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AMERICAN DIABETES ASSOCIATION

STANDARDS OF MEDICAL CARE IN DIABETES—2021

American Diabetes Association®

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Standards of Medical Care in Diabetes—2021

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THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

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—Norbert Freinkel, *Diabetes Care*, January-February 1978

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Introduction: *Standards of Medical Care in Diabetes—2021*

Diabetes Care 2020;44(Suppl. 1):S1–S2 | https://doi.org/10.2337/dc21-SINT

Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control. Ongoing diabetes self-management education and support are critical to preventing acute complications and reducing the risk of long-term complications. Significant evidence exists that supports a range of interventions to improve diabetes outcomes.

The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes," referred to as the Standards of Care, is intended to provide clinicians, patients, researchers, policy makers, and other interested individuals with the components of diabetes care, general treatment goals, and tools to evaluate the quality of care. The Standards of Care recommendations are not intended to preclude clinical judgment and must be applied in the context of excellent clinical care, with adjustments for individual preferences, comorbidities, and other patient factors. For more detailed information about the management of diabetes, please refer to *Medical Management of Type 1 Diabetes* (1) and *Medical Management of Type 2 Diabetes* (2).

The recommendations in the Standards of Care include screening, diagnostic, and therapeutic actions that are known or believed to favorably affect health outcomes of patients with diabetes. Many of these interventions have also been shown to be cost-effective (3,4).

The ADA strives to improve and update the Standards of Care to ensure that clinicians, health plans, and policy makers can continue to rely on it as the most authoritative source for current guidelines for diabetes care.

ADA STANDARDS, STATEMENTS, REPORTS, and REVIEWS

The ADA has been actively involved in the development and dissemination of diabetes care clinical practice recommendations and related documents for more than 30 years. The ADA's Standards of Medical Care is viewed as an important resource for health care professionals who care for people with diabetes.

Standards of Care

The annual Standards of Care supplement to* Diabetes Care *contains official ADA position, is authored by the ADA, and provides all of the ADA's current clinical practice recommendations.

To update the Standards of Care, the ADA's Professional Practice Committee (PPC) performs an extensive clinical diabetes literature search, supplemented with input from ADA staff and the medical community at large. The PPC updates the Standards of Care annually. However, the Standards of Care is a "living" document, where important updates are published online should the PPC determine that new evidence or regulatory changes (e.g., drug approvals, label changes) merit immediate inclusion. More information on the "living Standards" can be found on the ADA's professional website DiabetesPro at professional.diabetes.org/content-page/living-standards. The Standards of Care supersedes all previous ADA position statements—and the recommendations therein—on clinical topics within the purview of the Standards of Care; ADA position statements, while still containing valuable analysis, should not be considered the ADA's current position. The Standards of Care receives annual review and approval by the ADA's Board of Directors.

ADA Statement

An ADA statement is an official ADA point of view or belief that does not contain clinical practice recommendations and may be issued on advocacy, policy, economic, or medical issues related to diabetes.

ADA statements undergo a formal review process, including a review by the appropriate ADA national committee, ADA science and medicine staff, and the ADA's Board of Directors.

Consensus Report

A consensus report of a particular topic contains a comprehensive examination and is authored by an expert panel (i.e., consensus panel) and represents the panel's collective analysis, evaluation, and opinion.

The need for a consensus report arises when clinicians, scientists, regulators,

The "Standards of Medical Care in Diabetes" was originally approved in 1988. Most recent review/revision: December 2020.

Table 1—ADA evidence-grading system for "Standards of Medical Care in Diabetes"

Level of evidence	Description
A	Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, including • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis Compelling nonexperimental evidence, i.e., "all or none" rule developed by the Centre for Evidence-Based Medicine at the University of Oxford Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporated quality ratings in the analysis
B	Supportive evidence from well-conducted cohort studies • Evidence from a well-conducted prospective cohort study or registry • Evidence from a well-conducted meta-analysis of cohort studies Supportive evidence from a well-conducted case-control study
C	Supportive evidence from poorly controlled or uncontrolled studies • Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results • Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls) • Evidence from case series or case reports Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience

and/or policy makers desire guidance and/or clarity on a medical or scientific issue related to diabetes for which the evidence is contradictory, emerging, or incomplete. Consensus reports may also highlight gaps in evidence and propose areas of future research to address these gaps. A consensus report is not an ADA position but represents expert opinion only and is produced under the auspices of the ADA by invited experts. A consensus report may be developed after an ADA Clinical Conference or Research Symposium.

Scientific Review

A scientific review is a balanced review and analysis of the literature on a scientific or medical topic related to diabetes.

A scientific review is not an ADA position and does not contain clinical practice recommendations but is produced under the auspices of the ADA by invited experts. The scientific review may provide a scientific rationale for clinical practice recommendations in the Standards of Care. The category may also include task force and expert committee reports.

GRADING OF SCIENTIFIC EVIDENCE

Since the ADA first began publishing clinical practice guidelines, there has been considerable evolution in the evaluation of scientific evidence and in the development of evidence-based guidelines. In 2002, the ADA developed a classification system to grade the quality of scientific evidence supporting ADA recommendations. A 2015 analysis of the evidence cited in the Standards of Care found steady improvement in quality over the previous 10 years, with the 2014 Standards of Care for the first time having the majority of bulleted recommendations supported by **A** level or **B** level evidence (5). A grading system (**Table 1**) developed by the ADA and modeled after existing methods was used to clarify and codify the evidence that forms the basis for the recommendations. ADA recommendations are assigned ratings of **A**, **B**, or **C**, depending on the quality of the evidence in support of the recommendation. Expert opinion **E** is a separate category for recommendations in which there is no evidence from clinical trials, clinical trials may be impractical, or there is conflicting evidence. Recommendations with **A** level evidence are based on large well-designed clinical trials or well-done meta-analyses. Generally, these recommendations have the best chance of improving outcomes when applied to the population for which they are appropriate. Recommendations with lower levels of evidence may be equally important but are not as well supported.

Of course, published evidence is only one component of clinical decision-making. Clinicians care for patients, not populations; guidelines must always be interpreted with the individual patient in mind. Individual circumstances, such as comorbid and coexisting diseases, age, education, disability, and, above all, patients' values and preferences, must be considered and may lead to different treatment targets and strategies. Furthermore, conventional evidence hierarchies, such as the one adapted by the ADA, may miss nuances important in diabetes care. For example, although there is excellent evidence from clinical trials supporting the importance of achieving multiple risk factor control, the optimal way to achieve this result is less clear. It is difficult to assess each component of such a complex intervention.

References

1. American Diabetes Association. *Medical Management of Type 1 Diabetes*. 7th ed. Wang CC, Shah AC, Eds. Alexandria, VA, American Diabetes Association, 2017

2. American Diabetes Association. *Medical Management of Type 2 Diabetes*. 8th ed. Meneghini L, Ed. Alexandria, VA, American Diabetes Association, 2020

3. Zhou X, Siegel KR, Ng BP, Jawanda S, Proia KK, Zhang X, Albright AL, Zhang P. Cost-effectiveness of diabetes prevention interventions targeting high-risk individuals and whole populations: a systematic review. Diabetes Care 2020;43:1593–1616

4. Siegel KR, Ali MK, Zhou X, Ng BP, Jawanda S, Proia K, Zhang X, Gregg EW, Albright AL, Zhang P. Cost-effectiveness of interventions to manage diabetes: has the evidence changed since 2008? Diabetes Care 2020;43:1557–1592

5. Grant RW, Kirkman MS. Trends in the evidence level for the American Diabetes Association's "Standards of Medical Care in Diabetes" from 2005 to 2014. Diabetes Care 2015;38:6–8

Professional Practice Committee: *Standards of Medical Care in Diabetes—2021*

Diabetes Care 2021;44(Suppl. 1):S3| https://doi.org/10.2337/dc21-SPPC

The Professional Practice Committee (PPC) of the American Diabetes Association (ADA) is responsible for the "Standards of Medical Care in Diabetes," referred to as the Standards of Care. The PPC is a multidisciplinary expert committee comprising physicians, diabetes care and education specialists, and others who have expertise in a range of areas, including, but not limited to, adult and pediatric endocrinology, epidemiology, public health, cardiovascular risk management, microvascular complications, preconception and pregnancy care, weight management and diabetes prevention, and use of technology in diabetes management. Appointment to the PPC is based on excellence in clinical practice and research. Although the primary role of the PPC members is to review and update the Standards of Care, they may also be involved in ADA statements, reports, and reviews.

All members of the PPC are required to disclose potential conflicts of interest with industry and other relevant organizations. These disclosures are discussed at the outset of each Standards of Care revision meeting. Members of the committee, their employers, and their disclosed conflicts of interest are listed in "Disclosures: *Standards of Medical Care in Diabetes—2021*" (https://doi.org/10.2337/dc21-SPPC). The ADA funds development of the Standards of Care out of its general revenues and does not use industry support for this purpose.

Relevant literature was thoroughly reviewed through 1 July 2020; additionally, critical updates published through 1 September 2020 were considered. Recommendations were revised based on new evidence, new considerations for standard of care practices, or, in some cases, to clarify the prior recommendations or revise wording to match the strength of the published evidence. A table linking the changes in recommendations to new evidence can be reviewed online at professional.diabetes.org/SOC. The Standards of Care is approved by the ADA's Board of Directors, which includes health care professionals, scientists, and lay people.

Feedback from the larger clinical community was invaluable for the annual 2020 revision of the Standards of Care. Readers who wish to comment on the 2021 Standards of Care are invited to do so at professional.diabetes.org/SOC.

The PPC thanks the following individuals who provided their expertise in reviewing and/or consulting with the committee: Daniel DeSalvo, MD; Alison B. Evert, MS, RD, CDCES; Joy Hayes, MS, RDN, LD, CDCES; Ingrid M. Libman, MD, MPH, PhD; Aaron Michels, MD; Joshua J. Neumiller, PharmD, CDCES, FASCP; Richard Pratley, MD; Ellen W. Seely, MD; Dimitra Skondra, MD; Patti Urbanski, MEd, RD, LD, CDCES; Jenise C. Wong, MD, PhD; Jennifer Wyckoff, MD; and Ann Zmuda, DPM.

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Summary of Revisions: *Standards of Medical Care in Diabetes—2021*

American Diabetes Association

Diabetes Care 2021;44(Suppl. 1):S4–S6 | https://doi.org/10.2337/dc21-SREV

GENERAL CHANGES

The field of diabetes care is rapidly changing as new research, technology, and treatments that can improve the health and well-being of people with diabetes continue to emerge. With annual updates since 1989, the American Diabetes Association (ADA) has long been a leader in producing guidelines that capture the most current state of the field.

*Although levels of evidence for several recommendations have been updated, these changes are not outlined below where the clinical recommendation has remained the same. That is, changes in evidence level from, for example, **E** to **C** are not noted below. The 2021 Standards of Care contains, in addition to many minor changes that clarify recommendations or reflect new evidence, the following more substantive revisions.*

SECTION CHANGES

Section 1. Improving Care and Promoting Health in Populations

(https://doi.org/10.2337/dc21-S001)

Additional information has been included on social determinants of health in diabetes to reflect the evidence presented in "Social Determinants of Health in Diabetes: A Scientific Review," (https://doi.org/10.2337/dci20-0053), including a change to Recommendation 1.5.

The concept of "cost-related medication nonadherence" has been added to the "Cost Considerations" subsection.

Section 2. Classification and Diagnosis of Diabetes

(https://doi.org/10.2337/dc21-S002)

More discussion about use of the term LADA (latent autoimmune diabetes in adults) has been added to the section.

Guidance on use of point-of-care A1C assays for the diagnosis of diabetes has been clarified.

A recommendation about screening for diabetes and prediabetes in patients with HIV (Recommendation 2.14), as well as the in-text discussion on the topic, has been moved to this section. This content was previously in Section 4 "Comprehensive Medical Evaluation and Assessment of Comorbidities" (https://doi.org/10.2337/dc21-S004).

Additional evidence has been added to the subsection "Cystic Fibrosis–Related Diabetes" (CFRD) regarding early diagnosis and treatment of CFRD and reported increases in CFRD.

Additional evidence has also been added to the "Posttransplantation Diabetes Mellitus" subsection.

Section 3. Prevention or Delay of Type 2 Diabetes

(https://doi.org/10.2337/dc21-S003)

A new subsection, "Delivery and Dissemination of Lifestyle Behavior Change for Diabetes Prevention," was created to describe evidence for broader dissemination of and national efforts for lifestyle behavior change programs to prevent diabetes.

Additional guidance and evidence have been added to the newly named "Prevention of Vascular Disease and Mortality" subsection (previously called "Prevention of Cardiovascular Disease") and include data from longer-term follow up diabetes prevention studies.

Section 4. Comprehensive Medical Evaluation and Assessment of Comorbidities

(https://doi.org/10.2337/dc21-S004)

Regarding ongoing management, Recommendation 4.5 has been modified to include overall health status, risk of hypoglycemia, and cardiovascular risk using the risk calculator. Recommendation 4.6 was eliminated.

The "Immunizations" subsection has been significantly revised, and vaccine-specific recommendations were removed. **Table 4.5** was added containing Centers for Disease Control and Prevention–recommended vaccinations for people with diabetes. More information has been added to the discussion of each vaccine, including important considerations related to coronavirus disease 2019 (COVID-19).

The recommendation on pancreatitis was removed because the guidance is more appropriately covered in the discussion of the evidence in the subsection text.

Additional evidence on hearing impairment has been added to the "Sensory Impairment" subsection, and audiology has been added as a consideration to the table on referrals for initial care management (**Table 4.4**).

The HIV recommendation and discussion were removed from this section and can now be found in Section 2 "Classification

and Diagnosis of Diabetes" (https://doi.org/10.2337/dc21-S002).

More information on determining testosterone levels has been added to the "Low Testosterone in Men" subsection, and readers are now referred to the Endocrine Society Clinical Practice Guideline (https://doi.org/10.1210/jc.2018-00229) for more detailed recommendations.

Table 4.1, "Components of the Comprehensive Diabetes Medical Evaluation at Initial, Follow-up, and Annual Visits," was reorganized and revised to include a number of additional factors, including social determinants of health and identification of surrogate decision maker and advanced care plan.

Section 5. Facilitating Behavior Change and Well-being to Improve Health Outcomes

(https://doi.org/10.2337/dc21-S005)

Based on "Diabetes Self-management Education and Support in Adults With Type 2 Diabetes: A Consensus Report of the American Diabetes Association, the Association of Diabetes Care & Education Specialists, the Academy of Nutrition and Dietetics, the American Academy of Family Physicians, the American Academy of PAs, the American Association of Nurse Practitioners, and the American Pharmacists Association," published in June 2020 (https://doi.org/10.2337/dci20-0023), Recommendations 5.6 and 5.7 regarding barriers to diabetes self-management education and support (DSMES) have been added. The four critical times DSMES needs should be evaluated have been revised based on the consensus report. Additional evidence on the usefulness of DSMES and ways to address barriers has been included.

The "Carbohydrates" and "Fats" subsections have been revised to include additional guidance and studies related to these macronutrients.

Recommendation 5.29 has been added to the "Physical Activity" subsection to address baseline physical activity and sedentary time and to encourage the promotion of nonsedentary activities above baseline for sedentary individuals with diabetes.

Recommendation 5.34 has been added for smoking cessation, which can be addressed as part of diabetes education programs.

The concept of mindful self-compassion has been added to the "Diabetes Distress" subsection, discussing its effects on diabetes.

Section 6. Glycemic Targets

(https://doi.org/10.2337/dc21-S006)

The "A1C" subsection was retitled "Glycemic Assessment," with respective changes to Recommendations 6.1 and 6.2 to allow for other glycemic measures aside from A1C.

Recommendation 6.3 was removed.

The "Glycemic Goals" subsection has also been revised to include other glycemic measures, and the recommendation for glycemic goals for many nonpregnant adults without significant hypoglycemia has been divided in two parts (Recommendations 6.5a and 6.5b) to include time-in-range goals.

Figure 6.1 has been revised and no longer includes example patient-specific data.

More discussion has been added to the "A1C and Microvascular Complications" subsection.

Recommendation 6.9 regarding hypoglycemia assessment has been revised and now recommends that occurrence of and risk for hypoglycemia should be reviewed at every encounter and investigated as indicated.

Section 7. Diabetes Technology

(https://doi.org/10.2337/dc21-S007)

Recommendations 7.9–7.13 in the "Continuous Glucose Monitoring Devices" subsection have been revised, and "blinded" continuous glucose monitoring (CGM) is now referred to as "professional CGM," which is clinic-based and can include blinded and real-time devices. **Table 7.3** has been updated to reflect this change as well. Recommendations 7.9–7.11 now recommend CGM as useful for people with diabetes on multiple daily injections and continuous subcutaneous insulin infusions and other forms of insulin therapy (with different levels of evidence) not defined by type of diabetes or age.

Recommendation 7.14 regarding skin reactions with use of CGM has been added. This section has also been updated to include information on the evolving evidence and a new discussion on education and training.

The "Insulin Delivery" subsection has also been revised, and the recommendation on examination of insulin injection/infusion site was removed.

Recommendation 7.27 regarding inpatient use of devices was moved to later in the section where use in the inpatient setting is more fully discussed. The use of CGM in the hospital during the COVID-19 pandemic is also reviewed in the "Inpatient Care" subsection.

Recommendation 7.21 on insulin pump use for people with type 2 diabetes and other forms of diabetes with multiple daily injections has been added to the "Insulin Pumps" subsection, with additional discussion. Information on insulin pump use in older adults has been added as well.

The possible benefit of systems that combine technology and online coaching has been added to Recommendation 7.26.

Section 8. Obesity Management for the Treatment of Type 2 Diabetes

(https://doi.org/10.2337/dc21-S008)

The concept of patient-centered communication that uses nonjudgmental language has been added as Recommendation 8.1, with additional discussion in the "Assessment" subsection. The subsection on "Diet, Physical Activity, and Behavioral Therapy" has been updated, including more thorough discussion of health outcomes of weight loss. Based on the publication "Social Determinants of Health in Diabetes: A Scientific Review" (https://doi.org/10.2337/dci20-0053), considerations related to social determinants of health have been added in this subsection as well.

More detail has been added to the "Pharmacotherapy" subsection, particularly focused on assessing efficacy and safety.

Section 9. Pharmacologic Approaches to Glycemic Treatment

(https://doi.org/10.2337/dc21-S009)

Additional evidence has been added to the discussion of use of sensor-augmented insulin pumps.

The concept that improved technologies and treatments would require reconsideration of the role of pancreas and islet transplantation has been removed.

Recommendation 9.13 and the related discussion have been added cautioning providers of the potential for overbasalization with insulin therapy.

Table 9.1 has been updated.

Figure 9.1 has been revised to include a dedicated decision pathway for chronic kidney disease and a dedicated decision pathway for heart failure, with updates to reflect consensus interpretation of clinical trial data.

Figure 9.2 has also been revised to include assessment of adequacy of insulin dose and updates in regard to the use of glucagon-like peptide 1 receptor agonists.

Section 10. Cardiovascular Disease and Risk Management

(https://doi.org/10.2337/dc21-S010)

This section is endorsed for the third consecutive year by the American College of Cardiology.

The section has been revised to acknowledge that few trials have been specifically designed to assess the impact of cardiovascular risk reduction strategies in patients with type 1 diabetes.

A lower limit has been added to Recommendation 10.6 regarding pregnant patients with diabetes and preexisting hypertension.

ACE inhibitors or angiotensin receptor blockers as first-line therapy for hypertension in people with diabetes and coronary artery disease has been added as Recommendation 10.10, with additional discussion.

The ODYSSEY OUTCOMES trial has been added to the "Combination Therapy for LDL Cholesterol Lowering" subsection.

Recommendations 10.37 and 10.38 have been added to the "Antiplatelet Agents" subsection regarding long-term dual antiplatelet therapy and combination therapy with aspirin plus low dose rivaroxaban, respectively. New evidence from THEMIS, THEMIS-PCI, COMPASS, and VOYAGER PAD has also been added to the "Antiplatelet Agents" subsection.

Recommendations 10.43–10.47 regarding treatment in the "Cardiovascular Disease" subsection have been revised to include the evolving evidence from cardiovascular outcomes trials.

Table 10.3*A* is now titled "Cardiovascular and Cardiorenal Outcomes Trials of Available Antihyperglycemic Medications Completed After the Issuance of the FDA 2008 Guidelines: DPP-4 Inhibitors," and the CAROLINA trial has been added.

Table 10.3*B* is now titled "Cardiovascular and Cardiorenal Outcomes Trials of Available Antihyperglycemic Medications Completed After the Issuance of the FDA 2008 Guidelines: GLP-1 Receptor Agonists," and the PIONEER-6 trial has been added.

Table 10.3*C* is now titled "Cardiovascular and Cardiorenal Outcomes Trials of Available Antihyperglycemic Medications Completed After the Issuance of the FDA 2008 Guidelines: SGLT2 Inhibitors," and the CREDENCE and DAPA-HF trials have been added.

Section 11. Microvascular Complications and Foot Care

(https://doi.org/10.2337/dc21-S011)

Recommendation 11.3 on treatment for chronic kidney disease has been divided into three recommendations (11.3a, 11.3b, and 11.3c) to individualize treatment based on renal function and risk of cardiovascular disease.

Section 12. Older Adults

(https://doi.org/10.2337/dc21-S012)

Recommendations 12.4 and 12.5 and discussion in the "Hypoglycemia" subsection have been modified, and a new recommendation on the use of continuous glucose monitoring for the reduction of hypoglycemia has been added based on findings from the Wireless Innovation in Seniors with Diabetes Mellitus (WISDM) trial.

The reasonable A1C goal for older adults who are otherwise healthy with few coexisting chronic illnesses and intact cognitive function and functional status has been modified to A1C $<$7.0–7.5% (53–58 mmol/mol). This change is reflected in **Table 12.1** as well. Fasting or preprandial and bedtime glucose levels for healthy older adults have also been revised in this table.

Recommendation 12.12 and accompanying review of the evidence on weight loss has been added to the "Lifestyle Management" subsection.

In the "Pharmacologic Therapy" subsection, for the very complex older patient in poor health in **Table 12.2**, avoiding reliance on A1C and avoiding hypoglycemia and symptomatic hyperglycemia were added as a reasonable A1C/treatment goal.

The example treatment goal for older adults who are otherwise healthy with few coexisting chronic illnesses and intact cognitive function and functional status has been modified to A1C $<$7.0–7.5% (53–58 mmol/mol).

Additional considerations and discussion of findings have been added to the "Incretin-based Therapies" and "Sodium–Glucose Cotransporter 2 Inhibitors" subsections.

Section 13. Children and Adolescents

(https://doi.org/10.2337/dc21-S013)

To incorporate social determinants of health, a new recommendation on assessment of food security, housing stability/homelessness, health literacy, financial barriers, and social/community support and its application to treatment decisions has been added to the type 1 (Recommendation 13.12) and type 2 diabetes (Recommendation 13.105) sections.

Three new recommendations, one on real-time CGM (Recommendation 13.20), one on intermittently scanned CGM (Recommendation 13.21), and another on use of CGM metrics from the most recent 14 days (Recommendation 13.27), have been added to the type 1 diabetes "Glycemic Control" subsection.

For physical activity in youth with prediabetes and type 2 diabetes, Recommendation 13.58 has been changed to at least 60 min daily, with bone and muscle strength training at least 3 days per week.

Figure 13.1 has been revised to better represent current guidance for management of new-onset diabetes in youth with overweight or obesity with clinical suspicion of type 2 diabetes.

Section 14. Management of Diabetes in Pregnancy

(https://doi.org/10.2337/dc21-S0014)

The information on insulin requirements during pregnancy in the "Insulin Physiology" subsection has been clarified.

Lower limits have been added to the recommended glycemic targets for type 1 and type 2 diabetes in pregnancy, though they do not apply to diet-controlled type 2 diabetes in pregnancy.

More information on CGM in pregnancy, specifically on time in range and target ranges for women with type 1 diabetes in pregnancy, has been added.

The guidance on use of hybrid closed-loop systems during pregnancy has been updated with new considerations.

Recommendation 14.18 and narrative in the "Preeclampsia and Aspirin" subsection have been revised to include more information on aspirin dosing and the insufficient data available on its use for pregnant women with preexisting diabetes.

A lower limit has been added to Recommendation 14.19 regarding pregnant patients with diabetes and chronic hypertension.

Section 15. Diabetes Care in the Hospital

(https://doi.org/10.2337/dc21-S0015)

Additional information has been added on enteral and parenteral feeding and insulin requirements.

The "Glucocorticoid Therapy" subsection has been revised to include more guidance on use of NPH insulin with steroids.

Section 16. Diabetes Advocacy

(https://doi.org/10.2337/dc21-S016)

No changes have been made to this section.

1. Improving Care and Promoting Health in Populations: *Standards of Medical Care in Diabetes—2021*

American Diabetes Association

Diabetes Care 2021;44(Suppl. 1):S7–S14 | https://doi.org/10.2337/dc21-s001

The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc21-SPPC), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc21-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

DIABETES AND POPULATION HEALTH

Recommendations

1.1 Ensure treatment decisions are timely, rely on evidence-based guidelines, and are made collaboratively with patients based on individual preferences, prognoses, and comorbidities. **B**

1.2 Align approaches to diabetes management with the Chronic Care Model. This model emphasizes person-centered team care, integrated long-term treatment approaches to diabetes and comorbidities, and ongoing collaborative communication and goal setting between all team members. **A**

1.3 Care systems should facilitate team-based care and utilization of patient registries, decision support tools, and community involvement to meet patient needs. **B**

1.4 Assess diabetes health care maintenance (see **Table 4.1**) using reliable and relevant data metrics to improve processes of care and health outcomes, with attention to care costs. **B**

Population health is defined as "the health outcomes of a group of individuals, including the distribution of health outcomes within the group"; these outcomes can be measured in terms of health outcomes (mortality, morbidity, health, and functional status), disease burden (incidence and prevalence), and behavioral and metabolic factors (exercise, diet, A1C, etc.) (1). Clinical practice recommendations for health care providers are tools that can ultimately improve health across populations; however, for optimal outcomes, diabetes care must also be individualized for each patient. Thus, efforts to improve population health will require a combination of policy-level, system-level, and patient-level approaches. With such an integrated approach in

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mind, the American Diabetes Association (ADA) highlights the importance of *patient-centered care*, defined as care that considers individual patient comorbidities and prognoses; is respectful of and responsive to patient preferences, needs, and values; and ensures that patient values guide all clinical decisions (2). Further, social determinants of health (SDOH)—often out of direct control of the individual and potentially representing lifelong risk—contribute to medical and psychosocial outcomes and must be addressed to improve all health outcomes (3). Clinical practice recommendations, whether based on evidence or expert opinion, are intended to guide an overall approach to care. The science and art of medicine come together when the clinician is faced with making treatment recommendations for a patient who may not meet the eligibility criteria used in the studies on which guidelines are based. Recognizing that one size does not fit all, the standards presented here provide guidance for when and how to adapt recommendations for an individual.

Care Delivery Systems

The proportion of patients with diabetes who achieve recommended A1C, blood pressure, and LDL cholesterol levels has fluctuated in recent years (4). Glycemic control and control of cholesterol through dietary intake remain challenging. In 2013–2016, 64% of adults with diagnosed diabetes met individualized A1C target levels, 70% achieved recommended blood pressure control, 57% met the LDL cholesterol target level, and 85% were nonsmokers (4). Only 23% met targets for glycemic, blood pressure, and LDL cholesterol measures while also avoiding smoking (4). The mean A1C nationally among people with diabetes increased slightly from 7.3% in 2005–2008 to 7.5% in 2013–2016 based on the National Health and Nutrition Examination Survey (NHANES), with younger adults, women, and non-Hispanic Black individuals less likely to meet treatment targets (4). Certain segments of the population, such as young adults and patients with complex comorbidities, financial or other social hardships, and/or limited English proficiency, face particular challenges to goal-based care (5–7). Even after adjusting for these patient factors, the persistent variability in the quality of diabetes care across providers and practice settings indicates that substantial system-level improvements are still needed.

Diabetes poses a significant financial burden to individuals and society. It is estimated that the annual cost of diagnosed diabetes in 2017 was $327 billion, including $237 billion in direct medical costs and $90 billion in reduced productivity. After adjusting for inflation, economic costs of diabetes increased by 26% from 2012 to 2017 (8). This is attributed to the increased prevalence of diabetes and the increased cost per person with diabetes. Ongoing population health strategies are needed in order to reduce costs and provide optimized care.

Chronic Care Model

Numerous interventions to improve adherence to the recommended standards have been implemented. However, a major barrier to optimal care is a delivery system that is often fragmented, lacks clinical information capabilities, duplicates services, and is poorly designed for the coordinated delivery of chronic care. The Chronic Care Model (CCM) takes these factors into consideration and is an effective framework for improving the quality of diabetes care (9).

Six Core Elements. The CCM includes six core elements to optimize the care of patients with chronic disease:

1. Delivery system design (moving from a *reactive* to a *proactive* care delivery system where planned visits are coordinated through a team-based approach)
2. Self-management support
3. Decision support (basing care on evidence-based, effective care guidelines)
4. Clinical information systems (using registries that can provide patient-specific and population-based support to the care team)
5. Community resources and policies (identifying or developing resources to support healthy lifestyles)
6. Health systems (to create a quality-oriented culture)

A 5-year effectiveness study of the CCM in 53,436 primary care patients with type 2 diabetes suggested that the use of this model of care delivery reduced the cumulative incidence of diabetes-related complications and all-cause mortality (10). Patients who were enrolled in the CCM experienced a reduction in cardiovascular disease (CVD) risk by 56.6%, microvascular complications by 11.9%, and mortality by 66.1% (10). The same study suggested that health care utilization was lower in the CCM group, which resulted in health care savings of $7,294 per individual over the study period (11).

Redefining the roles of the health care delivery team and empowering patient self-management are fundamental to the successful implementation of the CCM (12). Collaborative, multidisciplinary teams are best suited to provide care for people with chronic conditions such as diabetes and to facilitate patients' self-management (13–15). There are references to guide the implementation of the CCM into diabetes care delivery, including opportunities and challenges (16).

Strategies for System-Level Improvement

Optimal diabetes management requires an organized, systematic approach and the involvement of a coordinated team of dedicated health care professionals working in an environment where patient-centered, high-quality care is a priority (7,17,18). While many diabetes processes of care have improved nationally in the past decade, the overall quality of care for patients with diabetes remains suboptimal (4). Efforts to increase the quality of diabetes care include providing care that is concordant with evidence-based guidelines (19); expanding the role of teams to implement more intensive disease management strategies (7,20,21); tracking medication-taking behavior at a systems level (22); redesigning the organization of the care process (23); implementing electronic health record tools (24,25); empowering and educating patients (26,27); removing financial barriers and reducing patient out-of-pocket costs for diabetes education, eye exams, diabetes technology, and necessary medications (7); assessing and addressing psychosocial issues (28,29); and identifying, developing, and engaging community resources and public policies that support healthy lifestyles (30). The National Diabetes Education Program maintains an online resource (www.cdc.gov/diabetes/ndep/training-tech-assistance/index.html) to help health care professionals design and implement more effective health care delivery systems for those with diabetes. Given the pluralistic needs of patients with diabetes and how the constant challenges they experience vary over the course of disease management (complex

insulin regimens, new technology, etc.), a diverse team with complementary expertise is consistently recommended (31).

Care Teams

The care team, which centers around the patient, should avoid therapeutic inertia and prioritize timely and appropriate intensification of lifestyle and/or pharmacologic therapy for patients who have not achieved the recommended metabolic targets (32–34). Strategies shown to improve care team behavior and thereby catalyze reductions in A1C, blood pressure, and/or LDL cholesterol include engaging in explicit and collaborative goal setting with patients (35,36); identifying and addressing language, numeracy, or cultural barriers to care (37–39); integrating evidence-based guidelines and clinical information tools into the process of care (19,40,41); soliciting performance feedback, setting reminders, and providing structured care (e.g., guidelines, formal case management, and patient education resources) (7); and incorporating care management teams including nurses, dietitians, pharmacists, and other providers (20,42). Initiatives such as the Patient-Centered Medical Home show promise for improving health outcomes by fostering comprehensive primary care and offering new opportunities for team-based chronic disease management (43).

Telemedicine

Telemedicine is a growing field that may increase access to care for patients with diabetes. The American Telemedicine Association defines telemedicine as the use of medical information exchanged from one site to another via electronic communications to improve a patient's clinical health status. Telemedicine includes a growing variety of applications and services using two-way video, smartphones, wireless tools, and other forms of telecommunications technology (44). Increasingly, evidence suggests that various telemedicine modalities may be effective at reducing A1C in patients with type 2 diabetes compared with usual care or in addition to usual care (45). For rural populations or those with limited physical access to health care, telemedicine has a growing body of evidence for its effectiveness, particularly with regard to glycemic control as measured by A1C (46–48). Interactive strategies that facilitate communication between providers and patients, including the use of web-based portals or text messaging and those that incorporate medication adjustment, appear more effective. Telemedicine and other virtual environments can also be used to offer diabetes self-management education and clinical support and remove geographic and transportation barriers for patients living in underresourced areas or with disabilities (49). There is limited data available on the cost-effectiveness of these strategies.

Behaviors and Well-being

Successful diabetes care also requires a systematic approach to supporting patients' behavior-change efforts. High-quality diabetes self-management education and support (DSMES) has been shown to improve patient self-management, satisfaction, and glucose outcomes. National DSMES standards call for an integrated approach that includes clinical content and skills, behavioral strategies (goal setting, problem solving), and engagement with psychosocial concerns (29). For more information on DSMES, see Section 5 "Facilitating Behavior Change and Well-being to Improve Health Outcomes" (https://doi.org/10.2337/dc21-S005).

Cost Considerations

The cost of diabetes medications, particularly insulin, is an ongoing barrier to achieving glycemic goals. Up to 25% of patients who are prescribed insulin report cost-related insulin underuse (50). Insulin underuse due to cost has also been termed cost-related medication nonadherence (CRN). The cost of insulin has continued to increase in recent years for reasons that are not entirely clear. There are recommendations from the ADA Insulin Access and Affordability Working Group for approaches to this issue from a systems level (51). Recommendations including concepts such as cost-sharing for insured people with diabetes should be based on the lowest price available, list price for insulins that closely reflect net price, and health plans that ensure that people with diabetes can access insulin without undue administrative burden or excessive cost (51). Reduction in CRN is associated with better biologic and psychologic outcomes, including quality of life.

Access to Care and Quality Improvement

The Affordable Care Act and Medicaid expansion have resulted in increased access to care for many individuals with diabetes with an emphasis on the protection of people with preexisting conditions, health promotion, and disease prevention (52). In fact, health insurance coverage increased from 84.7% in 2009 to 90.1% in 2016 for adults with diabetes aged 18–64 years. Coverage for those ≥65 years remained nearly universal (53). Patients who have either private or public insurance coverage are more likely to meet quality indicators for diabetes care (54). As mandated by the Affordable Care Act, the Agency for Healthcare Research and Quality developed a National Quality Strategy based on the triple aims that include improving the health of a population, overall quality and patient experience of care, and per capita cost (55,56). As health care systems and practices adapt to the changing landscape of health care, it will be important to integrate traditional disease-specific metrics with measures of patient experience, as well as cost, in assessing the quality of diabetes care (57,58). Information and guidance specific to quality improvement and practice transformation for diabetes care is available from the National Institute of Diabetes and Digestive and Kidney Diseases guidance on diabetes care and quality (59). Using patient registries and electronic health records, health systems can evaluate the quality of diabetes care being delivered and perform intervention cycles as part of quality improvement strategies (60). Improvement of health literacy and numeracy is also a necessary component to improve care (61,62). Critical to these efforts is provider adherence to clinical practice recommendations (see **Table 4.1**) and the use of accurate, reliable data metrics that include sociodemographic variables to examine health equity within and across populations (63).

In addition to quality improvement efforts, other strategies that simultaneously improve the quality of care and potentially reduce costs are gaining momentum and include reimbursement structures that, in contrast to visit-based billing, reward the provision of appropriate and high-quality care to achieve metabolic goals (64) and incentives that accommodate personalized care goals (7,65). (Also see COST CONSIDERATIONS above regarding CRN reduction.)

TAILORING TREATMENT FOR SOCIAL CONTEXT

Recommendations

1.5 Assess food insecurity, housing insecurity/homelessness, financial barriers, and social capital/social community support and apply that information to treatment decisions. **A**

1.6 Refer patients to local community resources when available. **B**

1.7 Provide patients with self-management support from lay health coaches, navigators, or community health workers when available. **A**

Health inequities related to diabetes and its complications are well documented, heavily influenced by SDOH, and have been associated with greater risk for diabetes, higher population prevalence, and poorer diabetes outcomes (66–70). SDOH are defined as the economic, environmental, political, and social conditions in which people live and are responsible for a major part of health inequality worldwide (71). Greater exposure to adverse SDOH over the life-course results in worse health (72). The ADA recognizes the association between social and environmental factors and the prevention and treatment of diabetes and has issued a call for research that seeks to better understand how these social determinants influence behaviors and how the relationships between these variables might be modified for the prevention and management of diabetes (73,74). While a comprehensive strategy to reduce diabetes-related health inequities in populations has not been formally studied, general recommendations from other chronic disease management and prevention models can be drawn upon to inform systems-level strategies in diabetes (75). For example, the National Academy of Medicine has published a framework for educating health care professionals on the importance of SDOH (76). Furthermore, there are resources available for the inclusion of standardized sociodemographic variables in electronic medical records to facilitate the measurement of health inequities as well as the impact of interventions designed to reduce those inequities (76–78).

SDOH are not always recognized and often go undiscussed in the clinical encounter (69). A study by Piette et al. (79) found that among patients with chronic illnesses, two-thirds of those who reported not taking medications as prescribed due to CRN never shared this with their physician. In a study using data from the National Health Interview Survey (NHIS), Patel et al. (69) found that one-half of adults with diabetes reported financial stress and one-fifth reported food insecurity. One population in which such issues must be considered is older adults, where social difficulties may impair the quality of life and increase the risk of functional dependency (80) (see Section 12 "Older Adults," https://doi.org/10.2337/dc21-S012, for a detailed discussion of social considerations in older adults). Creating systems-level mechanisms to screen for SDOH may help overcome structural barriers and communication gaps between patients and providers (69,81). In addition, brief, validated screening tools for some SDOH exist and could facilitate discussion around factors that significantly impact treatment during the clinical encounter. Below is a discussion of assessment and treatment considerations in the context of food insecurity, homelessness, limited English proficiency, limited health literacy, and low literacy.

Food Insecurity

Food insecurity is the unreliable availability of nutritious food and the inability to consistently obtain food without resorting to socially unacceptable practices. Over 18% of the U.S. population reported food insecurity between 2005 and 2014 (82). The rate is higher in some racial/ethnic minority groups, including African American and Latino populations, low-income households, and homes headed by a single mother. The rate of food insecurity in individuals with diabetes may be up to 20% (83). Additionally, the risk for type 2 diabetes is increased twofold in those with food insecurity (73) and has been associated with low adherence to taking medications appropriately and recommended self-care behaviors, depression, diabetes distress, and worse glycemic control when compared with individuals who are food secure (84,85). Older adults with food insecurity are more likely to have emergency department visits and hospitalizations compared with older adults who do not report food insecurity (86). Risk for food insecurity can be assessed with a validated two-item screening tool (87) that includes the statements: *1*) "Within the past 12 months we worried whether our food would run out before we got money to buy more" and *2*) "Within the past 12 months the food we bought just didn't last and we didn't have money to get more." An affirmative response to either statement had a sensitivity of 97% and specificity of 83%. Interventions such as food prescription programs are considered promising practices to address food insecurity by integrating community resources into primary care settings and directly deal with food deserts in underserved communities (88,89).

Treatment Considerations

In those with diabetes and food insecurity, the priority is mitigating the increased risk for uncontrolled hyperglycemia and severe hypoglycemia. Reasons for the increased risk of hyperglycemia include the steady consumption of inexpensive carbohydrate-rich processed foods, binge eating, financial constraints to filling diabetes medication prescriptions, and anxiety/depression leading to poor diabetes self-care behaviors. Hypoglycemia can occur as a result of inadequate or erratic carbohydrate consumption following the administration of sulfonylureas or insulin. See **Table 9.1** for drug-specific and patient factors, including cost and risk of hypoglycemia, which may be important considerations for adults with food insecurity and type 2 diabetes. Providers should consider these factors when making treatment decisions in people with food insecurity and seek local resources that might help patients with diabetes and their family members to more regularly obtain nutritious food (90).

Homelessness and Housing Insecurity

Homelessness/housing insecurity often accompanies many additional barriers to diabetes self-management, including food insecurity, literacy and numeracy deficiencies, lack of insurance, cognitive dysfunction, and mental health issues (91). The prevalence of diabetes in the homeless population is estimated to be around 8% (92). Additionally, patients with diabetes who are homeless need secure places to keep their diabetes supplies, as well as refrigerator access to properly store their

insulin and take it on a regular schedule. Risk for homelessness can be ascertained using a brief risk assessment tool developed and validated for use among veterans (93). Housing insecurity has also been shown to be directly associated with a person's ability to maintain their diabetes self-management (94). Given the potential challenges, providers who care for either homeless or housing-insecure individuals should be familiar with resources or have access to social workers that can facilitate stable housing for their patients as a way to improve diabetes care (95).

Migrant and Seasonal Agricultural Workers

Migrant and seasonal agricultural workers may have a higher risk of type 2 diabetes than the overall population. While migrant farmworker–specific data are lacking, most agricultural workers in the U.S. are Latino, a population with a high rate of type 2 diabetes. Living in severe poverty brings with it food insecurity, high chronic stress, and increased risk of diabetes; there is also an association between the use of certain pesticides and the incidence of diabetes (96).

Data from the Department of Labor indicates that there are 2.5–3 million agricultural workers in the U.S., and these agricultural workers travel throughout the country serving as the backbone for a multibillion-dollar agricultural industry. According to 2018 health center data, 174 health centers across the U.S. reported that they provided health care services to 579,806 adult agricultural patients, and 78,332 had encounters for diabetes (13.5%) (97).

Migrant farmworkers encounter numerous and overlapping barriers to receiving care. Migration, which may occur as frequently as every few weeks for farmworkers, disrupts care. Cultural and linguistic barriers, lack of transportation and money, lack of available work hours, unfamiliarity with new communities, lack of access to resources, and other barriers prevent migrant farmworkers from accessing health care. Without regular care, those with diabetes may suffer severe and often expensive complications that affect quality of life.

Health care providers should be attuned to the working and living conditions of all patients. If a migrant farmworker with diabetes presents for care, appropriate referrals should be initiated to social workers and community resources, as available, to assist with removing barriers to care.

Language Barriers

Providers who care for non–English speakers should develop or offer educational programs and materials in multiple languages with the specific goals of preventing diabetes and building diabetes awareness in people who cannot easily read or write in English. The National Standards for Culturally and Linguistically Appropriate Services in Health and Health Care (National CLAS Standards) provide guidance on how health care providers can reduce language barriers by improving their cultural competency, addressing health literacy, and ensuring communication with language assistance (98). The National CLAS Standards website (https://thinkculturalhealth.hhs.gov) offers a number of resources and materials that can be used to improve the quality of care delivery to non–English-speaking patients (98).

Health Literacy

Health literacy is defined as the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate decisions (61). Health literacy is strongly associated with patients being able to engage in complex disease management and self-care (99). Approximately 80 million adults in the U.S. are estimated to have limited or low health literacy (62). Clinicians and diabetes care and education specialists should ensure they provide easy-to-understand information and reduce unnecessary complexity when developing care plans with patients. Interventions addressing low health literacy in populations with diabetes seem effective in improving diabetes outcomes, including ones focusing primarily on patient education, self-care training, or disease management. Combining easily adapted materials with formal diabetes education demonstrates effectiveness on clinical and behavioral outcomes in populations with low literacy (100). However, evidence supporting these strategies is largely limited to observational studies, and more research is needed to investigate the most effective strategies for enhancing both acquisition and retention of diabetes knowledge, as well as to examine different media and strategies for delivering interventions to patients (37).

Social Capital/Community Support

Social capital, which comprises community and personal network instrumental support, promotes better health, whereas lack of social support is associated with poorer health outcomes in individuals with diabetes (74). Of particular concern are the SDOH of racism and discrimination, which are likely to be lifelong (101). These factors are rarely addressed in routine treatment or disease management but may drive underlying causes of nonadherence to regimen behaviors. Identification or development of community resources to support healthy lifestyles is a core element of the CCM (9) with particular need to incorporate relevant social support networks. There is currently a paucity of evidence regarding enhancement of these resources for those most likely to benefit from such intervention strategies.

Health care community linkages are receiving increasing attention from the American Medical Association, the Agency for Healthcare Research and Quality, and others as a means of promoting translation of clinical recommendations for lifestyle modification in real-world settings (102). Community health workers (CHWs) (103), peer supporters (104–106), and lay leaders (107) may assist in the delivery of DSMES services (76,108), particularly in underserved communities. A CHW is defined by the American Public Health Association as a "frontline public health worker who is a trusted member of and/or has an unusually close understanding of the community served" (109). CHWs can be part of a cost-effective, evidence-based strategy to improve the management of diabetes and cardiovascular risk factors in underserved communities and health care systems (110).

References

1. Kindig D, Stoddart G. What is population health? Am J Public Health 2003;93:380–383
2. Institute of Medicine, Committee on Quality of Health Care in America. *Crossing the Quality Chasm: A New Health System for the 21st Century.* Washington, DC, National Academies Press, 2001. PMID: 25057539
3. Haire-Joshu D, Hill-Briggs F. The next generation of diabetes translation: a path to health equity. Annu Rev Public Health 2019;40:391–410
4. Kazemian P, Shebl FM, McCann N, Walensky RP, Wexler DJ. Evaluation of the cascade of diabetes care in the United States, 2005-2016. JAMA Intern Med 2019;179:1376–1385

5. Kerr EA, Heisler M, Krein SL, et al. Beyond comorbidity counts: how do comorbidity type and severity influence diabetes patients' treatment priorities and self-management? J Gen Intern Med 2007;22:1635–1640
6. Fernandez A, Schillinger D, Warton EM, et al. Language barriers, physician-patient language concordance, and glycemic control among insured Latinos with diabetes: the Diabetes Study of Northern California (DISTANCE). J Gen Intern Med 2011;26:170–176
7. TRIAD Study Group. Health systems, patients factors, and quality of care for diabetes: a synthesis of findings from the TRIAD study. Diabetes Care 2010;33:940–947
8. American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. Diabetes Care 2018;41:917–928
9. Stellefson M, Dipnarine K, Stopka C. The chronic care model and diabetes management in US primary care settings: a systematic review. Prev Chronic Dis 2013;10:E26
10. Wan EYF, Fung CSC, Jiao FF, et al. Five-year effectiveness of the multidisciplinary Risk Assessment and Management Programme-Diabetes Mellitus (RAMP-DM) on diabetes-related complications and health service uses. A population-based and propensity-matched cohort study. Diabetes Care 2018;41:49–59
11. Jiao FF, Fung CSC, Wan EYF, et al. Five-year cost-effectiveness of the Multidisciplinary Risk Assessment and Management Programme-Diabetes Mellitus (RAMP-DM). Diabetes Care 2018;41: 250–257
12. Coleman K, Austin BT, Brach C, Wagner EH. Evidence on the Chronic Care Model in the new millennium. Health Aff (Millwood) 2009;28:75–85
13. Piatt GA, Anderson RM, Brooks MM, et al. 3-year follow-up of clinical and behavioral improvements following a multifaceted diabetes care intervention: results of a randomized controlled trial. Diabetes Educ 2010;36:301–309
14. Katon WJ, Lin EHB, Von Korff M, et al. Collaborative care for patients with depression and chronic illnesses. N Engl J Med 2010;363: 2611–2620
15. Parchman ML, Zeber JE, Romero RR, Pugh JA. Risk of coronary artery disease in type 2 diabetes and the delivery of care consistent with the chronic care model in primary care settings: a STARNet study. Med Care 2007;45:1129–1134
16. Del Valle KL, McDonnell ME. Chronic care management services for complex diabetes management: a practical overview. Curr Diab Rep 2018;18:135
17. Tricco AC, Ivers NM, Grimshaw JM, et al. Effectiveness of quality improvement strategies on the management of diabetes: a systematic review and meta-analysis. Lancet 2012;379: 2252–2261
18. Schmittdiel JA, Gopalan A, Lin MW, Banerjee S, Chau CV, Adams AS. Population health management for diabetes: health care system-level approaches for improving quality and addressing disparities. Curr Diab Rep 2017;17:31
19. O'Connor PJ, Bodkin NL, Fradkin J, et al. Diabetes performance measures: current status and future directions. Diabetes Care 2011;34:1651–1659
20. Jaffe MG, Lee GA, Young JD, Sidney S, Go AS. Improved blood pressure control associated with a large-scale hypertension program. JAMA 2013; 310:699–705
21. Peikes D, Chen A, Schore J, Brown R. Effects of care coordination on hospitalization, quality of care, and health care expenditures among Medicare beneficiaries: 15 randomized trials. JAMA 2009;301:603–618
22. Raebel MA, Schmittdiel J, Karter AJ, Konieczny JL, Steiner JF. Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases. Med Care 2013;51(Suppl. 3):S11–S21
23. Feifer C, Nemeth L, Nietert PJ, et al. Different paths to high-quality care: three archetypes of top-performing practice sites. Ann Fam Med 2007;5:233–241
24. Reed M, Huang J, Graetz I, et al. Outpatient electronic health records and the clinical care and outcomes of patients with diabetes mellitus. Ann Intern Med 2012;157:482–489
25. Cebul RD, Love TE, Jain AK, Hebert CJ. Electronic health records and quality of diabetes care. N Engl J Med 2011;365:825–833
26. Battersby M, Von Korff M, Schaefer J, et al. Twelve evidence-based principles for implementing self-management support in primary care. Jt Comm J Qual Patient Saf 2010;36:561–570
27. Grant RW, Wald JS, Schnipper JL, et al. Practice-linked online personal health records for type 2 diabetes mellitus: a randomized controlled trial. Arch Intern Med 2008;168:1776–1782
28. Young-Hyman D, de Groot M, Hill-Briggs F, Gonzalez JS, Hood K, Peyrot M. Psychosocial care for people with diabetes: a position statement of the American Diabetes Association. Diabetes Care 2016;39:2126–2140
29. Beck J, Greenwood DA, Blanton L, et al.; 2017 Standards Revision Task Force. 2017 National standards for diabetes self-management education and support. Diabetes Care 2017;40:1409–1419
30. Pullen-Smith B, Carter-Edwards L, Leathers KH. Community health ambassadors: a model for engaging community leaders to promote better health in North Carolina. J Public Health Manag Pract 2008;14(Suppl.):S73–S81
31. Handlow NE, Nolton B, Winter SE, Wessel CM, Pennock J. 180-LB: Impact of a multidisciplinary diabetes care team in primary care settings on glycemic control (Late-Breaking Abstract). Diabetes 2019;68(Suppl. 1). Accessed 30 September 2020. Available from https://doi.org/10.2337/db19-180-LB
32. Davidson MB. How our current medical care system fails people with diabetes: lack of timely, appropriate clinical decisions. Diabetes Care 2009;32:370–372
33. Selby JV, Uratsu CS, Fireman B, et al. Treatment intensification and risk factor control: toward more clinically relevant quality measures. Med Care 2009;47:395–402
34. Raebel MA, Ellis JL, Schroeder EB, et al. Intensification of antihyperglycemic therapy among patients with incident diabetes: a Surveillance Prevention and Management of Diabetes Mellitus (SUPREME-DM) study. Pharmacoepidemiol Drug Saf 2014;23:699–710
35. Grant RW, Pabon-Nau L, Ross KM, Youatt EJ, Pandiscio JC, Park ER. Diabetes oral medication initiation and intensification: patient views compared with current treatment guidelines. Diabetes Educ 2011;37:78–84
36. Tamhane S, Rodriguez-Gutierrez R, Hargraves I, Montori VM. Shared decision-making in diabetes care. Curr Diab Rep 2015;15:112
37. Schillinger D, Piette J, Grumbach K, et al. Closing the loop: physician communication with diabetic patients who have low health literacy. Arch Intern Med 2003;163:83–90
38. Rosal MC, Ockene IS, Restrepo A, et al. Randomized trial of a literacy-sensitive, culturally tailored diabetes self-management intervention for low-income Latinos: Latinos en Control. Diabetes Care 2011;34:838–844
39. Osborn CY, Cavanaugh K, Wallston KA, et al. Health literacy explains racial disparities in diabetes medication adherence. J Health Commun 2011;16(Suppl. 3):268–278
40. Garg AX, Adhikari NKJ, McDonald H, et al. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. JAMA 2005;293: 1223–1238
41. Smith SA, Shah ND, Bryant SC, et al.; Evidens Research Group. Chronic care model and shared care in diabetes: randomized trial of an electronic decision support system. Mayo Clin Proc 2008;83: 747–757
42. Stone RA, Rao RH, Sevick MA, et al. Active care management supported by home telemonitoring in veterans with type 2 diabetes: the DiaTel randomized controlled trial. Diabetes Care 2010;33:478–484
43. Bojadzievski T, Gabbay RA. Patient-centered medical home and diabetes. Diabetes Care 2011; 34:1047–1053
44. Telligen and gpTRAC (Great Plains Telehealth Resource & Assistance Center). Telehealth Start-Up and Resource Guide, Version 1.1, October 2014. Accessed 23 October 2020. Available from https://www.healthit.gov/sites/default/files/telehealthguide_final_0.pdf
45. Lee SWH, Chan CKY, Chua SS, Chaiyakunapruk N. Comparative effectiveness of telemedicine strategies on type 2 diabetes management: a systematic review and network meta-analysis. Sci Rep 2017;7:12680
46. Faruque LI, Wiebe N, Ehteshami-Afshar A, et al.; Alberta Kidney Disease Network. Effect of telemedicine on glycated hemoglobin in diabetes: a systematic review and meta-analysis of randomized trials. CMAJ 2017;189:E341–E364
47. Marcolino MS, Maia JX, Alkmim MBM, Boersma E, Ribeiro AL. Telemedicine application in the care of diabetes patients: systematic review and meta-analysis. PLoS One 2013;8:e79246
48. Heitkemper EM, Mamykina L, Travers J, Smaldone A. Do health information technology self-management interventions improve glycemic control in medically underserved adults with diabetes? A systematic review and meta-analysis. J Am Med Inform Assoc 2017;24:1024–1035
49. Reagan L, Pereira K, Jefferson V, et al. Diabetes self-management training in a virtual environment. Diabetes Educ 2017;43:413–421
50. Herkert D, Vijayakumar P, Luo J, et al. Cost-related insulin underuse among patients with diabetes. JAMA Intern Med 2019;179:112–114
51. Cefalu WT, Dawes DE, Gavlak G, et al.; Insulin Access and Affordability Working Group. Conclusions and recommendations. Diabetes Care 2018;41:1299–1311
52. Myerson R, Laiteerapong N. The Affordable Care Act and diabetes diagnosis and care:

exploring the potential impacts. Curr Diab Rep 2016;16:27
53. Casagrande SS, McEwen LN, Herman WH. Changes in health insurance coverage under the Affordable Care Act: a national sample of U.S. adults with diabetes, 2009 and 2016. Diabetes Care 2018;41:956–962
54. Doucette ED, Salas J, Scherrer JF. Insurance coverage and diabetes quality indicators among patients in NHANES. Am J Manag Care 2016;22:484–490
55. Stiefel M, Nolan K. Measuring the triple aim: a call for action. Popul Health Manag 2013;16:219–220
56. About the National Quality Strategy. Agency for Healthcare Research & Quality, 2017. Accessed 30 September 2020. Available from https://www.ahrq.gov/workingforquality/about/index.html
57. National Quality Forum. Accessed 30 September 2020. Available from http://www.qualityforum.org/Home.aspx
58. Burstin H, Johnson K. Getting to better care and outcomes for diabetes through measurement. Am J Manag Care 2016;22(4 Spec. No.):SP145–SP146
59. National Institute of Diabetes and Digestive and Kidney Diseases. Diabetes for Health Professionals. Accessed 26 October 2020. Available from https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/diabetes
60. O'Connor PJ, Sperl-Hillen JM, Fazio CJ, Averbeck BM, Rank BH, Margolis KL. Outpatient diabetes clinical decision support: current status and future directions. Diabet Med 2016;33:734–741
61. Institute of Medicine, Committee on Health Literacy. *Health Literacy: A Prescription to End Confusion*. Neilsen-Bohlman L, Panzer AM, Kindig DA, Eds. Washington, DC, National Academies Press, 2004. PMID: 25009856
62. Schaffler J, Leung K, Tremblay S, et al. The effectiveness of self-management interventions for individuals with low health literacy and/or low income: a descriptive systematic review. J Gen Intern Med 2018;33:510–523
63. Centers for Medicare & Medicaid Services. CMS Equity Plan for Medicare, 2017. Accessed 30 September 2020. Available from https://www.cms.gov/About-CMS/Agency-Information/OMH/equity-initiatives/equity-plan.html
64. Rosenthal MB, Cutler DM, Feder J. The ACO rules—striking the balance between participation and transformative potential. N Engl J Med 2011;365:e6
65. Washington AE, Lipstein SH. The Patient-Centered Outcomes Research Institute: promoting better information, decisions, and health. N Engl J Med 2011;365:e31
66. Hutchinson RN, Shin S. Systematic review of health disparities for cardiovascular diseases and associated factors among American Indian and Alaska Native populations. PLoS One 2014;9:e80973
67. Borschuk AP, Everhart RS. Health disparities among youth with type 1 diabetes: a systematic review of the current literature. Fam Syst Health 2015;33:297–313
68. Walker RJ, Strom Williams J, Egede LE. Influence of race, ethnicity and social determinants of health on diabetes outcomes. Am J Med Sci 2016;351:366–373
69. Patel MR, Piette JD, Resnicow K, Kowalski-Dobson T, Heisler M. Social determinants of health, cost-related nonadherence, and cost-reducing behaviors among adults with diabetes: findings from the National Health Interview Survey. Med Care 2016;54:796–803
70. Steve SL, Tung EL, Schlichtman JJ, Peek ME. Social disorder in adults with type 2 diabetes: building on race, place, and poverty. Curr Diab Rep 2016;16:72
71. Commission on Social Determinants of Health. Closing the gap in a generation: Health equity through action on the social determinants of health. Geneva, World Health Organization. Accessed 30 September 2020. Available from http://www.who.int/social_determinants/final_report/csdh_finalreport_2008.pdf
72. Dixon B, Peña M-M, Taveras EM. Lifecourse approach to racial/ethnic disparities in childhood obesity. Adv Nutr 2012;3:73–82
73. Hill JO, Galloway JM, Goley A, et al. Scientific statement. Socioecological determinants of prediabetes and type 2 diabetes. Diabetes Care 2013;36:2430–2439
74. Hill Briggs F, Adler NE, Berkowitz SA, et al. Social determinants of health and diabetes: a scientific review. Diabetes Care. 2 November 2020 [Epub ahead of print]. DOI: 10.2337/dci20-0053
75. The Secretary's Advisory Committee on National Health Promotion and Disease Prevention Objectives for 2020. Phase I. Report: Recommendations for the Framework and Format of Healthy People 2020. Accessed 1 October 2020. Available from https://www.healthypeople.gov/2010/hp2020/advisory/PhaseI/default.htm
76. National Academies of Sciences, Engineering, and Medicine. *A Framework for Educating Health Professionals to Address the Social Determinants of Health*. Washington, DC: National Academies Press, 2016. PMID: 27854400
77. Chin MH, Clarke AR, Nocon RS, et al. A roadmap and best practices for organizations to reduce racial and ethnic disparities in health care. J Gen Intern Med 2012;27:992–1000
78. National Quality Forum. National Voluntary Consensus Standards for Ambulatory Care—Measuring Healthcare Disparities, 2008. Accessed 1 October 2020. Available from https://www.qualityforum.org/Publications/2008/03/National_Voluntary_Consensus_Standards_for_Ambulatory_Care%E2%80%94Measuring_Healthcare_Disparities.aspx
79. Piette JD, Heisler M, Wagner TH. Cost-related medication underuse among chronically ill adults: the treatments people forgo, how often, and who is at risk. Am J Public Health 2004;94:1782–1787
80. Laiteerapong N, Karter AJ, Liu JY, et al. Correlates of quality of life in older adults with diabetes: the Diabetes & Aging Study. Diabetes Care 2011;34:1749–1753
81. O'Gurek DT, Henke C. A practical approach to screening for social determinants of health. Fam Pract Manag 2018;25:7–12
82. Walker RJ, Grusnick J, Garacci E, Mendez C, Egede LE. Trends in food insecurity in the USA for individuals with prediabetes, undiagnosed diabetes, and diagnosed diabetes. J Gen Intern Med 2019;34:33–35
83. Berkowitz SA, Karter AJ, Corbie-Smith G, et al. Food insecurity, food "deserts," and glycemic control in patients with diabetes: a longitudinal analysis. Diabetes Care 2018;41:1188–1195
84. Heerman WJ, Wallston KA, Osborn CY, et al. Food insecurity is associated with diabetes self-care behaviours and glycaemic control. Diabet Med 2016;33:844–850
85. Silverman J, Krieger J, Kiefer M, Hebert P, Robinson J, Nelson K. The relationship between food insecurity and depression, diabetes distress and medication adherence among low-income patients with poorly-controlled diabetes. J Gen Intern Med 2015;30:1476–1480
86. Schroeder EB, Zeng C, Sterrett AT, Kimpo TK, Paolino AR, Steiner JF. The longitudinal relationship between food insecurity in older adults with diabetes and emergency department visits, hospitalizations, hemoglobin A1c, and medication adherence. J Diabetes Complications 2019;33:289–295
87. Hager ER, Quigg AM, Black MM, et al. Development and validity of a 2-item screen to identify families at risk for food insecurity. Pediatrics 2010;126:e26–e32
88. Goddu AP, Roberson TS, Raffel KE, Chin MH, Peek ME. Food Rx: a community-university partnership to prescribe healthy eating on the South Side of Chicago. J Prev Interv Community 2015;43:148–162
89. Feinberg AT, Hess A, Passaretti M, Coolbaugh S, Lee TH. Prescribing Food as a Specialty Drug. NEJM Catalyst, 2018. Accessed 1 October 2020. Available from https://catalyst.nejm.org/doi/abs/10.1056/CAT.18.0212
90. Seligman HK, Schillinger D. Hunger and socioeconomic disparities in chronic disease. N Engl J Med 2010;363:6–9
91. White BM, Logan A, Magwood GS. Access to diabetes care for populations experiencing homelessness: an integrated review. Curr Diab Rep 2016;16:112
92. Bernstein RS, Meurer LN, Plumb EJ, Jackson JL. Diabetes and hypertension prevalence in homeless adults in the United States: a systematic review and meta-analysis. Am J Public Health 2015;105:e46–e60
93. Montgomery AE, Fargo JD, Kane V, Culhane DP. Development and validation of an instrument to assess imminent risk of homelessness among veterans. Public Health Rep 2014;129:428–436
94. Stahre M, VanEenwyk J, Siegel P, Njai R. housing insecurity and the association with health outcomes and unhealthy behaviors, Washington State, 2011. Prev Chronic Dis 2015;12:E109
95. Baxter AJ, Tweed EJ, Katikireddi SV, Thomson H. Effects of Housing First approaches on health and well-being of adults who are homeless or at risk of homelessness: systematic review and meta-analysis of randomised controlled trials. J Epidemiol Community Health 2019;73:379–387
96. Evangelou E, Ntritsos G, Chondrogiorgi M, et al. Exposure to pesticides and diabetes: a systematic review and meta-analysis. Environ Int 2016;91:60–68
97. Health Resources & Services Administration. 2018 Health Center Data. Accessed 1 October 2020. Available from https://bphc.hrsa.gov/uds/datacenter.aspx?q=tall&year=2018&state=&fd=mh
98. U.S. Department of Health & Human Services. National Standards for Culturally and Linguistically Appropriate Services (CLAS) in Health and Health Care. Accessed 1 October 2020. Available from

https://www.thinkculturalhealth.hhs.gov/assets/pdfs/enhancednationalclasstandards.pdf
99. Aaby A, Friis K, Christensen B, Rowlands G, Maindal HT. Health literacy is associated with health behaviour and self-reported health: a large population-based study in individuals with cardiovascular disease. Eur J Prev Cardiol 2017;24:1880–1888
100. White RO, Eden S, Wallston KA, et al. Health communication, self-care, and treatment satisfaction among low-income diabetes patients in a public health setting. Patient Educ Couns 2015;98:144–149
101. Williams DR, Lawrence JA, Davis BA. Racism and health: evidence and needed research. Annu Rev Public Health 2019;40:105–125
102. Agency for Healthcare Research and Quality. Clinical-Community Linkages, 2016. Accessed 1 October 2020. Available from http://www.ahrq.gov/professionals/prevention-chronic-care/improve/community/index.html
103. Egbujie BA, Delobelle PA, Levitt N, Puoane T, Sanders D, van Wyk B. Role of community health workers in type 2 diabetes mellitus self-management: a scoping review. PLoSOne 2018;13:e0198424
104. Heisler M, Vijan S, Makki F, Piette JD. Diabetes control with reciprocal peer support versus nurse care management: a randomized trial. Ann Intern Med 2010;153:507–515
105. Long JA, Jahnle EC, Richardson DM, Loewenstein G, Volpp KG. Peer mentoring and financial incentives to improve glucose control in African American veterans: a randomized trial. Ann Intern Med 2012;156:416–424
106. Fisher EB, Boothroyd RI, Elstad EA, et al. Peer support of complex health behaviors in prevention and disease management with special reference to diabetes: systematic reviews. Clin Diabetes Endocrinol 2017;3:4
107. Foster G, Taylor SJC, Eldridge SE, Ramsay J, Griffiths CJ. Self-management education programmes by lay leaders for people with chronic conditions. Cochrane Database Syst Rev 2007;4:CD005108
108. Piatt GA, Rodgers EA, Xue L, Zgibor JC. Integration and utilization of peer leaders for diabetes self-management support: results from Project SEED (Support, Education, and Evaluation in Diabetes). Diabetes Educ 2018;44:373–382
109. Understanding Scope and Competencies: A Contemporary Look at the United States Community Health Worker Field, CHW Central, 2018. Accessed 1 October 2020. Available from http://www.chwcentral.org/understanding-scope-and-competencies-contemporary-look-united-states-community-health-worker-field
110. Community Health Workers Help Patients Manage Diabetes, 2017. The Guide to Community Preventive Services (The Community Guide). Accessed 1 October 2020. Available from https://www.thecommunityguide.org/content/community-health-workers-help-patients-manage-diabetes

2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes—2021*

American Diabetes Association

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The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc21-SPPC), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc21-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

CLASSIFICATION

Diabetes can be classified into the following general categories:

1. Type 1 diabetes (due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency, including latent autoimmune diabetes of adulthood)
2. Type 2 diabetes (due to a progressive loss of adequate β-cell insulin secretion frequently on the background of insulin resistance)
3. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)
4. Gestational diabetes mellitus (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)

This section reviews most common forms of diabetes but is not comprehensive. For additional information, see the American Diabetes Association (ADA) position statement "Diagnosis and Classification of Diabetes Mellitus" (1).

Type 1 diabetes and type 2 diabetes are heterogeneous diseases in which clinical presentation and disease progression may vary considerably. Classification is important for determining therapy, but some individuals cannot be clearly classified as having type 1 or type 2 diabetes at the time of diagnosis. The traditional paradigms of type 2 diabetes occurring only in adults and type 1 diabetes only in children are no longer accurate, as both diseases occur in both age-groups. Children with type 1 diabetes typically present with the hallmark symptoms of polyuria/polydipsia, and approximately one-third present with diabetic ketoacidosis (DKA) (2). The onset of

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type 1 diabetes may be more variable in adults; they may not present with the classic symptoms seen in children and may experience temporary remission from the need for insulin (3–5). Occasionally, patients with type 2 diabetes may present with DKA (6), particularly ethnic and racial minorities (7). It is important for the provider to realize that classification of diabetes type is not always straightforward at presentation and that misdiagnosis is common (e.g., adults with type 1 diabetes misdiagnosed as having type 2 diabetes; individuals with maturity-onset diabetes of the young [MODY] misdiagnosed as having type 1 diabetes, etc.). Although difficulties in distinguishing diabetes type may occur in all age-groups at onset, the diagnosis becomes more obvious over time in people with β-cell deficiency.

In both type 1 and type 2 diabetes, various genetic and environmental factors can result in the progressive loss of β-cell mass and/or function that manifests clinically as hyperglycemia. Once hyperglycemia occurs, patients with all forms of diabetes are at risk for developing the same chronic complications, although rates of progression may differ. The identification of individualized therapies for diabetes in the future will require better characterization of the many paths to β-cell demise or dysfunction (8). Across the globe many groups are working on combining clinical, pathophysiological, and genetic characteristics to more precisely define the subsets of diabetes currently clustered into the type 1 diabetes versus type 2 diabetes nomenclature with the goal of optimizing treatment approaches. Many of these studies show great promise and may soon be incorporated into the diabetes classification system (9).

Characterization of the underlying pathophysiology is more precisely developed in type 1 diabetes than in type 2 diabetes. It is now clear from studies of first-degree relatives of patients with type 1 diabetes that the persistent presence of two or more islet autoantibodies is a near certain predictor of clinical hyperglycemia and diabetes. The rate of progression is dependent on the age at first detection of autoantibody, number of autoantibodies, autoantibody specificity, and autoantibody titer. Glucose and A1C levels rise well before the clinical onset of diabetes, making diagnosis feasible well before the onset of DKA. Three distinct stages of type 1 diabetes can be identified (**Table 2.1**) and serve as a framework for future research and regulatory decision-making (8,10). There is debate as to whether slowly progressive autoimmune diabetes with an adult onset should be termed latent autoimmune diabetes in adults (LADA) or type 1 diabetes. The clinical priority is awareness that slow autoimmune β-cell destruction can occur in adults leading to a long duration of marginal insulin secretory capacity. For the purpose of this classification, all forms of diabetes mediated by autoimmune β-cell destruction are included under the rubric of type 1 diabetes. Use of the term LADA is common and acceptable in clinical practice and has the practical impact of heightening awareness of a population of adults likely to develop overt autoimmune β-cell destruction (11), thus accelerating insulin initiation prior to deterioration of glucose control or development of DKA (4,12).

The paths to β-cell demise and dysfunction are less well defined in type 2 diabetes, but deficient β-cell insulin secretion, frequently in the setting of insulin resistance, appears to be the common denominator. Type 2 diabetes is associated with insulin secretory defects related to inflammation and metabolic stress among other contributors, including genetic factors. Future classification schemes for diabetes will likely focus on the pathophysiology of the underlying β-cell dysfunction (8,9,13–15).

DIAGNOSTIC TESTS FOR DIABETES

Diabetes may be diagnosed based on plasma glucose criteria, either the fasting plasma glucose (FPG) value or the 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT), or A1C criteria (16) (**Table 2.2**).

Generally, FPG, 2-h PG during 75-g OGTT, and A1C are equally appropriate for diagnostic screening. It should be noted that the tests do not necessarily detect diabetes in the same individuals. The efficacy of interventions for primary prevention of type 2 diabetes (17,18) has mainly been demonstrated among individuals who have impaired glucose tolerance (IGT) with or without elevated fasting glucose, not for individuals with isolated impaired fasting glucose (IFG) or for those with prediabetes defined by A1C criteria.

The same tests may be used to screen for and diagnose diabetes and to detect individuals with prediabetes (**Table 2.2** and **Table 2.5**) (19). Diabetes may be identified anywhere along the spectrum of clinical scenarios—in seemingly low-risk individuals who happen to have glucose testing, in individuals tested based on diabetes risk assessment, and in symptomatic patients.

Fasting and 2-Hour Plasma Glucose

The FPG and 2-h PG may be used to diagnose diabetes (**Table 2.2**). The concordance between the FPG and 2-h PG tests is imperfect, as is the concordance between A1C and either glucose-based test. Compared with FPG and A1C cut points, the 2-h PG value diagnoses more people with prediabetes and diabetes (20). In people in whom there is discordance between A1C values and glucose values, FPG and 2-h PG are more accurate (21).

A1C

Recommendations

2.1 To avoid misdiagnosis or missed diagnosis, the A1C test should be performed using a method that is certified by the NGSP and standardized to the Diabetes Control and Complications Trial (DCCT) assay. **B**

2.2 Marked discordance between measured A1C and plasma glucose levels should raise the possibility of A1C assay interference and consideration of using an assay without interference or plasma blood glucose criteria to diagnose diabetes. **B**

2.3 In conditions associated with an altered relationship between A1C and glycemia, such as hemoglobinopathies including sickle cell disease, pregnancy (second and third trimesters and the postpartum period), glucose-6-phosphate dehydrogenase deficiency, HIV, hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, only plasma blood glucose criteria should be used

Table 2.1—Staging of type 1 diabetes (8,10)

	Stage 1	Stage 2	Stage 3
Characteristics	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• New-onset hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple autoantibodies • No IGT or IFG	• Multiple autoantibodies • Dysglycemia: IFG and/or IGT • FPG 100–125 mg/dL (5.6–6.9 mmol/L) • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) • A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	• Clinical symptoms • Diabetes by standard criteria

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; 2-h PG, 2-h plasma glucose.

to diagnose diabetes. (See OTHER CONDITIONS ALTERING THE RELATIONSHIP OF A1C AND GLYCEMIA below for more information.) **B**

The A1C test should be performed using a method that is certified by the NGSP (www.ngsp.org) and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. Although point-of-care A1C assays may be NGSP certified and cleared by the U.S. Food and Drug Administration (FDA) for use in monitoring glycemic control in people with diabetes in both Clinical Laboratory Improvement Amendments (CLIA)-regulated and CLIA-waived settings, only those point-of-care A1C assays that are also cleared by the FDA for use in the diagnosis of diabetes should be used for this purpose, and only in the clinical settings for which they are cleared. As discussed in Section 6 "Glycemic Targets" (https://doi.org/10.2337/dc21-S006), point-of-care A1C assays may be more generally applied for assessment of glycemic control in the clinic.

A1C has several advantages compared with FPG and OGTT, including greater convenience (fasting not required), greater preanalytical stability, and less day-to-day perturbations during stress, changes in diet, or illness. However, these advantages may be offset by the lower sensitivity of A1C at the designated cut point, greater cost, limited availability of A1C testing in certain regions of the developing world, and the imperfect correlation between A1C and average glucose in certain individuals. The A1C test, with a diagnostic threshold of ≥6.5% (48 mmol/mol), diagnoses only 30% of the diabetes cases identified collectively using A1C, FPG, or 2-h PG, according to National Health and Nutrition Examination Survey (NHANES) data (22).

When using A1C to diagnose diabetes, it is important to recognize that A1C is an indirect measure of average blood glucose levels and to take other factors into consideration that may impact hemoglobin glycation independently of glycemia, such as hemodialysis, pregnancy, HIV treatment (23,24), age, race/ethnicity, pregnancy status, genetic background, and anemia/hemoglobinopathies. (See OTHER CONDITIONS ALTERING THE RELATIONSHIP OF A1C AND GLYCEMIA below for more information.)

Age

The epidemiologic studies that formed the basis for recommending A1C to diagnose diabetes included only adult populations (22). However, recent ADA clinical guidance concluded that A1C, FPG, or 2-h PG can be used to test for prediabetes or type 2 diabetes in children and adolescents (see SCREENING AND TESTING FOR PREDIABETES AND TYPE 2 DIABETES IN CHILDREN AND ADOLESCENTS below for additional information) (25).

Race/Ethnicity/Hemoglobinopathies

Hemoglobin variants can interfere with the measurement of A1C, although most assays in use in the U.S. are unaffected by the most common variants. Marked discrepancies between measured A1C and plasma glucose levels should prompt consideration that the A1C assay may not be reliable for that individual. For patients with a hemoglobin variant but normal red blood cell turnover, such as those with the sickle cell trait, an A1C assay without interference from hemoglobin variants should be used. An updated list of A1C assays with interferences is available at www.ngsp.org/interf.asp.

African Americans heterozygous for the common hemoglobin variant HbS may have, for any given level of mean glycemia, lower A1C by about 0.3% compared with those without the trait (26). Another genetic variant, X-linked glucose-6-phosphate dehydrogenase G202A, carried by 11% of African Americans, was associated with a decrease in A1C of about 0.8% in homozygous men and 0.7% in homozygous women compared with those without the variant (27).

Table 2.2—Criteria for the diagnosis of diabetes

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Even in the absence of hemoglobin variants, A1C levels may vary with race/ethnicity independently of glycemia (28–30). For example, African Americans may have higher A1C levels than non-Hispanic Whites with similar fasting and postglucose load glucose levels (31). Though conflicting data exists, African Americans may also have higher levels of fructosamine and glycated albumin and lower levels of 1,5-anhydroglucitol, suggesting that their glycemic burden (particularly postprandially) may be higher (32,33). Similarly, A1C levels may be higher for a given mean glucose concentration when measured with continuous glucose monitoring (34). Despite these and other reported differences, the association of A1C with risk for complications appears to be similar in African Americans and non-Hispanic Whites (35,36).

Other Conditions Altering the Relationship of A1C and Glycemia

In conditions associated with increased red blood cell turnover, such as sickle cell disease, pregnancy (second and third trimesters), glucose-6-phosphate dehydrogenase deficiency (37,38), hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, only plasma blood glucose criteria should be used to diagnose diabetes (39). A1C is less reliable than blood glucose measurement in other conditions such as the postpartum state (40–42), HIV treated with certain protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) (23), and iron-deficient anemia (43).

Confirming the Diagnosis

Unless there is a clear clinical diagnosis (e.g., patient in a hyperglycemic crisis or with classic symptoms of hyperglycemia and a random plasma glucose ≥200 mg/dL [11.1 mmol/L]), diagnosis requires two abnormal test results, either from the same sample (44) or in two separate test samples. If using two separate test samples, it is recommended that the second test, which may either be a repeat of the initial test or a different test, be performed without delay. For example, if the A1C is 7.0% (53 mmol/mol) and a repeat result is 6.8% (51 mmol/mol), the diagnosis of diabetes is confirmed. If two different tests (such as A1C and FPG) are both above the diagnostic threshold when analyzed from the same sample or in two different test samples, this also confirms the diagnosis. On the other hand, if a patient has discordant results from two different tests, then the test result that is above the diagnostic cut point should be repeated, with careful consideration of the possibility of A1C assay interference. The diagnosis is made on the basis of the confirmed test. For example, if a patient meets the diabetes criterion of the A1C (two results ≥6.5% [48 mmol/mol]) but not FPG (<126 mg/dL [7.0 mmol/L]), that person should nevertheless be considered to have diabetes.

Each of the tests has preanalytic and analytic variability, so it is possible that a test yielding an abnormal result (i.e., above the diagnostic threshold), when repeated, will produce a value below the diagnostic cut point. This scenario is likely for FPG and 2-h PG if the glucose samples remain at room temperature and are not centrifuged promptly. Because of the potential for preanalytic variability, it is critical that samples for plasma glucose be spun and separated immediately after they are drawn. If patients have test results near the margins of the diagnostic threshold, the health care professional should discuss signs and symptoms with the patient and repeat the test in 3–6 months.

Diagnosis

In a patient with classic symptoms, measurement of plasma glucose is sufficient to diagnose diabetes (symptoms of hyperglycemia or hyperglycemic crisis plus a random plasma glucose ≥200 mg/dL [11.1 mmol/L]). In these cases, knowing the plasma glucose level is critical because, in addition to confirming that symptoms are due to diabetes, it will inform management decisions. Some providers may also want to know the A1C to determine the chronicity of the hyperglycemia. The criteria to diagnose diabetes are listed in **Table 2.2**.

TYPE 1 DIABETES

Recommendations

2.4 Screening for type 1 diabetes risk with a panel of islet autoantibodies is currently recommended in the setting of a research trial or can be offered as an option for first-degree family members of a proband with type 1 diabetes. **B**

2.5 Persistence of autoantibodies is a risk factor for clinical diabetes and may serve as an indication for intervention in the setting of a clinical trial. **B**

Immune-Mediated Diabetes

This form, previously called "insulin-dependent diabetes" or "juvenile-onset diabetes," accounts for 5–10% of diabetes and is due to cellular-mediated autoimmune destruction of the pancreatic β-cells. Autoimmune markers include islet cell autoantibodies and autoantibodies to GAD (GAD65), insulin, the tyrosine phosphatases IA-2 and IA-2β, and zinc transporter 8 (ZnT8). Numerous clinical studies are being conducted to test various methods of preventing type 1 diabetes in those with evidence of islet autoimmunity (www.clinicaltrials.gov and www.trialnet.org/our-research/prevention-studies) (12,45–49). Stage 1 of type 1 diabetes is defined by the presence of two or more of these autoimmune markers. The disease has strong HLA associations, with linkage to the *DQA* and *DQB* genes. These HLA-DR/DQ alleles can be either predisposing or protective (**Table 2.1**). There are important genetic considerations, as most of the mutations that cause diabetes are dominantly inherited. The importance of genetic testing is in the genetic counseling that follows. Some mutations are associated with other conditions, which then may prompt additional screenings.

The rate of β-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults) (50). Children and adolescents may present with DKA as the first manifestation of the disease. Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or DKA with infection or other stress. Adults may retain sufficient β-cell function to prevent DKA for many years; such individuals may have remission or decreased insulin needs for months or years and eventually become dependent on insulin for survival and are at risk for DKA (3–5,51,52). At this latter stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide. Immune-mediated diabetes is the most common form of diabetes in childhood and adolescence, but it can occur at any age, even in the 8th and 9th decades of life.

Autoimmune destruction of β-cells has multiple genetic predispositions and is also related to environmental factors that are still poorly defined. Although patients are not typically obese when they present with type 1 diabetes, obesity is increasingly common in the general population, and there is evidence that it may also be a risk factor for type 1 diabetes. As such, obesity should not preclude the diagnosis. People with type 1 diabetes are also prone to other autoimmune disorders such as Hashimoto thyroiditis, Graves disease, celiac disease, Addison disease, vitiligo, autoimmune hepatitis, myasthenia gravis, and pernicious anemia (see Section 4 "Comprehensive Medical Evaluation and Assessment of Comorbidities," https://doi.org/10.2337/dc21-S004).

Idiopathic Type 1 Diabetes

Some forms of type 1 diabetes have no known etiologies. These patients have permanent insulinopenia and are prone to DKA but have no evidence of β-cell autoimmunity. However, only a minority of patients with type 1 diabetes fall into this category. Individuals with autoantibody-negative type 1 diabetes of African or Asian ancestry may suffer from episodic DKA and exhibit varying degrees of insulin deficiency between episodes (possibly ketosis-prone diabetes). This form of diabetes is strongly inherited and is not HLA associated. An absolute requirement for insulin replacement therapy in affected patients may be intermittent. Future research is needed to determine the cause of β-cell destruction in this rare clinical scenario.

Screening for Type 1 Diabetes Risk

The incidence and prevalence of type 1 diabetes is increasing (53). Patients with type 1 diabetes often present with acute symptoms of diabetes and markedly elevated blood glucose levels, and approximately one-third are diagnosed with life-threatening DKA (2). Multiple studies indicate that measuring islet autoantibodies in individuals genetically at risk for type 1 diabetes (e.g., relatives of those with type 1 diabetes or individuals from the general population with type 1 diabetes–associated genetic factors) identifies individuals who may develop type 1 diabetes (10). Such testing, coupled with education about diabetes symptoms and close follow-up, may enable earlier identification of type 1 diabetes onset. A study reported the risk of progression to type 1 diabetes from the time of seroconversion to autoantibody positivity in three pediatric cohorts from Finland, Germany, and the U.S. Of the 585 children who developed more than two autoantibodies, nearly 70% developed type 1 diabetes within 10 years and 84% within 15 years (45). These findings are highly significant because while the German group was recruited from offspring of parents with type 1 diabetes, the Finnish and American groups were recruited from the general population. Remarkably, the findings in all three groups were the same, suggesting that the same sequence of events led to clinical disease in both "sporadic" and familial cases of type 1 diabetes. Indeed, the risk of type 1 diabetes increases as the number of relevant autoantibodies detected increases (48,54,55). In The Environmental Determinants of Diabetes in the Young (TEDDY) study, type 1 diabetes developed in 21% of 363 subjects with at least one autoantibody at 3 years of age (56).

There is currently a lack of accepted and clinically validated screening programs outside of the research setting; thus, widespread clinical testing of asymptomatic low-risk individuals is not currently recommended due to lack of approved therapeutic interventions. However, one should consider referring relatives of those with type 1 diabetes for islet autoantibody testing for risk assessment in the setting of a clinical research study (see www.trialnet.org). Individuals who test positive should be counseled about the risk of developing diabetes, diabetes symptoms, and DKA prevention. Numerous clinical studies are being conducted to test various methods of preventing and treating stage 2 type 1 diabetes in those with evidence of autoimmunity with promising results (see www.clinicaltrials.gov and www.trialnet.org).

PREDIABETES AND TYPE 2 DIABETES

Recommendations

2.6 Screening for prediabetes and type 2 diabetes with an informal assessment of risk factors or validated tools should be considered in asymptomatic adults. **B**

2.7 Testing for prediabetes and/or type 2 diabetes in asymptomatic people should be considered in adults of any age with overweight or obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) and who have one or more additional risk factors for diabetes (**Table 2.3**). **B**

2.8 Testing for prediabetes and/or type 2 diabetes should be considered in women with overweight or obesity planning pregnancy and/or who have one or more additional risk factor for diabetes (**Table 2.3**). **C**

2.9 For all people, testing should begin at age 45 years. **B**

2.10 If tests are normal, repeat testing carried out at a minimum of 3-year intervals is reasonable, sooner with symptoms. **C**

2.11 To test for prediabetes and type 2 diabetes, fasting plasma glucose, 2-h plasma glucose during 75-g oral glucose tolerance test, and A1C are equally appropriate (**Table 2.2** and **Table 2.5**). **B**

2.12 In patients with prediabetes and type 2 diabetes, identify and treat other cardiovascular disease risk factors. **A**

2.13 Risk-based screening for prediabetes and/or type 2 diabetes should be considered after the onset of puberty or after 10 years of age, whichever occurs earlier, in children and adolescents with overweight (BMI ≥85th percentile) or obesity (BMI ≥95th percentile) and who have one or more risk factor for diabetes. (See **Table 2.4** for evidence grading of risk factors.) **B**

2.14 Patients with HIV should be screened for diabetes and prediabetes with a fasting glucose test before starting antiretroviral therapy, at the time of switching antiretroviral therapy, and 3−6 months after starting or switching antiretroviral therapy. If initial screening results are normal, fasting glucose should be checked annually. **E**

Prediabetes

"Prediabetes" is the term used for individuals whose glucose levels do not meet the criteria for diabetes but are too high to be considered normal (35,36). Patients

Table 2.3—Criteria for testing for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in adults with overweight or obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) who have one or more of the following risk factors:
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - History of CVD
   - Hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - Women with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. Patients with prediabetes (A1C ≥5.7% [39 mmol/mol], IGT, or IFG) should be tested yearly.
3. Women who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other patients, testing should begin at age 45 years.
5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.
6. HIV

CVD, cardiovascular disease; GDM, gestational diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

with prediabetes are defined by the presence of IFG and/or IGT and/or A1C 5.7–6.4% (39–47 mmol/mol) (**Table 2.5**). Prediabetes should not be viewed as a clinical entity in its own right but rather as an increased risk for diabetes and cardiovascular disease (CVD). Criteria for testing for diabetes or prediabetes in asymptomatic adults is outlined in **Table 2.3**. Prediabetes is associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension.

Diagnosis

IFG is defined as FPG levels from 100 to 125 mg/dL (from 5.6 to 6.9 mmol/L) (57,58) and IGT as 2-h PG during 75-g OGTT levels from 140 to 199 mg/dL (from 7.8 to 11.0 mmol/L) (59). It should be noted that the World Health Organization (WHO) and numerous other diabetes organizations define the IFG cutoff at 110 mg/dL (6.1 mmol/L).

As with the glucose measures, several prospective studies that used A1C to predict the progression to diabetes as defined by A1C criteria demonstrated a strong, continuous association between A1C and subsequent diabetes. In a systematic review of 44,203 individuals from 16 cohort studies with a follow-up interval averaging 5.6 years (range 2.8–12 years), those with A1C between 5.5% and 6.0% (between 37 and 42 mmol/mol) had a substantially increased risk of diabetes (5-year incidence from 9% to 25%). Those with an A1C range of 6.0–6.5% (42–48 mmol/mol) had a 5-year risk of developing diabetes between 25% and 50% and a relative risk 20 times higher compared with A1C of 5.0% (31 mmol/mol) (60). In a community-based study of African American and non-Hispanic White adults without diabetes, baseline A1C was a stronger predictor of subsequent diabetes and cardiovascular events than fasting glucose (61). Other analyses suggest that A1C of 5.7% (39 mmol/mol) or higher is associated with a diabetes risk similar to that of the high-risk participants in the Diabetes Prevention Program (DPP) (62), and A1C at baseline was a strong predictor of the development of glucose-defined diabetes during the DPP and its follow-up (63). Hence, it is reasonable to consider an A1C range of 5.7–6.4% (39–47 mmol/mol) as identifying individuals with prediabetes. Similar to those with IFG and/or IGT, individuals with A1C of 5.7–6.4% (39–47 mmol/mol) should be informed of their increased risk for diabetes and CVD and counseled about effective strategies to lower their risks (see Section 3 "Prevention or Delay of Type 2 Diabetes," https://doi.org/10.2337/dc21-S003). Similar to glucose measurements, the continuum of risk is curvilinear, so as A1C rises, the diabetes risk rises disproportionately (60). Aggressive interventions and vigilant follow-up should be pursued for those considered at very high risk (e.g., those with A1C >6.0% [42 mmol/mol]).

Table 2.5 summarizes the categories of prediabetes and **Table 2.3** the criteria for prediabetes testing. The ADA diabetes risk test is an additional option for assessment to determine the appropriateness of testing for diabetes or prediabetes in asymptomatic adults (**Fig. 2.1**) (diabetes.org/socrisktest). For additional background regarding risk factors and screening for prediabetes, see SCREENING AND TESTING FOR PREDIABETES AND TYPE 2 DIABETES IN ASYMPTOMATIC ADULTS and also SCREENING AND TESTING FOR PREDIABETES AND TYPE 2 DIABETES IN CHILDREN AND ADOLESCENTS below.

Table 2.4—Risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting (202)

Testing should be considered in youth* who have overweight (≥85th percentile) or obesity (≥95th percentile) **A** and who have one or more additional risk factors based on the strength of their association with diabetes:

- Maternal history of diabetes or GDM during the child's gestation **A**
- Family history of type 2 diabetes in first- or second-degree relative **A**
- Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander) **A**
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight) **B**

GDM, gestational diabetes mellitus. *After the onset of puberty or after 10 years of age, whichever occurs earlier. If tests are normal, repeat testing at a minimum of 3-year intervals (or more frequently if BMI is increasing or risk factor profile deteriorating) is recommended. Reports of type 2 diabetes before age 10 years exist, and this can be considered with numerous risk factors.

Type 2 Diabetes

Type 2 diabetes, previously referred to as "noninsulin-dependent diabetes" or "adult-onset diabetes," accounts for 90–95% of all diabetes. This form encompasses individuals who have relative (rather than absolute) insulin deficiency and have peripheral insulin resistance.

Table 2.5—Criteria defining prediabetes*

FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
A1C 5.7–6.4% (39–47 mmol/mol)

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose. *For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.

At least initially, and often throughout their lifetime, these individuals may not need insulin treatment to survive.

There are various causes of type 2 diabetes. Although the specific etiologies are not known, autoimmune destruction of β-cells does not occur, and patients do not have any of the other known causes of diabetes. Most, but not all, patients with type 2 diabetes have overweight or obesity. Excess weight itself causes some degree of insulin resistance. Patients who do not have obesity or overweight by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region.

DKA seldom occurs spontaneously in type 2 diabetes; when seen, it usually arises in association with the stress of another illness such as infection, myocardial infarction, or with the use of certain drugs (e.g., corticosteroids, atypical antipsychotics, and sodium–glucose cotransporter 2 inhibitors) (64,65). Type 2 diabetes frequently goes undiagnosed for many years because hyperglycemia develops gradually and, at earlier stages, is often not severe enough for the patient to notice the classic diabetes symptoms caused by hyperglycemia. Nevertheless, even undiagnosed patients are at increased risk of developing macrovascular and microvascular complications.

Patients with type 2 diabetes may have insulin levels that appear normal or elevated, yet the failure to normalize blood glucose reflects a relative defect in glucose-stimulated insulin secretion. Thus, insulin secretion is defective in these patients and insufficient to compensate for insulin resistance. Insulin resistance may improve with weight reduction, exercise, and/or pharmacologic treatment of hyperglycemia but is seldom restored to normal. Recent interventions with intensive diet and exercise or surgical weight loss have led to diabetes remission (66–72) (see Section 8 "Obesity Management for the Treatment of Type 2 Diabetes," https://doi.org/10.2337/dc21-S008).

The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity. It occurs more frequently in women with prior gestational diabetes mellitus (GDM), with hypertension or dyslipidemia, with polycystic ovary syndrome, and in certain racial/ethnic subgroups (African American, American Indian, Hispanic/Latino, and Asian American). It is often associated with a strong genetic predisposition or family history in first-degree relatives (more so than type 1 diabetes). However, the genetics of type 2 diabetes is poorly understood and under intense investigation in this era of precision medicine (13). In adults without traditional risk factors for type 2 diabetes and/or younger age, consider islet autoantibody testing (e.g., GAD65 autoantibodies) to exclude the diagnosis of type 1 diabetes.

Screening and Testing for Prediabetes and Type 2 Diabetes in Asymptomatic Adults

Screening for prediabetes and type 2 diabetes risk through an informal assessment of risk factors (**Table 2.3**) or with an assessment tool, such as the ADA risk test (**Fig. 2.1**) (online at diabetes.org/socrisktest), is recommended to guide providers on whether performing a diagnostic test (**Table 2.2**) is appropriate. Prediabetes and type 2 diabetes meet criteria for conditions in which early detection via screening is appropriate. Both conditions are common and impose significant clinical and public health burdens. There is often a long presymptomatic phase before the diagnosis of type 2 diabetes. Simple tests to detect preclinical disease are readily available. The duration of glycemic burden is a strong predictor of adverse outcomes. There are effective interventions that prevent progression from prediabetes to diabetes (see Section 3 "Prevention or Delay of Type 2 Diabetes," https://doi.org/10.2337/dc21-S003) and reduce the risk of diabetes complications (73) (see Section 10 "Cardiovascular Disease and Risk Management," https://doi.org/10.2337/dc21-S010, and Section 11 "Microvascular Complications and Foot Care," https://doi.org/10.2337/dc21-S011). In the most recent National Institutes of Health (NIH) Diabetes Prevention Program Outcomes Study (DPPOS) report, prevention of progression from prediabetes to diabetes (74) resulted in lower rates of developing retinopathy and nephropathy (75). Similar impact on diabetes complications was reported with screening, diagnosis, and comprehensive risk factor management in the U.K. Clinical Practice Research Datalink database (73). In that report, progression from prediabetes to diabetes augmented risk of complications.

Approximately one-quarter of people with diabetes in the U.S. and nearly half of Asian and Hispanic Americans with diabetes are undiagnosed (57,58). Although screening of asymptomatic individuals to identify those with prediabetes or diabetes might seem reasonable, rigorous clinical trials to prove the effectiveness of such screening have not been conducted and are unlikely to occur. Based on a population estimate, diabetes in women of childbearing age is underdiagnosed (76). Employing a probabilistic model, Peterson et al. (77) demonstrated cost and health benefits of preconception screening.

A large European randomized controlled trial compared the impact of screening for diabetes and intensive multifactorial intervention with that of screening and routine care (78). General practice patients between the ages of 40 and 69 years were screened for diabetes and randomly assigned by practice to intensive treatment of multiple risk factors or routine diabetes care. After 5.3 years of follow-up, CVD risk factors were modestly but significantly improved with intensive treatment compared with routine care, but the incidence of first CVD events or mortality was not significantly different between the groups (59). The

American Diabetes Association®
Connected for Life

Are you at risk for type 2 diabetes?

Diabetes Risk Test:

WRITE YOUR SCORE IN THE BOX.

1. How old are you? .....
Less than 40 years (0 points)
40–49 years (1 point)
50–59 years (2 points)
60 years or older (3 points)

2. Are you a man or a woman? .....
Man (1 point) Woman (0 points)

3. If you are a woman, have you ever been diagnosed with gestational diabetes?.....
Yes (1 point) No (0 points)

4. Do you have a mother, father, sister or brother with diabetes? .....
Yes (1 point) No (0 points)

5. Have you ever been diagnosed with high blood pressure? .....
Yes (1 point) No (0 points)

6. Are you physically active? .....
Yes (0 points) No (1 point)

7. What is your weight category? .....
See chart at right.

Height	Weight (lbs.)		
4' 10"	119–142	143–190	191+
4' 11"	124–147	148–197	198+
5' 0"	128–152	153–203	204+
5' 1"	132–157	158–210	211+
5' 2"	136–163	164–217	218+
5' 3"	141–168	169–224	225+
5' 4"	145–173	174–231	232+
5' 5"	150–179	180–239	240+
5' 6"	155–185	186–246	247+
5' 7"	159–190	191–254	255+
5' 8"	164–196	197–261	262+
5' 9"	169–202	203–269	270+
5' 10"	174–208	209–277	278+
5' 11"	179–214	215–285	286+
6' 0"	184–220	221–293	294+
6' 1"	189–226	227–301	302+
6' 2"	194–232	233–310	311+
6' 3"	200–239	240–318	319+
6' 4"	205–245	246–327	328+
	1 point	2 points	3 points

If you weigh less than the amount in the left column: 0 points

Adapted from Bang et al., Ann Intern Med 151:775–783, 2009 • Original algorithm was validated without gestational diabetes as part of the model.

ADD UP YOUR SCORE.

If you scored 5 or higher:

You are at increased risk for having type 2 diabetes. However, only your doctor can tell for sure if you do have type 2 diabetes or prediabetes, a condition in which blood glucose levels are higher than normal but not yet high enough to be diagnosed as diabetes. Talk to your doctor to see if additional testing is needed.

Type 2 diabetes is more common in African Americans, Hispanics/Latinos, Native Americans, Asian Americans, and Native Hawaiians and Pacific Islanders.

Higher body weight increases diabetes risk for everyone. Asian Americans are at increased diabetes risk at lower body weight than the rest of the general public (about 15 pounds lower).

Lower Your Risk

The good news is you can manage your risk for type 2 diabetes. Small steps make a big difference in helping you live a longer, healthier life.

If you are at high risk, your first step is to visit your doctor to see if additional testing is needed.

Visit diabetes.org or call 1-800-DIABETES (800-342-2383) for information, tips on getting started, and ideas for simple, small steps you can take to help lower your risk.

Learn more at diabetes.org/risktest | 1-800-DIABETES (800-342-2383)

Diabetes Risk Test | American Diabetes Association®

Figure 2.1—ADA risk test (diabetes.org/socrisktest).

excellent care provided to patients in the routine care group and the lack of an unscreened control arm limited the authors' ability to determine whether screening and early treatment improved outcomes compared with no screening and later treatment after clinical diagnoses. Computer simulation modeling studies suggest that major benefits are likely to accrue from the early diagnosis and treatment of hyperglycemia and cardiovascular risk factors in type 2 diabetes (79); moreover, screening, beginning at age 30 or 45 years and independent of risk factors, may be cost-effective (<$11,000 per quality-adjusted life year gained—2010 modeling data) (80). Cost-effectiveness of

screening has been reinforced in cohort studies (81,82).

Additional considerations regarding testing for type 2 diabetes and prediabetes in asymptomatic patients include the following.

Age

Age is a major risk factor for diabetes. Testing should begin at no later than age 45 years for all patients. Screening should be considered in adults of any age with overweight or obesity and one or more risk factors for diabetes.

BMI and Ethnicity

In general, BMI $\geq$25 kg/m^2 is a risk factor for diabetes. However, data suggest that the BMI cut point should be lower for the Asian American population (83,84). The BMI cut points fall consistently between 23 and 24 kg/m^2 (sensitivity of 80%) for nearly all Asian American subgroups (with levels slightly lower for Japanese Americans). This makes a rounded cut point of 23 kg/m^2 practical. An argument can be made to push the BMI cut point to lower than 23 kg/m^2 in favor of increased sensitivity; however, this would lead to an unacceptably low specificity (13.1%). Data from WHO also suggests that a BMI of $\geq$23 kg/m^2 should be used to define increased risk in Asian Americans (85). The finding that one-third to one-half of diabetes in Asian Americans is undiagnosed suggests that testing is not occurring at lower BMI thresholds (86,87).

Evidence also suggests that other populations may benefit from lower BMI cut points. For example, in a large multiethnic cohort study, for an equivalent incidence rate of diabetes, a BMI of 30 kg/m^2 in non-Hispanic Whites was equivalent to a BMI of 26 kg/m^2 in African Americans (88).

Medications

Certain medications, such as glucocorticoids, thiazide diuretics, some HIV medications (23), and atypical antipsychotics (66), are known to increase the risk of diabetes and should be considered when deciding whether to screen.

HIV

Individuals with HIV are at higher risk for developing prediabetes and diabetes on antiretroviral (ARV) therapies, so a screening protocol is recommended (89). The A1C test may underestimate glycemia in people with HIV; it is not recommended for diagnosis and may present challenges for monitoring (24). In those with prediabetes, weight loss through healthy nutrition and physical activity may reduce the progression toward diabetes. Among patients with HIV and diabetes, preventive health care using an approach used in patients without HIV is critical to reduce the risks of microvascular and macrovascular complications. Diabetes risk is increased with certain PIs and NRTIs. New-onset diabetes is estimated to occur in more than 5% of patients infected with HIV on PIs, whereas more than 15% may have prediabetes (90). PIs are associated with insulin resistance and may also lead to apoptosis of pancreatic β-cells. NRTIs also affect fat distribution (both lipohypertrophy and lipoatrophy), which is associated with insulin resistance. For patients with HIV and ARV-associated hyperglycemia, it may be appropriate to consider discontinuing the problematic ARV agents if safe and effective alternatives are available (91). Before making ARV substitutions, carefully consider the possible effect on HIV virological control and the potential adverse effects of new ARV agents. In some cases, antihyperglycemic agents may still be necessary.

Testing Interval

The appropriate interval between screening tests is not known (92). The rationale for the 3-year interval is that with this interval, the number of false-positive tests that require confirmatory testing will be reduced and individuals with false-negative tests will be retested before substantial time elapses and complications develop (92). In especially high-risk individuals, particularly with weight gain, shorter intervals between screening may be useful.

Community Screening

Ideally, testing should be carried out within a health care setting because of the need for follow-up and treatment. Community screening outside a health care setting is generally not recommended because people with positive tests may not seek, or have access to, appropriate follow-up testing and care. However, in specific situations where an adequate referral system is established beforehand for positive tests, community screening may be considered. Community testing may also be poorly targeted; i.e., it may fail to reach the groups most at risk and inappropriately test those at very low risk or even those who have already been diagnosed (93).

Screening in Dental Practices

Because periodontal disease is associated with diabetes, the utility of screening in a dental setting and referral to primary care as a means to improve the diagnosis of prediabetes and diabetes has been explored (94–96), with one study estimating that 30% of patients $\geq$30 years of age seen in general dental practices had dysglycemia (96,97). A similar study in 1,150 dental patients >40 years old in India reported 20.69% and 14.60% meeting criteria for prediabetes and diabetes using random blood glucose. Further research is needed to demonstrate the feasibility, effectiveness, and cost-effectiveness of screening in this setting.

Screening and Testing for Prediabetes and Type 2 Diabetes in Children and Adolescents

In the last decade, the incidence and prevalence of type 2 diabetes in children and adolescents has increased dramatically, especially in racial and ethnic minority populations (53). See **Table 2.4** for recommendations on risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting (25). See **Table 2.2** and **Table 2.5** for the criteria for the diagnosis of diabetes and prediabetes, respectively, which apply to children, adolescents, and adults. See Section 13 "Children and Adolescents" (https://doi.org/10.2337/dc21-S013) for additional information on type 2 diabetes in children and adolescents.

Some studies question the validity of A1C in the pediatric population, especially among certain ethnicities, and suggest OGTT or FPG as more suitable diagnostic tests (98). However, many of these studies do not recognize that diabetes diagnostic criteria are based on long-term health outcomes, and validations are not currently available in the pediatric population (99). The ADA acknowledges the limited data supporting A1C for diagnosing type 2 diabetes in children and adolescents. Although A1C is not recommended for diagnosis of diabetes in children with cystic fibrosis or symptoms suggestive of acute onset of type 1 diabetes and only A1C assays without

interference are appropriate for children with hemoglobinopathies, the ADA continues to recommend A1C for diagnosis of type 2 diabetes in this cohort to decrease barriers to screening (100,101).

CYSTIC FIBROSIS–RELATED DIABETES

Recommendations

2.15 Annual screening for cystic fibrosis–related diabetes (CFRD) with an oral glucose tolerance test should begin by age 10 years in all patients with cystic fibrosis not previously diagnosed with CFRD. **B**

2.16 A1C is not recommended as a screening test for cystic fibrosis–related diabetes. **B**

2.17 Patients with cystic fibrosis–related diabetes should be treated with insulin to attain individualized glycemic goals. **A**

2.18 Beginning 5 years after the diagnosis of cystic fibrosis–related diabetes, annual monitoring for complications of diabetes is recommended. **E**

Cystic fibrosis–related diabetes (CFRD) is the most common comorbidity in people with cystic fibrosis, occurring in about 20% of adolescents and 40–50% of adults (102). Diabetes in this population, compared with individuals with type 1 or type 2 diabetes, is associated with worse nutritional status, more severe inflammatory lung disease, and greater mortality. Insulin insufficiency is the primary defect in CFRD. Genetically determined β-cell function and insulin resistance associated with infection and inflammation may also contribute to the development of CFRD. Milder abnormalities of glucose tolerance are even more common and occur at earlier ages than CFRD. Whether individuals with IGT should be treated with insulin replacement has not currently been determined. Although screening for diabetes before the age of 10 years can identify risk for progression to CFRD in those with abnormal glucose tolerance, no benefit has been established with respect to weight, height, BMI, or lung function. OGTT is the recommended screening test; however, recent publications suggest that an A1C cut point threshold of 5.5% (5.8% in a second study) would detect more than 90% of cases and reduce patient screening burden (103,104). Ongoing studies are underway to validate this approach. Regardless of age, weight loss or failure of expected weight gain is a risk for CFRD and should prompt screening (103,104). The Cystic Fibrosis Foundation Patient Registry (105) evaluated 3,553 cystic fibrosis patients and diagnosed 445 (13%) with CFRD. Early diagnosis and treatment of CFRD was associated with preservation of lung function. The European Cystic Fibrosis Society Patient Registry reported an increase in CFRD with age (increased 10% per decade), genotype, decreased lung function, and female sex (106,107). Continuous glucose monitoring or HOMA of β-cell function (108) may be more sensitive than OGTT to detect risk for progression to CFRD; however, evidence linking these results to long-term outcomes is lacking, and these tests are not recommended for screening outside of the research setting (109).

CFRD mortality has significantly decreased over time, and the gap in mortality between cystic fibrosis patients with and without diabetes has considerably narrowed (110). There are limited clinical trial data on therapy for CFRD. The largest study compared three regimens: premeal insulin aspart, repaglinide, or oral placebo in cystic fibrosis patients with diabetes or abnormal glucose tolerance. Participants all had weight loss in the year preceding treatment; however, in the insulin-treated group, this pattern was reversed, and patients gained 0.39 ($\pm$ 0.21) BMI units ($P = 0.02$). The repaglinide-treated group had initial weight gain, but this was not sustained by 6 months. The placebo group continued to lose weight (110). Insulin remains the most widely used therapy for CFRD (111). The primary rationale for the use of insulin in patients with CFRD is to induce an anabolic state while promoting macronutrient retention and weight gain.

Additional resources for the clinical management of CFRD can be found in the position statement "Clinical Care Guidelines for Cystic Fibrosis–Related Diabetes: A Position Statement of the American Diabetes Association and a Clinical Practice Guideline of the Cystic Fibrosis Foundation, Endorsed by the Pediatric Endocrine Society" (112) and in the International Society for Pediatric and Adolescent Diabetes's 2014 clinical practice consensus guidelines (102).

POSTTRANSPLANTATION DIABETES MELLITUS

Recommendations

2.19 Patients should be screened after organ transplantation for hyperglycemia, with a formal diagnosis of posttransplantation diabetes mellitus being best made once a patient is stable on an immunosuppressive regimen and in the absence of an acute infection. **B**

2.20 The oral glucose tolerance test is the preferred test to make a diagnosis of posttransplantation diabetes mellitus. **B**

2.21 Immunosuppressive regimens shown to provide the best outcomes for patient and graft survival should be used, irrespective of posttransplantation diabetes mellitus risk. **E**

Several terms are used in the literature to describe the presence of diabetes following organ transplantation (113). "New-onset diabetes after transplantation" (NODAT) is one such designation that describes individuals who develop new-onset diabetes following transplant. NODAT excludes patients with pretransplant diabetes that was undiagnosed as well as posttransplant hyperglycemia that resolves by the time of discharge (114). Another term, "posttransplantation diabetes mellitus" (PTDM) (114,115), describes the presence of diabetes in the posttransplant setting irrespective of the timing of diabetes onset.

Hyperglycemia is very common during the early posttransplant period, with ~90% of kidney allograft recipients exhibiting hyperglycemia in the first few weeks following transplant (114–117). In most cases, such stress- or steroid-induced hyperglycemia resolves by the time of discharge (117,118). Although the use of immunosuppressive therapies is a major contributor to the development of PTDM, the risks of transplant rejection outweigh the risks of PTDM and the role of the diabetes care provider is to treat hyperglycemia appropriately regardless of the type of immunosuppression (114). Risk factors for PTDM include both general diabetes risks (such as age,

family history of diabetes, etc.) as well as transplant-specific factors, such as use of immunosuppressant agents (119). Whereas posttransplantation hyperglycemia is an important risk factor for subsequent PTDM, a formal diagnosis of PTDM is optimally made once the patient is stable on maintenance immunosuppression and in the absence of acute infection (117–120). In a recent study of 152 heart transplant recipients, 38% had PTDM at 1 year. Risk factors for PTDM included elevated BMI, discharge from the hospital on insulin, and glucose values in the 24 h prior to hospital discharge (121). In an Iranian cohort, 19% had PTDM after heart and lung transplant (122). The OGTT is considered the gold standard test for the diagnosis of PTDM (1 year posttransplant) (114,115,123,124). However, screening patients using fasting glucose and/or A1C can identify high-risk patients requiring further assessment and may reduce the number of overall OGTTs required.

Few randomized controlled studies have reported on the short- and long-term use of antihyperglycemic agents in the setting of PTDM (119,125,126). Most studies have reported that transplant patients with hyperglycemia and PTDM after transplantation have higher rates of rejection, infection, and rehospitalization (117,119,127). Insulin therapy is the agent of choice for the management of hyperglycemia, PTDM, and preexisting diabetes and diabetes in the hospital setting. After discharge, patients with preexisting diabetes could go back on their pretransplant regimen if they were in good control before transplantation. Those with previously poor control or with persistent hyperglycemia should continue insulin with frequent home self-monitoring of blood glucose to determine when insulin dose reductions may be needed and when it may be appropriate to switch to noninsulin agents.

No studies to date have established which noninsulin agents are safest or most efficacious in PTDM. The choice of agent is usually made based on the side effect profile of the medication and possible interactions with the patient's immunosuppression regimen (119). Drug dose adjustments may be required because of decreases in the glomerular filtration rate, a relatively common complication in transplant patients. A small short-term pilot study reported that metformin was safe to use in renal transplant recipients (128), but its safety has not been determined in other types of organ transplant. Thiazolidinediones have been used successfully in patients with liver and kidney transplants, but side effects include fluid retention, heart failure, and osteopenia (129, 130). Dipeptidyl peptidase 4 inhibitors do not interact with immunosuppressant drugs and have demonstrated safety in small clinical trials (131,132). Well-designed intervention trials examining the efficacy and safety of these and other antihyperglycemic agents in patients with PTDM are needed.

MONOGENIC DIABETES SYNDROMES

Recommendations

2.22 All children diagnosed with diabetes in the first 6 months of life should have immediate genetic testing for neonatal diabetes. **A**

2.23 Children and those diagnosed in early adulthood who have diabetes not characteristic of type 1 or type 2 diabetes that occurs in successive generations (suggestive of an autosomal dominant pattern of inheritance) should have genetic testing for maturity-onset diabetes of the young. **A**

2.24 In both instances, consultation with a center specializing in diabetes genetics is recommended to understand the significance of these mutations and how best to approach further evaluation, treatment, and genetic counseling. **E**

Monogenic defects that cause β-cell dysfunction, such as neonatal diabetes and MODY, represent a small fraction of patients with diabetes (<5%). **Table 2.6** describes the most common causes of monogenic diabetes. For a comprehensive list of causes, see *Genetic Diagnosis of Endocrine Disorders* (133).

Neonatal Diabetes

Diabetes occurring under 6 months of age is termed "neonatal" or "congenital" diabetes, and about 80–85% of cases can be found to have an underlying monogenic cause (134–137). Neonatal diabetes occurs much less often after 6 months of age, whereas autoimmune type 1 diabetes rarely occurs before 6 months of age. Neonatal diabetes can either be transient or permanent. Transient diabetes is most often due to overexpression of genes on chromosome 6q24, is recurrent in about half of cases, and may be treatable with medications other than insulin. Permanent neonatal diabetes is most commonly due to autosomal dominant mutations in the genes encoding the Kir6.2 subunit (*KCNJ11*) and SUR1 subunit (*ABCC8*) of the β-cell K_{ATP} channel. A recent report details a de novo mutation in *EIF2B1* affecting eIF2 signaling associated with permanent neonatal diabetes and hepatic dysfunction, similar to Wolcott-Rallison syndrome but with few severe comorbidities (138). Correct diagnosis has critical implications because most patients with K_{ATP}-related neonatal diabetes will exhibit improved glycemic control when treated with high-dose oral sulfonylureas instead of insulin. Insulin gene (*INS*) mutations are the second most common cause of permanent neonatal diabetes, and, while intensive insulin management is currently the preferred treatment strategy, there are important genetic counseling considerations, as most of the mutations that cause diabetes are dominantly inherited.

Maturity-Onset Diabetes of the Young

MODY is frequently characterized by onset of hyperglycemia at an early age (classically before age 25 years, although diagnosis may occur at older ages). MODY is characterized by impaired insulin secretion with minimal or no defects in insulin action (in the absence of coexistent obesity). It is inherited in an autosomal dominant pattern with abnormalities in at least 13 genes on different chromosomes identified to date. The most commonly reported forms are GCK-MODY (MODY2), HNF1A-MODY (MODY3), and HNF4A-MODY (MODY1).

For individuals with MODY, the treatment implications are considerable and warrant genetic testing (139,140). Clinically, patients with GCK-MODY exhibit mild, stable fasting hyperglycemia and do not require antihyperglycemic therapy except sometimes during pregnancy. Patients with HNF1A- or HNF4A-MODY usually respond well to low doses of sulfonylureas, which are considered first-line therapy. Mutations or deletions in *HNF1B* are associated with renal cysts

Table 2.6—Most common causes of monogenic diabetes (133)

	Gene	Inheritance	Clinical features
MODY	*GCK*	AD	GCK-MODY: stable, nonprogressive elevated fasting blood glucose; typically does not require treatment; microvascular complications are rare; small rise in 2-h PG level on OGTT (<54 mg/dL [3 mmol/L])
	HNF1A	AD	HNF1A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; lowered renal threshold for glucosuria; large rise in 2-h PG level on OGTT (>90 mg/dL [5 mmol/L]); sensitive to sulfonylureas
	HNF4A	AD	HNF4A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; may have large birth weight and transient neonatal hypoglycemia; sensitive to sulfonylureas
	HNF1B	AD	HNF1B-MODY: developmental renal disease (typically cystic); genitourinary abnormalities; atrophy of the pancreas; hyperuricemia; gout
Neonatal diabetes	*KCNJ11*	AD	Permanent or transient: IUGR; possible developmental delay and seizures; responsive to sulfonylureas
	INS	AD	Permanent: IUGR; insulin requiring
	ABCC8	AD	Permanent or transient: IUGR; rarely developmental delay; responsive to sulfonylureas
	6q24 (*PLAGL1, HYMA1*)	AD for paternal duplications	Transient: IUGR; macroglossia; umbilical hernia; mechanisms include UPD6, paternal duplication or maternal methylation defect; may be treatable with medications other than insulin
	GATA6	AD	Permanent: pancreatic hypoplasia; cardiac malformations; pancreatic exocrine insufficiency; insulin requiring
	EIF2AK3	AR	Permanent: Wolcott-Rallison syndrome: epiphyseal dysplasia; pancreatic exocrine insufficiency; insulin requiring
	EIF2B1	AD	Permanent diabetes: can be associated with fluctuating liver function (138)
	FOXP3	X-linked	Permanent: immunodysregulation, polyendocrinopathy; enteropathy X-linked (IPEX) syndrome: autoimmune diabetes, autoimmune thyroid disease, exfoliative dermatitis; insulin requiring

AD, autosomal dominant; AR, autosomal recessive; IUGR, intrauterine growth restriction; OGTT, oral glucose tolerance test; UPD6, uniparental disomy of chromosome 6; 2-h PG, 2-h plasma glucose.

and uterine malformations (renal cysts and diabetes [RCAD] syndrome). Other extremely rare forms of MODY have been reported to involve other transcription factor genes including *PDX1* (*IPF1*) and *NEUROD1*.

Diagnosis of Monogenic Diabetes

A diagnosis of one of the three most common forms of MODY, including GCK-MODY, HNF1A-MODY, and HNF4A-MODY, allows for more cost-effective therapy (no therapy for GCK-MODY; sulfonylureas as first-line therapy for HNF1A-MODY and HNF4A-MODY). Additionally, diagnosis can lead to identification of other affected family members. Genetic screening is increasingly available and cost-effective (138,140).

A diagnosis of MODY should be considered in individuals who have atypical diabetes and multiple family members with diabetes not characteristic of type 1 or type 2 diabetes, although admittedly "atypical diabetes" is becoming increasingly difficult to precisely define in the absence of a definitive set of tests for either type of diabetes (135–137, 139–145). In most cases, the presence of autoantibodies for type 1 diabetes precludes further testing for monogenic diabetes, but the presence of autoantibodies in patients with monogenic diabetes has been reported (146). Individuals in whom monogenic diabetes is suspected should be referred to a specialist for further evaluation if available, and consultation is available from several centers. Readily available commercial genetic testing following the criteria listed below now enables a cost-effective (147), often cost-saving, genetic diagnosis that is increasingly supported by health insurance. A biomarker screening pathway such as the combination of urinary C-peptide/creatinine ratio and antibody screening may aid in determining who should get genetic testing for MODY (148). It is critical to correctly diagnose one of the monogenic forms of diabetes because these patients may be incorrectly diagnosed with type 1 or type 2 diabetes, leading to suboptimal, even potentially harmful, treatment regimens and delays in diagnosing other family members (149). The correct diagnosis is especially critical for those with GCK-MODY mutations where multiple studies have shown that no complications ensue in the absence of glucose-lowering therapy (150). Genetic counseling is recommended to ensure that affected individuals understand the patterns of inheritance and the importance of a correct diagnosis.

The diagnosis of monogenic diabetes should be considered in children and adults diagnosed with diabetes in early adulthood with the following findings:

- Diabetes diagnosed within the first 6 months of life (with occasional cases presenting later, mostly *INS* and *ABCC8* mutations) (134,151)
- Diabetes without typical features of type 1 or type 2 diabetes (negative diabetes-associated autoantibodies, nonobese, lacking other metabolic features, especially with strong family history of diabetes)
- Stable, mild fasting hyperglycemia (100–150 mg/dL [5.5–8.5 mmol/L]), stable A1C between 5.6% and 7.6% (between 38 and 60 mmol/mol), especially if nonobese

PANCREATIC DIABETES OR DIABETES IN THE CONTEXT OF DISEASE OF THE EXOCRINE PANCREAS

Pancreatic diabetes includes both structural and functional loss of glucose-normalizing insulin secretion in the context of exocrine pancreatic dysfunction and is commonly misdiagnosed as type 2 diabetes. Hyperglycemia due to general pancreatic dysfunction has been called "type 3c diabetes" and, more recently, diabetes in the context of disease of the exocrine pancreas has been termed pancreoprivic diabetes (1). The diverse set of etiologies includes pancreatitis (acute and chronic), trauma or pancreatectomy, neoplasia, cystic fibrosis (addressed elsewhere in this chapter), hemochromatosis, fibrocalculous pancreatopathy, rare genetic disorders (152), and idiopathic forms (1), which is the preferred terminology. A distinguishing feature is concurrent pancreatic exocrine insufficiency (according to the monoclonal fecal elastase 1 test or direct function tests), pathological pancreatic imaging (endoscopic ultrasound, MRI, computed tomography), and absence of type 1 diabetes–associated autoimmunity (153–157). There is loss of both insulin and glucagon secretion and often higher-than-expected insulin requirements. Risk for microvascular complications is similar to other forms of diabetes. In the context of pancreatectomy, islet autotransplantation can be done to retain insulin secretion (158,159). In some cases, autotransplant can lead to insulin independence. In others, it may decrease insulin requirements (160).

GESTATIONAL DIABETES MELLITUS

Recommendations

2.25 Test for undiagnosed prediabetes and diabetes at the first prenatal visit in those with risk factors using standard diagnostic criteria. **B**

2.26 Test for gestational diabetes mellitus at 24–28 weeks of gestation in pregnant women not previously found to have diabetes. **A**

2.27 Test women with gestational diabetes mellitus for prediabetes or diabetes at 4–12 weeks postpartum, using the 75-g oral glucose tolerance test and clinically appropriate nonpregnancy diagnostic criteria. **B**

2.28 Women with a history of gestational diabetes mellitus should have lifelong screening for the development of diabetes or prediabetes at least every 3 years. **B**

2.29 Women with a history of gestational diabetes mellitus found to have prediabetes should receive intensive lifestyle interventions and/or metformin to prevent diabetes. **A**

Definition

For many years, GDM was defined as any degree of glucose intolerance that was first recognized during pregnancy (60), regardless of the degree of hyperglycemia. This definition facilitated a uniform strategy for detection and classification of GDM, but this definition has serious limitations (161). First, the best available evidence reveals that many, perhaps most, cases of GDM represent preexisting hyperglycemia that is detected by routine screening in pregnancy, as routine screening is not widely performed in nonpregnant women of reproductive age. It is the severity of hyperglycemia that is clinically important with regard to both short- and long-term maternal and fetal risks. Universal preconception and/or first trimester screening is hampered by lack of data and consensus regarding appropriate diagnostic thresholds and outcomes and cost-effectiveness (162,163). A compelling argument for further work in this area is the fact that hyperglycemia that would be diagnostic of diabetes outside of pregnancy and is present at the time of conception is associated with an increased risk of congenital malformations that is not seen with lower glucose levels (164,165).

The ongoing epidemic of obesity and diabetes has led to more type 2 diabetes in women of reproductive age, with an increase in the number of pregnant women with undiagnosed type 2 diabetes in early pregnancy (166–169). Because of the number of pregnant women with undiagnosed type 2 diabetes, it is reasonable to test women with risk factors for type 2 diabetes (170) (**Table 2.3**) at their initial prenatal visit, using standard diagnostic criteria (**Table 2.2**). Women found to have diabetes by the standard diagnostic criteria used outside of pregnancy should be classified as having diabetes complicating pregnancy (most often type 2 diabetes, rarely type 1 diabetes or monogenic diabetes) and managed accordingly. Women who meet the lower glycemic criteria for GDM should be diagnosed with that condition and managed accordingly. Other women should be rescreened for GDM between 24 and 28 weeks of gestation (see Section 14 "Management of Diabetes in Pregnancy," https://doi.org/10.2337/dc21-S014). The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) GDM diagnostic criteria for the 75-g OGTT as well as the GDM screening and diagnostic criteria used in the two-step approach were not derived from data in the first half of pregnancy, so the diagnosis of GDM in early pregnancy by either FPG or OGTT values is not evidence based (171) and further work is needed.

GDM is often indicative of underlying β-cell dysfunction (172), which confers marked increased risk for later development of diabetes, generally but not always type 2 diabetes, in the mother after delivery (173,174). As effective prevention interventions are available (175,176), women diagnosed with GDM should receive lifelong screening for prediabetes to allow interventions to reduce diabetes risk and for type 2 diabetes to allow treatment at the earliest possible time (177).

Diagnosis

GDM carries risks for the mother, fetus, and neonate. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (178), a large-scale multinational cohort study completed by more than 23,000 pregnant women, demonstrated that risk of adverse maternal, fetal, and neonatal outcomes continuously increased as a function of maternal glycemia at 24–28 weeks of gestation, even within ranges previously considered normal for pregnancy. For most complications, there was no threshold for risk. These results have led to careful reconsideration of the diagnostic criteria for GDM.

GDM diagnosis (**Table 2.7**) can be accomplished with either of two strategies:

1. The "one-step" 75-g OGTT derived from the IADPSG criteria, or
2. The older "two-step" approach with a 50-g (nonfasting) screen followed by a 100-g OGTT for those who screen

positive, based on the work of Carpenter and Coustan's interpretation of the older O'Sullivan (179) criteria.

Different diagnostic criteria will identify different degrees of maternal hyperglycemia and maternal/fetal risk, leading some experts to debate, and disagree on, optimal strategies for the diagnosis of GDM.

One-Step Strategy

The IADPSG defined diagnostic cut points for GDM as the average fasting, 1-h, and 2-h PG values during a 75-g OGTT in women at 24–28 weeks of gestation who participated in the HAPO study at which odds for adverse outcomes reached 1.75 times the estimated odds of these outcomes at the mean fasting, 1-h, and 2-h PG levels of the study population. This one-step strategy was anticipated to significantly increase the incidence of GDM (from 5–6% to 15–20%), primarily because only one abnormal value, not two, became sufficient to make the diagnosis (180). Many regional studies have investigated the impact of adopting the IADPSG criteria on prevalence and have seen a roughly one- to threefold increase (181). The anticipated increase in the incidence of GDM could have a substantial impact on costs and medical infrastructure needs and has the potential to "medicalize" pregnancies previously categorized as normal. A recent follow-up study of women participating in a blinded study of pregnancy OGTTs found that 11 years after their pregnancies, women who would have been diagnosed with GDM by the one-step approach, as compared with those without, were at 3.4-fold higher risk of developing prediabetes and type 2 diabetes and had children with a higher risk of obesity and increased body fat, suggesting that the larger group of women identified by the one-step approach would benefit from increased screening for diabetes and prediabetes that would accompany a history of GDM (182,183). The ADA recommends the IADPSG diagnostic criteria with the intent of optimizing gestational outcomes because these criteria are the only ones based on pregnancy outcomes rather than end points such as prediction of subsequent maternal diabetes.

The expected benefits of using IADPSG to the offspring are inferred from intervention trials that focused on women with lower levels of hyperglycemia than identified using older GDM diagnostic criteria. Those trials found modest benefits including reduced rates of large-for-gestational-age births and preeclampsia (184,185). It is important to note that 80–90% of women being treated for mild GDM in these two randomized controlled trials could be managed with lifestyle therapy alone. The OGTT glucose cutoffs in these two trials overlapped with the thresholds recommended by the IADPSG, and in one trial (185), the 2-h PG threshold (140 mg/dL [7.8 mmol/L]) was lower than the cutoff recommended by the IADPSG (153 mg/dL [8.5 mmol/L]). No randomized controlled trials of treating versus not treating GDM diagnosed by the IADPSG criteria but not the Carpenter-Coustan criteria have been published to date. Data are also lacking on how the treatment of lower levels of hyperglycemia affects a mother's future risk for the development of type 2 diabetes and her offspring's risk for obesity, diabetes, and other metabolic disorders. Additional well-designed clinical studies are needed to determine the optimal intensity of monitoring and treatment of women with GDM diagnosed by the one-step strategy (186,187).

Two-Step Strategy

In 2013, the NIH convened a consensus development conference to consider diagnostic criteria for diagnosing GDM (188). The 15-member panel had representatives from obstetrics and gynecology, maternal-fetal medicine, pediatrics, diabetes research, biostatistics, and other related fields. The panel recommended a two-step approach to screening that used a 1-h 50-g glucose load test (GLT) followed by a 3-h 100-g OGTT for those who screened positive. The American College of Obstetricians and Gynecologists (ACOG) recommends any of the commonly used thresholds of 130, 135, or 140 mg/dL for the 1-h 50-g GLT (189). A systematic review for the U.S. Preventive Services Task Force compared GLT cutoffs of 130 mg/dL (7.2 mmol/L) and 140 mg/dL (7.8 mmol/L) (190). The higher cutoff yielded sensitivity of 70–88% and specificity of 69–89%, while the lower cutoff was 88–99% sensitive and 66–77% specific. Data regarding a cutoff of 135 mg/dL are limited. As for other screening tests, choice of a cutoff is based upon the trade-off between sensitivity and specificity. The use of A1C at 24–28 weeks of gestation as a screening test for GDM does not function as well as the GLT (191).

Key factors cited by the NIH panel in their decision-making process were the lack of clinical trial data demonstrating

Table 2.7—Screening for and diagnosis of GDM

One-step strategy

Perform a 75-g OGTT, with plasma glucose measurement when patient is fasting and at 1 and 2 h, at 24–28 weeks of gestation in women not previously diagnosed with diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 h.

The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded:

- Fasting: 92 mg/dL (5.1 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 153 mg/dL (8.5 mmol/L)

Two-step strategy

Step 1: Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 h, at 24–28 weeks of gestation in women not previously diagnosed with diabetes.

If the plasma glucose level measured 1 h after the load is ≥130, 135, or 140 mg/dL (7.2, 7.5, or 7.8 mmol/L, respectively), proceed to a 100-g OGTT.

Step 2: The 100-g OGTT should be performed when the patient is fasting.

The diagnosis of GDM is made when at least two* of the following four plasma glucose levels (measured fasting and at 1, 2, and 3 h during OGTT) are met or exceeded (Carpenter-Coustan criteria [193]):

- Fasting: 95 mg/dL (5.3 mmol/L)
- 1 h: 180 mg/dL (10.0 mmol/L)
- 2 h: 155 mg/dL (8.6 mmol/L)
- 3 h: 140 mg/dL (7.8 mmol/L)

GDM, gestational diabetes mellitus; GLT, glucose load test; OGTT, oral glucose tolerance test.
*American College of Obstetricians and Gynecologists notes that one elevated value can be used for diagnosis (189).

the benefits of the one-step strategy and the potential negative consequences of identifying a large group of women with GDM, including medicalization of pregnancy with increased health care utilization and costs. Moreover, screening with a 50-g GLT does not require fasting and is therefore easier to accomplish for many women. Treatment of higher-threshold maternal hyperglycemia, as identified by the two-step approach, reduces rates of neonatal macrosomia, large-for-gestational-age births (192), and shoulder dystocia, without increasing small-for-gestational-age births. ACOG currently supports the two-step approach but notes that one elevated value, as opposed to two, may be used for the diagnosis of GDM (189). If this approach is implemented, the incidence of GDM by the two-step strategy will likely increase markedly. ACOG recommends either of two sets of diagnostic thresholds for the 3-h 100-g OGTT—Carpenter-Coustan or National Diabetes Data Group (193,194). Each is based on different mathematical conversions of the original recommended thresholds by O'Sullivan (179), which used whole blood and nonenzymatic methods for glucose determination. A secondary analysis of data from a randomized clinical trial of identification and treatment of mild GDM (195) demonstrated that treatment was similarly beneficial in patients meeting only the lower thresholds per Carpenter-Coustan (193) and in those meeting only the higher thresholds per National Diabetes Data Group (194). If the two-step approach is used, it would appear advantageous to use the Carpenter-Coustan lower diagnostic thresholds as shown in step 2 in **Table 2.7**.

Future Considerations

The conflicting recommendations from expert groups underscore the fact that there are data to support each strategy. A cost-benefit estimation comparing the two strategies concluded that the one-step approach is cost-effective only if patients with GDM receive postdelivery counseling and care to prevent type 2 diabetes (196). The decision of which strategy to implement must therefore be made based on the relative values placed on factors that have yet to be measured (e.g., willingness to change practice based on correlation studies rather than intervention trial results, available infrastructure, and importance of cost considerations).

As the IADPSG criteria ("one-step strategy") have been adopted internationally, further evidence has emerged to support improved pregnancy outcomes with cost savings (197), and IADPSG may be the preferred approach. Data comparing population-wide outcomes with one-step versus two-step approaches have been inconsistent to date (198,199). In addition, pregnancies complicated by GDM per the IADPSG criteria, but not recognized as such, have outcomes comparable to pregnancies with diagnosed GDM by the more stringent two-step criteria (200,201). There remains strong consensus that establishing a uniform approach to diagnosing GDM will benefit patients, caregivers, and policy makers. Longer-term outcome studies are currently underway.

References

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014;37(Suppl. 1):S81–S90
2. Dabelea D, Rewers A, Stafford JM, Standiford DA, Lawrence JM, Saydah S, et al. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for Diabetes in Youth study. Pediatrics 2014;133:e938–e945
3. Humphreys A, Bravis V, Kaur A, et al. Individual and diabetes presentation characteristics associated with partial remission status in children and adults evaluated up to 12 months following diagnosis of type 1 diabetes: an ADDRESS-2 (After Diagnosis Diabetes Research Support System-2) study analysis. Diabetes Res Clin Pract 2019;155: 107789
4. Thomas NJ, Lynam AL, Hill AV, et al. Type 1 diabetes defined by severe insulin deficiency occurs after 30 years of age and is commonly treated as type 2 diabetes. Diabetologia 2019; 62:1167–1172
5. Hope SV, Wienand-Barnett S, Shepherd M, et al. Practical classification guidelines for diabetes in patients treated with insulin: a cross-sectional study of the accuracy of diabetes diagnosis. Br J Gen Pract 2016;66:e315–e322
6. Zhong VW, Juhaeri J, Mayer-Davis EJ. Trends in hospital admission for diabetic ketoacidosis in adults with type 1 and type 2 diabetes in England, 1998-2013: a retrospective cohort study. Diabetes Care 2018;41:1870–1877
7. Newton CA, Raskin P. Diabetic ketoacidosis in type 1 and type 2 diabetes mellitus: clinical and biochemical differences. Arch Intern Med 2004; 164:1925–1931
8. Skyler JS, Bakris GL, Bonifacio E, et al. Differentiation of diabetes by pathophysiology, natural history, and prognosis. Diabetes 2017; 66:241–255
9. Lynam AL, Dennis JM, Owen KR, et al. Logistic regression has similar performance to optimised machine learning algorithms in a clinical setting: application to the discrimination between type 1 and type 2 diabetes in young adults. Diagn Progn Res 2020;4:6
10. Insel RA, Dunne JL, Atkinson MA, et al. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. Diabetes Care 2015;38:1964–1974
11. Zhu Y, Qian L, Liu Q, et al. Glutamic acid decarboxylase autoantibody detection by electrochemiluminescence assay identifies latent autoimmune diabetes in adults with poor islet function. Diabetes Metab J 2020;44:260–266
12. Lynam A, McDonald T, Hill A, et al. Development and validation of multivariable clinical diagnostic models to identify type 1 diabetes requiring rapid insulin therapy in adults aged 18-50 years. BMJ Open 2019;9:e031586
13. Chung WK, Erion K, Florez JC, et al. Precision medicine in diabetes: a consensus report from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2020;43:1617–1635
14. Gale EA. Declassifying diabetes. Diabetologia 2006;49:1989–1995
15. Schwartz SS, Epstein S, Corkey BE, Grant SFA, Gavin JR 3rd, Aguilar RB. The time is right for a new classification system for diabetes: rationale and implications of the β-cell-centric classification schema. Diabetes Care 2016;39:179–186
16. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327–1334
17. Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403
18. Tuomilehto J, Lindström J, Eriksson JG, et al.; Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343–1350
19. Chadha C, Pittas AG, Lary CW, et al.; D2d Research Group. Reproducibility of a prediabetes classification in a contemporary population. Metab Open 2020;6:100031
20. Meijnikman AS, De Block CEM, Dirinck E, et al. Not performing an OGTT results in significant underdiagnosis of (pre)diabetes in a high risk adult Caucasian population. Int J Obes 2017;41:1615–1620
21. Gonzalez A, Deng Y, Lane AN, et al. Impact of mismatches in HbA_{1c} vs glucose values on the diagnostic classification of diabetes and prediabetes. Diabet Med 2020;37:689–696
22. Cowie CC, Rust KF, Byrd-Holt DD, et al. Prevalence of diabetes and high risk for diabetes using A1C criteria in the U.S. population in 1988-2006. Diabetes Care 2010;33:562–568
23. Eckhardt BJ, Holzman RS, Kwan CK, Baghdadi J, Aberg JA. Glycated hemoglobin A_{1c} as screening for diabetes mellitus in HIV-infected individuals. AIDS Patient Care STDS 2012;26:197–201
24. Kim PS, Woods C, Georgoff P, et al. A1C underestimates glycemia in HIV infection. Diabetes Care 2009;32:1591–1593
25. Arslanian S, Bacha F, Grey M, Marcus MD, White NH, Zeitler P. Evaluation and management of youth-onset type 2 diabetes: a position statement by the American Diabetes Association. Diabetes Care 2018;41:2648–2668

26. Lacy ME, Wellenius GA, Sumner AE, et al. Association of sickle cell trait with hemoglobin A1c in African Americans. JAMA 2017;317:507–515
27. Wheeler E, Leong A, Liu C-T, et al.; EPIC-CVD Consortium; EPIC-InterAct Consortium; Lifelines Cohort Study. Impact of common genetic determinants of hemoglobin A1c on type 2 diabetes risk and diagnosis in ancestrally diverse populations: a transethnic genome-wide meta-analysis. PLoS Med 2017;14:e1002383
28. Ziemer DC, Kolm P, Weintraub WS, et al. Glucose-independent, black-white differences in hemoglobin A1c levels: a cross-sectional analysis of 2 studies. Ann Intern Med 2010;152:770–777
29. Kumar PR, Bhansali A, Ravikiran M, et al. Utility of glycated hemoglobin in diagnosing type 2 diabetes mellitus: a community-based study. J Clin Endocrinol Metab 2010;95:2832–2835
30. Herman WH. Are there clinical implications of racial differences in HbA_{1c}? Yes, to not consider can do great harm! Diabetes Care 2016;39:1458–1461
31. Herman WH, Ma Y, Uwaifo G, et al.; Diabetes Prevention Program Research Group. Differences in A1C by race and ethnicity among patients with impaired glucose tolerance in the Diabetes Prevention Program. Diabetes Care 2007;30:2453–2457
32. Selvin E, Steffes MW, Ballantyne CM, Hoogeveen RC, Coresh J, Brancati FL. Racial differences in glycemic markers: a cross-sectional analysis of community-based data. Ann Intern Med 2011;154:303–309
33. Herman WH, Dungan KM, Wolffenbuttel BHR, et al. Racial and ethnic differences in mean plasma glucose, hemoglobin A1c, and 1,5-anhydroglucitol in over 2000 patients with type 2 diabetes. J Clin Endocrinol Metab 2009;94:1689–1694
34. Bergenstal RM, Gal RL, Connor CG, et al.; T1D Exchange Racial Differences Study Group. Racial differences in the relationship of glucose concentrations and hemoglobin A1c levels. Ann Intern Med 2017;167:95–102
35. Selvin E, Rawlings AM, Bergenstal RM, Coresh J, Brancati FL. No racial differences in the association of glycated hemoglobin with kidney disease and cardiovascular outcomes. Diabetes Care 2013;36:2995–3001
36. Selvin E. Are there clinical implications of racial differences in HbA_{1c}? A difference, to be a difference, must make a difference. Diabetes Care 2016;39:1462–1467
37. Paterson AD. HbA1c for type 2 diabetes diagnosis in Africans and African Americans: personalized medicine NOW! PLoS Med 2017;14:e1002384
38. Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. Lancet 2008;371:64–74
39. Picón MJ, Murri M, Muñoz A, Fernández-García JC, Gomez-Huelgas R, Tinahones FJ. Hemoglobin A_{1c} versus oral glucose tolerance test in postpartum diabetes screening. Diabetes Care 2012;35:1648–1653
40. Göbl CS, Bozkurt L, Yarragudi R, Tura A, Pacini G, Kautzky-Willer A. Is early postpartum HbA1c an appropriate risk predictor after pregnancy with gestational diabetes mellitus? Acta Diabetol 2014;51:715–722
41. Megia A, Näf S, Herranz L, et al. The usefulness of HbA1c in postpartum reclassification of gestational diabetes. BJOG 2012;119:891–894
42. Welsh KJ, Kirkman MS, Sacks DB. Role of glycated proteins in the diagnosis and management of diabetes: research gaps and future directions. Diabetes Care 2016;39:1299–1306
43. Kim C, Bullard KM, Herman WH, Beckles GL. Association between iron deficiency and A1C Levels among adults without diabetes in the National Health and Nutrition Examination Survey, 1999–2006. Diabetes Care 2010;33:780–785
44. Selvin E, Wang D, Matsushita K, Grams ME, Coresh J. Prognostic implications of single-sample confirmatory testing for undiagnosed diabetes: a prospective cohort study. Ann Intern Med 2018;169:156–164
45. Ziegler AG, Rewers M, Simell O, et al. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. JAMA 2013;309:2473–2479
46. Ziegler A-G, Bonifacio E; BABYDIAB-BABYDIET Study Group. Age-related islet autoantibody incidence in offspring of patients with type 1 diabetes. Diabetologia 2012;55:1937–1943
47. Parikka V, Näntö-Salonen K, Saarinen M, et al. Early seroconversion and rapidly increasing autoantibody concentrations predict prepubertal manifestation of type 1 diabetes in children at genetic risk. Diabetologia 2012;55:1926–1936
48. Steck AK, Vehik K, Bonifacio E, et al.; TEDDY Study Group. Predictors of progression from the appearance of islet autoantibodies to early childhood diabetes: The Environmental Determinants of Diabetes in the Young (TEDDY). Diabetes Care 2015;38:808–813
49. McKeigue PM, Spiliopoulou A, McGurnaghan S, et al. Persistent C-peptide secretion in type 1 diabetes and its relationship to the genetic architecture of diabetes. BMC Med. 2019;17:165
50. Bogun MM, Bundy BN, Goland RS, Greenbaum CJ. C-Peptide levels in subjects followed longitudinally before and after type 1 diabetes diagnosis in TrialNet. Diabetes Care 2020;43:1836–1842
51. Mishra R, Hodge KM, Cousminer DL, Leslie RD, Grant SFA. A global perspective of latent autoimmune diabetes in adults. Trends Endocrinol Metab 2018;29:638–650
52. Buzzetti R, Zampetti S, Maddaloni E. Adult-onset autoimmune diabetes: current knowledge and implications for management. Nat Rev Endocrinol 2017;13:674–686
53. Dabelea D, Mayer-Davis EJ, Saydah S, et al.; SEARCH for Diabetes in Youth Study. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. JAMA 2014;311:1778–1786
54. Sosenko JM, Skyler JS, Palmer JP, et al.; Type 1 Diabetes TrialNet Study Group; Diabetes Prevention Trial-Type 1 Study Group. The prediction of type 1 diabetes by multiple autoantibody levels and their incorporation into an autoantibody risk score in relatives of type 1 diabetic patients. Diabetes Care 2013;36:2615–2620
55. Orban T, Sosenko JM, Cuthbertson D, et al.; Diabetes Prevention Trial-Type 1 Study Group. Pancreatic islet autoantibodies as predictors of type 1 diabetes in the Diabetes Prevention Trial-Type 1. Diabetes Care 2009;32:2269–2274
56. Jacobsen LM, Larsson HE, Tamura RN, et al.; TEDDY Study Group. Predicting progression to type 1 diabetes from ages 3 to 6 in islet autoantibody positive TEDDY children. Pediatr Diabetes 2019;20:263–270
57. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2011;34(Suppl. 1):S62–S69
58. Genuth S, Alberti KGMM, Bennett P, et al.; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003;26:3160–3167
59. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183–1197
60. Zhang X, Gregg EW, Williamson DF, et al. A1C level and future risk of diabetes: a systematic review. Diabetes Care 2010;33:1665–1673
61. Selvin E, Steffes MW, Zhu H, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 2010;362:800–811
62. Ackermann RT, Cheng YJ, Williamson DF, Gregg EW. Identifying adults at high risk for diabetes and cardiovascular disease using hemoglobin A1c National Health and Nutrition Examination Survey 2005-2006. Am J Prev Med 2011;40:11–17
63. Diabetes Prevention Program Research Group. HbA_{1c} as a predictor of diabetes and as an outcome in the diabetes prevention program: a randomized clinical trial. Diabetes Care 2015;38:51–58
64. Umpierrez G, Korytkowski M. Diabetic emergencies - ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. Nat Rev Endocrinol 2016;12:222–232
65. Fadini GP, Bonora BM, Avogaro A. SGLT2 inhibitors and diabetic ketoacidosis: data from the FDA Adverse Event Reporting System. Diabetologia 2017;60:1385–1389
66. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet 2018;391:541–551
67. Taheri S, Zaghloul H, Chagoury O, et al. Effect of intensive lifestyle intervention on bodyweight and glycaemia in early type 2 diabetes (DIADEM-I): an open-label, parallel-group, randomised controlled trial. Lancet Diabetes Endocrinol 2020;8:477–489
68. Lean MEJ, Leslie WS, Barnes AC, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. Lancet Diabetes Endocrinol 2019;7:344–355
69. Roth AE, Thornley CJ, Blackstone RP. Outcomes in bariatric and metabolic surgery: an updated 5-year review. Curr Obes Rep 2020;9:380–389
70. Conte C, Lapeyre-Mestre M, Hanaire H, Ritz P. Diabetes remission and relapse after bariatric surgery: a nationwide population-based study. Obes Surg. 31 August 2020 [Epub ahead of print]. DOI: 10.1007/s11695-020-04924-3

71. Yoshino M, Kayser BD, Yoshino J, et al. Effects of diet versus gastric bypass on metabolic function in diabetes. N Engl J Med 2020;383:721–732
72. Cresci B, Cosentino C, Monami M, Mannucci E. Metabolic surgery for the treatment of type 2 diabetes: a network meta-analysis of randomized controlled trials. Diabetes Obes Metab 2020;22:1378–1387
73. Palladino R, Tabak AG, Khunti K, et al. Association between pre-diabetes and microvascular and macrovascular disease in newly diagnosed type 2 diabetes. BMJ Open Diabetes Res Care 2020;8:e001061
74. Perreault L, Pan Q, Aroda VR, et al.; Diabetes Prevention Program Research Group. Exploring residual risk for diabetes and microvascular disease in the Diabetes Prevention Program Outcomes Study (DPPOS). Diabet Med 2017;34:1747–1755
75. Nathan DM, Bennett PH, Crandall JP, et al.; DPP Research Group. Does diabetes prevention translate into reduced long-term vascular complications of diabetes? Diabetologia 2019;62:1319–1328
76. Wei Y, Xu Q, Yang H, et al. Preconception diabetes mellitus and adverse pregnancy outcomes in over 6.4 million women: a population-based cohort study in China. PLoS Med 2019;16:e1002926
77. Peterson C, Grosse SD, Li R, et al. Preventable health and cost burden of adverse birth outcomes associated with pregestational diabetes in the United States. Am J Obstet Gynecol 2015;212:74.e1–74.e9
78. Griffin SJ, Borch-Johnsen K, Davies MJ, et al. Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. Lancet 2011;378:156–167
79. Herman WH, Ye W, Griffin SJ, et al. Early detection and treatment of type 2 diabetes reduce cardiovascular morbidity and mortality: a simulation of the results of the Anglo-Danish-Dutch Study of Intensive Treatment in People With Screen-Detected Diabetes in Primary Care (ADDITION-Europe). Diabetes Care 2015;38:1449–1455
80. Kahn R, Alperin P, Eddy D, et al. Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effectiveness analysis. Lancet 2010;375:1365–1374
81. Zhou X, Siegel KR, Ng BP, et al. Cost-effectiveness of diabetes prevention interventions targeting high-risk individuals and whole populations: a systematic review. Diabetes Care 2020;43:1593–1616
82. Chatterjee R, Narayan KMV, Lipscomb J, et al. Screening for diabetes and prediabetes should be cost-saving in patients at high risk. Diabetes Care 2013;36:1981–1987
83. Araneta MRG, Kanaya AM, Hsu WC, et al. Optimum BMI cut points to screen Asian Americans for type 2 diabetes. Diabetes 2015;38:814–820
84. Hsu WC, Araneta MRG, Kanaya AM, Chiang JL, Fujimoto W. BMI cut points to identify at-risk Asian Americans for type 2 diabetes screening. Diabetes Care 2015;38:150–158
85. Expert Consultation WHO; WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157–163
86. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and trends in diabetes among adults in the United States, 1988-2012. JAMA 2015;314:1021–1029
87. Centers for Disease Control and Prevention. National Diabetes Statistics Report: estimates of diabetes and its burden in the United States, 2020. Accessed 28 October 2020. Available from https://www.cdc.gov/diabetes/data/statistics/statistics-report.html
88. Chiu M, Austin PC, Manuel DG, Shah BR, Tu JV. Deriving ethnic-specific BMI cutoff points for assessing diabetes risk. Diabetes Care 2011;34:1741–1748
89. Schambelan M, Benson CA, Carr A, et al.; International AIDS Society-USA. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS Society-USA panel. J Acquir Immune Defic Syndr 2002;31:257–275
90. Monroe AK, Glesby MJ, Brown TT. Diagnosing and managing diabetes in HIV-infected patients: current concepts. Clin Infect Dis 2015;60:453–462
91. Wohl DA, McComsey G, Tebas P, et al. Current concepts in the diagnosis and management of metabolic complications of HIV infection and its therapy. Clin Infect Dis 2006;43:645–653
92. Johnson SL, Tabaei BP, Herman WH. The efficacy and cost of alternative strategies for systematic screening for type 2 diabetes in the U.S. population 45–74 years of age. Diabetes Care 2005;28:307–311
93. Tabaei BP, Burke R, Constance A, et al. Community-based screening for diabetes in Michigan. Diabetes Care 2003;26:668–670
94. Lalla E, Kunzel C, Burkett S, Cheng B, Lamster IB. Identification of unrecognized diabetes and pre-diabetes in a dental setting. J Dent Res 2011;90:855–860
95. Lalla E, Cheng B, Kunzel C, Burkett S, Lamster IB. Dental findings and identification of undiagnosed hyperglycemia. J Dent Res 2013;92:888–892
96. Herman WH, Taylor GW, Jacobson JJ, Burke R, Brown MB. Screening for prediabetes and type 2 diabetes in dental offices. J Public Health Dent 2015;75:175–182
97. Jadhav AN, Tarte PR, Puri SK. Dental clinic: potential source of high-risk screening for prediabetes and type 2 diabetes. Indian J Dent Res 2019;30:851–854
98. Buse JB, Kaufman FR, Linder B, Hirst K, El Ghormli L, Willi S; HEALTHY Study Group. Diabetes screening with hemoglobin A_{1c} versus fasting plasma glucose in a multiethnic middle-school cohort. Diabetes Care 2013;36:429–435
99. Kapadia C, Zeitler P; Drugs and Therapeutics Committee of the Pediatric Endocrine Society. Hemoglobin A_{1c} measurement for the diagnosis of type 2 diabetes in children. Int J Pediatr Endocrinol 2012;2012:31
100. Kester LM, Hey H, Hannon TS. Using hemoglobin A1c for prediabetes and diabetes diagnosis in adolescents: can adult recommendations be upheld for pediatric use? J Adolesc Health 2012;50:321–323
101. Wu E-L, Kazzi NG, Lee JM. Cost-effectiveness of screening strategies for identifying pediatric diabetes mellitus and dysglycemia. JAMA Pediatr 2013;167:32–39
102. Moran A, Pillay K, Becker D, Granados A, Hameed S, Acerini CL. ISPAD Clinical Practice Consensus Guidelines 2018: management of cystic fibrosis-related diabetes in children and adolescents. Pediatr Diabetes 2018;19(Suppl. 27):64–74
103. Gilmour JA. Response to the Letter to the Editor From Dr. Boudreau et al, "Validation of a Stepwise Approach Using Glycated Hemoglobin Levels to Reduce the Number of Required Oral Glucose Tolerance Tests to Screen for Cystic Fibrosis-Related Diabetes in Adults". Can J Diabetes 2019;43:163
104. Gilmour JA, Sykes J, Etchells E, Tullis E. Cystic fibrosis-related diabetes screening in adults: a gap analysis and evaluation of accuracy of glycated hemoglobin levels. Can J Diabetes 2019;43:13–18
105. Franck Thompson E, Watson D, Benoit CM, Landvik S, McNamara J. The association of pediatric cystic fibrosis-related diabetes screening on clinical outcomes by center: a CF Patient Registry study. J Cyst Fibros 2020;19:316–320
106. Olesen HV, Drevinek P, Gulmans VA, et al.; ECFSPR Steering Group. Cystic fibrosis related diabetes in Europe: prevalence, risk factors and outcome. J Cyst Fibros 2020;19:321–327
107. Prentice BJ, Chelliah A, Ooi CY, et al. Peak OGTT glucose is associated with lower lung function in young children with cystic fibrosis. J Cyst Fibros 2020;19:305–309
108. Mainguy C, Bellon G, Delaup V, et al. Sensitivity and specificity of different methods for cystic fibrosis-related diabetes screening: is the oral glucose tolerance test still the standard? J Pediatr Endocrinol Metab 2017;30:27–35
109. Ode KL, Moran A. New insights into cystic fibrosis-related diabetes in children. Lancet Diabetes Endocrinol 2013;1:52–58
110. Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W. Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. Diabetes Care 2009;32:1626–1631
111. Onady GM, Stolfi A. Insulin and oral agents for managing cystic fibrosis-related diabetes. Cochrane Database Syst Rev 2016;4:CD004730
112. Moran A, Brunzell C, Cohen RC, et al.; CFRD Guidelines Committee. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. Diabetes Care 2010;33:2697–2708
113. Shivaswamy V, Boerner B, Larsen J. Post-transplant diabetes mellitus: causes, treatment, and impact on outcomes. Endocr Rev 2016;37:37–61
114. Sharif A, Hecking M, de Vries APJ, et al. Proceedings from an international consensus meeting on posttransplantation diabetes mellitus: recommendations and future directions. Am J Transplant 2014;14:1992–2000
115. Hecking M, Werzowa J, Haidinger M, et al.; European-New-Onset Diabetes After Transplantation Working Group. Novel views on new-onset diabetes after transplantation: development, prevention and treatment. Nephrol Dial Transplant 2013;28:550–566

116. Ramirez SC, Maaske J, Kim Y, et al. The association between glycemic control and clinical outcomes after kidney transplantation. Endocr Pract 2014;20:894–900
117. Thomas MC, Moran J, Mathew TH, Russ GR, Rao MM. Early peri-operative hyperglycaemia and renal allograft rejection in patients without diabetes. BMC Nephrol 2000;1:1
118. Chakkera HA, Weil EJ, Castro J, et al. Hyperglycemia during the immediate period after kidney transplantation. Clin J Am Soc Nephrol 2009;4:853–859
119. Wallia A, Illuri V, Molitch ME. Diabetes care after transplant: definitions, risk factors, and clinical management. Med Clin North Am 2016;100:535–550
120. Gulsoy Kirnap N, Bozkus Y, Haberal M. Analysis of risk factors for posttransplant diabetes mellitus after kidney transplantation: single-center experience. Exp Clin Transplant 2020;18(Suppl. 1):36–40
121. Munshi VN, Saghafian S, Cook CB, Eric Steidley D, Hardaway B, Chakkera HA. Incidence, risk factors, and trends for postheart transplantation diabetes mellitus. Am J Cardiol 2020;125:436–440
122. Kgosidialwa O, Blake K, O'Connell O, Egan J, O'Neill J, Hatunic M. Post-transplant diabetes mellitus associated with heart and lung transplant. Ir J Med Sci 2020;189:185–189
123. Sharif A, Moore RH, Baboolal K. The use of oral glucose tolerance tests to risk stratify for new-onset diabetes after transplantation: an underdiagnosed phenomenon. Transplantation 2006;82:1667–1672
124. Hecking M, Kainz A, Werzowa J, et al. Glucose metabolism after renal transplantation. Diabetes Care 2013;36:2763–2771
125. Galindo RJ, Fried M, Breen T, Tamler R. Hyperglycemia management in patients with posttransplantation diabetes. Endocr Pract 2016;22:454–465
126. Jenssen T, Hartmann A. Emerging treatments for post-transplantation diabetes mellitus. Nat Rev Nephrol 2015;11:465–477
127. Thomas MC, Mathew TH, Russ GR, Rao MM, Moran J. Early peri-operative glycaemic control and allograft rejection in patients with diabetes mellitus: a pilot study. Transplantation 2001;72:1321–1324
128. Kurian B, Joshi R, Helmuth A. Effectiveness and long-term safety of thiazolidinediones and metformin in renal transplant recipients. Endocr Pract 2008;14:979–984
129. Budde K, Neumayer H-H, Fritsche L, Sulowicz W, Stompôr T, Eckland D. The pharmacokinetics of pioglitazone in patients with impaired renal function. Br J Clin Pharmacol 2003;55:368–374
130. Luther P, Baldwin D Jr. Pioglitazone in the management of diabetes mellitus after transplantation. Am J Transplant 2004;4:2135–2138
131. Strøm Halden TA, Åsberg A, Vik K, Hartmann A, Jenssen T. Short-term efficacy and safety of sitagliptin treatment in long-term stable renal recipients with new-onset diabetes after transplantation. Nephrol Dial Transplant 2014;29:926–933
132. Lane JT, Odegaard DE, Haire CE, Collier DS, Wrenshall LE, Stevens RB. Sitagliptin therapy in kidney transplant recipients with new-onset diabetes after transplantation. Transplantation 2011;92:e56–e57
133. Carmody D, Støy J, Greeley SA, Bell GI, Philipson LH. A clinical guide to monogenic diabetes. In *Genetic Diagnosis of Endocrine Disorders*. 2nd ed. Weiss RE, Refetoff S, Eds. Philadelphia, PA, Elsevier, 2016
134. De Franco E, Flanagan SE, Houghton JAL, et al. The effect of early, comprehensive genomic testing on clinical care in neonatal diabetes: an international cohort study. Lancet 2015;386:957–963
135. Sanyoura M, Letourneau L, Knight Johnson AE, et al. GCK-MODY in the US Monogenic Diabetes Registry: description of 27 unpublished variants. Diabetes Res Clin Pract 2019;151:231–236
136. Carmody D, Naylor RN, Bell CD, et al. GCK-MODY in the US National Monogenic Diabetes Registry: frequently misdiagnosed and unnecessarily treated. Acta Diabetol 2016;53:703–708
137. Timsit J, Saint-Martin C, Dubois-Laforgue D, Bellanné-Chantelot C. Searching for maturity-onset diabetes of the young (MODY): when and what for? Can J Diabetes 2016;40:455–461
138. De Franco E, Caswell R, Johnson MB, et al. De novo mutations in *EIF2B1* affecting eIF2 signaling cause neonatal/early-onset diabetes and transient hepatic dysfunction. Diabetes 2020;69:477–483
139. Shields BM, Hicks S, Shepherd MH, Colclough K, Hattersley AT, Ellard S. Maturity-onset diabetes of the young (MODY): how many cases are we missing? Diabetologia 2010;53:2504–2508
140. Awa WL, Schober E, Wiegand S, et al. Reclassification of diabetes type in pediatric patients initially classified as type 2 diabetes mellitus: 15 years follow-up using routine data from the German/Austrian DPV database. Diabetes Res Clin Pract 2011;94:463–467
141. Shepherd M, Shields B, Hammersley S, et al.; UNITED Team. Systematic population screening, using biomarkers and genetic testing, identifies 2.5% of the U.K. pediatric diabetes population with monogenic diabetes. Diabetes Care 2016;39:1879–1888
142. SEARCH Study Group. SEARCH for Diabetes in Youth: a multicenter study of the prevalence, incidence and classification of diabetes mellitus in youth. Control Clin Trials 2004;25:458–471
143. Pihoker C, Gilliam LK, Ellard S, et al.; SEARCH for Diabetes in Youth Study Group. Prevalence, characteristics and clinical diagnosis of maturity onset diabetes of the young due to mutations in HNF1A, HNF4A, and glucokinase: results from the SEARCH for Diabetes in Youth. J Clin Endocrinol Metab 2013;98:4055–4062
144. Draznin B (Ed.). *Atypical Diabetes: Pathophysiology, Clinical Presentations, and Treatment Options*. Arlington, American Diabetes Association, 2018
145. DiabetesGenes. MODY Probability Calculator. Accessed 28 October 2020. Available from https://www.diabetesgenes.org/mody-probability-calculator/
146. Urbanová J, Rypáčková B, Procházková Z, et al. Positivity for islet cell autoantibodies in patients with monogenic diabetes is associated with later diabetes onset and higher HbA1c level. Diabet Med 2014;31:466–471
147. Naylor RN, John PM, Winn AN, et al. Cost-effectiveness of MODY genetic testing: translating genomic advances into practical health applications. Diabetes Care 2014;37:202–209
148. Shields BM, Shepherd M, Hudson M, et al.; UNITED study team. Population-based assessment of a biomarker-based screening pathway to aid diagnosis of monogenic diabetes in young-onset patients. Diabetes Care 2017;40:1017–1025
149. Hattersley A, Bruining J, Shield J, Njolstad P, Donaghue KC. The diagnosis and management of monogenic diabetes in children and adolescents. Pediatr Diabetes 2009;10(Suppl. 12):33–42
150. Rubio-Cabezas O, Hattersley AT, Njølstad PR, et al.; International Society for Pediatric and Adolescent Diabetes. ISPAD Clinical Practice Consensus Guidelines 2014. The diagnosis and management of monogenic diabetes in children and adolescents. Pediatr Diabetes 2014;15(Suppl. 20):47–64
151. Greeley SAW, Naylor RN, Philipson LH, Bell GI. Neonatal diabetes: an expanding list of genes allows for improved diagnosis and treatment. Curr Diab Rep 2011;11:519–532
152. Le Bodic L, Bignon JD, Raguénès O, et al. The hereditary pancreatitis gene maps to long arm of chromosome 7. Hum Mol Genet 1996;5:549–554
153. Hardt PD, Brendel MD, Kloer HU, Bretzel RG. Is pancreatic diabetes (type 3c diabetes) underdiagnosed and misdiagnosed? Diabetes Care 2008;31(Suppl. 2):S165–S169
154. Woodmansey C, McGovern AP, McCullough KA, et al. Incidence, demographics, and clinical characteristics of diabetes of the exocrine pancreas (type 3c): a retrospective cohort study. Diabetes Care 2017;40:1486–1493
155. Duggan SN, Ewald N, Kelleher L, Griffin O, Gibney J, Conlon KC. The nutritional management of type 3c (pancreatogenic) diabetes in chronic pancreatitis. Eur J Clin Nutr 2017;71:3–8
156. Makuc J. Management of pancreatogenic diabetes: challenges and solutions. Diabetes Metab Syndr Obes 2016;9:311–315
157. Andersen DK, Korc M, Petersen GM, et al. Diabetes, pancreatogenic diabetes, and pancreatic cancer. Diabetes 2017;66:1103–1110
158. Bellin MD, Gelrud A, Arreaza-Rubin G, et al. Total pancreatectomy with islet autotransplantation: summary of an NIDDK workshop. Ann Surg 2015;261:21–29
159. Anazawa T, Okajima H, Masui T, Uemoto S. Current state and future evolution of pancreatic islet transplantation. Ann Gastroenterol Surg 2018;3:34–42
160. Quartuccio M, Hall E, Singh V, et al. Glycemic predictors of insulin independence after total pancreatectomy with islet autotransplantation. J Clin Endocrinol Metab 2017;102:801–809
161. Huvinen E, Koivusalo SB, Meinilä J, et al. Effects of a lifestyle intervention during pregnancy and first postpartum year: findings from the RADIEL study. J Clin Endocrinol Metab 2018;103:1669–1677
162. Yefet E, Jeda E, Tzur A, Nachum Z. Markers for undiagnosed type 2 diabetes mellitus during pregnancy-A population-based retrospective cohort study. J Diabetes 2020;12:205–214
163. Kattini R, Hummelen R, Kelly L. Early gestational diabetes mellitus screening with glycated hemoglobin: a systematic review. J Obstet Gynaecol Can. 5 April 2020 [Epub ahead of print]. DOI: 10.1016/j.jogc.2019.12.015

164. Rosenn B, Miodovnik M, Combs CA, Khoury J, Siddiqi TA. Glycemic thresholds for spontaneous abortion and congenital malformations in insulin-dependent diabetes mellitus. Obstet Gynecol 1994;84:515–520
165. Schaefer UM, Songster G, Xiang A, Berkowitz K, Buchanan TA, Kjos SL. Congenital malformations in offspring of women with hyperglycemia first detected during pregnancy. Am J Obstet Gynecol 1997;177:1165–1171
166. Poltavskiy E, Kim DJ, Bang H. Comparison of screening scores for diabetes and prediabetes. Diabetes Res Clin Pract 2016;118:146–153
167. Feig DS, Hwee J, Shah BR, Booth GL, Bierman AS, Lipscombe LL. Trends in incidence of diabetes in pregnancy and serious perinatal outcomes: a large, population-based study in Ontario, Canada, 1996–2010. Diabetes Care 2014;37:1590–1596
168. Peng TY, Ehrlich SF, Crites Y, et al. Trends and racial and ethnic disparities in the prevalence of pregestational type 1 and type 2 diabetes in Northern California: 1996-2014. Am J Obstet Gynecol 2017;216:177.e1–177.e8
169. Jovanovič L, Liang Y, Weng W, Hamilton M, Chen L, Wintfeld N. Trends in the incidence of diabetes, its clinical sequelae, and associated costs in pregnancy. Diabetes Metab Res Rev 2015;31:707–716
170. Mission JF, Catov J, Deihl TE, Feghali M, Scifres C. Early pregnancy diabetes screening and diagnosis: prevalence, rates of abnormal test results, and associated factors. Obstet Gynecol 2017;130:1136–1142
171. McIntyre HD, Sacks DA, Barbour LA, et al. Issues with the diagnosis and classification of hyperglycemia in early pregnancy. Diabetes Care 2016;39:53–54
172. Buchanan TA, Xiang A, Kjos SL, Watanabe R. What is gestational diabetes? Diabetes Care 2007;30(Suppl. 2):S105–S111
173. Noctor E, Crowe C, Carmody LA, et al.; ATLANTIC-DIP investigators. Abnormal glucose tolerance post-gestational diabetes mellitus as defined by the International Association of Diabetes and Pregnancy Study Groups criteria. Eur J Endocrinol 2016;175:287–297
174. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. Diabetes Care 2002;25:1862–1868
175. Ratner RE, Christophi CA, Metzger BE, et al.; Diabetes Prevention Program Research Group. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. J Clin Endocrinol Metab 2008;93:4774–4779
176. Aroda VR, Christophi CA, Edelstein SL, et al.; Diabetes Prevention Program Research Group. The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the Diabetes Prevention Program outcomes study 10-year follow-up. J Clin Endocrinol Metab 2015;100:1646–1653
177. Wang C, Wei Y, Zhang X, et al. A randomized clinical trial of exercise during pregnancy to prevent gestational diabetes mellitus and improve pregnancy outcome in overweight and obese pregnant women. Am J Obstet Gynecol 2017;216:340–351
178. Metzger BE, Lowe LP, Dyer AR, et al.; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991–2002
179. O'Sullivan JB, Mahan CM. Criteria for the oral glucose tolerance test in pregnancy. Diabetes 1964;13:278–285
180. Sacks DA, Hadden DR, Maresh M, et al.; HAPO Study Cooperative Research Group. Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel-recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. Diabetes Care 2012;35:526–528
181. Brown FM, Wyckoff J. Application of one-step IADPSG versus two-step diagnostic criteria for gestational diabetes in the real world: impact on health services, clinical care, and outcomes. Curr Diab Rep 2017;17:85
182. Lowe WL Jr, Scholtens DM, Lowe LP, et al.; HAPO Follow-up Study Cooperative Research Group. Association of gestational diabetes with maternal disorders of glucose metabolism and childhood adiposity. JAMA 2018;320:1005–1016
183. Lowe WL, Scholtens DM, Kuang A, et al.; HAPO Follow-up Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): maternal gestational diabetes mellitus and childhood glucose metabolism. Diabetes Care 2019;42:372–380
184. Landon MB, Spong CY, Thom E, et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med 2009;361:1339–1348
185. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS; Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 2005;352:2477–2486
186. Tam WH, Ma RCW, Ozaki R, et al. In utero exposure to maternal hyperglycemia increases childhood cardiometabolic risk in offspring. Diabetes Care 2017;40:679–686
187. Landon MB, Rice MM, Varner MW, et al.; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (MFMU) Network. Mild gestational diabetes mellitus and long-term child health. Diabetes Care 2015;38:445–452
188. Vandorsten JP, Dodson WC, Espeland MA, et al. NIH consensus development conference: diagnosing gestational diabetes mellitus. NIH Consens State Sci Statements 2013;29:1–31
189. Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 190: gestational diabetes mellitus. Obstet Gynecol 2018;131:e49–e64
190. Donovan L, Hartling L, Muise M, Guthrie A, Vandermeer B, Dryden DM. Screening tests for gestational diabetes: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2013;159:115–122
191. Khalafallah A, Phuah E, Al-Barazan AM, et al. Glycosylated haemoglobin for screening and diagnosis of gestational diabetes mellitus. BMJ Open 2016;6:e011059
192. Horvath K, Koch K, Jeitler K, et al. Effects of treatment in women with gestational diabetes mellitus: systematic review and meta-analysis. BMJ 2010;340:c1395
193. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. Am J Obstet Gynecol 1982;144:768–773
194. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979;28:1039–1057
195. Harper LM, Mele L, Landon MB, et al.; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network. Carpenter-Coustan compared with National Diabetes Data Group criteria for diagnosing gestational diabetes. Obstet Gynecol 2016;127:893–898
196. Werner EF, Pettker CM, Zuckerwise L, et al. Screening for gestational diabetes mellitus: are the criteria proposed by the international association of the Diabetes and Pregnancy Study Groups cost-effective? Diabetes Care 2012;35:529–535
197. Duran A, Sáenz S, Torrejón MJ, et al. Introduction of IADPSG criteria for the screening and diagnosis of gestational diabetes mellitus results in improved pregnancy outcomes at a lower cost in a large cohort of pregnant women: the St. Carlos Gestational Diabetes Study. Diabetes Care 2014;37:2442–2450
198. Wei Y, Yang H, Zhu W, et al. International Association of Diabetes and Pregnancy Study Group criteria is suitable for gestational diabetes mellitus diagnosis: further evidence from China. Chin Med J (Engl) 2014;127:3553–3556
199. Feldman RK, Tieu RS, Yasumura L. Gestational diabetes screening: the International Association of the Diabetes and Pregnancy Study Groups compared with Carpenter-Coustan screening. Obstet Gynecol 2016;127:10–17
200. Ethridge JK Jr, Catalano PM, Waters TP. Perinatal outcomes associated with the diagnosis of gestational diabetes made by the International Association of the Diabetes and Pregnancy Study Groups criteria. Obstet Gynecol 2014;124:571–578
201. Mayo K, Melamed N, Vandenberghe H, Berger H. The impact of adoption of the international association of diabetes in pregnancy study group criteria for the screening and diagnosis of gestational diabetes. Am J Obstet Gynecol 2015;212:224.e1–224.e9
202. Hutchins J, Barajas RA, Hale D, Escaname E, Lynch J. Type 2 diabetes in a 5-year-old and single center experience of type 2 diabetes in youth under 10. Pediatr Diabetes 2017;18:674–677

3. Prevention or Delay of Type 2 Diabetes: *Standards of Medical Care in Diabetes—2021*

American Diabetes Association

Diabetes Care 2021;44(Suppl. 1):S34–S39 | https://doi.org/10.2337/dc21-S003

The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc21-SPPC), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc21-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

For guidelines related to screening for increased risk for type 2 diabetes (prediabetes), please refer to Section 2 "Classification and Diagnosis of Diabetes" (https://doi.org/10.2337/dc21-S002). For guidelines related to screening, diagnosis, and management of type 2 diabetes in youth, please refer to Section 13 "Children and Adolescents" (https://doi.org/10.2337/dc21-S013).

Recommendation

3.1 At least annual monitoring for the development of type 2 diabetes in those with prediabetes is suggested. **E**

Screening for prediabetes and type 2 diabetes risk through an informal assessment of risk factors (**Table 2.3**) or with an assessment tool, such as the American Diabetes Association risk test (**Fig. 2.1**), is recommended to guide providers on whether performing a diagnostic test for prediabetes (**Table 2.5**) and previously undiagnosed type 2 diabetes (**Table 2.2**) is appropriate (see Section 2 "Classification and Diagnosis of Diabetes," https://doi.org/10.2337/dc21-S002). Testing high-risk patients for prediabetes is warranted because the laboratory assessment is safe and reasonable in cost, substantial time exists before the development of type 2 diabetes and its complications during which one can intervene, and there is an effective means of preventing type 2 diabetes in those determined to have prediabetes with an A1C 5.7–6.4% (39–47 mmol/mol), impaired glucose tolerance, or impaired fasting glucose. Using A1C to screen for prediabetes may be problematic in the presence of certain hemoglobinopathies or conditions that affect red blood cell turnover. See Section 2 "Classification and Diagnosis of Diabetes" (https://doi.org/10.2337/dc21-S002) and Section 6 "Glycemic Targets" (https://care.diabetesjournals.org/lookup/doi/10.2337/dc21-S006) for additional details on the appropriate use of the A1C test.

LIFESTYLE BEHAVIOR CHANGE FOR DIABETES PREVENTION

Recommendations

3.2 Refer patients with prediabetes to an intensive lifestyle behavior change program modeled on the Diabetes Prevention Program to achieve and maintain

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7% loss of initial body weight and increase moderate-intensity physical activity (such as brisk walking) to at least 150 min/week. **A**

3.3 A variety of eating patterns can be considered to prevent diabetes in individuals with prediabetes. **B**

3.4 Based on patient preference, certified technology-assisted diabetes prevention programs may be effective in preventing type 2 diabetes and should be considered. **B**

3.5 Given the cost-effectiveness of lifestyle behavior modification programs for diabetes prevention **A**, such diabetes prevention programs should be covered by third-party payers.

The Diabetes Prevention Program

Several major randomized controlled trials, including the Diabetes Prevention Program (DPP) (1), the Finnish Diabetes Prevention Study (DPS) (2), and the Da Qing Diabetes Prevention Study (Da Qing study) (3), demonstrate that lifestyle/behavioral therapy featuring an individualized reduced-calorie meal plan is highly effective in preventing type 2 diabetes and improving other cardiometabolic markers (such as blood pressure, lipids, and inflammation) (4). The strongest evidence for diabetes prevention in the U.S. comes from the DPP trial (1). The DPP demonstrated that an intensive lifestyle intervention could reduce the risk of incident type 2 diabetes by 58% over 3 years. Follow-up of three large studies of lifestyle intervention for diabetes prevention has shown sustained reduction in the risk of conversion to type 2 diabetes: 39% reduction at 30 years in the Da Qing study (5), 43% reduction at 7 years in the Finnish DPS (2), and 34% reduction at 10 years (6) and 27% reduction at 15 years (7) in the U.S. Diabetes Prevention Program Outcomes Study (DPPOS).

The two major goals of the DPP intensive lifestyle intervention were to achieve and maintain a minimum of 7% weight loss and 150 min of physical activity per week similar in intensity to brisk walking. The DPP lifestyle intervention was a goal-based intervention: all participants were given the same weight loss and physical activity goals, but individualization was permitted in the specific methods used to achieve the goals (8). Although weight loss was the most important factor to reduce the risk of incident diabetes, it was also found that achieving the target behavioral goal of at least 150 min of physical activity per week, even without weight loss, reduced the incidence of type 2 diabetes by 44% (9).

The 7% weight loss goal was selected because it was feasible to achieve and maintain and likely to lessen the risk of developing diabetes. Participants were encouraged to achieve the 7% weight loss during the first 6 months of the intervention. However, longer-term (4-year) data reveal maximal prevention of diabetes observed at about 7–10% weight loss (9). The recommended pace of weight loss was 1–2 lb/week. Calorie goals were calculated by estimating the daily calories needed to maintain the participant's initial weight and subtracting 500–1,000 calories/day (depending on initial body weight). The initial focus was on reducing total dietary fat. After several weeks, the concept of calorie balance and the need to restrict calories as well as fat was introduced (8).

The goal for physical activity was selected to approximate at least 700 kcal/week expenditure from physical activity. For ease of translation, this goal was described as at least 150 min of moderate-intensity physical activity per week similar in intensity to brisk walking. Participants were encouraged to distribute their activity throughout the week with a minimum frequency of three times per week and at least 10 min per session. A maximum of 75 min of strength training could be applied toward the total 150 min/week physical activity goal (8).

To implement the weight loss and physical activity goals, the DPP used an individual model of treatment rather than a group-based approach. This choice was based on a desire to intervene before participants had the possibility of developing diabetes or losing interest in the program. The individual approach also allowed for tailoring of interventions to reflect the diversity of the population (8).

The DPP intervention was administered as a structured core curriculum followed by a more flexible maintenance program of individual sessions, group classes, motivational campaigns, and restart opportunities. The 16-session core curriculum was completed within the first 24 weeks of the program and included sections on lowering calories, increasing physical activity, self-monitoring, maintaining healthy lifestyle behaviors, and psychological, social, and motivational challenges. Further details are available regarding the core curriculum sessions (8).

Nutrition

The dietary counseling for weight loss in the DPP intervention included a reduction of total dietary fat and calories to prevent diabetes for those at high risk for developing type 2 diabetes with an overweight or obese BMI (1,8,9). However, evidence suggests that there is not an ideal percentage of calories from carbohydrate, protein, and fat for all people to prevent diabetes; therefore, macronutrient distribution should be based on an individualized assessment of current eating patterns, preferences, and metabolic goals (10). Based on other intervention trials, a variety of eating patterns characterized by the totality of food and beverages consumed (10,11) may also be appropriate for patients with prediabetes (10), including Mediterranean-style and low-carbohydrate eating plans (12–15). Observational studies have also shown that vegetarian, plant-based (may include some animal products), and Dietary Approaches to Stop Hypertension (DASH) eating patterns are associated with a lower risk of developing type 2 diabetes (16–19). Evidence suggests that the overall quality of food consumed (as measured by the Healthy Eating Index, Alternative Healthy Eating Index, and DASH score), with an emphasis on whole grains, legumes, nuts, fruits, and vegetables and minimal refined and processed foods, is also associated with a lower risk of type 2 diabetes (18,20–23). As is the case for those with diabetes, individualized medical nutrition therapy (see Section 5 "Facilitating Behavior Change and Well-being to Improve Health Outcomes," https://doi.org/10.2337/dc21-S005, for more detailed information) is effective in lowering A1C in individuals diagnosed with prediabetes (24).

Physical Activity

Just as 150 min/week of moderate-intensity physical activity, such as brisk walking, showed beneficial effects in those with prediabetes (1), moderate-intensity physical activity has been shown to improve insulin sensitivity and reduce abdominal fat in children and young adults (25,26). On the basis of these findings, providers are encouraged to promote a DPP-style program, including a focus on physical activity, to all individuals who have been identified to be at an increased risk of

type 2 diabetes. In addition to aerobic activity, an exercise regimen designed to prevent diabetes may include resistance training (8,27,28). Breaking up prolonged sedentary time may also be encouraged, as it is associated with moderately lower postprandial glucose levels (29,30). The preventive effects of exercise appear to extend to the prevention of gestational diabetes mellitus (GDM) (31).

Delivery and Dissemination of Lifestyle Behavior Change for Diabetes Prevention

Because the intensive lifestyle intervention in the DPP was effective in preventing type 2 diabetes for those at high risk for the disease and lifestyle behavior change programs for diabetes prevention were shown to be cost-effective, broader efforts to disseminate scalable lifestyle behavior change programs for diabetes prevention with coverage by third-party payers ensued (32–36). Group delivery of DPP content in community or primary care settings has demonstrated the potential to reduce overall program costs while still producing weight loss and diabetes risk reduction (37–41).

The Centers for Disease Control and Prevention (CDC) developed the National Diabetes Prevention Program (National DPP), a resource designed to bring such evidence-based lifestyle change programs for preventing type 2 diabetes to communities (www.cdc.gov/diabetes/prevention/index.htm). This online resource includes locations of CDC-recognized diabetes prevention lifestyle change programs (available at https://nccd.cdc.gov/DDT_DPRP/Programs.aspx). To be eligible for this program, patients must have a BMI in the overweight range and be at risk for diabetes based on laboratory testing or a positive risk test (available at www.cdc.gov/prediabetes/takethetest/). Results from the CDC's National DPP during the first 4 years of implementation are promising and demonstrate cost-efficacy (42). The CDC has also developed the Diabetes Prevention Impact Tool Kit (available at https://nccd.cdc.gov/toolkit/diabetesimpact) to help organizations assess the economics of providing or covering the National DPP lifestyle change program (43). In an effort to expand preventive services using a cost-effective model that began in April 2018, the Centers for Medicare & Medicaid Services expanded Medicare reimbursement coverage for the National DPP lifestyle intervention to organizations recognized by the CDC that become Medicare suppliers for this service (online at https://innovation.cms.gov/innovation-models/medicare-diabetes-prevention-program). The locations of Medicare DPPs are available online at https://innovation.cms.gov/innovation-models/medicare-diabetes-prevention-program/mdpp-map. To qualify for Medicare coverage, patients must have a BMI in the overweight range and laboratory testing consistent with prediabetes in the last year. Medicaid coverage of the DPP lifestyle intervention is also expanding on a state-by-state basis.

While CDC-recognized lifestyle change programs and Medicare DPP services have the advantages of having met minimum quality standards and being reimbursed by various payers, there have been lower retention rates in such programs reported for younger adults and racial/ethnic minority populations (44). Therefore, other programs and modalities of lifestyle behavior changes for achieving the goals for diabetes prevention may also be appropriate and efficacious based on patient preferences and availability. The use of community health workers to support DPP efforts has been shown to be effective with cost savings (45,46) (see Section 1 "Improving Care and Promoting Health in Populations," https://doi.org/10.2337/dc21-S001, for more information). The use of community health workers may facilitate adoption of lifestyle behavior changes for diabetes prevention while bridging barriers related to social determinants of health, though coverage by third-party payers sometimes remains problematic. Registered dietitian nutritionists (RDN) can help individuals with prediabetes reach their goals of improving eating habits, increasing moderate-intensity physical activity, and achieving 7–10% loss of initial body weight (10,47–49). Individualized medical nutrition therapy (see Section 5 "Facilitating Behavior Change and Well-being to Improve Health Outcomes," https://doi.org/10.2337/dc21-S005, for more detailed information) is also effective in improving glycemia in individuals diagnosed with prediabetes (24,47). Furthermore, these trials involving medical nutrition therapy for patients with prediabetes found significant reductions in weight, waist circumference, and glycemia. Individuals with prediabetes can benefit from being referred to an RDN for individualized medical nutrition therapy upon diagnosis and at regular intervals throughout their treatment regimen (49,50). Other allied health professionals, like pharmacists and diabetes care and education specialists, also have the capability of delivering lifestyle behavior change programs and may be considered for diabetes prevention efforts (51,52).

Technology-assisted programs may effectively deliver the DPP lifestyle program, reducing weight and, therefore, diabetes risk (53–58). Such technology-assisted programs may deliver content through smartphone, web-based applications, and telehealth, and may be an acceptable and efficacious option to bridge barriers particularly for low-income and rural patients; however, not all programs are effective in helping people reach targets for diabetes prevention (53,59–61). The CDC Diabetes Prevention Recognition Program (DPRP) (www.cdc.gov/diabetes/prevention/requirements-recognition.htm) certifies technology-assisted modalities as effective vehicles for DPP-based programs; such programs must use an approved curriculum, include interaction with a coach, and attain the DPRP outcomes of participation, physical activity reporting, and weight loss. Therefore, providers should consider referring patients with prediabetes to certified technology–assisted DPP programs based on patient preference.

PHARMACOLOGIC INTERVENTIONS

Recommendations

3.6 Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI $\geq$35 kg/m^2, those aged $<$60 years, and women with prior gestational diabetes mellitus. **A**

3.7 Long-term use of metformin may be associated with biochemical vitamin B12 deficiency; consider periodic measurement of vitamin B12 levels in metformin-treated patients, especially in those with anemia or peripheral neuropathy. **B**

Because weight loss through behavior changes in diet and exercise alone can be difficult to maintain long term (6), people

being treated with weight loss therapy may benefit from support and additional pharmacotherapeutic options, if needed. Various pharmacologic agents used to treat diabetes have been evaluated for diabetes prevention. Metformin, α-glucosidase inhibitors, liraglutide, thiazolidinediones, and insulin have been shown to lower the risk of diabetes in those with prediabetes (62–67); whereas diabetes prevention was not seen with nateglinide (68). In addition, several weight loss medications like orlistat and phenteramine-topiramate have also been shown in research studies to decrease the incidence of diabetes to various degrees in those with prediabetes (69,70). Studies of other pharmacologic agents have shown some efficacy in diabetes prevention with valsartan but no efficacy with ramipril, anti-inflammatory drugs, or vitamin D in preventing diabetes (71–75). However, no pharmacologic agent has been approved by the U.S. Food and Drug Administration specifically for diabetes prevention. The risk versus benefit of each medication must be weighed. Metformin has the strongest evidence base (1) and demonstrated long-term safety as pharmacologic therapy for diabetes prevention (76). For other drugs, cost, side effects, and durable efficacy require consideration.

Metformin was overall less effective than lifestyle modification in the DPP, though group differences declined over time in the DPPOS (7), and metformin may be cost-saving over a 10-year period (34). During initial follow-up in the DPP, metformin was as effective as lifestyle modification in participants with BMI ≥35 kg/m^2 and in younger participants aged 25–44 years (1). In the DPP, for women with a history of GDM, metformin and intensive lifestyle modification led to an equivalent 50% reduction in diabetes risk (77), and both interventions remained highly effective during a 10-year follow-up period (78). By the time of the 15-year follow-up (DPPOS), exploratory analyses demonstrated that participants with a higher baseline fasting glucose (≥110 mg/dL vs. 95–109 mg/dL) and women with a history of GDM (vs. women without a history of GDM) experienced higher risk reductions with metformin (compared with the placebo arm) (79). In the Indian Diabetes Prevention Programme (IDPP-1), metformin and the lifestyle intervention reduced diabetes risk similarly at 30 months; of note, the lifestyle intervention in IDPP-1 was less intensive than that in the DPP (80). Based on findings from the DPP, metformin should be recommended as an option for high-risk individuals (e.g., those with a history of GDM or those with BMI ≥35 kg/m^2). Consider monitoring vitamin B12 levels in those taking metformin chronically to check for possible deficiency (81,82) (see Section 9 "Pharmacologic Approaches to Glycemic Treatment," https://doi.org/10.2337/dc21-S009, for more details).

PREVENTION OF VASCULAR DISEASE AND MORTALITY

Recommendation

3.8 Prediabetes is associated with heightened cardiovascular risk; therefore, screening for and treatment of modifiable risk factors for cardiovascular disease are suggested. **B**

People with prediabetes often have other cardiovascular risk factors, including hypertension and dyslipidemia (83), and are at increased risk for cardiovascular disease (84,85). Evaluation for tobacco use and referral for tobacco cessation, if indicated, should be part of routine care for those at risk for diabetes. Of note, the years immediately following smoking cessation may represent a time of increased risk for diabetes (86–88), a time when patients should be monitored for diabetes development and receive the concurrent evidence-based lifestyle behavior change for diabetes prevention described in this section. See Section 5 "Facilitating Behavior Change and Well-being to Improve Health Outcomes" (https://doi.org/10.2337/dc21-S005) for more detailed information. The lifestyle interventions for weight loss in study populations at risk for type 2 diabetes have shown a reduction in cardiovascular risk factors and the need for medications used to treat these cardiovascular risk factors (89,90). In longer-term follow-up, lifestyle interventions for diabetes prevention also prevented the development of microvascular complications among women enrolled in the DPPOS and in the study population enrolled in the China Da Qing Diabetes Prevention Outcome Study (7,91). The lifestyle intervention in the latter study was also efficacious in preventing cardiovascular disease and mortality at 23 and 30 years of follow-up (3,5). Treatment goals and therapies for hypertension and dyslipidemia in the primary prevention of cardiovascular disease for people with prediabetes should be based on their level of cardiovascular risk, and increased vigilance is warranted to identify and treat these and other cardiovascular risk factors (92).

References

1. Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403
2. Lindström J, Ilanne-Parikka P, Peltonen M, et al.; Finnish Diabetes Prevention Study Group. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet 2006;368:1673–1679
3. Li G, Zhang P, Wang J, et al. Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. Lancet Diabetes Endocrinol 2014;2:474–480
4. Nathan DM, Bennett PH, Crandall JP, et al.; Research Group. Does diabetes prevention translate into reduced long-term vascular complications of diabetes? Diabetologia 2019;62:1319–1328
5. Gong Q, Zhang P, Wang J, et al.; Da Qing Diabetes Prevention Study Group. Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the Da Qing Diabetes Prevention Outcome Study. Lancet Diabetes Endocrinol 2019;7:452–461
6. Knowler WC, Fowler SE, Hamman RF, et al.; Diabetes Prevention Program Research Group. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet 2009;374:1677–1686
7. Nathan DM, Barrett-Connor E, Crandall JP, et al. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications: the DPP Outcomes Study. Lancet Diabetes Endocrinol 2015;3:866–875
8. Diabetes Prevention Program (DPP) Research Group. The Diabetes Prevention Program (DPP): description of lifestyle intervention. Diabetes Care 2002;25:2165–2171
9. Hamman RF, Wing RR, Edelstein SL, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. Diabetes Care 2006;29:2102–2107
10. Evert AB, Dennison M, Gardner CD, et al. Nutrition therapy for adults with diabetes or prediabetes: a consensus report. Diabetes Care 2019;42:731–754
11. Department of Health and Human Services and Department of Agriculture. Dietary Guidelines for Americans 2015–2020, Eighth Edition. Accessed 5 October 2020. Available from https://health.gov/dietaryguidelines/2015/guidelines
12. Salas-Salvadó J, Guasch-Ferré M, Lee C-H, Estruch R, Clish CB, Ros E. Protective effects of

the Mediterranean diet on type 2 diabetes and metabolic syndrome. J Nutr 2016;146:920S–927S
13. Bloomfield HE, Koeller E, Greer N, MacDonald R, Kane R, Wilt TJ. Effects on health outcomes of a Mediterranean diet with no restriction on fat intake: a systematic review and meta-analysis. Ann Intern Med 2016;165:491–500
14. Estruch R, Ros E, Salas-Salvadó J, Covas M-I, Corella D, Arós F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med 2018;21:e34
15. Stentz FB, Brewer A, Wan J, et al. Remission of pre-diabetes to normal glucose tolerance in obese adults with high protein versus high carbohydrate diet: randomized control trial. BMJ Open Diabetes Res Care 2016;4:e000258
16. Chiu THT, Pan W-H, Lin M-N, Lin C-L. Vegetarian diet, change in dietary patterns, and diabetes risk: a prospective study. Nutr Diabetes 2018;8:12
17. Lee Y, Park K. Adherence to a vegetarian diet and diabetes risk: a systematic review and meta-analysis of observational studies. Nutrients 2017;9:E603
18. Qian F, Liu G, Hu FB, Bhupathiraju SN, Sun Q. Association between plant-based dietary patterns and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA Intern Med 2019;179:1335–1344
19. Esposito K, Chiodini P, Maiorino MI, Bellastella G, Panagiotakos D, Giugliano D. Which diet for prevention of type 2 diabetes? A meta-analysis of prospective studies. Endocrine 2014;47:107–116
20. Ley SH, Hamdy O, Mohan V, Hu FB. Prevention and management of type 2 diabetes: dietary components and nutritional strategies. Lancet 2014;383:1999–2007
21. Jacobs S, Harmon BE, Boushey CJ, et al. A priori-defined diet quality indexes and risk of type 2 diabetes: the Multiethnic Cohort. Diabetologia 2015;58:98–112
22. Chiuve SE, Fung TT, Rimm EB, et al. Alternative dietary indices both strongly predict risk of chronic disease. J Nutr 2012;142:1009–1018
23. Schwingshackl L, Bogensberger B, Hoffmann G. Diet quality as assessed by the Healthy Eating Index, Alternate Healthy Eating Index, Dietary Approaches to Stop Hypertension score, and Health Outcomes: an updated systematic review and meta-analysis of cohort studies. J Acad Nutr Diet 2018;118:74–100.e11
24. Parker AR, Byham-Gray L, Denmark R, Winkle PJ. The effect of medical nutrition therapy by a registered dietitian nutritionist in patients with prediabetes participating in a randomized controlled clinical research trial. J Acad Nutr Diet 2014;114:1739–1748
25. Fedewa MV, Gist NH, Evans EM, Dishman RK. Exercise and insulin resistance in youth: a meta-analysis. Pediatrics 2014;133:e163–e174
26. Davis CL, Pollock NK, Waller JL, et al. Exercise dose and diabetes risk in overweight and obese children: a randomized controlled trial. JAMA 2012;308:1103–1112
27. Sigal RJ, Alberga AS, Goldfield GS, et al. Effects of aerobic training, resistance training, or both on percentage body fat and cardiometabolic risk markers in obese adolescents: the healthy eating aerobic and resistance training in youth randomized clinical trial. JAMA Pediatr 2014;168:1006–1014
28. Dai X, Zhai L, Chen Q, et al. Two-year-supervised resistance training prevented diabetes incidence in people with prediabetes: a randomised control trial. Diabetes Metab Res Rev 2019;35:e3143
29. Thorp AA, Kingwell BA, Sethi P, Hammond L, Owen N, Dunstan DW. Alternating bouts of sitting and standing attenuate postprandial glucose responses. Med Sci Sports Exerc 2014;46:2053–2061
30. Healy GN, Dunstan DW, Salmon J, et al. Breaks in sedentary time: beneficial associations with metabolic risk. Diabetes Care 2008;31:661–666
31. Russo LM, Nobles C, Ertel KA, Chasan-Taber L, Whitcomb BW. Physical activity interventions in pregnancy and risk of gestational diabetes mellitus: a systematic review and meta-analysis. Obstet Gynecol 2015;125:576–582
32. Herman WH, Hoerger TJ, Brandle M, et al.; Diabetes Prevention Program Research Group. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. Ann Intern Med 2005;142:323–332
33. Chen F, Su W, Becker SH, et al. Clinical and economic impact of a digital, remotely-delivered intensive behavioral counseling program on Medicare beneficiaries at risk for diabetes and cardiovascular disease. PLoS One 2016;11:e0163627
34. Diabetes Prevention Program Research Group. The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the DPP/DPPOS. Diabetes Care 2012;35:723–730
35. Alva ML, Hoerger TJ, Jeyaraman R, Amico P, Rojas-Smith L. Impact of the YMCA of the USA Diabetes Prevention Program on Medicare spending and utilization. Health Aff (Millwood) 2017;36:417–424
36. Zhou X, Siegel KR, Ng BP, et al. Cost-effectiveness of diabetes prevention interventions targeting high-risk individuals and whole populations: a systematic review. Diabetes Care 2020;43:1593–1616
37. Ackermann RT, Finch EA, Brizendine E, Zhou H, Marrero DG. Translating the Diabetes Prevention Program into the community. The DEPLOY Pilot Study. Am J Prev Med 2008;35:357–363
38. Balk EM, Earley A, Raman G, Avendano EA, Pittas AG, Remington PL. Combined diet and physical activity promotion programs to prevent type 2 diabetes among persons at increased risk: a systematic review for the Community Preventive Services Task Force. Ann Intern Med 2015;163:437–451
39. Li R, Qu S, Zhang P, et al. Economic evaluation of combined diet and physical activity promotion programs to prevent type 2 diabetes among persons at increased risk: a systematic review for the Community Preventive Services Task Force. Ann Intern Med 2015;163:452–460
40. Gilmer T, O'Connor PJ, Schiff JS, et al. Cost-effectiveness of a community-based Diabetes Prevention Program with participation incentives for Medicaid beneficiaries. Health Serv Res 2018;53:4704–4724
41. Ackermann RT, Kang R, Cooper AJ, et al. Effect on health care expenditures during nationwide implementation of the Diabetes Prevention Program as a health insurance benefit. Diabetes Care 2019;42:1776–1783
42. Ely EK, Gruss SM, Luman ET, et al. A national effort to prevent type 2 diabetes: participant-level evaluation of CDC's National Diabetes Prevention Program. Diabetes Care 2017;40:1331–1341
43. Lanza A, Soler R, Smith B, Hoerger T, Neuwahl S, Zhang P. The Diabetes Prevention Impact Tool Kit: an online tool kit to assess the cost-effectiveness of preventing type 2 diabetes. J Public Health Manag Pract 2019;25:E1–E5
44. Cannon MJ, Masalovich S, Ng BP, et al. Retention among participants in the National Diabetes Prevention Program lifestyle change program, 2012–2017. Diabetes Care 2020;43:2042–2049
45. The Community Guide. Diabetes prevention: interventions engaging community health workers, 2016. Accessed 5 October 2020. Available from https://www.thecommunityguide.org/findings/diabetes-prevention-interventions-engaging-community-health-workers
46. Jacob V, Chattopadhyay SK, Hopkins DP, et al. Economics of community health workers for chronic disease: findings from community guide systematic reviews. Am J Prev Med 2019;56:e95–e106
47. Raynor HA, Davidson PG, Burns H, et al. Medical nutrition therapy and weight loss questions for the Evidence Analysis Library prevention of type 2 diabetes project: systematic reviews. J Acad Nutr Diet 2017;117:1578–1611
48. Sun Y, You W, Almeida F, Estabrooks P, Davy B. The effectiveness and cost of lifestyle interventions including nutrition education for diabetes prevention: a systematic review and meta-analysis. J Acad Nutr Diet 2017;117:404–421.e36
49. Briggs Early K, Stanley K. Position of the Academy of Nutrition and Dietetics: the role of medical nutrition therapy and registered dietitian nutritionists in the prevention and treatment of prediabetes and type 2 diabetes. J Acad Nutr Diet 2018;118:343–353
50. Powers MA, Bardsley JK, Cypress M, et al. Diabetes self-management education and support in adults with type 2 diabetes: a consensus report of the American Diabetes Association, the Association of Diabetes Care & Education Specialists, the Academy of Nutrition and Dietetics, the American Academy of Family Physicians, the American Academy of PAs, the American Association of Nurse Practitioners, and the American Pharmacists Association. Diabetes Care 2020;43:1636–1649
51. Hudspeth BD. Power of prevention: the pharmacist's role in prediabetes management. Diabetes Spectr 2018;31:320–323
52. Butcher MK, Vanderwood KK, Hall TO, Gohdes D, Helgerson SD, Harwell TS. Capacity of diabetes education programs to provide both diabetes self-management education and to implement diabetes prevention services. J Public Health Manag Pract 2011;17:242–247
53. Grock S, Ku J-H, Kim J, Moin T. A review of technology-assisted interventions for diabetes prevention. Curr Diab Rep 2017;17:107
54. Sepah SC, Jiang L, Peters AL. Translating the Diabetes Prevention Program into an online

social network: validation against CDC standards. Diabetes Educ 2014;40:435–443
55. Bian RR, Piatt GA, Sen A, et al. The effect of technology-mediated diabetes prevention interventions on weight: a meta-analysis. J Med Internet Res 2017;19:e76
56. Sepah SC, Jiang L, Peters AL. Long-term outcomes of a Web-based diabetes prevention program: 2-year results of a single-arm longitudinal study. J Med Internet Res 2015;17:e92
57. Moin T, Damschroder LJ, AuYoung M, et al. Results from a trial of an online diabetes prevention program intervention. Am J Prev Med 2018;55:583–591
58. Michaelides A, Major J, Pienkosz E Jr, Wood M, Kim Y, Toro-Ramos T. Usefulness of a novel mobile diabetes prevention program delivery platform with human coaching: 65-week observational follow-up. JMIR Mhealth Uhealth 2018; 6:e93
59. Kim SE, Castro Sweet CM, Cho E, Tsai J, Cousineau MR. Evaluation of a digital diabetes prevention program adapted for low-income patients, 2016-2018. Prev Chronic Dis 2019; 27:E155
60. Vadheim LM, Patch K, Brokaw SM, et al. Telehealth delivery of the diabetes prevention program to rural communities. Transl Behav Med 2017;7:286–291
61. Fischer HH, Durfee MJ, Raghunath SG, Ritchie ND. Short message service text message support for weight loss in patients with prediabetes: pragmatic trial. JMIR Diabetes 2019;4: e12985
62. Chiasson J-L, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trail Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. Lancet 2002;359:2072–2077
63. le Roux CW, Astrup A, Fujioka K, et al.; SCALE Obesity Prediabetes NN8022-1839 Study Group. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. Lancet 2017;389:1399–1409
64. Gerstein HC, Yusuf S, Bosch J, et al.; DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet 2006;368:1096–1105
65. DeFronzo RA, Tripathy D, Schwenke DC, et al.; ACT NOW Study. Pioglitazone for diabetes prevention in impaired glucose tolerance. N Engl J Med 2011;364:1104–1115
66. Kawamori R, Tajima N, Iwamoto Y, Kashiwagi A, Shimamoto K, Kaku K; Voglibose Ph-3 Study Group. Voglibose for prevention of type 2 diabetes mellitus: a randomised, double-blind trial in Japanese individuals with impaired glucose tolerance. Lancet 2009;373:1607–1614
67. Gerstein HC, Bosch J, Dagenais GR, et al.; ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012;367:319–328
68. Holman RR, Haffner SM, McMurray JJ, et al.; NAVIGATOR Study Group. Effect of nateglinide on the incidence of diabetes and cardiovascular events. N Engl J Med 2010;362:1463–1476
69. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of Diabetes in Obese Subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care 2004;27:155–161
70. Garvey WT, Ryan DH, Henry R, et al. Prevention of type 2 diabetes in subjects with prediabetes and metabolic syndrome treated with phentermine and topiramate extended release. Diabetes Care 2014;37:912–921
71. McMurray JJ, Holman RR, Haffner SM, et al.; NAVIGATOR Study Group. Effect of valsartan on the incidence of diabetes and cardiovascular events. N Engl J Med 2010;362:1477–1490
72. Bosch J, Yusuf S, Gerstein HC, et al.; DREAM Trial Investigators. Effect of ramipril on the incidence of diabetes. N Engl J Med 2006;355:1551–1562
73. Everett BM, Donath MY, Pradhan AD, Thuren T, Pais P, Nicolau JC, et al. Anti-inflammatory therapy with canakinumab for the prevention and management of diabetes. J Am Coll Cardiol 2018;29:2392–2401
74. Pittas AG, Dawson-Hughes B, Sheehan P, et al.; D2d Research Group. Vitamin D supplementation and prevention of type 2 diabetes. N Engl J Med 2019;381:520–530
75. Ray KK, Colhoun HM, Szarek M, et al.; ODYSSEY OUTCOMES Committees and Investigators. Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial. Lancet Diabetes Endocrinol 2019;7:618–628
76. Diabetes Prevention Program Research Group. Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study. Diabetes Care 2012;35:731–737
77. Ratner RE, Christophi CA, Metzger BE, et al.; Diabetes Prevention Program Research Group. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. J Clin Endocrinol Metab 2008;93:4774–4779
78. Aroda VR, Christophi CA, Edelstein SL, et al.; Diabetes Prevention Program Research Group. The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the Diabetes Prevention Program Outcomes Study 10-year follow-up. J Clin Endocrinol Metab 2015;100:1646–1653
79. Diabetes Prevention Program Research Group. Long-term effects of metformin on diabetes prevention: identification of subgroups that benefited most in the Diabetes Prevention Program and Diabetes Prevention Program Outcomes Study. Diabetes Care 2019;42:601–608
80. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V; Indian Diabetes Prevention Programme (IDPP). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia 2006; 49:289–297
81. Griffin SJ, Bethel MA, Holman RR, et al. Metformin in non-diabetic hyperglycaemia: the GLINT feasibility RCT. Health Technol Assess 2018;22:1–64
82. Aroda VR, Edelstein SL, Goldberg RB, et al.; Diabetes Prevention Program Research Group. Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes Study. J Clin Endocrinol Metab 2016; 101:1754–1761
83. Ali MK, Bullard KM, Saydah S, Imperatore G, Gregg EW. Cardiovascular and renal burdens of prediabetes in the USA: analysis of data from serial cross-sectional surveys, 1988-2014. Lancet Diabetes Endocrinol 2018;6:392–403
84. Pan Y, Chen W, Wang Y. Prediabetes and outcome of ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. J Stroke Cerebrovasc Dis 2019;28:683–692
85. Huang Y, Cai X, Mai W, Li M, Hu Y. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. BMJ 2016;355:i5953
86. Yeh H-C, Duncan BB, Schmidt MI, Wang N-Y, Brancati FL. Smoking, smoking cessation, and risk for type 2 diabetes mellitus: a cohort study. Ann Intern Med 2010;152:10–17
87. Oba S, Noda M, Waki K, et al.; Japan Public Health Center-based Prospective Study Group. Smoking cessation increases short-term risk of type 2 diabetes irrespective of weight gain: the Japan Public Health Center-Based Prospective Study [published correction appears in PLoS One 2013;8:10.1371/annotation/23aa7c42-9a4d-42a7-8f50-9d0ac4b85396]. PLoS One 2012;7: e17061
88. Hu Y, Zong G, Liu G, Wang M, Rosner B, Pan A, et al. Smoking cessation, weight change, type 2 diabetes, and mortality. N Engl J Med. 2018 16; 379:623–632
89. Orchard TJ, Temprosa M, Barrett-Connor E, et al.; Diabetes Prevention Program Outcomes Study Research Group. Long-term effects of the Diabetes Prevention Program interventions on cardiovascular risk factors: a report from the DPP Outcomes Study. Diabet Med 2013;30:46–55
90. Salas-Salvadó J, Díaz-López A, Ruiz-Canela M, et al.; PREDIMED-Plus investigators. Effect of a lifestyle intervention program with energy-restricted Mediterranean diet and exercise on weight loss and cardiovascular risk factors: one-year results of the PREDIMED-Plus Trial. Diabetes Care 2019;42:777–788
91. Gong Q, Gregg EW, Wang J, et al. Long-term effects of a randomised trial of a 6-year lifestyle intervention in impaired glucose tolerance on diabetes-related microvascular complications: the China Da Qing Diabetes Prevention Outcome Study. Diabetologia 2011;54:300–307
92. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;140:e596–e646

4. Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Medical Care in Diabetes—2021*

American Diabetes Association

Diabetes Care 2021;44(Suppl. 1):S40–S52 | https://doi.org/10.2337/dc21-S004

The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc21-SPPC), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence grading system for ADA's clinical practice recommendations, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc21-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

PATIENT-CENTERED COLLABORATIVE CARE

Recommendations

4.1 A patient-centered communication style that uses person-centered and strength-based language and active listening; elicits patient preferences and beliefs; and assesses literacy, numeracy, and potential barriers to care should be used to optimize patient health outcomes and health-related quality of life. **B**

4.2 People with diabetes can benefit from a coordinated multidisciplinary team that may draw from diabetes care and education specialists, primary care providers, subspecialty providers, nurses, dietitians, exercise specialists, pharmacists, dentists, podiatrists, and mental health professionals. **E**

A successful medical evaluation depends on beneficial interactions between the patient and the care team. The Chronic Care Model (1–3) (see Section 1 "Improving Care and Promoting Health in Populations," https://doi.org/10.2337/dc21-S001) is a patient-centered approach to care that requires a close working relationship between the patient and clinicians involved in treatment planning. People with diabetes should receive health care from a coordinated interdisciplinary team that may include diabetes care and education specialists, physicians, nurse practitioners, physician assistants, nurses, dietitians, exercise specialists, pharmacists, dentists, podiatrists, and mental health professionals. Individuals with diabetes must assume an active role in their care. The patient, family or support people, physicians, and health care team should together formulate the management plan, which includes lifestyle

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management (see Section 5 "Facilitating Behavior Change and Well-being to Improve Health Outcomes," https://doi.org/10.2337/dc21-S005).

The goals of treatment for diabetes are to prevent or delay complications and optimize quality of life (**Fig. 4.1**). Treatment goals and plans should be created with patients based on their individual preferences, values, and goals. This individualized management plan should take into account the patient's age, cognitive abilities, school/work schedule and conditions, health beliefs, support systems, eating patterns, physical activity, social situation, financial concerns, cultural factors, literacy and numeracy (mathematical literacy), diabetes history (duration, complications, current use of medications), comorbidities, health priorities, other medical conditions, preferences for care, and life expectancy. Various strategies and techniques should be used to support patients' self-management efforts, including providing education on problem-solving skills for all aspects of diabetes management.

Provider communication with patients and families should acknowledge that multiple factors impact glycemic management but also emphasize that collaboratively developed treatment plans and a healthy lifestyle can significantly improve disease outcomes and well-being (4–7). Thus, the goal of provider-patient communication is to establish a collaborative relationship and to assess and address self-management barriers without blaming patients for "noncompliance" or "nonadherence" when the outcomes of self-management are not optimal (8). The familiar terms "noncompliance" and "nonadherence" denote a passive, obedient role for a person with diabetes in "following doctor's orders" that is at odds with the active role people with diabetes take in directing the day-to-day decision-making, planning, monitoring, evaluation, and problem-solving involved in diabetes self-management. Using a nonjudgmental approach that normalizes periodic lapses in self-management may help minimize patients' resistance to reporting problems with self-management. Empathizing and using active listening techniques, such as open-ended questions, reflective statements, and summarizing what the patient said, can help facilitate communication. Patients' perceptions about their own ability, or self-efficacy, to self-manage diabetes are one important psychosocial factor related to improved diabetes self-management and treatment outcomes in diabetes (9–13) and should be a target of ongoing assessment, patient education, and treatment planning.

Language has a strong impact on perceptions and behavior. The use of empowering language in diabetes care and education can help to inform and motivate people, yet language that shames and judges may undermine this effort. The American Diabetes Association (ADA) and the Association of Diabetes Care & Education Specialists (formerly called American Association of Diabetes Educators) joint consensus report, "The Use of Language in Diabetes Care and Education," provides the authors' expert opinion regarding the use of language by

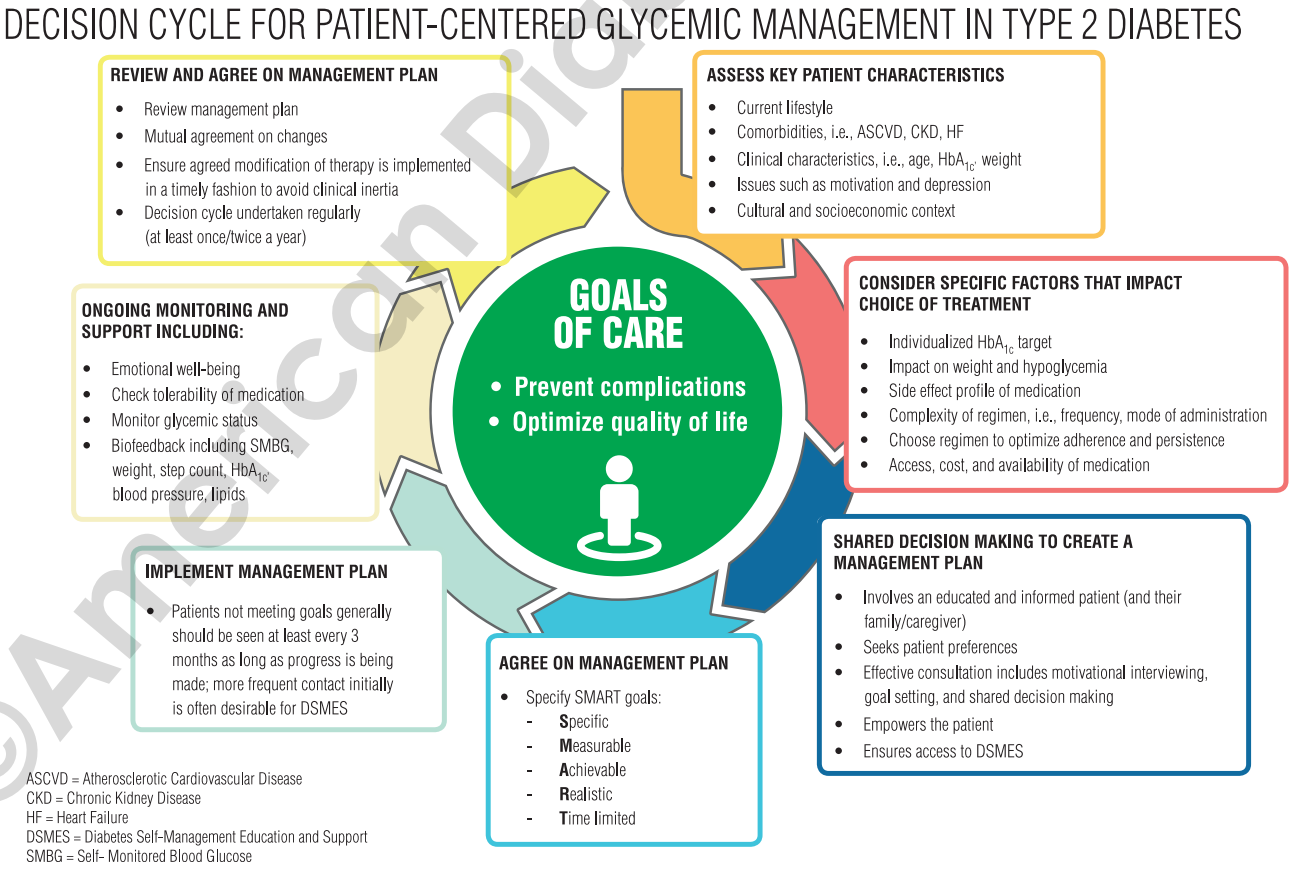

Figure 4.1—Decision cycle for patient-centered glycemic management in type 2 diabetes. Reprinted from Davies et al. (101).

health care professionals when speaking or writing about diabetes for people with diabetes or for professional audiences (14). Although further research is needed to address the impact of language on diabetes outcomes, the report includes five key consensus recommendations for language use:

- Use language that is neutral, nonjudgmental, and based on facts, actions, or physiology/biology.
- Use language free from stigma.
- Use language that is strength based, respectful, and inclusive and that imparts hope.
- Use language that fosters collaboration between patients and providers.
- Use language that is person centered (e.g., "person with diabetes" is preferred over "diabetic").

COMPREHENSIVE MEDICAL EVALUATION

Recommendations

4.3 A complete medical evaluation should be performed at the initial visit to:
- Confirm the diagnosis and classify diabetes. **A**
- Evaluate for diabetes complications and potential comorbid conditions. **A**
- Review previous treatment and risk factor control in patients with established diabetes. **A**
- Begin patient engagement in the formulation of a care management plan. **A**
- Develop a plan for continuing care. **A**

4.4 A follow-up visit should include most components of the initial comprehensive medical evaluation (see **Table 4.1**). **A**

4.5 Ongoing management should be guided by the assessment of overall health status, diabetes complications, cardiovascular risk (see THE RISK CALCULATOR, Section 10 "Cardiovascular Disease and Risk Management," https://doi.org/10.2337/dc21-010), hypoglycemia risk, and shared decision-making to set therapeutic goals. **B**

The comprehensive medical evaluation includes the initial and follow-up evaluations, assessment of complications, psychosocial assessment, management of comorbid conditions, and engagement of the patient throughout the process. While a comprehensive list is provided in **Table 4.1**, in clinical practice the provider may need to prioritize the components of the medical evaluation given the available resources and time. The goal is to provide the health care team information so it can optimally support a patient. In addition to the medical history, physical examination, and laboratory tests, providers should assess diabetes self-management behaviors, nutrition, social determinants of health, and psychosocial health (see Section 5 "Facilitating Behavior Change and Well-being to Improve Health Outcomes," https://doi.org/10.2337/dc21-S005) and give guidance on routine immunizations. The assessment of sleep pattern and duration should be considered; a meta-analysis found that poor sleep quality, short sleep, and long sleep were associated with higher A1C in people with type 2 diabetes (15). Interval follow-up visits should occur at least every 3–6 months individualized to the patient, and then at least annually.

Lifestyle management and psychosocial care are the cornerstones of diabetes management. Patients should be referred for diabetes self-management education and support, medical nutrition therapy, and assessment of psychosocial/emotional health concerns if indicated. Patients should receive recommended preventive care services (e.g., immunizations, cancer screening, etc.); smoking cessation counseling; and ophthalmological, dental, and podiatric referrals.

The assessment of risk of acute and chronic diabetes complications and treatment planning are key components of initial and follow-up visits (**Table 4.2**). The risk of atherosclerotic cardiovascular disease and heart failure (see Section 10 "Cardiovascular Disease and Risk Management," https://doi.org/10.2337/dc21-S010), chronic kidney disease staging (see Section 11 "Microvascular Complications and Foot Care," https://doi.org/10.2337/dc21-S011), presence of retinopathy, and risk of treatment-associated hypoglycemia (**Table 4.3**) should be used to individualize targets for glycemia (see Section 6 "Glycemic Targets," https://doi.org/10.2337/dc21-S006), blood pressure, and lipids and to select specific glucose-lowering medication (see Section 9 "Pharmacologic Approaches to Glycemic Treatment," https://doi.org/10.2337/dc21-S009), antihypertension medication, and statin treatment intensity.

Additional referrals should be arranged as necessary (**Table 4.4**). Clinicians should ensure that individuals with diabetes are appropriately screened for complications and comorbidities. Discussing and implementing an approach to glycemic control with the patient is a part, not the sole goal, of the patient encounter.

IMMUNIZATIONS

Recommendation

4.6 Provide routinely recommended vaccinations for children and adults with diabetes as indicated by age (see **Table 4.5** for highly recommended vaccinations for adults with diabetes). **A**

The importance of routine vaccinations for people living with diabetes has been elevated by the coronavirus disease 2019 (COVID-19) pandemic. Preventing avoidable infections not only directly prevents morbidity but also reduces hospitalizations, which may additionally reduce risk of acquiring infections such as COVID-19. Children and adults with diabetes should receive vaccinations according to age-appropriate recommendations (16,17). The Centers for Disease Control and Prevention (CDC) provides vaccination schedules specifically for children, adolescents, and adults with diabetes (see https://www.cdc.gov/vaccines/). The CDC Advisory Committee on Immunization Practices (ACIP) makes recommendations based on its own review and rating of the evidence, provided in **Table 4.5** for selected vaccinations. The ACIP evidence review has evolved over time with the adoption of Grading of Recommendations Assessment, Development and Evaluation (GRADE) in 2010 and then the Evidence to Decision or Evidence to Recommendation (EtR) frameworks in 2018 (18). Here we discuss the particular importance of specific vaccines.

Influenza

Influenza is a common, preventable infectious disease associated with high mortality and morbidity in vulnerable populations, including youth, older adults, and people with chronic diseases. Influenza vaccination in people with diabetes has been found to significantly reduce

Table 4.1 – Components of the comprehensive diabetes medical evaluation at initial, follow-up, and annual visits

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
PAST MEDICAL AND FAMILY HISTORY	**Diabetes history**			
	▪ Characteristics at onset (e.g., age, symptoms)	✓		
	▪ Review of previous treatment regimens and response	✓		
	▪ Assess frequency/cause/severity of past hospitalizations	✓		
	Family history			
	▪ Family history of diabetes in a first-degree relative	✓		
	▪ Family history of autoimmune disorder	✓		
	Personal history of complications and common comorbidities			
	▪ Comorbid conditions (e.g., obesity, OSA, NAFLD)	✓		✓
	▪ High blood pressure or abnormal lipids	✓		✓
	▪ Macrovascular and microvascular complications	✓		✓
	▪ Hypoglycemia: awareness/frequency/causes/timing of episodes	✓	✓	✓
	▪ Presence of hemoglobinopathies or anemias	✓		✓
	▪ Last dental visit	✓		✓
	▪ Last dilated eye exam	✓		✓
	▪ Visits to specialists	✓	✓	✓
	Interval history			
	▪ Changes in medical/family history since last visit		✓	✓
BEHAVIORAL FACTORS	▪ Eating patterns and weight history	✓	✓	✓
	▪ Assess familiarity with carbohydrate counting (e.g., type 1 diabetes, type 2 diabetes treated with MDI)	✓		
	▪ Physical activity and sleep behaviors	✓	✓	✓
	▪ Tobacco, alcohol, and substance use	✓		✓
MEDICATIONS AND VACCINATIONS	▪ Current medication regimen	✓	✓	✓
	▪ Medication-taking behavior	✓	✓	✓
	▪ Medication intolerance or side effects	✓	✓	✓
	▪ Complementary and alternative medicine use	✓	✓	✓
	▪ Vaccination history and needs	✓		✓
TECHNOLOGY USE	▪ Assess use of health apps, online education, patient portals, etc.	✓		✓
	▪ Glucose monitoring (meter/CGM): results and data use	✓	✓	✓
	▪ Review insulin pump settings and use	✓	✓	✓
SOCIAL LIFE ASSESSMENT	**Social network**			
	▪ Identify existing social supports	✓		✓
	▪ Identify surrogate decision maker, advanced care plan	✓		✓
	▪ Identify social determinants of health (e.g., food security, housing stability & homelessness, transportation access, financial security, community safety)	✓		✓

Continued on p. S44

Table 4.1 (cont.)– Components of the comprehensive diabetes medical evaluation at initial, follow-up, and annual visits

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
PHYSICAL EXAMINATION	▪ Height, weight, and BMI; growth/pubertal development in children and adolescents	✓	✓	✓
	▪ Blood pressure determination	✓	✓	✓
	▪ Orthostatic blood pressure measures (when indicated)	✓		
	▪ Fundoscopic examination (refer to eye specialist)	✓		✓
	▪ Thyroid palpation	✓		✓
	▪ Skin examination (e.g., acanthosis nigricans, insulin injection or insertion sites, lipodystrophy)	✓	✓	✓
	▪ Comprehensive foot examination			
	• Visual inspection (e.g., skin integrity, callous formation, foot deformity or ulcer, toenails)**	✓		✓
	• Screen for PAD (pedal pulses–refer for ABI if diminished)	✓		✓
	• Determination of temperature, vibration or pinprick sensation, and 10-g monofilament exam	✓		✓
	▪ Screen for depression, anxiety, and disordered eating	✓		✓
	▪ Consider assessment for cognitive impairment*	✓		✓
	▪ Consider assessment for functional performance*	✓		✓
LABORATORY EVALUATION	▪ A1C, if the results are not available within the past 3 months	✓	✓	✓
	▪ If not performed/available within the past year	✓		✓
	• Lipid profile, including total, LDL, and HDL cholesterol and triglycerides#	✓		✓^
	• Liver function tests#	✓		✓
	• Spot urinary albumin–to–creatinine ratio	✓		✓
	• Serum creatinine and estimated glomerular filtration rate+	✓		✓
	• Thyroid-stimulating hormone in patients with type 1 diabetes#	✓		✓
	• Vitamin B12 if on metformin (when indicated)	✓		✓
	• Serum potassium levels in patients on ACE inhibitors, ARBs, or diuretics+	✓		✓

ABI, ankle-brachial pressure index; ARBs, angiotensin receptor blockers; CGM, continuous glucose monitors; MDI, multiple daily injections; NAFLD, nonalcoholic fatty liver disease; OSA, obstructive sleep apnea; PAD, peripheral arterial disease

*at 65 years of age or older

+may be needed more frequently in patients with known chronic kidney disease or with changes in medications that affect kidney function and serum potassium (see Table 11.1)

#may also need to be checked after initiation or dose changes of medications that affect these laboratory values (i.e., diabetes medications, blood pressure medications, cholesterol medications, or thyroid medications)

^in people without dyslipidemia and not on cholesterol lowering therapy, testing may be less frequent

**should be performed at every visit in patients with sensory loss, previous foot ulcers, or amputations

influenza and diabetes-related hospital admissions (19). Given the benefits of the annual influenza vaccination, it is recommended for all individuals ≥6 months of age who do not have a contraindication. Influenza vaccination is critically important in the next year as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza viruses will both be active in the U.S. during the 2020–2021 season (20). The live attenuated influenza vaccine (LAIV), which is delivered by nasal spray, is an option for patients beginning at age 2 years through age 49 years, for those who are not pregnant, but patients with chronic conditions such as diabetes are cautioned against taking the LAIV and are instead recommended to receive the inactive or recombinant influenza vaccination. For individuals ≥65 years of age, there may be additional benefit from the high-dose quadrivalent inactivated influenza vaccine (20).

Pneumococcal Pneumonia

Like influenza, pneumococcal pneumonia is a common, preventable disease. People with diabetes are at increased risk for the bacteremic form of pneumococcal infection and have been reported to have a high risk of nosocomial bacteremia, with a mortality rate as high as 50% (21). There are two vaccination types, the 23-valent pneumococcal polysaccharide vaccine (PPSV23) and the 13-valent pneumococcal conjugate vaccine (PCV13), with distinct schedules for children and adults.

All children are recommended to receive a four-dose series of PCV13 by 15 months of age. For children with diabetes who have incomplete series by ages 2–5 years, the CDC recommends a catch-up schedule to ensure that these children have four doses. Children with diabetes between 6–18 years of age are also advised to receive one dose of PPSV23, preferably after receipt of PCV13.

Table 4.2—Assessment and treatment plan*

Assessing risk of diabetes complications
• ASCVD and heart failure history
• ASCVD risk factors and 10-year ASCVD risk assessment
• Staging of chronic kidney disease (see **Table 11.1**)
• Hypoglycemia risk (see **Table 4.3**)
Goal setting
• Set A1C/blood glucose target
• If hypertension is present, establish blood pressure target
• Diabetes self-management goals
Therapeutic treatment plans
• Lifestyle management
• Pharmacologic therapy: glucose lowering
• Pharmacologic therapy: cardiovascular disease risk factors and renal
• Use of glucose monitoring and insulin delivery devices
• Referral to diabetes education and medical specialists (as needed)

ASCVD, atherosclerotic cardiovascular disease. *Assessment and treatment planning are essential components of initial and all follow-up visits.

For adults with diabetes, one dose of PPSV23 is recommended between the ages of 19–64 years and another dose at ≥65 years of age. The PCV13 is no longer routinely recommended for patients over 65 years of age because of the declining rates of pneumonia due to these strains (22). Older patients should have a shared decision-making discussion with their provider to determine individualized risks and benefits. PCV13 is recommended for patients with immunocompromising conditions such as asplenia, advanced kidney disease, cochlear implants, or cerebrospinal fluid leaks (23). Some older patients residing in assisted living facilities may also consider PCV13. If the PCV13 is to be administered, it should be given prior to the next dose of PPSV23.

Hepatitis B

Compared with the general population, people with type 1 or type 2 diabetes have higher rates of hepatitis B. This may be due to contact with infected blood or through improper equipment use (glucose monitoring devices or infected needles). Because of the higher likelihood of transmission, hepatitis B vaccine is recommended for adults with diabetes aged <60 years. For adults aged ≥60 years, hepatitis B vaccine may be administered at the discretion of the treating clinician based on the patient's likelihood of acquiring hepatitis B infection.

COVID-19

During the coming year, it is expected that vaccines for COVID-19 will become available and that people with diabetes should be a priority population. The COVID-19 vaccine will likely become a routine part of the annual preventive schedule for people with diabetes.

ASSESSMENT OF COMORBIDITIES

Besides assessing diabetes-related complications, clinicians and their patients need to be aware of common comorbidities that affect people with diabetes and may complicate management (24–28). Diabetes comorbidities are conditions that affect people with diabetes more often than age-matched people without diabetes. This section discusses many of the common comorbidities observed in patients with diabetes but is not necessarily inclusive of all the conditions that have been reported.

Table 4.3—Assessment of hypoglycemia risk

Factors that increase risk of treatment-associated hypoglycemia
• Use of insulin or insulin secretagogues (i.e., sulfonylureas, meglitinides)
• Impaired kidney or hepatic function
• Longer duration of diabetes
• Frailty and older age
• Cognitive impairment
• Impaired counterregulatory response, hypoglycemia unawareness
• Physical or intellectual disability that may impair behavioral response to hypoglycemia
• Alcohol use
• Polypharmacy (especially ACE inhibitors, angiotensin receptor blockers, nonselective β-blockers)
In addition to individual risk factors, consider use of comprehensive risk prediction models (102).

See references 103–107.

Autoimmune Diseases

Recommendations

4.7 Patients with type 1 diabetes should be screened for autoimmune thyroid disease soon after diagnosis and periodically thereafter. **B**

4.8 Adult patients with type 1 diabetes should be screened for celiac disease in the presence of gastrointestinal symptoms, signs, or laboratory manifestations suggestive of celiac disease. **B**

People with type 1 diabetes are at increased risk for other autoimmune diseases, with thyroid disease, celiac disease, and pernicious anemia (vitamin B12 deficiency) being among the most common (29). Other associated conditions include autoimmune hepatitis, primary adrenal insufficiency (Addison disease), dermatomyositis, and myasthenia gravis (30–33). Type 1 diabetes may also occur with other autoimmune diseases in the context of specific genetic disorders or polyglandular autoimmune syndromes (34). Given the high prevalence, nonspecific symptoms, and insidious onset of primary hypothyroidism, routine screening for thyroid dysfunction is recommended for all patients with type 1 diabetes. Screening for celiac disease should be considered in adult patients with suggestive symptoms (e.g., diarrhea, malabsorption, abdominal pain) or signs (e.g., osteoporosis, vitamin deficiencies, iron deficiency anemia) (35,36). Measurement of vitamin B12 levels should be considered for patients with type 1 diabetes and peripheral neuropathy or unexplained anemia.

Cancer

Diabetes is associated with increased risk of cancers of the liver, pancreas, endometrium, colon/rectum, breast, and bladder (37). The association may result from

Table 4.4—Referrals for initial care management

- Eye care professional for annual dilated eye exam
- Family planning for women of reproductive age
- Registered dietitian nutritionist for medical nutrition therapy
- Diabetes self-management education and support
- Dentist for comprehensive dental and periodontal examination
- Mental health professional, if indicated
- Audiology, if indicated

shared risk factors between type 2 diabetes and cancer (older age, obesity, and physical inactivity) but may also be due to diabetes-related factors (38), such as underlying disease physiology or diabetes treatments, although evidence for these links is scarce. Patients with diabetes should be encouraged to undergo recommended age- and sex-appropriate cancer screenings and to reduce their modifiable cancer risk factors (obesity, physical inactivity, and smoking). New onset of atypical diabetes (lean body habitus, negative family history) in a middle-aged or older patient may precede the diagnosis of pancreatic adenocarcinoma (39). However, in the absence of other symptoms (e.g., weight loss, abdominal pain), routine screening of all such patients is not currently recommended.

Cognitive Impairment/Dementia

Recommendation

4.9 In the presence of cognitive impairment, diabetes treatment regimens should be simplified as much as possible and tailored to minimize the risk of hypoglycemia. **B**

Diabetes is associated with a significantly increased risk and rate of cognitive decline and an increased risk of dementia (40,41). A recent meta-analysis of prospective observational studies in people with diabetes showed 73% increased risk of all types of dementia, 56% increased risk of Alzheimer dementia, and 127% increased risk of vascular dementia compared with individuals without diabetes (42). The reverse is also true: people with Alzheimer dementia are more likely to develop diabetes than people without Alzheimer dementia. In a 15-year prospective study of community-dwelling people >60 years of age, the presence of diabetes at baseline significantly increased the age- and sex-adjusted incidence of all-cause dementia, Alzheimer dementia, and vascular dementia compared with rates in those with normal glucose tolerance (43). See Section 12 "Older Adults" (https://doi.org/10.2337/dc21-S012) for a more detailed discussion regarding screening for cognitive impairment.

Hyperglycemia

In those with type 2 diabetes, the degree and duration of hyperglycemia are related to dementia. More rapid cognitive decline is associated with both increased A1C and longer duration of diabetes (42). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study found that each 1% higher A1C level was associated with lower cognitive function in individuals with type 2 diabetes (44). However, the ACCORD study found no difference in cognitive outcomes in participants randomly assigned to intensive and standard glycemic control, supporting the recommendation that intensive glucose control should not be advised for the improvement of cognitive function in individuals with type 2 diabetes (45).

Hypoglycemia

In type 2 diabetes, severe hypoglycemia is associated with reduced cognitive function, and those with poor cognitive function have more severe hypoglycemia. In a long-term study of older patients with type 2 diabetes, individuals with one or more recorded episodes of severe hypoglycemia had a stepwise increase in risk of dementia (46). Likewise, the ACCORD trial found that as cognitive function decreased, the risk of severe hypoglycemia increased (47). Tailoring glycemic therapy may help to prevent hypoglycemia in individuals with cognitive dysfunction. See Section 12 "Older Adults" (https://doi.org/10.2337/dc21-S012) for more detailed discussion of hypoglycemia in older patients with type 1 and type 2 diabetes.

Nutrition

In one study, adherence to the Mediterranean diet correlated with improved cognitive function (48). However, a recent Cochrane review found insufficient evidence to recommend any specific dietary change for the prevention or treatment of cognitive dysfunction (49).

Statins

A systematic review has reported that data do not support an adverse effect of statins on cognition (50). The U.S. Food and Drug Administration postmarketing surveillance databases have also revealed a low reporting rate for cognitive-related adverse events, including cognitive dysfunction or dementia, with statin therapy, similar to rates seen with other commonly prescribed cardiovascular medications (50). Therefore, fear of cognitive decline should not be a barrier to statin use in individuals with diabetes and a high risk for cardiovascular disease.

Nonalcoholic Fatty Liver Disease

Recommendation

4.10 Patients with type 2 diabetes or prediabetes and elevated liver enzymes (ALT) or fatty liver on ultrasound should be evaluated for presence of nonalcoholic steatohepatitis and liver fibrosis. **C**

Diabetes is associated with the development of nonalcoholic fatty liver disease, including its more severe manifestations of nonalcoholic steatohepatitis, liver fibrosis, cirrhosis, and hepatocellular carcinoma (51). Elevations of hepatic transaminase concentrations are associated with higher BMI, waist circumference, and triglyceride levels and lower HDL cholesterol levels. Noninvasive tests, such as elastography or fibrosis biomarkers, may be used to assess risk of fibrosis, but referral to a liver specialist and liver biopsy may be required for definitive diagnosis (52). Interventions that improve metabolic abnormalities in patients with diabetes (weight loss, glycemic control, and treatment with specific drugs for hyperglycemia or dyslipidemia) are also beneficial for fatty liver disease (53,54). Pioglitazone, vitamin E treatment, and liraglutide treatment of biopsy-proven nonalcoholic steatohepatitis have each been shown to improve liver histology, but effects on longer-term clinical

Table 4.5—Highly recommended immunizations for adult patients with diabetes (Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention)

Vaccination	Age-group recommendations	Frequency	GRADE evidence type*	Reference
Hepatitis B	<60 years of age; ≥60 years of age discuss with doctor	Two- or three-dose series	2	Centers for Disease Control and Prevention (CDC). Use of hepatitis B vaccination for adults with diabetes mellitus: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2011;60:1709–1711
Human papilloma virus (HPV)	≤26 years of age; 27–45 years of age may also be vaccinated against HPV after a discussion with their health care provider	Three doses over 6 months	2 for females, 3 for males	Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee on Immunization Practices. MMWR 2019;68:698–702
Influenza	All patients; advised not to receive live attenuated influenza vaccine	Annual	–	Demicheli V, Jefferson T, Di Pietrantonj C, Ferroni E, Thorning S, Thomas RE, Rivetti A. Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev 2018;2:CD004876
Pneumonia (PPSV23 [Pneumovax])	19–64 years of age, vaccinate with Pneumovax	One dose	2	CDC. Updated recommendations for prevention of invasive pneumococcal disease among adults using the 23-valent pneumococcal polysaccaride vaccine (PPSV23). MMWR 2010;59:1102–1106
	≥65 years of age, obtain second dose of Pneumovax, at least 5 years from prior Pneumovax vaccine	One dose; if PCV13 has been given, then give PPSV23 ≥1 year after PCV13 and ≥5 years after any PPSV23 at age <65 years	2	Falkenhorst G, Remschmidt C, Harder T, Hummers-Pradier E, Wichmann O, Bogdan C. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine (PPV23) against pneumococcal disease in the elderly: systematic review and meta-analysis. PLoS ONE 2017;12:e0169368
Pneumonia (PCV13 [Prevnar])	19–64 years of age, no recommendation	None		
	≥65 years of age, without an immunocompromising condition (e.g., chronic renal failure), cochlear implant, or cerebrospinal fluid leak, have shared decision-making discussion with doctor	One dose	3	Matanock A, Lee G, Gierke R, Kobayashi M, Leidner A, Pilishvili T. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: updated recommendations of the Advisory Committee on Immunization Practices. MMWR 2019;68:1069–1075

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Table 4.5—Continued

Vaccination	Age-group recommendations	Frequency	GRADE evidence type*	Reference
Tetanus, diphtheria, pertussis (TDAP)	All adults; pregnant women should have an extra dose	Booster every 10 years	2 for effectiveness, 3 for safety	Havers FP, Moro PL, Hunter P, Hariri S, Bernstein H. Use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines: updated recommendations of the Advisory Committee on Immunization Practices—United States, 2019. MMWR 2020;69:77–83
Zoster	≥50 years of age	Two-dose Shingrix, even if previously vaccinated	1	Dooling KL, Guo A, Patel M, et al. Recommendations of the Advisory Committee on Immunization Practices for use of herpes zoster vaccines. MMWR 2018;67:103–108

GRADE, Grading of Recommendations Assessment, Development and Evaluation; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine. *Evidence type: 1 = randomized controlled trials (RCTs), or overwhelming evidence from observational studies; 2 = RCTs with important limitations, or exceptionally strong evidence from observational studies; 3 = observational studies, or RCTs with notable limitations; and 4 = clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations. For a comprehensive list, refer to the Centers for Disease Control and Prevention at https://www.cdc.gov/vaccines/.

outcomes are not known (55–57). Treatment with other glucagon-like peptide 1 receptor agonists and with sodium–glucose cotransporter 2 inhibitors has shown promise in preliminary studies, although benefits may be mediated, at least in part, by weight loss (57–59).

Hepatitis C Infection

Infection with hepatitis C virus (HCV) is associated with a higher prevalence of type 2 diabetes, which is present in up to one-third of individuals with chronic HCV infection. HCV may impair glucose metabolism by several mechanisms, including directly via viral proteins and indirectly by altering proinflammatory cytokine levels (60). The use of newer direct-acting antiviral drugs produces a sustained virological response (cure) in nearly all cases and has been reported to improve glucose metabolism in individuals with diabetes (61). A meta-analysis of mostly observational studies found a mean reduction in A1C levels of 0.45% (95% CI −0.60 to −0.30) and reduced requirement for glucose-lowering medication use following successful eradication of HCV infection (62).

Pancreatitis

Diabetes is linked to diseases of the exocrine pancreas such as pancreatitis, which may disrupt the global architecture or physiology of the pancreas, often resulting in both exocrine and endocrine dysfunction. Up to half of patients with diabetes may have some degree of impaired exocrine pancreas function (63). People with diabetes are at an approximately twofold higher risk of developing acute pancreatitis (64).

Conversely, prediabetes and/or diabetes has been found to develop in approximately one-third of patients after an episode of acute pancreatitis (65); thus, the relationship is likely bidirectional. Postpancreatitis diabetes may include either new-onset disease or previously unrecognized diabetes (66). Studies of patients treated with incretin-based therapies for diabetes have also reported that pancreatitis may occur more frequently with these medications, but results have been mixed and causality has not been established (67–69).

Islet autotransplantation should be considered for patients requiring total pancreatectomy for medically refractory chronic pancreatitis to prevent postsurgical diabetes. Approximately one-third of patients undergoing total pancreatectomy with islet autotransplantation are insulin free 1 year postoperatively, and observational studies from different centers have demonstrated islet graft function up to a decade after the surgery in some patients (70–74). Both patient and disease factors should be carefully considered when deciding the indications and timing of this surgery. Surgeries should be performed in skilled facilities that have demonstrated expertise in islet autotransplantation.

Fractures

Age-specific hip fracture risk is significantly increased in both people with type 1 diabetes (relative risk 6.3) and those with type 2 diabetes (relative risk 1.7) in both sexes (75). Type 1 diabetes is associated with osteoporosis, but in type 2 diabetes, an increased risk of hip fracture is seen despite higher bone mineral density (BMD) (76). In three large observational studies of older adults, femoral neck BMD T-score and the World Health Organization Fracture Risk Assessment Tool (FRAX) score were associated with hip and nonspine fractures. Fracture risk was higher in participants with diabetes compared with those without diabetes for a given T-score and age or for a given FRAX score (77). Providers should assess fracture history and risk factors in older patients with diabetes and recommend measurement of BMD if appropriate for the patient's age and sex. Fracture prevention strategies for people with diabetes are the same as for the general population and may include vitamin D supplementation. For patients with type 2 diabetes with fracture risk

factors, thiazolidinediones (78) and sodium–glucose cotransporter 2 inhibitors (79) should be used with caution.

Sensory Impairment

Hearing impairment, both in high-frequency and low- to midfrequency ranges, is more common in people with diabetes than in those without, with stronger associations found in studies of younger people (80). Proposed pathophysiologic mechanisms include the combined contributions of hyperglycemia and oxidative stress to cochlear microangiopathy and auditory neuropathy (81). In a National Health and Nutrition Examination Survey (NHANES) analysis, hearing impairment was about twice as prevalent in people with diabetes compared with those without, after adjusting for age and other risk factors for hearing impairment (82). Low HDL cholesterol, coronary heart disease, peripheral neuropathy, and general poor health have been reported as risk factors for hearing impairment for people with diabetes, but an association of hearing loss with blood glucose levels has not been consistently observed (83). In the Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort, time-weighted mean A1C was associated with increased risk of hearing impairment when tested after long-term (>20 years) follow-up (84). Impairment in smell, but not taste, has also been reported in individuals with diabetes (85).

Low Testosterone in Men

Recommendation

4.11 In men with diabetes who have symptoms or signs of hypogonadism, such as decreased sexual desire (libido) or activity, or erectile dysfunction, consider screening with a morning serum testosterone level. **B**

Mean levels of testosterone are lower in men with diabetes compared with age-matched men without diabetes, but obesity is a major confounder (86,87). Testosterone replacement in men with symptomatic hypogonadism may have benefits including improved sexual function, well-being, muscle mass and strength, and bone density (88). In men with diabetes who have symptoms or signs of low testosterone (hypogonadism), a morning total testosterone level should be measured using an accurate and reliable assay (89). In men who have total testosterone levels close to the lower limit, it is reasonable to determine free testosterone concentrations either directly from equilibrium dialysis assays or by calculations that use total testosterone, sex hormone binding globulin, and albumin concentrations (89). Please see the Endocrine Society Clinical Practice Guideline for detailed recommendations (89). Further tests (such as luteinizing hormone and follicle-stimulating hormone levels) may be needed to determine if the patient has hypogonadism. Testosterone replacement in older men with hypogonadism has been associated with increased coronary artery plaque volume, with no conclusive evidence that testosterone supplementation is associated with increased cardiovascular risk in hypogonadal men (89).

Obstructive Sleep Apnea

Age-adjusted rates of obstructive sleep apnea, a risk factor for cardiovascular disease, are significantly higher (4- to 10-fold) with obesity, especially with central obesity (90). The prevalence of obstructive sleep apnea in the population with type 2 diabetes may be as high as 23%, and the prevalence of any sleep-disordered breathing may be as high as 58% (91,92). In obese participants enrolled in the Action for Health in Diabetes (Look AHEAD) trial, it exceeded 80% (93). Patients with symptoms suggestive of obstructive sleep apnea (e.g., excessive daytime sleepiness, snoring, witnessed apnea) should be considered for screening (94). Sleep apnea treatment (lifestyle modification, continuous positive airway pressure, oral appliances, and surgery) significantly improves quality of life and blood pressure control. The evidence for a treatment effect on glycemic control is mixed (95).

Periodontal Disease

Periodontal disease is more severe, and may be more prevalent, in patients with diabetes than in those without and has been associated with higher A1C levels (96–98). Longitudinal studies suggest that people with periodontal disease have higher rates of incident diabetes. Current evidence suggests that periodontal disease adversely affects diabetes outcomes, although evidence for treatment benefits remains controversial (28,99). In a randomized clinical trial, intensive periodontal treatment was associated with better glycemic control (A1C 8.3% vs. 7.8% in control subjects and the intensive-treatment group, respectively) and reduction in inflammatory markers after 12 months of follow-up (100).

References

1. Stellefson M, Dipnarine K, Stopka C. The chronic care model and diabetes management in US primary care settings: a systematic review. Prev Chronic Dis 2013;10:E26
2. Coleman K, Austin BT, Brach C, Wagner EH. Evidence on the Chronic Care Model in the new millennium. Health Aff (Millwood) 2009;28:75–85
3. Gabbay RA, Bailit MH, Mauger DT, Wagner EH, Siminerio L. Multipayer patient-centered medical home implementation guided by the chronic care model. Jt Comm J Qual Patient Saf 2011;37:265–273
4. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853
5. Nathan DM, Genuth S, Lachin J, et al.; Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
6. Lachin JM, Genuth S, Nathan DM, Zinman B, Rutledge BN; DCCT/EDIC Research Group. Effect of glycemic exposure on the risk of microvascular complications in the Diabetes Control and Complications Trial—revisited. Diabetes 2008;57:995–1001
7. White NH, Cleary PA, Dahms W, Goldstein D, Malone J, Tamborlane WV; Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Beneficial effects of intensive therapy of diabetes during adolescence: outcomes after the conclusion of the Diabetes Control and Complications Trial (DCCT). J Pediatr 2001;139:804–812
8. Anderson RM, Funnell MM. Compliance and adherence are dysfunctional concepts in diabetes care. Diabetes Educ 2000;26:597–604
9. Sarkar U, Fisher L, Schillinger D. Is self-efficacy associated with diabetes self-management across race/ethnicity and health literacy? Diabetes Care 2006;29:823–829
10. King DK, Glasgow RE, Toobert DJ, et al. Self-efficacy, problem solving, and social-environmental support are associated with diabetes self-management behaviors. Diabetes Care 2010;33:751–753
11. Nouwen A, Urquhart Law G, Hussain S, McGovern S, Napier H. Comparison of the role of self-efficacy and illness representations in relation to dietary self-care and diabetes distress in adolescents with type 1 diabetes. Psychol Health 2009;24:1071–1084

12. Beckerle CM, Lavin MA. Association of self-efficacy and self-care with glycemic control in diabetes. Diabetes Spectr 2013;26:172–178
13. Iannotti RJ, Schneider S, Nansel TR, et al. Self-efficacy, outcome expectations, and diabetes self-management in adolescents with type 1 diabetes. J Dev Behav Pediatr 2006;27:98–105
14. Dickinson JK, Guzman SJ, Maryniuk MD, et al. The use of language in diabetes care and education. Diabetes Care 2017;40:1790–1799
15. Lee SWH, Ng KY, Chin WK. The impact of sleep amount and sleep quality on glycemic control in type 2 diabetes: a systematic review and meta-analysis. Sleep Med Rev 2017;31:91–101
16. Robinson CL, Bernstein H, Poehling K, Romero JR, Szilagyi P. Advisory Committee on Immunization Practices recommended immunization schedule for children and adolescents aged 18 years or younger - United States, 2020. MMWR Morb Mortal Wkly Rep 2020;69:130–132
17. Freedman MS, Hunter P, Ault K, Kroger A. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older - United States, 2020. MMWR Morb Mortal Wkly Rep 2020;69:133–135
18. Lee G, Carr W; ACIP Evidence-Based Recommendations Work Group; ACIP Evidence Based Recommendations Work Group. Updated framework for development of evidence-based recommendations by the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep 2018;67:1271–1272
19. Goeijenbier M, van Sloten TT, Slobbe L, et al. Benefits of flu vaccination for persons with diabetes mellitus: a review. Vaccine 2017;35:5095–5101
20. Grohskopf LA, Alyanak E, Broder KR, Blanton LH, Fry AM, Jernigan DB, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices - United States, 2020-21 influenza season. MMWR Recomm Rep 2020;69:1–24
21. Smith SA, Poland GA. Use of influenza and pneumococcal vaccines in people with diabetes. Diabetes Care 2000;23:95–108
22. Matanock A, Lee G, Gierke R, Kobayashi M, Leidner A, Pilishvili T. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: updated recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep 2019;68:1069–1075
23. Ahmed SS, Pondo T, Xing W, et al. Early impact of 13-valent pneumococcal conjugate vaccine use on invasive pneumococcal disease among adults with and without underlying medical conditions—United States. Clin Infect Dis 2020;70:2484–2492
24. Selvin E, Coresh J, Brancati FL. The burden and treatment of diabetes in elderly individuals in the U.S. Diabetes Care 2006;29:2415–2419
25. Grant RW, Ashburner JM, Hong CS, Chang Y, Barry MJ, Atlas SJ. Defining patient complexity from the primary care physician's perspective: a cohort study [published correction appears in Ann Intern Med 2012;157:152]. Ann Intern Med 2011;155:797–804
26. Tinetti ME, Fried TR, Boyd CM. Designing health care for the most common chronic condition—multimorbidity. JAMA 2012;307:2493–2494
27. Sudore RL, Karter AJ, Huang ES, et al. Symptom burden of adults with type 2 diabetes across the disease course: Diabetes & Aging Study. J Gen Intern Med 2012;27:1674–1681
28. Borgnakke WS, Ylöstalo PV, Taylor GW, Genco RJ. Effect of periodontal disease on diabetes: systematic review of epidemiologic observational evidence. J Periodontol 2013;84(Suppl.):S135–S152
29. Nederstigt C, Uitbeijerse BS, Janssen LGM, Corssmit EPM, de Koning EJP, Dekkers OM. Associated auto-immune disease in type 1 diabetes patients: a systematic review and meta-analysis. Eur J Endocrinol 2019;180:135–144
30. De Block CE, De Leeuw IH, Van Gaal LF. High prevalence of manifestations of gastric autoimmunity in parietal cell antibody-positive type 1 (insulin-dependent) diabetic patients. The Belgian Diabetes Registry. J Clin Endocrinol Metab 1999;84:4062–4067
31. Triolo TM, Armstrong TK, McFann K, et al. Additional autoimmune disease found in 33% of patients at type 1 diabetes onset. Diabetes Care 2011;34:1211–1213
32. Hughes JW, Riddlesworth TD, DiMeglio LA, Miller KM, Rickels MR, McGill JB; T1D Exchange Clinic Network. Autoimmune diseases in children and adults with type 1 diabetes from the T1D Exchange Clinic Registry. J Clin Endocrinol Metab 2016;101:4931–4937
33. Kahaly GJ, Hansen MP. Type 1 diabetes associated autoimmunity. Autoimmun Rev 2016;15:644–648
34. Eisenbarth GS, Gottlieb PA. Autoimmune polyendocrine syndromes. N Engl J Med 2004;350:2068–2079
35. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA; American College of Gastroenterology. ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol 2013;108:656–676; quiz 677
36. Husby S, Murray JA, Katzka DA. AGA clinical practice update on diagnosis and monitoring of celiac disease-changing utility of serology and histologic measures: expert review. Gastroenterology 2019;156:885–889
37. Suh S, Kim K-W. Diabetes and cancer: is diabetes causally related to cancer? Diabetes Metab J 2011;35:193–198
38. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. CA Cancer J Clin 2010;60:207–221
39. Aggarwal G, Kamada P, Chari ST. Prevalence of diabetes mellitus in pancreatic cancer compared to common cancers. Pancreas 2013;42:198–201
40. Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes–systematic overview of prospective observational studies. Diabetologia 2005;48:2460–2469
41. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol 2006;5:64–74
42. Gudala K, Bansal D, Schifano F, Bhansali A. Diabetes mellitus and risk of dementia: a meta-analysis of prospective observational studies. J Diabetes Investig 2013;4:640–650
43. Ohara T, Doi Y, Ninomiya T, et al. Glucose tolerance status and risk of dementia in the community: the Hisayama study. Neurology 2011;77:1126–1134
44. Cukierman-Yaffe T, Gerstein HC, Williamson JD, et al.; Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) Investigators. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) trial. Diabetes Care 2009;32:221–226
45. Launer LJ, Miller ME, Williamson JD, et al.; ACCORD MIND investigators. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. Lancet Neurol 2011;10:969–977
46. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA 2009;301:1565–1572
47. Punthakee Z, Miller ME, Launer LJ, et al.; ACCORD Group of Investigators; ACCORD-MIND Investigators. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. Diabetes Care 2012;35:787–793
48. Scarmeas N, Stern Y, Mayeux R, Manly JJ, Schupf N, Luchsinger JA. Mediterranean diet and mild cognitive impairment. Arch Neurol 2009;66:216–225
49. Ooi CP, Loke SC, Yassin Z, Hamid T-A. Carbohydrates for improving the cognitive performance of independent-living older adults with normal cognition or mild cognitive impairment. Cochrane Database Syst Rev 2011;4:CD007220
50. Richardson K, Schoen M, French B, et al. Statins and cognitive function: a systematic review. Ann Intern Med 2013;159:688–697
51. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. Gastroenterology 2004;126:460–468
52. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328–357
53. American Gastroenterological Association. American Gastroenterological Association medical position statement: nonalcoholic fatty liver disease. Gastroenterology 2002;123:1702–1704
54. Cusi K, Orsak B, Bril F, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. Ann Intern Med 2016;165:305–315
55. Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med 2006;355:2297–2307
56. Sanyal AJ, Chalasani N, Kowdley KV, et al.; NASH CRN. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010;362:1675–1685
57. Armstrong MJ, Gaunt P, Aithal GP, et al.; LEAN trial team. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised,

placebo-controlled phase 2 study. Lancet 2016; 387:679–690
58. Shimizu M, Suzuki K, Kato K, et al. Evaluation of the effects of dapagliflozin, a sodium-glucose co-transporter-2 inhibitor, on hepatic steatosis and fibrosis using transient elastography in patients with type 2 diabetes and non-alcoholic fatty liver disease. Diabetes Obes Metab 2019; 21:285–292
59. Kuchay MS, Krishan S, Mishra SK, et al. Effect of dulaglutide on liver fat in patients with type 2 diabetes and NAFLD: randomised controlled trial (D-LIFT trial). Diabetologia 2020;63:2434–2445
60. Lecube A, Hernández C, Genescà J, Simó R. Proinflammatory cytokines, insulin resistance, and insulin secretion in chronic hepatitis C patients: a case-control study. Diabetes Care 2006;29:1096–1101
61. Hum J, Jou JH, Green PK, et al. Improvement in glycemic control of type 2 diabetes after successful treatment of hepatitis C virus. Diabetes Care 2017;40:1173–1180
62. Carnovale C, Pozzi M, Dassano A, et al. The impact of a successful treatment of hepatitis C virus on glyco-metabolic control in diabetic patients: a systematic review and meta-analysis. Acta Diabetol 2019;56:341–354
63. Piciucchi M, Capurso G, Archibugi L, Delle Fave MM, Capasso M, Delle Fave G. Exocrine pancreatic insufficiency in diabetic patients: prevalence, mechanisms, and treatment. Int J Endocrinol 2015;2015:595649
64. Lee Y-K, Huang M-Y, Hsu C-Y, Su Y-C. Bidirectional relationship between diabetes and acute pancreatitis: a population-based cohort study in Taiwan. Medicine (Baltimore) 2016;95: e2448
65. Das SLM, Singh PP, Phillips ARJ, Murphy R, Windsor JA, Petrov MS. Newly diagnosed diabetes mellitus after acute pancreatitis: a systematic review and meta-analysis. Gut 2014;63: 818–831
66. Petrov MS. Diabetes of the exocrine pancreas: American Diabetes Association-compliant lexicon. Pancreatology 2017;17:523–526
67. Thomsen RW, Pedersen L, Møller N, Kahlert J, Beck-Nielsen H, Sørensen HT. Incretin-based therapy and risk of acute pancreatitis: a nationwide population-based case-control study. Diabetes Care 2015;38:1089–1098
68. Tkáč I, Raz I. Combined analysis of three large interventional trials with gliptins indicates increased incidence of acute pancreatitis in patients with type 2 diabetes. Diabetes Care 2017; 40:284–286
69. Egan AG, Blind E, Dunder K, et al. Pancreatic safety of incretin-based drugs–FDA and EMA assessment. N Engl J Med 2014;370:794–797
70. Bellin MD, Gelrud A, Arreaza-Rubin G, et al. Total pancreatectomy with islet autotransplantation: summary of an NIDDK workshop. Ann Surg 2015;261:21–29
71. Sutherland DER, Radosevich DM, Bellin MD, et al. Total pancreatectomy and islet autotransplantation for chronic pancreatitis. J Am Coll Surg 2012;214:409–424; discussion 424–426
72. Quartuccio M, Hall E, Singh V, et al. Glycemic predictors of insulin independence after total pancreatectomy with islet autotransplantation. J Clin Endocrinol Metab 2017;102:801–809
73. Webb MA, Illouz SC, Pollard CA, et al. Islet auto transplantation following total pancreatectomy: a long-term assessment of graft function. Pancreas 2008;37:282–287
74. Wu Q, Zhang M, Qin Y, et al. Systematic review and meta-analysis of islet autotransplantation after total pancreatectomy in chronic pancreatitis patients. Endocr J 2015;62:227–234
75. Janghorbani M, Van Dam RM, Willett WC, Hu FB. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. Am J Epidemiol 2007;166:495–505
76. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes–a meta-analysis. Osteoporos Int 2007;18:427–444
77. Schwartz AV, Vittinghoff E, Bauer DC, et al.; Study of Osteoporotic Fractures (SOF) Research Group; Osteoporotic Fractures in Men (MrOS) Research Group; Health, Aging, and Body Composition (Health ABC) Research Group. Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes. JAMA 2011; 305:2184–2192
78. Kahn SE, Zinman B, Lachin JM, et al.; Diabetes Outcome Progression Trial (ADOPT) Study Group. Rosiglitazone-associated fractures in type 2 diabetes: an analysis from A Diabetes Outcome Progression Trial (ADOPT). Diabetes Care 2008;31:845–851
79. Taylor SI, Blau JE, Rother KI. Possible adverse effects of SGLT2 inhibitors on bone. Lancet Diabetes Endocrinol 2015;3:8–10
80. Baiduc RR, Helzner EP. Epidemiology of diabetes and hearing loss. Semin Hear 2019;40: 281–291
81. Helzner EP, Contrera KJ. Type 2 diabetes and hearing impairment. Curr Diab Rep 2016; 16:3
82. Bainbridge KE, Hoffman HJ, Cowie CC. Diabetes and hearing impairment in the United States: audiometric evidence from the National Health and Nutrition Examination Survey, 1999 to 2004. Ann Intern Med 2008;149:1–10
83. Bainbridge KE, Hoffman HJ, Cowie CC. Risk factors for hearing impairment among U.S. adults with diabetes: National Health and Nutrition Examination Survey 1999-2004. Diabetes Care 2011;34:1540–1545
84. Schade DS, Lorenzi GM, Braffett BH, et al.; DCCT/EDIC Research Group. Hearing impairment and type 1 diabetes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Cohort. Diabetes Care 2018;41:2495–2501
85. Rasmussen VF, Vestergaard ET, Hejlesen O, Andersson CUN, Cichosz SL. Prevalence of taste and smell impairment in adults with diabetes: across-sectional analysis of data from the National Health and Nutrition Examination Survey (NHANES). Prim Care Diabetes 2018;12:453–459
86. Dhindsa S, Miller MG, McWhirter CL, et al. Testosterone concentrations in diabetic and nondiabetic obese men. Diabetes Care 2010;33: 1186–1192
87. Grossmann M. Low testosterone in men with type 2 diabetes: significance and treatment. J Clin Endocrinol Metab 2011;96:2341–2353
88. Bhasin S, Cunningham GR, Hayes FJ, et al.; Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95: 2536–2559
89. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2018;103:1715–1744
90. Li C, Ford ES, Zhao G, Croft JB, Balluz LS, Mokdad AH. Prevalence of self-reported clinically diagnosed sleep apnea according to obesity status in men and women: National Health and Nutrition Examination Survey, 2005-2006. Prev Med 2010;51:18–23
91. West SD, Nicoll DJ, Stradling JR. Prevalence of obstructive sleep apnoea in men with type 2 diabetes. Thorax 2006;61:945–950
92. Resnick HE, Redline S, Shahar E, et al.; Sleep Heart Health Study. Diabetes and sleep disturbances: findings from the Sleep Heart Health Study. Diabetes Care 2003;26:702–709
93. Foster GD, Sanders MH, Millman R, et al.; Sleep AHEAD Research Group. Obstructive sleep apnea among obese patients with type 2 diabetes. Diabetes Care 2009;32:1017–1019
94. Bibbins-Domingo K, Grossman DC, Curry SJ, et al.; US Preventive Services Task Force. Screening for obstructive sleep apnea in adults: US Preventive Services Task Force recommendation statement. JAMA 2017;317:407–414
95. Shaw JE, Punjabi NM, Wilding JP, Alberti KGMM, Zimmet PZ; International Diabetes Federation Taskforce on Epidemiology and Prevention. Sleep-disordered breathing and type 2 diabetes: a report from the International Diabetes Federation Taskforce on Epidemiology and Prevention. Diabetes Res Clin Pract 2008;81: 2–12
96. Khader YS, Dauod AS, El-Qaderi SS, Alkafajei A, Batayha WQ. Periodontal status of diabetics compared with nondiabetics: a meta-analysis. J Diabetes Complications 2006;20:59–68
97. Casanova L, Hughes FJ, Preshaw PM. Diabetes and periodontal disease: a two-way relationship. Br Dent J 2014;217:433–437
98. Eke PI, Thornton-Evans GO, Wei L, Borgnakke WS, Dye BA, Genco RJ. Periodontitis in US Adults: National Health and Nutrition Examination Survey 2009-2014. J Am Dent Assoc 2018;149:576–588.e6
99. Simpson TC, Weldon JC, Worthington HV, et al. Treatment of periodontal disease for glycaemic control in people with diabetes mellitus. Cochrane Database Syst Rev 2015;11: CD004714
100. D'Aiuto F, Gkranias N, Bhowruth D, et al.; TASTE Group. Systemic effects of periodontitis treatment in patients with type 2 diabetes: a 12 month, single-centre, investigator-masked, randomised trial. Lancet Diabetes Endocrinol 2018;6:954–965
101. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018: a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669–2701
102. Karter AJ, Warton EM, Lipska KJ, et al. Development and validation of a tool to identify patients with type 2 diabetes at high risk of hypoglycemia-related emergency department or hospital use. JAMA Intern Med 2017;177:1461–1470

103. Lipska KJ, Ross JS, Wang Y, et al. National trends in US hospital admissions for hyperglycemia and hypoglycemia among Medicare beneficiaries, 1999 to 2011. JAMA Intern Med 2014; 174:1116–1124
104. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. Arch Intern Med 1997;157:1681–1686
105. Abdelhafiz AH, Rodríguez-Mañas L, Morley JE, Sinclair AJ. Hypoglycemia in older people - a less well recognized risk factor for frailty. Aging Dis 2015;6:156–167
106. Yun J-S, Ko S-H, Ko S-H, et al. Presence of macroalbuminuria predicts severe hypoglycemia in patients with type 2 diabetes: a 10-year follow-up study. Diabetes Care 2013;36:1283–1289
107. Chelliah A, Burge MR. Hypoglycaemia in elderly patients with diabetes mellitus: causes and strategies for prevention. Drugs Aging 2004;21:511–530

5. Facilitating Behavior Change and Well-being to Improve Health Outcomes: *Standards of Medical Care in Diabetes—2021*

American Diabetes Association

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The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc21-SPPC), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc21-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Effective behavior management and psychological well-being are foundational to achieving treatment goals for people with diabetes (1,2). Essential to achieving these goals are diabetes self-management education and support (DSMES), medical nutrition therapy (MNT), routine physical activity, smoking cessation counseling when needed, and psychosocial care. Following an initial comprehensive medical evaluation (see Section 4 "Comprehensive Medical Evaluation and Assessment of Comorbidities," https://doi.org/10.2337/dc21-S004), patients and providers are encouraged to engage in person-centered collaborative care (3–6), which is guided by shared decision-making in treatment regimen selection, facilitation of obtaining needed medical and psychosocial resources, and shared monitoring of agreed-upon regimen and lifestyle (7). Reevaluation during routine care should include not only assessment of medical health, but also behavioral and mental health outcomes, especially during times of deterioration in health and well-being.

DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT

Recommendations

5.1 In accordance with the national standards for diabetes self-management education and support, all people with diabetes should participate in diabetes self-management education and receive the support needed to facilitate the knowledge, decision-making, and skills mastery necessary for diabetes self-care. **A**

5.2 There are four critical times to evaluate the need for diabetes self-management education to promote skills acquisition in support of regimen implementation, medical nutrition therapy, and well-being: at diagnosis, annually

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and/or when not meeting treatment targets, when complicating factors develop (medical, physical, psychosocial), and when transitions in life and care occur. **E**

5.3 Clinical outcomes, health status, and well-being are key goals of diabetes self-management education and support that should be measured as part of routine care. **C**

5.4 Diabetes self-management education and support should be patient centered, may be given in group or individual settings and/or use technology, and should be communicated with the entire diabetes care team. **A**

5.5 Because diabetes self-management education and support can improve outcomes and reduce costs **B**, reimbursement by third-party payers is recommended. **C**

5.6 Barriers to diabetes self-management education and support exist at the health system, payor, provider, and patient levels **A** and efforts need to be made to identify and address them. **E**

5.7 Some barriers to diabetes self-management education and support access may be mitigated through telemedicine approaches. **B**

DSMES services facilitate the knowledge, decision-making, and skills mastery necessary for optimal diabetes self-care and incorporate the needs, goals, and life experiences of the person with diabetes. The overall objectives of DSMES are to support informed decision-making, self-care behavior, problem-solving, and active collaboration with the health care team to improve clinical outcomes, health status, and well-being in a cost-effective manner (2). Providers are encouraged to consider the burden of treatment and the patient's level of confidence/self-efficacy for management behaviors as well as the level of social and family support when providing DSMES. Patient performance of self-management behaviors, including its effect on clinical outcomes, health status, and quality of life, as well as the psychosocial factors impacting the person's ability to self-manage, should be monitored as part of routine clinical care. A randomized controlled trial testing a decision-making education and skill-building program (8) showed that addressing these targets improved health outcomes in a population in need of health care resources. Furthermore, following a DSMES curriculum improves quality of care (9).

In addition, in response to the growing literature that associates potentially judgmental words with increased feelings of shame and guilt, providers are encouraged to consider the impact that language has on building therapeutic relationships and to choose positive, strength-based words and phrases that put people first (4,10). Patient performance of self-management behaviors, as well as psychosocial factors with the potential to impact the person's self-management, should be monitored. Please see Section 4 "Comprehensive Medical Evaluation and Assessment of Comorbidities" (https://doi.org/10.2337/dc21-S004) for more on use of language.

DSMES and the current national standards guiding it (2,11) are based on evidence of benefit. Specifically, DSMES helps people with diabetes to identify and implement effective self-management strategies and cope with diabetes at four critical time points (see below) (2). Ongoing DSMES helps people with diabetes to maintain effective self-management throughout a lifetime of diabetes as they face new challenges and as advances in treatment become available (12).

Four critical time points have been defined when the need for DSMES is to be evaluated by the medical care provider and/or multidisciplinary team, with referrals made as needed (2):

1. At diagnosis
2. Annually and/or when not meeting treatment targets
3. When complicating factors (health conditions, physical limitations, emotional factors, or basic living needs) develop that influence self-management
4. When transitions in life and care occur

DSMES focuses on supporting patient empowerment by providing people with diabetes the tools to make informed self-management decisions (13). Diabetes care requires an approach that places the person with diabetes and his or her family/support system at the center of the care model, working in collaboration with health care professionals. Patient-centered care is respectful of and responsive to individual patient preferences, needs, and values. It ensures that patient values guide all decision-making (14).

Evidence for the Benefits

Studies have found that DSMES is associated with improved diabetes knowledge and self-care behaviors (14,15), lower A1C (14,16–19), lower self-reported weight (20,21), improved quality of life (17,22), reduced all-cause mortality risk (23), healthy coping (5,24), and reduced health care costs (25–27). Better outcomes were reported for DSMES interventions that were more than 10 h over the course of 6–12 months (18), included ongoing support (12,28), were culturally (29,30) and age appropriate (31,32), were tailored to individual needs and preferences, and addressed psychosocial issues and incorporated behavioral strategies (13,24,33,34). Individual and group approaches are effective (21,35, 36), with a slight benefit realized by those who engage in both (18).

Emerging evidence demonstrates the benefit of telemedicine or internet-based DSMES services for diabetes prevention and the management of type 2 diabetes (37–43). Technology-enabled diabetes self-management solutions improve A1C most effectively when there is two-way communication between the patient and the health care team, individualized feedback, use of patient-generated health data, and education (39).

Current research supports diabetes care and education specialists including nurses, dietitians, and pharmacists as providers of DSMES who may also tailor curriculum to the person's needs (44–46). Members of the DSMES team should have specialized clinical knowledge in diabetes and behavior change principles. Certification as a diabetes care and education specialist (see https://www.cbdce.org/) and/or board certification in advanced diabetes management (see www.diabeteseducator.org/education/certification/bc_adm) demonstrates an individual's specialized training in and understanding of diabetes management and support (11), and engagement with qualified providers has been shown to improve disease-related outcomes. Additionally, there is growing evidence for the role of community health workers (47,48), as well as peer (47–51) and lay leaders (52), in providing ongoing support.

Evidence suggests people with diabetes who completed more than 10 hours of DSMES over the course of 6–12 months and those who participated on an ongoing basis had significant reductions in mortality (23) and A1C (decrease of 0.57%) (18) compared with those who spent less time with a diabetes care and education specialist. Given individual needs and access to resources, a variety of culturally adapted DSMES programs need to be offered in a variety of settings. Use of technology to facilitate access to DSMES services, support self-management decisions, and decrease therapeutic inertia suggests that these approaches need broader adoption.

DSMES is associated with an increased use of primary care and preventive services (25,53,54) and less frequent use of acute care and inpatient hospital services (20). Patients who participate in DSMES are more likely to follow best practice treatment recommendations, particularly among the Medicare population, and have lower Medicare and insurance claim costs (26,53). Despite these benefits, reports indicate that only 5–7% of individuals eligible for DSMES through Medicare or a private insurance plan actually receive it (55,56). Barriers to DSMES exist at the health system, payor, provider, and patient levels. This low participation may be due to lack of referral or other identified barriers such as logistical issues (accessibility, timing, costs) and the lack of a perceived benefit (56). Health system, programmatic, and payor barriers include lack of administrative leadership support, limited numbers of DSMES providers, not having referral to DSMES services effectively embedded in the health system service structure, and limited reimbursement rates (57). Thus, in addition to educating referring providers about the benefits of DSMES and the critical times to refer, efforts need to be made to identify and address all of the various potential barriers (2). Alternative and innovative models of DSMES delivery need to be explored and evaluated, including the integration of technology-enabled diabetes and cardiometabolic health services (58,59).

Reimbursement

Medicare reimburses DSMES when that service meets the national standards (2,11) and is recognized by the American Diabetes Association (ADA) or Association of Diabetes Care & Education Specialists (ADCES). DSMES is also covered by most health insurance plans. Ongoing support has been shown to be instrumental for improving outcomes when it is implemented after the completion of education services. DSMES is frequently reimbursed when performed in person. However, although DSMES can also be provided via phone calls and telehealth, these remote versions may not always be reimbursed. Some barriers to DSMES access may be mitigated through telemedicine approaches. Changes in reimbursement policies that increase DSMES access and utilization will result in a positive impact to beneficiaries' clinical outcomes, quality of life, health care utilization, and costs (60–62). During the time of the coronavirus disease 2019 (COVID-19) pandemic, reimbursement policies have changed (https://professional.diabetes.org/content-page/dsmes-and-mnt-during-covid-19-national-pandemic), and these changes may provide a new reimbursement paradigm for future provision of DSMES through telehealth channels.

MEDICAL NUTRITION THERAPY

Please refer to the ADA consensus report "Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report" for more information on nutrition therapy (46). For many individuals with diabetes, the most challenging part of the treatment plan is determining what to eat. There is not a "one-size-fits-all" eating pattern for individuals with diabetes, and meal planning should be individualized. Nutrition therapy plays an integral role in overall diabetes management, and each person with diabetes should be actively engaged in education, self-management, and treatment planning with his or her health care team, including the collaborative development of an individualized eating plan (46,63). All providers should refer people with diabetes for individualized MNT provided by a registered dietitian nutritionist (RD/RDN) who is knowledgeable and skilled in providing diabetes-specific MNT (64) at diagnosis and as needed throughout the life span, similar to DSMES. MNT delivered by an RD/RDN is associated with A1C absolute decreases of 1.0–1.9% for people with type 1 diabetes (65) and 0.3–2.0% for people with type 2 diabetes (65). See **Table 5.1** for specific nutrition recommendations. Because of the progressive nature of type 2 diabetes, behavior modification alone may not be adequate to maintain euglycemia over time. However, after medication is initiated, nutrition therapy continues to be an important component and RD/RDNs providing MNT in diabetes care should assess and monitor medication changes in relation to the nutrition care plan (46,63).

Goals of Nutrition Therapy for Adults With Diabetes

1. To promote and support healthful eating patterns, emphasizing a variety of nutrient-dense foods in appropriate portion sizes, to improve overall health and:
   - achieve and maintain body weight goals
   - attain individualized glycemic, blood pressure, and lipid goals
   - delay or prevent the complications of diabetes
2. To address individual nutrition needs based on personal and cultural preferences, health literacy and numeracy, access to healthful foods, willingness and ability to make behavioral changes, and existing barriers to change
3. To maintain the pleasure of eating by providing nonjudgmental messages about food choices while limiting food choices only when indicated by scientific evidence
4. To provide an individual with diabetes the practical tools for developing healthy eating patterns rather than focusing on individual macronutrients, micronutrients, or single foods

Eating Patterns and Meal Planning

Evidence suggests that there is not an ideal percentage of calories from carbohydrate, protein, and fat for people with diabetes. Therefore, macronutrient distribution should be based on an individualized assessment of current eating patterns, preferences, and metabolic goals. Consider personal preferences (e.g., tradition, culture, religion, health beliefs and goals, economics) as well as metabolic goals when working with individuals to determine the best eating pattern for them (46,66,67). Members of the health care team should complement MNT by providing evidence-based guidance that helps people with diabetes make healthy food choices that meet their

Table 5.1—Medical nutrition therapy recommendations

Topic	Recommendation
Effectiveness of nutrition therapy	**5.8** An individualized medical nutrition therapy program as needed to achieve treatment goals, provided by a registered dietitian nutritionist (RD/RDN), preferably one who has comprehensive knowledge and experience in diabetes care, is recommended for all people with type 1 or type 2 diabetes, prediabetes, and gestational diabetes mellitus. **A** **5.9** Because diabetes medical nutrition therapy can result in cost savings **B** and improved outcomes (e.g., A1C reduction, reduced weight, decrease in cholesterol) **A**, medical nutrition therapy should be adequately reimbursed by insurance and other payers. **E**
Energy balance	**5.10** For all patients with overweight or obesity, lifestyle modification to achieve and maintain a minimum weight loss of 5% is recommended for all patients with diabetes and prediabetes. **A**
Eating patterns and macronutrient distribution	**5.11** There is no single ideal dietary distribution of calories among carbohydrates, fats, and proteins for people with diabetes; therefore, meal plans should be individualized while keeping total calorie and metabolic goals in mind. **E** **5.12** A variety of eating patterns can be considered for the management of type 2 diabetes and to prevent diabetes in individuals with prediabetes. **B**
Carbohydrates	**5.13** Carbohydrate intake should emphasize nutrient-dense carbohydrate sources that are high in fiber and minimally processed. Eating plans should emphasize nonstarchy vegetables, minimal added sugars, fruits, whole grains, as well as dairy products. **B** **5.14** Reducing overall carbohydrate intake for individuals with diabetes has demonstrated the most evidence for improving glycemia and may be applied in a variety of eating patterns that meet individual needs and preferences. **B** **5.15** For people with diabetes who are prescribed a flexible insulin therapy program, education on how to use carbohydrate counting **A** and on dosing for fat and protein content **B** should be used to determine mealtime insulin dosing. **5.16** For adults using fixed insulin doses, consistent pattern of carbohydrate intake with respect to time and amount, while considering the insulin action time, can result in improved glycemia and reduce the risk for hypoglycemia. **B** **5.17** People with diabetes and those at risk are advised to replace sugar-sweetened beverages (including fruit juices) with water as much as possible in order to control glycemia and weight and reduce their risk for cardiovascular disease and fatty liver **B** and should minimize the consumption of foods with added sugar that have the capacity to displace healthier, more nutrient-dense food choices. **A**
Protein	**5.18** In individuals with type 2 diabetes, ingested protein appears to increase insulin response without increasing plasma glucose concentrations. Therefore, carbohydrate sources high in protein should be avoided when trying to treat or prevent hypoglycemia. **B**
Dietary fat	**5.19** An eating plan emphasizing elements of a Mediterranean-style eating pattern rich in monounsaturated and polyunsaturated fats may be considered to improve glucose metabolism and lower cardiovascular disease risk. **B** **5.20** Eating foods rich in long-chain n-3 fatty acids, such as fatty fish (EPA and DHA) and nuts and seeds (ALA), is recommended to prevent or treat cardiovascular disease. **B**
Micronutrients and herbal supplements	**5.21** There is no clear evidence that dietary supplementation with vitamins, minerals (such as chromium and vitamin D), herbs, or spices (such as cinnamon or aloe vera) can improve outcomes in people with diabetes who do not have underlying deficiencies, and they are not generally recommended for glycemic control. **C**
Alcohol	**5.22** Adults with diabetes who drink alcohol should do so in moderation (no more than one drink per day for adult women and no more than two drinks per day for adult men). **C** **5.23** Educating people with diabetes about the signs, symptoms, and self-management of delayed hypoglycemia after drinking alcohol, especially when using insulin or insulin secretagogues, is recommended. The importance of glucose monitoring after drinking alcoholic beverages to reduce hypoglycemia risk should be emphasized. **B**
Sodium	**5.24** As for the general population, people with diabetes and prediabetes should limit sodium consumption to $<$2,300 mg/day. **B**
Nonnutritive sweeteners	**5.25** The use of nonnutritive sweeteners may have the potential to reduce overall calorie and carbohydrate intake if substituted for caloric (sugar) sweeteners and without compensation by intake of additional calories from other food sources. For those who consume sugar-sweetened beverages regularly, a low-calorie or nonnutritive-sweetened beverage may serve as a short-term replacement strategy, but overall, people are encouraged to decrease both sweetened and nonnutritive-sweetened beverages and use other alternatives, with an emphasis on water intake. **B**

individualized needs and improve overall health. A variety of eating patterns are acceptable for the management of diabetes (46,66,68,69). Until the evidence surrounding comparative benefits of different eating patterns in specific individuals strengthens, health care providers should focus on the key factors that are common among the patterns: *1*) emphasize nonstarchy vegetables, *2*) minimize added sugars and refined grains, and *3*) choose whole foods over highly processed foods to the extent possible (46). An individualized eating pattern also considers the individual's health status, skills, resources, food preferences, and health goals. Referral to an RD/RDN is essential to assess the overall nutrition status of, and to work collaboratively with, the patient to create a personalized meal plan that coordinates and aligns with the overall treatment plan, including physical activity and medication use. The Mediterranean-style (67,70–72), low-carbohydrate (73–75), and vegetarian or plant-based (71,72,76,77) eating patterns are all examples of healthful eating patterns that have shown positive results in research, but individualized meal planning should focus on personal preferences, needs, and goals.

Reducing overall carbohydrate intake for individuals with diabetes has demonstrated the most evidence for improving glycemia and may be applied in a variety of eating patterns that meet individual needs and preferences (46). For individuals with type 2 diabetes not meeting glycemic targets or for whom reducing glucose-lowering drugs is a priority, reducing overall carbohydrate intake with a low- or very-low-carbohydrate eating pattern is a viable option (73–75). As research studies on low-carbohydrate eating plans generally indicate challenges with long-term sustainability, it is important to reassess and individualize meal plan guidance regularly for those interested in this approach, recognizing that insulin and other diabetes medications may need to be adjusted to prevent hypoglycemia and blood pressure will need to be monitored. Very-low-carbohydrate eating patterns are not recommended at this time for women who are pregnant or lactating, people with or at risk for disordered eating, or people who have renal disease, and they should be used with caution in patients taking sodium–glucose cotransporter 2 inhibitors due to the potential risk of ketoacidosis (78,79). There is inadequate research in type 1 diabetes to support one eating pattern over another at this time.

A randomized controlled trial found that two meal planning approaches were effective in helping achieve improved A1C, particularly for individuals with an A1C between 7% and 10% (80). The diabetes plate method is a commonly used visual approach for providing basic meal planning guidance. This simple graphic (featuring a 9-inch plate) shows how to portion foods (1/2 of the plate for nonstarchy vegetables, 1/4 of the plate for protein, and 1/4 of the plate for carbohydrates). Carbohydrate counting is a more advanced skill that helps plan for and track how much carbohydrate is consumed at meals and snacks. Meal planning approaches should be customized to the individual, including their numeracy level (80).

Weight Management

Management and reduction of weight is important for people with type 1 diabetes, type 2 diabetes, or prediabetes and overweight or obesity. To support weight loss and improve A1C, cardiovascular disease (CVD) risk factors, and well-being in adults with overweight/obesity and prediabetes or diabetes, MNT and DSMES services should include an individualized eating plan in a format that results in an energy deficit in combination with enhanced physical activity (46). Lifestyle intervention programs should be intensive and have frequent follow-up to achieve significant reductions in excess body weight and improve clinical indicators. There is strong and consistent evidence that modest persistent weight loss can delay the progression from prediabetes to type 2 diabetes (66,81,82) (see Section 3 "Prevention or Delay of Type 2 Diabetes," https://doi.org/10.2337/dc20-S003) and is beneficial to the management of type 2 diabetes (see Section 8 "Obesity Management for the Treatment of Type 2 Diabetes," https://doi.org/10.2337/dc20-S008).

In prediabetes, the weight loss goal is 7–10% for preventing progression to type 2 diabetes (83). In conjunction with support for healthy lifestyle behaviors, medication-assisted weight loss can be considered for people at risk for type 2 diabetes when needed to achieve and sustain 7–10% weight loss (84,85). People with prediabetes at a healthy weight should also be considered for behavioral interventions to help establish routine aerobic and resistance exercise (83,86,87) as well as to establish healthy eating patterns. Services delivered by practitioners familiar with diabetes and its management, such as an RD/RDN, have been found to be effective (64).

For many individuals with overweight and obesity with type 2 diabetes, 5% weight loss is needed to achieve beneficial outcomes in glycemic control, lipids, and blood pressure (88). It should be noted, however, that the clinical benefits of weight loss are progressive, and more intensive weight loss goals (i.e., 15%) may be appropriate to maximize benefit depending on need, feasibility, and safety (89,90). In select individuals with type 2 diabetes, an overall healthy eating plan that results in energy deficit in conjunction with weight loss medications and/or metabolic surgery should be considered to help achieve weight loss and maintenance goals, lower A1C, and reduce CVD risk (84,91,92). Overweight and obesity are also increasingly prevalent in people with type 1 diabetes and present clinical challenges regarding diabetes treatment and CVD risk factors (93,94). Sustaining weight loss can be challenging (88,95) but has long-term benefits; maintaining weight loss for 5 years is associated with sustained improvements in A1C and lipid levels (96). MNT guidance from an RD/RDN with expertise in diabetes and weight management, throughout the course of a structured weight loss plan, is strongly recommended.

People with diabetes and prediabetes should be screened and evaluated during DSMES and MNT encounters for disordered eating, and nutrition therapy should be individualized to accommodate disorders (46). Disordered eating can make following an eating plan challenging, and individuals should be referred to a mental health professional as needed. Studies have demonstrated that a variety of eating plans, varying in macronutrient composition, can be used effectively and safely in the short term (1–2 years) to achieve weight loss in people with diabetes. This includes structured low-calorie meal plans with meal replacements (89,96,97), the Mediterranean-style eating pattern (98), and low-carbohydrate meal plans with additional

support (99,100). However, no single approach has been proven to be consistently superior (46,101–103), and more data are needed to identify and validate those meal plans that are optimal with respect to long-term outcomes and patient acceptability. The importance of providing guidance on an individualized meal plan containing nutrient-dense foods, such as vegetables, fruits, legumes, dairy, lean sources of protein (including plant-based sources as well as lean meats, fish, and poultry), nuts, seeds, and whole grains, cannot be overemphasized (102), as well as guidance on achieving the desired energy deficit (104–107). Any approach to meal planning should be individualized considering the health status, personal preferences, and ability of the person with diabetes to sustain the recommendations in the plan.

Carbohydrates

Studies examining the ideal amount of carbohydrate intake for people with diabetes are inconclusive, although monitoring carbohydrate intake and considering the blood glucose response to dietary carbohydrate are key for improving postprandial glucose management (108,109). The literature concerning glycemic index and glycemic load in individuals with diabetes is complex, often with varying definitions of low and high glycemic index foods (110,111). The glycemic index ranks carbohydrate foods on their postprandial glycemic response, and glycemic load takes into account both the glycemic index of foods and the amount of carbohydrate eaten. Studies have found mixed results regarding the effect of glycemic index and glycemic load on fasting glucose levels and A1C, with one systematic review finding no significant impact on A1C (112), while two others demonstrated A1C reductions of 0.15% (110) to 0.5% (113).

Reducing overall carbohydrate intake for individuals with diabetes has demonstrated evidence for improving glycemia and may be applied in a variety of eating patterns that meet individual needs and preferences (46). For people with type 2 diabetes, low-carbohydrate and very-low-carbohydrate eating patterns, in particular, have been found to reduce A1C and the need for antihyperglycemic medications (46,67,114,115). Systematic reviews and meta-analyses of randomized controlled trials found carbohydrate-restricted eating patterns, particularly those considered very low carbohydrate (<26% total energy), were effective in reducing A1C in the short term (<6 months), with less difference in eating patterns beyond 1 year (73,74,103,115). Part of the challenge in interpreting low-carbohydrate research has been due to the wide range of definitions for a low-carbohydrate eating plan (75,113). Weight reduction was also a goal in many low-carbohydrate studies, which further complicates evaluating the distinct contribution of the eating pattern (40,99,103,116). As research studies on low-carbohydrate eating plans generally indicate challenges with long-term sustainability (115), it is important to reassess and individualize meal plan guidance regularly for those interested in this approach. Providers should maintain consistent medical oversight and recognize that insulin and other diabetes medications may need to be adjusted to prevent hypoglycemia and blood pressure will need to be monitored. In addition, very-low-carbohydrate eating plans are not currently recommended for women who are pregnant or lactating, children, people who have renal disease, or people with or at risk for disordered eating, and these plans should be used with caution in those taking sodium–glucose cotransporter 2 inhibitors because of the potential risk of ketoacidosis (78,79). There is inadequate research about dietary patterns for type 1 diabetes to support one eating plan over another at this time (117).

Most individuals with diabetes report a moderate intake of carbohydrate (44–46% of total calories) (66). Efforts to modify habitual eating patterns are often unsuccessful in the long term; people generally go back to their usual macronutrient distribution (66). Thus, the recommended approach is to individualize meal plans with a macronutrient distribution that is more consistent with personal preference and usual intake to increase the likelihood for long-term maintenance.

As for all individuals in developed countries, both children and adults with diabetes are encouraged to minimize intake of refined carbohydrates and added sugars and instead focus on carbohydrates from vegetables, legumes, fruits, dairy (milk and yogurt), and whole grains. People with diabetes and those at risk for diabetes are encouraged to consume at least the amount of dietary fiber recommended for the general public. The Dietary Guidelines for Americans recommend a minimum of 14 g of fiber/1,000 kcal, with at least half of grain consumption being whole, intact grains (118). Regular intake of sufficient dietary fiber is associated with lower all-cause mortality in people with diabetes (119,120), and prospective cohort studies have found dietary fiber intake is inversely associated with risk of type 2 diabetes (121,122). The consumption of sugar-sweetened beverages and processed food products with high amounts of refined grains and added sugars is strongly discouraged (118,123,124).

Individuals with type 1 or type 2 diabetes taking insulin at mealtime should be offered intensive and ongoing education on the need to couple insulin administration with carbohydrate intake. For people whose meal schedule or carbohydrate consumption is variable, regular counseling to help them understand the complex relationship between carbohydrate intake and insulin needs is important. In addition, education on using the insulin-to-carbohydrate ratios for meal planning can assist them with effectively modifying insulin dosing from meal to meal and improving glycemic management (66,108,125–128). Results from recent high-fat and/or high-protein mixed meals studies continue to support previous findings that glucose response to mixed meals high in protein and/or fat along with carbohydrate differs among individuals; therefore, a cautious approach to increasing insulin doses for high-fat and/or high-protein mixed meals is recommended to address delayed hyperglycemia that may occur 3 h or more after eating (46). Checking glucose 3 h after eating may help to determine if additional insulin adjustments are required (129,130). Continuous glucose monitoring or self-monitoring of blood glucose should guide decision-making for administration of additional insulin. For individuals on a fixed daily insulin schedule, meal planning should emphasize a relatively fixed carbohydrate consumption pattern with respect to both time and amount, while considering insulin action time (46).

Protein

There is no evidence that adjusting the daily level of protein intake (typically

1–1.5 g/kg body wt/day or 15–20% total calories) will improve health, and research is inconclusive regarding the ideal amount of dietary protein to optimize either glycemic management or CVD risk (111,131). Therefore, protein intake goals should be individualized based on current eating patterns. Some research has found successful management of type 2 diabetes with meal plans including slightly higher levels of protein (20–30%), which may contribute to increased satiety (132).

Historically, low-protein eating plans were advised for individuals with diabetic kidney disease (DKD) (with albuminuria and/or reduced estimated glomerular filtration rate); however, new evidence does not suggest that people with DKD need to restrict protein to less than the generally recommended protein intake (46). Reducing the amount of dietary protein below the recommended daily allowance of 0.8 g/kg is not recommended because it does not alter glycemic measures, cardiovascular risk measures, or the rate at which glomerular filtration rate declines and may increase risk for malnutrition (133,134).

In individuals with type 2 diabetes, protein intake may enhance or increase the insulin response to dietary carbohydrates (135). Therefore, use of carbohydrate sources high in protein (such as milk and nuts) to treat or prevent hypoglycemia should be avoided due to the potential concurrent rise in endogenous insulin.

Fats

The ideal amount of dietary fat for individuals with diabetes is controversial. New evidence suggests that there is not an ideal percentage of calories from fat for people with or at risk for diabetes and that macronutrient distribution should be individualized according to the patient's eating patterns, preferences, and metabolic goals (46). The type of fats consumed is more important than total amount of fat when looking at metabolic goals and CVD risk, and it is recommended that the percentage of total calories from saturated fats should be limited (98,118,136–138). Multiple randomized controlled trials including patients with type 2 diabetes have reported that a Mediterranean-style eating pattern (98, 139–144), rich in polyunsaturated and monounsaturated fats, can improve both glycemic management and blood lipids.

Evidence does not conclusively support recommending n-3 (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) supplements for all people with diabetes for the prevention or treatment of cardiovascular events (46,145,146). In individuals with type 2 diabetes, two systematic reviews with n-3 and n-6 fatty acids concluded that the dietary supplements did not improve glycemic management (111,147). In the ASCEND trial (A Study of Cardiovascular Events iN Diabetes), when compared with placebo, supplementation with n-3 fatty acids at the dose of 1 g/day did not lead to cardiovascular benefit in people with diabetes without evidence of CVD (148). However, results from the Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial (REDUCE-IT) did find that supplementation with 4 g/day of pure EPA significantly lowered the risk of adverse cardiovascular events. This trial of 8,179 participants, in which over 50% had diabetes, found a 5% absolute reduction in cardiovascular events for individuals with established atherosclerotic CVD taking a preexisting statin with residual hypertriglyceridemia (135–499 mg/dL) (149). See Section 10 "Cardiovascular Disease and Risk Management" (https://doi.org/10.2337/dc21-S010) for more information. People with diabetes should be advised to follow the guidelines for the general population for the recommended intakes of saturated fat, dietary cholesterol, and *trans* fat (118). *Trans* fats should be avoided. In addition, as saturated fats are progressively decreased in the diet, they should be replaced with unsaturated fats and not with refined carbohydrates (143).

Sodium

As for the general population, people with diabetes are advised to limit their sodium consumption to <2,300 mg/day (46). Restriction below 1,500 mg, even for those with hypertension, is generally not recommended (150–152). Sodium recommendations should take into account palatability, availability, affordability, and the difficulty of achieving low-sodium recommendations in a nutritionally adequate diet (153).

Micronutrients and Supplements

There continues to be no clear evidence of benefit from herbal or nonherbal (i.e., vitamin or mineral) supplementation for people with diabetes without underlying deficiencies (46). Metformin is associated with vitamin B12 deficiency per a report from the Diabetes Prevention Program Outcomes Study (DPPOS), suggesting that periodic testing of vitamin B12 levels should be considered in patients taking metformin, particularly in those with anemia or peripheral neuropathy (154). Routine supplementation with antioxidants, such as vitamins E and C and carotene, is not advised due to lack of evidence of efficacy and concern related to long-term safety. In addition, there is insufficient evidence to support the routine use of herbal supplements and micronutrients, such as cinnamon (155), curcumin, vitamin D (156), aloe vera, or chromium, to improve glycemia in people with diabetes (46,157). However, for special populations, including pregnant or lactating women, older adults, vegetarians, and people following very-low-calorie or low-carbohydrate diets, a multivitamin may be necessary.

Alcohol

Moderate alcohol intake does not have major detrimental effects on long-term blood glucose management in people with diabetes. Risks associated with alcohol consumption include hypoglycemia and/or delayed hypoglycemia (particularly for those using insulin or insulin secretagogue therapies), weight gain, and hyperglycemia (for those consuming excessive amounts) (46,157). People with diabetes should be educated about these risks and encouraged to monitor blood glucose frequently after drinking alcohol to minimize such risks. People with diabetes can follow the same guidelines as those without diabetes if they choose to drink. For women, no more than one drink per day, and for men, no more than two drinks per day is recommended (one drink is equal to a 12-oz beer, a 5-oz glass of wine, or 1.5 oz of distilled spirits).

Nonnutritive Sweeteners

The U.S. Food and Drug Administration has approved many nonnutritive sweeteners for consumption by the general public, including people with diabetes (46,158). For some people with diabetes who are accustomed to regularly consuming sugar-sweetened products, nonnutritive sweeteners (containing few or no calories) may be an acceptable substitute for nutritive sweeteners (those containing calories, such as sugar, honey, and agave syrup) when consumed in moderation (159,160). Use of nonnutritive

sweeteners does not appear to have a significant effect on glycemic management (66,66a), but they can reduce overall calorie and carbohydrate intake (66), as long as individuals are not compensating with additional calories from other food sources (46). There is mixed evidence from systematic reviews and meta-analyses for nonnutritive sweetener use with regard to weight management, with some finding benefit in weight loss (161,162), while other research suggests an association with weight gain (163). The addition of nonnutritive sweeteners to diets poses no benefit for weight loss or reduced weight gain without energy restriction (163a). Low-calorie or nonnutritive-sweetened beverages may serve as a short-term replacement strategy; however, people with diabetes should be encouraged to decrease both sweetened and nonnutritive-sweetened beverages, with an emphasis on water intake (160). Additionally, some research has found that higher nonnutritive-sweetened beverage and sugar-sweetened beverage consumption may be positively associated with the development of type 2 diabetes, although substantial heterogeneity makes interpreting the results difficult (164–166).

PHYSICAL ACTIVITY

Recommendations

5.26 Children and adolescents with type 1 or type 2 diabetes or prediabetes should engage in 60 min/day or more of moderate- or vigorous-intensity aerobic activity, with vigorous muscle-strengthening and bone-strengthening activities at least 3 days/week. **C**

5.27 Most adults with type 1 **C** and type 2 **B** diabetes should engage in 150 min or more of moderate- to vigorous-intensity aerobic activity per week, spread over at least 3 days/week, with no more than 2 consecutive days without activity. Shorter durations (minimum 75 min/week) of vigorous-intensity or interval training may be sufficient for younger and more physically fit individuals.

5.28 Adults with type 1 **C** and type 2 **B** diabetes should engage in 2–3 sessions/week of resistance exercise on nonconsecutive days.

5.29 All adults, and particularly those with type 2 diabetes, should decrease the amount of time spent in daily sedentary behavior. **B** Prolonged sitting should be interrupted every 30 min for blood glucose benefits. **C**

5.30 Flexibility training and balance training are recommended 2–3 times/week for older adults with diabetes. Yoga and tai chi may be included based on individual preferences to increase flexibility, muscular strength, and balance. **C**

5.31 Evaluate baseline physical activity and sedentary time. Promote increase in nonsedentary activities above baseline for sedentary individuals with type 1 **E** and type 2 **B** diabetes. Examples include walking, yoga, housework, gardening, swimming, and dancing.

Physical activity is a general term that includes all movement that increases energy use and is an important part of the diabetes management plan. Exercise is a more specific form of physical activity that is structured and designed to improve physical fitness. Both physical activity and exercise are important. Exercise has been shown to improve blood glucose control, reduce cardiovascular risk factors, contribute to weight loss, and improve well-being (167). Physical activity is as important for those with type 1 diabetes as it is for the general population, but its specific role in the prevention of diabetes complications and the management of blood glucose is not as clear as it is for those with type 2 diabetes. A recent study suggested that the percentage of people with diabetes who achieved the recommended exercise level per week (150 min) varied by race. Objective measurement by accelerometer showed that 44.2%, 42.6%, and 65.1% of Whites, African Americans, and Hispanics, respectively, met the threshold (168). It is important for diabetes care management teams to understand the difficulty that many patients have reaching recommended treatment targets and to identify individualized approaches to improve goal achievement.

Moderate to high volumes of aerobic activity are associated with substantially lower cardiovascular and overall mortality risks in both type 1 and type 2 diabetes (169). A recent prospective observational study of adults with type 1 diabetes suggested that higher amounts of physical activity led to reduced cardiovascular mortality after a mean follow-up time of 11.4 years for patients with and without chronic kidney disease (170). Additionally, structured exercise interventions of at least 8 weeks' duration have been shown to lower A1C by an average of 0.66% in people with type 2 diabetes, even without a significant change in BMI (171). There are also considerable data for the health benefits (e.g., increased cardiovascular fitness, greater muscle strength, improved insulin sensitivity, etc.) of regular exercise for those with type 1 diabetes (172). A recent study suggested that exercise training in type 1 diabetes may also improve several important markers such as triglyceride level, LDL, waist circumference, and body mass (173). In adults with type 2 diabetes, higher levels of exercise intensity are associated with greater improvements in A1C and in cardiorespiratory fitness (174); sustained improvements in cardiorespiratory fitness and weight loss have also been associated with a lower risk of heart failure (175). Other benefits include slowing the decline in mobility among overweight patients with diabetes (176). The ADA position statement "Physical Activity/Exercise and Diabetes" reviews the evidence for the benefits of exercise in people with type 1 and type 2 diabetes and offers specific recommendations (177). Physical activity and exercise should be recommended and prescribed to all individuals with diabetes as part of management of glycemia and overall health. Specific recommendations and precautions will vary by the type of diabetes, age, activity done, and presence of diabetes-related health complications. Recommendations should be tailored to meet the specific needs of each individual (177).

Exercise and Children

All children, including children with diabetes or prediabetes, should be encouraged to engage in regular physical activity. Children should engage in at least 60 min of moderate to vigorous aerobic activity every day, with muscle- and bone-strengthening activities at least 3 days per week (178). In general, youth with type 1 diabetes benefit from being physically active, and an active lifestyle

should be recommended to all (179). Youth with type 1 diabetes who engage in more physical activity may have better health outcomes and health-related quality of life (180,181).

Frequency and Type of Physical Activity

People with diabetes should perform aerobic and resistance exercise regularly (177). Aerobic activity bouts should ideally last at least 10 min, with the goal of ~30 min/day or more, most days of the week for adults with type 2 diabetes. Daily exercise, or at least not allowing more than 2 days to elapse between exercise sessions, is recommended to decrease insulin resistance, regardless of diabetes type (182,183). A study in adults with type 1 diabetes found a dose-response inverse relationship between self-reported bouts of physical activity per week with A1C, BMI, hypertension, dyslipidemia, and diabetes-related complications, such as hypoglycemia, diabetic ketoacidosis, retinopathy and microalbuminuria (184). Over time, activities should progress in intensity, frequency, and/or duration to at least 150 min/week of moderate-intensity exercise. Adults able to run at 6 miles/h (9.7 km/h) for at least 25 min can benefit sufficiently from shorter-intensity activity (75 min/week) (177). Many adults, including most with type 2 diabetes, may be unable or unwilling to participate in such intense exercise and should engage in moderate exercise for the recommended duration. Adults with diabetes should engage in 2–3 sessions/week of resistance exercise on nonconsecutive days (185). Although heavier resistance training with free weights and weight machines may improve glycemic control and strength (186), resistance training of any intensity is recommended to improve strength, balance, and the ability to engage in activities of daily living throughout the life span. Providers and staff should help patients set stepwise goals toward meeting the recommended exercise targets. As individuals intensify their exercise program, medical monitoring may be indicated to ensure safety and evaluate the effects on glucose management. (See the section PHYSICAL ACTIVITY AND GLYCEMIC CONTROL below)

Recent evidence supports that all individuals, including those with diabetes, should be encouraged to reduce the amount of time spent being sedentary—waking behaviors with low energy expenditure (e.g., working at a computer, watching television)—by breaking up bouts of sedentary activity (>30 min) by briefly standing, walking, or performing other light physical activities (187,188). Participating in leisure-time activity and avoiding extended sedentary periods may help prevent type 2 diabetes for those at risk (189,190) and may also aid in glycemic control for those with diabetes.

A systematic review and meta-analysis found higher frequency of regular leisure-time physical activity was more effective in reducing A1C levels (191). A wide range of activities, including yoga, tai chi, and other types, can have significant impacts on A1C, flexibility, muscle strength, and balance (167,192–194). Flexibility and balance exercises may be particularly important in older adults with diabetes to maintain range of motion, strength, and balance (177).

Physical Activity and Glycemic Control

Clinical trials have provided strong evidence for the A1C-lowering value of resistance training in older adults with type 2 diabetes (195) and for an additive benefit of combined aerobic and resistance exercise in adults with type 2 diabetes (196). If not contraindicated, patients with type 2 diabetes should be encouraged to do at least two weekly sessions of resistance exercise (exercise with free weights or weight machines), with each session consisting of at least one set (group of consecutive repetitive exercise motions) of five or more different resistance exercises involving the large muscle groups (195).

For type 1 diabetes, although exercise in general is associated with improvement in disease status, care needs to be taken in titrating exercise with respect to glycemic management. Each individual with type 1 diabetes has a variable glycemic response to exercise. This variability should be taken into consideration when recommending the type and duration of exercise for a given individual (172).

Women with preexisting diabetes, particularly type 2 diabetes, and those at risk for or presenting with gestational diabetes mellitus should be advised to engage in regular moderate physical activity prior to and during their pregnancies as tolerated (177).

Pre-exercise Evaluation

As discussed more fully in Section 10 "Cardiovascular Disease and Risk Management" (https://doi.org/10.2337/dc21-S010), the best protocol for assessing asymptomatic patients with diabetes for coronary artery disease remains unclear. The ADA consensus report "Screening for Coronary Artery Disease in Patients With Diabetes" (197) concluded that routine testing is not recommended. However, providers should perform a careful history, assess cardiovascular risk factors, and be aware of the atypical presentation of coronary artery disease, such as recent patient-reported or tested decrease in exercise tolerance, in patients with diabetes. Certainly, high-risk patients should be encouraged to start with short periods of low-intensity exercise and slowly increase the intensity and duration as tolerated. Providers should assess patients for conditions that might contraindicate certain types of exercise or predispose to injury, such as uncontrolled hypertension, untreated proliferative retinopathy, autonomic neuropathy, peripheral neuropathy, and a history of foot ulcers or Charcot foot. The patient's age and previous physical activity level should be considered when customizing the exercise regimen to the individual's needs. Those with complications may need a more thorough evaluation prior to starting an exercise program (198).

Hypoglycemia

In individuals taking insulin and/or insulin secretagogues, physical activity may cause hypoglycemia if the medication dose or carbohydrate consumption is not adjusted for the exercise bout and post-bout impact on glucose. Individuals on these therapies may need to ingest some added carbohydrate if pre-exercise glucose levels are <90 mg/dL (5.0 mmol/L), depending on whether they are able to lower insulin doses during the workout (such as with an insulin pump or reduced pre-exercise insulin dosage), the time of day exercise is done, and the intensity and duration of the activity (172,198). In some patients, hypoglycemia after exercise may occur and last for several hours due to increased insulin sensitivity. Hypoglycemia is less common in patients with diabetes who are not treated with insulin or insulin secretagogues, and no routine preventive measures for hypoglycemia are usually advised in these cases. Intense activities

may actually raise blood glucose levels instead of lowering them, especially if pre-exercise glucose levels are elevated (172). Because of the variation in glycemic response to exercise bouts, patients need to be educated to check blood glucose levels before and after periods of exercise and about the potential prolonged effects (depending on intensity and duration) (see the section DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT above).

Exercise in the Presence of Microvascular Complications

See Section 11 "Microvascular Complications and Foot Care" (https://doi.org/10.2337/dc21-S011) for more information on these long-term complications.

Retinopathy

If proliferative diabetic retinopathy or severe nonproliferative diabetic retinopathy is present, then vigorous-intensity aerobic or resistance exercise may be contraindicated because of the risk of triggering vitreous hemorrhage or retinal detachment (199). Consultation with an ophthalmologist prior to engaging in an intense exercise regimen may be appropriate.

Peripheral Neuropathy

Decreased pain sensation and a higher pain threshold in the extremities can result in an increased risk of skin breakdown, infection, and Charcot joint destruction with some forms of exercise. Therefore, a thorough assessment should be done to ensure that neuropathy does not alter kinesthetic or proprioceptive sensation during physical activity, particularly in those with more severe neuropathy. Studies have shown that moderate-intensity walking may not lead to an increased risk of foot ulcers or reulceration in those with peripheral neuropathy who use proper footwear (200). In addition, 150 min/week of moderate exercise was reported to improve outcomes in patients with prediabetic neuropathy (201). All individuals with peripheral neuropathy should wear proper footwear and examine their feet daily to detect lesions early. Anyone with a foot injury or open sore should be restricted to non–weight-bearing activities.

Autonomic Neuropathy

Autonomic neuropathy can increase the risk of exercise-induced injury or adverse events through decreased cardiac responsiveness to exercise, postural hypotension, impaired thermoregulation, impaired night vision due to impaired papillary reaction, and greater susceptibility to hypoglycemia (202). Cardiovascular autonomic neuropathy is also an independent risk factor for cardiovascular death and silent myocardial ischemia (203). Therefore, individuals with diabetic autonomic neuropathy should undergo cardiac investigation before beginning physical activity more intense than that to which they are accustomed.

Diabetic Kidney Disease

Physical activity can acutely increase urinary albumin excretion. However, there is no evidence that vigorous-intensity exercise accelerates the rate of progression of DKD, and there appears to be no need for specific exercise restrictions for people with DKD in general (199).

SMOKING CESSATION: TOBACCO AND E-CIGARETTES

Recommendations

5.32 Advise all patients not to use cigarettes and other tobacco products or e-cigarettes. **A**

5.33 After identification of tobacco or e-cigarette use, include smoking cessation counseling and other forms of treatment as a routine component of diabetes care. **A**

5.34 Address smoking cessation as part of diabetes education programs for those in need. **B**

Results from epidemiologic, case-control, and cohort studies provide convincing evidence to support the causal link between cigarette smoking and health risks (204). Recent data show tobacco use is higher among adults with chronic conditions (205) as well as in adolescents and young adults with diabetes (206). People with diabetes who smoke (and people with diabetes exposed to second-hand smoke) have a heightened risk of CVD, premature death, microvascular complications, and worse glycemic control when compared with those who do not smoke (207–209). Smoking may have a role in the development of type 2 diabetes (210–213).

The routine and thorough assessment of tobacco use is essential to prevent smoking or encourage cessation. Numerous large randomized clinical trials have demonstrated the efficacy and cost-effectiveness of brief counseling in smoking cessation, including the use of telephone quit lines, in reducing tobacco use. Pharmacologic therapy to assist with smoking cessation in people with diabetes has been shown to be effective (214), and for the patient motivated to quit, the addition of pharmacologic therapy to counseling is more effective than either treatment alone (215). Special considerations should include assessment of level of nicotine dependence, which is associated with difficulty in quitting and relapse (216). Although some patients may gain weight in the period shortly after smoking cessation (217), recent research has demonstrated that this weight gain does not diminish the substantial CVD benefit realized from smoking cessation (218). One study in people who smoke who had newly diagnosed type 2 diabetes found that smoking cessation was associated with amelioration of metabolic parameters and reduced blood pressure and albuminuria at 1 year (219).

In recent years, e-cigarettes have gained public awareness and popularity because of perceptions that e-cigarette use is less harmful than regular cigarette smoking (220,221). However, in light of recent Centers for Disease Control and Prevention evidence (222) of deaths related to e-cigarette use, no persons should be advised to use e-cigarettes, either as a way to stop smoking tobacco or as a recreational drug.

Diabetes education programs offer potential to systematically reach and engage individuals with diabetes in smoking cessation efforts. A cluster randomized trial found statistically significant increases in quit rates and long-term abstinence rates (>6 months) when smoking cessation interventions were offered through diabetes education clinics, regardless of motivation to quit at baseline (223).

PSYCHOSOCIAL ISSUES

Recommendations

5.35 Psychosocial care should be integrated with a collaborative, patient-centered approach and provided to all people with diabetes, with the goals of optimizing health outcomes and health-related quality of life. **A**

5.36 Psychosocial screening and follow-up may include, but are not limited to, attitudes about diabetes, expectations for medical management and outcomes, affect or mood, general and diabetes-related quality of life, available resources (financial, social, and emotional), and psychiatric history. **E**

5.37 Providers should consider assessment for symptoms of diabetes distress, depression, anxiety, disordered eating, and cognitive capacities using appropriate standardized and validated tools at the initial visit, at periodic intervals, and when there is a change in disease, treatment, or life circumstance. Including caregivers and family members in this assessment is recommended. **B**

5.38 Consider screening older adults (aged ≥65 years) with diabetes for cognitive impairment and depression. **B**

Please refer to the ADA position statement "Psychosocial Care for People With Diabetes" for a list of assessment tools and additional details (1).

Complex environmental, social, behavioral, and emotional factors, known as psychosocial factors, influence living with diabetes, both type 1 and type 2, and achieving satisfactory medical outcomes and psychological well-being. Thus, individuals with diabetes and their families are challenged with complex, multifaceted issues when integrating diabetes care into daily life (128).

Emotional well-being is an important part of diabetes care and self-management. Psychological and social problems can impair the individual's (11,224–228) or family's (227) ability to carry out diabetes care tasks and therefore potentially compromise health status. There are opportunities for the clinician to routinely assess psychosocial status in a timely and efficient manner for referral to appropriate services (229,230). A systematic review and meta-analysis showed that psychosocial interventions modestly but significantly improved A1C (standardized mean difference –0.29%) and mental health outcomes (231). However, there was a limited association between the effects on A1C and mental health, and no intervention characteristics predicted benefit on both outcomes.

Screening

Key opportunities for psychosocial screening occur at diabetes diagnosis, during regularly scheduled management visits, during hospitalizations, with new onset of complications, during significant transitions in care such as from pediatric to adult care teams (232), or when problems with achieving A1C goals, quality of life, or self-management are identified (2). Patients are likely to exhibit psychological vulnerability at diagnosis, when their medical status changes (e.g., end of the honeymoon period), when the need for intensified treatment is evident, and when complications are discovered. Significant changes in life circumstances, often called social determinants of health, are known to considerably affect a person's ability to self-manage their illness. Thus, screening for social determinants of health (e.g., loss of employment, birth of a child, or other family-based stresses) should also be incorporated into routine care (233).

Providers can start with informal verbal inquires, for example, by asking whether there have been persistent changes in mood during the past 2 weeks or since the patient's last visit and whether the person can identify a triggering event or change in circumstances. Providers should also ask whether there are new or different barriers to treatment and self-management, such as feeling overwhelmed or stressed by having diabetes (see the section DIABETES DISTRESS below), changes in finances, or competing medical demands (e.g., the diagnosis of a comorbid condition). In circumstances where persons other than the patient are significantly involved in diabetes management, these issues should be explored with nonmedical care providers (232). Standardized and validated tools for psychosocial monitoring and assessment can also be used by providers (1), with positive findings leading to referral to a mental health provider specializing in diabetes for comprehensive evaluation, diagnosis, and treatment.

Diabetes Distress

Recommendation

5.39 Routinely monitor people with diabetes for diabetes distress, particularly when treatment targets are not met and/or at the onset of diabetes complications. **B**

Diabetes distress is very common and is distinct from other psychological disorders (227,234,235). Diabetes distress refers to significant negative psychological reactions related to emotional burdens and worries specific to an individual's experience in having to manage a severe, complicated, and demanding chronic disease such as diabetes (234–236). The constant behavioral demands (medication dosing, frequency, and titration; monitoring blood glucose, food intake, eating patterns, and physical activity) of diabetes self-management and the potential or actuality of disease progression are directly associated with reports of diabetes distress (234). The prevalence of diabetes distress is reported to be 18–45% with an incidence of 38–48% over 18 months in persons with type 2 diabetes (236). In the second Diabetes Attitudes, Wishes and Needs (DAWN2) study, significant diabetes distress was reported by 45% of the participants, but only 24% reported that their health care teams asked them how diabetes affected their lives (227). High levels of diabetes distress significantly impact medication-taking behaviors and are linked to higher A1C, lower self-efficacy, and poorer dietary and exercise behaviors (5,234,236). DSMES has been shown to reduce diabetes distress (5). It may be helpful to provide counseling regarding expected diabetes-related versus generalized psychological distress, both at diagnosis and when disease state or treatment changes occur (237).

A randomized controlled trial tested the effects of participation in a standardized 8-week mindful self-compassion program versus a control group among patients with type 1 and type 2 diabetes. Mindful self-compassion training increased self-compassion, reduced depression and diabetes distress, and improved A1C in the intervention group (238).

Diabetes distress should be routinely monitored (239) using person-based diabetes-specific validated measures (1). If diabetes distress is identified, the person should be referred for specific diabetes education to address areas of diabetes self-care causing the patient

distress and impacting clinical management. People whose self-care remains impaired after tailored diabetes education should be referred by their care team to a behavioral health provider for evaluation and treatment.

Other psychosocial issues known to affect self-management and health outcomes include attitudes about the illness, expectations for medical management and outcomes, available resources (financial, social, and emotional) (240), and psychiatric history.

Referral to a Mental Health Specialist

Indications for referral to a mental health specialist familiar with diabetes management may include positive screening for overall stress related to work-life balance, diabetes distress, diabetes management difficulties, depression, anxiety, disordered eating, and cognitive dysfunction (see **Table 5.2** for a complete list). It is preferable to incorporate psychosocial assessment and treatment into routine care rather than waiting for a specific problem or deterioration in metabolic or psychological status to occur (33,227). Providers should identify behavioral and mental health providers, ideally those who are knowledgeable about diabetes treatment and the psychosocial aspects of diabetes, to whom they can refer patients. The ADA provides a list of mental health providers who have received additional education in diabetes at the ADA Mental Health Provider Directory (professional.diabetes.org/mhp_listing). Ideally, psychosocial care providers should be embedded in diabetes care settings. Although the provider may not feel qualified to treat psychological problems (241), optimizing the patient-provider relationship as a foundation may increase the likelihood of the patient accepting referral for other services. Collaborative care interventions and a team approach have demonstrated efficacy in diabetes self-management, outcomes of depression, and psychosocial functioning (5,6).

Psychosocial/Emotional Distress

Clinically significant psychopathologic diagnoses are considerably more prevalent in people with diabetes than in those without (242,243). Symptoms, both clinical and subclinical, that interfere with the person's ability to carry out daily diabetes self-management tasks must be addressed. In addition to impacting a person's ability to carry out self-management, and the association of mental health diagnosis and poorer short-term glycemic stability, symptoms of emotional distress are associated with mortality risk (242). Providers should consider an assessment of symptoms of depression, anxiety, disordered eating, and cognitive capacities using appropriate standardized/validated tools at the initial visit, at periodic intervals when patient distress is suspected, and when there is a change in health, treatment, or life circumstance. Inclusion of caregivers and family members in this assessment is recommended. Diabetes distress is addressed as an independent condition (see the section DIABETES DISTRESS above), as this state is very common and expected and is distinct from the psychological disorders discussed below (1). A list of age-appropriate screening and evaluation measures is provided in the ADA position statement "Psychosocial Care for People with Diabetes" (1).

Anxiety Disorders

Recommendations

5.40 Consider screening for anxiety in people exhibiting anxiety or worries regarding diabetes complications, insulin administration, and taking of medications, as well as fear of hypoglycemia and/or hypoglycemia unawareness that interferes with self-management behaviors, and in those who express fear, dread, or irrational thoughts and/or show anxiety symptoms such as avoidance behaviors, excessive repetitive behaviors, or social withdrawal. Refer for treatment if anxiety is present. **B**

5.41 People with hypoglycemia unawareness, which can co-occur with fear of hypoglycemia, should be treated using blood glucose awareness training (or other evidence-based intervention) to help re-establish awareness of symptoms of hypoglycemia and reduce fear of hypoglycemia. **A**

Anxiety symptoms and diagnosable disorders (e.g., generalized anxiety disorder, body dysmorphic disorder, obsessive-compulsive disorder, specific phobias, and posttraumatic stress disorder) are common in people with diabetes (244). The Behavioral Risk Factor Surveillance System (BRFSS) estimated the lifetime prevalence of generalized anxiety disorder to be 19.5% in people with either type 1 or type 2 diabetes (245). Common diabetes-specific concerns include fears related to hypoglycemia (246,247), not meeting blood glucose targets (244), and insulin injections or infusion (248). Onset of complications presents another critical point in the disease course when anxiety can occur (1). People with diabetes who exhibit excessive diabetes self-management behaviors well beyond what is prescribed or needed to achieve glycemic

Table 5.2—Situations that warrant referral of a person with diabetes to a mental health provider for evaluation and treatment

- If self-care remains impaired in a person with diabetes distress after tailored diabetes education
- If a person has a positive screen on a validated screening tool for depressive symptoms
- In the presence of symptoms or suspicions of disordered eating behavior, an eating disorder, or disrupted patterns of eating
- If intentional omission of insulin or oral medication to cause weight loss is identified
- If a person has a positive screen for anxiety or fear of hypoglycemia
- If a serious mental illness is suspected
- In youth and families with behavioral self-care difficulties, repeated hospitalizations for diabetic ketoacidosis, or significant distress
- If a person screens positive for cognitive impairment
- Declining or impaired ability to perform diabetes self-care behaviors
- Before undergoing bariatric or metabolic surgery and after surgery if assessment reveals an ongoing need for adjustment support

targets may be experiencing symptoms of obsessive-compulsive disorder (249).

General anxiety is a predictor of injection-related anxiety and associated with fear of hypoglycemia (247,250). Fear of hypoglycemia and hypoglycemia unawareness often co-occur. Interventions aimed at treating one often benefit both (251). Fear of hypoglycemia may explain avoidance of behaviors associated with lowering glucose such as increasing insulin doses or frequency of monitoring. If fear of hypoglycemia is identified and a person does not have symptoms of hypoglycemia, a structured program of blood glucose awareness training delivered in routine clinical practice can improve A1C, reduce the rate of severe hypoglycemia, and restore hypoglycemia awareness (252,253). If not available within the practice setting, a structured program targeting both fear of hypoglycemia and unawareness should be sought out and implemented by a qualified behavioral practitioner (251,253–255).

Depression

Recommendations

5.42 Providers should consider annual screening of all patients with diabetes, especially those with a self-reported history of depression, for depressive symptoms with age-appropriate depression screening measures, recognizing that further evaluation will be necessary for individuals who have a positive screen. **B**

5.43 Beginning at diagnosis of complications or when there are significant changes in medical status, consider assessment for depression. **B**

5.44 Referrals for treatment of depression should be made to mental health providers with experience using cognitive behavioral therapy, interpersonal therapy, or other evidence-based treatment approaches in conjunction with collaborative care with the patient's diabetes treatment team. **A**

History of depression, current depression, and antidepressant medication use are risk factors for the development of type 2 diabetes, especially if the individual has other risk factors such as obesity and family history of type 2 diabetes (256–258). Elevated depressive symptoms and depressive disorders affect one in four patients with type 1 or type 2 diabetes (226). Thus, routine screening for depressive symptoms is indicated in this high-risk population including people with type 1 or type 2 diabetes, gestational diabetes mellitus, and postpartum diabetes. Regardless of diabetes type, women have significantly higher rates of depression than men (259).

Routine monitoring with appropriate validated measures (1) can help to identify if referral is warranted. Adult patients with a history of depressive symptoms or disorder need ongoing monitoring of depression recurrence within the context of routine care (256). Integrating mental and physical health care can improve outcomes. When a patient is in psychological therapy (talk or cognitive behavioral therapy), the mental health provider should be incorporated into the diabetes treatment team (260). As with DSMES, person-centered collaborative care approaches have been shown to improve both depression and medical outcomes (261).

Various randomized controlled trials have shown improvements in diabetes and depression health outcomes when depression is simultaneously treated (261,262). It is important to note that medical regimen should also be monitored in response to reduction in depressive symptoms. People may agree to or adopt previously refused treatment strategies (improving ability to follow recommended treatment behaviors), which may include increased physical activity and intensification of regimen behaviors and monitoring, resulting in changed glucose profiles.

Disordered Eating Behavior

Recommendations

5.45 Providers should consider reevaluating the treatment regimen of people with diabetes who present with symptoms of disordered eating behavior, an eating disorder, or disrupted patterns of eating. **B**

5.46 Consider screening for disordered or disrupted eating using validated screening measures when hyperglycemia and weight loss are unexplained based on self-reported behaviors related to medication dosing, meal plan, and physical activity. In addition, a review of the medical regimen is recommended to identify potential treatment-related effects on hunger/caloric intake. **B**

Estimated prevalence of disordered eating behavior and diagnosable eating disorders in people with diabetes varies (263–265). For people with type 1 diabetes, insulin omission causing glycosuria in order to lose weight is the most commonly reported disordered eating behavior (266,267); in people with type 2 diabetes, bingeing (excessive food intake with an accompanying sense of loss of control) is most commonly reported. For people with type 2 diabetes treated with insulin, intentional omission is also frequently reported (268). People with diabetes and diagnosable eating disorders have high rates of comorbid psychiatric disorders (269). People with type 1 diabetes and eating disorders have high rates of diabetes distress and fear of hypoglycemia (270).

When evaluating symptoms of disordered or disrupted eating (when the individual exhibits eating behavior that is nonvolitional and maladaptive) in people with diabetes, etiology and motivation for the behavior should be considered (265,271). Mixed intervention results point to the need for treatment of eating disorders and disordered eating behavior in context. More rigorous methods to identify underlying mechanisms of action that drive change in eating and treatment behaviors as well as associated mental distress are needed (272). Adjunctive medication such as glucagon-like peptide 1 receptor agonists (273) may help individuals not only to meet glycemic targets but also to regulate hunger and food intake, thus having the potential to reduce uncontrollable hunger and bulimic symptoms.

Serious Mental Illness

Recommendations

5.47 Incorporate active monitoring of diabetes self-care activities into treatment goals for people with diabetes and serious mental illness. **B**

5.48 In people who are prescribed atypical antipsychotic medications,

screen for prediabetes and diabetes 4 months after medication initiation and at least annually thereafter. **B**

5.49 If a second-generation antipsychotic medication is prescribed for adolescents or adults with diabetes, changes in weight, glycemic control, and cholesterol levels should be carefully monitored and the treatment regimen should be reassessed. **C**

Studies of individuals with serious mental illness, particularly schizophrenia and other thought disorders, show significantly increased rates of type 2 diabetes (274). People with schizophrenia should be monitored for type 2 diabetes because of the known comorbidity. Disordered thinking and judgment can be expected to make it difficult to engage in behavior that reduces risk factors for type 2 diabetes, such as restrained eating for weight management. Coordinated management of diabetes or prediabetes and serious mental illness is recommended to achieve diabetes treatment targets. In addition, those taking second-generation (atypical) antipsychotics, such as olanzapine, require greater monitoring because of an increase in risk of type 2 diabetes associated with this medication (275–277). Because of this increased risk, people should be screened for prediabetes or diabetes 4 months after medication initiation and at least annually thereafter. Serious mental illness is often associated with the inability to evaluate and utilize information to make judgments about treatment options. When a person has an established diagnosis of a mental illness that impacts judgment, activities of daily living, and ability to establish a collaborative relationship with care providers, it is wise to include a nonmedical caretaker in decision-making regarding the medical regimen. This person can help improve the patient's ability to follow the agreed-upon regimen through both monitoring and caretaking functions (278).

References

1. Young-Hyman D, de Groot M, Hill-Briggs F, Gonzalez JS, Hood K, Peyrot M. Psychosocial care for people with diabetes: a position statement of the American Diabetes Association. Diabetes Care 2016;39:2126–2140
2. Powers MA, Bardsley JK, Cypress M, et al. Diabetes self-management education and support in adults with type 2 diabetes: a consensus report of the American Diabetes Association, the Association of Diabetes Care & Education Specialists, the Academy of Nutrition and Dietetics, the American Academy of Family Physicians, the American Academy of PAs, the American Association of Nurse Practitioners, and the American Pharmacists Association. Diabetes Care 2020;43:1636–1649
3. Rutten GEHM, Alzaid A. Person-centred type 2 diabetes care: time for a paradigm shift. Lancet Diabetes Endocrinol 2018;6:264–266
4. Dickinson JK, Guzman SJ, Maryniuk MD, et al. The use of language in diabetes care and education. Diabetes Care 2017;40:1790–1799
5. Fisher L, Hessler D, Glasgow RE, et al. REDEEM: a pragmatic trial to reduce diabetes distress. Diabetes Care 2013;36:2551–2558
6. Huang Y, Wei X, Wu T, Chen R, Guo A. Collaborative care for patients with depression and diabetes mellitus: a systematic review and meta-analysis. BMC Psychiatry 2013;13:260
7. Hill-Briggs F. Problem solving in diabetes self-management: a model of chronic illness self-management behavior. Ann Behav Med 2003;25:182–193
8. Fitzpatrick SL, Golden SH, Stewart K, et al. Effect of DECIDE (Decision-making Education for Choices In Diabetes Everyday) program delivery modalities on clinical and behavioral outcomes in urban African Americans with type 2 diabetes: a randomized trial. Diabetes Care 2016;39:2149–2157
9. Brunisholz KD, Briot P, Hamilton S, et al. Diabetes self-management education improves quality of care and clinical outcomes determined by a diabetes bundle measure. J Multidiscip Healthc 2014;7:533–542
10. Dickinson JK, Maryniuk MD. Building therapeutic relationships: choosing words that put people first. Clin Diabetes 2017;35:51–54
11. Beck J, Greenwood DA, Blanton L, et al.; 2017 Standards Revision Task Force. 2017 National Standards for Diabetes Self-Management Education and Support. Diabetes Care 2017;40:1409–1419
12. Tang TS, Funnell MM, Brown MB, Kurlander JE. Self-management support in "real-world" settings: an empowerment-based intervention. Patient Educ Couns 2010;79:178–184
13. Marrero DG, Ard J, Delamater AM, et al. Twenty-first century behavioral medicine: a context for empowering clinicians and patients with diabetes: a consensus report. Diabetes Care 2013;36:463–470
14. Norris SL, Lau J, Smith SJ, Schmid CH, Engelgau MM. Self-management education for adults with type 2 diabetes: a meta-analysis of the effect on glycemic control. Diabetes Care 2002;25:1159–1171
15. Haas L, Maryniuk M, Beck J, et al.; 2012 Standards Revision Task Force. National Standards for Diabetes Self-Management Education and Support. Diabetes Care 2013;37(Suppl. 1):S144–S153
16. Frosch DL, Uy V, Ochoa S, Mangione CM. Evaluation of a behavior support intervention for patients with poorly controlled diabetes. Arch Intern Med 2011;171:2011–2017
17. Cooke D, Bond R, Lawton J, et al.; U.K. NIHR DAFNE Study Group. Structured type 1 diabetes education delivered within routine care: impact on glycemic control and diabetes-specific quality of life. Diabetes Care 2013;36:270–272
18. Chrvala CA, Sherr D, Lipman RD. Diabetes self-management education for adults with type 2 diabetes mellitus: a systematic review of the effect on glycemic control. Patient Educ Couns 2016;99:926–943
19. Marincic PZ, Salazar MV, Hardin A, et al. Diabetes self-management education and medical nutrition therapy: a multisite study documenting the efficacy of registered dietitian nutritionist interventions in the management of glycemic control and diabetic dyslipidemia through retrospective chart review. J Acad Nutr Diet 2019;119:449–463
20. Steinsbekk A, Rygg LØ, Lisulo M, Rise MB, Fretheim A. Group based diabetes self-management education compared to routine treatment for people with type 2 diabetes mellitus. A systematic review with meta-analysis. BMC Health Serv Res 2012;12:213
21. Deakin T, McShane CE, Cade JE, Williams RDRR. Group based training for self-management strategies in people with type 2 diabetes mellitus. Cochrane Database Syst Rev 20052:CD003417
22. Cochran J, Conn VS. Meta-analysis of quality of life outcomes following diabetes self-management training. Diabetes Educ 2008;34:815–823
23. He X, Li J, Wang B, et al. Diabetes self-management education reduces risk of all-cause mortality in type 2 diabetes patients: a systematic review and meta-analysis. Endocrine 2017;55:712–731
24. Thorpe CT, Fahey LE, Johnson H, Deshpande M, Thorpe JM, Fisher EB. Facilitating healthy coping in patients with diabetes: a systematic review. Diabetes Educ 2013;39:33–52
25. Robbins JM, Thatcher GE, Webb DA, Valdmanis VG. Nutritionist visits, diabetes classes, and hospitalization rates and charges: the Urban Diabetes Study. Diabetes Care 2008;31:655–660
26. Duncan I, Ahmed T, Li QE, et al. Assessing the value of the diabetes educator. Diabetes Educ 2011;37:638–657
27. Strawbridge LM, Lloyd JT, Meadow A, Riley GF, Howell BL. One-year outcomes of diabetes self-management training among Medicare beneficiaries newly diagnosed with diabetes. Med Care 2017;55:391–397
28. Piatt GA, Anderson RM, Brooks MM, et al. 3-year follow-up of clinical and behavioral improvements following a multifaceted diabetes care intervention: results of a randomized controlled trial. Diabetes Educ 2010;36:301–309
29. Glazier RH, Bajcar J, Kennie NR, Willson K. A systematic review of interventions to improve diabetes care in socially disadvantaged populations. Diabetes Care 2006;29:1675–1688
30. Hawthorne K, Robles Y, Cannings-John R, Edwards AGK. Culturally appropriate health education for type 2 diabetes mellitus in ethnic minority groups. Cochrane Database Syst Rev 1996;3:CD006424
31. Chodosh J, Morton SC, Mojica W, et al. Meta-analysis: chronic disease self-management programs for older adults. Ann Intern Med 2005;143:427–438
32. Sarkisian CA, Brown AF, Norris KC, Wintz RL, Mangione CM. A systematic review of diabetes

self-care interventions for older, African American, or Latino adults. Diabetes Educ 2003;29:467–479
33. Peyrot M, Rubin RR. Behavioral and psychosocial interventions in diabetes: a conceptual review. Diabetes Care 2007;30:2433–2440
34. Naik AD, Palmer N, Petersen NJ, et al. Comparative effectiveness of goal setting in diabetes mellitus group clinics: randomized clinical trial. Arch Intern Med 2011;171:453–459
35. Duke S-AS, Colagiuri S, Colagiuri R. Individual patient education for people with type 2 diabetes mellitus. Cochrane Database Syst Rev 2009;1:CD005268
36. Odgers-Jewell K, Ball LE, Kelly JT, Isenring EA, Reidlinger DP, Thomas R. Effectiveness of group-based self-management education for individuals with type 2 diabetes: a systematic review with meta-analyses and meta-regression. Diabet Med 2017;34:1027–1039
37. Pereira K, Phillips B, Johnson C, Vorderstrasse A. Internet delivered diabetes self-management education: a review. Diabetes Technol Ther 2015;17:55–63
38. Sepah SC, Jiang L, Peters AL. Long-term outcomes of a web-based diabetes prevention program: 2-year results of a single-arm longitudinal study. J Med Internet Res 2015;17:e92
39. Greenwood DA, Gee PM, Fatkin KJ, Peeples M. A systematic review of reviews evaluating technology-enabled diabetes self-management education and support. J Diabetes Sci Technol 2017;11:1015–1027
40. Athinarayanan SJ, Adams RN, Hallberg SJ, et al. Long-term effects of a novel continuous remote care intervention including nutritional ketosis for the management of type 2 diabetes: a 2-year non-randomized clinical trial. Front Endocrinol (Lausanne) 2019;10:348
41. Kumar S, Moseson H, Uppal J, Juusola JL. A diabetes mobile app with in-app coaching from a certified diabetes educator reduces A1C for individuals with type 2 diabetes. Diabetes Educ 2018;44:226–236
42. Hallberg SJ, McKenzie AL, Williams PT, et al. Effectiveness and safety of a novel care model for the management of type 2 diabetes at 1 year: an open-label, non-randomized, controlled study. Diabetes Ther 2018;9:583–612
43. Xu T, Pujara S, Sutton S, Rhee M Telemedicine in the management of type 1 diabetes. Prev Chronic Dis 2018;15:E13
44. van Eikenhorst L, Taxis K, van Dijk L, de Gier H. Pharmacist-led self-management interventions to improve diabetes outcomes. A systematic literature review and meta-analysis. Front Pharmacol 2017;8:891
45. Tshiananga JKT, Kocher S, Weber C, Erny-Albrecht K, Berndt K, Neeser K. The effect of nurse-led diabetes self-management education on glycosylated hemoglobin and cardiovascular risk factors: a meta-analysis. Diabetes Educ 2012;38:108–123
46. Evert AB, Dennison M, Gardner CD, et al. Nutrition therapy for adults with diabetes or prediabetes: a consensus report. Diabetes Care 2019;42:731–754
47. Shah M, Kaselitz E, Heisler M. The role of community health workers in diabetes: update on current literature. Curr Diab Rep 2013;13:163–171
48. Spencer MS, Kieffer EC, Sinco B, et al. Outcomes at 18 months from a community health worker and peer leader diabetes self-management program for Latino adults. Diabetes Care 2018;41:1414–1422
49. Heisler M, Vijan S, Makki F, Piette JD. Diabetes control with reciprocal peer support versus nurse care management: a randomized trial. Ann Intern Med 2010;153:507–515
50. Long JA, Jahnle EC, Richardson DM, Loewenstein G, Volpp KG. Peer mentoring and financial incentives to improve glucose control in African American veterans: a randomized trial. Ann Intern Med 2012;156:416–424
51. Fisher EB, Boothroyd RI, Elstad EA, et al. Peer support of complex health behaviors in prevention and disease management with special reference to diabetes: systematic reviews. Clin Diabetes Endocrinol 2017;3:4
52. Foster G, Taylor SJC, Eldridge SE, Ramsay J, Griffiths CJ. Self-management education programmes by lay leaders for people with chronic conditions. Cochrane Database Syst Rev 2007;4:CD005108
53. Duncan I, Birkmeyer C, Coughlin S, Li QE, Sherr D, Boren S. Assessing the value of diabetes education. Diabetes Educ 2009;35:752–760
54. Johnson TM, Murray MR, Huang Y. Associations between self-management education and comprehensive diabetes clinical care. Diabetes Spectr 2010;23:41–46
55. Strawbridge LM, Lloyd JT, Meadow A, Riley GF, Howell BL. Use of Medicare's diabetes self-management training benefit. Health Educ Behav 2015;42:530–538
56. Horigan G, Davies M, Findlay-White F, Chaney D, Coates V. Reasons why patients referred to diabetes education programmes choose not to attend: a systematic review. Diabet Med 2017;34:14–26
57. Carey ME, Agarwal S, Horne R, Davies M, Slevin M, Coates V. Exploring organizational support for the provision of structured self-management education for people with type 2 diabetes: findings from a qualitative study. Diabet Med 2019;36:761–770
58. Greenwood DA, Howell F, Scher L, et al. A framework for optimizing technology-enabled diabetes and cardiometabolic care and education: the role of the diabetes care and education specialist. Diabetes Educ 2020;46:315–322
59. Isaacs D, Cox C, Schwab K, et al. Technology integration: the role of the diabetes care and education specialist in practice. Diabetes Educ 2020;46:323–334
60. Center for Health Law and Policy Innovation. Reconsidering cost-sharing for diabetes self-management education: recommendations for policy reform. Accessed 25 October 2020. Available from https://www.chlpi.org/health_library/reconsidering-cost-sharing-diabetes-self-management-education-recommendations-policy-reform/
61. Turner RM, Ma Q, Lorig K, Greenberg J, DeVries AR. Evaluation of a diabetes self-management program: claims analysis on comorbid illnesses, health care utilization, and cost. J Med Internet Res 2018;20:e207
62. Centers for Medicare & Medicaid Services. COVID-19 Frequently Asked Questions (FAQs) on Medicare Fee-for-Service (FFS) Billing. Accessed 25 October 2020. Available from https://www.cms.gov/files/document/03092020-covid-19-faqs-508.pdf
63. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669–2701
64. Briggs Early K, Stanley K. Position of the Academy of Nutrition and Dietetics: the role of medical nutrition therapy and registered dietitian nutritionists in the prevention and treatment of prediabetes and type 2 diabetes. J Acad Nutr Diet 2018;118:343–353
65. Franz MJ, MacLeod J, Evert A, et al. Academy of Nutrition and Dietetics Nutrition practice guideline for type 1 and type 2 diabetes in adults: systematic review of evidence for medical nutrition therapy effectiveness and recommendations for integration into the nutrition care process. J Acad Nutr Diet 2017;117:1659–1679
66. MacLeod J, Franz MJ, Handu D, et al. Academy of Nutrition and Dietetics Nutrition practice guideline for type 1 and type 2 diabetes in adults: nutrition intervention evidence reviews and recommendations. J Acad Nutr Diet 2017;117:1637–1658
66a. Grotz VL, Pi-Sunyer X, Porte D, Roberts A, Richard Trout J. A 12-week randomized clinical trial investigating the potential for sucralose to affect glucose homeostasis. Regul Toxicol Pharmacol 2017;88:22–33
67. Schwingshackl L, Chaimani A, Hoffmann G, Schwedhelm C, Boeing H. A network meta-analysis on the comparative efficacy of different dietary approaches on glycaemic control in patients with type 2 diabetes mellitus. Eur J Epidemiol 2018;33:157–170
68. Schwingshackl L, Schwedhelm C, Hoffmann G, et al. Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr 2017;105:1462–1473
69. Benson G, Hayes J. An update on the Mediterranean, vegetarian, and DASH eating patterns in people with type 2 diabetes. Diabetes Spectr 2020;33:125–132
70. Esposito K, Maiorino MI, Ciotola M, et al. Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: a randomized trial. Ann Intern Med 2009;151:306–314
71. de Carvalho GB, Dias-Vasconcelos NL, Santos RKF, Brandão-Lima PN, da Silva DG, Pires LV. Effect of different dietary patterns on glycemic control in individuals with type 2 diabetes mellitus: a systematic review. Crit Rev Food Sci Nutr 2020;60:1999–2010
72. Papamichou D, Panagiotakos DB, Itsiopoulos C. Dietary patterns and management of type 2 diabetes: a systematic review of randomised clinical trials. Nutr Metab Cardiovasc Dis 2019;29:531–543
73. Sainsbury E, Kizirian NV, Partridge SR, Gill T, Colagiuri S, Gibson AA. Effect of dietary carbohydrate restriction on glycemic control in adults with diabetes: a systematic review and meta-analysis. Diabetes Res Clin Pract 2018;139:239–252
74. van Zuuren EJ, Fedorowicz Z, Kuijpers T, Pijl H. Effects of low-carbohydrate- compared with low-fat-diet interventions on metabolic control in people with type 2 diabetes: a systematic

review including GRADE assessments. Am J Clin Nutr 2018;108:300–331
75. Snorgaard O, Poulsen GM, Andersen HK, Astrup A. Systematic review and meta-analysis of dietary carbohydrate restriction in patients with type 2 diabetes. BMJ Open Diabetes Res Care 2017;5:e000354
76. Rinaldi S, Campbell EE, Fournier J, O'Connor C, Madill J. A comprehensive review of the literature supporting recommendations from the Canadian Diabetes Association for the use of a plant-based diet for management of type 2 diabetes. Can J Diabetes 2016;40:471–477
77. Pawlak R. Vegetarian diets in the prevention and management of diabetes and its complications. Diabetes Spectr 2017;30:82–88
78. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections. Accessed 25 October 2020. Available from https://www.fda.gov/Drugs/DrugSafety/ucm475463.htm
79. Blau JE, Tella SH, Taylor SI, Rother KI. Ketoacidosis associated with SGLT2 inhibitor treatment: analysis of FAERS data. Diabetes Metab Res Rev 2017;33
80. Bowen ME, Cavanaugh KL, Wolff K, et al. The diabetes nutrition education study randomized controlled trial: a comparative effectiveness study of approaches to nutrition in diabetes self-management education. Patient Educ Couns 2016;99:1368–1376
81. Mudaliar U, Zabetian A, Goodman M, et al. Cardiometabolic risk factor changes observed in diabetes prevention programs in US settings: a systematic review and meta-analysis. PLoS Med 2016;13:e1002095
82. Balk EM, Earley A, Raman G, Avendano EA, Pittas AG, Remington PL. Combined diet and physical activity promotion programs to prevent type 2 diabetes among persons at increased risk: a systematic review for the Community Preventive Services Task Force. Ann Intern Med 2015;163:437–451
83. Hamman RF, Wing RR, Edelstein SL, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. Diabetes Care 2006;29:2102–2107
84. Garvey WT, Ryan DH, Bohannon NJV, et al. Weight-loss therapy in type 2 diabetes: effects of phentermine and topiramate extended release. Diabetes Care 2014;37:3309–3316
85. Kahan S, Fujioka K. Obesity pharmacotherapy in patients with type 2 diabetes. Diabetes Spectr 2017;30:250–257
86. Jeon CY, Lokken RP, Hu FB, van Dam RM. Physical activity of moderate intensity and risk of type 2 diabetes: a systematic review. Diabetes Care 2007;30:744–752
87. Duncan GE, Perri MG, Theriaque DW, Hutson AD, Eckel RH, Stacpoole PW. Exercise training, without weight loss, increases insulin sensitivity and postheparin plasma lipase activity in previously sedentary adults. Diabetes Care 2003;26:557–562
88. Franz MJ, Boucher JL, Rutten-Ramos S, VanWormer JJ. Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta-analysis of randomized clinical trials. J Acad Nutr Diet 2015;115:1447–1463
89. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet 2018;391:541–551
90. Wing RR, Lang W, Wadden TA, et al.; Look AHEAD Research Group. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care 2011;34:1481–1486
91. Sjöström L, Peltonen M, Jacobson P, et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. JAMA 2014;311:2297–2304
92. Cefalu WT, Leiter LA, de Bruin TWA, Gause-Nilsson I, Sugg J, Parikh SJ. Dapagliflozin's effects on glycemia and cardiovascular risk factors in high-risk patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension. Diabetes Care 2015;38:1218–1227
93. Prinz N, Schwandt A, Becker M, et al. Trajectories of body mass index from childhood to young adulthood among patients with type 1 diabetes—a longitudinal group-based modeling approach based on the DPV Registry. J Pediatr 2018;201:78–85.e4
94. Lipman TH, Levitt Katz LE, Ratcliffe SJ, et al. Increasing incidence of type 1 diabetes in youth: twenty years of the Philadelphia Pediatric Diabetes Registry. Diabetes Care 2013;36:1597–1603
95. Sumithran P, Prendergast LA, Delbridge E, et al. Long-term persistence of hormonal adaptations to weight loss. N Engl J Med 2011;365:1597–1604
96. Hamdy O, Mottalib A, Morsi A, et al. Long-term effect of intensive lifestyle intervention on cardiovascular risk factors in patients with diabetes in real-world clinical practice: a 5-year longitudinal study. BMJ Open Diabetes Res Care 2017;5:e000259
97. Mottalib A, Salsberg V, Mohd-Yusof B-N, et al. Effects of nutrition therapy on HbA1c and cardiovascular disease risk factors in overweight and obese patients with type 2 diabetes. Nutr J 2018;17:42
98. Estruch R, Ros E, Salas-Salvadó J, et al.; PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med 2018;378:e34
99. Saslow LR, Daubenmier JJ, Moskowitz JT, et al. Twelve-month outcomes of a randomized trial of a moderate-carbohydrate versus very low-carbohydrate diet in overweight adults with type 2 diabetes mellitus or prediabetes. Nutr Diabetes 2017;7:304
100. Yancy WS Jr, Crowley MJ, Dar MS, et al. Comparison of group medical visits combined with intensive weight management vs group medical visits alone for glycemia in patients with type 2 diabetes: a noninferiority randomized clinical trial. JAMA Intern Med 2019;180:70–79
101. Emadian A, Andrews RC, England CY, Wallace V, Thompson JL. The effect of macronutrients on glycaemic control: a systematic review of dietary randomised controlled trials in overweight and obese adults with type 2 diabetes in which there was no difference in weight loss between treatment groups. Br J Nutr 2015;114:1656–1666
102. Gardner CD, Trepanowski JF, Del Gobbo LC, et al. Effect of low-fat vs low-carbohydrate diet on 12-month weight loss in overweight adults and the association with genotype pattern or insulin secretion: the DIETFITS randomized clinical trial. JAMA 2018;319:667–679
103. Korsmo-Haugen H-K, Brurberg KG, Mann J, Aas A-M. Carbohydrate quantity in the dietary management of type 2 diabetes: a systematic review and meta-analysis. Diabetes Obes Metab 2019;21:15–27
104. Sacks FM, Bray GA, Carey VJ, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med 2009;360:859–873
105. de Souza RJ, Bray GA, Carey VJ, et al. Effects of 4 weight-loss diets differing in fat, protein, and carbohydrate on fat mass, lean mass, visceral adipose tissue, and hepatic fat: results from the POUNDS LOST trial. Am J Clin Nutr 2012;95:614–625
106. Johnston BC, Kanters S, Bandayrel K, et al. Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. JAMA 2014;312:923–933
107. Fox CS, Golden SH, Anderson C, et al.; American Heart Association Diabetes Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council on Cardiovascular Surgery and Anesthesia, Council on Quality of Care and Outcomes Research; American Diabetes Association. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care 2015;38:1777–1803
108. DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. BMJ 2002;325:746
109. Delahanty LM, Nathan DM, Lachin JM, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications. Association of diet with glycated hemoglobin during intensive treatment of type 1 diabetes in the Diabetes Control and Complications Trial. Am J Clin Nutr 2009;89:518–524
110. Zafar MI, Mills KE, Zheng J, et al. Low-glycemic index diets as an intervention for diabetes: a systematic review and meta-analysis. Am J Clin Nutr 2019;110:891–902
111. Wheeler ML, Dunbar SA, Jaacks LM, et al. Macronutrients, food groups, and eating patterns in the management of diabetes: a systematic review of the literature, 2010. Diabetes Care 2012;35:434–445
112. Vega-López S, Venn BJ, Slavin JL. Relevance of the glycemic index and glycemic load for body weight, diabetes, and cardiovascular disease. Nutrients 2018;10:E1361
113. Thomas D, Elliott EJ. Low glycaemic index, or low glycaemic load, diets for diabetes mellitus. Cochrane Database Syst Rev 2009;1:CD006296
114. Meng Y, Bai H, Wang S, Li Z, Wang Q, Chen L. Efficacy of low carbohydrate diet for type 2 diabetes mellitus management: a systematic

review and meta-analysis of randomized controlled trials. Diabetes Res Clin Pract 2017;131:124–131
115. Kirkpatrick CF, Bolick JP, Kris-Etherton PM, et al. Review of current evidence and clinical recommendations on the effects of low-carbohydrate and very-low-carbohydrate (including ketogenic) diets for the management of body weight and other cardiometabolic risk factors: a scientific statement from the National Lipid Association Nutrition and Lifestyle Task Force. J Clin Lipidol 2019;13:689–711.e1
116. Tay J, Luscombe-Marsh ND, Thompson CH, et al. Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial. Am J Clin Nutr 2015;102:780–790
117. Turton JL, Raab R, Rooney KB. Low-carbohydrate diets for type 1 diabetes mellitus: a systematic review. PLoS One 2018;13:e0194987
118. U.S. Department of Agriculture and U.S. Department of Health and Human Services. Dietary guidelines for Americans 2015-2020, Eighth Edition, 2015. Accessed 25 October 2020. Available from https://health.gov/dietaryguidelines/2015/guidelines/
119. He M, van Dam RM, Rimm E, Hu FB, Qi L. Whole-grain, cereal fiber, bran, and germ intake and the risks of all-cause and cardiovascular disease-specific mortality among women with type 2 diabetes mellitus. Circulation 2010;121:2162–2168
120. Burger KNJ, Beulens JWJ, van der Schouw YT, et al. Dietary fiber, carbohydrate quality and quantity, and mortality risk of individuals with diabetes mellitus. PLoS One 2012;7:e43127
121. Partula V, Deschasaux M, Druesne-Pecollo N, et al.; The Milieu Intérieur Consortium. Associations between consumption of dietary fibers and the risk of cardiovascular diseases, cancers, type 2 diabetes, and mortality in the prospective NutriNet-Santé cohort. Am J Clin Nutr 2020;112:195–207
122. Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te Morenga L. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. Lancet 2019;393:434–445
123. Nansel TR, Lipsky LM, Liu A. Greater diet quality is associated with more optimal glycemic control in a longitudinal study of youth with type 1 diabetes. Am J Clin Nutr 2016;104:81–87
124. Katz ML, Mehta S, Nansel T, Quinn H, Lipsky LM, Laffel LMB. Associations of nutrient intake with glycemic control in youth with type 1 diabetes: differences by insulin regimen. Diabetes Technol Ther 2014;16:512–518
125. Rossi MCE, Nicolucci A, Di Bartolo P, et al. Diabetes Interactive Diary: a new telemedicine system enabling flexible diet and insulin therapy while improving quality of life: an open-label, international, multicenter, randomized study. Diabetes Care 2010;33:109–115
126. Laurenzi A, Bolla AM, Panigoni G, et al. Effects of carbohydrate counting on glucose control and quality of life over 24 weeks in adult patients with type 1 diabetes on continuous subcutaneous insulin infusion: a randomized, prospective clinical trial (GIOCAR). Diabetes Care 2011;34:823–827
127. Sämann A, Mühlhauser I, Bender R, Kloos Ch, Müller UA. Glycaemic control and severe hypoglycaemia following training in flexible, intensive insulin therapy to enable dietary freedom in people with type 1 diabetes: a prospective implementation study. Diabetologia 2005;48:1965–1970
128. Bell KJ, Barclay AW, Petocz P, Colagiuri S, Brand-Miller JC. Efficacy of carbohydrate counting in type 1 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2014;2:133–140
129. Bell KJ, Toschi E, Steil GM, Wolpert HA. Optimized mealtime insulin dosing for fat and protein in type 1 diabetes: application of a model-based approach to derive insulin doses for open-loop diabetes management. Diabetes Care 2016;39:1631–1634
130. Campbell MD, Walker M, King D, et al. Carbohydrate counting at meal time followed by a small secondary postprandial bolus injection at 3 hours prevents late hyperglycemia, without hypoglycemia, after a high-carbohydrate, high-fat meal in type 1 diabetes. Diabetes Care 2016;39:e141–e142
131. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Diabetes Care 2014;37:2864–2883
132. Ley SH, Hamdy O, Mohan V, Hu FB. Prevention and management of type 2 diabetes: dietary components and nutritional strategies. Lancet 2014;383:1999–2007
133. Pan Y, Guo LL, Jin HM. Low-protein diet for diabetic nephropathy: a meta-analysis of randomized controlled trials. Am J Clin Nutr 2008;88:660–666
134. Robertson L, Waugh N, Robertson A. Protein restriction for diabetic renal disease. Cochrane Database Syst Rev 2007;4:CD002181
135. Layman DK, Clifton P, Gannon MC, Krauss RM, Nuttall FQ. Protein in optimal health: heart disease and type 2 diabetes. Am J Clin Nutr 2008;87:1571S–1575S
136. Ros E. Dietary cis-monounsaturated fatty acids and metabolic control in type 2 diabetes. Am J Clin Nutr 2003;78(Suppl.):617S–625S
137. Forouhi NG, Imamura F, Sharp SJ, et al. Association of plasma phospholipid n-3 and n-6 polyunsaturated fatty acids with type 2 diabetes: the EPIC-InterAct case-cohort study. PLoS Med 2016;13:e1002094
138. Wang DD, Li Y, Chiuve SE, et al. Association of specific dietary fats with total and cause-specific mortality. JAMA Intern Med 2016;176:1134–1145
139. Brehm BJ, Lattin BL, Summer SS, et al. One-year comparison of a high-monounsaturated fat diet with a high-carbohydrate diet in type 2 diabetes. Diabetes Care 2009;32:215–220
140. Shai I, Schwarzfuchs D, Henkin Y, et al.; Dietary Intervention Randomized Controlled Trial (DIRECT) Group. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med 2008;359:229–241
141. Brunerova L, Smejkalova V, Potockova J, Andel M. A comparison of the influence of a high-fat diet enriched in monounsaturated fatty acids and conventional diet on weight loss and metabolic parameters in obese non-diabetic and type 2 diabetic patients. Diabet Med 2007;24:533–540
142. Bloomfield HE, Koeller E, Greer N, MacDonald R, Kane R, Wilt TJ. Effects on health outcomes of a Mediterranean Diet with no restriction on fat intake: a systematic review and meta-analysis. Ann Intern Med 2016;165:491–500
143. Sacks FM, Lichtenstein AH, Wu JHY, et al.; American Heart Association. Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. Circulation 2017;136:e1–e23
144. Jacobson TA, Maki KC, Orringer CE, et al.; NLA Expert Panel. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 2. J Clin Lipidol 2015;9:S1–S122.e1
145. Holman RR, Paul S, Farmer A, Tucker L, Stratton IM, Neil HA; Atorvastatin in Factorial with Omega-3 EE90 Risk Reduction in Diabetes Study Group. Atorvastatin in Factorial with Omega-3 EE90 Risk Reduction in Diabetes (AFORRD): a randomised controlled trial. Diabetologia 2009;52:50–59
146. Bosch J, Gerstein HC, Dagenais GR, et al.; ORIGIN Trial Investigators. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. N Engl J Med 2012;367:309–318
147. Brown TJ, Brainard J, Song F, Wang X, Abdelhamid A, Hooper L; PUFAH Group. Omega-3, omega-6, and total dietary polyunsaturated fat for prevention and treatment of type 2 diabetes mellitus: systematic review and meta-analysis of randomised controlled trials. BMJ 2019;366:l4697
148. ASCEND Study Collaborative Group; Bowman L, Mafham M, Wallendszus K, et al. Effects of n-3 fatty acid supplements in diabetes mellitus. N Engl J Med 2018;379:1540–1550
149. Bhatt DL, Steg PG, Miller M, et al.; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med 2019;380:11–22
150. Thomas MC, Moran J, Forsblom C, et al.; FinnDiane Study Group. The association between dietary sodium intake, ESRD, and all-cause mortality in patients with type 1 diabetes. Diabetes Care 2011;34:861–866
151. Ekinci EI, Clarke S, Thomas MC, et al. Dietary salt intake and mortality in patients with type 2 diabetes. Diabetes Care 2011;34:703–709
152. Lennon SL, DellaValle DM, Rodder SG, et al. 2015 Evidence Analysis Library evidence-based nutrition practice guideline for the management of hypertension in adults. J Acad Nutr Diet 2017;117:1445–1458.e17
153. Maillot M, Drewnowski A. A conflict between nutritionally adequate diets and meeting the 2010 dietary guidelines for sodium. Am J Prev Med 2012;42:174–179
154. Aroda VR, Edelstein SL, Goldberg RB, et al.; Diabetes Prevention Program Research Group. Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes Study. J Clin Endocrinol Metab 2016;101:1754–1761
155. Allen RW, Schwartzman E, Baker WL, Coleman CI, Phung OJ. Cinnamon use in type 2 diabetes: an updated systematic review and meta-analysis. Ann Fam Med 2013;11:452–459
156. Mitri J, Pittas AG. Vitamin D and diabetes. Endocrinol Metab Clin North Am 2014;43:205–232
157. Mozaffarian D. Dietary and policy priorities for cardiovascular disease, diabetes, and obesity:

a comprehensive review. Circulation 2016;133:187–225
158. National Agricultural Library, U.S. Department of Agriculture. Nutritive and Nonnutritive Sweetener Resources. Accessed 20 September 2020. Available from https://www.nal.usda.gov/fnic/nutritive-and-nonnutritive-sweetener-resources
159. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;140:e596–e646
160. Johnson RK, Lichtenstein AH, Anderson CAM, et al.; American Heart Association Nutrition Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Quality of Care and Outcomes Research; Stroke Council. Low-calorie sweetened beverages and cardiometabolic health: a science advisory from the American Heart Association. Circulation 2018;138:e126–e140
161. Miller PE, Perez V. Low-calorie sweeteners and body weight and composition: a meta-analysis of randomized controlled trials and prospective cohort studies. Am J Clin Nutr 2014;100:765–777
162. Rogers PJ, Hogenkamp PS, de Graaf C, et al. Does low-energy sweetener consumption affect energy intake and body weight? A systematic review, including meta-analyses, of the evidence from human and animal studies. Int J Obes 2016;40:381–394
163. Azad MB, Abou-Setta AM, Chauhan BF, et al. Nonnutritive sweeteners and cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials and prospective cohort studies. CMAJ 2017;189:E929–E939
163a. Mattes RD, Popkin BM. Nonnutritive sweetener consumption in humans: effects on appetite and food intake and their putative mechanisms. Am J Clin Nutr 2009;89:1–14
164. Hirahatake KM, Jacobs DR, Shikany JM, et al. Cumulative intake of artificially sweetened and sugar-sweetened beverages and risk of incident type 2 diabetes in young adults: the Coronary Artery Risk Development In Young Adults (CARDIA) Study. Am J Clin Nutr 2019;110:733–741
165. Löfvenborg JE, Andersson T, Carlsson P-O, et al. Sweetened beverage intake and risk of latent autoimmune diabetes in adults (LADA) and type 2 diabetes. Eur J Endocrinol 2016;175:605–614
166. Daher MI, Matta JM, Abdel Nour AM. Nonnutritive sweeteners and type 2 diabetes: should we ring the bell? Diabetes Res Clin Pract 2019;155:107786
167. 2018 Physical Activity Guidelines Advisory Committee. *2018 Physical Activity Guidelines Advisory Committee Scientific Report*. Washington, DC, U.S. Department of Health and Human Services, 2018
168. Bazargan-Hejazi S, Arroyo JS, Hsia S, Brojeni NR, Pan D. A racial comparison of differences between self-reported and objectively measured physical activity among US adults with diabetes. Ethn Dis 2017;27:403–410
169. Sluik D, Buijsse B, Muckelbauer R, et al. Physical activity and mortality in individuals with diabetes mellitus: a prospective study and meta-analysis. Arch Intern Med 2012;172:1285–1295
170. Tikkanen-Dolenc H, Wadén J, Forsblom C, et al.; FinnDiane Study Group. Physical activity reduces risk of premature mortality in patients with type 1 diabetes with and without kidney disease. Diabetes Care 2017;40:1727–1732
171. Boulé NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. JAMA 2001;286:1218–1227
172. Peters AL, Laffel L (Eds.). *American Diabetes Association/JDRF Type 1 Diabetes Sourcebook*. Alexandria, VA, American Diabetes Association, 2013
173. Ostman C, Jewiss D, King N, Smart NA. Clinical outcomes to exercise training in type 1 diabetes: a systematic review and meta-analysis. Diabetes Res Clin Pract 2018;139:380–391
174. Boulé NG, Kenny GP, Haddad E, Wells GA, Sigal RJ. Meta-analysis of the effect of structured exercise training on cardiorespiratory fitness in type 2 diabetes mellitus. Diabetologia 2003;46:1071–1081
175. Pandey A, Patel KV, Bahnson JL, et al.; Look AHEAD Research Group. Association of intensive lifestyle intervention, fitness, and body mass index with risk of heart failure in overweight or obese adults with type 2 diabetes mellitus: an analysis from the Look AHEAD trial. Circulation 2020;141:1295–1306
176. Rejeski WJ, Ip EH, Bertoni AG, et al.; Look AHEAD Research Group. Lifestyle change and mobility in obese adults with type 2 diabetes. N Engl J Med 2012;366:1209–1217
177. Colberg SR, Sigal RJ, Yardley JE, et al. Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. Diabetes Care 2016;39:2065–2079
178. Janssen I, Leblanc AG. Systematic review of the health benefits of physical activity and fitness in school-aged children and youth. Int J Behav Nutr Phys Act 2010;7:40
179. Riddell MC, Gallen IW, Smart CE, et al. Exercise management in type 1 diabetes: a consensus statement. Lancet Diabetes Endocrinol 2017;5:377–390
180. Anderson BJ, Laffel LM, Domenger C, et al. Factors associated with diabetes-specific health-related quality of life in youth with type 1 diabetes: the Global TEENs study. Diabetes Care 2017;40:1002–1009
181. Adolfsson P, Riddell MC, Taplin CE, et al. ISPAD Clinical Practice Consensus Guidelines 2018: exercise in children and adolescents with diabetes. Pediatr Diabetes 2018;19(Suppl. 27):205–226
182. Jelleyman C, Yates T, O'Donovan G, et al. The effects of high-intensity interval training on glucose regulation and insulin resistance: a meta-analysis. Obes Rev 2015;16:942–961
183. Little JP, Gillen JB, Percival ME, et al. Low-volume high-intensity interval training reduces hyperglycemia and increases muscle mitochondrial capacity in patients with type 2 diabetes. J Appl Physiol (1985) 2011;111:1554–1560
184. Bohn B, Herbst A, Pfeifer M, et al.; DPV Initiative. Impact of physical activity on glycemic control and prevalence of cardiovascular risk factors in adults with type 1 diabetes: a cross-sectional multicenter study of 18,028 patients. Diabetes Care 2015;38:1536–1543
185. U.S. Department of Health and Human Services. Physical Activity Guidelines for Americans, 2nd ed. Accessed 25 October 2020. Available from https://health.gov/sites/default/files/2019-09/Physical_Activity_Guidelines_2nd_edition.pdf
186. Willey KA, Singh MAF. Battling insulin resistance in elderly obese people with type 2 diabetes: bring on the heavy weights. Diabetes Care 2003;26:1580–1588
187. Katzmarzyk PT, Church TS, Craig CL, Bouchard C. Sitting time and mortality from all causes, cardiovascular disease, and cancer. Med Sci Sports Exerc 2009;41:998–1005
188. Dempsey PC, Larsen RN, Sethi P, et al. Benefits for type 2 diabetes of interrupting prolonged sitting with brief bouts of light walking or simple resistance activities. Diabetes Care 2016;39:964–972
189. Wang Y, Lee D-C, Brellenthin AG, et al. Leisure-time running reduces the risk of incident type 2 diabetes. Am J Med 2019;132:1225–1232
190. Schellenberg ES, Dryden DM, Vandermeer B, Ha C, Korownyk C. Lifestyle interventions for patients with and at risk for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013;159:543–551
191. Pai L-W, Li T-C, Hwu Y-J, Chang S-C, Chen L-L, Chang P-Y. The effectiveness of regular leisure-time physical activities on long-term glycemic control in people with type 2 diabetes: a systematic review and meta-analysis. Diabetes Res Clin Pract 2016;113:77–85
192. Cui J, Yan J-H, Yan L-M, Pan L, Le J-J, Guo Y-Z. Effects of yoga in adults with type 2 diabetes mellitus: a meta-analysis. J Diabetes Investig 2017;8:201–209
193. Lee MS, Jun JH, Lim H-J, Lim H-S. A systematic review and meta-analysis of tai chi for treating type 2 diabetes. Maturitas 2015;80:14–23
194. Rees JL, Johnson ST, Boulé NG. Aquatic exercise for adults with type 2 diabetes: a meta-analysis. Acta Diabetol 2017;54:895–904
195. Colberg SR, Sigal RJ, Fernhall B, et al.; American College of Sports Medicine; American Diabetes Association. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement executive summary. Diabetes Care 2010;33:2692–2696
196. Church TS, Blair SN, Cocreham S, et al. Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial. JAMA 2010;304:2253–2262
197. Bax JJ, Young LH, Frye RL, Bonow RO, Steinberg HO, Barrett EJ. Screening for coronary artery disease in patients with diabetes. Diabetes Care 2007;30:2729–2736
198. Peters A, Laffel L, Colberg SR, Riddell MC. Physical activity: regulation of glucose metabolism, clinical management strategies, and weight control. In *American Diabetes Association/JDRF*

Type 1 Diabetes Sourcebook. Alexandria, VA, American Diabetes Association, 2013
199. Colberg SR. *Exercise and Diabetes: A Clinician's Guide to Prescribing Physical Activity*. 1st ed. Alexandria, VA, American Diabetes Association, 2013
200. Lemaster JW, Reiber GE, Smith DG, Heagerty PJ, Wallace C. Daily weight-bearing activity does not increase the risk of diabetic foot ulcers. Med Sci Sports Exerc 2003;35:1093–1099
201. Smith AG, Russell J, Feldman EL, et al. Lifestyle intervention for pre-diabetic neuropathy. Diabetes Care 2006;29:1294–1299
202. Spallone V, Ziegler D, Freeman R, et al.; Toronto Consensus Panel on Diabetic Neuropathy. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. Diabetes Metab Res Rev 2011; 27:639–653
203. Pop-Busui R, Evans GW, Gerstein HC, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care 2010;33:1578–1584
204. Suarez L, Barrett-Connor E. Interaction between cigarette smoking and diabetes mellitus in the prediction of death attributed to cardiovascular disease. Am J Epidemiol 1984;120:670–675
205. Stanton CA, Keith DR, Gaalema DE, et al. Trends in tobacco use among US adults with chronic health conditions: National Survey on Drug Use and Health 2005-2013. Prev Med 2016; 92:160–168
206. Bae J. Differences in cigarette use behaviors by age at the time of diagnosis with diabetes from young adulthood to adulthood: results from the National Longitudinal Study of Adolescent Health. J Prev Med Public Health 2013;46: 249–260
207. Śliwińska-Mossoń M, Milnerowicz H. The impact of smoking on the development of diabetes and its complications. Diab Vasc Dis Res 2017;14:265–276
208. Kar D, Gillies C, Zaccardi F, et al. Relationship of cardiometabolic parameters in non-smokers, current smokers, and quitters in diabetes: a systematic review and meta-analysis. Cardiovasc Diabetol 2016;15:158
209. Pan A, Wang Y, Talaei M, Hu FB. Relation of smoking with total mortality and cardiovascular events among patients with diabetes mellitus: a meta-analysis and systematic review. Circulation 2015;132:1795–1804
210. Jankowich M, Choudhary G, Taveira TH, Wu W-C. Age-, race-, and gender-specific prevalence of diabetes among smokers. Diabetes Res Clin Pract 2011;93:e101–e105
211. Akter S, Goto A, Mizoue T. Smoking and the risk of type 2 diabetes in Japan: a systematic review and meta-analysis. J Epidemiol 2017;27: 553–561
212. Liu X, Bragg F, Yang L, et al.; China Kadoorie Biobank Collaborative Group. Smoking and smoking cessation in relation to risk of diabetes in Chinese men and women: a 9-year prospective study of 0·5 million people. Lancet Public Health 2018;3:e167–e176
213. Yeh H-C, Duncan BB, Schmidt MI, Wang N-Y, Brancati FL. Smoking, smoking cessation, and risk for type 2 diabetes mellitus: a cohort study. Ann Intern Med 2010;152:10–17
214. Tonstad S, Lawrence D. Varenicline in smokers with diabetes: a pooled analysis of 15 randomized, placebo-controlled studies of varenicline. J Diabetes Investig 2017;8:93–100
215. West R. Tobacco smoking: health impact, prevalence, correlates and interventions. Psychol Health 2017;32:1018–1036
216. Ranney L, Melvin C, Lux L, McClain E, Lohr KN. Systematic review: smoking cessation intervention strategies for adults and adults in special populations. Ann Intern Med 2006;145:845–856
217. Tian J, Venn A, Otahal P, Gall S. The association between quitting smoking and weight gain: a systematic review and meta-analysis of prospective cohort studies. Obes Rev 2015;16:883–901
218. Clair C, Rigotti NA, Porneala B, et al. Association of smoking cessation and weight change with cardiovascular disease among adults with and without diabetes. JAMA 2013;309:1014–1021
219. Voulgari C, Katsilambros N, Tentolouris N. Smoking cessation predicts amelioration of microalbuminuria in newly diagnosed type 2 diabetes mellitus: a 1-year prospective study. Metabolism 2011;60:1456–1464
220. Huerta TR, Walker DM, Mullen D, Johnson TJ, Ford EW. Trends in e-cigarette awareness and perceived harmfulness in the U.S. Am J Prev Med 2017;52:339–346
221. Pericot-Valverde I, Gaalema DE, Priest JS, Higgins ST. E-cigarette awareness, perceived harmfulness, and ever use among U.S. adults. Prev Med 2017;104:92–99
222. Centers for Disease Control and Prevention. Outbreak of lung injury associated with e-cigarette use, or vaping, products. Accessed 27 October 2020. Available from https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html
223. Reid RD, Malcolm J, Wooding E, et al. Prospective, cluster-randomized trial to implement the Ottawa Model for Smoking Cessation in diabetes education programs in Ontario, Canada. Diabetes Care 2018;41:406–412
224. Anderson RJ, Grigsby AB, Freedland KE, et al. Anxiety and poor glycemic control: a meta-analytic review of the literature. Int J Psychiatry Med 2002;32:235–247
225. Delahanty LM, Grant RW, Wittenberg E, et al. Association of diabetes-related emotional distress with diabetes treatment in primary care patients with type 2 diabetes. Diabet Med 2007; 24:48–54
226. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care 2001;24:1069–1078
227. Nicolucci A, Kovacs Burns K, Holt RIG, et al.; DAWN2 Study Group. Diabetes Attitudes, Wishes and Needs second study (DAWN2™): cross-national benchmarking of diabetes-related psychosocial outcomes for people with diabetes. Diabet Med 2013;30:767–777
228. Ducat L, Philipson LH, Anderson BJ. The mental health comorbidities of diabetes. JAMA 2014;312:691–692
229. Gonzalvo JD, Hamm J, Eaves S, et al. A practical approach to mental health for the diabetes educator. AADE Pract 2019;7:29–44
230. Robinson DJ, Coons M, Haensel H, Vallis M, Yale J-F; Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes and mental health. Can J Diabetes 2018;42(Suppl. 1):S130–S141
231. Harkness E, Macdonald W, Valderas J, Coventry P, Gask L, Bower P. Identifying psychosocial interventions that improve both physical and mental health in patients with diabetes: a systematic review and meta-analysis. Diabetes Care 2010;33:926–930
232. Weissberg-Benchell J, Shapiro JB. A review of interventions aimed at facilitating successful transition planning and transfer to adult care among youth with chronic illness. Pediatr Ann 2017;46:e182–e187
233. O'Gurek DT, Henke C. A practical approach to screening for social determinants of health. Fam Pract Manag 2018;25:7–12
234. Fisher L, Hessler DM, Polonsky WH, Mullan J. When is diabetes distress clinically meaningful?: establishing cut points for the Diabetes Distress Scale. Diabetes Care 2012;35:259–264
235. Fisher L, Glasgow RE, Strycker LA. The relationship between diabetes distress and clinical depression with glycemic control among patients with type 2 diabetes. Diabetes Care 2010;33:1034–1036
236. Aikens JE. Prospective associations between emotional distress and poor outcomes in type 2 diabetes. Diabetes Care 2012;35:2472–2478
237. Fisher L, Skaff MM, Mullan JT, et al. Clinical depression versus distress among patients with type 2 diabetes: not just a question of semantics. Diabetes Care 2007;30:542–548
238. Friis AM, Johnson MH, Cutfield RG, Consedine NS. Kindness matters: a randomized controlled trial of a mindful self-compassion intervention improves depression, distress, and HbA_{1c} among patients with diabetes. Diabetes Care 2016;39:1963–1971
239. Snoek FJ, Bremmer MA, Hermanns N. Constructs of depression and distress in diabetes: time for an appraisal. Lancet Diabetes Endocrinol 2015;3:450–460
240. Gary TL, Safford MM, Gerzoff RB, et al. Perception of neighborhood problems, health behaviors, and diabetes outcomes among adults with diabetes in managed care: the Translating Research Into Action for Diabetes (TRIAD) study. Diabetes Care 2008;31:273–278
241. Beverly EA, Hultgren BA, Brooks KM, Ritholz MD, Abrahamson MJ, Weinger K. Understanding physicians' challenges when treating type 2 diabetic patients' social and emotional difficulties: a qualitative study. Diabetes Care 2011;34:1086–1088
242. Naicker K, Johnson JA, Skogen JC, et al. Type 2 diabetes and comorbid symptoms of depression and anxiety: longitudinal associations with mortality risk. Diabetes Care 2017;40:352–358
243. de Groot M, Golden SH, Wagner J. Psychological conditions in adults with diabetes. Am Psychol 2016;71:552–562
244. Smith KJ, Béland M, Clyde M, et al. Association of diabetes with anxiety: a systematic review and meta-analysis. J Psychosom Res 2013; 74:89–99
245. Li C, Barker L, Ford ES, Zhang X, Strine TW, Mokdad AH. Diabetes and anxiety in US adults: findings from the 2006 Behavioral Risk Factor

Surveillance System. Diabet Med 2008;25:878–881
246. Cox DJ, Irvine A, Gonder-Frederick L, Nowacek G, Butterfield J. Fear of hypoglycemia: quantification, validation, and utilization. Diabetes Care 1987;10:617–621
247. Wild D, von Maltzahn R, Brohan E, Christensen T, Clauson P, Gonder-Frederick L. A critical review of the literature on fear of hypoglycemia in diabetes: implications for diabetes management and patient education. Patient Educ Couns 2007;68:10–15
248. Zambanini A, Newson RB, Maisey M, Feher MD. Injection related anxiety in insulin-treated diabetes. Diabetes Res Clin Pract 1999;46:239–246
249. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. Arlington, VA, American Psychiatric Association, 2013
250. Mitsonis C, Dimopoulos N, Psarra V. P01-138 Clinical implications of anxiety in diabetes: a critical review of the evidence base. Eur Psychiatry 2009;24:S526
251. Yeoh E, Choudhary P, Nwokolo M, Ayis S, Amiel SA. Interventions that restore awareness of hypoglycemia in adults with type 1 diabetes: a systematic review and meta-analysis. Diabetes Care 2015;38:1592–1609
252. Cox DJ, Gonder-Frederick L, Polonsky W, Schlundt D, Kovatchev B, Clarke W. Blood glucose awareness training (BGAT-2): long-term benefits. Diabetes Care 2001;24:637–642
253. Gonder-Frederick LA, Schmidt KM, Vajda KA, et al. Psychometric properties of the Hypoglycemia Fear Survey-II for adults with type 1 diabetes. Diabetes Care 2011;34:801–806
254. Cox DJ, Kovatchev B, Koev D, et al. Hypoglycemia anticipation, awareness and treatment training (HAATT) reduces occurrence of severe hypoglycemia among adults with type 1 diabetes mellitus. Int J Behav Med 2004;11:212–218
255. Lamounier RN, Geloneze B, Leite SO, et al.; HAT Brazil study group. Hypoglycemia incidence and awareness among insulin-treated patients with diabetes: the HAT study in Brazil. Diabetol Metab Syndr 2018;10:83
256. Lustman PJ, Griffith LS, Clouse RE. Depression in adults with diabetes. Results of 5-yr follow-up study. Diabetes Care 1988;11:605–612
257. de Groot M, Crick KA, Long M, Saha C, Shubrook JH. Lifetime duration of depressive disorders in patients with type 2 diabetes. Diabetes Care 2016;39:2174–2181
258. Rubin RR, Ma Y, Marrero DG, et al.; Diabetes Prevention Program Research Group. Elevated depression symptoms, antidepressant medicine use, and risk of developing diabetes during the diabetes prevention program. Diabetes Care 2008;31:420–426
259. Clouse RE, Lustman PJ, Freedland KE, Griffith LS, McGill JB, Carney RM. Depression and coronary heart disease in women with diabetes. Psychosom Med 2003;65:376–383
260. Katon WJ, Lin EHB, Von Korff M, et al. Collaborative care for patients with depression and chronic illnesses. N Engl J Med 2010;363:2611–2620
261. Katon WJ, Von Korff M, Lin EHB, et al. The Pathways Study: a randomized trial of collaborative care in patients with diabetes and depression. Arch Gen Psychiatry 2004;61:1042–1049
262. Atlantis E, Fahey P, Foster J. Collaborative care for comorbid depression and diabetes: a systematic review and meta-analysis. BMJ Open 2014;4:e004706
263. Pinhas-Hamiel O, Hamiel U, Levy-Shraga Y. Eating disorders in adolescents with type 1 diabetes: challenges in diagnosis and treatment. World J Diabetes 2015;6:517–526
264. Papelbaum M, Appolinário JC, Moreira RdeO, Ellinger VCM, Kupfer R, Coutinho WF. Prevalence of eating disorders and psychiatric comorbidity in a clinical sample of type 2 diabetes mellitus patients. Rev Bras Psiquiatr 2005;27:135–138
265. Young-Hyman DL, Davis CL. Disordered eating behavior in individuals with diabetes: importance of context, evaluation, and classification. Diabetes Care 2010;33:683–689
266. Pinhas-Hamiel O, Hamiel U, Greenfield Y, et al. Detecting intentional insulin omission for weight loss in girls with type 1 diabetes mellitus. Int J Eat Disord 2013;46:819–825
267. Goebel-Fabbri AE, Fikkan J, Franko DL, Pearson K, Anderson BJ, Weinger K. Insulin restriction and associated morbidity and mortality in women with type 1 diabetes. Diabetes Care 2008;31:415–419
268. Weinger K, Beverly EA. Barriers to achieving glycemic targets: who omits insulin and why? Diabetes Care 2010;33:450–452
269. Hudson JI, Hiripi E, Pope HG Jr, Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. Biol Psychiatry 2007;61:348–358
270. Martyn-Nemeth P, Quinn L, Hacker E, Park H, Kujath AS. Diabetes distress may adversely affect the eating styles of women with type 1 diabetes. Acta Diabetol 2014;51:683–686
271. Peterson CM, Fischer S, Young-Hyman D. Topical review: a comprehensive risk model for disordered eating in youth with type 1 diabetes. J Pediatr Psychol 2015;40:385–390
272. Banting R, Randle-Phillips C. A systematic review of psychological interventions for comorbid type 1 diabetes mellitus and eating disorders. Diabetes Manag (Lond) 2018;8:1–18
273. Garber AJ. Novel GLP-1 receptor agonists for diabetes. Expert Opin Investig Drugs 2012;21:45–57
274. Suvisaari J, Perälä J, Saarni SI, et al. Type 2 diabetes among persons with schizophrenia and other psychotic disorders in a general population survey. Eur Arch Psychiatry Clin Neurosci 2008;258:129–136
275. Koro CE, Fedder DO, L'Italien GJ, et al. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. BMJ 2002;325:243
276. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 2004;27:596–601
277. Holt RIG. Association between antipsychotic medication use and diabetes. Curr Diab Rep 2019;19:96–96
278. Kruse J, Schmitz N, Thefeld W; German National Health Interview and Examination Survey. On the association between diabetes and mental disorders in a community sample: results from the German National Health Interview and Examination Survey. Diabetes Care 2003;26:1841–1846

6. Glycemic Targets: *Standards of Medical Care in Diabetes—2021*

American Diabetes Association

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The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc21-SPPC), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc21-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

ASSESSMENT OF GLYCEMIC CONTROL

Glycemic control is assessed by the A1C measurement, continuous glucose monitoring (CGM), and self-monitoring of blood glucose (SMBG). A1C is the metric used to date in clinical trials demonstrating the benefits of improved glycemic control. Patient SMBG can be used with self-management and medication adjustment, particularly in individuals taking insulin. CGM serves an important role in assessing the effectiveness and safety of treatment in many patients with type 1 diabetes, including prevention of hypoglycemia, and in selected patients with type 2 diabetes, such as in those on intensive insulin regimens and in those on regimens associated with hypoglycemia.

Glycemic Assessment

Recommendations

6.1 Assess glycemic status (A1C or other glycemic measurement) *at least* two times a year in patients who are meeting treatment goals (and who have stable glycemic control). **E**

6.2 Assess glycemic status at least quarterly, and as needed, in patients whose therapy has recently changed and/or who are not meeting glycemic goals. **E**

A1C reflects average glycemia over approximately 3 months. The performance of the test is generally excellent for National Glycohemoglobin Standardization Program (NGSP)-certified assays (see www.ngsp.org). The test is the primary tool for assessing glycemic control and has strong predictive value for diabetes complications (1–3). Thus, A1C testing should be performed routinely in all patients with diabetes at initial assessment and as part of continuing care. Measurement approximately every 3 months determines whether patients' glycemic targets have been reached and maintained. The frequency of A1C testing should depend on the clinical situation, the treatment regimen, and the clinician's judgment. The use of point-of-care A1C testing may provide an opportunity for more timely treatment changes during encounters

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between patients and providers. Patients with type 2 diabetes with stable glycemia well within target may do well with A1C testing or other glucose assessment only twice per year. Unstable or intensively managed patients or people not at goal with treatment adjustments may require testing more frequently (every 3 months with interim assessments as needed) (4).

A1C Limitations

The A1C test is an indirect measure of average glycemia and, as such, is subject to limitations. As with any laboratory test, there is variability in the measurement of A1C. Although A1C variability is lower on an intraindividual basis than that of blood glucose measurements, clinicians should exercise judgment when using A1C as the sole basis for assessing glycemic control, particularly if the result is close to the threshold that might prompt a change in medication therapy. For example, conditions that affect red blood cell turnover (hemolytic and other anemias, glucose-6-phosphate dehydrogenase deficiency, recent blood transfusion, use of drugs that stimulate erythropoesis, end-stage kidney disease, and pregnancy) may result in discrepancies between the A1C result and the patient's true mean glycemia. Hemoglobin variants must be considered, particularly when the A1C result does not correlate with the patient's CGM or SMBG levels. However, most assays in use in the U.S. are accurate in individuals heterozygous for the most common variants (see www.ngsp.org/interf.asp). Other measures of average glycemia such as fructosamine and 1,5-anhydroglucitol are available, but their translation into average glucose levels and their prognostic significance are not as clear as for A1C and CGM. Though some variability in the relationship between average glucose levels and A1C exists among different individuals, generally the association between mean glucose and A1C within an individual correlates over time (5).

A1C does not provide a measure of glycemic variability or hypoglycemia. For patients prone to glycemic variability, especially patients with type 1 diabetes or type 2 diabetes with severe insulin deficiency, glycemic control is best evaluated by the combination of results from SMBG or CGM and A1C. A1C may also inform the accuracy of the patient's CGM or meter (or the patient's reported SMBG results) and the adequacy of the SMBG monitoring.

Correlation Between SMBG and A1C

Table 6.1 shows the correlation between A1C levels and mean glucose levels based on the international A1C-Derived Average Glucose (ADAG) study, which assessed the correlation between A1C and frequent SMBG and CGM in 507 adults (83% non-Hispanic Whites) with type 1, type 2, and no diabetes (6), and an empirical study of the average blood glucose levels at premeal, postmeal, and bedtime associated with specified A1C levels using data from the ADAG trial (7). The American Diabetes Association (ADA) and the American Association for Clinical Chemistry have determined that the correlation ($r = 0.92$) in the ADAG trial is strong enough to justify reporting both the A1C result and the estimated average glucose (eAG) result when a clinician orders the A1C test. Clinicians should note that the mean plasma glucose numbers in **Table 6.1** are based on ~2,700 readings per A1C in the ADAG trial. In a recent report, mean glucose measured with CGM versus central laboratory–measured A1C in 387 participants in three randomized trials demonstrated that A1C may underestimate or overestimate mean glucose in individuals (5). Thus, as suggested, a patient's SMBG or CGM profile has considerable potential for optimizing his or her glycemic management (5).

Table 6.1—Estimated average glucose (eAG)

A1C (%)	mg/dL*	mmol/L
5	97 (76–120)	5.4 (4.2–6.7)
6	126 (100–152)	7.0 (5.5–8.5)
7	154 (123–185)	8.6 (6.8–10.3)
8	183 (147–217)	10.2 (8.1–12.1)
9	212 (170–249)	11.8 (9.4–13.9)
10	240 (193–282)	13.4 (10.7–15.7)
11	269 (217–314)	14.9 (12.0–17.5)
12	298 (240–347)	16.5 (13.3–19.3)

Data in parentheses are 95% CI. A calculator for converting A1C results into eAG, in either mg/dL or mmol/L, is available at professional.diabetes.org/eAG. *These estimates are based on ADAG data of ~2,700 glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, or no diabetes. The correlation between A1C and average glucose was 0.92 (6,7). Adapted from Nathan et al. (6).

A1C Differences in Ethnic Populations and Children

In the ADAG study, there were no significant differences among racial and ethnic groups in the regression lines between A1C and mean glucose, although the study was underpowered to detect a difference and there was a trend toward a difference between the African and African American and the non-Hispanic White cohorts, with higher A1C values observed in Africans and African Americans compared with non-Hispanic Whites for a given mean glucose. Other studies have also demonstrated higher A1C levels in African Americans than in Whites at a given mean glucose concentration (8,9).

A1C assays are available that do not demonstrate a statistically significant difference in individuals with hemoglobin variants. Other assays have statistically significant interference, but the difference is not clinically significant. Use of an assay with such statistically significant interference may explain a report that for any level of mean glycemia, African Americans heterozygous for the common hemoglobin variant HbS had lower A1C by about 0.3 percentage points when compared with those without the trait (10,11). Another genetic variant, X-linked glucose-6-phosphate dehydrogenase G202A, carried by 11% of African Americans, was associated with a decrease in A1C of about 0.8% in hemizygous men and 0.7% in homozygous women compared with those without the trait (12).

A small study comparing A1C to CGM data in children with type 1 diabetes found a highly statistically significant correlation between A1C and mean blood glucose, although the correlation ($r = 0.7$) was significantly lower than in the ADAG trial (13). Whether there are clinically meaningful differences in how A1C relates to average glucose in children or in different ethnicities is an area for further study (8,14,15). Until further evidence is available, it seems prudent to establish A1C goals in these populations with consideration of individualized CGM, SMBG, and A1C results. This limitation does not interfere with the usefulness of CGM for insulin dose adjustments.

Glucose Assessment by Continuous Glucose Monitoring

Recommendations

6.3 Standardized, single-page glucose reports from continuous glucose monitoring (CGM) devices with visual cues, such as the ambulatory glucose profile (AGP), should be considered as a standard printout for all CGM devices. **E**

6.4 Time in range (TIR) is associated with the risk of microvascular complications, should be an acceptable end point for clinical trials moving forward, and can be used for assessment of glycemic control. Additionally, time below target (<70 and <54 mg/dL [3.9 and 3.0 mmol/L]) and time above target (>180 mg/dL [10.0 mmol/L]) are useful parameters for reevaluation of the treatment regimen. **C**

CGM is rapidly improving diabetes management. As stated in the recommendations, time in range (TIR) is a useful metric of glycemic control and glucose patterns and it correlates well with A1C in most studies (16–21). New data support that increased TIR correlates with the risk of complications. The studies supporting this assertion are reviewed in more detail in Section 7 "Diabetes Technology" (https://doi.org/10.2337/dc21-S007); they include cross-sectional data and cohort studies (22–24) demonstrating TIR as an acceptable end point for clinical trials moving forward and that it can be used for assessment of glycemic control. Additionally, time below target (<70 and <54 mg/dL [3.9 and 3.0 mmol/L]) and time above target (>180 mg/dL [10.0 mmol/L]) are useful parameters for reevaluation of the treatment regimen.

For many people with diabetes, glucose monitoring is key for achieving glycemic targets. Major clinical trials of insulin-treated patients have included SMBG as part of multifactorial interventions to demonstrate the benefit of intensive glycemic control on diabetes complications (25). SMBG is thus an integral component of effective therapy of patients taking insulin. In recent years, CGM has emerged as a complementary method for assessing glucose levels. Both approaches to glucose monitoring allow patients to evaluate individual response to therapy and assess whether glycemic targets are being safely achieved. The international consensus on TIR provides guidance on standardized CGM metrics (see **Table 6.2**) and considerations for clinical interpretation and care (26). To make these metrics more actionable, standardized reports with visual cues, such as the ambulatory glucose profile (see **Fig. 6.1**), are recommended (26) and may help the patient and the provider better interpret the data to guide treatment decisions (16,19). SMBG and CGM can be useful to guide medical nutrition therapy and physical activity, prevent hypoglycemia, and aid medication management. While A1C is currently the primary measure to guide glucose management and a valuable risk marker for developing diabetes complications, the glucose management indicator (GMI) along with the other CGM metrics provide for a more personalized diabetes management plan. The incorporation of these metrics into clinical practice is in evolution, and optimization and harmonization of CGM terminology will evolve to suit patient and provider needs. The patient's specific needs and goals should dictate SMBG frequency and timing and consideration of CGM use. Please refer to Section 7 "Diabetes Technology" (https://doi.org/10.2337/dc21-S007) for a fuller discussion of the use of SMBG and CGM.

With the advent of new technology, CGM has evolved rapidly in both accuracy and affordability. As such, many patients have these data available to assist with both self-management and assessment by providers. Reports can be generated from CGM that will allow the provider to determine TIR and to assess hypoglycemia, hyperglycemia, and glycemic variability. As discussed in a recent consensus document, a report formatted as shown in **Fig. 6.1** can be generated (26). Published data suggest a strong correlation between TIR and A1C, with a goal of 70% TIR aligning with an A1C of ~7% in two prospective studies (18,27).

GLYCEMIC GOALS

For glycemic goals in older adults, please refer to Section 12, "Older Adults" (https://doi.org/10.2337/dc21-S012). For glycemic goals in children, please refer to Section 13 "Children and Adolescents" (https://doi.org/10.2337/dc21-S013). For glycemic goals in pregnant women, please refer to Section 14 "Management of Diabetes in Pregnancy" (https://doi.org/10.2337/dc21-S014). Overall, regardless of the population being served, it is critical for the glycemic targets to be woven into the overall patient-centered strategy. For example, in a very young child safety and simplicity may outweigh the need for perfect control in the short run. Simplification may decrease parental anxiety and build trust and confidence, which could support further strengthening of glycemic targets and self-efficacy. Similarly, in healthy older adults, there is no empiric need to loosen control. However, the provider needs to work with an individual and should consider adjusting targets or simplifying the regimen if this change is needed to improve safety and adherence.

Recommendations

6.5a An A1C goal for many nonpregnant adults of <7% (53 mmol/mol) without significant hypoglycemia is appropriate. **A**

6.5b If using ambulatory glucose profile/glucose management indicator to assess glycemia, a parallel goal is a time in range of >70% with time below range <4% (**Fig. 6.1**). **B**

6.6 On the basis of provider judgment and patient preference, achievement of lower A1C levels than the goal of 7% may be acceptable, and even beneficial, if it can be achieved safely without significant hypoglycemia or other adverse effects of treatment. **C**

6.7 Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with limited life expectancy, or where the harms of treatment are greater than the benefits. **B**

6.8 Reassess glycemic targets over time based on the criteria in **Fig. 6.2** and in older adults (**Table 12.1**). **E**

A1C and Microvascular Complications

Hyperglycemia defines diabetes, and glycemic control is fundamental to diabetes management. The Diabetes Control and Complications Trial (DCCT) (25), a prospective randomized controlled trial of intensive (mean A1C about 7% [53 mmol/mol])

Table 6.2—Standardized CGM metrics for clinical care

1. Number of days CGM device is worn (recommend 14 days)	
2. Percentage of time CGM device is active (recommend 70% of data from 14 days)	
3. Mean glucose	
4. Glucose management indicator	
5. Glycemic variability (%CV) target ≤36%*	
6. TAR: % of readings and time >250 mg/dL (>13.9 mmol/L)	Level 2 hyperglycemia
7. TAR: % of readings and time 181–250 mg/dL (10.1–13.9 mmol/L)	Level 1 hyperglycemia
8. TIR: % of readings and time 70–180 mg/dL (3.9–10.0 mmol/L)	In range
9. TBR: % of readings and time 54–69 mg/dL (3.0–3.8 mmol/L)	Level 1 hypoglycemia
10. TBR: % of readings and time <54 mg/dL (<3.0 mmol/L)	Level 2 hypoglycemia

CGM, continuous glucose monitoring; CV, coefficient of variation; TAR, time above range; TBR, time below range; TIR, time in range. *Some studies suggest that lower %CV targets (<33%) provide additional protection against hypoglycemia for those receiving insulin or sulfonylureas. Adapted from Battelino et al. (26).

versus standard (mean A1C about 9% [75 mmol/mol]) glycemic control in patients with type 1 diabetes, showed definitively that better glycemic control is associated with 50–76% reductions in rates of development and progression of microvascular (retinopathy, neuropathy, and diabetic kidney disease) complications. Follow-up of the DCCT cohorts in the Epidemiology of Diabetes Interventions and Complications (EDIC) study (28,29) demonstrated persistence of these microvascular benefits over two decades despite the fact that the glycemic separation between the treatment groups diminished and disappeared during follow-up.

The Kumamoto Study (30) and UK Prospective Diabetes Study (UKPDS) (31,32) confirmed that intensive glycemic control significantly decreased rates of microvascular complications in patients with short-duration type 2 diabetes. Long-term follow-up of the UKPDS cohorts showed enduring effects of early glycemic control on most microvascular complications (33).

Therefore, achieving A1C targets of <7% (53 mmol/mol) has been shown to reduce microvascular complications of type 1 and type 2 diabetes when instituted early in the course of disease (1,34). Epidemiologic analyses of the DCCT (25) and UKPDS (35) demonstrate a curvilinear relationship between A1C and microvascular complications. Such analyses suggest that, on a population level, the greatest number of complications will be averted by taking patients from very poor control to fair/good control. These analyses also suggest that further lowering of A1C from 7% to 6% [53 mmol/mol to 42 mmol/mol] is associated with further reduction in the risk of microvascular complications, although the absolute risk reductions become much smaller. The implication of these findings is that there is no need to deintensify therapy for an individual with an A1C between 6% and 7% and low hypoglycemia risk with a long life expectancy. There are now newer agents that do not cause hypoglycemia, making it possible to maintain glucose control without risk of hypoglycemia (see Section 9 "Pharmacologic Approaches to Glycemic Treatment," https://doi.org/10.2337/dc21-S009).

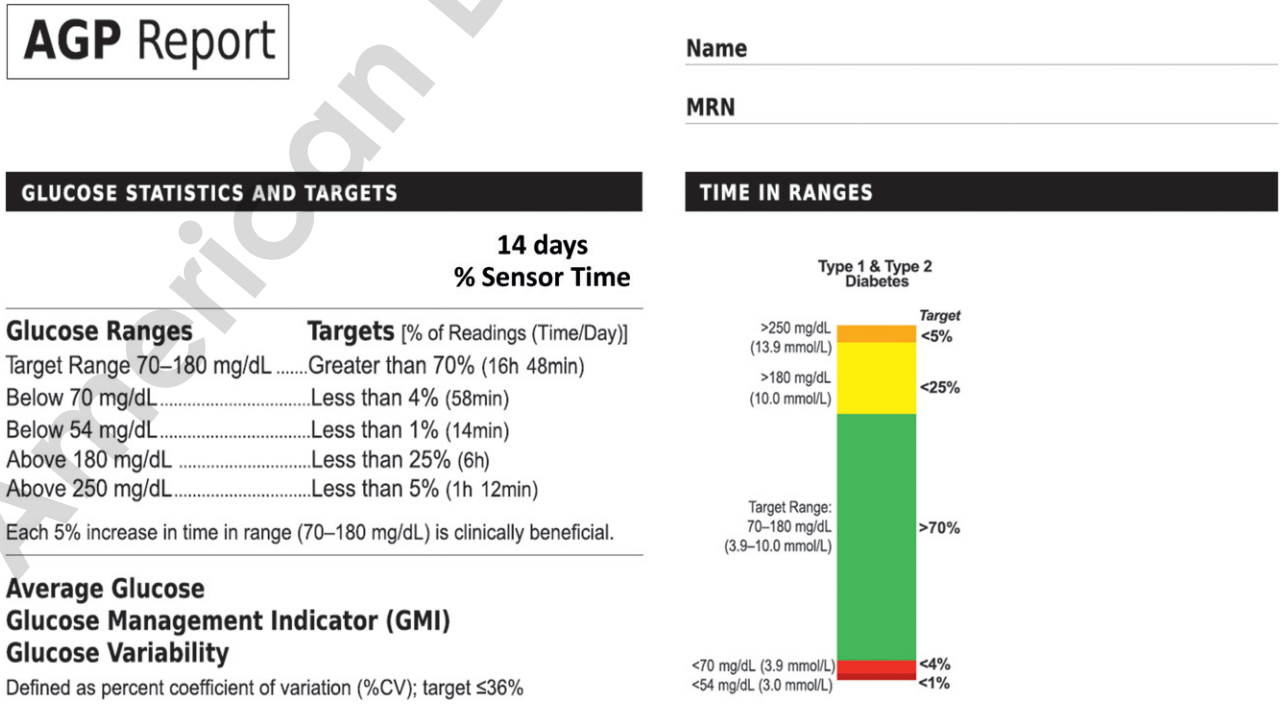

Figure 6.1—Key points included in standard ambulatory glucose profile (AGP) report. Adapted from Battelino et al. (26).

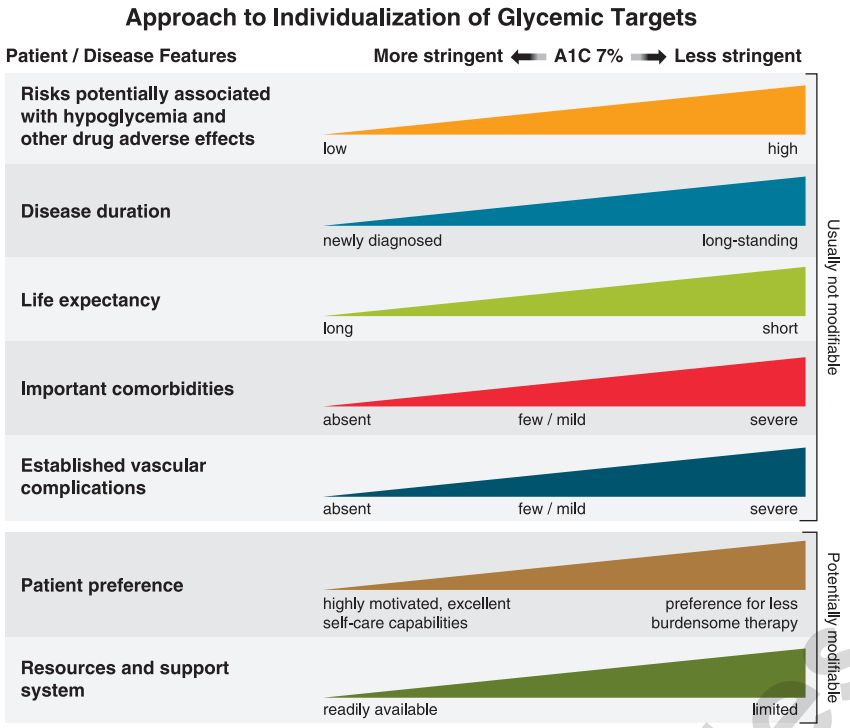

Figure 6.2—Patient and disease factors used to determine optimal glycemic targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. A1C 7% = 53 mmol/mol. Adapted with permission from Inzucchi et al. (59).

Given the substantially increased risk of hypoglycemia in type 1 diabetes and with polypharmacy in type 2 diabetes, the risks of lower glycemic targets may outweigh the potential benefits on microvascular complications. Three landmark trials (Action to Control Cardiovascular Risk in Diabetes [ACCORD], Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE], and Veterans Affairs Diabetes Trial [VADT]) were conducted to test the effects of near normalization of blood glucose on cardiovascular outcomes in individuals with long-standing type 2 diabetes and either known cardiovascular disease (CVD) or high cardiovascular risk. These trials showed that lower A1C levels were associated with reduced onset or progression of some microvascular complications (36–38).

The concerning mortality findings in the ACCORD trial (39), discussed below, and the relatively intense efforts required to achieve near euglycemia should also be considered when setting glycemic targets for individuals with long-standing diabetes, such as those studied in ACCORD, ADVANCE, and VADT. Findings from these studies suggest caution is needed in treating diabetes aggressively to near-normal A1C goals in people with long-standing type 2 diabetes with or at significant risk of CVD. These landmark studies need to be considered with an important caveat; glucagon like peptide 1 (GLP-1) receptor agonists and sodium–glucose cotransporter 2 (SGLT2) inhibitors were not approved at the time of these trials. As such, these agents with established cardiovascular and renal benefit appear to be safe in this group of high-risk patients. Clinical trials examining these agents for cardiovascular safety were not designed to test higher versus lower A1C; therefore, beyond post hoc analysis of these trials, we do not have evidence that it is the glucose lowering by these agents that confers the CVD and renal benefit (40). As such, on the basis of physician judgment and patient preferences, select patients, especially those with little comorbidity and long life expectancy, may benefit from adopting more intensive glycemic targets if they can achieve them safely without hypoglycemia or significant therapeutic burden.

A1C and Cardiovascular Disease Outcomes

Cardiovascular Disease and Type 1 Diabetes

CVD is a more common cause of death than microvascular complications in populations with diabetes. There is evidence for a cardiovascular benefit of intensive glycemic control after long-term follow-up of cohorts treated early in the course of type 1 diabetes. In the DCCT, there was a trend toward lower risk of CVD events with intensive control. In the 9-year post-DCCT follow-up of the EDIC cohort, participants previously randomized to the intensive arm had a significant 57% reduction in the risk of nonfatal myocardial infarction (MI), stroke, or cardiovascular death compared with those previously randomized to the standard arm (41). The benefit of intensive glycemic control in this cohort with type 1 diabetes has been shown to persist for several decades (42) and to be associated with a modest reduction in all-cause mortality (43).

Cardiovascular Disease and Type 2 Diabetes

In type 2 diabetes, there is evidence that more intensive treatment of glycemia in newly diagnosed patients may reduce long-term CVD rates. In addition, data from the Swedish National Diabetes Registry (44) and the Joint Asia Diabetes Evaluation (JADE) demonstrate greater proportions of people with diabetes being diagnosed at <40 years of age and a demonstrably increased burden of heart disease and years of life lost in people diagnosed at a younger age (45–48). Thus, for prevention of both microvascular and macrovascular complications of diabetes, there is a major call to overcome therapeutic inertia and treat to target for an individual patient (47,49). During the UKPDS, there was a 16% reduction in CVD events (combined fatal or nonfatal MI and sudden death) in the intensive glycemic control arm that did not reach statistical significance (P = 0.052), and there was no suggestion of benefit on other CVD outcomes (e.g., stroke). Similar to the DCCT/EDIC, after 10 years of observational follow-up, those originally randomized to intensive glycemic control had significant long-term reductions in MI (15% with sulfonylurea or insulin as initial pharmacotherapy, 33% with metformin as initial pharmacotherapy) and in all-cause mortality (13% and 27%, respectively) (33).

ACCORD, ADVANCE, and VADT suggested no significant reduction in CVD outcomes with intensive glycemic control in participants followed for shorter durations (3.5–5.6 years) and who had

more advanced type 2 diabetes than UKPDS participants. All three trials were conducted in relatively older participants with longer known duration of diabetes (mean duration 8–11 years) and either CVD or multiple cardiovascular risk factors. The target A1C among intensive-control subjects was <6% (42 mmol/mol) in ACCORD, <6.5% (48 mmol/mol) in ADVANCE, and a 1.5% reduction in A1C compared with control subjects in VADT, with achieved A1C of 6.4% vs. 7.5% (46 mmol/mol vs. 58 mmol/mol) in ACCORD, 6.5% vs. 7.3% (48 mmol/mol vs. 56 mmol/mol) in ADVANCE, and 6.9% vs. 8.4% (52 mmol/mol vs. 68 mmol/mol) in VADT. Details of these studies are reviewed extensively in the joint ADA position statement, "Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials" (50).

The glycemic control comparison in ACCORD was halted early due to an increased mortality rate in the intensive compared with the standard treatment arm (1.41% vs. 1.14% per year; hazard ratio 1.22 [95% CI 1.01–1.46]), with a similar increase in cardiovascular deaths. Analysis of the ACCORD data did not identify a clear explanation for the excess mortality in the intensive treatment arm (39).

Longer-term follow-up has shown no evidence of cardiovascular benefit or harm in the ADVANCE trial (51). The end-stage renal disease rate was lower in the intensive treatment group over follow-up. However, 10-year follow-up of the VADT cohort (52) showed a reduction in the risk of cardiovascular events (52.7 [control group] vs. 44.1 [intervention group] events per 1,000 person-years) with no benefit in cardiovascular or overall mortality. Heterogeneity of mortality effects across studies was noted, which may reflect differences in glycemic targets, therapeutic approaches, and, importantly, population characteristics (53).

Mortality findings in ACCORD (39) and subgroup analyses of VADT (54) suggest that the potential risks of intensive glycemic control may outweigh its benefits in higher-risk patients. In all three trials, severe hypoglycemia was significantly more likely in participants who were randomly assigned to the intensive glycemic control arm. Those patients with long duration of diabetes, a known history of hypoglycemia, advanced atherosclerosis, or advanced age/frailty may benefit from less aggressive targets (55,56).

As discussed further below, severe hypoglycemia is a potent marker of high absolute risk of cardiovascular events and mortality (57). Providers should be vigilant in preventing hypoglycemia and should not aggressively attempt to achieve near-normal A1C levels in patients in whom such targets cannot be safely and reasonably achieved. As discussed in Section 9 "Pharmacologic Approaches to Glycemic Treatment" (https://doi.org/10.2337/dc21-S009), addition of specific (SGLT2) inhibitors or GLP-1 receptor agonists that have demonstrated CVD benefit is recommended for use in patients with established CVD, chronic kidney disease, and heart failure. As outlined in more detail in Section 9 "Pharmacologic Approaches to Glycemic Treatment" (https://doi.org/10.2337/dc21-S009) and Section 10 "Cardiovascular Disease and Risk Management" (https://doi.org/10.2337/dc21-S010), the cardiovascular benefits of SGLT2 inhibitors or GLP-1 receptor agonists are not dependent upon A1C lowering; therefore, initiation can be considered in people with type 2 diabetes and CVD independent of the current A1C or A1C goal or metformin therapy. Based on these considerations, the following two strategies are offered (58):

1. If already on dual therapy or multiple glucose-lowering therapies and not on an SGLT2 inhibitor or GLP-1 receptor agonist, consider switching to one of these agents with proven cardiovascular benefit.
2. Introduce SGLT2 inhibitors or GLP-1 receptor agonists in patients with CVD at A1C goal (independent of metformin) for cardiovascular benefit, independent of baseline A1C or individualized A1C target.

Setting and Modifying A1C Goals

Numerous factors must be considered when setting glycemic targets. The ADA proposes general targets appropriate for many patients but emphasizes the importance of individualization based on key patient characteristics. Glycemic targets must be individualized in the context of shared decision-making to address the needs and preferences of each patient and the individual characteristics that influence risks and benefits of therapy for each patient in order to optimize patient engagement and self-efficacy.

The factors to consider in individualizing goals are depicted in **Fig. 6.2**. This figure is not designed to be applied rigidly but to be used as a broad construct to guide clinical decision-making (59) and engage in shared decision-making in people with type 1 and type 2 diabetes. More stringent targets may be recommended if they can be achieved safely and with acceptable burden of therapy and if life expectancy is sufficient to reap benefits of stringent targets. Less stringent targets (A1C up to 8% [64 mmol/mol]) may be recommended if the life expectancy of the patient is such that the benefits of an intensive goal may not be realized, or if the risks and burdens outweigh the potential benefits. Severe or frequent hypoglycemia is an absolute indication for the modification of treatment regimens, including setting higher glycemic goals.

Diabetes is a chronic disease that progresses over decades. Thus, a goal that might be appropriate for an individual early in the course of their diabetes may change over time. Newly diagnosed patients and/or those without comorbidities that limit life expectancy may benefit from intensive control proven to prevent microvascular complications. Both DCCT/EDIC and UKPDS demonstrated metabolic memory, or a legacy effect, in which a finite period of intensive control yielded benefits that extended for decades after that control ended. Thus, a finite period of intensive control to near-normal A1C may yield enduring benefits even if control is subsequently deintensified as patient characteristics change. Over time, comorbidities may emerge, decreasing life expectancy and thereby decreasing the potential to reap benefits from intensive control. Also, with longer duration of disease, diabetes may become more difficult to control, with increasing risks and burdens of therapy. Thus, A1C targets should be reevaluated over time to balance the risks and benefits as patient factors change.

Recommended glycemic targets for many nonpregnant adults are shown in **Table 6.3**. The recommendations include blood glucose levels that appear to correlate with achievement of an A1C of <7% (53 mmol/mol). Pregnancy recommendations are discussed in more detail in Section 14 "Management of Diabetes in Pregnancy" (https://doi.org/10.2337/dc21-S014).

The issue of preprandial versus postprandial SMBG targets is complex (60). Elevated postchallenge (2-h oral glucose tolerance test) glucose values have been associated with increased cardiovascular risk independent of fasting plasma glucose in some epidemiologic studies, whereas intervention trials have not shown postprandial glucose to be a cardiovascular risk factor independent of A1C. In people with diabetes, surrogate measures of vascular pathology, such as endothelial dysfunction, are negatively affected by postprandial hyperglycemia. It is clear that postprandial hyperglycemia, like preprandial hyperglycemia, contributes to elevated A1C levels, with its relative contribution being greater at A1C levels that are closer to 7% (53 mmol/mol). However, outcome studies have clearly shown A1C to be the primary predictor of complications, and landmark trials of glycemic control such as the DCCT and UKPDS relied overwhelmingly on preprandial SMBG. Additionally, a randomized controlled trial in patients with known CVD found no CVD benefit of insulin regimens targeting postprandial glucose compared with those targeting preprandial glucose (61). Therefore, it is reasonable for postprandial testing to be recommended for individuals who have premeal glucose values within target but A1C values above target. In addition, when intensifying insulin therapy, measuring postprandial plasma glucose 1–2 h after the start of a meal and using treatments aimed at reducing postprandial plasma glucose values to <180 mg/dL (10.0 mmol/L) may help to lower A1C.

An analysis of data from 470 participants in the ADAG study (237 with type 1 diabetes and 147 with type 2 diabetes) found that the glucose ranges highlighted in **Table 6.1** are adequate to meet targets and decrease hypoglycemia (7,62). These findings support that premeal glucose targets may be relaxed without undermining overall glycemic control as measured by A1C. These data prompted the revision in the ADA-recommended premeal glucose target to 80–130 mg/dL (4.4–7.2 mmol/L) but did not affect the definition of hypoglycemia.

HYPOGLYCEMIA

Recommendations

6.9 Occurrence and risk for hypoglycemia should be reviewed at every encounter and investigated as indicated. **C**

6.10 Glucose (approximately 15–20 g) is the preferred treatment for the conscious individual with blood glucose <70 mg/dL (3.9 mmol/L), although any form of carbohydrate that contains glucose may be used. Fifteen minutes after treatment, if self-monitoring of blood glucose (SMBG) shows continued hypoglycemia, the treatment should be repeated. Once the SMBG or glucose pattern is trending up, the individual should consume a meal or snack to prevent recurrence of hypoglycemia. **B**

6.11 Glucagon should be prescribed for all individuals at increased risk of level 2 or 3 hypoglycemia so that it is available should it be needed. Caregivers, school personnel, or family members of these individuals should know where it is and when and how to administer it. Glucagon administration is not limited to health care professionals. **E**

6.12 Hypoglycemia unawareness or one or more episodes of level 3 hypoglycemia should trigger hypoglycemia avoidance education and reevaluation of the treatment regimen. **E**

6.13 Insulin-treated patients with hypoglycemia unawareness, one level 3 hypoglycemic event, or a pattern of unexplained level 2 hypoglycemia should be advised to raise their glycemic targets to strictly avoid hypoglycemia for at least several weeks in order to partially reverse hypoglycemia unawareness and reduce risk of future episodes. **A**

6.14 Ongoing assessment of cognitive function is suggested with increased vigilance for hypoglycemia by the clinician, patient, and caregivers if low cognition or declining cognition is found. **B**

Hypoglycemia is the major limiting factor in the glycemic management of type 1 and type 2 diabetes. Recommendations regarding the classification of hypoglycemia are outlined in **Table 6.4** (63–68). Level 1 hypoglycemia is defined as a measurable glucose concentration <70 mg/dL (3.9 mmol/L) but ≥54 mg/dL (3.0 mmol/L). A blood glucose concentration of 70 mg/dL (3.9 mmol/L) has been recognized as a threshold for neuroendocrine responses to falling glucose in people without diabetes. Because many people with diabetes demonstrate impaired counterregulatory responses to hypoglycemia and/or experience hypoglycemia unawareness, a measured glucose level <70 mg/dL (3.9 mmol/L) is considered clinically important (independent of the severity of acute hypoglycemic symptoms). Level 2 hypoglycemia (defined as a blood glucose concentration <54 mg/dL [3.0 mmol/L]) is the threshold at which neuroglycopenic symptoms begin to occur and requires immediate action to resolve the hypoglycemic event. If a patient has level 2 hypoglycemia without adrenergic or neuroglycopenic symptoms, they likely have hypoglycemia unawareness (discussed further below). This clinical scenario warrants investigation and review of the medical regimen. Lastly, level 3 hypoglycemia is defined as a severe event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery.

Symptoms of hypoglycemia include, but are not limited to, shakiness,

Table 6.3—Summary of glycemic recommendations for many nonpregnant adults with diabetes

A1C	<7.0% (53 mmol/mol)*#
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for individual patients. #CGM may be used to assess glycemic target as noted in Recommendation 6.5b and **Fig. 6.1**. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations (as per **Fig. 6.2**). †Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

Table 6.4—Classification of hypoglycemia

	Glycemic criteria/description
Level 1	Glucose <70 mg/dL (3.9 mmol/L) and ≥54 mg/dL (3.0 mmol/L)
Level 2	Glucose <54 mg/dL (3.0 mmol/L)
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia

Reprinted from Agiostratidou et al. (63).

irritability, confusion, tachycardia, and hunger. Hypoglycemia may be inconvenient or frightening to patients with diabetes. Level 3 hypoglycemia may be recognized or unrecognized and can progress to loss of consciousness, seizure, coma, or death. Hypoglycemia is reversed by administration of rapid-acting glucose or glucagon. Hypoglycemia can cause acute harm to the person with diabetes or others, especially if it causes falls, motor vehicle accidents, or other injury. Recurrent level 2 hypoglycemia and/or level 3 hypoglycemia is an urgent medical issue and requires intervention with medical regimen adjustment, behavioral intervention, and, in some cases, use of technology to assist with hypoglycemia prevention and identification (64,69–72). A large cohort study suggested that among older adults with type 2 diabetes, a history of level 3 hypoglycemia was associated with greater risk of dementia (73). Conversely, in a substudy of the ACCORD trial, cognitive impairment at baseline or decline in cognitive function during the trial was significantly associated with subsequent episodes of level 3 hypoglycemia (74). Evidence from DCCT/EDIC, which involved adolescents and younger adults with type 1 diabetes, found no association between frequency of level 3 hypoglycemia and cognitive decline (75).

Studies of rates of level 3 hypoglycemia that rely on claims data for hospitalization, emergency department visits, and ambulance use substantially underestimate rates of level 3 hypoglycemia (76) yet reveal a high burden of hypoglycemia in adults over 60 years of age in the community (77). African Americans are at substantially increased risk of level 3 hypoglycemia (77,78). In addition to age and race, other important risk factors found in a community-based epidemiologic cohort of older Black and White adults with type 2 diabetes include insulin use, poor or moderate versus good glycemic control, albuminuria, and poor cognitive function (77). Level 3 hypoglycemia was associated with mortality in participants in both the standard and the intensive glycemia arms of the ACCORD trial, but the relationships between hypoglycemia, achieved A1C, and treatment intensity were not straightforward. An association of level 3 hypoglycemia with mortality was also found in the ADVANCE trial (79). An association between self-reported level 3 hypoglycemia and 5-year mortality has also been reported in clinical practice (80).

Young children with type 1 diabetes and the elderly, including those with type 1 and type 2 diabetes (73,81), are noted as particularly vulnerable to hypoglycemia because of their reduced ability to recognize hypoglycemic symptoms and effectively communicate their needs. Individualized glucose targets, patient education, dietary intervention (e.g., bedtime snack to prevent overnight hypoglycemia when specifically needed to treat low blood glucose), exercise management, medication adjustment, glucose monitoring, and routine clinical surveillance may improve patient outcomes (82). CGM with automated low glucose suspend has been shown to be effective in reducing hypoglycemia in type 1 diabetes (83). For patients with type 1 diabetes with level 3 hypoglycemia and hypoglycemia unawareness that persists despite medical treatment, human islet transplantation may be an option, but the approach remains experimental (84,85).

In 2015, the ADA changed its preprandial glycemic target from 70–130 mg/dL (3.9–7.2 mmol/L) to 80–130 mg/dL (4.4–7.2 mmol/L). This change reflects the results of the ADAG study, which demonstrated that higher glycemic targets corresponded to A1C goals (7). An additional goal of raising the lower range of the glycemic target was to limit overtreatment and provide a safety margin in patients titrating glucose-lowering drugs such as insulin to glycemic targets.

Hypoglycemia Treatment

Providers should continue to counsel patients to treat hypoglycemia with fast-acting carbohydrates at the hypoglycemia alert value of 70 mg/dL (3.9 mmol/L) or less. This should be reviewed at each patient visit. Hypoglycemia treatment requires ingestion of glucose- or carbohydrate-containing foods (86–88). The acute glycemic response correlates better with the glucose content of food than with the carbohydrate content of food. Pure glucose is the preferred treatment, but any form of carbohydrate that contains glucose will raise blood glucose. Added fat may retard and then prolong the acute glycemic response. In type 2 diabetes, ingested protein may increase insulin response without increasing plasma glucose concentrations (89). Therefore, carbohydrate sources high in protein should not be used to treat or prevent hypoglycemia. Ongoing insulin activity or insulin secretagogues may lead to recurrent hypoglycemia unless more food is ingested after recovery. Once the glucose returns to normal, the individual should be counseled to eat a meal or snack to prevent recurrent hypoglycemia.

Glucagon

The use of glucagon is indicated for the treatment of hypoglycemia in people unable or unwilling to consume carbohydrates by mouth. Those in close contact with, or having custodial care of, people with hypoglycemia-prone diabetes (family members, roommates, school personnel, childcare providers, correctional institution staff, or coworkers) should be instructed on the use of glucagon, including where the glucagon product is kept and when and how to administer it. An individual does not need to be a health care professional to safely administer glucagon. In addition to traditional glucagon injection powder that requires reconstitution prior to injection, intranasal glucagon and glucagon solution for subcutaneous injection are available. Care should be taken to ensure that glucagon products are not expired.

Hypoglycemia Prevention

Hypoglycemia prevention is a critical component of diabetes management.

SMBG and, for some patients, CGM are essential tools to assess therapy and detect incipient hypoglycemia. Patients should understand situations that increase their risk of hypoglycemia, such as when fasting for tests or procedures, when meals are delayed, during and after the consumption of alcohol, during and after intense exercise, and during sleep. Hypoglycemia may increase the risk of harm to self or others, such as with driving. Teaching people with diabetes to balance insulin use and carbohydrate intake and exercise are necessary, but these strategies are not always sufficient for prevention.

In type 1 diabetes and severely insulin-deficient type 2 diabetes, hypoglycemia unawareness (or hypoglycemia-associated autonomic failure) can severely compromise stringent diabetes control and quality of life. This syndrome is characterized by deficient counterregulatory hormone release, especially in older adults, and a diminished autonomic response, which are both risk factors for, and caused by, hypoglycemia. A corollary to this "vicious cycle" is that several weeks of avoidance of hypoglycemia has been demonstrated to improve counterregulation and hypoglycemia awareness in many patients (90). Hence, patients with one or more episodes of clinically significant hypoglycemia may benefit from at least short-term relaxation of glycemic targets and availability of glucagon (91).

Use of CGM Technology in Hypoglycemia Prevention

With the advent of CGM and CGM-assisted pump therapy, there has been a promise of alarm-based prevention of hypoglycemia (92,93). To date, there have been a number of randomized controlled trials in adults with type 1 diabetes and studies in adults and children with type 1 diabetes using real-time CGM (see Section 7 "Diabetes Technology," https://doi.org/10.2337/dc21-S007). These studies had differing A1C at entry and differing primary end points and thus must be interpreted carefully. Real-time CGM studies can be divided into studies with elevated A1C with the primary end point of A1C reduction and studies with A1C near target with the primary end point of reduction in hypoglycemia (93–109). In people with type 1 and type 2 diabetes with A1C above target, CGM improved A1C between 0.3% and 0.6%. For studies targeting hypoglycemia, most studies demonstrated a significant reduction in time spent between 54 and 70 mg/dL. A recent report in people with type 1 diabetes over the age of 60 years revealed a small but statistically significant decrease in hypoglycemia (110). No study to date has reported a decrease in level 3 hypoglycemia. In a single study using intermittently scanned CGM, adults with type 1 diabetes with A1C near goal and impaired awareness of hypoglycemia demonstrated no change in A1C and decreased level 2 hypoglycemia (100). For people with type 2 diabetes, studies examining the impact of CGM on hypoglycemic events are limited; a recent meta-analysis does not reflect a significant impact on hypoglycemic events in type 2 diabetes (111), whereas improvements in A1C were observed in most studies (111–117). Overall, real-time CGM appears to be a useful tool for decreasing time spent in a hypoglycemic range in people with impaired awareness. For type 2 diabetes, other strategies to assist patients with insulin dosing can improve A1C with minimal hypoglycemia (118).

INTERCURRENT ILLNESS

For further information on management of patients with hyperglycemia in the hospital, see Section 15 "Diabetes Care in the Hospital" (https://doi.org/10.2337/dc21-S015).

Stressful events (e.g., illness, trauma, surgery, etc.) may worsen glycemic control and precipitate diabetic ketoacidosis or nonketotic hyperglycemic hyperosmolar state, life-threatening conditions that require immediate medical care to prevent complications and death. Any condition leading to deterioration in glycemic control necessitates more frequent monitoring of blood glucose; ketosis-prone patients also require urine or blood ketone monitoring. If accompanied by ketosis, vomiting, or alteration in the level of consciousness, marked hyperglycemia requires temporary adjustment of the treatment regimen and immediate interaction with the diabetes care team. The patient treated with noninsulin therapies or medical nutrition therapy alone may require insulin. Adequate fluid and caloric intake must be ensured. Infection or dehydration is more likely to necessitate hospitalization of individuals with diabetes versus those without diabetes.

A physician with expertise in diabetes management should treat the hospitalized patient. For further information on the management of diabetic ketoacidosis and the nonketotic hyperglycemic hyperosmolar state, please refer to the ADA consensus report "Hyperglycemic Crises in Adult Patients With Diabetes" (119).

References

1. Laiteerapong N, Ham SA, Gao Y, et al. The legacy effect in type 2 diabetes: impact of early glycemic control on future complications (The Diabetes & Aging Study). Diabetes Care 2019;42:416–426
2. Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–412
3. Little RR, Rohlfing CL, Sacks DB; National Glycohemoglobin Standardization Program (NGSP) Steering Committee. Status of hemoglobin A1c measurement and goals for improvement: from chaos to order for improving diabetes care. Clin Chem 2011;57:205–214
4. Jovanovič L, Savas H, Mehta M, Trujillo A, Pettitt DJ. Frequent monitoring of A1C during pregnancy as a treatment tool to guide therapy. Diabetes Care 2011;34:53–54
5. Beck RW, Connor CG, Mullen DM, Wesley DM, Bergenstal RM. The fallacy of average: how using HbA_{1c} alone to assess glycemic control can be misleading. Diabetes Care 2017;40:994–999
6. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ; A1c-Derived Average Glucose Study Group. Translating the A1C assay into estimated average glucose values. Diabetes Care 2008;31:1473–1478
7. Wei N, Zheng H, Nathan DM. Empirically establishing blood glucose targets to achieve HbA_{1c} goals. Diabetes Care 2014;37:1048–1051
8. Selvin E. Are there clinical implications of racial differences in HbA_{1c}? A difference, to be a difference, must make a difference. Diabetes Care 2016;39:1462–1467
9. Bergenstal RM, Gal RL, Connor CG, et al.; T1D Exchange Racial Differences Study Group. Racial differences in the relationship of glucose concentrations and hemoglobin A1C levels. Ann Intern Med 2017;167:95–102
10. Lacy ME, Wellenius GA, Sumner AE, et al. Association of sickle cell trait with hemoglobin A1C in African Americans. JAMA 2017;317:507–515
11. Rohlfing C, Hanson S, Little RR. Measurement of hemoglobin A1c in patients with sickle cell trait. JAMA 2017;317:2237–2238
12. Wheeler E, Leong A, Liu C-T, et al.; EPIC-CVD Consortium; EPIC-InterAct Consortium; Lifelines Cohort Study. Impact of common genetic determinants of hemoglobin A1c on type 2 diabetes risk and diagnosis in ancestrally diverse populations: a transethnic genome-wide meta-analysis. PLoS Med 2017;14:e1002383
13. Wilson DM, Kollman; Diabetes Research in Children Network (DirecNet) Study Group. Relationship of A1C to glucose concentrations in children with type 1 diabetes: assessments by

high-frequency glucose determinations by sensors. Diabetes Care 2008;31:381–385
14. Buse JB, Kaufman FR, Linder B, Hirst K, El Ghormli L, Willi S; HEALTHY Study Group. Diabetes screening with hemoglobin A_{1c} versus fasting plasma glucose in a multiethnic middle-school cohort. Diabetes Care 2013;36:429–435
15. Kamps JL, Hempe JM, Chalew SA. Racial disparity in A1C independent of mean blood glucose in children with type 1 diabetes. Diabetes Care 2010;33:1025–1027
16. Advani A. Positioning time in range in diabetes management. Diabetologia 2020;63:242–252
17. Avari P, Uduku C, George D, Herrero P, Reddy M, Oliver N. Differences for percentage times in glycemic range between continuous glucose monitoring and capillary blood glucose monitoring in adults with type 1 diabetes: analysis of the REPLACE-BG dataset. Diabetes Technol Ther 2020;22:222–227
18. Vigersky RA, McMahon C. The relationship of hemoglobin A1C to time-in-range in patients with diabetes. Diabetes Technol Ther 2019;21:81–85
19. Kröger J, Reichel A, Siegmund T, Ziegler R. Clinical recommendations for the use of the ambulatory glucose profile in diabetes care. J Diabetes Sci Technol 2020;14:586–594
20. Livingstone R, Boyle JG, Petrie JR. How tightly controlled do fluctuations in blood glucose levels need to be to reduce the risk of developing complications in people with type 1 diabetes? Diabet Med 2020;37:513–521
21. Messer LH, Berget C, Vigers T, et al. Real world hybrid closed-loop discontinuation: predictors and perceptions of youth discontinuing the 670G system in the first 6 months. Pediatr Diabetes 2020;21:319–327
22. Mayeda L, Katz R, Ahmad I, et al. Glucose time in range and peripheral neuropathy in type 2 diabetes mellitus and chronic kidney disease. BMJ Open Diabetes Res Care 2020;8:e000991
23. Yoo JH, Choi MS, Ahn J, et al. Association between continuous glucose monitoring-derived time in range, other core metrics, and albuminuria in type 2 diabetes. Diabetes Technol Ther 2020;22:768–776
24. Lu J, Ma X, Shen Y, et al. Time in range is associated with carotid intima-media thickness in type 2 diabetes. Diabetes Technol Ther 2020;22:72–78
25. Nathan DM, Genuth S, Lachin J, et al.; Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
26. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care 2019;42:1593–1603
27. Beck RW, Bergenstal RM, Cheng P, et al. The relationships between time in range, hyperglycemia metrics, and HbA1c. J Diabetes Sci Technol 2019;13:614–626
28. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group; Lachin JM, White NH, Hainsworth DP, Sun W, Cleary PA, et al. Effect of intensive diabetes therapy on the progression of diabetic retinopathy in patients with type 1 diabetes: 18 years of follow-up in the DCCT/EDIC. Diabetes 2015;64:631–642
29. Lachin JM, Genuth S, Cleary P, Davis MD, Nathan DM; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 2000;342:381–389
30. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995;28:103–117
31. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854–865
32. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853
33. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589
34. Lind M, Pivodic A, Svensson A-M, Ólafsdóttir AF, Wedel H, Ludvigsson J. HbA_{1c} level as a risk factor for retinopathy and nephropathy in children and adults with type 1 diabetes: Swedish population based cohort study. BMJ 2019;366:l4894
35. Adler AI, Stratton IM, Neil HAW, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000;321:412–419
36. Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–139
37. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572
38. Ismail-Beigi F, Craven T, Banerji MA, et al.; ACCORD trial group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010;376:419–430
39. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
40. Buse JB, Bain SC, Mann JFE, et al.; LEADER Trial Investigators. Cardiovascular risk reduction with liraglutide: an exploratory mediation analysis of the LEADER trial. Diabetes Care 2020;43:1546–1552
41. Nathan DM, Cleary PA, Backlund J-YC, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643–2653
42. Nathan DM, Zinman B, Cleary PA, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications and Pittsburgh Epidemiology of Diabetes Complications experience (1983-2005). Arch Intern Med 2009;169:1307–1316
43. Orchard TJ, Nathan DM, Zinman B, et al.; Writing Group for the DCCT/EDIC Research Group. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. JAMA 2015;313:45–53
44. Di Angelantonio E, Kaptoge S, Wormser D, et al.; Emerging Risk Factors Collaboration. Association of cardiometabolic multimorbidity with mortality. JAMA 2015;314:52–60
45. Yeung RO, Zhang Y, Luk A, et al. Metabolic profiles and treatment gaps in young-onset type 2 diabetes in Asia (the JADE programme): a cross-sectional study of a prospective cohort. Lancet Diabetes Endocrinol 2014;2:935–943
46. Sattar N, Rawshani A, Franzén S, et al. Age at diagnosis of type 2 diabetes mellitus and associations with cardiovascular and mortality risks. Circulation 2019;139:2228–2237
47. Zabala A, Darsalia V, Holzmann MJ, et al. Risk of first stroke in people with type 2 diabetes and its relation to glycaemic control: a nationwide observational study. Diabetes Obes Metab 2020;22:182–190
48. Zoungas S, Woodward M, Li Q, et al.; ADVANCE Collaborative group. Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complications and death in type 2 diabetes. Diabetologia 2014;57:2465–2474
49. Gabbay RA, Beebe C, Cuddeback J, et al. Addressing therapeutic inertia in 2020 and beyond: a 3-year initiative of the American Diabetes Association. Clinical Diabetes 2020;38:371–381
50. Skyler JS, Bergenstal R, Bonow RO, et al.; American Diabetes Association; American College of Cardiology Foundation; American Heart Association. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. Diabetes Care 2009;32:187–192
51. Zoungas S, Chalmers J, Neal B, et al.; ADVANCE-ON Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. N Engl J Med 2014;371:1392–1406
52. Hayward RA, Reaven PD, Wiitala WL, et al.; VADT Investigators. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;372:2197–2206
53. CONTROL Group; Turnbull FM, Abraira C, Anderson RJ, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009;52:2288–2298
54. Duckworth WC, Abraira C, Moritz TE, et al.; Investigators of the VADT. The duration of

diabetes affects the response to intensive glucose control in type 2 subjects: the VA Diabetes Trial. J Diabetes Complications 2011;25:355–361
55. Lipska KJ, Ross JS, Miao Y, Shah ND, Lee SJ, Steinman MA. Potential overtreatment of diabetes mellitus in older adults with tight glycemic control. JAMA Intern Med 2015;175:356–362
56. Vijan S, Sussman JB, Yudkin JS, Hayward RA. Effect of patients' risks and preferences on health gains with plasma glucose level lowering in type 2 diabetes mellitus. JAMA Intern Med 2014;174:1227–1234
57. Lee AK, Warren B, Lee CJ, et al. The association of severe hypoglycemia with incident cardiovascular events and mortality in adults with type 2 diabetes. Diabetes Care 2018;41:104–111
58. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018: a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669–2701
59. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140–149
60. American Diabetes Association. Postprandial blood glucose. Diabetes Care 2001;24:775–778
61. Raz I, Wilson PWF, Strojek K, et al. Effects of prandial versus fasting glycemia on cardiovascular outcomes in type 2 diabetes: the HEART2D trial. Diabetes Care 2009;32:381–386
62. Albers JW, Herman WH, Pop-Busui R, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of prior intensive insulin treatment during the Diabetes Control and Complications Trial (DCCT) on peripheral neuropathy in type 1 diabetes during the Epidemiology of Diabetes Interventions and Complications (EDIC) study. Diabetes Care 2010;33:1090–1096
63. Agiostratidou G, Anhalt H, Ball D, et al. Standardizing clinically meaningful outcome measures beyond HbA_{1c} for type 1 diabetes: a consensus report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. Diabetes Care 2017;40:1622–1630
64. Lamounier RN, Geloneze B, Leite SO, et al.; HAT Brazil study group. Hypoglycemia incidence and awareness among insulin-treated patients with diabetes: the HAT study in Brazil. Diabetol Metab Syndr 2018;10:83
65. Li P, Geng Z, Ladage VP, Wu J, Lorincz I, Doshi JA. Early hypoglycaemia and adherence after basal insulin initiation in a nationally representative sample of Medicare beneficiaries with type 2 diabetes. Diabetes Obes Metab 2019;21:2486–2495
66. Shivaprasad C, Aiswarya Y, Kejal S, et al. Comparison of CGM-derived measures of glycemic variability between pancreatogenic diabetes and type 2 diabetes mellitus. J Diabetes Sci Technol. 7 July 2019 [Epub ahead of print]. DOI: 10.1177/1932296819860133
67. Hendrieckx C, Ivory N, Singh H, Frier BM, Speight J. Impact of severe hypoglycaemia on psychological outcomes in adults with type 2 diabetes: a systematic review. Diabet Med 2019;36:1082–1091
68. Yang W, Ma J, Yuan G, et al. Determining the optimal fasting glucose target for patients with type 2 diabetes: results of the multicentre, open-label, randomized-controlled FPG GOAL trial. Diabetes Obes Metab 2019;21:1973–1977
69. Amiel SA, Choudhary P, Jacob P, et al. Hypoglycaemia Awareness Restoration Programme for People with Type 1 Diabetes and Problematic Hypoglycaemia Persisting Despite Optimised Self-care (HARPdoc): protocol for a group randomised controlled trial of a novel intervention addressing cognitions. BMJ Open 2019;9:e030356
70. Harris SM, Joyce H, Miller A, Connor C, Amiel SA, Mulnier H. The attitude of healthcare professionals plays an important role in the uptake of diabetes self-management education: analysis of the Barriers to Uptake of Type 1 Diabetes Education (BUD1E) study survey. Diabet Med 2018;35:1189–1196
71. Choudhary P, Amiel SA. Hypoglycaemia in type 1 diabetes: technological treatments, their limitations and the place of psychology. Diabetologia 2018;61:761–769
72. Hopkins D, Lawrence I, Mansell P, et al. Improved biomedical and psychological outcomes 1 year after structured education in flexible insulin therapy for people with type 1 diabetes: the U.K. DAFNE experience. Diabetes Care 2012;35:1638–1642
73. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA 2009;301:1565–1572
74. Punthakee Z, Miller ME, Launer LJ, et al.; ACCORD Group of Investigators; ACCORD-MIND Investigators. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. Diabetes Care 2012;35:787–793
75. Jacobson AM, Musen G, Ryan CM, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group. Long-term effect of diabetes and its treatment on cognitive function. N Engl J Med 2007;356:1842–1852
76. Karter AJ, Moffet HH, Liu JY, Lipska KJ. Surveillance of hypoglycemia-limitations of emergency department and hospital utilization data. JAMA Intern Med 2018;178:987–988
77. Lee AK, Lee CJ, Huang ES, Sharrett AR, Coresh J, Selvin E. Risk factors for severe hypoglycemia in black and white adults with diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. Diabetes Care 2017;40:1661–1667
78. Karter AJ, Lipska KJ, O'Connor PJ, et al.; SUPREME-DM Study Group. High rates of severe hypoglycemia among African American patients with diabetes: the Surveillance, Prevention, and Management of Diabetes Mellitus (SUPREME-DM) network. J Diabetes Complications 2017;31:869–873
79. Zoungas S, Patel A, Chalmers J, et al.; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. N Engl J Med 2010;363:1410–1418
80. McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA. Increased mortality of patients with diabetes reporting severe hypoglycemia. Diabetes Care 2012;35:1897–1901
81. DuBose SN, Weinstock RS, Beck RW, et al. Hypoglycemia in older adults with type 1 diabetes. Diabetes Technol Ther 2016;18:765–771
82. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care 2013;36:1384–1395
83. Bergenstal RM, Klonoff DC, Garg SK, et al.; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med 2013;369:224–232
84. Hering BJ, Clarke WR, Bridges ND, et al.; Clinical Islet Transplantation Consortium. Phase 3 trial of transplantation of human islets in type 1 diabetes complicated by severe hypoglycemia. Diabetes Care 2016;39:1230–1240
85. Harlan DM. Islet transplantation for hypoglycemia unawareness/severe hypoglycemia: caveat emptor. Diabetes Care 2016;39:1072–1074
86. McTavish L, Wiltshire E. Effective treatment of hypoglycemia in children with type 1 diabetes: a randomized controlled clinical trial. Pediatr Diabetes 2011;12:381–387
87. McTavish L, Corley B, Weatherall M, Wiltshire E, Krebs JD. Weight-based carbohydrate treatment of hypoglycaemia in people with type 1 diabetes using insulin pump therapy: a randomized crossover clinical trial. Diabet Med 2018;35:339–346
88. Georgakopoulos K, Katsilambros N, Fragaki M, et al. Recovery from insulin-induced hypoglycemia after saccharose or glucose administration. Clin Physiol Biochem 1990;8:267–272
89. Layman DK, Clifton P, Gannon MC, Krauss RM, Nuttall FQ. Protein in optimal health: heart disease and type 2 diabetes. Am J Clin Nutr 2008;87:1571S–1575S
90. Cryer PE. Diverse causes of hypoglycemia-associated autonomic failure in diabetes. N Engl J Med 2004;350:2272–2279
91. Mitchell BD, He X, Sturdy IM, Cagle AP, Settles JA. Glucagon prescription patterns in patients with either type 1 or 2 diabetes with newly prescribed insulin. Endocr Pract 2016;22:123–135
92. Hermanns N, Heinemann L, Freckmann G, Waldenmaier D, Ehrmann D. Impact of CGM on the management of hypoglycemia problems: overview and secondary analysis of the HypoDE study. J Diabetes Sci Technol 2019;13:636–644
93. Heinemann L, Freckmann G, Ehrmann D, et al. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. Lancet 2018;391:1367–1377
94. Beck RW, Riddlesworth T, Ruedy K, et al.; DIAMOND Study Group. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. JAMA 2017;317:371–378
95. Lind M, Polonsky W, Hirsch IB, et al. Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1

diabetes treated with multiple daily insulin injections: the GOLD randomized clinical trial. JAMA 2017;317:379–387
96. Sequeira PA, Montoya L, Ruelas V, et al. Continuous glucose monitoring pilot in low-income type 1 diabetes patients. Diabetes Technol Ther 2013;15:855–858
97. Tumminia A, Crimi S, Sciacca L, et al. Efficacy of real-time continuous glucose monitoring on glycaemic control and glucose variability in type 1 diabetic patients treated with either insulin pumps or multiple insulin injection therapy: a randomized controlled crossover trial. Diabetes Metab Res Rev 2015;31:61–68
98. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. Lancet 2016;388:2254–2263
99. Hermanns N, Schumann B, Kulzer B, Haak T. The impact of continuous glucose monitoring on low interstitial glucose values and low blood glucose values assessed by point-of-care blood glucose meters: results of a crossover trial. J Diabetes Sci Technol 2014;8:516–522
100. Reddy M, Jugnee N, El Laboudi A, Spanudakis E, Anantharaja S, Oliver N. A randomized controlled pilot study of continuous glucose monitoring and flash glucose monitoring in people with type 1 diabetes and impaired awareness of hypoglycaemia. Diabet Med 2018;35:483–490
101. Riddlesworth T, Price D, Cohen N, Beck RW. Hypoglycemic event frequency and the effect of continuous glucose monitoring in adults with type 1 diabetes using multiple daily insulin injections. Diabetes Ther 2017;8:947–951
102. van Beers CAJ, DeVries JH, Kleijer SJ, et al. Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycaemia (IN CONTROL): a randomised, open-label, crossover trial. Lancet Diabetes Endocrinol 2016;4:893–902
103. Battelino T, Conget I, Olsen B, et al.; SWITCH Study Group. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. Diabetologia 2012;55:3155–3162
104. Deiss D, Bolinder J, Riveline J-P, et al. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. Diabetes Care 2006;29:2730–2732
105. Tamborlane WV, Beck RW, Bode BW, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008;359:1464–1476
106. O'Connell MA, Donath S, O'Neal DN, et al. Glycaemic impact of patient-led use of sensor-guided pump therapy in type 1 diabetes: a randomised controlled trial. Diabetologia 2009;52:1250–1257
107. Beck RW, Hirsch IB, Laffel L, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. Diabetes Care 2009;32:1378–1383
108. Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes Care 2011;34:795–800
109. Ludvigsson J, Hanas R. Continuous subcutaneous glucose monitoring improved metabolic control in pediatric patients with type 1 diabetes: a controlled crossover study. Pediatrics 2003;111:933–938
110. Pratley RE, Kanapka LG, Rickels MR, et al.; Wireless Innovation for Seniors With Diabetes Mellitus (WISDM) Study Group. Effect of continuous glucose monitoring on hypoglycemia in older adults with type 1 diabetes: a randomized clinical trial. JAMA 2020;323:2397–2406
111. Dicembrini I, Mannucci E, Monami M, Pala L. Impact of technology on glycemic control in type 2 diabetes: a meta-analysis of randomized trials on continuous glucose monitoring and continuous subcutaneous insulin infusion. Diabetes Obes Metab 2019;21:2619–2625
112. Beck RW, Riddlesworth TD, Ruedy K, et al.; DIAMOND Study Group. Continuous glucose monitoring versus usual care in patients with type 2 diabetes receiving multiple daily insulin injections: a randomized trial. Ann Intern Med 2017;167:365–374
113. Ehrhardt NM, Chellappa M, Walker MS, Fonda SJ, Vigersky RA. The effect of real-time continuous glucose monitoring on glycemic control in patients with type 2 diabetes mellitus. J Diabetes Sci Technol 2011;5:668–675
114. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline J-P, Rayman G. Flash glucose-sensing technology as a replacement for blood glucose monitoring for the management of insulin-treated type 2 diabetes: a multicenter, open-label randomized controlled trial. Diabetes Ther 2017;8:55–73
115. Yoo HJ, An HG, Park SY, et al. Use of a real time continuous glucose monitoring system as a motivational device for poorly controlled type 2 diabetes. Diabetes Res Clin Pract 2008;82:73–79
116. Garg S, Zisser H, Schwartz S, et al. Improvement in glycemic excursions with a transcutaneous, real-time continuous glucose sensor: a randomized controlled trial. Diabetes Care 2006;29:44–50
117. New JP, Ajjan R, Pfeiffer AFH, Freckmann G. Continuous glucose monitoring in people with diabetes: the randomized controlled Glucose Level Awareness in Diabetes Study (GLADIS). Diabet Med 2015;32:609–617
118. Bergenstal RM, Johnson M, Passi R, et al. Automated insulin dosing guidance to optimise insulin management in patients with type 2 diabetes: a multicentre, randomised controlled trial. Lancet 2019;393:1138–1148
119. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009;32:1335–1343

7. Diabetes Technology: *Standards of Medical Care in Diabetes—2021*

American Diabetes Association

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The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc21-SPPC), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc21-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Diabetes technology is the term used to describe the hardware, devices, and software that people with diabetes use to help manage their condition, from lifestyle to blood glucose levels. Historically, diabetes technology has been divided into two main categories: insulin administered by syringe, pen, or pump, and blood glucose monitoring as assessed by meter or continuous glucose monitor. More recently, diabetes technology has expanded to include hybrid devices that both monitor glucose and deliver insulin, some automatically, as well as software that serves as a medical device, providing diabetes self-management support. Diabetes technology, when coupled with education and follow-up, can improve the lives and health of people with diabetes; however, the complexity and rapid change of the diabetes technology landscape can also be a barrier to patient and provider implementation.

Recommendation

7.1 Use of technology should be individualized based on a patient's needs, desires, skill level, and availability of devices. **E**

Technology is rapidly changing, but there is no "one-size-fits-all" approach to technology use in people with diabetes. Insurance coverage can lag behind device availability, patient interest in devices and willingness to change can vary, and providers may have trouble keeping up with newly released technology. Not-for-profit websites can help providers and patients make decisions as to the initial choice of devices. Other sources, including health care providers and device manufacturers, can help people troubleshoot when difficulties arise.

SELF-MONITORING OF BLOOD GLUCOSE

Recommendations

7.2 People who are on insulin using self-monitoring of blood glucose should be encouraged to test when appropriate based on their insulin regimen. This may

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include testing when fasting, prior to meals and snacks, at bedtime, prior to exercise, when low blood glucose is suspected, after treating low blood glucose until they are normoglycemic, and prior to and while performing critical tasks such as driving. **B**

7.3 Providers should be aware of the differences in accuracy among glucose meters—only U.S. Food and Drug Administration–approved meters with proven accuracy should be used, with unexpired strips, purchased from a pharmacy or licensed distributor. **E**

7.4 When prescribed as part of a diabetes self-management education and support program, self-monitoring of blood glucose may help to guide treatment decisions and/or self-management for patients taking less frequent insulin injections. **B**

7.5 Although self-monitoring of blood glucose in patients on noninsulin therapies has not consistently shown clinically significant reductions in A1C, it may be helpful when altering diet, physical activity, and/or medications (particularly medications that can cause hypoglycemia) in conjunction with a treatment adjustment program. **E**

7.6 When prescribing self-monitoring of blood glucose, ensure that patients receive ongoing instruction and regular evaluation of technique, results, and their ability to use data, including uploading/sharing data (if applicable), from self-monitoring of blood glucose devices to adjust therapy. **E**

7.7 Health care providers should be aware of medications and other factors, such as high-dose vitamin C and hypoxemia, that can interfere with glucose meter accuracy and provide clinical management as indicated. **E**

Major clinical trials of insulin-treated patients have included self-monitoring of blood glucose (SMBG) as part of multifactorial interventions to demonstrate the benefit of intensive glycemic control on diabetes complications (1). SMBG is thus an integral component of effective therapy of patients taking insulin. In recent years, continuous glucose monitoring (CGM) has emerged as a method for the assessment of glucose levels (discussed below). Glucose monitoring allows patients to evaluate their individual response to therapy and assess whether glycemic targets are being safely achieved. Integrating results into diabetes management can be a useful tool for guiding medical nutrition therapy and physical activity, preventing hypoglycemia, or adjusting medications (particularly prandial insulin doses). The patient's specific needs and goals should dictate SMBG frequency and timing or the consideration of CGM use.

Meter Standards

Glucose meters meeting U.S. Food and Drug Administration (FDA) guidance for meter accuracy provide the most reliable data for diabetes management. There are several current standards for accuracy of blood glucose monitors, but the two most used are those of the International Organization for Standardization (ISO) (ISO 15197:2013) and the FDA. The current ISO and FDA standards are compared in **Table 7.1**. In Europe, currently marketed monitors must meet current ISO standards. In the U.S., currently marketed monitors must meet the standard under which they were approved, which may not be the current standard. Moreover, the monitoring of current accuracy is left to the manufacturer and not routinely checked by an independent source.

Patients assume their glucose monitor is accurate because it is FDA cleared, but often that is not the case. There is substantial variation in the accuracy of widely used blood glucose monitoring systems (2,3). The Diabetes Technology Society Blood Glucose Monitoring System Surveillance Program provides information on the performance of devices used for SMBG (https://diabetestechnology.org/surveillance). In one analysis, only 6 of the top 18 glucose meters met the accuracy standard (4).

There are single-meter studies in which benefits have been found with individual meter systems, but few that compare meters in a head-to-head manner. Certain meter system characteristics, such as the use of lancing devices that are less painful (5) and the ability to reapply blood to a strip with an insufficient initial sample, may also be beneficial to patients (6) and may make SMBG less burdensome for patients to perform.

Counterfeit Strips

Patients should be advised against purchasing or reselling preowned or secondhand test strips, as these may give incorrect results. Only unopened and unexpired vials of glucose test strips should be used to ensure SMBG accuracy.

Optimizing SMBG Monitor Use

SMBG accuracy is dependent on the instrument and user, so it is important to evaluate each patient's monitoring technique, both initially and at regular intervals thereafter. Optimal use of SMBG requires proper review and interpretation of the data, by both the patient and the provider, to ensure that data are used in an effective and timely manner. In patients with type 1 diabetes, there is a correlation between greater SMBG frequency and lower A1C (7). Among patients who check their blood glucose at least once daily, many report taking no action when results are high or low (8). Patients should be taught how to use SMBG data to adjust food intake, exercise, or pharmacologic therapy to achieve specific goals. Some meters now provide advice to the user in real time, when monitoring glucose levels (9), while others can be used as a part of integrated health platforms (10).

The ongoing need for and frequency of SMBG should be reevaluated at each routine visit to avoid overuse, particularly if SMBG is not being used effectively for self-management (8,11,12).

Patients on Intensive Insulin Regimens

SMBG is especially important for insulin-treated patients to monitor for and prevent hypoglycemia and hyperglycemia. Most patients using intensive insulin regimens (multiple daily injections or insulin pump therapy) should be encouraged to assess glucose levels using SMBG (and/or CGM) prior to meals and snacks, at bedtime, occasionally postprandially, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to and while performing critical tasks such as driving. For many patients using SMBG, this will require checking up to 6–10 times daily, although individual needs may vary. A database study of almost 27,000 children and adolescents with type 1 diabetes showed that, after adjustment for multiple confounders, increased daily frequency of SMBG was significantly associated with lower A1C

Table 7.1—Comparison of ISO 15197:2013 and FDA blood glucose meter accuracy standards

Setting	FDA (206,207)	ISO 15197:2013 (208)
Home use	95% within 15% for all BG in the usable BG range† 99% within 20% for all BG in the usable BG range†	95% within 15% for BG ≥100 mg/dL 95% within 15 mg/dL for BG <100 mg/dL 99% in A or B region of consensus error grid‡
Hospital use	95% within 12% for BG ≥75 mg/dL 95% within 12 mg/dL for BG <75 mg/dL 98% within 15% for BG ≥75 mg/dL 98% within 15 mg/dL for BG <75 mg/dL	

BG, blood glucose; FDA, U.S. Food and Drug Administration; ISO, International Organization for Standardization. To convert mg/dL to mmol/L, see http://endmemo.com/medical/unitconvert/Glucose.php. †The range of blood glucose values for which the meter has been proven accurate and will provide readings (other than low, high, or error). ‡Values outside of the "clinically acceptable" A and B regions are considered "outlier" readings and may be dangerous to use for therapeutic decisions (209).

(−0.2% per additional check per day) and with fewer acute complications (13).

Patients Using Basal Insulin and/or Oral Agents

The evidence is insufficient regarding when to prescribe SMBG and how often monitoring is needed for insulin-treated patients who do not use intensive insulin regimens, such as those with type 2 diabetes using basal insulin with or without oral agents. However, for patients using basal insulin, assessing fasting glucose with SMBG to inform dose adjustments to achieve blood glucose targets results in lower A1C (14,15).

In people with type 2 diabetes not using insulin, routine glucose monitoring may be of limited additional clinical benefit. By itself, even when combined with education, it has showed limited improvement in outcomes (16–19). However, for some individuals, glucose monitoring can provide insight into the impact of diet, physical activity, and medication management on glucose levels. Glucose monitoring may also be useful in assessing hypoglycemia, glucose levels during intercurrent illness, or discrepancies between measured A1C and glucose levels when there is concern an A1C result may not be reliable in specific individuals. It may be useful when coupled with a treatment adjustment program. In a year-long study of insulin-naive patients with suboptimal initial glycemic stability, a group trained in structured SMBG (a paper tool was used at least quarterly to collect and interpret seven-point SMBG profiles taken on 3 consecutive days) reduced their A1C by 0.3% more than the control group (20). A trial of once-daily SMBG that included enhanced patient feedback through messaging found no clinically or statistically significant change in A1C at 1 year (19). Meta-analyses have suggested that SMBG can reduce A1C by 0.25–0.3% at 6 months (21–23), but the effect was attenuated at 12 months in one analysis (21). Reductions in A1C were greater (−0.3%) in trials where structured SMBG data were used to adjust medications, but A1C was not changed significantly without such structured diabetes therapy adjustment (23). A key consideration is that performing SMBG alone does not lower blood glucose levels. To be useful, the information must be integrated into clinical and self-management plans.

Glucose Meter Inaccuracy

Although many meters function well under a variety of circumstances, providers and people with diabetes need to be aware of factors that can impair meter accuracy. A meter reading that seems discordant with clinical reality needs to be retested or tested in a laboratory. Providers in intensive care unit settings need to be particularly aware of the potential for abnormal meter readings, and laboratory-based values should be used if there is any doubt. Some meters give error messages if meter readings are likely to be false (24).

Oxygen. Currently available glucose monitors utilize an enzymatic reaction linked to an electrochemical reaction, either glucose oxidase or glucose dehydrogenase (25). Glucose oxidase monitors are sensitive to the oxygen available and should only be used with capillary blood in patients with normal oxygen saturation. Higher oxygen tensions (i.e., arterial blood or oxygen therapy) may result in false low glucose readings, and low oxygen tensions (i.e., high altitude, hypoxia, or venous blood readings) may lead to false high glucose readings. Glucose dehydrogenase–based monitors are not sensitive to oxygen.

Temperature. Because the reaction is sensitive to temperature, all monitors have an acceptable temperature range (25). Most will show an error if the temperature is unacceptable, but a few will provide a reading and a message indicating that the value may be incorrect.

Interfering Substances. There are a few physiologic and pharmacologic factors that interfere with glucose readings. Most interfere only with glucose oxidase systems (25). They are listed in **Table 7.2**.

Table 7.2—Interfering substances for glucose readings

Glucose oxidase monitors
Uric acid
Galactose
Xylose
Acetaminophen
L-DOPA
Ascorbic acid
Glucose dehydrogenase monitors
Icodextrin (used in peritoneal dialysis)

CONTINUOUS GLUCOSE MONITORING DEVICES

See **Table 7.3** for definitions of types of CGM devices.

Recommendations

7.8 When prescribing continuous glucose monitoring (CGM) devices, robust diabetes education, training, and support are required for optimal CGM device implementation and ongoing use. People using CGM devices need to have the ability to perform self-monitoring of blood glucose in order to calibrate their monitor and/or verify readings if discordant from their symptoms. **B**

7.9 When used properly, real-time continuous glucose monitors in conjunction with multiple daily injections and continuous subcutaneous insulin infusion **A** and other forms of insulin therapy **C** are a useful tool to lower and/or maintain A1C levels and/or reduce

hypoglycemia in adults and youth with diabetes.

7.10 When used properly, intermittently scanned continuous glucose monitors in conjunction with multiple daily injections and continuous subcutaneous insulin infusion **B** and other forms of insulin therapy **C** can be useful and may lower A1C levels and/or reduce hypoglycemia in adults and youth with diabetes to replace self-monitoring of blood glucose.

7.11 In patients on multiple daily injections and continuous subcutaneous insulin infusion, real-time continuous glucose monitoring (CGM) devices should be used as close to daily as possible for maximal benefit. **A** Intermittently scanned CGM devices should be scanned frequently, at a minimum once every 8 h.

7.12 When used as an adjunct to pre- and postprandial self-monitoring of blood glucose, continuous glucose monitoring can help to achieve A1C targets in diabetes and pregnancy. **B**

7.13 Use of professional continuous glucose monitoring (CGM) and/or intermittent real-time or intermittently scanned CGM can be helpful in identifying and correcting patterns of hyper- and hypoglycemia and improving A1C levels in people with diabetes on noninsulin as well as basal insulin regimens. **C**

7.14 Skin reactions, either due to irritation or allergy, should be assessed and addressed to aid in successful use of devices. **E**

7.15 People who have been using continuous glucose monitors should have continued access across third-party payers. **E**

CGM measures interstitial glucose (which correlates well with plasma glucose, although at times can lag if glucose levels are rising or falling rapidly). There are two basic types of CGM devices: those that are owned by the user, unblinded, and intended for frequent/continuous use (real-time [rt]CGM and intermittently scanned [is]CGM) and those that are owned and applied in/by the clinic, which provide data that is blinded or unblinded for a discrete period of time (professional CGM). **Table 7.3** provides the definitions for the types of CGM devices. For devices that provide patients unblinded data, most of the published randomized controlled trials (RCTs) have been performed using rtCGM devices that have alarms and alerts. The RCT results have largely been positive, in terms of reducing either A1C levels and/or episodes of hypoglycemia, as long as participants regularly wear the devices (26–29). These devices provide glucose readings continuously to a smartphone or reader that can be viewed by the patient and/or a caregiver. It is difficult to determine how much the need to swipe a device to obtain a result, combined with a lack of alarms and alerts, matters in terms of outcomes, although results from these devices (isCGM) have not shown consistent improvements in glycemic outcomes (30). However, data from longitudinal trials (without a control group for comparison) show improvement in A1C levels (31). There is one small study in patients at risk for hypoglycemia that compared rtCGM with isCGM (32). The study showed improvement in time spent in hypoglycemia with rtCGM compared with isCGM. The newest version of the isCGM system has an optional alert for a high or low glucose value (without the capacity for providing predictive alerts), but it still requires that the device be swiped to reveal the glucose level and trend arrows, and RCT data are lacking in terms of added benefit. This device (FreeStyle Libre 2) and one rtCGM (Dexcom G6) have both been designated as integrated continuous glucose monitoring (iCGM) devices (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm?id=682). This is a higher standard, set by the FDA, so these devices can be reliably integrated with other digitally connected devices, including automated insulin dosing systems.

Some real-time systems require calibration by the user, which varies in frequency depending on the device. Additionally, for some CGM systems, the FDA suggests SMBG for making treatment decisions. Devices that require SMBG confirmation are called "adjunctive," while those that do not are called "nonadjunctive." An RCT of 226 adults suggested that a CGM device could be used safely and effectively without regular confirmatory SMBG in patients with well-controlled type 1 diabetes at low risk of severe hypoglycemia (33). Two CGM devices are approved by the FDA for making treatment decisions without SMBG calibration or confirmation (34,35). For patients with type 1 diabetes using rtCGM, an important predictor of A1C lowering for all age-groups was frequency of sensor use (26). In this study, overall use was highest in those aged ≥25 years (who had the most improvement in A1C) and lower in younger age-groups.

The abundance of data provided by CGM offers opportunities to analyze patient data more granularly than was previously possible, providing additional information to aid in achieving glycemic targets. A variety of metrics have been proposed (27) and are discussed in Section 6 "Glycemic Targets" (https://doi.org/10.21337/dc21-S006). CGM is essential for creating the ambulatory glucose profile (AGP) and providing data on time in range, percentage of time spent above and below range, and variability

Table 7.3—Continuous glucose monitoring (CGM) devices

Type of CGM	Description
Real-time CGM (rtCGM)	CGM systems that measure and display glucose levels continuously
Intermittently scanned CGM (isCGM)	CGM systems that measure glucose levels continuously but only display glucose values when swiped by a reader or a smartphone
Professional CGM	CGM devices that are placed on the patient in the provider's office (or with remote instruction) and worn for a discrete period of time (generally 7–14 days). Data may be blinded or visible to the person wearing the device. The data are used to assess glycemic patterns and trends. These devices are not fully owned by the patient—they are a clinic-based device, as opposed to the patient-owned rtCGM/isCGM devices.

(36). Access to CGM devices should be considered from the outset of the diagnosis of diabetes that requires insulin management (37,38). This allows for close tracking of glucose levels with adjustments of insulin dosing and lifestyle modifications and removes the burden of frequent SMBG monitoring. Interruption of access to CGM is associated with a worsening of outcomes (39); therefore, it is important for individuals on CGM to have consistent access to the devices.

Education and Training

In general, no device used in diabetes management works optimally without education, training, and follow-up. Device companies offer online tutorials and training videos as well as written material on their use. Patients vary in terms of comfort level with technology, and some prefer in-person training and support. Programs that involve training and support have been shown to improve outcomes in both adults and children using isCGM (40–42). Individuals using CGM should also be trained on how to use SMBG, for use with devices that require calibration, for testing if CGM values seem incongruent with the patient's sense of their glucose levels, and if the CGM device fails or is not available.

Real-time CGM Device Use in Adults and Children With Diabetes

Data exist to support the use of real-time CGM in adults and children, both those on multiple daily injections (MDI) and those on continuous subcutaneous insulin infusion (CSII). This is true in studies both in people with type 1 diabetes and those with type 2 diabetes, although data in individuals with type 2 diabetes is primarily in adults.

In terms of RCTs in people with type 1 diabetes, there are four studies in adults with A1C as the primary outcome (28,29,43–45), three studies in adults with hypoglycemia as the primary outcome (46–48), four studies in adults and children with A1C as the primary outcome (26,49–51), and three studies in adults and children with hypoglycemia as a primary outcome (52–54).

Primary Outcome: A1C Reduction—Adults

In general, A1C reduction was shown in studies where the baseline A1C was higher. In two larger studies in adults with type 1 diabetes that assessed the benefit of rtCGM in patients on MDI, there were significant reductions in A1C: −0.6% in one (28,43) and −0.43% in the other (29). No reduction in A1C was seen in a small study performed in underserved, less well-educated adults with type 1 diabetes (44). In the adult subset of the JDRF CGM study, there was a significant reduction in A1C of −0.53% (55) in patients who were primarily treated with insulin pump therapy. Better adherence in wearing the rtCGM device resulted in a greater likelihood of an improvement in glycemic control (26,45).

Primary Outcome: Hypoglycemia—Adults

In studies in adults where reduction in episodes of hypoglycemia was the primary end point, significant reductions were seen in individuals with type 1 diabetes on MDI or CSII (46–48). In one study in patients who were at higher risk for episodes of hypoglycemia (48), there was a reduction in rates of all levels of hypoglycemia (see Section 6 "Glycemic Targets," https://doi.org/10.2337/dc21-S006, for hypoglycemia definitions). rtCGM may be particularly useful in insulin-treated patients with hypoglycemia unawareness and/or frequent hypoglycemic episodes, although studies have not been powered to show consistent reductions in severe (level 3) hypoglycemia (26,49,50).

Impact on Glycemic Control—Children

When data from adult and pediatric participants are analyzed together, rtCGM use in RCTs has been associated with reduction in A1C levels (49–51). Yet, in the JDRF CGM trial, when youth were analyzed by age-group (8- to 14-year-olds and 15- to 24-year-olds), no change in A1C was seen, likely due to poor rtCGM adherence (26). Indeed, in a secondary analysis of that RCT's data in both pediatric cohorts, those who used the sensor ≥6 days/week had an improvement in their glycemic control (56). One critical component to success with CGM is near-daily wearing of the device (49,55, 57–59). One RCT showed no improvement in glycemic outcomes in children aged 4–10 years of age, regardless of how often it was worn (60).

Though data from small observational studies demonstrate that rtCGM can be worn by patients <8 years old and the use of rtCGM provides insight to glycemic patterns (61,62), an RCT in children aged 4–9 years did not demonstrate improvements in glycemic control following 6 months of rtCGM use (60). However, observational feasibility studies of toddlers demonstrated a high degree of parental satisfaction and sustained use of the devices despite the inability to change the degree of glycemic control attained (63).

Registry data have also shown an association between rtCGM use and lower A1C levels (55,64), even when limiting assessment of rtCGM use to participants on injection therapy (64).

Impact on Hypoglycemia—Children

There are no studies solely including pediatric patients that assess rates of hypoglycemia as the primary outcome. Some of the studies where pediatric and adult patients were combined together did show potential reductions in hypoglycemia (16,65,66).

Real-time CGM Use in Type 2 Diabetes

Studies in people with type 2 diabetes are heterogeneous in design: in two, participants were using basal insulin with oral agents or oral agents alone (67,68); in one, individuals were on MDI alone (69). The findings in studies with MDI alone (69) and in two studies in people using oral agents with or without insulin (67,68) showed significant reductions in A1C levels. The Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes (DIAMOND) study in people with type 2 diabetes on MDI showed a reduction in A1C but no reduction in hypoglycemia (69). Studies in individuals with type 2 diabetes on oral agents with or without insulin did not show reductions in rates of hypoglycemia (67,68).

Intermittently Scanned CGM Device Use in Adults and Children With Diabetes

The original isCGM device (to which the majority of the published data applies) did not provide alarms and alerts but is an option used by many patients. There are relatively few RCT data proving benefit in people with diabetes, but there are multiple longitudinal and observational studies. One RCT, designed to show a reduction in episodes of hypoglycemia in patients with type 1 diabetes at higher risk for hypoglycemia, showed a significant benefit in terms of time spent in a hypoglycemic range ($P < 0.0001$) (46). Another RCT, assessing the ability of

isCGM to prevent episodes of recurrent, severe hypoglycemia, showed no benefit (70). In one RCT of isCGM in people with type 2 diabetes on a variety of insulin regimens and with an initial A1C of ~8.8%, no reduction in A1C was seen; however, the time spent in a hypoglycemic range was reduced by 43% (71). In a study of isCGM in individuals with type 2 diabetes on MDI, the A1C was reduced by 0.82% in the intervention group and 0.33% in the control group ($P = 0.005$) with no change in rates of hypoglycemia (72). Multiple observational studies have shown benefit in terms of A1C reduction, reductions in hypoglycemia, and/or improvements in quality of life in both children and adults (31,41,73–78). An observational study from Belgium showed no improvements in A1C or quality of life after a year of isCGM use, with a reduction in episodes of severe hypoglycemia and time absent from work compared with patient recall of events during the 6 months prior to starting CGM (79).

There are several published reviews of data available on isCGM (80–83). The Norwegian Institute of Public Health conducted an assessment of isCGM clinical effectiveness, cost-effectiveness, and safety for individuals with type 1 and type 2 diabetes, based on data available to January 2017 (80). The authors concluded that, although there were few quality data available at the time of the report, isCGM may increase treatment satisfaction, increase time in range, and reduce frequency of nocturnal hypoglycemia, without differences in A1C or quality of life or serious adverse events. The Canadian Agency for Drugs and Technologies in Health reviewed existing data on isCGM performance and accuracy, hypoglycemia, effect on A1C, and patient satisfaction and quality of life and concluded that the system could replace SMBG, particularly in patients who require frequent monitoring (81). A 2020 systematic review of RCTs assessing efficacy and patient satisfaction with isCGM revealed improvements in A1C levels in some subgroups of patients (e.g., those with type 2 diabetes) but concluded that additional benefit in terms of time in range, glycemic variability, and hypoglycemia was unclear (30). Benefit was enhanced in individuals with type 1 diabetes when combined with a structured education program. Another review showed some benefits in terms of A1C reduction as well as improvement in quality of life (84). A review that included studies conducted using a variety of trial designs, including prospective and retrospective cohort studies, showed overall a reduction in A1C (−0.26%) in people with type 1 and type 2 diabetes, but there was no difference in time in range or hypoglycemic episodes (83).

Other benefits are discussed in a review (82) that supported the use of isCGM as a more affordable alternative to rtCGM systems for individuals with diabetes who are on intensive insulin therapy. In many cases, isCGM is the preferred alternative compared with SMBG (85,86). It can also improve adherence to monitoring in patients who are in extremely poor control (87).

Real-time CGM Device Use in Pregnancy

One well-designed RCT showed a reduction in A1C levels in adult women with type 1 diabetes on MDI or CSII who were pregnant using CGM in addition to standard care, including optimization of pre- and postprandial glucose targets (88). It demonstrated the value of CGM in pregnancy complicated by type 1 diabetes by showing a mild improvement in A1C without an increase in hypoglycemia as well as reductions in large-for-gestational-age births, length of stay, and neonatal hypoglycemia (88). An observational cohort study that evaluated the glycemic variables reported using CGM found that lower mean glucose, lower standard deviation, and a higher percentage of time in target range were associated with lower risk of large-for-gestational-age births and other adverse neonatal outcomes (89). Use of the CGM-reported mean glucose is superior to use of estimated A1C, glucose management indicator, and other calculations to estimate A1C given the changes to A1C that occur in pregnancy (90). Two studies employing intermittent use of rtCGM showed no difference in neonatal outcomes in women with type 1 diabetes (91) or gestational diabetes mellitus (92).

Use of Professional and Intermittent CGM

Professional CGM devices, which provide retrospective data, either blinded or unblinded, for analysis, can be used to identify patterns of hypo- and hyperglycemia (93). Professional CGM can be helpful to evaluate patients when either rtCGM or isCGM is not available to the patient or the patient prefers a blinded analysis or a shorter experience with unblinded data. It can be particularly useful to evaluate periods of hypoglycemia in patients on agents that can cause hypoglycemia in order to make medication dose adjustments. It can also be useful to evaluate patients for periods of hyperglycemia.

There are some data showing benefit of intermittent use of CGM (rtCGM or isCGM) in individuals with type 2 diabetes on noninsulin and/or basal insulin therapies (68,94). In these RCTs, patients with type 2 diabetes not on intensive insulin regimens used CGM intermittently compared with patients randomized to SMBG. Both early (68) and late improvements in A1C were found (68,94).

Use of professional or intermittent CGM should always be coupled with analysis and interpretation for the patient, along with education as needed to adjust medication and change lifestyle behaviors.

Side Effects of CGM Devices

Contact dermatitis (both irritant and allergic) has been reported with all devices that attach to the skin (95–97). In some cases this has been linked to the presence of isobornyl acrylate, which is a skin sensitizer and can cause an additional spreading allergic reaction (98–100). Patch testing can be done to identify the cause of the contact dermatitis in some cases (101). Identifying and eliminating tape allergens is important to ensure comfortable use of devices and enhance patient adherence (102–105). In some instances, use of an implanted sensor can help avoid skin reactions in those who are sensitive to tape (106,107).

INSULIN DELIVERY

Insulin Syringes and Pens

Recommendations

7.16 For people with diabetes who require insulin, insulin syringes or insulin pens may be used for insulin delivery with consideration of patient preference, insulin type and dosing regimen,

cost, and self-management capabilities. **B**

7.17 Insulin pens or insulin injection aids may be considered for patients with dexterity issues or vision impairment to facilitate the administration of accurate insulin doses. **C**

7.18 Smart pens may be useful for some patients to help with dose capture and dosing recommendations. **E**

7.19 U.S. Food and Drug Administration–approved insulin dose calculators/decision support systems may be helpful for titrating insulin doses. **E**

Injecting insulin with a syringe or pen is the insulin delivery method used by most people with diabetes (108,109), although inhaled insulin is also available. Others use insulin pumps or automated insulin delivery devices (see sections on those topics below). For patients with diabetes who use insulin, insulin syringes and pens are both able to deliver insulin safely and effectively for the achievement of glycemic targets. When choosing among delivery systems, patient preferences, cost, insulin type and dosing regimen, and self-management capabilities should be considered. It is important to note that while many insulin types are available for purchase as either pens or vials, others may only be available in one form or the other and there may be significant cost differences between pens and vials (see **Table 9.3** for a list of insulin product costs with dosage forms). Insulin pens may allow people with vision impairment or dexterity issues to dose insulin accurately (110–112), while insulin injection aids are also available to help with these issues. (For a helpful list of injection aids, see http://main.diabetes.org/dforg/pdfs/2018/2018-cg-injection-aids.pdf.) Inhaled insulin can be useful in people who have an aversion to injections.

The most common syringe sizes are 1 mL, 0.5 mL, and 0.3 mL, allowing doses of up to 100 units, 50 units, and 30 units of U-100 insulin, respectively. In a few parts of the world, insulin syringes still have U-80 and U-40 markings for older insulin concentrations and veterinary insulin, and U-500 syringes are available for the use of U-500 insulin. Syringes are generally used once but may be reused by the same individual in resource-limited settings with appropriate storage and cleansing (113).

Insulin pens offer added convenience by combining the vial and syringe into a single device. Insulin pens, allowing push-button injections, come as disposable pens with prefilled cartridges or reusable insulin pens with replaceable insulin cartridges. Pens vary with respect to dosing increment and minimal dose, which can range from half-unit doses to 2-unit dose increments. U-500 pens come in 5-unit dose increments. Some reusable pens include a memory function, which can recall dose amounts and timing. "Smart" pens that can be programmed to calculate insulin doses and provide downloadable data reports are also available. These pens are useful to assist patient insulin dosing in real time as well as for allowing clinicians to retrospectively review the insulin doses that were given and make insulin dose adjustments (114).

Needle thickness (gauge) and length is another consideration. Needle gauges range from 22 to 33, with higher gauge indicating a thinner needle. A thicker needle can give a dose of insulin more quickly, while a thinner needle may cause less pain. Needle length ranges from 4 to 12.7 mm, with some evidence suggesting shorter needles may lower the risk of intramuscular injection. When reused, needles may be duller and thus injection more painful. Proper insulin injection technique is a requisite for obtaining the full benefits of insulin therapy. Concerns with technique and use of the proper technique are outlined in Section 9 "Pharmacologic Approaches to Glycemic Treatment" (https://doi.org/10.2337/dc21-S009).

Bolus calculators have been developed to aid in dosing decisions (115–119). These are subject to FDA approval to ensure safety in terms of dosing recommendations. People who are interested in using these systems should be encouraged to use those that are FDA approved. Provider input and education can be helpful for setting the initial dosing calculations with ongoing follow-up for adjustments as needed.

Insulin Pumps

Recommendations

7.20 Insulin pump therapy may be considered as an option for all adults and youth with type 1 diabetes who are able to safely manage the device. **A**

7.21 Insulin pump therapy may be considered as an option for adults and youth with type 2 diabetes and other forms of diabetes who are on multiple daily injections who are able to safely manage the device. **B**

7.22 Individuals with diabetes who have been successfully using continuous subcutaneous insulin infusion should have continued access across third-party payers. **E**

CSII, or insulin pumps, have been available in the U.S. for over 40 years. These devices deliver rapid-acting insulin throughout the day to help manage blood glucose levels. Most insulin pumps use tubing to deliver insulin through a cannula, while a few attach directly to the skin, without tubing.

Most studies comparing MDI with CSII have been relatively small and of short duration. However, a recent systematic review and meta-analysis concluded that pump therapy has modest advantages for lowering A1C (−0.30% [95% CI −0.58 to −0.02]) and for reducing severe hypoglycemia rates in children and adults (120). There is no consensus to guide choosing which form of insulin administration is best for a given patient, and research to guide this decision-making is needed (121). Thus, the choice of MDI or an insulin pump is often based upon the individual characteristics of the patient and which is most likely to benefit them. Newer systems, such as sensor-augmented pumps and automatic insulin delivery systems, are discussed elsewhere in this section.

Adoption of pump therapy in the U.S. shows geographical variations, which may be related to provider preference or center characteristics (122,123) and socioeconomic status, as pump therapy is more common in individuals of higher socioeconomic status as reflected by race/ethnicity, private health insurance, family income, and education (123,124). Given the additional barriers to optimal diabetes care observed in disadvantaged groups (125), addressing the differences in access to insulin pumps and other diabetes technology may contribute to fewer health disparities.

Pump therapy can be successfully started at the time of diagnosis (126,127). Practical aspects of pump therapy initiation include assessment of patient and family

readiness (although there is no consensus on which factors to consider in adults [128] or pediatric patients), selection of pump type and initial pump settings, patient/family education of potential pump complications (e.g., diabetic ketoacidosis [DKA] with infusion set failure), transition from MDI, and introduction of advanced pump settings (e.g., temporary basal rates, extended/square/dual wave bolus).

Older individuals with type 1 diabetes benefit from ongoing insulin pump therapy. There are no data to suggest that measurement of C-peptide levels or antibodies predicts success with insulin pump therapy (129,130). Additionally, frequency of follow-up does not influence outcomes. Access to insulin pump therapy should be allowed/continued in older adults as it is in younger people.

Complications of the pump can be caused by issues with infusion sets (dislodgement, occlusion), which place patients at risk for ketosis and DKA and thus must be recognized and managed early (131); lipohypertrophy or, less frequently, lipoatrophy (132,133); and pump site infection (134). Discontinuation of pump therapy is relatively uncommon today; the frequency has decreased over the past few decades, and its causes have changed (134,135). Current reasons for attrition are problems with cost, wearability, dislike for the pump, suboptimal glycemic control, or mood disorders (e.g., anxiety or depression) (136).

Insulin Pumps in Youth

The safety of insulin pumps in youth has been established for over 15 years (137). Studying the effectiveness of CSII in lowering A1C has been challenging because of the potential selection bias of observational studies. Participants on CSII may have a higher socioeconomic status that may facilitate better glycemic control (138) versus MDI. In addition, the fast pace of development of new insulins and technologies quickly renders comparisons obsolete. However, RCTs comparing CSII and MDI with insulin analogs demonstrate a modest improvement in A1C in participants on CSII (139,140). Observational studies, registry data, and meta-analysis have also suggested an improvement of glycemic control in participants on CSII (141–143). Although hypoglycemia was a major adverse effect of intensified insulin regimen in the Diabetes Control and Complications Trial (DCCT) (144), data suggest that CSII may reduce the rates of severe hypoglycemia compared with MDI (143,145–147).

There is also evidence that CSII may reduce DKA risk (143,148) and diabetes complications, in particular, retinopathy and peripheral neuropathy in youth, compared with MDI (65). Finally, treatment satisfaction and quality-of-life measures improved on CSII compared with MDI (149,150). Therefore, CSII can be used safely and effectively in youth with type 1 diabetes to assist with achieving targeted glycemic control while reducing the risk of hypoglycemia and DKA, improving quality of life, and preventing long-term complications. Based on patient–provider shared decision-making, insulin pumps may be considered in all pediatric patients with type 1 diabetes. In particular, pump therapy may be the preferred mode of insulin delivery for children under 7 years of age (66). Because of a paucity of data in adolescents and youth with type 2 diabetes, there is insufficient evidence to make recommendations.

Common barriers to pump therapy adoption in children and adolescents are concerns regarding the physical interference of the device, discomfort with the idea of having a device on the body, therapeutic effectiveness, and financial burden (141,151).

Insulin Pumps in Patients With Type 2 and Other Types of Diabetes

Traditional insulin pumps can be considered for the treatment of people with type 2 diabetes who are on MDI as well as those who have other types of diabetes resulting in insulin deficiency, for instance, those who have had a pancreatectomy and/or individuals with cystic fibrosis (152–156). Similar to data on insulin pump use in people with type 1 diabetes, reductions in A1C levels are not consistently seen in individuals with type 2 diabetes when compared with MDI, although they have been in some studies (154,157). Use of insulin pumps in insulin-requiring patients with any type of diabetes may improve patient satisfaction and simplify therapy (130,152).

For patients judged to be clinically insulin deficient who are treated with an intensive insulin regimen, the presence or absence of measurable C-peptide levels does not correlate with response to therapy (130). Another pump option in people with type 2 diabetes is a disposable patchlike device, which provides a continuous, subcutaneous infusion of rapid-acting insulin (basal) as well as 2-unit increments of bolus insulin at the press of a button (153,155,158). Use of an insulin pump as a means for insulin delivery is an individual choice for people with diabetes and should be considered an option in patients who are capable of safely using the device.

Combined Insulin Pump and Sensor Systems

Recommendations

7.23 Sensor-augmented pump therapy with automatic low glucose suspend may be considered for adults and youth with diabetes to prevent/mitigate episodes of hypoglycemia. **B**

7.24 Automated insulin delivery systems may be considered in youth and adults with type 1 diabetes to improve glycemic control. **A**

7.25 Individual patients may be using systems not approved by the U.S. Food and Drug Administration, such as do-it-yourself closed-loop systems and others; providers cannot prescribe these systems but should provide safety information/troubleshooting/backup advice for the individual devices to enhance patient safety. **E**

Sensor-Augmented Pumps

Sensor-augmented pumps that suspend insulin when glucose is low or predicted to go low within the next 30 min have been approved by the FDA. The Automation to Simulate Pancreatic Insulin Response (ASPIRE) trial of 247 patients with type 1 diabetes and documented nocturnal hypoglycemia showed that sensor-augmented insulin pump therapy with a low glucose suspend function significantly reduced nocturnal hypoglycemia over 3 months without increasing A1C levels (51). In a different sensor-augmented pump, predictive low glucose suspend reduced time spent with glucose $<$70 mg/dL from 3.6% at baseline to 2.6% (3.2% with sensor-augmented pump therapy without predictive low glucose suspend) without rebound hyperglycemia during a 6-week randomized crossover trial (159). These devices may offer

the opportunity to reduce hypoglycemia for those with a history of nocturnal hypoglycemia. Additional studies have been performed, in adults and children, showing the benefits of this technology (160–162).

Automated Insulin Delivery Systems

Automated insulin delivery systems increase and decrease insulin delivery based on sensor-derived glucose level to begin to approximate physiologic insulin delivery. These systems consist of three components: an insulin pump, a continuous glucose sensor, and an algorithm that determines insulin delivery. With these systems, insulin delivery can not only be suspended but also increased or decreased based on sensor glucose values. While eventually insulin delivery in closed-loop systems may be truly automated, currently meals must be announced. A so-called hybrid approach, hybrid closed-loop, has been adopted in first-generation closed-loop systems and requires users to bolus for meals and snacks. Multiple studies, using a variety of systems with varying algorithms, pump, and sensors, have been performed in adults and children (163–173). Evidence suggests such systems may reduce A1C levels and improve time in range (174–178). They may lower the risk of exercise-related hypoglycemia (179) and may have psychosocial benefits (180–183). Use of these systems depends on patient preference and selection of patients (and/or caregivers) who are capable of safely and effectively using the devices.

Some people with type 1 diabetes have been using "do-it-yourself" (DIY) systems that combine a pump and an rtCGM with a controller and an algorithm designed to automate insulin delivery (184–187). These systems are not approved by the FDA, although there are efforts underway to obtain regulatory approval for them. The information on how to set up and manage these systems is freely available on the internet, and there are internet groups where people inform each other as to how to set up and use them. Although these systems cannot be prescribed by providers, it is important to keep patients safe if they are using these methods for automated insulin delivery. Part of this entails making sure people have a "backup plan" in case of pump failure. Additionally, in most DIY systems, insulin doses are adjusted based on the pump settings for basal rates, carbohydrate ratios, correction doses, and insulin activity. Therefore, these settings can be evaluated and changed based on the patient's insulin requirements.

Digital Health Technology

Recommendation

7.26 Systems that combine technology and online coaching can be beneficial in treating prediabetes and diabetes for some individuals. **B**

Increasingly, people are turning to the internet for advice, coaching, connection, and health care. Diabetes, in part because it is both common and numeric, lends itself to the development of apps and online programs. The FDA approves and monitors clinically validated, digital, usually online, health technologies intended to treat a medical or psychological condition; these are known as digital therapeutics or "digiceuticals" (188). Other applications, such as those that assist in displaying or storing data, encourage a healthy lifestyle or provide limited clinical data support. Therefore, it is possible to find apps that have been fully reviewed and approved and others designed and promoted by people with relatively little skill or knowledge in the clinical treatment of diabetes.

An area of particular importance is that of online privacy and security. There are established cloud-based data collection programs, such as Tidepool, Glooko, and others, that have been developed with appropriate data security features and are compliant with the U.S. Health Insurance Portability and Accountability Act of 1996. These programs can be useful for monitoring patients, both by the patients themselves as well as their health care team (189). Consumers should read the policy regarding data privacy and sharing before entering data into an application and learn how they can control the way their data will be used (some programs offer the ability to share more or less information, such as being part of a registry or data repository or not).

There are many online programs that offer lifestyle counseling to aid with weight loss and increase physical activity (190). Many of these include a health coach and can create small groups of similar patients in social networks. There are programs that aim to treat prediabetes and prevent progression to diabetes, often following the model of the Diabetes Prevention Program (191,192). Others assist in improving diabetes outcomes by remotely monitoring patient clinical data (for instance, wireless monitoring of glucose levels, weight, or blood pressure) and providing feedback and coaching (193–198). There are text messaging approaches that tie into a variety of different types of lifestyle and treatment programs, which vary in terms of their effectiveness (199,200). For many of these interventions, there are limited RCT data and long-term follow-up is lacking. But for an individual patient, opting into one of these programs can be helpful and, for many, is an attractive option.

Inpatient Care

Recommendation

7.27 Patients using diabetes devices should be allowed to use them in an inpatient setting when proper supervision is available. **E**

Patients who are comfortable using their diabetes devices, such as insulin pumps and sensors, should be given the chance to use them in an inpatient setting if they are competent to do so (201,202). Patients who are familiar with treating their own glucose levels can often adjust insulin doses more knowledgably than inpatient staff who do not personally know the patient or their management style. However, this should occur based on the hospital's policies for diabetes management, and there should be supervision to be sure that the individual can adjust their insulin doses in a hospitalized setting where factors such as infection, certain medications, immobility, changes in diet, and other factors can impact insulin sensitivity and the response to insulin.

With the advent of the coronavirus disease 2019 pandemic, the FDA has allowed CGM use in the hospital for patient monitoring (203). This approach has been employed to reduce the use of personal protective equipment and more closely monitor patients, so that medical personnel do not have to go into a patient room solely for the purpose of measuring a glucose level. Studies are underway to assess the effectiveness of this approach, which may ultimately lead to the routine use of CGM for monitoring hospitalized patients (204,205).

The Future

The pace of development in diabetes technology is extremely rapid. New

approaches and tools are available each year. It is hard for research to keep up with these advances because by the time a study is completed, newer versions of the devices are already on the market. The most important component in all of these systems is the patient. Technology selection must be appropriate for the individual. Simply having a device or application does not change outcomes unless the human being engages with it to create positive health benefits. This underscores the need for the health care team to assist the patient in device/program selection and to support its use through ongoing education and training. Expectations must be tempered by reality—we do not yet have technology that completely eliminates the self-care tasks necessary for treating diabetes, but the tools described in this section can make it easier to manage.

References

1. Diabetes Control and Complications Trial Research Group; Nathan DM, Genuth S, Lachin J, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
2. King F, Ahn D, Hsiao V, Porco T, Klonoff DC. A review of blood glucose monitor accuracy. Diabetes Technol Ther 2018;20:843–856
3. Brazg RL, Klaff LJ, Parkin CG. Performance variability of seven commonly used self-monitoring of blood glucose systems: clinical considerations for patients and providers. J Diabetes Sci Technol 2013;7:144–152
4. Klonoff DC, Parkes JL, Kovatchev BP, et al. Investigation of the accuracy of 18 marketed blood glucose monitors. Diabetes Care 2018;41:1681–1688
5. Grady M, Lamps G, Shemain A, Cameron H, Murray L. Clinical evaluation of a new, lower pain, one touch lancing device for people with diabetes: virtually pain-free testing and improved comfort compared to current lancing systems. J Diabetes Sci Technol. 17 July 2019 [Epub ahead of print]. DOI: 10.1177/1932296819856665
6. Harrison B, Brown D. Accuracy of a blood glucose monitoring system that recognizes insufficient sample blood volume and allows application of more blood to the same test strip. Expert Rev Med Devices 2020;17:75–82
7. Miller KM, Beck RW, Bergenstal RM, et al.; T1D Exchange Clinic Network. Evidence of a strong association between frequency of self-monitoring of blood glucose and hemoglobin A_{1c} levels in T1D exchange clinic registry participants. Diabetes Care 2013;36:2009–2014
8. Grant RW, Huang ES, Wexler DJ, et al. Patients who self-monitor blood glucose and their unused testing results. Am J Manag Care 2015;21:e119–e129
9. Katz LB, Stewart L, Guthrie B, Cameron H. Patient satisfaction with a new, high accuracy blood glucose meter that provides personalized guidance, insight, and encouragement. J Diabetes Sci Technol 2020;14:318–323
10. Shaw RJ, Yang Q, Barnes A, et al. Self-monitoring diabetes with multiple mobile health devices. J Am Med Inform Assoc 2020;27:667–676
11. Gellad WF, Zhao X, Thorpe CT, Mor MK, Good CB, Fine MJ. Dual use of Department of Veterans Affairs and Medicare benefits and use of test strips in veterans with type 2 diabetes mellitus. JAMA Intern Med 2015;175:26–34
12. Endocrine Society and Choosing Wisely. Five things physicians and patients should question. Accessed 1 November 2020. Available from http://www.choosingwisely.org/societies/endocrine-society/
13. Ziegler R, Heidtmann B, Hilgard D, Hofer S, Rosenbauer J, Holl R; DPV-Wiss-Initiative. Frequency of SMBG correlates with HbA1c and acute complications in children and adolescents with type 1 diabetes. Pediatr Diabetes 2011;12:11–17
14. Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetologia 2008;51:408–416
15. Garber AJ. Treat-to-target trials: uses, interpretation and review of concepts. Diabetes Obes Metab 2014;16:193–205
16. Farmer A, Wade A, Goyder E, et al. Impact of self monitoring of blood glucose in the management of patients with non-insulin treated diabetes: open parallel group randomised trial. BMJ 2007;335:132
17. O'Kane MJ, Bunting B, Copeland M, Coates VE; ESMON study group. Efficacy of self monitoring of blood glucose in patients with newly diagnosed type 2 diabetes (ESMON study): randomised controlled trial. BMJ 2008;336:1174–1177
18. Simon J, Gray A, Clarke P, Wade A, Neil A, Farmer A; Diabetes Glycaemic Education and Monitoring Trial Group. Cost effectiveness of self monitoring of blood glucose in patients with non-insulin treated type 2 diabetes: economic evaluation of data from the DiGEM trial. BMJ 2008;336:1177–1180
19. Young LA, Buse JB, Weaver MA, et al.; Monitor Trial Group. Glucose self-monitoring in non-insulin-treated patients with type 2 diabetes in primary care settings: a randomized trial. JAMA Intern Med 2017;177:920–929
20. Polonsky WH, Fisher L, Schikman CH, et al. Structured self-monitoring of blood glucose significantly reduces A1C levels in poorly controlled, noninsulin-treated type 2 diabetes: results from the Structured Testing Program study. Diabetes Care 2011;34:262–267
21. Malanda UL, Welschen LMC, Riphagen II, Dekker JM, Nijpels G, Bot SDM. Self-monitoring of blood glucose in patients with type 2 diabetes mellitus who are not using insulin. Cochrane Database Syst Rev 2012;1:CD005060
22. Willett LR. ACP Journal Club. Meta-analysis: self-monitoring in non-insulin-treated type 2 diabetes improved HbA_{1c} by 0.25%. Ann Intern Med 2012;156:JC6–JC12
23. Mannucci E, Antenore A, Giorgino F, Scavini M. Effects of structured versus unstructured self-monitoring of blood glucose on glucose control in patients with non-insulin-treated type 2 diabetes: a meta-analysis of randomized controlled trials. J Diabetes Sci Technol 2018;12:183–189
24. Sai S, Urata M, Ogawa I. Evaluation of linearity and interference effect on SMBG and POCT devices, showing drastic high values, low values, or error messages. J Diabetes Sci Technol 2019;13:734–743
25. Ginsberg BH. Factors affecting blood glucose monitoring: sources of errors in measurement. J Diabetes Sci Technol 2009;3:903–913
26. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group; Tamborlane WV, Beck RW, Bode BW, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008;359:1464–1476
27. Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. Diabetes Care 2017;40:1631–1640
28. Beck RW, Riddlesworth T, Ruedy K, et al.; DIAMOND Study Group. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. JAMA 2017;317:371–378
29. Lind M, Polonsky W, Hirsch IB, et al. Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections: the GOLD randomized clinical trial. JAMA 2017;317:379–387
30. Cowart K, Updike W, Bullers K. Systematic review of randomized controlled trials evaluating glycemic efficacy and patient satisfaction of intermittent-scanned continuous glucose monitoring in patients with diabetes. Diabetes Technol Ther 2020;22:337–345
31. Evans M, Welsh Z, Ells S, Seibold A. The impact of flash glucose monitoring on glycaemic control as measured by HbA1c: a meta-analysis of clinical trials and real-world observational studies. Diabetes Ther 2020;11:83–95
32. Reddy M, Jugnee N, El Laboudi A, Spanudakis E, Anantharaja S, Oliver N. A randomized controlled pilot study of continuous glucose monitoring and flash glucose monitoring in people with type 1 diabetes and impaired awareness of hypoglycaemia. Diabet Med 2018;35:483–490
33. Aleppo G, Ruedy KJ, Riddlesworth TD, et al.; REPLACE-BG Study Group. REPLACE-BG: a randomized trial comparing continuous glucose monitoring with and without routine blood glucose monitoring in adults with well-controlled type 1 diabetes. Diabetes Care 2017;40:538–545
34. U.S. Food and Drug Administration. FDA news release: FDA expands indication for continuous glucose monitoring system, first to replace fingerstick testing for diabetes treatment decisions. 2016. Accessed 1 November 2020. Available from https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm534056.htm
35. U.S. Food and Drug Administration. FDA news release:. FDA approves first continuous glucose monitoring system for adults not requiring blood sample calibration. 2017. Accessed 1 November 2020. Available from https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm577890.htm
36. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring

data interpretation: recommendations from the international consensus on time in range. Diabetes Care 2019;42:1593–1603
37. Prahalad P, Addala A, Scheinker D, Hood KK, Maahs DM. CGM initiation soon after type 1 diabetes diagnosis results in sustained CGM use and wear time. Diabetes Care 2020;43:e3–e4
38. Patton SR, Noser AE, Youngkin EM, Majidi S, Clements MA. Early initiation of diabetes devices relates to improved glycemic control in children with recent-onset type 1 diabetes mellitus. Diabetes Technol Ther 2019;21:379–384
39. Addala A, Maahs DM, Scheinker D, Chertow S, Leverenz B, Prahalad P. Uninterrupted continuous glucose monitoring access is associated with a decrease in HbA1c in youth with type 1 diabetes and public insurance. Pediatr Diabetes 2020;21:1301–1309
40. Hermanns N, Ehrmann D, Schipfer M, Kröger J, Haak T, Kulzer B. The impact of a structured education and treatment programme (FLASH) for people with diabetes using a flash sensor-based glucose monitoring system: results of a randomized controlled trial. Diabetes Res Clin Pract 2019;150:111–121
41. Pintus D, Ng SM. FreeStyle Libre flash glucose monitoring improves patient quality of life measures in children with type 1 diabetes mellitus (T1DM) with appropriate provision of education and support by healthcare professionals. Diabetes Metab Syndr 2019;13:2923–2926
42. Hilliard ME, Levy W, Anderson BJ, et al. Benefits and barriers of continuous glucose monitoring in young children with type 1 diabetes. Diabetes Technol Ther 2019;21:493–498
43. Riddlesworth T, Price D, Cohen N, Beck RW. Hypoglycemic event frequency and the effect of continuous glucose monitoring in adults with type 1 diabetes using multiple daily insulin injections. Diabetes Ther 2017;8:947–951
44. Sequeira PA, Montoya L, Ruelas V, et al. Continuous glucose monitoring pilot in low-income type 1 diabetes patients. Diabetes Technol Ther 2013;15:855–858
45. Tumminia A, Crimi S, Sciacca L, et al. Efficacy of real-time continuous glucose monitoring on glycaemic control and glucose variability in type 1 diabetic patients treated with either insulin pumps or multiple insulin injection therapy: a randomized controlled crossover trial. Diabetes Metab Res Rev 2015;31:61–68
46. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. Lancet 2016;388:2254–2263
47. Hermanns N, Schumann B, Kulzer B, Haak T. The impact of continuous glucose monitoring on low interstitial glucose values and low blood glucose values assessed by point-of-care blood glucose meters: results of a crossover trial. J Diabetes Sci Technol 2014;8:516–522
48. van Beers CAJ, DeVries JH, Kleijer SJ, et al. Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycaemia (IN CONTROL): a randomised, open-label, crossover trial. Lancet Diabetes Endocrinol 2016;4:893–902
49. Battelino T, Conget I, Olsen B, et al.; SWITCH Study Group. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. Diabetologia 2012;55:3155–3162
50. Deiss D, Bolinder J, Riveline J-P, et al. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. Diabetes Care 2006;29:2730–2732
51. O'Connell MA, Donath S, O'Neal DN, et al. Glycaemic impact of patient-led use of sensor-guided pump therapy in type 1 diabetes: a randomised controlled trial. Diabetologia 2009;52:1250–1257
52. Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes Care 2011;34:795–800
53. Heinemann L, Freckmann G, Ehrmann D, et al. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. Lancet 2018;391:1367–1377
54. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group; Beck RW, Hirsch IB, Laffel L, et al. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. Diabetes Care 2009;32:1378–1383
55. Wong JC, Foster NC, Maahs DM, et al.; T1D Exchange Clinic Network. Real-time continuous glucose monitoring among participants in the T1D Exchange clinic registry. Diabetes Care 2014;37:2702–2709
56. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group; Beck RW, Buckingham B, Miller K, et al. Factors predictive of use and of benefit from continuous glucose monitoring in type 1 diabetes. Diabetes Care 2009;32:1947–1953
57. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Effectiveness of continuous glucose monitoring in a clinical care environment: evidence from the Juvenile Diabetes Research Foundation continuous glucose monitoring (JDRF-CGM) trial. Diabetes Care 2010;33:17–22
58. Chase HP, Beck RW, Xing D, et al. Continuous glucose monitoring in youth with type 1 diabetes: 12-month follow-up of the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized trial. Diabetes Technol Ther 2010;12:507–515
59. Pickup JC, Freeman SC, Sutton AJ. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. BMJ 2011;343:d3805
60. Mauras N, Beck R, Xing D, et al.; Diabetes Research in Children Network (DirecNet) Study Group. A randomized clinical trial to assess the efficacy and safety of real-time continuous glucose monitoring in the management of type 1 diabetes in young children aged 4 to <10 years. Diabetes Care 2012;35:204–210
61. Jeha GS, Karaviti LP, Anderson B, et al. Continuous glucose monitoring and the reality of metabolic control in preschool children with type 1 diabetes. Diabetes Care 2004;27:2881–2886
62. Gandrud LM, Xing D, Kollman C, et al. The Medtronic Minimed Gold continuous glucose monitoring system: an effective means to discover hypo- and hyperglycemia in children under 7 years of age. Diabetes Technol Ther 2007;9:307–316
63. Tsalikian E, Fox L, Weinzimer S, et al.; Diabetes Research in Children Network Study Group. Feasibility of prolonged continuous glucose monitoring in toddlers with type 1 diabetes. Pediatr Diabetes 2012;13:301–307
64. Foster NC, Miller KM, Tamborlane WV, Bergenstal RM, Beck RW; T1D Exchange Clinic Network. Continuous glucose monitoring in patients with type 1 diabetes using insulin injections. Diabetes Care 2016;39:e81–e82
65. Zabeen B, Craig ME, Virk SA, et al. Insulin pump therapy is associated with lower rates of retinopathy and peripheral nerve abnormality. PLoS One 2016;11:e0153033
66. Sundberg F, Barnard K, Cato A, et al. ISPAD Guidelines. Managing diabetes in preschool children. Pediatr Diabetes 2017;18:499–517
67. Yoo HJ, An HG, Park SY, et al. Use of a real time continuous glucose monitoring system as a motivational device for poorly controlled type 2 diabetes. Diabetes Res Clin Pract 2008;82:73–79
68. Ehrhardt NM, Chellappa M, Walker MS, Fonda SJ, Vigersky RA. The effect of real-time continuous glucose monitoring on glycemic control in patients with type 2 diabetes mellitus. J Diabetes Sci Technol 2011;5:668–675
69. Beck RW, Riddlesworth TD, Ruedy K, et al.; DIAMOND Study Group. Continuous glucose monitoring versus usual care in patients with type 2 diabetes receiving multiple daily insulin injections: a randomized trial. Ann Intern Med 2017;167:365–374
70. Davis TME, Dwyer P, England M, Fegan PG, Davis WA. Efficacy of intermittently scanned continuous glucose monitoring in the prevention of recurrent severe hypoglycemia. Diabetes Technol Ther 2020;22:367–373
71. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline J-P, Rayman G. Flash glucose-sensing technology as a replacement for blood glucose monitoring for the management of insulin-treated type 2 diabetes: a multicenter, open-label randomized controlled trial. Diabetes Ther 2017;8:55–73
72. Yaron M, Roitman E, Aharon-Hananel G, et al. Effect of flash glucose monitoring technology on glycemic control and treatment satisfaction in patients with type 2 diabetes. Diabetes Care 2019;42:1178–1184
73. Paris I, Henry C, Pirard F, Gérard A-C, Colin IM. The new FreeStyle Libre flash glucose monitoring system improves the glycaemic control in a cohort of people with type 1 diabetes followed in real-life conditions over a period of one year. Endocrinol Diabetes Metab 2018;1:e00023
74. Vergier J, Samper M, Dalla-Vale F, et al. Evaluation of flash glucose monitoring after long-term use: a pediatric survey. Prim Care Diabetes 2019;13:63–70
75. Landau Z, Abiri S, Gruber N, et al. Use of flash glucose-sensing technology (FreeStyle Libre) in youth with type 1 diabetes: AWeSoMe study group real-life observational experience. Acta Diabetol 2018;55:1303–1310
76. Deja G, Kłeczek M, Chumięcki M, Strzała-Kłeczek A, Deja R, Jarosz-Chobot P. The usefulness of the FlashStyle Libre system in glycemic

control in children with type 1 diabetes during summer camp. Pediatr Endocrinol Diabetes Metab 2018;24:11–19
77. Kröger J, Fasching P, Hanaire H. Three European retrospective real-world chart review studies to determine the effectiveness of flash glucose monitoring on HbA1c in adults with type 2 diabetes. Diabetes Ther 2020;11:279–291
78. Messaaoui A, Tenoutasse S, Crenier L. Flash glucose monitoring accepted in daily life of children and adolescents with type 1 diabetes and reduction of severe hypoglycemia in real-life use. Diabetes Technol Ther 2019;21:329–335
79. Charleer S, De Block C, Van Huffel L, et al. Quality of life and glucose control after 1 year of nationwide reimbursement of intermittently scanned continuous glucose monitoring in adults living with type 1 diabetes (FUTURE): a prospective observational real-world cohort study. Diabetes Care 2020;43:389–397
80. Norwegian Institute of Public Health. FreeStyle Libre flash glucose self-monitoring system: a single-technology assessment. 2017. Accessed 1 November 2020. Available from http://www.fhi.no/en/publ/2017/freestyle-libre-systemet-for-egenmaling-av-blodsukker-en-hurtigmetodevurder/
81. Palylyk-Colwell E, Ford C. Flash glucose monitoring system for diabetes. In *CADTH Issues in Emerging Health Technologies*. Ottawa, ON, Canadian Agency for Drugs and Technologies in Health, 2016. Accessed 1 November 2020. Available from http://www.ncbi.nlm.nih.gov/books/NBK476439/
82. Leelarathna L, Wilmot EG. Flash forward: a review of flash glucose monitoring. Diabet Med 2018;35:472–482
83. Castellana M, Parisi C, Di Molfetta S, et al. Efficacy and safety of flash glucose monitoring in patients with type 1 and type 2 diabetes: a systematic review and meta-analysis. BMJ Open Diabetes Res Care 2020;8:e001092
84. Ang E, Lee ZX, Moore S, Nana M. Flash glucose monitoring (FGM): a clinical review on glycaemic outcomes and impact on quality of life. J Diabetes Complications 2020;34:107559
85. Al Hayek AA, Robert AA, Al Dawish MA. Acceptability of the FreeStyle Libre flash glucose monitoring system: the experience of young patients with type 1 diabetes. Clin Med Insights Endocrinol Diabetes 2020;13:1179551420910122
86. Babaya N, Noso S, Hiromine Y, et al. Flash glucose monitoring in type 1 diabetes: a comparison with self-monitoring blood glucose. J Diabetes Investig 2020;11:1222–1229
87. Halbron M, Bourron O, Andreelli F, et al. Insulin pump combined with flash glucose monitoring: a therapeutic option to improve glycemic control in severely nonadherent patients with type 1 diabetes. Diabetes Technol Ther 2019;21:409–412
88. Feig DS, Donovan LE, Corcoy R, et al.; CONCEPTT Collaborative Group. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. Lancet 2017;390:2347–2359
89. Kristensen K, Ögge LE, Sengpiel V, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes: an observational cohort study of 186 pregnancies. Diabetologia 2019;62:1143–1153
90. Law GR, Gilthorpe MS, Secher AL, et al. Translating HbA_{1c} measurements into estimated average glucose values in pregnant women with diabetes. Diabetologia 2017;60:618–624
91. Secher AL, Ringholm L, Andersen HU, Damm P, Mathiesen ER. The effect of real-time continuous glucose monitoring in pregnant women with diabetes: a randomized controlled trial. Diabetes Care 2013;36:1877–1883
92. Wei Q, Sun Z, Yang Y, Yu H, Ding H, Wang S. Effect of a CGMS and SMBG on maternal and neonatal outcomes in gestational diabetes mellitus: a randomized controlled trial. Sci Rep 2016;6:19920
93. Ajjan RA, Jackson N, Thomson SA. Reduction in HbA1c using professional flash glucose monitoring in insulin-treated type 2 diabetes patients managed in primary and secondary care settings: a pilot, multicentre, randomised controlled trial. Diab Vasc Dis Res 2019;16:385–395
94. Wada E, Onoue T, Kobayashi T, et al. Flash glucose monitoring helps achieve better glycemic control than conventional self-monitoring of blood glucose in non-insulin-treated type 2 diabetes: a randomized controlled trial. BMJ Open Diabetes Res Care 2020;8:e001115
95. Pleus S, Ulbrich S, Zschornack E, Kamann S, Haug C, Freckmann G. Documentation of skin-related issues associated with continuous glucose monitoring use in the scientific literature. Diabetes Technol Ther 2019;21:538–545
96. Herman A, de Montjoye L, Baeck M. Adverse cutaneous reaction to diabetic glucose sensors and insulin pumps: irritant contact dermatitis or allergic contact dermatitis? Contact Dermat 2020;83:25–30
97. Rigo RS, Levin LE, Belsito DV, Garzon MC, Gandica R, Williams KM. Cutaneous reactions to continuous glucose monitoring and continuous subcutaneous insulin infusion devices in type 1 diabetes mellitus. J Diabetes Sci Technol. 9 May 2020 [Epub ahead of print]. DOI: 10.1177/1932296820918894
98. Kamann S, Aerts O, Heinemann L. Further evidence of severe allergic contact dermatitis from isobornyl acrylate while using a continuous glucose monitoring system. J Diabetes Sci Technol 2018;12:630–633
99. Aerts O, Herman A, Bruze M, Goossens A, Mowitz M FreeStyle Libre: contact irritation versus contact allergy. Lancet 2017;390:1644
100. Herman A, Aerts O, Baeck M, et al. Allergic contact dermatitis caused by isobornyl acrylate in Freestyle® Libre, a newly introduced glucose sensor. Contact Dermat 2017;77:367–373
101. Hyry HSI, Liippo JP, Virtanen HM. Allergic contact dermatitis caused by glucose sensors in type 1 diabetes patients. Contact Dermat 2019;81:161–166
102. Asarani NAM, Reynolds AN, Boucher SE, de Bock M, Wheeler BJ. Cutaneous complications with continuous or flash glucose monitoring use: systematic review of trials and observational studies. J Diabetes Sci Technol 2020;14:328–337
103. Lombardo F, Salzano G, Crisafulli G, et al. Allergic contact dermatitis in pediatric patients with type 1 diabetes: an emerging issue. Diabetes Res Clin Pract 2020;162:108089
104. Oppel E, Kamann S, Heinemann L, Reichl F-X, Högg C. The implanted glucose monitoring system Eversense: an alternative for diabetes patients with isobornyl acrylate allergy. Contact Dermat 2020;82:101–104
105. Freckmann G, Buck S, Waldenmaier D, et al. Skin reaction report form: development and design of a standardized report form for skin reactions due to medical devices for diabetes management. J Diabetes Sci Technol. 22 March 2020 [Epub ahead of print]. DOI: 10.1177/1932296820911105
106. Deiss D, Irace C, Carlson G, Tweden KS, Kaufman FR. Real-world safety of an implantable continuous glucose sensor over multiple cycles of use: a post-market registry study. Diabetes Technol Ther 2020;22:48–52
107. Sanchez P, Ghosh-Dastidar S, Tweden KS, Kaufman FR. Real-world data from the first U.S. commercial users of an implantable continuous glucose sensor. Diabetes Technol Ther 2019;21:677–681
108. Lasalvia P, Barahona-Correa JE, Romero-Alvernia DM, et al. Pen devices for insulin self-administration compared with needle and vial: systematic review of the literature and meta-analysis. J Diabetes Sci Technol 2016;10:959–966
109. Hanas R, de Beaufort C, Hoey H, Anderson B. Insulin delivery by injection in children and adolescents with diabetes. Pediatr Diabetes 2011;12:518–526
110. Pfützner A, Schipper C, Niemeyer M, et al. Comparison of patient preference for two insulin injection pen devices in relation to patient dexterity skills. J Diabetes Sci Technol 2012;6:910–916
111. Williams AS, Schnarrenberger PA. A comparison of dosing accuracy: visually impaired and sighted people using insulin pens. J Diabetes Sci Technol 2010;4:514–521
112. Reinauer KM, Joksch G, Renn W, Eggstein M. Insulin pens in elderly diabetic patients. Diabetes Care 1990;13:1136–1137
113. Thomas DR, Fischer RG, Nicholas WC, Beghe C, Hatten KW, Thomas JN. Disposable insulin syringe reuse and aseptic practices in diabetic patients. J Gen Intern Med 1989;4:97–100
114. Gomez-Peralta F, Abreu C, Gomez-Rodriguez S, et al. Efficacy of *Insulclock* in patients with poorly controlled type 1 diabetes mellitus: a pilot, randomized clinical trial. Diabetes Technol Ther 2020;22:686–690
115. Bailey TS, Stone JY. A novel pen-based Bluetooth-enabled insulin delivery system with insulin dose tracking and advice. Expert Opin Drug Deliv 2017;14:697–703
116. Eiland L, McLarney M, Thangavelu T, Drincic A App-based insulin calculators: current and future state. Curr Diab Rep 2018;18:123
117. Huckvale K, Adomaviciute S, Prieto JT, Leow MK-S, Car J. Smartphone apps for calculating insulin dose: a systematic assessment. BMC Med 2015;13:106
118. Breton MD, Patek SD, Lv D, et al. Continuous glucose monitoring and insulin informed advisory system with automated titration and dosing of insulin reduces glucose variability in type 1 diabetes mellitus. Diabetes Technol Ther 2018;20:531–540
119. Bergenstal RM, Johnson M, Passi R, et al. Automated insulin dosing guidance to optimise insulin management in patients with type 2 diabetes: a multicentre, randomised controlled trial. Lancet 2019;393:1138–1148

120. Yeh H-C, Brown TT, Maruthur N, et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. Ann Intern Med 2012;157:336–347
121. Pickup JC. The evidence base for diabetes technology: appropriate and inappropriate meta-analysis. J Diabetes Sci Technol 2013;7: 1567–1574
122. Blackman SM, Raghinaru D, Adi S, et al. Insulin pump use in young children in the T1D Exchange clinic registry is associated with lower hemoglobin A1c levels than injection therapy. Pediatr Diabetes 2014;15:564–572
123. Lin MH, Connor CG, Ruedy KJ, et al.; Pediatric Diabetes Consortium. Race, socioeconomic status, and treatment center are associated with insulin pump therapy in youth in the first year following diagnosis of type 1 diabetes. Diabetes Technol Ther 2013;15:929–934
124. Willi SM, Miller KM, DiMeglio LA, et al.; T1D Exchange Clinic Network. Racial-ethnic disparities in management and outcomes among children with type 1 diabetes. Pediatrics 2015;135: 424–434
125. Redondo MJ, Libman I, Cheng P, et al.; Pediatric Diabetes Consortium. Racial/ethnic minority youth with recent-onset type 1 diabetes have poor prognostic factors. Diabetes Care 2018;41:1017–1024
126. Ramchandani N, Ten S, Anhalt H, et al. Insulin pump therapy from the time of diagnosis of type 1 diabetes. Diabetes Technol Ther 2006;8: 663–670
127. Berghaeuser MA, Kapellen T, Heidtmann B, Haberland H, Klinkert C, Holl RW; German working group for insulin pump treatment in paediatric patients. Continuous subcutaneous insulin infusion in toddlers starting at diagnosis of type 1 diabetes mellitus. A multicenter analysis of 104 patients from 63 centres in Germany and Austria. Pediatr Diabetes 2008;9:590–595
128. Peters AL, Ahmann AJ, Battelino T, et al. Diabetes technology-continuous subcutaneous insulin infusion therapy and continuous glucose monitoring in adults: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2016;101:3922–3937
129. Gill M, Chhabra H, Shah M, Zhu C, Grunberger G. C-peptide and beta-cell autoantibody testing prior to initiating continuous subcutaneous insulin infusion pump therapy did not improve utilization or medical costs among older adults with diabetes mellitus. Endocr Pract 2018; 24:634–645
130. Vigersky RA, Huang S, Cordero TL, et al.; OpT2mise Study Group. Improved HbA1c, total daily insulin dose, and treatment satisfaction with insulin pump therapy compared to multiple daily insulin injections in patients with type 2 diabetes irrespective of baseline C-peptide levels. Endocr Pract 2018;24:446–452
131. Wheeler BJ, Heels K, Donaghue KC, Reith DM, Ambler GR. Insulin pump-associated adverse events in children and adolescents—a prospective study. Diabetes Technol Ther 2014;16:558–562
132. Kordonouri O, Lauterborn R, Deiss D. Lipohypertrophy in young patients with type 1 diabetes. Diabetes Care 2002;25:634
133. Kordonouri O, Hartmann R, Remus K, Bläsig S, Sadeghian E, Danne T. Benefit of supplementary fat plus protein counting as compared with conventional carbohydrate counting for insulin bolus calculation in children with pump therapy. Pediatr Diabetes 2012;13:540–544
134. Guinn TS, Bailey GJ, Mecklenburg RS. Factors related to discontinuation of continuous subcutaneous insulin-infusion therapy. Diabetes Care 1988;11:46–51
135. Wong JC, Boyle C, DiMeglio LA, et al.; T1D Exchange Clinic Network. Evaluation of pump discontinuation and associated factors in the T1D Exchange clinic registry. J Diabetes Sci Technol 2017;11:224–232
136. Wong JC, Dolan LM, Yang TT, Hood KK. Insulin pump use and glycemic control in adolescents with type 1 diabetes: predictors of change in method of insulin delivery across two years. Pediatr Diabetes 2015;16:592–599
137. Plotnick LP, Clark LM, Brancati FL, Erlinger T. Safety and effectiveness of insulin pump therapy in children and adolescents with type 1 diabetes. Diabetes Care 2003;26:1142–1146
138. Redondo MJ, Connor CG, Ruedy KJ, et al.; Pediatric Diabetes Consortium. Pediatric Diabetes Consortium Type 1 Diabetes New Onset (NeOn) Study: factors associated with HbA1c levels one year after diagnosis. Pediatr Diabetes 2014;15:294–302
139. Doyle EA, Weinzimer SA, Steffen AT, Ahern JAH, Vincent M, Tamborlane WVA. A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine. Diabetes Care 2004;27:1554–1558
140. Alemzadeh R, Ellis JN, Holzum MK, Parton EA, Wyatt DT. Beneficial effects of continuous subcutaneous insulin infusion and flexible multiple daily insulin regimen using insulin glargine in type 1 diabetes. Pediatrics 2004;114:e91–e95
141. Sherr JL, Hermann JM, Campbell F, et al.; T1D Exchange Clinic Network, the DPV Initiative, and the National Paediatric Diabetes Audit and the Royal College of Paediatrics and Child Health registries. Use of insulin pump therapy in children and adolescents with type 1 diabetes and its impact on metabolic control: comparison of results from three large, transatlantic paediatric registries. Diabetologia 2016;59:87–91
142. Jeitler K, Horvath K, Berghold A, et al. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. Diabetologia 2008;51:941–951
143. Karges B, Schwandt A, Heidtmann B, et al. Association of insulin pump therapy vs insulin injection therapy with severe hypoglycemia, ketoacidosis, and glycemic control among children, adolescents, and young adults with type 1 diabetes. JAMA 2017;318:1358–1366
144. The DCCT Research Group. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. Am J Med 1991;90:450–459
145. Haynes A, Hermann JM, Miller KM, et al.; T1D Exchange, WACDD and DPV registries. Severe hypoglycemia rates are not associated with HbA1c: a cross-sectional analysis of 3 contemporary pediatric diabetes registry databases. Pediatr Diabetes 2017;18:643–650
146. Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. Diabet Med 2008;25:765–774
147. Birkebaek NH, Drivvoll AK, Aakeson K, et al. Incidence of severe hypoglycemia in children with type 1 diabetes in the Nordic countries in the period 2008-2012: association with hemoglobin A_{1c} and treatment modality. BMJ Open Diabetes Res Care 2017;5:e000377
148. Maahs DM, Hermann JM, Holman N, et al.; National Paediatric Diabetes Audit and the Royal College of Paediatrics and Child Health, the DPV Initiative, and the T1D Exchange Clinic Network. Rates of diabetic ketoacidosis: international comparison with 49,859 pediatric patients with type 1 diabetes from England, Wales, the U.S., Austria, and Germany. Diabetes Care 2015;38:1876–1882
149. Weintrob N, Benzaquen H, Galatzer A, et al. Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens in children with type 1 diabetes: a randomized open crossover trial. Pediatrics 2003;112:559–564
150. Opipari-Arrigan L, Fredericks EM, Burkhart N, Dale L, Hodge M, Foster C. Continuous subcutaneous insulin infusion benefits quality of life in preschool-age children with type 1 diabetes mellitus. Pediatr Diabetes 2007;8:377–383
151. Commissariat PV, Boyle CT, Miller KM, et al. Insulin pump use in young children with type 1 diabetes: sociodemographic factors and parent-reported barriers. Diabetes Technol Ther 2017; 19:363–369
152. Grunberger G, Sze D, Ermakova A, Sieradzan R, Oliveria T, Miller EM. Treatment intensification with insulin pumps and other technologies in patients with type 2 diabetes: results of a physician survey in the United States. Clin Diabetes 2020;38:47–55
153. Grunberger G, Rosenfeld CR, Bode BW, et al. Effectiveness of V-Go® for patients with type 2 diabetes in a real-world setting: a prospective observational study. Drugs Real World Outcomes 2020;7:31–40
154. Layne JE, Parkin CG, Zisser H. Efficacy of a tubeless patch pump in patients with type 2 diabetes previously treated with multiple daily injections. J Diabetes Sci Technol 2017;11:178–179
155. Raval AD, Nguyen MH, Zhou S, Grabner M, Barron J, Quimbo R. Effect of V-Go versus multiple daily injections on glycemic control, insulin use, and diabetes medication costs among individuals with type 2 diabetes mellitus. J Manag Care Spec Pharm 2019;25:1111–1123
156. Leahy JJL, Aleppo G, Fonseca VA, et al. Optimizing postprandial glucose management in adults with insulin-requiring diabetes: report and recommendations. J Endocr Soc 2019;3:1942–1957
157. Reznik Y, Cohen O, Aronson R, et al.; OpT2mise Study Group. Insulin pump treatment compared with multiple daily injections for treatment of type 2 diabetes (OpT2mise): a randomised open-label controlled trial. Lancet 2014;384: 1265–1272
158. Winter A, Lintner M, Knezevich E. V-Go insulin delivery system versus multiple daily insulin injections for patients with uncontrolled type 2 diabetes mellitus. J Diabetes Sci Technol 2015;9:1111–1116
159. Forlenza GP, Li Z, Buckingham BA, et al. Predictive low-glucose suspend reduces hypoglycemia

in adults, adolescents, and children with type 1 diabetes in an at-home randomized crossover study: results of the PROLOG trial. Diabetes Care 2018;41:2155–2161
160. Wood MA, Shulman DI, Forlenza GP, et al. In-clinic evaluation of the MiniMed 670G system "suspend before low" feature in children with type 1 diabetes. Diabetes Technol Ther 2018;20:731–737
161. Beato-Víbora PI, Quirós-López C, Lázaro-Martín L, et al. Impact of sensor-augmented pump therapy with predictive low-glucose suspend function on glycemic control and patient satisfaction in adults and children with type 1 diabetes. Diabetes Technol Ther 2018;20:738–743
162. Brown SA, Beck RW, Raghinaru D, et al.; iDCL Trial Research Group. Glycemic outcomes of use of CLC versus PLGS in type 1 diabetes: a randomized controlled trial. Diabetes Care 2020;43:1822–1828
163. Bergenstal RM, Garg S, Weinzimer SA, et al. Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. JAMA 2016;316:1407–1408
164. Garg SK, Weinzimer SA, Tamborlane WV, et al. Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. Diabetes Technol Ther 2017;19:155–163
165. Tauschmann M, Thabit H, Bally L, et al.; APCam11 Consortium. Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. Lancet 2018;392:1321–1329
166. Ekhlaspour L, Forlenza GP, Chernavvsky D, et al. Closed loop control in adolescents and children during winter sports: use of the Tandem Control-IQ AP system. Pediatr Diabetes 2019;20:759–768
167. Buckingham BA, Christiansen MP, Forlenza GP, et al. Performance of the Omnipod personalized model predictive control algorithm with meal bolus challenges in adults with type 1 diabetes. Diabetes Technol Ther 2018;20:585–595
168. Renard E, Tubiana-Rufi N, Bonnemaison-Gilbert E, et al. Closed-loop driven by control-to-range algorithm outperforms threshold-low-glucose-suspend insulin delivery on glucose control albeit not on nocturnal hypoglycaemia in prepubertal patients with type 1 diabetes in a supervised hotel setting. Diabetes Obes Metab 2019;21:183–187
169. Forlenza GP, Ekhlaspour L, Breton M, et al. Successful at-home use of the Tandem Control-IQ artificial pancreas system in young children during a randomized controlled trial. Diabetes Technol Ther 2019;21:159–169
170. Anderson SM, Buckingham BA, Breton MD, et al. Hybrid closed-loop control is safe and effective for people with type 1 diabetes who are at moderate to high risk for hypoglycemia. Diabetes Technol Ther 2019;21:356–363
171. Forlenza GP, Pinhas-Hamiel O, Liljenquist DR, et al. Safety evaluation of the MiniMed 670G system in children 7-13 years of age with type 1 diabetes. Diabetes Technol Ther 2019;21:11–19
172. Karageorgiou V, Papaioannou TG, Bellos I, et al. Effectiveness of artificial pancreas in the non-adult population: a systematic review and network meta-analysis. Metabolism 2019;90:20–30
173. Brown S, Raghinaru D, Emory E, Kovatchev B. First look at Control-IQ: a new-generation automated insulin delivery system. Diabetes Care 2018;41:2634–2636
174. Brown SA, Kovatchev BP, Raghinaru D, et al.; iDCL Trial Research Group. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. N Engl J Med 2019;381:1707–1717
175. Kaur H, Schneider N, Pyle L, Campbell K, Akturk HK, Shah VN. Efficacy of hybrid closed-loop system in adults with type 1 diabetes and gastroparesis. Diabetes Technol Ther 2019;21:736–739
176. Sherr JL, Buckingham BA, Forlenza GP, et al. Safety and performance of the Omnipod hybrid closed-loop system in adults, adolescents, and children with type 1 diabetes over 5 days under free-living conditions. Diabetes Technol Ther 2020;22:174–184
177. Lal RA, Basina M, Maahs DM, Hood K, Buckingham B, Wilson DM. One year clinical experience of the first commercial hybrid closed-loop system. Diabetes Care 2019;42:2190–2196
178. Kovatchev B, Anderson SM, Raghinaru D, et al.; iDCL Study Group. Randomized controlled trial of mobile closed-loop control. Diabetes Care 2020;43:607–615
179. Sherr JL, Cengiz E, Palerm CC, et al. Reduced hypoglycemia and increased time in target using closed-loop insulin delivery during nights with or without antecedent afternoon exercise in type 1 diabetes. Diabetes Care 2013;36:2909–2914
180. Troncone A, Bonfanti R, Iafusco D, et al. Evaluating the experience of children with type 1 diabetes and their parents taking part in an artificial pancreas clinical trial over multiple days in a diabetes camp setting. Diabetes Care 2016;39:2158–2164
181. Barnard KD, Wysocki T, Allen JM, et al. Closing the loop overnight at home setting: psychosocial impact for adolescents with type 1 diabetes and their parents. BMJ Open Diabetes Res Care 2014;2:e000025
182. Barnard KD, Wysocki T, Thabit H, et al.; Angela Consortium. Psychosocial aspects of closed- and open-loop insulin delivery: closing the loop in adults with type 1 diabetes in the home setting. Diabet Med 2015;32:601–608
183. Weissberg-Benchell J, Hessler D, Polonsky WH, Fisher L. Psychosocial impact of the bionic pancreas during summer camp. J Diabetes Sci Technol 2016;10:840–844
184. Lewis D. History and perspective on DIY closed looping. J Diabetes Sci Technol 2019;13:790–793
185. Hng T-M, Burren D. Appearance of do-it-yourself closed-loop systems to manage type 1 diabetes. Intern Med J 2018;48:1400–1404
186. Petruzelkova L, Soupal J, Plasova V, et al. Excellent glycemic control maintained by open-source hybrid closed-loop AndroidAPS during and after sustained physical activity. Diabetes Technol Ther 2018;20:744–750
187. Kesavadev J, Srinivasan S, Saboo B, Krishna B M, Krishnan G. The do-it-yourself artificial pancreas: a comprehensive review. Diabetes Ther 2020;11:1217–1235
188. Fleming GA, Petrie JR, Bergenstal RM, Holl RW, Peters AL, Heinemann L. Diabetes digital app technology: benefits, challenges, and recommendations. A consensus report by the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) Diabetes Technology Working Group. Diabetes Care 2020;43:250–260
189. Wong JC, Izadi Z, Schroeder S, et al. A pilot study of use of a software platform for the collection, integration, and visualization of diabetes device data by health care providers in a multidisciplinary pediatric setting. Diabetes Technol Ther 2018;20:806–816
190. Chao DY, Lin TM, Ma W-Y. Enhanced self-efficacy and behavioral changes among patients with diabetes: cloud-based mobile health platform and mobile app service. JMIR Diabetes 2019;4:e11017
191. Sepah SC, Jiang L, Peters AL. Translating the Diabetes Prevention Program into an online social network: validation against CDC standards. Diabetes Educ 2014;40:435–443
192. Kaufman N, Ferrin C, Sugrue D. Using digital health technology to prevent and treat diabetes. Diabetes Technol Ther 2019;21(S1):S79–S94
193. Öberg U, Isaksson U, Jutterström L, Orre CJ, Hörnsten Å. Perceptions of persons with type 2 diabetes treated in Swedish primary health care: qualitative study on using ehealth services for self-management support. JMIR Diabetes 2018;3:e7
194. Bollyky JB, Bravata D, Yang J, Williamson M, Schneider J. Remote lifestyle coaching plus a connected glucose meter with certified diabetes educator support improves glucose and weight loss for people with type 2 diabetes. J Diabetes Res 2018;2018:3961730
195. Wilhide Iii CC, Peeples MM, Anthony Kouyaté RC. Evidence-based mhealth chronic disease mobile app intervention design: development of a framework. JMIR Res Protoc 2016;5:e25
196. Dixon RF, Zisser H, Layne JE, et al. A virtual type 2 diabetes clinic using continuous glucose monitoring and endocrinology visits. J Diabetes Sci Technol 2020;14:908–911
197. Yang Y, Lee EY, Kim H-S, Lee S-H, Yoon K-H, Cho J-H. Effect of a mobile phone-based glucose-monitoring and feedback system for type 2 diabetes management in multiple primary care clinic settings: cluster randomized controlled trial. JMIR Mhealth Uhealth. 2020;8:e16266
198. Levine BJ, Close KL, Gabbay RA. Reviewing U.S. connected diabetes care: the newest member of the team. Diabetes Technol Ther 2020;22:1–9
199. McGill DE, Volkening LK, Butler DA, Wasserman RM, Anderson BJ, Laffel LM. Text-message responsiveness to blood glucose monitoring reminders is associated with HbA_{1c} benefit in teenagers with type 1 diabetes. Diabet Med 2019;36:600–605
200. Shen Y, Wang F, Zhang X, et al. Effectiveness of internet-based interventions on glycemic control in patients with type 2 diabetes: meta-analysis of randomized controlled trials. J Med Internet Res 2018;20:e172
201. Stone MP, Agrawal P, Chen X, et al. Retrospective analysis of 3-month real-world glucose data after the MiniMed 670G system commercial launch. Diabetes Technol Ther 2018;20:689–692
202. Umpierrez GE, Klonoff DC. Diabetes technology update: use of insulin pumps and continuous glucose monitoring in the hospital. Diabetes Care 2018;41:1579–1589
203. U.S. Food and Drug Administration. Enforcement Policy for Non-Invasive Remote Monitoring Devices Used to Support Patient Monitoring During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency

(Revised): Guidance for Industry and Food and Drug Administration Staff. June 2020. Accessed 2 September 2020. Available from https://www.fda.gov/media/136290/download
204. Ushigome E, Yamazaki M, Hamaguchi M, et al. Usefulness and safety of remote continuous glucose monitoring for a severe COVID-19 patient with diabetes. Diabetes Technol Ther. 15 July 2020 [Epub ahead of print]. DOI: 10.1089/dia.2020.0237
205. Galindo RJ, Aleppo G, Klonoff DC, et al. Implementation of continuous glucose monitoring in the hospital: emergent considerations for remote glucose monitoring during the COVID-19 pandemic. J Diabetes Sci Technol 2020;14:822–832
206. U.S. Food and Drug Administration. Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use: Guidance for Industry and Food and Drug Administration Staff. 2019. Accessed 1 November 2020. Available from http://www.fda.gov/regulatory-information/search-fda-guidance-documents/self-monitoring-blood-glucose-test-systems-over-counter-use-0
207. U.S. Food and Drug Administration. Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use: Guidance for Industry and Food and Drug Administration Staff. 2016. Accessed 1 November 2020. Available from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/blood-glucose-monitoring-test-systems-prescription-point-care-use
208. International Standards Organization. ISO 15197:2013. In vitro diagnostic test systems – requirements for blood glucose monitoring systems for self-testing in managing diabetes mellitus. Accessed 1 November 2020. Available from http://www.iso.org/cms/render/live/en/sites/isoorg/contents/data/standard/05/49/54976.html
209. Parkes JL, Slatin SL, Pardo S, Ginsberg BH. A new consensus error grid to evaluate the clinical significance of inaccuracies in the measurement of blood glucose. Diabetes Care 2000;23:1143–1148

8. Obesity Management for the Treatment of Type 2 Diabetes: *Standards of Medical Care in Diabetes—2021*

American Diabetes Association

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The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc21-SPPC), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc21-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

There is strong and consistent evidence that obesity management can delay the progression from prediabetes to type 2 diabetes (1–5) and is highly beneficial in the treatment of type 2 diabetes (6–17). In patients with type 2 diabetes who also have overweight or obesity, modest and sustained weight loss has been shown to improve glycemic control and reduce the need for glucose-lowering medications (6–8). Several studies have demonstrated that in patients with type 2 diabetes and obesity, more intensive dietary energy restriction with very-low-calorie diets can substantially reduce A1C and fasting glucose and promote sustained diabetes remission through at least 2 years (10,18–21). The goal of this section is to provide evidence-based recommendations for obesity management, including dietary, behavioral, pharmacologic, and surgical interventions, in patients with type 2 diabetes. This section focuses on obesity management in adults. Further discussion on obesity in older individuals and children can be found in Section 12 "Older Adults" (https://doi.org/10.2337/dc21-S012) and Section 13 "Children and Adolescents" (https://doi.org/10.2337/dc21-S013), respectively.

ASSESSMENT

Recommendations

8.1 Use patient-centered, nonjudgmental language that fosters collaboration between patients and providers, including people-first language (e.g., "person with obesity" rather than "obese person"). **E**

8.2 Measure height and weight and calculate BMI at annual visits or more frequently. Assess weight trajectory to inform treatment considerations. **E**

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8.3 Based on clinical considerations, such as the presence of comorbid heart failure or significant unexplained weight gain or loss, weight may need to be monitored and evaluated more frequently. **B** If deterioration of medical status is associated with significant weight gain or loss, inpatient evaluation should be considered, especially focused on associations between medication use, food intake, and glycemic status. **E**

8.4 Accommodations should be made to provide privacy during weighing. **E**

A patient-centered communication style that uses inclusive and nonjudgmental language and active listening, elicits patient preferences and beliefs, and assesses potential barriers to care should be used to optimize patient health outcomes and health-related quality of life. Use people-first language (e.g., "person with obesity" rather than "obese person") to avoid defining patients by their condition (22,23,23a).

Height and weight should be measured and used to calculate BMI at annual visits or more frequently when appropriate (19). BMI, calculated as weight in kilograms divided by the square of height in meters (kg/m^2), will be calculated automatically by most electronic medical records. Use BMI to document weight status (overweight: BMI 25–29.9 kg/m^2; obesity class I: BMI 30–34.9 kg/m^2; obesity class II: BMI 35–39.9 kg/m^2; obesity class III: BMI $\geq$40 kg/m^2). Note that misclassification can occur, particularly in very muscular or frail individuals. In some populations, notably Asian and Asian American populations, the BMI cut points to define overweight and obesity are lower than in other populations due to differences in body composition and cardiometabolic risk (**Table 8.1**) (24,25). Clinical considerations, such as the presence of comorbid heart failure or unexplained weight change, may warrant more frequent weight measurement and evaluation (26,27). If weighing is questioned or refused, the practitioner should be mindful of possible prior stigmatizing experiences and query for concerns, and the value of weight monitoring should be explained as a part of the medical evaluation process that helps to inform treatment decisions (28,29). Accommodations should be made to ensure privacy during weighing, particularly for those patients who report or exhibit a high level of weight-related distress or dissatisfaction. Scales should be situated in a private area or room. Weight should be measured and reported nonjudgmentally. Care should be taken to regard a patient's weight (and weight changes) and BMI as sensitive health information. Additionally, assessing weight gain pattern and trajectory can further inform risk stratification and treatment options (30). Providers should advise patients with overweight or obesity and those with increasing weight trajectories that, in general, higher BMIs increase the risk of diabetes, cardiovascular disease, and all-cause mortality, as well as other adverse health and quality of life outcomes. Providers should assess readiness to engage in behavioral changes for weight loss and jointly determine behavioral and weight-loss goals and patient-appropriate intervention strategies (31). Strategies may include dietary changes, physical activity, behavioral therapy, pharmacologic therapy, medical devices, and metabolic surgery (**Table 8.1**). The latter three strategies may be prescribed for carefully selected patients as adjuncts to dietary changes, physical activity, and behavioral counseling.

DIET, PHYSICAL ACTIVITY, AND BEHAVIORAL THERAPY

Recommendations

8.5 Diet, physical activity, and behavioral therapy designed to achieve and maintain $\geq$5% weight loss is recommended for most patients with type 2 diabetes who have overweight or obesity and are ready to achieve weight loss. Greater benefits in control of diabetes and cardiovascular risk may be gained from even greater weight loss. **B**

8.6 Such interventions should include a high frequency of counseling ($\geq$16 sessions in 6 months) and focus on dietary changes, physical activity, and behavioral strategies to achieve a 500–750 kcal/day energy deficit. **A**

8.7 An individual's preferences, motivation, and life circumstances should be considered, along with medical status, when weight loss interventions are recommended. **C**

8.8 Behavioral changes that create an energy deficit, regardless of macronutrient composition, will result in weight loss. Dietary recommendations should be individualized to the patient's preferences and nutritional needs. **A**

8.9 Evaluate systemic, structural, and socioeconomic factors that may impact dietary patterns and food choices, such as food insecurity and hunger, access to healthful food options, cultural circumstances, and social determinants of health. **C**

8.10 For patients who achieve short-term weight-loss goals, long-term ($\geq$1 year) weight-maintenance programs are recommended when available. Such programs should, at minimum, provide monthly contact and support, recommend ongoing monitoring of body weight (weekly or more frequently) and other self-monitoring strategies, and encourage high levels of physical activity (200–300 min/week). **A**

8.11 Short-term dietary intervention using structured, very-low-calorie diets (800–1,000 kcal/day) may be prescribed for carefully selected patients by trained practitioners in medical settings with close monitoring. Long-term, comprehensive weight-maintenance strategies and counseling should be integrated to maintain weight loss. **B**

Among patients with both type 2 diabetes and overweight or obesity who have inadequate glycemic, blood pressure, and lipid control and/or other obesity-related medical conditions, modest and sustained weight loss improves glycemic control, blood pressure, and lipids and may reduce the need for medications to control these risk factors (6–8,32). Greater weight loss may produce even greater benefits (20,21). For a more detailed discussion of lifestyle management approaches and recommendations see Section 5 "Facilitating Behavior Change and Well-being to Improve Health Outcomes" (https://doi.org/10.2337/dc21-S005). For a detailed discussion of nutrition interventions, please also refer to "Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report" (33).

Table 8.1—Treatment options for overweight and obesity in type 2 diabetes

	BMI category (kg/m^2)		
Treatment	25.0–26.9 (or 23.0–24.9*)	27.0–29.9 (or 25.0–27.4*)	≥30.0 (or ≥27.5*)
Diet, physical activity, and behavioral therapy	†	†	†
Pharmacotherapy		†	†
Metabolic surgery			†

*Recommended cut points for Asian American individuals (expert opinion). †Treatment may be indicated for select motivated patients.

Look AHEAD Trial

Although the Action for Health in Diabetes (Look AHEAD) trial did not show that the intensive lifestyle intervention reduced cardiovascular events in adults with type 2 diabetes and overweight or obesity (34), it did confirm the feasibility of achieving and maintaining long-term weight loss in patients with type 2 diabetes. In the intensive lifestyle intervention group, mean weight loss was 4.7% at 8 years (35). Approximately 50% of intensive lifestyle intervention participants lost and maintained ≥5% of their initial body weight, and 27% lost and maintained ≥10% of their initial body weight at 8 years (35). Participants assigned to the intensive lifestyle group required fewer glucose-, blood pressure–, and lipid-lowering medications than those randomly assigned to standard care. Secondary analyses of the Look AHEAD trial and other large cardiovascular outcome studies document additional benefits of weight loss in patients with type 2 diabetes, including improvements in mobility, physical and sexual function, and health-related quality of life (26). Moreover, several subgroups had improved cardiovascular outcomes, including those who achieved >10% weight loss (36) and those with moderately or poorly controlled diabetes (A1C >6.8%) at baseline (37).

Lifestyle Interventions

Significant weight loss can be attained with lifestyle programs that achieve a 500–750 kcal/day energy deficit, which in most cases is approximately 1,200–1,500 kcal/day for women and 1,500–1,800 kcal/day for men, adjusted for the individual's baseline body weight. Clinical benefits typically begin upon achieving 3–5% weight loss (19,38), and the benefits of weight loss are progressive; more intensive weight-loss goals (>5%, >7%, >15%, etc.) may be pursued if needed to achieve further health improvements and/or if the patient is more motivated and more intensive goals can be feasibly and safely attained.

Dietary interventions may differ by macronutrient goals and food choices as long as they create the necessary energy deficit to promote weight loss (19,39–41). Use of meal replacement plans prescribed by trained practitioners, with close patient monitoring, can be beneficial. Within the intensive lifestyle intervention group of the Look AHEAD trial, for example, use of a partial meal replacement plan was associated with improvements in diet quality and weight loss (38). The diet choice should be based on the patient's health status and preferences, including a determination of food availability and other cultural circumstances that could affect dietary patterns (42).

Intensive behavioral lifestyle interventions should include ≥16 sessions in 6 months and focus on dietary changes, physical activity, and behavioral strategies to achieve an ~500–750 kcal/day energy deficit. Interventions should be provided by trained interventionists in either individual or group sessions (38). Assessing an individual's motivation level, life circumstances, and willingness to implement lifestyle changes to achieve weight loss should be considered along with medical status when weight-loss interventions are recommended and initiated (31,43).

Patients with type 2 diabetes and overweight or obesity who have lost weight should be offered long-term (≥1 year) comprehensive weight-loss maintenance programs that provide at least monthly contact with trained interventionists and focus on ongoing monitoring of body weight (weekly or more frequently) and/or other self-monitoring strategies such as tracking intake, steps, etc.; continued focus on dietary and behavioral changes; and participation in high levels of physical activity (200–300 min/week) (44). Some commercial and proprietary weight-loss programs have shown promising weight-loss results, though most lack evidence of effectiveness, many do not satisfy guideline recommendations, and some promote unscientific and possibly dangerous practices (45,46).

When provided by trained practitioners in medical settings with ongoing monitoring, short-term (generally up to 3 months) intensive dietary intervention may be prescribed for carefully selected patients, such as those requiring weight loss prior to surgery and persons needing greater weight loss and glycemic improvements. When integrated with behavioral support and counseling, structured very-low-calorie diets, typically 800–1,000 kcal/day utilizing high-protein foods and meal replacement products, may increase the pace and/or magnitude of initial weight loss and glycemic improvements compared with standard behavioral interventions (20,21). As weight regain is common, such interventions should include long-term, comprehensive weight-maintenance strategies and counseling to maintain weight loss and behavioral changes (47,48).

Health disparities adversely affect groups of people who have systematically experienced greater obstacles to health based on their race or ethnicity, socioeconomic status, gender, disability, or other factors. Overwhelming research shows that these disparities may significantly affect health outcomes, including increasing the risk for diabetes and diabetes-related complications. Health care providers should evaluate systemic, structural, and socioeconomic factors that may impact food choices, access to healthful foods, and dietary patterns; other behavioral patterns, such as neighborhood safety and availability of safe outdoor spaces for physical activity; environmental exposures; access to health care; social contexts; and, ultimately, diabetes risk and outcomes. For a detailed discussion of social determinants of health, please refer to "Social Determinants of Health: A Scientific Review" (49).

Table 8.2—Medications approved by the FDA for the treatment of obesity

Medication name	Typical adult maintenance dose	Average wholesale price (30-day supply) (118)	National Average Drug Acquisition Cost (30-day supply) (119)	1-Year (52- or 56-week) mean weight loss (% loss from baseline)		Common side effects (120–124)	Possible safety concerns/ considerations (120–124)
				Treatment arms	Weight loss (% loss from baseline)		
Short-term treatment (≤12 weeks)							
Sympathomimetic amine anorectic							
Phentermine (125)	8–37.5 mg q.d.*	$5–$46 (37.5 mg dose)	$3 (37.5 mg dose)	15 mg q.d.† 7.5 mg q.d.† PBO	6.1 5.5 1.2	Dry mouth, insomnia, dizziness, irritability, increased blood pressure, elevated heart rate	• Contraindicated for use in combination with monoamine oxidase inhibitors
Long-term treatment (>12 weeks)							
Lipase inhibitor							
Orlistat (3)	60 mg t.i.d. (OTC) 120 mg t.i.d. (Rx)	$41−$82 $823	$41 $556	120 mg t.i.d.‡ PBO	9.6 5.6	Abdominal pain, flatulence, fecal urgency	• Potential malabsorption of fat-soluble vitamins (A, D, E, K) and of certain medications (e.g., cyclosporine, thyroid hormone, anticonvulsants, etc.) • Rare cases of severe liver injury reported • Cholelithiasis • Nephrolithiasis
Sympathomimetic amine anorectic/antiepileptic combination							
Phentermine/ topiramate ER (126)	7.5 mg/46 mg q.d.§	$223 (7.5 mg/ 46 mg dose)	$179 (7.5 mg/ 46 mg dose)	15 mg/92 mg q.d.‖ 7.5 mg/46 mg q.d.‖ PBO	9.8 7.8 1.2	Constipation, paresthesia, insomnia, nasopharyngitis, xerostomia, increased blood pressure	• Contraindicated for use in combination with monoamine oxidase inhibitors • Birth defects • Cognitive impairment • Acute angle-closure glaucoma
Opioid antagonist/antidepressant combination							
Naltrexone/ bupropion ER (15)	16 mg/180 mg b.i.d.	$334	$266	16 mg/180 mg b.i.d. PBO	5.0 1.8	Constipation, nausea, headache, xerostomia, insomnia, elevated heart rate and blood pressure	• Contraindicated in patients with uncontrolled hypertension and/or seizure disorders • Contraindicated for use with chronic opioid therapy • Acute angle-closure glaucoma **Black box warning:** • Risk of suicidal behavior/ideation in persons younger than 24 years old who have depression

Continued on p. S104

Table 8.2—Continued

Medication name	Typical adult maintenance dose	Average wholesale price (30-day supply) (118)	National Average Drug Acquisition Cost (30-day supply) (119)	1-Year (52- or 56-week) mean weight loss (% loss from baseline)		Common side effects (120–124)	Possible safety concerns/ considerations (120–124)
				Treatment arms	Weight loss (% loss from baseline)		
Glucagon-like peptide 1 receptor agonist							
Liraglutide (16)**	3 mg q.d.	$1,557	$1,243	3.0 mg q.d. 1.8 mg q.d. PBO	6.0 4.7 2.0	Gastrointestinal side effects (nausea, vomiting, diarrhea, esophageal reflux), injection site reactions, elevated heart rate	• Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected. • Use caution in patients with kidney disease when initiating or increasing dose due to potential risk of acute kidney injury **Black box warning:** • Risk of thyroid C-cell tumors in rodents; human relevance not determined

All medications are contraindicated in women who are or may become pregnant. Women of reproductive potential must be counseled regarding the use of reliable methods of contraception. Select safety and side effect information is provided; for a comprehensive discussion of safety considerations, please refer to the prescribing information for each agent. b.i.d., twice daily; ER, extended release; OTC, over the counter; PBO, placebo; q.d., daily; Rx, prescription; t.i.d., three times daily. *Use lowest effective dose; maximum appropriate dose is 37.5 mg. †Duration of treatment was 28 weeks in a general obese adult population. **Agent has demonstrated cardiovascular safety in a dedicated cardiovascular outcome trial (127). ‡Enrolled participants had normal (79%) or impaired (21%) glucose tolerance. §Maximum dose, depending on response, is 15 mg/92 mg q.d. ||Approximately 68% of enrolled participants had type 2 diabetes or impaired glucose tolerance.

PHARMACOTHERAPY

Recommendations

8.12 When choosing glucose-lowering medications for patients with type 2 diabetes and overweight or obesity, consider the medication's effect on weight. **B**

8.13 Whenever possible, minimize medications for comorbid conditions that are associated with weight gain. **E**

8.14 Weight-loss medications are effective as adjuncts to diet, physical activity, and behavioral counseling for selected patients with type 2 diabetes and BMI $\geq$27 kg/m^2. Potential benefits and risks must be considered. **A**

8.15 If a patient's response to weight-loss medication is effective (typically defined as >5% weight loss after 3 months' use), further weight loss is likely with continued use. When early response is insufficient (typically <5% weight loss after 3 months' use), or if there are significant safety or tolerability issues, consider discontinuation of the medication and evaluate alternative medications or treatment approaches. **A**

Glucose-Lowering Therapy

A meta-analysis of 227 randomized controlled trials of glucose-lowering treatments in type 2 diabetes found that A1C changes were not associated with baseline BMI, indicating that patients with obesity can benefit from the same types of treatments for diabetes as normal-weight patients (50). As numerous effective medications are available, when considering medication regimens health care providers should consider each medication's effect on weight. Agents associated with varying degrees of weight loss include metformin, α-glucosidase inhibitors, sodium–glucose cotransporter 2 inhibitors, glucagon-like peptide 1 receptor agonists, and amylin mimetics. Dipeptidyl peptidase 4 inhibitors are weight neutral. In contrast, insulin secretagogues, thiazolidinediones, and insulin are often associated with weight gain (see Section 9 "Pharmacologic Approaches to Glycemic Treatment," https://doi.org/10.2337/dc21-s009).

Concomitant Medications

Providers should carefully review the patient's concomitant medications and, whenever possible, minimize or provide alternatives for medications that promote weight gain. Examples of medications associated with weight gain include antipsychotics (e.g., clozapine, olanzapine, risperidone, etc.), some antidepressants (e.g., tricyclic antidepressants, some selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors), glucocorticoids, injectable progestins, some anticonvulsants (e.g., gabapentin, pregabalin), and possibly sedating antihistamines and anticholinergics (51).

Approved Weight-Loss Medications

The U.S. Food and Drug Administration (FDA) has approved medications for both short-term and long-term weight management as adjuncts to diet, exercise, and behavioral therapy. Nearly all FDA-approved medications for weight loss have been shown to improve glycemic control in patients with type 2 diabetes and delay progression to type 2 diabetes in patients at risk (52). Phentermine and other older adrenergic agents are indicated for short-term (≤12 weeks) treatment (53). Four weight-loss medications are FDA approved for long-term use (>12 weeks) in patients with BMI $\geq$27 kg/m^2 with one or more obesity-associated comorbid condition (e.g., type 2 diabetes, hypertension, and/or dyslipidemia) who are motivated to lose weight (52). Medications approved by the FDA for the treatment of obesity are summarized in **Table 8.2**. The rationale for weight-loss medication use is to help patients adhere to dietary recommendations, in most cases by modulating appetite or satiety. Providers should be knowledgeable about the product label and should balance the potential benefits of successful weight loss against the potential risks of the medication for each patient. These medications are contraindicated in women who are pregnant or actively trying to conceive and not recommended for use in women who are nursing. Women of reproductive potential should receive counseling regarding the use of reliable methods of contraception.

Assessing Efficacy and Safety

Upon initiating weight-loss medication, assess efficacy and safety at least monthly for the first 3 months and at least quarterly thereafter. Modeling from published clinical trials consistently shows that early responders have improved long-term outcomes (54–56). Unless clinical circumstances (such as poor tolerability) or other considerations (such as financial expense or patient preference) suggest otherwise, those who achieve sufficient early weight loss upon starting a chronic weight-loss medication (typically defined as >5% weight loss after 3 months' use) should continue the medication. When early use appears ineffective (typically <5% weight loss after 3 months' use), it is unlikely that continued use will improve weight outcomes; as such, it should be recommended to discontinue the medication and consider other treatment options.

MEDICAL DEVICES FOR WEIGHT LOSS

Several minimally invasive medical devices have been approved by the FDA for short-term weight loss (57,58). It remains to be seen how these are used for obesity treatment. Given the high cost, limited insurance coverage, and paucity of data in people with diabetes at this time, medical devices for weight loss are currently not considered to be the standard of care for obesity management in people with type 2 diabetes.

METABOLIC SURGERY

Recommendations

8.16 Metabolic surgery should be a recommended option to treat type 2 diabetes in screened surgical candidates with BMI $\geq$40 kg/m^2 (BMI $\geq$37.5 kg/m^2 in Asian Americans) and in adults with BMI 35.0–39.9 kg/m^2 (32.5–37.4 kg/m^2 in Asian Americans) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with nonsurgical methods. **A**

8.17 Metabolic surgery may be considered as an option to treat type 2 diabetes in adults with BMI 30.0–34.9 kg/m^2 (27.5–32.4 kg/m^2 in Asian Americans) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with nonsurgical methods. **A**

8.18 Metabolic surgery should be performed in high-volume centers with multidisciplinary teams knowledgeable about and experienced in the management of diabetes and gastrointestinal surgery. **E**

8.19 Long-term lifestyle support and routine monitoring of micronutrient and nutritional status must be provided to patients after surgery, according to guidelines for postoperative management of metabolic surgery by national and international professional societies. **C**

8.20 People being considered for metabolic surgery should be evaluated for comorbid psychological conditions and social and situational circumstances that have the potential to interfere with surgery outcomes. **B**

8.21 People who undergo metabolic surgery should routinely be evaluated to assess the need for ongoing mental health services to help with the adjustment to medical and psychosocial changes after surgery. **C**

Several gastrointestinal (GI) operations, including partial gastrectomies and bariatric procedures (44), promote dramatic and durable weight loss and improvement of type 2 diabetes in many patients. Given the magnitude and rapidity of the effect of GI surgery on hyperglycemia and experimental evidence that rearrangements of GI anatomy similar to those in some metabolic procedures directly affect glucose homeostasis (45), GI interventions have been suggested as treatments for type 2 diabetes, and in that context they are termed "metabolic surgery."

A substantial body of evidence has now been accumulated, including data from numerous randomized controlled (nonblinded) clinical trials, demonstrating that metabolic surgery achieves superior glycemic control and reduction of cardiovascular risk factors in patients with type 2 diabetes and obesity compared with various lifestyle/medical interventions (17). Improvements in microvascular complications of diabetes, cardiovascular disease, and cancer have been observed only in nonrandomized observational studies (59–70). Cohort studies attempting to match surgical and nonsurgical subjects suggest that the procedure may reduce longer-term mortality (60,71).

While several surgical options are available, the overwhelming majority of procedures in the U.S. are vertical sleeve gastrectomy and Roux-en-Y gastric bypass (RYGB). Both procedures result in an anatomically smaller stomach pouch and often robust changes in enteroendocrine hormones. On the basis of this mounting evidence, several organizations and government agencies have recommended expanding the indications for metabolic surgery to include patients with type 2 diabetes who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with reasonable nonsurgical methods at BMIs as low as 30 kg/m^2 (27.5 kg/m^2 for Asian Americans) (72–79). Randomized controlled trials have documented diabetes remission during postoperative follow-up ranging from 1 to 5 years in 30–63% of patients with RYGB, which generally leads to greater degrees and lengths of remission compared with other bariatric surgeries (17,80). Available data suggest an erosion of diabetes remission over time (81): 35–50% or more of patients who initially achieve remission of diabetes eventually experience recurrence. However, the median disease-free period among such individuals following RYGB is 8.3 years (82,83). With or without diabetes relapse, the majority of patients who undergo surgery maintain substantial improvement of glycemic control from baseline for at least 5 years (84,85) to 15 years (60,61,83,86–88).

Exceedingly few presurgical predictors of success have been identified, but younger age, shorter duration of diabetes (e.g., $<$8 years) (89), nonuse of insulin, maintenance of weight loss, and better glycemic control are consistently associated with higher rates of diabetes remission and/or lower risk of weight regain (60,87,89,90). Greater baseline visceral fat area may also help to predict better postoperative outcomes, especially among Asian American patients with type 2 diabetes, who typically have more visceral fat compared with Caucasians with diabetes of the same BMI (91). Beyond improving glycemia, metabolic surgery has been shown to confer additional health benefits in randomized controlled trials, including substantial reductions in cardiovascular disease risk factors (17), reductions in incidence of microvascular disease (92), and enhancements in quality of life (84,89,93).

Although metabolic surgery has been shown to improve the metabolic profiles of patients with type 1 diabetes and morbid obesity, establishing the role of metabolic surgery in such patients will require larger and longer studies (94).

Metabolic surgery is more expensive than nonsurgical management strategies, but retrospective analyses and modeling studies suggest that metabolic surgery may be cost-effective or even cost-saving for patients with type 2 diabetes. However, results are largely dependent on assumptions about the long-term effectiveness and safety of the procedures (95,96).

Adverse Effects

The safety of metabolic surgery has improved significantly over the past several decades, with continued refinement of minimally invasive approaches (laparoscopic surgery), enhanced training and credentialing, and involvement of multidisciplinary teams. Mortality rates with metabolic operations are typically 0.1–0.5%, similar to cholecystectomy or hysterectomy (97–101). Morbidity has also dramatically declined with laparoscopic approaches. Major complications and need for operative reintervention occur in 2–6% of those undergoing bariatric surgery, with other minor complications in up to 15% (97–106). These rates compare favorably with those for other commonly performed elective operations (101). Empirical data suggest that proficiency of the operating surgeon is an important factor for determining mortality, complications, reoperations, and readmissions (107). Accordingly, metabolic surgery should be performed in high-volume centers with multidisciplinary teams knowledgeable about and experienced in the management of diabetes and GI surgery.

Longer-term concerns include dumping syndrome (nausea, colic, and diarrhea), vitamin and mineral deficiencies, anemia, osteoporosis, and severe hypoglycemia (108). Long-term nutritional and micronutrient deficiencies and related complications occur with variable frequency

depending on the type of procedure and require lifelong vitamin/nutritional supplementation; thus, long-term lifestyle support and routine monitoring of micronutrient and nutritional status should be provided to patients after surgery (109,110). Postprandial hypoglycemia is most likely to occur with RYGB (110,111). The exact prevalence of symptomatic hypoglycemia is unknown. In one study, it affected 11% of 450 patients who had undergone RYGB or vertical sleeve gastrectomy (108). Patients who undergo metabolic surgery may be at increased risk for substance use, including drug and alcohol use and cigarette smoking. Additional potential risks of metabolic surgery that have been described include worsening or new-onset depression and/or anxiety, need for additional GI surgery, and suicidal ideation (112–115).

People with diabetes presenting for metabolic surgery also have increased rates of depression and other major psychiatric disorders (116). Candidates for metabolic surgery with histories of alcohol, tobacco, or substance abuse or significant depression, suicidal ideation, or other mental health conditions should therefore first be assessed by a mental health professional with expertise in obesity management prior to consideration for surgery (117). Surgery should be postponed in patients with alcohol or substance abuse disorders, significant depression, suicidal ideation, or other mental health conditions until these conditions have been fully addressed. Individuals with preoperative psychopathology should be assessed regularly following metabolic surgery to optimize mental health management and to ensure that psychiatric symptoms do not interfere with weight loss and lifestyle changes.

References

1. Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403
2. Garvey WT, Ryan DH, Henry R, et al. Prevention of type 2 diabetes in subjects with prediabetes and metabolic syndrome treated with phentermine and topiramate extended release. Diabetes Care 2014;37:912–921
3. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of Diabetes in Obese Subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care 2004;27:155–161
4. le Roux CW, Astrup A, Fujioka K, et al.; SCALE Obesity Prediabetes NN8022-1839 Study Group. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. Lancet 2017;389:1399–1409
5. Booth H, Khan O, Prevost T, et al. Incidence of type 2 diabetes after bariatric surgery: population-based matched cohort study. Lancet Diabetes Endocrinol 2014;2:963–968
6. UKPDS Group. UK Prospective Diabetes Study 7: response of fasting plasma glucose to diet therapy in newly presenting type II diabetic patients. Metabolism 1990;39:905–912
7. Goldstein DJ. Beneficial health effects of modest weight loss. Int J Obes Relat Metab Disord 1992; 16:397–415
8. Pastors JG, Warshaw H, Daly A, Franz M, Kulkarni K. The evidence for the effectiveness of medical nutrition therapy in diabetes management. Diabetes Care 2002;25:608–613
9. Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Diabetologia 2011;54:2506–2514
10. Jackness C, Karmally W, Febres G, et al. Very low-calorie diet mimics the early beneficial effect of Roux-en-Y gastric bypass on insulin sensitivity and β-cell function in type 2 diabetic patients. Diabetes 2013;62:3027–3032
11. Rothberg AE, McEwen LN, Kraftson AT, Fowler CE, Herman WH. Very-low-energy diet for type 2 diabetes: an underutilized therapy? J Diabetes Complications 2014;28:506–510
12. Hollander PA, Elbein SC, Hirsch IB, et al. Role of orlistat in the treatment of obese patients with type 2 diabetes. A 1-year randomized double-blind study. Diabetes Care 1998;21:1288–1294
13. Garvey WT, Ryan DH, Bohannon NJV, et al. Weight-loss therapy in type 2 diabetes: effects of phentermine and topiramate extended release. Diabetes Care 2014;37:3309–3316
14. O'Neil PM, Smith SR, Weissman NJ, et al. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. Obesity (Silver Spring) 2012;20:1426–1436
15. Hollander P, Gupta AK, Plodkowski R, et al.; COR-Diabetes Study Group. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. Diabetes Care 2013;36:4022–4029
16. Davies MJ, Bergenstal R, Bode B, et al.; NN8022-1922 Study Group. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. JAMA 2015;314:687–699
17. Rubino F, Nathan DM, Eckel RH, et al.; Delegates of the 2nd Diabetes Surgery Summit. Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by international diabetes organizations. Diabetes Care 2016; 39:861–877
18. Steven S, Hollingsworth KG, Al-Mrabeh A, et al. Very low-calorie diet and 6 months of weight stability in type 2 diabetes: pathophysiological changes in responders and nonresponders. Diabetes Care 2016;39:808–815
19. Jensen MD, Ryan DH, Apovian CM, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Obesity Society. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. J Am Coll Cardiol 2014;63(25 Pt B):2985–3023
20. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet 2018;391:541–551
21. Lean MEJ, Leslie WS, Barnes AC, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. Lancet Diabetes Endocrinol 2019;7:344–355
22. AMA Manual of Style Committee. *AMA Manual of Style: A Guide for Authors and Editors*. 11th ed. New York, Oxford University Press, 2020
23. American Medical Association. Person-First Language for Obesity H-440.821. Accessed16 September 2020. Available from https://policysearch.ama-assn.org/policyfinder/detail/obesity?uri=%2FAMADoc%2FHOD.xml-H-440.821.xml
23a. Rubino F, Puhl RM, Cummings DE, et al. Joint international consensus statement for ending stigma of obesity. Nat Med 2020;26:485–497
24. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157–163
25. Araneta MRG, Kanaya A, Hsu WC, et al. Optimum BMI cut points to screen Asian Americans for type 2 diabetes. Diabetes Care 2015; 38:814–820
26. Yancy CW, Jessup M, Bozkurt B, et al.; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147–e239
27. Bosch X, Monclús E, Escoda O, et al. Unintentional weight loss: clinical characteristics and outcomes in a prospective cohort of 2677 patients. PLoS One. 2017;12:e0175125
28. Wilding JPH. The importance of weight management in type 2 diabetes mellitus. Int J Clin Pract 2014;68:682–691
29. Van Gaal L, Scheen A. Weight management in type 2 diabetes: current and emerging approaches to treatment. Diabetes Care 2015;38: 1161–1172
30. Kushner RF, Batsis JA, Butsch WS, et al. Weight history in clinical practice: the state of the science and future directions. Obesity (Silver Spring) 2020;28:9–17
31. Warren J, Smalley B, Barefoot N. Higher motivation for weight loss in African American than Caucasian rural patients with hypertension and/or diabetes. Ethn Dis 2016;26:77–84
32. Rothberg AE, McEwen LN, Kraftson AT, et al. Impact of weight loss on waist circumference and the components of the metabolic syndrome. BMJ Open Diabetes Res Care 2017;5:e000341
33. Evert AB, Dennison M, Gardner CD, et al. Nutrition therapy for adults with diabetes or prediabetes: a consensus report. Diabetes Care 2019;42:731–754

34. Look AHEAD Research Group; Wing RR, Bolin P, Brancati FL, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369:145–154
35. Look AHEAD Research Group. Eight-year weight losses with an intensive lifestyle intervention: the Look AHEAD study. Obesity (Silver Spring) 2014;22:5–13
36. Gregg EW, Jakicic JM, Blackburn G, et al.; Look AHEAD Research Group. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. Lancet Diabetes Endocrinol 2016;4:913–921
37. Baum A, Scarpa J, Bruzelius E, Tamler R, Basu S, Faghmous J. Targeting weight loss interventions to reduce cardiovascular complications of type 2 diabetes: a machine learning-based post-hoc analysis of heterogeneous treatment effects in the Look AHEAD trial. Lancet Diabetes Endocrinol 2017;5:808–815
38. Franz MJ, Boucher JL, Rutten-Ramos S, VanWormer JJ. Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta-analysis of randomized clinical trials. J Acad Nutr Diet 2015;115:1447–1463
39. Sacks FM, Bray GA, Carey VJ, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med 2009;360:859–873
40. de Souza RJ, Bray GA, Carey VJ, et al. Effects of 4 weight-loss diets differing in fat, protein, and carbohydrate on fat mass, lean mass, visceral adipose tissue, and hepatic fat: results from the POUNDS LOST trial. Am J Clin Nutr 2012;95:614–625
41. Johnston BC, Kanters S, Bandayrel K, et al. Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. JAMA 2014;312:923–933
42. Leung CW, Epel ES, Ritchie LD, Crawford PB, Laraia BA. Food insecurity is inversely associated with diet quality of lower-income adults. J Acad Nutr Diet 2014;114:1943–53.e2
43. Kahan S, Manson JE. Obesity treatment, beyond the guidelines: practical suggestions for clinical practice. JAMA 2019;321:1349–1350
44. Donnelly JE, Blair SN, Jakicic JM, Manore MM, Rankin JW, Smith BK; American College of Sports Medicine. American College of Sports Medicine Position Stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. Med Sci Sports Exerc 2009;41:459–471
45. Gudzune KA, Doshi RS, Mehta AK, et al. Efficacy of commercial weight-loss programs: an updated systematic review. Ann Intern Med 2015;162:501–512
46. Bloom B, Mehta AK, Clark JM, Gudzune KA. Guideline-concordant weight-loss programs in an urban area are uncommon and difficult to identify through the internet. Obesity (Silver Spring) 2016;24:583–588
47. Tsai AG, Wadden TA. The evolution of very-low-calorie diets: an update and meta-analysis. Obesity (Silver Spring) 2006;14:1283–1293
48. Johansson K, Neovius M, Hemmingsson E. Effects of anti-obesity drugs, diet, and exercise on weight-loss maintenance after a very-low-calorie diet or low-calorie diet: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr 2014;99:14–23
49. Hill-Briggs F, Adler NE, Berkowitz SA, et al. Social determinants of health and diabetes: a scientific review. Diabetes Care. 2 November 2020 [Epub ahead of print]. DOI: 10.2337/dci20-0053
50. Cai X, Yang W, Gao X, Zhou L, Han X, Ji L. Baseline body mass index and the efficacy of hypoglycemic treatment in type 2 diabetes: a meta-analysis. PLoS One 2016;11:e0166625
51. Domecq JP, Prutsky G, Leppin A, et al. Clinical review: drugs commonly associated with weight change: a systematic review and meta-analysis. J Clin Endocrinol Metab 2015;100:363–370
52. Kahan S, Fujioka K. Obesity pharmacotherapy in patients with type 2 diabetes. Diabetes Spectr 2017;30:250–257
53. Drugs.com. Phentermine [FDA prescribing information]. Accessed 29 October 2020. Available from https://www.drugs.com/pro/phentermine.html
54. Apovian CM, Aronne LJ, Bessesen DH, et al.; Endocrine Society. Pharmacological management of obesity: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2015;100:342–362
55. Fujioka K, O'Neil PM, Davies M, et al. Early weight loss with liraglutide 3.0 mg predicts 1-year weight loss and is associated with improvements in clinical markers. Obesity (Silver Spring) 2016;24:2278–2288
56. Fujioka K, Plodkowski R, O'Neil PM, Gilder K, Walsh B, Greenway FL. The relationship between early weight loss and weight loss at 1 year with naltrexone ER/bupropion ER combination therapy. Int J Obes 2016;40:1369–1375
57. Sullivan S. Endoscopic medical devices for primary obesity treatment in patients with diabetes. Diabetes Spectr 2017;30:258–264
58. Greenway FL, Aronne LJ, Raben A, et al. A randomized, double-blind, placebo-controlled study of Gelesis100: a novel nonsystemic oral hydrogel for weight loss. Obesity (Silver Spring) 2019;27:205–216
59. Sjöström L, Lindroos A-K, Peltonen M, et al.; Swedish Obese Subjects Study Scientific Group. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med 2004;351:2683–2693
60. Sjöström L, Peltonen M, Jacobson P, et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. JAMA 2014;311:2297–2304
61. Adams TD, Davidson LE, Litwin SE, et al. Health benefits of gastric bypass surgery after 6 years. JAMA 2012;308:1122–1131
62. Sjöström L, Narbro K, Sjöström CD, et al.; Swedish Obese Subjects Study. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med 2007;357:741–752
63. Sjöström L, Gummesson A, Sjöström CD, et al.; Swedish Obese Subjects Study. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. Lancet Oncol 2009;10:653–662
64. Sjöström L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. JAMA 2012;307:56–65
65. Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. N Engl J Med 2007;357:753–761
66. Arterburn DE, Olsen MK, Smith VA, et al. Association between bariatric surgery and long-term survival. JAMA 2015;313:62–70
67. Adams TD, Arterburn DE, Nathan DM, Eckel RH. Clinical outcomes of metabolic surgery: microvascular and macrovascular complications. Diabetes Care 2016;39:912–923
68. Sheng B, Truong K, Spitler H, Zhang L, Tong X, Chen L. The long-term effects of bariatric surgery on type 2 diabetes remission, microvascular and macrovascular complications, and mortality: a systematic review and meta-analysis. Obes Surg 2017;27:2724–2732
69. Fisher DP, Johnson E, Haneuse S, et al. Association between bariatric surgery and macrovascular disease outcomes in patients with type 2 diabetes and severe obesity. JAMA 2018;320:1570–1582
70. Billeter AT, Scheurlen KM, Probst P, et al. Meta-analysis of metabolic surgery versus medical treatment for microvascular complications in patients with type 2 diabetes mellitus. Br J Surg 2018;105:168–181
71. Aminian A, Zajichek A, Arterburn DE, et al. Association of metabolic surgery with major adverse cardiovascular outcomes in patients with type 2 diabetes and obesity. JAMA 2019;322:1271–1282
72. Rubino F, Kaplan LM, Schauer PR, Cummings DE; Diabetes Surgery Summit Delegates. The Diabetes Surgery Summit consensus conference: recommendations for the evaluation and use of gastrointestinal surgery to treat type 2 diabetes mellitus. Ann Surg 2010;251:399–405
73. Cummings DE, Cohen RV. Beyond BMI: the need for new guidelines governing the use of bariatric and metabolic surgery. Lancet Diabetes Endocrinol 2014;2:175–181
74. Zimmet P, Alberti KGMM, Rubino F, Dixon JB. IDF's view of bariatric surgery in type 2 diabetes. Lancet 2011;378:108–110
75. Kasama K, Mui W, Lee WJ, et al. IFSO-APC consensus statements 2011. Obes Surg 2012;22:677–684
76. Wentworth JM, Burton P, Laurie C, Brown WA, O'Brien PE. Five-year outcomes of a randomized trial of gastric band surgery in overweight but not obese people with type 2 diabetes. Diabetes Care 2017;40:e44–e45
77. Cummings DE, Arterburn DE, Westbrook EO, et al. Gastric bypass surgery vs intensive lifestyle and medical intervention for type 2 diabetes: the CROSSROADS randomised controlled trial. Diabetologia 2016;59:945–953
78. Liang Z, Wu Q, Chen B, Yu P, Zhao H, Ouyang X. Effect of laparoscopic Roux-en-Y gastric bypass surgery on type 2 diabetes mellitus with hypertension: a randomized controlled trial. Diabetes Res Clin Pract 2013;101:50–56
79. Aminian A, Chang J, Brethauer SA, Kim JJ; American Society for Metabolic and Bariatric Surgery Clinical Issues Committee. ASMBS updated position statement on bariatric surgery in class I obesity (BMI 30–35 kg/m^2). Surg Obes Relat Dis 2018;14:1071–1087

80. Isaman DJM, Rothberg AE, Herman WH. Reconciliation of type 2 diabetes remission rates in studies of Roux-en-Y gastric bypass. Diabetes Care 2016;39:2247–2253
81. Ikramuddin S, Korner J, Lee W-J, et al. Durability of addition of Roux-en-Y gastric bypass to lifestyle intervention and medical management in achieving primary treatment goals for uncontrolled type 2 diabetes in mild to moderate obesity: a randomized control trial. Diabetes Care 2016;39:1510–1518
82. Sjöholm K, Pajunen P, Jacobson P, et al. Incidence and remission of type 2 diabetes in relation to degree of obesity at baseline and 2 year weight change: the Swedish Obese Subjects (SOS) study. Diabetologia 2015;58:1448–1453
83. Arterburn DE, Bogart A, Sherwood NE, et al. A multisite study of long-term remission and relapse of type 2 diabetes mellitus following gastric bypass. Obes Surg 2013;23:93–102
84. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. Lancet 2015;386:964–973
85. Schauer PR, Bhatt DL, Kirwan JP, et al.; STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes—5-year outcomes. N Engl J Med 2017;376:641–651
86. Cohen RV, Pinheiro JC, Schiavon CA, Salles JE, Wajchenberg BL, Cummings DE. Effects of gastric bypass surgery in patients with type 2 diabetes and only mild obesity. Diabetes Care 2012;35:1420–1428
87. Brethauer SA, Aminian A, Romero-Talamás H, et al. Can diabetes be surgically cured? Long-term metabolic effects of bariatric surgery in obese patients with type 2 diabetes mellitus. Ann Surg 2013;258:628–636; discussion 636–637
88. Hsu C-C, Almulaifi A, Chen J-C, et al. Effect of bariatric surgery vs medical treatment on type 2 diabetes in patients with body mass index lower than 35: five-year outcomes. JAMA Surg 2015;150:1117–1124
89. Schauer PR, Bhatt DL, Kirwan JP, et al.; STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes—3-year outcomes. N Engl J Med 2014;370:2002–2013
90. Hariri K, Guevara D, Jayaram A, Kini SU, Herron DM, Fernandez-Ranvier G. Preoperative insulin therapy as a marker for type 2 diabetes remission in obese patients after bariatric surgery. Surg Obes Relat Dis 2018;14:332–337
91. Yu H, Di J, Bao Y, et al. Visceral fat area as a new predictor of short-term diabetes remission after Roux-en-Y gastric bypass surgery in Chinese patients with a body mass index less than 35 kg/m^2. Surg Obes Relat Dis 2015;11:6–11
92. O'Brien R, Johnson E, Haneuse S, et al. Microvascular outcomes in patients with diabetes after bariatric surgery versus usual care: a matched cohort study. Ann Intern Med 2018;169:300–310
93. Halperin F, Ding S-A, Simonson DC, et al. Roux-en-Y gastric bypass surgery or lifestyle with intensive medical management in patients with type 2 diabetes: feasibility and 1-year results of a randomized clinical trial. JAMA Surg 2014;149:716–726
94. Kirwan JP, Aminian A, Kashyap SR, Burguera B, Brethauer SA, Schauer PR. Bariatric surgery in obese patients with type 1 diabetes. Diabetes Care 2016;39:941–948
95. Rubin JK, Hinrichs-Krapels S, Hesketh R, Martin A, Herman WH, Rubino F. Identifying barriers to appropriate use of metabolic/bariatric surgery for type 2 diabetes treatment: Policy Lab results. Diabetes Care 2016;39:954–963
96. Fouse T, Schauer P. The socioeconomic impact of morbid obesity and factors affecting access to obesity surgery. Surg Clin North Am 2016;96:669–679
97. Longitudinal Assessment of Bariatric Surgery (LABS) Consortium; Flum DR, Belle SH, King WC, et al.. Perioperative safety in the longitudinal assessment of bariatric surgery. N Engl J Med 2009;361:445–454
98. Courcoulas AP, Christian NJ, Belle SH, et al.; Longitudinal Assessment of Bariatric Surgery (LABS) Consortium. Weight change and health outcomes at 3 years after bariatric surgery among individuals with severe obesity. JAMA 2013;310:2416–2425
99. Arterburn DE, Courcoulas AP. Bariatric surgery for obesity and metabolic conditions in adults. BMJ 2014;349:g3961
100. Young MT, Gebhart A, Phelan MJ, Nguyen NT. Use and outcomes of laparoscopic sleeve gastrectomy vs laparoscopic gastric bypass: analysis of the American College of Surgeons NSQIP. J Am Coll Surg 2015;220:880–885
101. Aminian A, Brethauer SA, Kirwan JP, Kashyap SR, Burguera B, Schauer PR. How safe is metabolic/diabetes surgery? Diabetes Obes Metab 2015;17:198–201
102. Birkmeyer NJO, Dimick JB, Share D, et al.; Michigan Bariatric Surgery Collaborative. Hospital complication rates with bariatric surgery in Michigan. JAMA 2010;304:435–442
103. Altieri MS, Yang J, Telem DA, et al. Lap band outcomes from 19,221 patients across centers and over a decade within the state of New York. Surg Endosc 2016;30:1725–1732
104. Hutter MM, Schirmer BD, Jones DB, et al. First report from the American College of Surgeons Bariatric Surgery Center Network: laparoscopic sleeve gastrectomy has morbidity and effectiveness positioned between the band and the bypass. Ann Surg 2011;254:410–420; discussion 420–422
105. Nguyen NT, Slone JA, Nguyen X-MT, Hartman JS, Hoyt DB. A prospective randomized trial of laparoscopic gastric bypass versus laparoscopic adjustable gastric banding for the treatment of morbid obesity: outcomes, quality of life, and costs. Ann Surg 2009;250:631–641
106. Courcoulas AP, King WC, Belle SH, et al. Seven-year weight trajectories and health outcomes in the Longitudinal Assessment of Bariatric Surgery (LABS) study. JAMA Surg 2018;153:427–434
107. Birkmeyer JD, Finks JF, O'Reilly A, et al.; Michigan Bariatric Surgery Collaborative. Surgical skill and complication rates after bariatric surgery. N Engl J Med 2013;369:1434–1442
108. Service GJ, Thompson GB, Service FJ, Andrews JC, Collazo-Clavell ML, Lloyd RV. Hyperinsulinemic hypoglycemia with nesidioblastosis after gastric-bypass surgery. N Engl J Med 2005;353:249–254
109. Mechanick JI, Kushner RF, Sugerman HJ, et al.; American Association of Clinical Endocrinologists; Obesity Society; American Society for Metabolic & Bariatric Surgery. American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery medical guidelines for clinical practice for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient. Obesity (Silver Spring) 2009;17(Suppl. 1):S1–S70
110. Mechanick JI, Youdim A, Jones DB, et al.; American Association of Clinical Endocrinologists; Obesity Society; American Society for Metabolic & Bariatric Surgery. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient—2013 update: cosponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery. Obesity (Silver Spring) 2013;21(Suppl. 1):S1–S27
111. Lee CJ, Clark JM, Schweitzer M, et al. Prevalence of and risk factors for hypoglycemic symptoms after gastric bypass and sleeve gastrectomy. Obesity (Silver Spring) 2015;23:1079–1084
112. Conason A, Teixeira J, Hsu C-H, Puma L, Knafo D, Geliebter A. Substance use following bariatric weight loss surgery. JAMA Surg 2013;148:145–150
113. Bhatti JA, Nathens AB, Thiruchelvam D, Grantcharov T, Goldstein BI, Redelmeier DA. Self-harm emergencies after bariatric surgery: a population-based cohort study. JAMA Surg 2016;151:226–232
114. Peterhänsel C, Petroff D, Klinitzke G, Kersting A, Wagner B. Risk of completed suicide after bariatric surgery: a systematic review. Obes Rev 2013;14:369–382
115. Jakobsen GS, Småstuen MC, Sandbu R, et al. Association of bariatric surgery vs medical obesity treatment with long-term medical complications and obesity-related comorbidities. JAMA 2018;319:291–301
116. Young-Hyman D, Peyrot M. *Psychosocial Care for People with Diabetes*. 1st ed. Alexandria, VA, American Diabetes Association, 2012
117. Greenberg I, Sogg S, M Perna F. Behavioral and psychological care in weight loss surgery: best practice update. Obesity (Silver Spring) 2009;17:880–884
118. Truven Health Analytics. Introduction to RED BOOK Online. Accessed 13 October 2020. Available from https://www.micromedexsolutions.com/micromedex2/4.34.0/WebHelp/RED_BOOK/Introduction_to_REDB_BOOK_Online.htm
119. Data.Medicaid.gov. NADAC (National Average Drug Acquisition Cost), 2019. Accessed 13 October 2020. Available from https://data.medicaid.gov/Drug-Pricing-and-Payment/NADAC-National-Average-Drug-Acquisition-Cost-/a4y5-998d
120. U.S. National Library of Medicine. Phentermine – phentermine hydrochloride capsule. Accessed 13 October 2020. Available from https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=737eef3b-9a6b-4ab3-a25c-49d84d2a0197

121. Nalpropion Pharmaceuticals. Contrave (naltrexone HCl/bupropion HCl) Extended-Release Tablets. Accessed 13 October 2020. Available from https://contrave.com
122. CHEPLAPHARM and H2-Pharma. Xenical (orlistat). Accessed 13 October 2020. Available from https://xenical.com
123. VIVUS, Inc. Qsymia (phentermine and topiramate extended-release) capsules. Accessed 13 October 2020. Available from https://qsymia.com
124. Novo Nordisk. Saxenda (liraglutide injection 3 mg). Accessed 13 October 2020. Available from https://www.saxenda.com
125. Aronne LJ, Wadden TA, Peterson C, Winslow D, Odeh S, Gadde KM. Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults. Obesity (Silver Spring) 2013;21:2163–2171
126. Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. Lancet 2011; 377:1341–1352
127. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375: 311–322

9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes—2021*

American Diabetes Association

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The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc21-SPPC), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc21-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

PHARMACOLOGIC THERAPY FOR TYPE 1 DIABETES

Recommendations

9.1 Most people with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion. **A**

9.2 Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk. **A**

9.3 Patients with type 1 diabetes should receive education on how to match prandial insulin doses to carbohydrate intake, premeal blood glucose, and anticipated physical activity. **C**

Insulin Therapy

Because the hallmark of type 1 diabetes is absent or near-absent β-cell function, insulin treatment is essential for individuals with type 1 diabetes. In addition to hyperglycemia, insulinopenia can contribute to other metabolic disturbances like hypertriglyceridemia and ketoacidosis as well as tissue catabolism that can be life threatening. Severe metabolic decompensation can be, and was, mostly prevented with once or twice daily injections for the six or seven decades after the discovery of insulin. However, over the past three decades, evidence has accumulated supporting more intensive insulin replacement, using multiple daily injections of insulin or continuous subcutaneous administration through an insulin pump, as providing the best combination of effectiveness and safety for people with type 1 diabetes. The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive therapy with multiple daily injections or continuous subcutaneous insulin infusion (CSII) reduced A1C and was associated with improved long-term outcomes (1–3). The study

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was carried out with short-acting (regular) and intermediate-acting (NPH) human insulins. In this landmark trial, lower A1C with intensive control (7%) led to ~50% reductions in microvascular complications over 6 years of treatment. However, intensive therapy was associated with a higher rate of severe hypoglycemia than conventional treatment (62 compared with 19 episodes per 100 patient-years of therapy). Follow-up of subjects from the DCCT more than 10 years after the active treatment component of the study demonstrated less macrovascular as well as less microvascular complications in the group that received intensive treatment (2,4).

Over the last 25 years, rapid-acting and long-acting insulin analogs have been developed that have distinct pharmacokinetics compared with recombinant human insulins: basal insulin analogs have longer duration of action with flatter, more constant plasma concentrations and activity profiles than NPH insulin; rapid-acting analogs (RAA) have a quicker onset and peak and shorter duration of action than regular human insulin. In people with type 1 diabetes, treatment with analog insulins is associated with less hypoglycemia and weight gain as well as lower A1C compared with human insulins (5–7). More recently, two new injectable insulin formulations with enhanced rapid action profiles have been introduced. Inhaled human insulin has a rapid peak and shortened duration of action compared with RAA and may cause less hypoglycemia and weight gain (8), and faster-acting insulin aspart and insulin lispro-aabc may reduce prandial excursions better than RAA (9,9a,9b); further investigation is needed to establish a clear place for these agents in diabetes management. In addition, new longer-acting basal analogs (U-300 glargine or degludec) may confer a lower hypoglycemia risk compared with U-100 glargine in patients with type 1 diabetes (10,11). Despite the advantages of insulin analogs in patients with type 1 diabetes, for some patients the expense and/or intensity of treatment required for their use is prohibitive. There are multiple approaches to insulin treatment, and the central precept in the management of type 1 diabetes is that some form of insulin be given in a planned regimen tailored to the individual patient to keep them safe and out of diabetic ketoacidosis and to avoid significant hypoglycemia, with every effort made to reach the patient's glycemic targets.

Most studies comparing multiple daily injections with CSII have been relatively small and of short duration. However, a recent systematic review and meta-analysis concluded that pump therapy has modest advantages for lowering A1C (−0.30% [95% CI −0.58 to −0.02]) and for reducing severe hypoglycemia rates in children and adults (12). However, there is no consensus to guide the choice of injection or pump therapy in a given patient, and research to guide this decision-making is needed (13). The arrival of continuous glucose monitors to clinical practice has proven beneficial in specific circumstances. Reduction of nocturnal hypoglycemia in people with type 1 diabetes using insulin pumps with glucose sensors is improved by automatic suspension of insulin delivery at a preset glucose level (13–15). When choosing among insulin delivery systems, patient preferences, cost, insulin type and dosing regimen, and self-management capabilities should be considered (See Section 7 "Diabetes Technology," https://doi.org/10.2337/dc21-S007).

The U.S. Food and Drug Administration (FDA) has now approved two hybrid closed-loop pump systems. The safety and efficacy of hybrid closed-loop systems has been supported in the literature in adolescents and adults with type 1 diabetes (16,17), and recent evidence suggests that a closed-loop system is superior to sensor-augmented pump therapy for glycemic control and reduction of hypoglycemia over 3 months of comparison in children and adults with type 1 diabetes (18). In the International Diabetes Closed Loop (iDCL) trial, a 6-month trial in patients with type 1 diabetes at least 14 years of age, the use of a closed-loop system was associated with a greater percentage of time spent in the target glycemic range, reduced mean glucose and A1C levels, and lower percentage of time spent in hypoglycemia compared with use of a sensor-augmented pump (19).

Intensive insulin management using a version of CSII and continuous glucose monitoring should be considered in most patients. Automated insulin delivery systems may be considered in adults with type 1 diabetes who have the skills to use them in order to improve time in range and reduce A1C and hypoglycemia (19). See Section 7 "Diabetes Technology" (https://doi.org/10.2337/dc21-S007) for a full discussion of insulin delivery devices.

In general, patients with type 1 diabetes require 50% of their daily insulin as basal and 50% as prandial. Total daily insulin requirements can be estimated based on weight, with typical doses ranging from 0.4 to 1.0 units/kg/day. Higher amounts are required during puberty, pregnancy, and medical illness. The *American Diabetes Association/JDRF Type 1 Diabetes Sourcebook* notes 0.5 units/kg/day as a typical starting dose in patients with type 1 diabetes who are metabolically stable, with half administered as prandial insulin given to control blood glucose after meals and the other half as basal insulin to control glycemia in the periods between meal absorption (20); this guideline provides detailed information on intensification of therapy to meet individualized needs. In addition, the American Diabetes Association position statement "Type 1 Diabetes Management Through the Life Span" provides a thorough overview of type 1 diabetes treatment (21).

Typical multidose regimens for patients with type 1 diabetes combine premeal use of shorter-acting insulins with a longer-acting formulation, usually at night. The long-acting basal dose is titrated to regulate overnight, fasting glucose. Postprandial glucose excursions are best controlled by a well-timed injection of prandial insulin. The optimal time to administer prandial insulin varies, based on the pharmacokinetics of the formulation (regular, RAA, inhaled), the premeal blood glucose level, and carbohydrate consumption. Recommendations for prandial insulin dose administration should therefore be individualized. Physiologic insulin secretion varies with glycemia, meal size, and tissue demands for glucose. To approach this variability in people using insulin treatment, strategies have evolved to adjust prandial doses based on predicted needs. Thus, education of patients on how to adjust prandial insulin to account for carbohydrate intake, premeal glucose levels, and anticipated activity can be effective and should be offered to most patients (22,23). For individuals in whom carbohydrate counting is effective, estimates of the fat and protein content of meals can be incorporated into their prandial dosing for added benefit (24).

Insulin Injection Technique

Ensuring that patients and/or caregivers understand correct insulin injection technique is important to optimize glucose control and insulin use safety. Thus, it is important that insulin be delivered into the proper tissue in the correct way. Recommendations have been published elsewhere outlining best practices for insulin injection (25). Proper insulin injection technique includes injecting into appropriate body areas, injection site rotation, appropriate care of injection sites to avoid infection or other complications, and avoidance of intramuscular (IM) insulin delivery.

Exogenously delivered insulin should be injected into subcutaneous tissue, not intramuscularly. Recommended sites for insulin injection include the abdomen, thigh, buttock, and upper arm. Because insulin absorption from IM sites differs according to the activity of the muscle, inadvertent IM injection can lead to unpredictable insulin absorption and variable effects on glucose, with IM injection being associated with frequent and unexplained hypoglycemia in several reports. Risk for IM insulin delivery is increased in younger, leaner patients when injecting into the limbs rather than truncal sites (abdomen and buttocks) and when using longer needles. Recent evidence supports the use of short needles (e.g., 4-mm pen needles) as effective and well tolerated when compared with longer needles, including a study performed in adults with obesity (26).

Injection site rotation is additionally necessary to avoid lipohypertrophy, an accumulation of subcutaneous fat in response to the adipogenic actions of insulin at a site of multiple injections. Lipohypertrophy appears as soft, smooth raised areas several centimeters in breadth and can contribute to erratic insulin absorption, increased glycemic variability, and unexplained hypoglycemic episodes. Patients and/or caregivers should receive education about proper injection site rotation and to recognize and avoid areas of lipohypertrophy. As noted in **Table 4.1**, examination of insulin injection sites for the presence of lipohypertrophy, as well as assessment of injection device use and injection technique, are key components of a comprehensive diabetes medical evaluation and treatment plan. Proper insulin injection technique may lead to more effective use of this therapy and, as such, holds the potential for improved clinical outcomes.

Noninsulin Treatments for Type 1 Diabetes

Injectable and oral glucose-lowering drugs have been studied for their efficacy as adjuncts to insulin treatment of type 1 diabetes. Pramlintide is based on the naturally occurring β-cell peptide amylin and is approved for use in adults with type 1 diabetes. Results from randomized controlled studies show variable reductions of A1C (0–0.3%) and body weight (1–2 kg) with addition of pramlintide to insulin (27,28). Similarly, results have been reported for several agents currently approved only for the treatment of type 2 diabetes. The addition of metformin in adults with type 1 diabetes caused small reductions in body weight and lipid levels but did not improve A1C (29,30). The addition of the glucagon-like peptide 1 (GLP-1) receptor agonist (RA) liraglutide or exenatide to insulin therapy caused small (0.2%) reductions in A1C compared with insulin alone in people with type 1 diabetes and also reduced body weight by ~3 kg (31). Similarly, the addition of a sodium–glucose cotransporter 2 (SGLT2) inhibitor to insulin therapy has been associated with improvements in A1C and body weight when compared with insulin alone (32,33); however, SGLT2 inhibitor use in type 1 diabetes is associated with a two- to fourfold increase in ketoacidosis. The risks and benefits of adjunctive agents continue to be evaluated, but only pramlintide is approved for treatment of type 1 diabetes.

SURGICAL TREATMENT FOR TYPE 1 DIABETES

Pancreas and Islet Transplantation

Successful pancreas and islet transplantation can normalize glucose levels and mitigate microvascular complications of type 1 diabetes. However, patients receiving these treatments require lifelong immunosuppression to prevent graft rejection and/or recurrence of autoimmune islet destruction. Given the potential adverse effects of immunosuppressive therapy, pancreas transplantation should be reserved for patients with type 1 diabetes undergoing simultaneous renal transplantation, following renal transplantation, or for those with recurrent ketoacidosis or severe hypoglycemia despite intensive glycemic management (34).

PHARMACOLOGIC THERAPY FOR TYPE 2 DIABETES

Recommendations

- **9.4** Metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes. **A**
- **9.5** Once initiated, metformin should be continued as long as it is tolerated and not contraindicated; other agents, including insulin, should be added to metformin. **A**
- **9.6** Early combination therapy can be considered in some patients at treatment initiation to extend the time to treatment failure. **A**
- **9.7** The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high. **E**
- **9.8** A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include effect on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences (**Table 9.1** and **Fig. 9.1**). **E**
- **9.9** Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit (**Table 9.1**, **Table 10.3*B***, **Table 10.3*C***) is recommended as part of the glucose-lowering regimen independent of A1C and in consideration of patient-specific factors (**Fig. 9.1** and Section 10). **A**
- **9.10** In patients with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible. **A**
- **9.11** Recommendation for treatment intensification for patients not meeting treatment goals should not be delayed. **A**

9.12 The medication regimen and medication-taking behavior should be reevaluated at regular intervals (every 3–6 months) and adjusted as needed to incorporate specific factors that impact choice of treatment (**Fig. 4.1** and **Table 9.1**). **E**

9.13 Clinicians should be aware of the potential for overbasalization with insulin therapy. Clinical signals that may prompt evaluation of overbasalization include basal dose more than ~0.5 IU/kg, high bedtime-morning or post-preprandial glucose differential, hypoglycemia (aware or unaware), and high variability. Indication of overbasalization should prompt reevaluation to further individualize therapy. **E**

The American Diabetes Association/European Association for the Study of Diabetes consensus report "Management of Hyperglycemia in Type 2 Diabetes, 2018" and the 2019 update (35,36) recommend a patient-centered approach to choosing appropriate pharmacologic treatment of blood glucose. This includes consideration of efficacy and key patient factors: *1*) important comorbidities such as atherosclerotic cardiovascular disease (ASCVD) and indicators of high ASCVD risk, chronic kidney disease (CKD), and heart failure (see Section 10 "Cardiovascular Disease and Risk Management," https://doi.org/10.2337/dc21-S010, and Section 11 "Microvascular Complications and Foot Care," https://doi.org/10.2337/dc21-S011), *2*) hypoglycemia risk, *3*) effects on body weight, *4*) side effects, *5*) cost, and *6*) patient preferences. Lifestyle modifications that improve health (see Section 5 "Facilitating Behavior Change and Well-being to Improve Health Outcomes," https://doi.org/10.2337/dc21-S005) should be emphasized along with any pharmacologic therapy. Section 12 "Older Adults" (https://doi.org/10.2337/dc21-S012) and Section 13 "Children and Adolescents" (https://doi.org/10.2337/dc21-S013) have recommendations specific for older adults and for children and adolescents with type 2 diabetes, respectively. Section 10 "Cardiovascular Disease and Risk Management" (https://doi.org/10.2337/dc21-S010) and Section 11 "Microvascular Complications and Foot Care" (https://doi.org/10.2337/dc21-S011) have recommendations for the use of glucose-lowering drugs in the management of cardiovascular and renal disease, respectively.

Initial Therapy

Metformin should be started at the time type 2 diabetes is diagnosed unless there are contraindications; for many patients this will be monotherapy in combination with lifestyle modifications. Additional and/or alternative agents may be considered in special circumstances, such as in individuals with established or increased risk of cardiovascular or renal complications (see Section 10 "Cardiovascular Disease and Risk Management," https://doi.org/10.2337/dc21-S010, and **Fig. 9.1**). Metformin is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death (37). Metformin is available in an immediate-release form for twice-daily dosing or as an extended-release form that can be given once daily. Compared with sulfonylureas, metformin as first-line therapy has beneficial effects on A1C, weight, and cardiovascular mortality (38); there is little systematic data available for other oral agents as initial therapy of type 2 diabetes.

The principal side effects of metformin are gastrointestinal intolerance due to bloating, abdominal discomfort, and diarrhea; these can be mitigated by gradual dose titration. The drug is cleared by renal filtration, and very high circulating levels (e.g., as a result of overdose or acute renal failure) have been associated with lactic acidosis. However, the occurrence of this complication is now known to be very rare, and metformin may be safely used in patients with reduced estimated glomerular filtration rates (eGFR); the FDA has revised the label for metformin to reflect its safety in patients with eGFR $\geq$30 mL/min/1.73 m^2 (39). A randomized trial confirmed previous observations that metformin use is associated with vitamin B12 deficiency and worsening of symptoms of neuropathy (40). This is compatible with a report from the Diabetes Prevention Program Outcomes Study (DPPOS) suggesting periodic testing of vitamin B12 (41).

In patients with contraindications or intolerance to metformin, initial therapy should be based on patient factors; consider a drug from another class depicted in **Fig. 9.1**. When A1C is $\geq$1.5% (12.5 mmol/mol) above the glycemic target (see Section 6 "Glycemic Targets," https://doi.org/10.2337/dc21-S006, for appropriate targets), many patients will require dual combination therapy to achieve their target A1C level (42). Insulin has the advantage of being effective where other agents are not and should be considered as part of any combination regimen when hyperglycemia is severe, especially if catabolic features (weight loss, hypertriglyceridemia, ketosis) are present. It is common practice to initiate insulin therapy for patients who present with blood glucose levels $\geq$300 mg/dL (16.7 mmol/L) or A1C >10% (86 mmol/mol) or if the patient has symptoms of hyperglycemia (i.e., polyuria or polydipsia) or evidence of catabolism (weight loss) (**Fig. 9.2**). As glucose toxicity resolves, simplifying the regimen and/or changing to oral agents is often possible. However, there is evidence that patients with uncontrolled hyperglycemia associated with type 2 diabetes can also be effectively treated with a sulfonylurea (43).

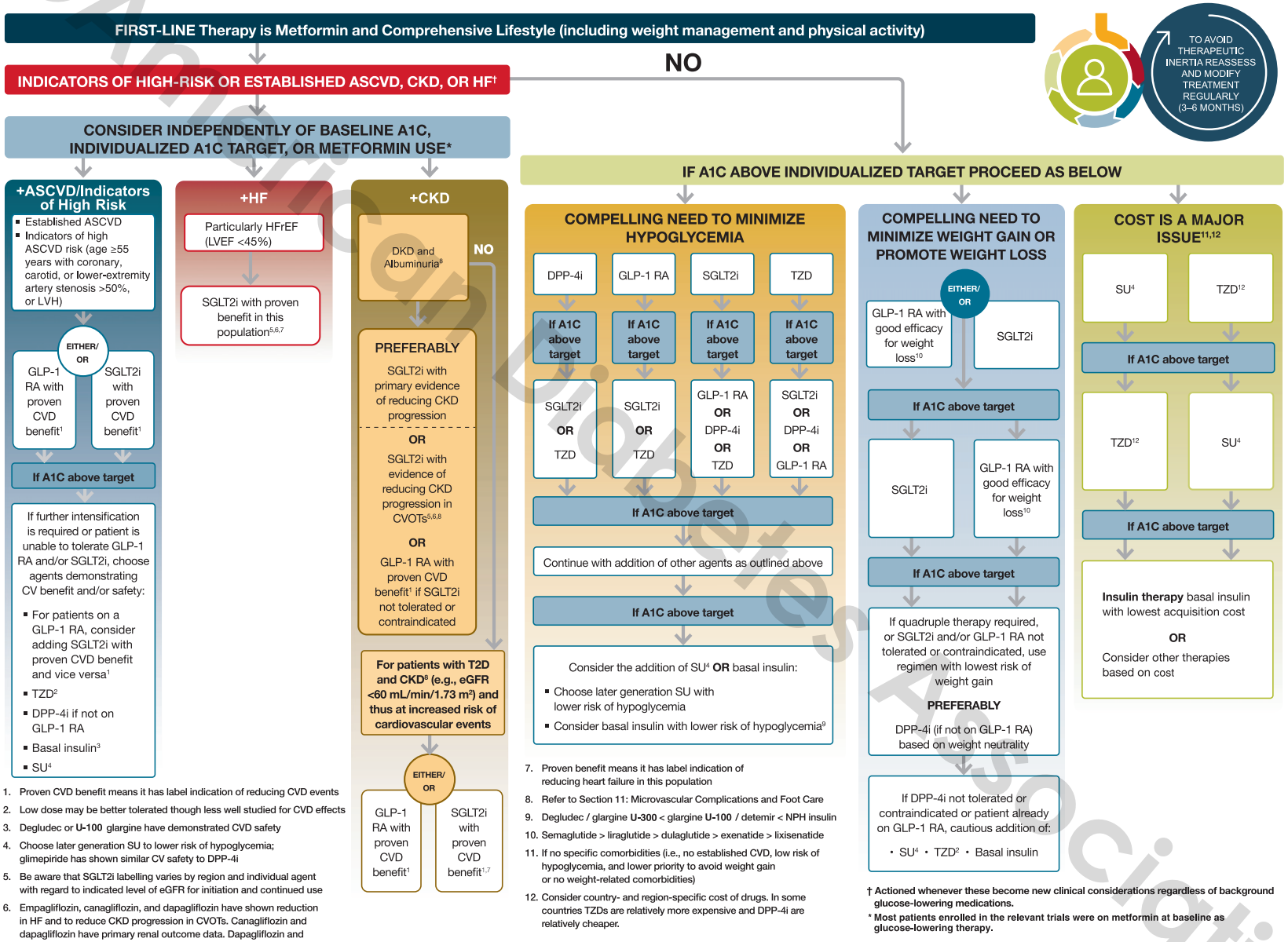
Combination Therapy

Because type 2 diabetes is a progressive disease in many patients, maintenance of glycemic targets with monotherapy is often possible for only a few years, after which combination therapy is necessary. Current recommendations have been to use stepwise addition of medications to metformin to maintain A1C at target. This allows a clearer assessment of the positive and negative effects of new drugs and reduces patient risk and expense (44); based on these factors, sequential addition of oral agents to metformin has been the standard of care. However, there are data to support initial combination therapy for more rapid attainment of glycemic goals (45,46) and later combination therapy for longer durability of glycemic effect (47). The VERIFY (Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of type 2 diabetes) trial demonstrated that initial combination therapy is superior to sequential addition of medications for extending primary and secondary failure (48). In the VERIFY trial, participants receiving the initial combination of metformin and the dipeptidyl peptidase 4 (DPP-4) inhibitor vildagliptin had a slower decline of glycemic control

Table 9.1—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

	Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
				ASCVD	HF			Progression of DKD	Dosing/use considerations*	
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30 mL/min/1.73 m^2	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT-2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin, dapagliflozin‡	High	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin	▪ Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	▪ Should be discontinued before any scheduled surgery to avoid potential risk for DKA ▪ DKA risk (all agents, rare in T2D) ▪ Risk of bone fractures (canagliflozin) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol ▪ Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral: exenatide once weekly, lixisenatide Benefit: dulaglutide†, liraglutide†, semaglutide†	Neutral	High	SQ; oral (semaglutide)	Benefit on renal end points in CVOTs, driven by albuminuria outcomes: liraglutide, semaglutide, dulaglutide	▪ Exenatide, lixisenatide: avoid for eGFR <30 mL/min/1.73 m^2 ▪ No dose adjustment for dulaglutide, liraglutide, semaglutide ▪ Caution when initiating or increasing dose due to potential risk of nausea, vomiting, diarrhea, or dehydration. Monitor renal function in patients reporting severe adverse GI reactions when initiating or increasing dose of therapy.	▪ **FDA Black Box:** Risk of thyroid C-cell tumors in rodents; human relevance not determined **(liraglutide, albiglutide, dulaglutide, exenatide extended release, semaglutide)** ▪ GI side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected.
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	High	Oral	Neutral	▪ Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment ▪ No dose adjustment required for linagliptin	▪ Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected. ▪ Joint pain
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	▪ No dose adjustment required ▪ Generally not recommended in renal impairment due to potential for fluid retention	▪ **FDA Black Box:** Congestive heart failure **(pioglitazone, rosiglitazone)** ▪ Fluid retention (edema; heart failure) ▪ Benefit in NASH ▪ Risk of bone fractures ▪ Bladder cancer (pioglitazone) ▪ ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: not recommended ▪ Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin: Human insulin	Highest	Yes	Gain	Neutral	Neutral	Low (SQ)	SQ; inhaled	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin: Analogs						High	SQ			

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVOT, cardiovascular outcomes trial; DPP-4, dipeptidyl peptidase 4; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; HF, heart failure; NASH, nonalcoholic steatohepatitis; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2D, type 2 diabetes. *For agent-specific dosing recommendations, please refer to the manufacturers' prescribing information. †FDA-approved for cardiovascular disease benefit. ‡FDA-approved for heart failure indication. §FDA-approved for chronic kidney disease indication.

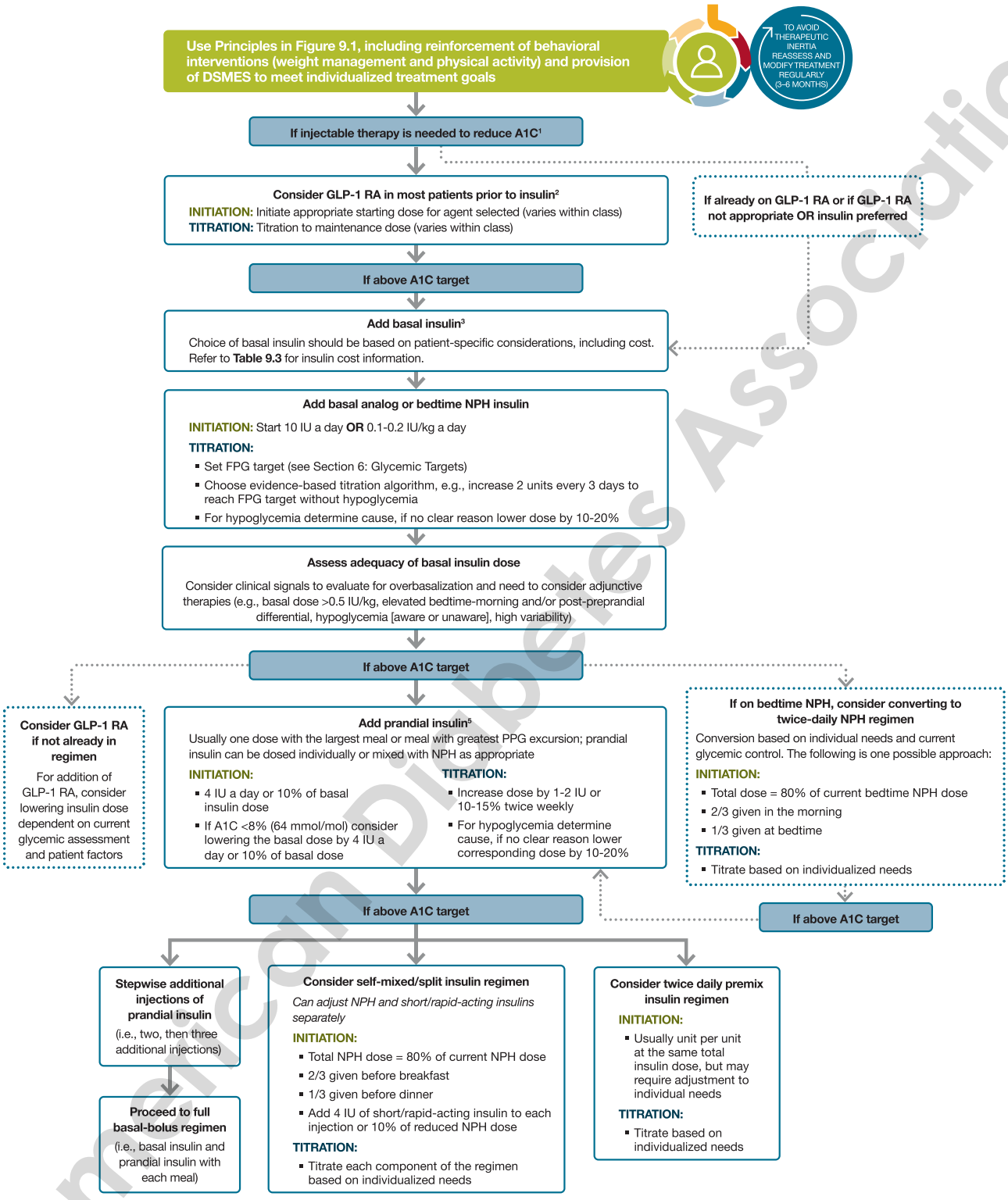


1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or **U-100** glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine **U-300** < glargine **U-100** / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

*** Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.**

Figure 9.1—Glucose-lowering medication in type 2 diabetes: 2021 ADA Professional Practice Committee (PPC) adaptation of Davies et al. (35) and Buse et al. (36). For appropriate context, see **Fig. 4.1**. The 2021 ADA PPC adaptation of the **Fig. 9.1** "Indicators of high-risk or established ASCVD, CKD, or HF" pathway has been adapted based on trial populations studied. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione.



1. Consider insulin as the first injectable if evidence of ongoing catabolism, symptoms of hyperglycemia are present, when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high, or a diagnosis of type 1 diabetes is a possibility.
2. When selecting GLP-1 RA, consider: patient preference, A1C lowering, weight-lowering effect, or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit. Oral or injectable GLP-1 RA are appropriate.
3. For patients on GLP-1 RA and basal insulin combination, consider use of a fixed-ratio combination product (iDegLira or iGlarLixi).
4. Consider switching from evening NPH to a basal analog if the patient develops hypoglycemia and/or frequently forgets to administer NPH in the evening and would be better managed with an AM dose of a long-acting basal insulin.
5. If adding prandial insulin to NPH, consider initiation of a self-mixed or premixed insulin regimen to decrease the number of injections required.

Figure 9.2—Intensifying to injectable therapies. DSMES, diabetes self-management education and support; FPG, fasting plasma glucose; FRC, fixed-ratio combination; GLP-1 RA, glucagon-like peptide 1 receptor agonist; max, maximum; PPG, postprandial glucose. Adapted from Davies et al. (35).

compared with metformin alone and with vildagliptin added sequentially to metformin. These results have not been generalized to oral agents other than vildagliptin, but they suggest that more intensive early treatment has some benefits and should be considered through a shared decision-making process with patients, as appropriate. Moreover, since the absolute effectiveness of most oral medications rarely exceeds 1%, initial combination therapy should be considered in patients presenting with A1C levels 1.5–2.0% above target.

Recommendations for treatment intensification for patients not meeting treatment goals should not be delayed. Shared decision-making is important in discussions regarding treatment intensification. The choice of medication added to metformin is based on the clinical characteristics of the patient and their preferences. Important clinical characteristics include the presence of established ASCVD or indicators of high ASCVD risk, heart failure, CKD, other comorbidities, and risk for specific adverse drug effects, as well as safety, tolerability, and cost. Although there are numerous trials comparing dual therapy with metformin alone, there is little evidence to support one combination over another. A comparative effectiveness meta-analysis suggests that each new class of noninsulin agents added to initial therapy with metformin generally lowers A1C approximately 0.7–1.0% (49,50). If the A1C target is not achieved after approximately 3 months, metformin can be combined with any one of the preferred six treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 RA, or basal insulin; the choice of which agent to add is based on drug-specific effects and patient factors (**Fig. 9.1** and **Table 9.1**).

For patients with established ASCVD or indicators of high ASCVD risk (such as patients $\geq$55 years of age with coronary, carotid, or lower-extremity artery stenosis $>$50% or left ventricular hypertrophy), heart failure, or CKD, an SGLT2 inhibitor or GLP-1 RA with demonstrated CVD benefit (**Table 9.1**, **Table 10.3*B***, **Table 10.3*C***, and Section 10 "Cardiovascular Disease and Risk Management," https://doi.org/10.2337/dc21-S010) is recommended as part of the glucose-lowering regimen independent of A1C, independent of metformin use, and in consideration of patient-specific factors (**Fig. 9.1**). For patients without established ASCVD, indicators of high ASCVD risk, heart failure, or CKD, the choice of a second agent to add to metformin is not yet guided by empiric evidence comparing across multiple classes. Rather, drug choice is based on efficacy, avoidance of side effects (particularly hypoglycemia and weight gain), cost, and patient preferences (51). Similar considerations are applied in patients who require a third agent to achieve glycemic goals. A recent systematic review and network meta-analysis suggests greatest reductions in A1C level with insulin regimens and specific GLP-1 RAs added to metformin-based background therapy (52). In all cases, treatment regimens need to be continuously reviewed for efficacy, side effects, and patient burden (**Table 9.1**). In some instances, patients will require medication reduction or discontinuation. Common reasons for this include ineffectiveness, intolerable side effects, expense, or a change in glycemic goals (e.g., in response to development of comorbidities or changes in treatment goals). Section 12 "Older Adults" (https://doi.org/10.2337/dc21-S012) has a full discussion of treatment considerations in older adults, in whom changes of glycemic goals and de-escalation of therapy are common.

The need for the greater potency of injectable medications is common, particularly in people with a longer duration of diabetes. The addition of basal insulin, either human NPH or one of the long-acting insulin analogs, to oral agent regimens is a well-established approach that is effective for many patients. In addition, recent evidence supports the utility of GLP-1 RAs in patients not at glycemic goal. While most GLP-1 RAs are injectable, an oral formulation of semaglutide is now commercially available (53). In trials comparing the addition of an injectable GLP-1 RA or insulin in patients needing further glucose lowering, glycemic efficacy of injectable GLP-1 RA was similar or greater than that of basal insulin (54–60). GLP-1 RAs in these trials had a lower risk of hypoglycemia and beneficial effects on body weight compared with insulin, albeit with greater gastrointestinal side effects. Thus, trial results support GLP-1 RAs as the preferred option for patients requiring the potency of an injectable therapy for glucose control (**Fig. 9.2**). However, high costs and tolerability issues are important barriers to GLP-1 RA use.

Cost for diabetes medicine has increased dramatically over the past two decades, and an increasing proportion is now passed on to patients and their families (61). **Table 9.2** provides cost information for currently approved noninsulin therapies. Of note, prices listed are average wholesale prices (AWP) (62) and National Average Drug Acquisition Costs (NADAC) (63), separate measures to allow for a comparison of drug prices, but do not account for discounts, rebates, or other price adjustments often involved in prescription sales that affect the actual cost incurred by the patient. Medication costs can be a major source of stress for patients with diabetes and contribute to worse adherence to medications (64); cost-reducing strategies may improve adherence in some cases (65).

Cardiovascular Outcomes Trials

There are now multiple large randomized controlled trials reporting statistically significant reductions in cardiovascular events in patients with type 2 diabetes treated with an SGLT2 inhibitor (empagliflozin, canagliflozin, dapagliflozin) or GLP-1 RA (liraglutide, semaglutide, dulaglutide); see Section 10 "Cardiovascular Disease and Risk Management" (https://doi.org/10.2337/dc21-S010) for details. The subjects enrolled in the cardiovascular outcomes trials using empagliflozin, canagliflozin, dapagliflozin, liraglutide, and semaglutide had A1C $\geq$6.5%, and more than 70% were taking metformin at baseline. Thus, a practical extension of these results to clinical practice is to use these drugs preferentially in patients with type 2 diabetes and established ASCVD or indicators of high ASCVD risk. For these patients, incorporating one of the SGLT2 inhibitors or GLP-1 RAs that have been demonstrated to have cardiovascular disease benefit is recommended (**Table 9.1**). In cardiovascular outcomes trials, empagliflozin, canagliflozin, dapagliflozin, liraglutide, semaglutide, and dulaglutide all had beneficial effects on indices of CKD, while dedicated renal outcomes studies have demonstrated benefit of specific SGLT2 inhibitors. See Section 11 "Microvascular Complications and Foot Care" (https://doi.org/10.2337/dc21-S011) for discussion of how CKD may impact treatment choices. Additional large randomized trials of other agents in these classes are ongoing.

Table 9.2—Median monthly (30-day) AWP and NADAC of maximum approved daily dose of noninsulin glucose-lowering agents in the U.S.

Class	Compound(s)	Dosage strength/product (if applicable)	Median AWP (min, max)†	Median NADAC (min, max)†	Maximum approved daily dose*
Biguanides	• Metformin	850 mg (IR)	$108 ($6, $109)	$3	2,550 mg
		1,000 mg (IR)	$87 ($4, $88)	$2	2,000 mg
		1,000 mg (ER)	$242 ($242, $7,214)	$188 ($188, $572)	2,000 mg
Sulfonylureas (2nd generation)	• Glimepiride	4 mg	$74 ($71, $198)	$4	8 mg
	• Glipizide	10 mg (IR)	$75 ($67, $97)	$5	40 mg (IR)
		10 mg (XL)	$48	$11	20 mg (XL)
	• Glyburide	6 mg (micronized)	$52 ($48, $71)	$10	12 mg (micronized)
		5 mg	$93 ($63, $103)	$11	20 mg
Thiazolidinediones	• Pioglitazone	45 mg	$348 ($283, $349)	$5	45 mg
	• Rosiglitazone	4 mg	$407	$330	8 mg
α-Glucosidase inhibitors	• Acarbose	100 mg	$106 ($104, $106)	$28	300 mg
	• Miglitol	100 mg	$241	$311	300 mg
Meglitinides (glinides)	• Nateglinide	120 mg	$155	$31	360 mg
	• Repaglinide	2 mg	$878 ($162, $897)	$38	16 mg
DPP-4 inhibitors	• Alogliptin	25 mg	$234	$175	25 mg
	• Saxagliptin	5 mg	$530	$424	5 mg
	• Linagliptin	5 mg	$555	$444	5 mg
	• Sitagliptin	100 mg	$568	$456	100 mg
SGLT2 inhibitors	• Ertugliflozin	15 mg	$354	$284	15 mg
	• Dapagliflozin	10 mg	$621	$496	10 mg
	• Empagliflozin	25 mg	$627	$501	25 mg
	• Canagliflozin	300 mg	$622	$499	300 mg
GLP-1 RAs	• Exenatide (extended release)	2 mg powder for suspension or pen	$882	$706	2 mg**
	• Exenatide	10 μg pen	$752	$720	20 μg
	• Dulaglutide	4.5/0.5 mL pen	$957	$766	4.5 mg**
	• Semaglutide	1 mg pen	$973	$779	1 mg**
		14 mg (tablet)	$927	$738	14 mg
	• Liraglutide	18 mg/3 mL pen	$1,161	$930	1.8 mg
	• Lixisenatide	300 μg/3 mL pen	$774	N/A	20 μg
Bile acid sequestrant	• Colesevelam	625 mg tabs	$710 ($674, $712)	$105	3.75 g
		3.75 g suspension	$804	$318	3.75 g
Dopamine-2 agonist	• Bromocriptine	0.8 mg	$960	$772	4.8 mg
Amylin mimetic	• Pramlintide	120 μg pen	$2702	$2,097	120 μg/injection††

AWP, average wholesale price; DPP-4, dipeptidyl peptidase 4; ER and XL, extended release; GLP-1 RA, glucagon-like peptide 1 receptor agonist; IR, immediate release; max, maximum; min, minimum; N/A, data not available; NADAC, National Average Drug Acquisition Cost; SGLT2, sodium–glucose cotransporter 2. †Calculated for 30-day supply (AWP [62] or NADAC [63] unit price × number of doses required to provide maximum approved daily dose × 30 days); median AWP or NADAC listed alone when only one product and/or price. *Utilized to calculate median AWP and NADAC (min, max); generic prices used, if available commercially. **Administered once weekly. ††AWP and NADAC calculated based on 120 mg three times daily.

Insulin Therapy

Many patients with type 2 diabetes eventually require and benefit from insulin therapy (**Fig. 9.2**). See the section INSULIN INJECTION TECHNIQUE, above, for guidance on how to administer insulin safely and effectively. The progressive nature of type 2 diabetes should be regularly and objectively explained to patients, and providers should avoid using insulin as a threat or describing it as a sign of personal failure or punishment. Rather, the utility and importance of insulin to maintain glycemic control once progression of the disease overcomes the effect of other agents should be emphasized. Educating and involving patients in insulin management is beneficial. For example, instruction of patients in self-titration of insulin doses based on glucose monitoring improves glycemic control in patients with type 2 diabetes initiating insulin (66). Comprehensive education regarding self-monitoring of blood glucose, diet, and the avoidance and appropriate treatment of hypoglycemia are critically important in any patient using insulin.

Basal Insulin

Basal insulin alone is the most convenient initial insulin regimen and can be added to metformin and other oral agents. Starting doses can be estimated based on body weight (0.1–0.2 units/kg/day) and the degree of hyperglycemia, with individualized titration over days to weeks as needed. The principal action of basal insulin is to restrain hepatic glucose production and limit hyperglycemia overnight and between meals (67,68). Control of fasting glucose can be achieved with human NPH insulin or a long-acting insulin analog. In clinical trials, long-acting basal analogs (U-100 glargine or detemir) have been demonstrated to reduce the risk of symptomatic and nocturnal hypoglycemia compared with NPH insulin (69–74), although these advantages are modest and may not persist (75). Longer-acting basal analogs (U-300 glargine or degludec) may convey a lower hypoglycemia risk compared with U-100 glargine when used in

Table 9.3—Median cost of insulin products in the U.S. calculated as AWP (62) and NADAC (63) per 1,000 units of specified dosage form/product

Insulins	Compounds	Dosage form/product	Median AWP (min, max)*	Median NADAC*
Rapid-acting	• Lispro follow-on product	U-100 vial	$157	$125
		U-100 prefilled pen	$202	$161
	• Lispro	U-100 vial	$165†	$132†
		U-100 cartridges	$408	$326
		U-100 prefilled pen	$212†	$170†
		U-200 prefilled pen	$424	$339
	• Lispro-aabc	U-100 vial	$330	N/A
		U-100 prefilled pen	$424	N/A
		U-200 prefilled pen	$424	N/A
	• Glulisine	U-100 vial	$341	$272
		U-100 prefilled pen	$439	$350
	• Aspart	U-100 vial	$174†	$139†
		U-100 cartridges	$215	$344
		U-100 prefilled pen	$223†	$179†
	• Aspart ("faster acting product")	U-100 vial	$347	$278
		U-100 cartridge	$430	N/A
		U-100 prefilled pen	$447	$356
	• Inhaled insulin	Inhalation cartridges	$924	$606
Short-acting	• human regular	U-100 vial	$165††	$133††
Intermediate-acting	• human NPH	U-100 vial	$165††	$133††
		U-100 prefilled pen	$208	$167
Concentrated human regular insulin	• U-500 human regular insulin	U-500 vial	$178	$143
		U-500 prefilled pen	$229	$183
Long-acting	• Glargine follow-on product	U-100 prefilled pen	$190 (118, 261)	$210
		U-100 vial	$190 (118, 261)	N/A
	• Glargine	U-100 vial; U-100 prefilled pen	$340	$272
		U-300 prefilled pen	$340	$272
	• Detemir	U-100 vial; U-100 prefilled pen	$370	$296
	• Degludec	U-100 vial; U-100 prefilled pen; U-200 prefilled pen	$407	$325
Premixed insulin products	• NPH/regular 70/30	U-100 vial	$165††	$133††
		U-100 prefilled pen	$208	$167
	• Lispro 50/50	U-100 vial	$342	$273
		U-100 prefilled pen	$424	$338
	• Lispro 75/25	U-100 vial	$342	$274
		U-100 prefilled pen	$212	$340
	• Aspart 70/30	U-100 vial	$180	$144
		U-100 prefilled pen	$224	$179
Premixed insulin/GLP-1 RA products	• Glargine/Lixisenatide	100/33 prefilled pen	$589	$471
	• Degludec/Liraglutide	100/3.6 prefilled pen	$874	$701

AWP, average wholesale price; GLP-1 RA, glucagon-like peptide 1 receptor agonist; N/A, not available; NADAC, National Average Drug Acquisition Cost. *AWP or NADAC calculated as in **Table 9.2**. †Generic prices used when available. ††AWP and NADAC data presented do not include vials of regular human insulin and NPH available at Walmart for approximately $25/vial; median listed alone when only one product and/or price.

combination with oral agents (76–82). Despite evidence for reduced hypoglycemia with newer, longer-acting basal insulin analogs in clinical trial settings, in practice these effects may be modest compared with NPH insulin (83). Clinicians should be aware of the potential for overbasalization with insulin therapy. Clinical signals that may prompt evaluation of overbasalization include basal dose greater than ~0.5 IU/kg, high bedtime-morning or post-preprandial glucose differential (e.g. bedtime-morning glucose differential ≥50 mg/dL), hypoglycemia (aware or unaware), and high variability. Indication of overbasalization should prompt reevaluation to further individualize therapy (84).

The cost of insulin has been rising steadily over the past two decades, at a pace several fold that of other medical expenditures (85). This expense contributes significant burden to patients as insulin has become a growing "out-of-pocket" cost for people with diabetes, and direct patient costs contribute to treatment nonadherence (85). Therefore, consideration of cost is an important component of effective management. For many patients with type 2 diabetes (e.g., individuals with relaxed A1C goals, low rates of hypoglycemia, and prominent insulin resistance, as well as those with cost concerns), human insulin (NPH and regular) may be the appropriate choice of therapy, and clinicians should be familiar with its use (83). Human regular insulin, NPH, and 70/30 NPH/regular products can be purchased for considerably less than the AWP and NADAC prices listed in **Table 9.3** at select pharmacies.

Prandial Insulin

Many individuals with type 2 diabetes require doses of insulin before meals, in

addition to basal insulin, to reach glycemic targets. A dose of 4 units or 10% of the amount of basal insulin at the largest meal or the meal with the greatest postprandial excursion is a safe estimate for initiating therapy. The prandial insulin regimen can then be intensified based on patient needs (see **Fig. 9.2**). People with type 2 diabetes are generally more insulin resistant than those with type 1 diabetes, require higher daily doses (~1 unit/kg), and have lower rates of hypoglycemia (86). Titration can be based on home glucose monitoring or A1C. With significant additions to the prandial insulin dose, particularly with the evening meal, consideration should be given to decreasing basal insulin. Meta-analyses of trials comparing rapid-acting insulin analogs with human regular insulin in patients with type 2 diabetes have not reported important differences in A1C or hypoglycemia (87,88).

Concentrated Insulins

Several concentrated insulin preparations are currently available. U-500 regular insulin is, by definition, five times more concentrated than U-100 regular insulin. Regular U-500 has distinct pharmacokinetics with delayed onset and longer duration of action, has characteristics more like an intermediate-acting (NPH) insulin, and can be used as two or three daily injections (89). U-300 glargine and U-200 degludec are three and two times as concentrated as their U-100 formulations and allow higher doses of basal insulin administration per volume used. U-300 glargine has a longer duration of action than U-100 glargine but modestly lower efficacy per unit administered (90,91). The FDA has also approved a concentrated formulation of rapid-acting insulin lispro, U-200 (200 units/mL) and insulin lispro-aabc (U-200). These concentrated preparations may be more convenient and comfortable for patients to inject and may improve adherence in those with insulin resistance who require large doses of insulin. While U-500 regular insulin is available in both prefilled pens and vials, other concentrated insulins are available only in prefilled pens to minimize the risk of dosing errors.

Inhaled Insulin

Inhaled insulin is available as a rapid-acting insulin; studies in people with type 1 diabetes suggest rapid pharmacokinetics (8). A pilot study found evidence that compared with injectable rapid-acting insulin, supplemental doses of inhaled insulin taken based on postprandial glucose levels may improve blood glucose management without additional hypoglycemia or weight gain (92), although results from a larger study are needed for confirmation. Inhaled insulin is contraindicated in patients with chronic lung disease, such as asthma and chronic obstructive pulmonary disease, and is not recommended in patients who smoke or who recently stopped smoking. All patients require spirometry (forced expiratory volume in 1 s [FEV_1]) testing to identify potential lung disease prior to and after starting inhaled insulin therapy.

Combination Injectable Therapy

If basal insulin has been titrated to an acceptable fasting blood glucose level (or if the dose is >0.5 units/kg/day with indications of need for other therapy) and A1C remains above target, consider advancing to combination injectable therapy (**Fig. 9.2**). This approach can use a GLP-1 RA added to basal insulin or multiple doses of insulin. The combination of basal insulin and GLP-1 RA has potent glucose-lowering actions and less weight gain and hypoglycemia compared with intensified insulin regimens (93–95), with one study suggesting greater durability of glycemic effect compared with addition of basal insulin alone (47). Two different once-daily, fixed dual-combination products containing basal insulin plus a GLP-1 RA are available: insulin glargine plus lixisenatide and insulin degludec plus liraglutide.

Intensification of insulin treatment can be done by adding doses of prandial to basal insulin. Starting with a single prandial dose with the largest meal of the day is simple and effective, and it can be advanced to a regimen with multiple prandial doses if necessary (96). Alternatively, in a patient on basal insulin in whom additional prandial coverage is desired, the regimen can be converted to two doses of a premixed insulin. Each approach has advantages and disadvantages. For example, basal/prandial regimens offer greater flexibility for patients who eat on irregular schedules. On the other hand, two doses of premixed insulin is a simple, convenient means of spreading insulin across the day. Moreover, human insulins, separately, self-mixed, or as premixed NPH/regular (70/30) formulations, are less costly alternatives to insulin analogs. **Figure 9.2** outlines these options as well as recommendations for further intensification, if needed, to achieve glycemic goals. When initiating combination injectable therapy, metformin therapy should be maintained, while sulfonylureas and DPP-4 inhibitors are typically weaned or discontinued. In patients with suboptimal blood glucose control, especially those requiring large insulin doses, adjunctive use of a thiazolidinedione or an SGLT2 inhibitor may help to improve control and reduce the amount of insulin needed, though potential side effects should be considered. Once a basal/bolus insulin regimen is initiated, dose titration is important, with adjustments made in both mealtime and basal insulins based on the blood glucose levels and an understanding of the pharmacodynamic profile of each formulation (pattern control). As people with type 2 diabetes get older, it may become necessary to simplify complex insulin regimens because of a decline in self-management ability (see Section 12 "Older Adults," https://doi.org/10.2337/dc21-S012).

References

1. Cleary PA, Orchard TJ, Genuth S, et al.; DCCT/EDIC Research Group. The effect of intensive glycemic treatment on coronary artery calcification in type 1 diabetic participants of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. Diabetes 2006; 55:3556–3565

2. Nathan DM, Cleary PA, Backlund J-YC, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643–2653

3. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Mortality in type 1 diabetes in the DCCT/EDIC versus the general population. Diabetes Care 2016;39:1378–1383

4. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. JAMA 2002;287:2563–2569

5. Tricco AC, Ashoor HM, Antony J, et al. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis. BMJ 2014; 349:g5459

6. Bartley PC, Bogoev M, Larsen J, Philotheou A. Long-term efficacy and safety of insulin detemir

compared to Neutral Protamine Hagedorn insulin in patients with type 1 diabetes using a treat-to-target basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. Diabet Med 2008;25:442–449
7. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. JAMA 2003;289:2254–2264
8. Bode BW, McGill JB, Lorber DL, Gross JL, Chang PC, Bregman DB; Affinity 1 Study Group. Inhaled technosphere insulin compared with injected prandial insulin in type 1 diabetes: a randomized 24-week trial. Diabetes Care 2015;38:2266–2273
9. Russell-Jones D, Bode BW, De Block C, et al. Fast-acting insulin aspart improves glycemic control in basal-bolus treatment for type 1 diabetes: results of a 26-week multicenter, active-controlled, treat-to-target, randomized, parallel-group trial (onset 1). Diabetes Care 2017;40:943–950
9a. Klaff L, Cao D, Dellva MA, et al. Ultra rapid lispro improves postprandial glucose control compared with lispro in patients with type 1 diabetes: results from the 26-week PRONTO-T1D study. Diabetes Obes Metab 2020;22:1799–1807
9b. Blevins T, Zhang Q, Frias JP, Jinnouchi H, Chang AM; PRONTO-T2D Investigators. Randomized double-blind clinical trial comparing ultra rapid lispro with lispro in a basal-bolus regimen in patients with type 2 diabetes: PRONTO-T2D. Diabetes Care 2020;43:2991–2998
10. Lane W, Bailey TS, Gerety G, et al.; Group Information; SWITCH 1. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 1 diabetes: the SWITCH 1 randomized clinical trial. JAMA 2017;318:33–44
11. Home PD, Bergenstal RM, Bolli GB, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 1 diabetes: a randomized, phase 3a, open-label clinical trial (EDITION 4). Diabetes Care 2015;38:2217–2225
12. Yeh H-C, Brown TT, Maruthur N, et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. Ann Intern Med 2012;157:336–347
13. Pickup JC. The evidence base for diabetes technology: appropriate and inappropriate meta-analysis. J Diabetes Sci Technol 2013;7:1567–1574
14. Bergenstal RM, Klonoff DC, Garg SK, et al.; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med 2013;369:224–232
15. Buckingham BA, Raghinaru D, Cameron F, et al.; In Home Closed Loop Study Group. Predictive low-glucose insulin suspension reduces duration of nocturnal hypoglycemia in children without increasing ketosis. Diabetes Care 2015;38:1197–1204
16. Bergenstal RM, Garg S, Weinzimer SA, et al. Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. JAMA 2016;316:1407–1408
17. Garg SK, Weinzimer SA, Tamborlane WV, et al. Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. Diabetes Technol Ther 2017;19:155–163
18. Tauschmann M, Thabit H, Bally L, et al.; APCam11 Consortium. Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. Lancet 2018;392:1321–1329
19. Brown SA, Kovatchev BP, Raghinaru D, et al.; iDCL Trial Research Group. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. N Engl J Med 2019;381:1707–1717
20. Peters AL, Laffel L (Eds.). *American Diabetes Association/JDRF Type 1 Diabetes Sourcebook*. Alexandria, VA, American Diabetes Association, 2013
21. Chiang JL, Kirkman MS, Laffel LMB, Peters AL; Type 1 Diabetes Sourcebook Authors. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. Diabetes Care 2014;37:2034–2054
22. Bell KJ, Barclay AW, Petocz P, Colagiuri S, Brand-Miller JC. Efficacy of carbohydrate counting in type 1 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2014;2:133–140
23. Vaz EC, Porfírio GJM, Nunes HRC, Nunes-Nogueira VDS. Effectiveness and safety of carbohydrate counting in the management of adult patients with type 1 diabetes mellitus: a systematic review and meta-analysis. Arch Endocrinol Metab 2018;62:337–345
24. Bell KJ, Smart CE, Steil GM, Brand-Miller JC, King B, Wolpert HA. Impact of fat, protein, and glycemic index on postprandial glucose control in type 1 diabetes: implications for intensive diabetes management in the continuous glucose monitoring era. Diabetes Care 2015;38:1008–1015
25. Frid AH, Kreugel G, Grassi G, et al. New insulin delivery recommendations. Mayo Clin Proc 2016;91:1231–1255
26. Bergenstal RM, Strock ES, Peremislov D, Gibney MA, Parvu V, Hirsch LJ. Safety and efficacy of insulin therapy delivered via a 4mm pen needle in obese patients with diabetes. Mayo Clin Proc 2015;90:329–338
27. Ratner RE, Dickey R, Fineman M, et al. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in type 1 diabetes mellitus: a 1-year, randomized controlled trial. Diabet Med 2004;21:1204–1212
28. Edelman S, Garg S, Frias J, et al. A double-blind, placebo-controlled trial assessing pramlintide treatment in the setting of intensive insulin therapy in type 1 diabetes. Diabetes Care 2006;29:2189–2195
29. Meng H, Zhang A, Liang Y, Hao J, Zhang X, Lu J. Effect of metformin on glycaemic control in patients with type 1 diabetes: a meta-analysis of randomized controlled trials. Diabetes Metab Res Rev 2018;34:e2983
30. Petrie JR, Chaturvedi N, Ford I, et al.; REMOVAL Study Group. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol 2017;5:597–609
31. Wang W, Liu H, Xiao S, Liu S, Li X, Yu P. Effects of insulin plus glucagon-like peptide-1 receptor agonists (GLP-1RAs) in treating type 1 diabetes mellitus: a systematic review and meta-analysis. Diabetes Ther 2017;8:727–738
32. Dandona P, Mathieu C, Phillip M, et al.; DEPICT-1 Investigators. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial. Lancet Diabetes Endocrinol 2017;5:864–876
33. Rosenstock J, Marquard J, Laffel LM, et al. Empagliflozin as adjunctive to insulin therapy in type 1 diabetes: the EASE trials. Diabetes Care 2018;41:2560–2569
34. Dean PG, Kukla A, Stegall MD, Kudva YC. Pancreas transplantation. BMJ. 2017;357:j1321
35. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669–2701
36. Buse JB, Wexler DJ, Tsapas A, et al. 2019 update to: management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2020;43:487–493
37. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589
38. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2016;164:740–751
39. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. Accessed 6 March 2020. Available from https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-revises-warnings-regarding-use-diabetes-medicine-metformin-certain
40. Out M, Kooy A, Lehert P, Schalkwijk CA, Stehouwer CDA. Long-term treatment with metformin in type 2 diabetes and methylmalonic acid: post hoc analysis of a randomized controlled 4.3 year trial. J Diabetes Complications 2018;32:171–178
41. Aroda VR, Edelstein SL, Goldberg RB, et al.; Diabetes Prevention Program Research Group. Long-term metformin use and vitamin B12 deficiency in the diabetes prevention program outcomes study. J Clin Endocrinol Metab 2016;101:1754–1761
42. Henry RR, Murray AV, Marmolejo MH, Hennicken D, Ptaszynska A, List JF. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. Int J Clin Pract 2012;66:446–456
43. Babu A, Mehta A, Guerrero P, et al. Safe and simple emergency department discharge therapy for patients with type 2 diabetes mellitus and severe hyperglycemia. Endocr Pract 2009;15:696–704
44. Cahn A, Cefalu WT. Clinical considerations for use of initial combination therapy in type 2 diabetes. Diabetes Care 2016;39(Suppl. 2):S137–S145
45. Abdul-Ghani MA, Puckett C, Triplitt C, et al. Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes. Results from the Efficacy and Durability of Initial Combination Therapy

for Type 2 Diabetes (EDICT): a randomized trial. Diabetes Obes Metab 2015;17:268–275
46. Phung OJ, Sobieraj DM, Engel SS, Rajpathak SN. Early combination therapy for the treatment of type 2 diabetes mellitus: systematic review and meta-analysis. Diabetes Obes Metab 2014; 16:410–417
47. Aroda VR, González-Galvez G, Grøn R, et al. Durability of insulin degludec plus liraglutide versus insulin glargine U100 as initial injectable therapy in type 2 diabetes (DUAL VIII): a multicentre, open-label, phase 3b, randomised controlled trial. Lancet Diabetes Endocrinol 2019;7: 596–605
48. Matthews DR, Paldánius PM, Proot P, Chiang Y, Stumvoll M, Prato SD. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. Lancet 2019;394: 1519–1529
49. Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med 2011;154:602–613
50. Maloney A, Rosenstock J, Fonseca V. A model-based meta-analysis of 24 antihyperglycemic drugs for type 2 diabetes: comparison of treatment effects at therapeutic doses. Clin Pharmacol Ther 2019;105:1213–1223
51. Vijan S, Sussman JB, Yudkin JS, Hayward RA. Effect of patients' risks and preferences on health gains with plasma glucose level lowering in type 2 diabetes mellitus. JAMA Intern Med 2014;174: 1227–1234
52. Tsapas A, Avgerinos I, Karagiannis T, et al. Comparative effectiveness of glucose-lowering drugs for type 2 diabetes: a systematic review and network meta-analysis. Ann Intern Med 2020;173:278–286
53. Pratley R, Amod A, Hoff ST, et al.; PIONEER 4 investigators. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. Lancet 2019;394:39–50
54. Singh S, Wright EE Jr, Kwan AYM, et al. Glucagon-like peptide-1 receptor agonists compared with basal insulins for the treatment of type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Obes Metab 2017;19:228–238
55. Levin PA, Nguyen H, Wittbrodt ET, Kim SC. Glucagon-like peptide-1 receptor agonists: a systematic review of comparative effectiveness research. Diabetes Metab Syndr Obes 2017;10:123–139
56. Abd El Aziz MS, Kahle M, Meier JJ, Nauck MA. A meta-analysis comparing clinical effects of short- or long-acting GLP-1 receptor agonists versus insulin treatment from head-to-head studies in type 2 diabetic patients. Diabetes Obes Metab 2017;19:216–227
57. Giorgino F, Benroubi M, Sun J-H, Zimmermann AG, Pechtner V. Efficacy and safety of once-weekly dulaglutide versus insulin glargine in patients with type 2 diabetes on metformin and glimepiride (AWARD-2). Diabetes Care 2015;38:2241–2249
58. Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. Lancet Diabetes Endocrinol 2017;5:355–366
59. Davies M, Heller S, Sreenan S, et al. Once-weekly exenatide versus once- or twice-daily insulin detemir: randomized, open-label, clinical trial of efficacy and safety in patients with type 2 diabetes treated with metformin alone or in combination with sulfonylureas. Diabetes Care 2013;36:1368–1376
60. Diamant M, Van Gaal L, Stranks S, et al. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. Lancet 2010;375:2234–2243
61. Riddle MC, Herman WH. The cost of diabetes care—an elephant in the room. Diabetes Care 2018;41:929–932
62. Truven Health Analytics. Micromedex 2.0: Introduction to RED BOOK Online. Accessed 10 September 2020. Available from https://www.micromedexsolutions.com/micromedex2/4.34.0/WebHelp/RED_BOOK/Introduction_to_REDB_BOOK_Online.htm
63. Centers for Medicare & Medicaid Services. NADAC (National Average Drug Acquisition Cost) drug pricing and payment. Accessed 2 October 2020. Available from https://data.medicaid.gov/Drug-Pricing-and-Payment/NADAC-National-Average-Drug-Acquisition-Cost-/a4y5-998d
64. Kang H, Lobo JM, Kim S, Sohn M-W. Cost-related medication non-adherence among U.S. adults with diabetes. Diabetes Res Clin Pract 2018;143:24–33
65. Patel MR, Piette JD, Resnicow K, Kowalski-Dobson T, Heisler M. Social determinants of health, cost-related nonadherence, and cost-reducing behaviors among adults with diabetes: findings from the National Health Interview Survey. Med Care 2016;54:796–803
66. Blonde L, Merilainen M, Karwe V, Raskin P; TITRATE Study Group. Patient-directed titration for achieving glycaemic goals using a once-daily basal insulin analogue: an assessment of two different fasting plasma glucose targets - the TITRATE study. Diabetes Obes Metab 2009;11: 623–631
67. Porcellati F, Lucidi P, Cioli P, et al. Pharmacokinetics and pharmacodynamics of insulin glargine given in the evening as compared with in the morning in type 2 diabetes. Diabetes Care 2015;38:503–512
68. Wang Z, Hedrington MS, Gogitidze Joy N, et al. Dose-response effects of insulin glargine in type 2 diabetes. Diabetes Care 2010;33:1555–1560
69. Singh SR, Ahmad F, Lal A, Yu C, Bai Z, Bennett H. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. CMAJ 2009;180:385–397
70. Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. Cochrane Database Syst Rev 2007;2: CD005613
71. Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues versus NPH human insulin in type 2 diabetes: a meta-analysis. Diabetes Res Clin Pract 2008;81:184–189
72. Owens DR, Traylor L, Mullins P, Landgraf W. Patient-level meta-analysis of efficacy and hypoglycaemia in people with type 2 diabetes initiating insulin glargine 100U/mL or neutral protamine Hagedorn insulin analysed according to concomitant oral antidiabetes therapy. Diabetes Res Clin Pract 2017;124(Suppl. C):57–65
73. Riddle MC, Rosenstock J, Gerich J; Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003;26:3080–3086
74. Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetes Care 2006; 29:1269–1274
75. Yki-Järvinen H, Kauppinen-Mäkelin R, Tiikkainen M, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. Diabetologia 2006;49:442–451
76. Bolli GB, Riddle MC, Bergenstal RM, et al.; on behalf of the EDITION 3 study investigators. New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naïve people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). Diabetes Obes Metab 2015;17:386–394
77. Terauchi Y, Koyama M, Cheng X, et al. New insulin glargine 300 U/ml versus glargine 100 U/ml in Japanese people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 2). Diabetes Obes Metab 2016;18:366–374
78. Yki-Järvinen H, Bergenstal RM, Bolli GB, et al. Glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus insulin glargine 100 U/ml in people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: the EDITION 2 randomized 12-month trial including 6-month extension. Diabetes Obes Metab 2015;17:1142–1149
79. Marso SP, McGuire DK, Zinman B, et al.; DEVOTE Study Group. Efficacy and safety of degludec versus glargine in type 2 diabetes. N Engl J Med 2017;377:723–732
80. Rodbard HW, Cariou B, Zinman B, et al.; BEGIN Once Long trial investigators. Comparison of insulin degludec with insulin glargine in insulin-naive subjects with type 2 diabetes: a 2-year randomized, treat-to-target trial. Diabet Med 2013; 30:1298–1304
81. Wysham C, Bhargava A, Chaykin L, et al. Effect of insulin degludec vs insulin glargine u100 on hypoglycemia in patients with type 2 diabetes: the SWITCH 2 randomized clinical trial. JAMA 2017;318:45–56
82. Zinman B, Philis-Tsimikas A, Cariou B, et al.; NN1250-3579 (BEGIN Once Long) Trial Investigators. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). Diabetes Care 2012;35:2464–2471
83. Lipska KJ, Parker MM, Moffet HH, Huang ES, Karter AJ. Association of initiation of basal insulin analogs vs neutral protamine hagedorn insulin with hypoglycemia-related emergency department visits or hospital admissions and with glycemic control in patients with type 2 diabetes. JAMA 2018;320:53–62

84. Cowart K. Overbasalization: addressing hesitancy in treatment intensification beyond basal insulin. Clin Diabetes 2020;38:304–310
85. Cefalu WT, Dawes DE, Gavlak G, et al.; Insulin Access and Affordability Working Group. Insulin Access and Affordability Working Group: conclusions and recommendations. Diabetes Care 2018;41:1299–1311
86. McCall AL. Insulin therapy and hypoglycemia. Endocrinol Metab Clin North Am 2012;41:57–87
87. Mannucci E, Monami M, Marchionni N. Short-acting insulin analogues vs. regular human insulin in type 2 diabetes: a meta-analysis. Diabetes Obes Metab 2009;11:53–59
88. Heller S, Bode B, Kozlovski P, Svendsen AL. Meta-analysis of insulin aspart versus regular human insulin used in a basal-bolus regimen for the treatment of diabetes mellitus. J Diabetes 2013;5:482–491
89. Wysham C, Hood RC, Warren ML, Wang T, Morwick TM, Jackson JA. Effect of total daily dose on efficacy, dosing, and safety of 2 dose titration regimens of human regular U500 insulin in severely insulin-resistant patients with type 2 diabetes. Endocr Pract 2016;22:653–665
90. Riddle MC, Yki-Järvinen H, Bolli GB, et al. One-year sustained glycaemic control and less hypoglycaemia with new insulin glargine 300 U/ml compared with 100 U/ml in people with type 2 diabetes using basal plus meal-time insulin: the EDITION 1 12-month randomized trial, including 6-month extension. Diabetes Obes Metab 2015;17:835–842
91. Yki-Järvinen H, Bergenstal R, Ziemen M, et al.; EDITION 2 Study Investigators. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). Diabetes Care 2014;37:3235–3243
92. Akturk HK, Snell-Bergeon JK, Rewers A, et al. Improved postprandial glucose with inhaled technosphere insulin compared with insulin aspart in patients with type 1 diabetes on multiple daily injections: the STAT study. Diabetes Technol Ther 2018;20:639–647
93. Diamant M, Nauck MA, Shaginian R, et al.; 4B Study Group. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. Diabetes Care 2014;37:2763–2773
94. Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. Lancet 2014;384:2228–2234
95. Maiorino MI, Chiodini P, Bellastella G, Capuano A, Esposito K, Giugliano D. Insulin and glucagon-like peptide 1 receptor agonist combination therapy in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabetes Care 2017;40:614–624
96. Rodbard HW, Visco VE, Andersen H, Hiort LC, Shu DHW. Treatment intensification with stepwise addition of prandial insulin aspart boluses compared with full basal-bolus therapy (FullSTEP Study): a randomised, treat-to-target clinical trial. Lancet Diabetes Endocrinol 2014;2:30–37

10. Cardiovascular Disease and Risk Management: *Standards of Medical Care in Diabetes—2021*

American Diabetes Association

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The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc21-SPPC), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc21-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

For prevention and management of diabetes complications in children and adolescents, please refer to Section 13 "Children and Adolescents" (https://doi.org/10.2337/dc21-S013).

Atherosclerotic cardiovascular disease (ASCVD)—defined as coronary heart disease (CHD), cerebrovascular disease, or peripheral arterial disease presumed to be of atherosclerotic origin—is the leading cause of morbidity and mortality for individuals with diabetes and results in an estimated $37.3 billion in cardiovascular-related spending per year associated with diabetes (1). Common conditions coexisting with type 2 diabetes (e.g., hypertension and dyslipidemia) are clear risk factors for ASCVD, and diabetes itself confers independent risk. Numerous studies have shown the efficacy of controlling individual cardiovascular risk factors in preventing or slowing ASCVD in people with diabetes. Furthermore, large benefits are seen when multiple cardiovascular risk factors are addressed simultaneously. Under the current paradigm of aggressive risk factor modification in patients with diabetes, there is evidence that measures of 10-year coronary heart disease (CHD) risk among U.S. adults with diabetes have improved significantly over the past decade (2) and that ASCVD morbidity and mortality have decreased (3,4).

Heart failure is another major cause of morbidity and mortality from cardiovascular disease. Recent studies have found that rates of incident heart failure hospitalization (adjusted for age and sex) were twofold higher in patients with diabetes compared with those without (5,6). People with diabetes may have heart failure with preserved ejection fraction (HFpEF) or with reduced ejection fraction (HFrEF). Hypertension is often a precursor of heart failure of either type, and ASCVD can coexist with either type (7), whereas prior myocardial infarction (MI) is often a major factor in HFrEF. Rates of heart failure hospitalization have been improved in recent trials including patients with type 2 diabetes, most of whom also had ASCVD, with sodium–glucose cotransporter 2 (SGLT2) inhibitors (8–10).

This section has received endorsement from the American College of Cardiology.

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For prevention and management of both ASCVD and heart failure, cardiovascular risk factors should be systematically assessed at least annually in all patients with diabetes. These risk factors include obesity/overweight, hypertension, dyslipidemia, smoking, a family history of premature coronary disease, chronic kidney disease, and the presence of albuminuria. Modifiable abnormal risk factors should be treated as described in these guidelines. Notably, the majority of evidence supporting interventions to reduce cardiovascular risk in diabetes comes from trials of patients with type 2 diabetes. Few trials have been specifically designed to assess the impact of cardiovascular risk reduction strategies in patients with type 1 diabetes.

THE RISK CALCULATOR

The American College of Cardiology/American Heart Association ASCVD risk calculator (Risk Estimator Plus) is generally a useful tool to estimate 10-year risk of a first ASCVD event (available online at tools.acc.org/ASCVD-Risk-Estimator-Plus). The calculator includes diabetes as a risk factor, since diabetes itself confers increased risk for ASCVD, although it should be acknowledged that these risk calculators do not account for the duration of diabetes or the presence of diabetes complications, such as albuminuria. Although some variability in calibration exists in various subgroups, including by sex, race, and diabetes, the overall risk prediction does not differ in those with or without diabetes (11–14), validating the use of risk calculators in people with diabetes. The 10-year risk of a first ASCVD event should be assessed to better stratify ASCVD risk and help guide therapy, as described below.

Recently, risk scores and other cardiovascular biomarkers have been developed for risk stratification of secondary prevention patients (i.e., those who are already high risk because they have ASCVD) but are not yet in widespread use (15,16). With newer, more expensive lipid-lowering therapies now available, use of these risk assessments may help target these new therapies to "higher risk" ASCVD patients in the future.

HYPERTENSION/BLOOD PRESSURE CONTROL

Hypertension, defined as a sustained blood pressure ≥140/90 mmHg, is common among patients with either type 1 or type 2 diabetes. Hypertension is a major risk factor for both ASCVD and microvascular complications. Moreover, numerous studies have shown that antihypertensive therapy reduces ASCVD events, heart failure, and microvascular complications. Please refer to the American Diabetes Association (ADA) position statement "Diabetes and Hypertension" for a detailed review of the epidemiology, diagnosis, and treatment of hypertension (17).

Screening and Diagnosis

Recommendations

10.1 Blood pressure should be measured at every routine clinical visit. Patients found to have elevated blood pressure (≥140/90 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. **B**

10.2 All hypertensive patients with diabetes should monitor their blood pressure at home. **B**

Blood pressure should be measured at every routine clinical visit by a trained individual and should follow the guidelines established for the general population: measurement in the seated position, with feet on the floor and arm supported at heart level, after 5 min of rest. Cuff size should be appropriate for the upper-arm circumference. Elevated values should be confirmed on a separate day. Postural changes in blood pressure and pulse may be evidence of autonomic neuropathy and therefore require adjustment of blood pressure targets. Orthostatic blood pressure measurements should be checked on initial visit and as indicated.

Home blood pressure self-monitoring and 24-h ambulatory blood pressure monitoring may provide evidence of white coat hypertension, masked hypertension, or other discrepancies between office and "true" blood pressure (17). In addition to confirming or refuting a diagnosis of hypertension, home blood pressure assessment may be useful to monitor antihypertensive treatment. Studies of individuals without diabetes found that home measurements may better correlate with ASCVD risk than office measurements (18,19). Moreover, home blood pressure monitoring may improve patient medication adherence and thus help reduce cardiovascular risk (20).

Treatment Goals

Recommendations

10.3 For patients with diabetes and hypertension, blood pressure targets should be individualized through a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications, and patient preferences. **C**

10.4 For individuals with diabetes and hypertension at higher cardiovascular risk (existing atherosclerotic cardiovascular disease [ASCVD] or 10-year ASCVD risk ≥15%), a blood pressure target of <130/80 mmHg may be appropriate, if it can be safely attained. **C**

10.5 For individuals with diabetes and hypertension at lower risk for cardiovascular disease (10-year atherosclerotic cardiovascular disease risk <15%), treat to a blood pressure target of <140/90 mmHg. **A**

10.6 In pregnant patients with diabetes and preexisting hypertension, a blood pressure target of 110–135/85 mmHg is suggested in the interest of reducing the risk for accelerated maternal hypertension **A** and minimizing impaired fetal growth. **E**

Randomized clinical trials have demonstrated unequivocally that treatment of hypertension to blood pressure <140/90 mmHg reduces cardiovascular events as well as microvascular complications (21–27). Therefore, patients with type 1 or type 2 diabetes who have hypertension should, at a minimum, be treated to blood pressure targets of <140/90 mmHg. The benefits and risks of intensifying antihypertensive therapy to target blood pressures lower than <140/90 mmHg (e.g., <130/80 or <120/80 mmHg) have been evaluated in large randomized clinical trials and meta-analyses of clinical trials. Notably, there is an absence of high-quality data available to guide blood pressure targets in type 1 diabetes.

Randomized Controlled Trials of Intensive Versus Standard Blood Pressure Control

The Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial provides the strongest direct assessment of the benefits and risks of intensive blood pressure control among people with type 2 diabetes (28). In ACCORD BP, compared with standard blood pressure control (target systolic blood pressure <140 mmHg), intensive blood pressure control (target systolic blood pressure <120 mmHg) did not reduce total major atherosclerotic cardiovascular events but did reduce the risk of stroke, at the expense of increased adverse events (**Table 10.1**). The ACCORD BP results suggest that blood pressure targets more intensive than <140/90 mmHg are not likely to improve cardiovascular outcomes among most people with type 2 diabetes but may be reasonable for patients who may derive the most benefit and have been educated about added treatment burden, side effects, and costs, as discussed below.

Additional studies, such as the Systolic Blood Pressure Intervention Trial (SPRINT) and the Hypertension Optimal Treatment (HOT) trial, also examined effects of intensive versus standard control (**Table 10.1**), though the relevance of their results to people with diabetes is less clear. The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation–Blood Pressure (ADVANCE BP) trial did not explicitly test blood pressure targets (29); the achieved blood pressure in the intervention group was higher than that achieved in the ACCORD BP intensive arm and would be consistent with a target blood pressure of <140/90 mmHg. Notably, ACCORD BP and SPRINT measured blood pressure using automated office blood pressure measurement, which yields values that are generally lower than typical office blood pressure readings by approximately 5–10 mmHg (30), suggesting that implementing the ACCORD BP or SPRINT

Table 10.1—Randomized controlled trials of intensive versus standard hypertension treatment strategies

Clinical trial	Population	Intensive	Standard	Outcomes
ACCORD BP (28)	4,733 participants with T2D aged 40–79 years with prior evidence of CVD or multiple cardiovascular risk factors	SBP target: <120 mmHg Achieved (mean) SBP/DBP: 119.3/64.4 mmHg	SBP target: 130–140 mmHg Achieved (mean) SBP/DBP: 13.5/70.5 mmHg	• No benefit in primary end point: composite of nonfatal MI, nonfatal stroke, and CVD death • Stroke risk reduced 41% with intensive control, not sustained through follow-up beyond the period of active treatment • Adverse events more common in intensive group, particularly elevated serum creatinine and electrolyte abnormalities
ADVANCE BP (29)	11,140 participants with T2D aged 55 years and older with prior evidence of CVD or multiple cardiovascular risk factors	Intervention: a single-pill, fixed-dose combination of perindopril and indapamide Achieved (mean) SBP/DBP: 136/73 mmHg	Control: placebo Achieved (mean) SBP/DBP: 141.6/75.2 mmHg	• Intervention reduced risk of primary composite end point of major macrovascular and microvascular events (9%), death from any cause (14%), and death from CVD (18%) • 6-year observational follow-up found reduction in risk of death in intervention group attenuated but still significant (198)
HOT (199)	18,790 participants, including 1,501 with diabetes	DBP target: ≤80 mmHg	DBP target: ≤90 mmHg	• In the overall trial, there was no cardiovascular benefit with more intensive targets • In the subpopulation with diabetes, an intensive DBP target was associated with a significantly reduced risk (51%) of CVD events
SPRINT (40)	9,361 participants without diabetes	SBP target: <120 mmHg Achieved (mean): 121.4 mmHg	SBP target: <140 mmHg Achieved (mean): 136.2 mmHg	• Intensive SBP target lowered risk of the primary composite outcome 25% (MI, ACS, stroke, heart failure, and death due to CVD) • Intensive target reduced risk of death 27% • Intensive therapy increased risks of electrolyte abnormalities and AKI

ACCORD BP, Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial; ACS, acute coronary syndrome; ADVANCE BP, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation–Blood Pressure trial; AKI, acute kidney injury; CVD, cardiovascular disease; DBP, diastolic blood pressure; HOT, Hypertension Optimal Treatment trial; MI, myocardial infarction; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial; T2D, type 2 diabetes. Data from this table can also be found in the ADA position statement "Diabetes and Hypertension" (17).

protocols in an outpatient clinic might require a systolic blood pressure target higher than <120 mmHg, such as <130 mmHg.

A number of post hoc analyses have attempted to explain the apparently divergent results of ACCORD BP and SPRINT. Some investigators have argued that the divergent results are not due to differences between people with and without diabetes but rather are due to differences in study design or to characteristics other than diabetes (31–33). Others have opined that the divergent results are most readily explained by the lack of benefit of intensive blood pressure control on cardiovascular mortality in ACCORD BP, which may be due to differential mechanisms underlying cardiovascular disease in type 2 diabetes, to chance, or both (34). Interestingly, a post hoc analysis has found that intensive blood pressure lowering increased the risk of incident chronic kidney disease in both ACCORD BP and SPRINT, with the absolute risk of incident chronic kidney disease being higher in individuals with type 2 diabetes (35).

Meta-analyses of Trials

To clarify optimal blood pressure targets in patients with diabetes, meta-analyses have stratified clinical trials by mean baseline blood pressure or mean blood pressure attained in the intervention (or intensive treatment) arm. Based on these analyses, antihypertensive treatment appears to be beneficial when mean baseline blood pressure is ≥140/90 mmHg or mean attained intensive blood pressure is ≥130/80 mmHg (17,21,22,24–26). Among trials with lower baseline or attained blood pressure, antihypertensive treatment reduced the risk of stroke, retinopathy, and albuminuria, but effects on other ASCVD outcomes and heart failure were not evident. Taken together, these meta-analyses consistently show that treating patients with baseline blood pressure ≥140 mmHg to targets <140 mmHg is beneficial, while more-intensive targets may offer additional (though probably less robust) benefits.

Individualization of Treatment Targets

Patients and clinicians should engage in a shared decision-making process to determine individual blood pressure targets (17). This approach acknowledges that the benefits and risks of intensive blood pressure targets are uncertain and may vary across patients and is consistent with a patient-focused approach to care that values patient priorities and provider judgment (36). Secondary analyses of ACCORD BP and SPRINT suggest that clinical factors can help determine individuals more likely to benefit and less likely to be harmed by intensive blood pressure control (37,38).

Absolute benefit from blood pressure reduction correlated with absolute baseline cardiovascular risk in SPRINT and in earlier clinical trials conducted at higher baseline blood pressure levels (11,38). Extrapolation of these studies suggests that patients with diabetes may also be more likely to benefit from intensive blood pressure control when they have high absolute cardiovascular risk. Therefore, it may be reasonable to target blood pressure <130/80 mmHg among patients with diabetes and either clinically diagnosed cardiovascular disease (particularly stroke, which was significantly reduced in ACCORD BP) or 10-year ASCVD risk ≥15%, if it can be attained safely. This approach is consistent with guidelines from the American College of Cardiology/American Heart Association, which advocate a blood pressure target <130/80 mmHg for all patients, with or without diabetes (39).

Potential adverse effects of antihypertensive therapy (e.g., hypotension, syncope, falls, acute kidney injury, and electrolyte abnormalities) should also be taken into account (28,35,40,41). Patients with older age, chronic kidney disease, and frailty have been shown to be at higher risk of adverse effects of intensive blood pressure control (41). In addition, patients with orthostatic hypotension, substantial comorbidity, functional limitations, or polypharmacy may be at high risk of adverse effects, and some patients may prefer higher blood pressure targets to enhance quality of life. Patients with low absolute cardiovascular risk (10-year ASCVD risk <15%) or with a history of adverse effects of intensive blood pressure control or at high risk of such adverse effects should have a higher blood pressure target. In such patients, a blood pressure target of <140/90 mmHg is recommended, if it can be safely attained.

Pregnancy and Antihypertensive Medications

There are few randomized controlled trials of antihypertensive therapy in pregnant women with diabetes. A 2014 Cochrane systematic review of antihypertensive therapy for mild to moderate chronic hypertension that included 49 trials and over 4,700 women did not find any conclusive evidence for or against blood pressure treatment to reduce the risk of preeclampsia for the mother or effects on perinatal outcomes such as preterm birth, small-for-gestational-age infants, or fetal death (42). The more recent Control of Hypertension in Pregnancy Study (CHIPS) (43) enrolled mostly women with chronic hypertension. In CHIPS, targeting a diastolic blood pressure of 85 mmHg during pregnancy was associated with reduced likelihood of developing accelerated maternal hypertension and no demonstrable adverse outcome for infants compared with targeting a higher diastolic blood pressure. The mean systolic blood pressure achieved in the more intensively treated group was 133.1 ± 0.5 mmHg, and the mean diastolic blood pressure achieved in that group was 85.3 ± 0.3 mmHg. A similar approach is supported by the International Society for the Study of Hypertension in Pregnancy, which specifically recommends use of antihypertensive therapy to maintain systolic blood pressure between 110 and 140 mmHg and diastolic blood pressure between 80 and 85 mmHg (44). Current evidence supports controlling blood pressure to 110–135/85 mmHg to reduce the risk of accelerated maternal hypertension but also to minimize impairment of fetal growth. During pregnancy, treatment with ACE inhibitors, angiotensin receptor blockers, and spironolactone are contraindicated as they may cause fetal damage. Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, and long-acting nifedipine, while hydralzine may be considered in the acute management of hypertension in pregnancy or severe preeclampsia (45). Diuretics are not recommended for blood pressure control in pregnancy but may be used during late-stage pregnancy if needed for volume control (45,46). The American College of Obstetricians and Gynecologists also recommends that postpartum patients with gestational hypertension, preeclampsia, and superimposed preeclampsia have their blood pressures observed for 72 h in the hospital and for 7–10 days postpartum. Long-term follow-up is recommended for these women as they have increased lifetime cardiovascular risk (47). See Section

14 "Management of Diabetes in Pregnancy" (https://doi.org/10.2337/dc21-S014) for additional information.

Treatment Strategies

Lifestyle Intervention

Recommendation

10.7 For patients with blood pressure >120/80 mmHg, lifestyle intervention consists of weight loss when indicated, a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern including reducing sodium and increasing potassium intake, moderation of alcohol intake, and increased physical activity. **A**

Lifestyle management is an important component of hypertension treatment because it lowers blood pressure, enhances the effectiveness of some antihypertensive medications, promotes other aspects of metabolic and vascular health, and generally leads to few adverse effects. Lifestyle therapy consists of reducing excess body weight through caloric restriction (see Section 8 "Obesity Management for the Treatment of Type 2 Diabetes," https://doi.org/10.2337/dc21-S008), restricting sodium intake (<2,300 mg/day), increasing consumption of fruits and vegetables (8–10 servings per day) and low-fat dairy products (2–3 servings per day), avoiding excessive alcohol consumption (no more than 2 servings per day in men and no more than 1 serving per day in women) (48), and increasing activity levels (49).

These lifestyle interventions are reasonable for individuals with diabetes and mildly elevated blood pressure (systolic >120 mmHg or diastolic >80 mmHg) and should be initiated along with pharmacologic therapy when hypertension is diagnosed (**Fig. 10.1**) (49). A lifestyle therapy plan should be developed in collaboration with the patient and discussed as part of diabetes management.

Pharmacologic Interventions

Recommendations

10.8 Patients with confirmed office-based blood pressure ≥140/90 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals. **A**

10.9 Patients with confirmed office-based blood pressure ≥160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single-pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. **A**

10.10 Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes. **A** ACE inhibitors or angiotensin receptor blockers are recommended first-line therapy for hypertension in people with diabetes and coronary artery disease. **A**

10.11 Multiple-drug therapy is generally required to achieve blood pressure targets. However, combinations of ACE inhibitors and angiotensin receptor blockers and combinations of ACE inhibitors or angiotensin receptor blockers with direct renin inhibitors should not be used. **A**

10.12 An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin-to-creatinine ratio ≥300 mg/g creatinine **A** or 30–299 mg/g creatinine. **B** If one class is not tolerated, the other should be substituted. **B**

10.13 For patients treated with an ACE inhibitor, angiotensin receptor blocker, or diuretic, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored at least annually. **B**

Initial Number of Antihypertensive Medications. Initial treatment for people with diabetes depends on the severity of hypertension (**Fig. 10.1**). Those with blood pressure between 140/90 mmHg and 159/99 mmHg may begin with a single drug. For patients with blood pressure ≥160/100 mmHg, initial pharmacologic treatment with two antihypertensive medications is recommended in order to more effectively achieve adequate blood pressure control (50–52). Single-pill antihypertensive combinations may improve medication adherence in some patients (53).

Classes of Antihypertensive Medications. Initial treatment for hypertension should include any of the drug classes demonstrated to reduce cardiovascular events in patients with diabetes: ACE inhibitors (54,55), angiotensin receptor blockers (ARBs) (54,55), thiazide-like diuretics (56), or dihydropyridine calcium channel blockers (57). In patients with diabetes and established coronary artery disease, ACE inhibitors or ARBs are recommended first-line therapy for hypertension (58–60). For patients with albuminuria (urine albumin-to-creatinine ratio [UACR] ≥30 mg/g), initial treatment should include an ACE inhibitor or ARB in order to reduce the risk of progressive kidney disease (17) (**Fig. 10.1**). In the absence of albuminuria, risk of progressive kidney disease is low, and ACE inhibitors and ARBs have not been found to afford superior cardioprotection when compared with thiazide-like diuretics or dihydropyridine calcium channel blockers (61). β-Blockers are indicated in the setting of prior MI, active angina, or HfrEF but have not been shown to reduce mortality as blood pressure–lowering agents in the absence of these conditions (23,62,63).

Multiple-Drug Therapy. Multiple-drug therapy is often required to achieve blood pressure targets (**Fig. 10.1**), particularly in the setting of diabetic kidney disease. However, the use of both ACE inhibitors and ARBs in combination, or the combination of an ACE inhibitor or ARB and a direct renin inhibitor, is not recommended given the lack of added ASCVD benefit and increased rate of adverse events—namely, hyperkalemia, syncope, and acute kidney injury (AKI) (64–66). Titration of and/or addition of further blood pressure medications should be made in a timely fashion to overcome therapeutic inertia in achieving blood pressure targets.

Bedtime Dosing. Growing evidence suggests that there is an association between the absence of nocturnal blood pressure dipping and the incidence of ASCVD. A meta-analysis of randomized clinical trials found a small benefit of evening versus morning dosing of antihypertensive medications with regard to blood pressure control but had no data on clinical effects (67). In two subgroup analyses of a single subsequent randomized controlled trial, moving at least one antihypertensive

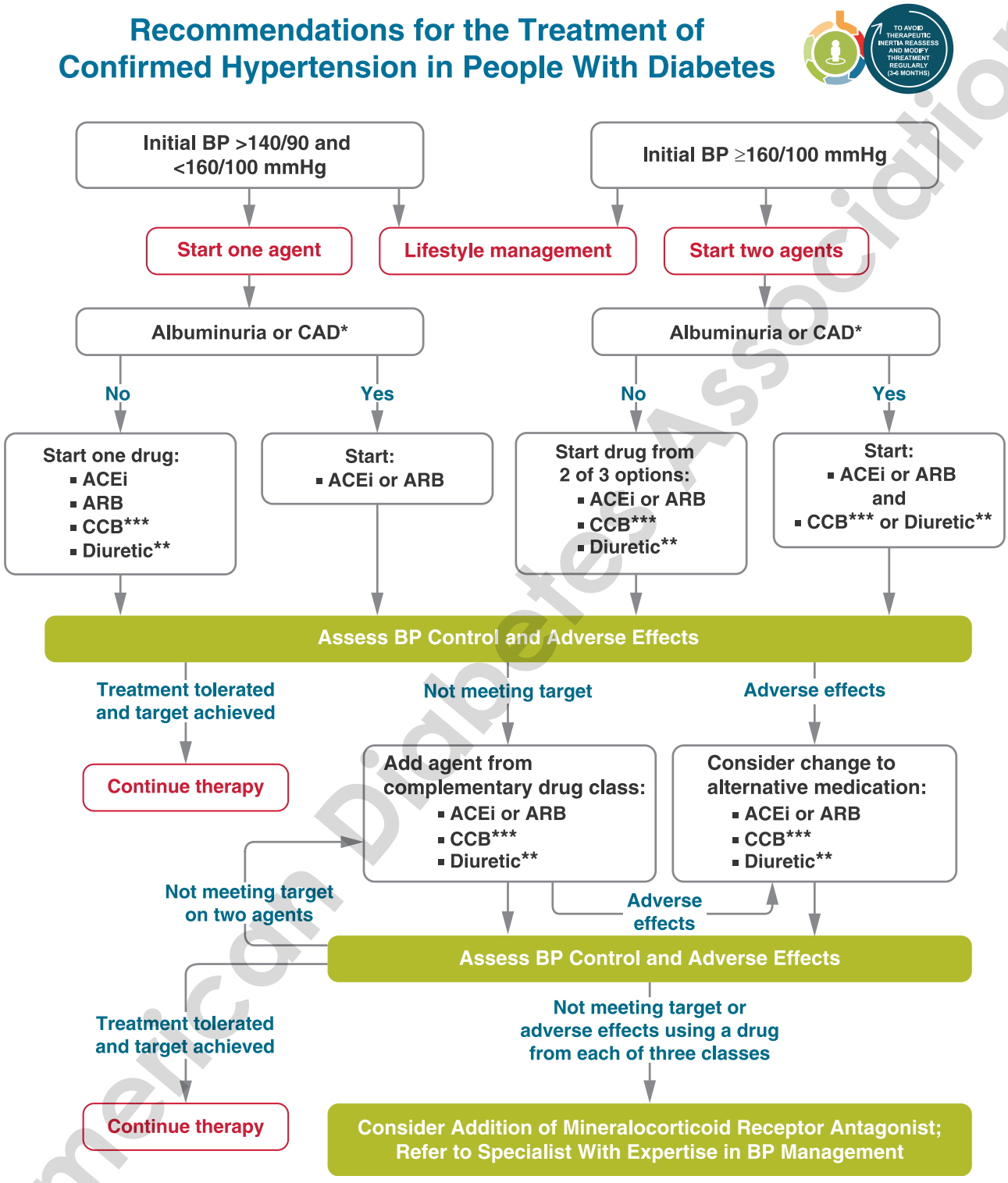

Figure 10.1—Recommendations for the treatment of confirmed hypertension in people with diabetes. *An ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB) is suggested to treat hypertension for patients with coronary artery disease (CAD) or urine albumin-to-creatinine ratio 30–299 mg/g creatinine and strongly recommended for patients with urine albumin-to-creatinine ratio ≥300 mg/g creatinine. **Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred. ***Dihydropyridine calcium channel blocker (CCB). BP, blood pressure. Adapted from de Boer et al. (17).

medication to bedtime significantly reduced cardiovascular events, but results were based on a small number of events (68).

Hyperkalemia and Acute Kidney Injury. Treatment with ACE inhibitors or ARBs can cause AKI and hyperkalemia, while diuretics can cause AKI and either hypokalemia or hyperkalemia (depending on mechanism of action) (69,70). Detection and management of these abnormalities is important because AKI and hyperkalemia each increase the risks of cardiovascular events and death (71). Therefore, serum creatinine and potassium should be monitored during treatment with an ACE

inhibitor, ARB, or diuretic, particularly among patients with reduced glomerular filtration who are at increased risk of hyperkalemia and AKI (69,70,72).

Resistant Hypertension

Recommendation

10.14 Patients with hypertension who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for mineralocorticoid receptor antagonist therapy. **B**

Resistant hypertension is defined as blood pressure ≥140/90 mmHg despite a therapeutic strategy that includes appropriate lifestyle management plus a diuretic and two other antihypertensive drugs belonging to different classes at adequate doses. Prior to diagnosing resistant hypertension, a number of other conditions should be excluded, including medication nonadherence, white coat hypertension, and secondary hypertension. In general, barriers to medication adherence (such as cost and side effects) should be identified and addressed (**Fig. 10.1**). Mineralocorticoid receptor antagonists are effective for management of resistant hypertension in patients with type 2 diabetes when added to existing treatment with an ACE inhibitor or ARB, thiazide-like diuretic, and dihydropyridine calcium channel blocker (73). Mineralocorticoid receptor antagonists also reduce albuminuria and have additional cardiovascular benefits (74–77). However, adding a mineralocorticoid receptor antagonist to a regimen including an ACE inhibitor or ARB may increase the risk for hyperkalemia, emphasizing the importance of regular monitoring for serum creatinine and potassium in these patients, and long-term outcome studies are needed to better evaluate the role of mineralocorticoid receptor antagonists in blood pressure management.

LIPID MANAGEMENT

Lifestyle Intervention

Recommendations

10.15 Lifestyle modification focusing on weight loss (if indicated); application of a Mediterranean style or Dietary Approaches to Stop Hypertension (DASH) eating pattern; reduction of saturated fat and *trans* fat; increase of dietary n-3 fatty acids, viscous fiber, and plant stanols/sterols intake; and increased physical activity should be recommended to improve the lipid profile and reduce the risk of developing atherosclerotic cardiovascular disease in patients with diabetes. **A**

10.16 Intensify lifestyle therapy and optimize glycemic control for patients with elevated triglyceride levels (≥150 mg/dL [1.7 mmol/L]) and/or low HDL cholesterol (<40 mg/dL [1.0 mmol/L] for men, <50 mg/dL [1.3 mmol/L] for women). **C**

Lifestyle intervention, including weight loss (78), increased physical activity, and medical nutrition therapy, allows some patients to reduce ASCVD risk factors. Nutrition intervention should be tailored according to each patient's age, diabetes type, pharmacologic treatment, lipid levels, and medical conditions.

Recommendations should focus on application of a Mediterranean style diet (79) or Dietary Approaches to Stop Hypertension (DASH) eating pattern, reducing saturated and *trans* fat intake and increasing plant stanols/sterols, n-3 fatty acids, and viscous fiber (such as in oats, legumes, and citrus) intake (80). Glycemic control may also beneficially modify plasma lipid levels, particularly in patients with very high triglycerides and poor glycemic control. See Section 5 "Facilitating Behavior Change and Well-being to Improve Health Outcomes" (https://doi.org/10.2337/dc21-S005) for additional nutrition information.

Ongoing Therapy and Monitoring With Lipid Panel

Recommendations

10.17 In adults not taking statins or other lipid-lowering therapy, it is reasonable to obtain a lipid profile at the time of diabetes diagnosis, at an initial medical evaluation, and every 5 years thereafter if under the age of 40 years, or more frequently if indicated. **E**

10.18 Obtain a lipid profile at initiation of statins or other lipid-lowering therapy, 4–12 weeks after initiation or a change in dose, and annually thereafter as it may help to monitor the response to therapy and inform medication adherence. **E**

In adults with diabetes, it is reasonable to obtain a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) at the time of diagnosis, at the initial medical evaluation, and at least every 5 years thereafter in patients under the age of 40 years. In younger patients with longer duration of disease (such as those with youth-onset type 1 diabetes), more frequent lipid profiles may be reasonable. A lipid panel should also be obtained immediately before initiating statin therapy. Once a patient is taking a statin, LDL cholesterol levels should be assessed 4–12 weeks after initiation of statin therapy, after any change in dose, and on an individual basis (e.g., to monitor for medication adherence and efficacy). If LDL cholesterol levels are not responding in spite of medication adherence, clinical judgment is recommended to determine the need for and timing of lipid panels. In individual patients, the highly variable LDL cholesterol–lowering response seen with statins is poorly understood (81). Clinicians should attempt to find a dose or alternative statin that is tolerable if side effects occur. There is evidence for benefit from even extremely low, less than daily statin doses (82).

STATIN TREATMENT

Primary Prevention

Recommendations

10.19 For patients with diabetes aged 40–75 years without atherosclerotic cardiovascular disease, use moderate-intensity statin therapy in addition to lifestyle therapy. **A**

10.20 For patients with diabetes aged 20–39 years with additional atherosclerotic cardiovascular disease risk factors, it may be reasonable to initiate statin therapy in addition to lifestyle therapy. **C**

10.21 In patients with diabetes at higher risk, especially those with multiple atherosclerotic cardiovascular disease risk factors or aged 50–70 years, it is reasonable to use high-intensity statin therapy. **B**

10.22 In adults with diabetes and 10-year atherosclerotic cardiovascular disease risk of 20% or higher, it may be reasonable to add ezetimibe to maximally tolerated statin therapy to reduce LDL cholesterol levels by 50% or more. **C**

Secondary Prevention

Recommendations

10.23 For patients of all ages with diabetes and atherosclerotic cardiovascular disease, high-intensity statin therapy should be added to lifestyle therapy. **A**

10.24 For patients with diabetes and atherosclerotic cardiovascular disease considered very high risk using specific criteria, if LDL cholesterol is ≥70 mg/dL on maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor). **A** Ezetimibe may be preferred due to lower cost.

10.25 For patients who do not tolerate the intended intensity, the maximally tolerated statin dose should be used. **E**

10.26 In adults with diabetes aged >75 years already on statin therapy, it is reasonable to continue statin treatment. **B**

10.27 In adults with diabetes aged >75 years, it may be reasonable to initiate statin therapy after discussion of potential benefits and risks. **C**

10.28 Statin therapy is contraindicated in pregnancy. **B**

Initiating Statin Therapy Based on Risk

Patients with type 2 diabetes have an increased prevalence of lipid abnormalities, contributing to their high risk of ASCVD. Multiple clinical trials have demonstrated the beneficial effects of statin therapy on ASCVD outcomes in subjects with and without CHD (83,84). Subgroup analyses of patients with diabetes in larger trials (85–89) and trials in patients with diabetes (90,91) showed significant primary and secondary prevention of ASCVD events and CHD death in patients with diabetes. Meta-analyses, including data from over 18,000 patients with diabetes from 14 randomized trials of statin therapy (mean follow-up 4.3 years), demonstrate a 9% proportional reduction in all-cause mortality and 13% reduction in vascular mortality for each 1 mmol/L (39 mg/dL) reduction in LDL cholesterol (92).

Accordingly, statins are the drugs of choice for LDL cholesterol lowering and cardioprotection. **Table 10.2** shows the two statin dosing intensities that are recommended for use in clinical practice: high-intensity statin therapy will achieve approximately a ≥50% reduction in LDL cholesterol, and moderate-intensity statin regimens achieve 30–49% reductions in LDL cholesterol. Low-dose statin therapy is generally not recommended in patients with diabetes but is sometimes the only dose of statin that a patient can tolerate. For patients who do not tolerate the intended intensity of statin, the maximally tolerated statin dose should be used.

As in those without diabetes, absolute reductions in ASCVD outcomes (CHD death and nonfatal MI) are greatest in people with high baseline ASCVD risk (known ASCVD and/or very high LDL cholesterol levels), but the overall benefits of statin therapy in people with diabetes at moderate or even low risk for ASCVD are convincing (93,94). The *relative* benefit of lipid-lowering therapy has been uniform across most subgroups tested (84,92), including subgroups that varied with respect to age and other risk factors.

Primary Prevention (Patients Without ASCVD)

For primary prevention, moderate-dose statin therapy is recommended for those 40 years and older (86,93,94), though high-intensity therapy may be considered on an individual basis in the context of additional ASCVD risk factors. The evidence is strong for patients with diabetes aged 40–75 years, an age-group well represented in statin trials showing benefit. Since risk is enhanced in patients with diabetes, as noted above, patients who also have multiple other coronary risk factors have increased risk, equivalent to that of those with ASCVD. As such, recent guidelines recommend that in patients with diabetes who are at higher risk, especially those with multiple ASCVD risk factors or aged 50–70 years, it is reasonable to prescribe high-intensity statin therapy (12,95). Furthermore, for patients with diabetes whose ASCVD risk is ≥20%, i.e., an ASCVD risk equivalent, the same high-intensity statin therapy is recommended as for those with documented ASCVD (12). In those individuals, it may also be reasonable to add ezetimibe to maximally tolerated statin therapy if needed to reduce LDL cholesterol levels by 50% or more (12). The evidence is lower for patients aged >75 years; relatively few older patients with diabetes have been enrolled in primary prevention trials. However, heterogeneity by age has not been seen in the relative benefit of lipid-lowering therapy in trials that included older participants (84,91,92), and because older age confers higher risk, the absolute benefits are actually greater (84,96). Moderate-intensity statin therapy is recommended in patients with diabetes who are 75 years or older. However, the risk-benefit profile should be routinely evaluated in this population, with downward titration of

Table 10.2—High-intensity and moderate-intensity statin therapy*

High-intensity statin therapy (lowers LDL cholesterol by ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30–49%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 1–4 mg

*Once-daily dosing. XL, extended release.

dose performed as needed. See Section 12 "Older Adults" (https://doi.org/10.2337/dc21-S012) for more details on clinical considerations for this population.

Age <40 Years and/or Type 1 Diabetes. Very little clinical trial evidence exists for patients with type 2 diabetes under the age of 40 years or for patients with type 1 diabetes of any age. For pediatric recommendations, see Section 13 "Children and Adolescents" (https://doi.org/10.2337/dc21-S013). In the Heart Protection Study (lower age limit 40 years), the subgroup of ~600 patients with type 1 diabetes had a proportionately similar, although not statistically significant, reduction in risk as patients with type 2 diabetes (86). Even though the data are not definitive, similar statin treatment approaches should be considered for patients with type 1 or type 2 diabetes, particularly in the presence of other cardiovascular risk factors. Patients below the age of 40 have lower risk of developing a cardiovascular event over a 10-year horizon; however, their lifetime risk of developing cardiovascular disease and suffering an MI, stroke, or cardiovascular death is high. For patients who are younger than 40 years of age and/or have type 1 diabetes with other ASCVD risk factors, it is recommended that the patient and health care provider discuss the relative benefits and risks and consider the use of moderate-intensity statin therapy. Please refer to "Type 1 Diabetes Mellitus and Cardiovascular Disease: A Scientific Statement From the American Heart Association and American Diabetes Association" (97) for additional discussion.

Secondary Prevention (Patients With ASCVD)

Because risk is high in patients with ASCVD, intensive therapy is indicated and has been shown to be of benefit in multiple large randomized cardiovascular outcomes trials (92,96,98,99). High-intensity statin therapy is recommended for all patients with diabetes and ASCVD. This recommendation is based on the Cholesterol Treatment Trialists' Collaboration involving 26 statin trials, of which 5 compared high-intensity versus moderate-intensity statins. Together, they found reductions in nonfatal cardiovascular events with more intensive therapy, in patients with and without diabetes (84,88,98).

Over the past few years, there have been multiple large randomized trials investigating the benefits of adding nonstatin agents to statin therapy, including those that evaluated further lowering of LDL cholesterol with ezetimibe (96,100) and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (99). Each trial found a significant benefit in the reduction of ASCVD events that was directly related to the degree of further LDL cholesterol lowering. These large trials included a significant number of participants with diabetes. For very high-risk patients with ASCVD who are on high-intensity (and maximally tolerated) statin therapy and have an LDL cholesterol ≥70 mg/dL, the addition of nonstatin LDL-lowering therapy can be considered following a clinician-patient discussion about the net benefit, safety, and cost. Definition of very high-risk patients with ASCVD includes the use of specific criteria (major ASCVD events and high-risk conditions); refer to the 2018 American College of Cardiology/American Heart Association multisociety guideline on the management of blood cholesterol for further details regarding this definition of risk (12).

Please see 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines (12) for recommendations for primary and secondary prevention and for statin and combination treatment in adults with diabetes (101).

Combination Therapy for LDL Cholesterol Lowering

Statins and Ezetimibe

The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was a randomized controlled trial in 18,144 patients comparing the addition of ezetimibe to simvastatin therapy versus simvastatin alone. Individuals were ≥50 years of age, had experienced a recent acute coronary syndrome (ACS) and were treated for an average of 6 years. Overall, the addition of ezetimibe led to a 6.4% relative benefit and a 2% absolute reduction in major adverse cardiovascular events (atherosclerotic cardiovascular events), with the degree of benefit being directly proportional to the change in LDL cholesterol, which was 70 mg/dL in the statin group on average and 54 mg/dL in the combination group (96). In those with diabetes (27% of participants), the combination of moderate-intensity simvastatin (40 mg) and ezetimibe (10 mg) showed a significant reduction of major adverse cardiovascular events with an absolute risk reduction of 5% (40% vs. 45% cumulative incidence at 7 years) and a relative risk reduction of 14% (hazard ratio [HR] 0.86 [95% CI 0.78–0.94]) over moderate-intensity simvastatin (40 mg) alone (100).

Statins and PCSK9 Inhibitors

Placebo-controlled trials evaluating the addition of the PCSK9 inhibitors evolocumab and alirocumab to maximally tolerated doses of statin therapy in participants who were at high risk for ASCVD demonstrated an average reduction in LDL cholesterol ranging from 36% to 59%. These agents have been approved as adjunctive therapy for patients with ASCVD or familial hypercholesterolemia who are receiving maximally tolerated statin therapy but require additional lowering of LDL cholesterol (102,103).

The effects of PCSK9 inhibition on ASCVD outcomes was investigated in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial, which enrolled 27,564 patients with prior ASCVD and an additional high-risk feature who were receiving their maximally tolerated statin therapy (two-thirds were on high-intensity statin) but who still had LDL cholesterol ≥70 mg/dL or non-HDL cholesterol ≥100 mg/dL (99). Patients were randomized to receive subcutaneous injections of evolocumab (either 140 mg every 2 weeks or 420 mg every month based on patient preference) versus placebo. Evolocumab reduced LDL cholesterol by 59% from a median of 92 to 30 mg/dL in the treatment arm.

During the median follow-up of 2.2 years, the composite outcome of cardiovascular death, MI, stroke, hospitalization for angina, or revascularization occurred in 11.3% vs. 9.8% of the placebo and evolocumab groups, respectively, representing a 15% relative risk reduction ($P < 0.001$). The combined end point of cardiovascular death, MI, or stroke was reduced by 20%, from 7.4% to 5.9% ($P < 0.001$). Importantly, similar benefits were seen in a prespecified subgroup of

patients with diabetes, comprising 11,031 patients (40% of the trial) (104).

In the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), 18,924 patients (28.8% of whom had diabetes) with recent acute coronary syndrome were randomized to the PCSK9 inhibitor alirocumab or placebo every 2 weeks in addition to maximally tolerated statin therapy, with alirocumab dosing titrated between 75 and 150 mg to achieve LDL cholesterol levels between 25 and 50 mg/dL (105).

Over a median follow-up of 2.8 years, a composite primary end point (comprising death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospital admission) occurred in 903 patients (9.5%) in the alirocumab group and in 1,052 patients (11.1%) in the placebo group (HR 0.85 [95% CI 0.78–0.93]; $P < 0.001$). Combination therapy with alirocumab plus statin therapy resulted in a greater absolute reduction in the incidence of the primary end point in patients with diabetes (2.3% [95% CI 0.4–4.2]) than in those with prediabetes (1.2% [0.0–2.4]) or normoglycemia (1.2% [–0.3 to 2.7]) (106).

Treatment of Other Lipoprotein Fractions or Targets

Recommendations

10.29 For patients with fasting triglyceride levels ≥500 mg/dL, evaluate for secondary causes of hypertriglyceridemia and consider medical therapy to reduce the risk of pancreatitis. **C**

10.30 In adults with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175–499 mg/dL), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that raise triglycerides. **C**

10.31 In patients with atherosclerotic cardiovascular disease or other cardiovascular risk factors on a statin with controlled LDL cholesterol but elevated triglycerides (135–499 mg/dL), the addition of icosapent ethyl can be considered to reduce cardiovascular risk. **A**

Hypertriglyceridemia should be addressed with dietary and lifestyle changes including weight loss and abstinence from alcohol (107). Severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL and especially >1,000 mg/dL) may warrant pharmacologic therapy (fibric acid derivatives and/or fish oil) and reduction in dietary fat to reduce the risk of acute pancreatitis. Moderate- or high-intensity statin therapy should also be used as indicated to reduce risk of cardiovascular events (see STATIN TREATMENT). In patients with moderate hypertriglyceridemia, lifestyle interventions, treatment of secondary factors, and avoidance of medications that might raise triglycerides are recommended.

The Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) enrolled 8,179 adults receiving statin therapy with moderately elevated triglycerides (135–499 mg/dL, median baseline of 216 mg/dL) who had either established cardiovascular disease (secondary prevention cohort) or diabetes plus at least one other cardiovascular risk factor (primary prevention cohort). Patients were randomized to icosapent ethyl 4 g/day (2 g twice daily with food) versus placebo. The trial met its primary end point, demonstrating a 25% relative risk reduction ($P < 0.001$) for the primary end point composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. This reduction in risk was seen in patients with or without diabetes at baseline. The composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was reduced by 26% ($P < 0.001$). Additional ischemic end points were significantly lower in the icosapent ethyl group than in the placebo group, including cardiovascular death, which was reduced by 20% ($P = 0.03$). The proportions of patients experiencing adverse events and serious adverse events were similar between the active and placebo treatment groups. It should be noted that data are lacking with other n-3 fatty acids, and results of the REDUCE-IT trial should not be extrapolated to other products (108).

Low levels of HDL cholesterol, often associated with elevated triglyceride levels, are the most prevalent pattern of dyslipidemia in individuals with type 2 diabetes. However, the evidence for the use of drugs that target these lipid fractions is substantially less robust than that for statin therapy (109). In a large trial in patients with diabetes, fenofibrate failed to reduce overall cardiovascular outcomes (110).

Other Combination Therapy

Recommendations

10.32 Statin plus fibrate combination therapy has not been shown to improve atherosclerotic cardiovascular disease outcomes and is generally not recommended. **A**

10.33 Statin plus niacin combination therapy has not been shown to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended. **A**

Statin and Fibrate Combination Therapy

Combination therapy (statin and fibrate) is associated with an increased risk for abnormal transaminase levels, myositis, and rhabdomyolysis. The risk of rhabdomyolysis is more common with higher doses of statins and renal insufficiency and appears to be higher when statins are combined with gemfibrozil (compared with fenofibrate) (111).

In the ACCORD study, in patients with type 2 diabetes who were at high risk for ASCVD, the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal MI, or nonfatal stroke as compared with simvastatin alone. Prespecified subgroup analyses suggested heterogeneity in treatment effects with possible benefit for men with both a triglyceride level ≥204 mg/dL (2.3 mmol/L) and an HDL cholesterol level ≤34 mg/dL (0.9 mmol/L) (112). A prospective trial of a newer fibrate in this specific population of patients is ongoing (113).

Statin and Niacin Combination Therapy

The Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial randomized over 3,000 patients (about one-third with diabetes) with established ASCVD, low LDL cholesterol levels

(<180 mg/dL [4.7 mmol/L]), low HDL cholesterol levels (men <40 mg/dL [1.0 mmol/L] and women <50 mg/dL [1.3 mmol/L]), and triglyceride levels of 150–400 mg/dL (1.7–4.5 mmol/L) to statin therapy plus extended-release niacin or placebo. The trial was halted early due to lack of efficacy on the primary ASCVD outcome (first event of the composite of death from CHD, nonfatal MI, ischemic stroke, hospitalization for an ACS, or symptom-driven coronary or cerebral revascularization) and a possible increase in ischemic stroke in those on combination therapy (114).

The much larger Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial also failed to show a benefit of adding niacin to background statin therapy (115). A total of 25,673 patients with prior vascular disease were randomized to receive 2 g of extended-release niacin and 40 mg of laropiprant (an antagonist of the prostaglandin D2 receptor DP1 that has been shown to improve adherence to niacin therapy) versus a matching placebo daily and followed for a median follow-up period of 3.9 years. There was no significant difference in the rate of coronary death, MI, stroke, or coronary revascularization with the addition of niacin–laropiprant versus placebo (13.2% vs. 13.7%; rate ratio 0.96; $P = 0.29$). Niacin–laropiprant was associated with an increased incidence of new-onset diabetes (absolute excess, 1.3 percentage points; $P < 0.001$) and disturbances in diabetes control among those with diabetes. In addition, there was an increase in serious adverse events associated with the gastrointestinal system, musculoskeletal system, skin, and, unexpectedly, infection and bleeding.

Therefore, combination therapy with a statin and niacin is not recommended given the lack of efficacy on major ASCVD outcomes and increased side effects.

Diabetes Risk With Statin Use

Several studies have reported a modestly increased risk of incident diabetes with statin use (116,117), which may be limited to those with diabetes risk factors. An analysis of one of the initial studies suggested that although statin use was associated with diabetes risk, the cardiovascular event rate reduction with statins far outweighed the risk of incident diabetes even for patients at highest risk for diabetes (118). The absolute risk increase was small (over 5 years of follow-up, 1.2% of participants on placebo developed diabetes and 1.5% on rosuvastatin developed diabetes) (118). A meta-analysis of 13 randomized statin trials with 91,140 participants showed an odds ratio of 1.09 for a new diagnosis of diabetes, so that (on average) treatment of 255 patients with statins for 4 years resulted in one additional case of diabetes while simultaneously preventing 5.4 vascular events among those 255 patients (117).

Lipid-Lowering Agents and Cognitive Function

Although concerns regarding a potential adverse impact of lipid-lowering agents on cognitive function have been raised, several lines of evidence point against this association, as detailed in a 2018 European Atherosclerosis Society Consensus Panel statement (119). First, there are three large randomized trials of statin versus placebo where specific cognitive tests were performed, and no differences were seen between statin and placebo (120–123). In addition, no change in cognitive function has been reported in studies with the addition of ezetimibe (96) or PCSK9 inhibitors (99,124) to statin therapy, including among patients treated to very low LDL cholesterol levels. In addition, the most recent systematic review of the U.S. Food and Drug Administration's (FDA's) postmarketing surveillance databases, randomized controlled trials, and cohort, case-control, and cross-sectional studies evaluating cognition in patients receiving statins found that published data do not reveal an adverse effect of statins on cognition (125). Therefore, a concern that statins or other lipid-lowering agents might cause cognitive dysfunction or dementia is not currently supported by evidence and should not deter their use in individuals with diabetes at high risk for ASCVD (125).

ANTIPLATELET AGENTS

Recommendations

10.34 Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of atherosclerotic cardiovascular disease. **A**

10.35 For patients with atherosclerotic cardiovascular disease and documented aspirin allergy, clopidogrel (75 mg/day) should be used. **B**

10.36 Dual antiplatelet therapy (with low-dose aspirin and a P2Y12 inhibitor) is reasonable for a year after an acute coronary syndrome and may have benefits beyond this period. **A**

10.37 Long-term treatment with dual antiplatelet therapy should be considered for patients with prior coronary intervention, high ischemic risk, and low bleeding risk to prevent major adverse cardiovascular events. **A**

10.38 Combination therapy with aspirin plus low-dose rivaroxaban should be considered for patients with stable coronary and/or peripheral artery disease and low bleeding risk to prevent major adverse limb and cardiovascular events. **A**

10.39 Aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk, after a comprehensive discussion with the patient on the benefits versus the comparable increased risk of bleeding. **A**

Risk Reduction

Aspirin has been shown to be effective in reducing cardiovascular morbidity and mortality in high-risk patients with previous MI or stroke (secondary prevention) and is strongly recommended. In primary prevention, however, among patients with no previous cardiovascular events, its net benefit is more controversial (126,127).

Previous randomized controlled trials of aspirin specifically in patients with diabetes failed to consistently show a significant reduction in overall ASCVD end points, raising questions about the efficacy of aspirin for primary prevention in people with diabetes, although some sex differences were suggested (128–130).

The Antithrombotic Trialists' Collaboration published an individual patient–level meta-analysis (126) of the six large trials of aspirin for primary prevention in

the general population. These trials collectively enrolled over 95,000 participants, including almost 4,000 with diabetes. Overall, they found that aspirin reduced the risk of serious vascular events by 12% (relative risk 0.88 [95% CI 0.82–0.94]). The largest reduction was for nonfatal MI, with little effect on CHD death (relative risk 0.95 [95% CI 0.78–1.15]) or total stroke.

Most recently, the ASCEND (A Study of Cardiovascular Events iN Diabetes) trial randomized 15,480 patients with diabetes but no evident cardiovascular disease to aspirin 100 mg daily or placebo (131). The primary efficacy end point was vascular death, MI, or stroke or transient ischemic attack. The primary safety outcome was major bleeding (i.e., intracranial hemorrhage, sight-threatening bleeding in the eye, gastrointestinal bleeding, or other serious bleeding). During a mean follow-up of 7.4 years, there was a significant 12% reduction in the primary efficacy end point (8.5% vs. 9.6%; $P = 0.01$). In contrast, major bleeding was significantly increased from 3.2% to 4.1% in the aspirin group (rate ratio 1.29; $P = 0.003$), with most of the excess being gastrointestinal bleeding and other extracranial bleeding. There were no significant differences by sex, weight, or duration of diabetes or other baseline factors including ASCVD risk score.

Two other large randomized trials of aspirin for primary prevention, in patients without diabetes (ARRIVE [Aspirin to Reduce Risk of Initial Vascular Events]) (132) and in the elderly (ASPREE [Aspirin in Reducing Events in the Elderly]) (133), which included 11% with diabetes, found no benefit of aspirin on the primary efficacy end point and an increased risk of bleeding. In ARRIVE, with 12,546 patients over a period of 60 months follow-up, the primary end point occurred in 4.29% vs. 4.48% of patients in the aspirin versus placebo groups (HR 0.96 [95% CI 0.81–1.13]; $P = 0.60$). Gastrointestinal bleeding events (characterized as mild) occurred in 0.97% of patients in the aspirin group vs. 0.46% in the placebo group (HR 2.11 [95% CI 1.36–3.28]; $P = 0.0007$). In ASPREE, including 19,114 individuals, for cardiovascular disease (fatal CHD, MI, stroke, or hospitalization for heart failure) after a median of 4.7 years of follow-up, the rates per 1,000 person-years were 10.7 vs. 11.3 events in aspirin vs. placebo groups (HR 0.95 [95% CI 0.83–1.08]). The rate of major hemorrhage per 1,000 person-years was 8.6 events vs. 6.2 events, respectively (HR 1.38 [95% CI 1.18–1.62]; $P < 0.001$).

Thus, aspirin appears to have a modest effect on ischemic vascular events, with the absolute decrease in events depending on the underlying ASCVD risk. The main adverse effect is an increased risk of gastrointestinal bleeding. The excess risk may be as high as 5 per 1,000 per year in real-world settings. However, for adults with ASCVD risk >1% per year, the number of ASCVD events prevented will be similar to the number of episodes of bleeding induced, although these complications do not have equal effects on long-term health (134).

Recommendations for using aspirin as primary prevention include both men and women aged ≥50 years with diabetes and at least one additional major risk factor (family history of premature ASCVD, hypertension, dyslipidemia, smoking, or chronic kidney disease/albuminuria) who are not at increased risk of bleeding (e.g., older age, anemia, renal disease) (135–138). Noninvasive imaging techniques such as coronary calcium scoring may potentially help further tailor aspirin therapy, particularly in those at low risk (139,140). For patients over the age of 70 years (with or without diabetes), the balance appears to have greater risk than benefit (131,133). Thus, for primary prevention, the use of aspirin needs to be carefully considered and may generally not be recommended. Aspirin may be considered in the context of high cardiovascular risk with low bleeding risk, but generally not in older adults. Aspirin therapy for primary prevention may be considered in the context of shared decision-making, which carefully weighs the cardiovascular benefits with the fairly comparable increase in risk of bleeding. For patients with documented ASCVD, use of aspirin for secondary prevention has far greater benefit than risk; for this indication, aspirin is still recommended (126).

Aspirin Use in People <50 Years of Age

Aspirin is not recommended for those at low risk of ASCVD (such as men and women aged <50 years with diabetes with no other major ASCVD risk factors) as the low benefit is likely to be outweighed by the risks of bleeding. Clinical judgment should be used for those at intermediate risk (younger patients with one or more risk factors or older patients with no risk factors) until further research is available. Patients' willingness to undergo long-term aspirin therapy should also be considered (141). Aspirin use in patients aged <21 years is generally contraindicated due to the associated risk of Reye syndrome.

Aspirin Dosing

Average daily dosages used in most clinical trials involving patients with diabetes ranged from 50 mg to 650 mg but were mostly in the range of 100–325 mg/day. There is little evidence to support any specific dose, but using the lowest possible dose may help to reduce side effects (142). In the U.S., the most common low-dose tablet is 81 mg. Although platelets from patients with diabetes have altered function, it is unclear what, if any, effect that finding has on the required dose of aspirin for cardioprotective effects in the patient with diabetes. Many alternate pathways for platelet activation exist that are independent of thromboxane A_2 and thus are not sensitive to the effects of aspirin (143). "Aspirin resistance" has been described in patients with diabetes when measured by a variety of ex vivo and in vitro methods (platelet aggregometry, measurement of thromboxane B_2) (144), but other studies suggest no impairment in aspirin response among patients with diabetes (145). A recent trial suggested that more frequent dosing regimens of aspirin may reduce platelet reactivity in individuals with diabetes (146); however, these observations alone are insufficient to empirically recommend that higher doses of aspirin be used in this group at this time. Another recent meta-analysis raised the hypothesis that low-dose aspirin efficacy is reduced in those weighing more than 70 kg (147); however, the ASCEND trial found benefit of low-dose aspirin in those in this weight range, which would thus not validate this suggested hypothesis (131). It appears that 75–162 mg/day is optimal.

Indications for P2Y12 Receptor Antagonist Use

A P2Y12 receptor antagonist in combination with aspirin is reasonable for at least 1 year in patients following an ACS and may have benefits beyond

this period. Evidence supports use of either ticagrelor or clopidogrel if no percutaneous coronary intervention was performed and clopidogrel, ticagrelor, or prasugrel if a percutaneous coronary intervention was performed (148). In patients with diabetes and prior MI (1–3 years before), adding ticagrelor to aspirin significantly reduces the risk of recurrent ischemic events including cardiovascular and CHD death (149). Similarly, the addition of ticagrelor to aspirin reduced the risk of ischemic cardiovascular events compared with aspirin alone in patients with diabetes and stable coronary artery disease (150,151). However, a higher incidence of major bleeding, including intracranial hemorrhage, was noted with dual antiplatelet therapy. The net clinical benefit (ischemic benefit vs. bleeding risk) was improved with ticagrelor therapy in the large prespecified subgroup of patients with history of percutaneous coronary intervention, while no net benefit was seen in patients without prior percutaneous coronary intervention (151).

Combination Antiplatelet and Anticoagulation Therapy

Combination therapy with aspirin plus low dose rivaroxaban may be considered for patients with stable coronary and/or peripheral artery disease to prevent major adverse limb and cardiovascular complications. In the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial of 27,395 patients with established coronary artery disease and/or peripheral artery disease, aspirin plus rivaroxaban 2.5 mg twice daily was superior to aspirin plus placebo in the reduction of cardiovascular ischemic events including major adverse limb events. The absolute benefits of combination therapy appeared larger in patients with diabetes, who comprised 10,341 of the trial participants (152,153). A similar treatment strategy was evaluated in the Vascular Outcomes Study of ASA (acetylsalicylic acid) Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral Artery Disease (VOYAGER PAD) trial (154), in which 6,564 patients with peripheral artery disease who had undergone revascularization were randomly assigned to receive rivaroxaban 2.5 mg twice daily plus aspirin or placebo plus aspirin. Rivaroxaban treatment in this group of patients was also associated with a significantly lower incidence of ischemic cardiovascular events, including major adverse limb events. However, an increased risk of major bleeding was noted with rivaroxaban added to aspirin treatment in both COMPASS and VOYAGER PAD.

The risks and benefits of dual antiplatelet or antiplatelet plus anticoagulant treatment strategies should be thoroughly discussed with eligible patients, and shared decision-making should be used to determine an individually appropriate treatment approach.

CARDIOVASCULAR DISEASE

Screening

Recommendations

10.40 In asymptomatic patients, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as atherosclerotic cardiovascular disease risk factors are treated. **A**

10.41 Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort); signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; or electrocardiogram abnormalities (e.g., Q waves). **E**

Treatment

Recommendations

10.42 Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease or established kidney disease, a sodium–glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit (**Table 10.3*B*** and **Table 10.3*C***) is recommended as part of the comprehensive cardiovascular risk reduction and/or glucose-lowering regimens. **A**

10.42a In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, multiple atherosclerotic cardiovascular disease risk factors, or diabetic kidney disease, a sodium–glucose cotransporter 2 inhibitor with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events and/or heart failure hospitalization. **A**

10.42b In patients with type 2 diabetes and established atherosclerotic cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease, a glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events. **A**

10.43 In patients with type 2 diabetes and established heart failure with reduced ejection fraction, a sodium–glucose cotransporter 2 inhibitor with proven benefit in this patient population is recommended to reduce risk of worsening heart failure and cardiovascular death. **A**

10.44 In patients with known atherosclerotic cardiovascular disease, particularly coronary artery disease, ACE inhibitor or angiotensin receptor blocker therapy is recommended to reduce the risk of cardiovascular events. **A**

10.45 In patients with prior myocardial infarction, β-blockers should be continued for 3 years after the event. **B**

10.46 Treatment of patients with heart failure with reduced ejection fraction should include a β-blocker with proven cardiovascular outcomes benefit, unless otherwise contraindicated. **A**

10.47 In patients with type 2 diabetes with stable heart failure, metformin may be continued for glucose lowering if estimated glomerular filtration rate remains >30 mL/min/1.73 m^2 but should be avoided in unstable or hospitalized patients with heart failure. **B**

Table 10.3*A*—Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: DPP-4 inhibitors

	SAVOR-TIMI 53 (194) (n = 16,492)	EXAMINE (200) (n = 5,380)	TECOS (196) (n = 14,671)	CARMELINA (197,201) (n = 6,979)	CAROLINA (173,202) (n = 6,042)
Intervention	Saxagliptin/placebo	Alogliptin/placebo	Sitagliptin/placebo	Linagliptin/placebo	Linagliptin/ glimepiride
Main inclusion criteria	Type 2 diabetes and history of or multiple risk factors for CVD	Type 2 diabetes and ACS within 15–90 days before randomization	Type 2 diabetes and preexisting CVD	Type 2 diabetes and high CV and renal risk	Type 2 diabetes and high CV risk
A1C inclusion criteria (%)	≥6.5	6.5–11.0	6.5–8.0	6.5–10.0	6.5–8.5
Age (years) ††	65.1	61.0	65.4	65.8	64.0
Race (% White)	75.2	72.7	67.9	80.2	73.0
Sex (% male)	66.9	67.9	70.7	62.9	60.0
Diabetes duration (years)††	10.3	7.1	11.6	14.7	6.2
Median follow-up (years)	2.1	1.5	3.0	2.2	6.3
Statin use (%)	78	91	80	71.8	64.1
Metformin use (%)	70	66	82	54.8	82.5
Prior CVD/CHF (%)	78/13	100/28	74/18	57/26.8	34.5/4.5
Mean baseline A1C (%)	8.0	8.0	7.2	7.9	7.2
Mean difference in A1C between groups at end of treatment (%)	−0.3^	−0.3^	−0.3^	−0.36^	0
Year started/reported	2010/2013	2009/2013	2008/2015	2013/2018	2010/2019
Primary outcome§	3-point MACE 1.00 (0.89–1.12)	3-point MACE 0.96 (95% UL ≤1.16)	4-point MACE 0.98 (0.89–1.08)	3-point MACE 1.02 (0.89–1.17)	3-point MACE 0.98 (0.84–1.14)
Key secondary outcome§	Expanded MACE 1.02 (0.94–1.11)	4-point MACE 0.95 (95% UL ≤1.14)	3-point MACE 0.99 (0.89–1.10)	Kidney composite (ESRD, sustained ≥40% decrease in eGFR, or renal death) 1.04 (0.89–1.22)	4-point MACE 0.99 (0.86–1.14)
Cardiovascular death§	1.03 (0.87–1.22)	0.85 (0.66–1.10)	1.03 (0.89–1.19)	0.96 (0.81–1.14)	1.00 (0.81–1.24)
MI§	0.95 (0.80–1.12)	1.08 (0.88–1.33)	0.95 (0.81–1.11)	1.12 (0.90–1.40)	1.03 (0.82–1.29)
Stroke§	1.11 (0.88–1.39)	0.91 (0.55–1.50)	0.97 (0.79–1.19)	0.91 (0.67–1.23)	0.86 (0.66–1.12)
HF hospitalization§	1.27 (1.07–1.51)	1.19 (0.90–1.58)	1.00 (0.83–1.20)	0.90 (0.74–1.08)	1.21 (0.92–1.59)
Unstable angina hospitalization§	1.19 (0.89–1.60)	0.90 (0.60–1.37)	0.90 (0.70–1.16)	0.87 (0.57–1.31)	1.07 (0.74–1.54)
All-cause mortality§	1.11 (0.96–1.27)	0.88 (0.71–1.09)	1.01 (0.90–1.14)	0.98 (0.84–1.13)	0.91 (0.78–1.06)
Worsening nephropathy§‖	1.08 (0.88–1.32)	—	—	Kidney composite (see above)	—

—, not assessed/reported; ACS, acute coronary syndrome; CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GLP-1, glucagon-like peptide 1; HF, heart failure; MACE, major adverse cardiac event; MI, myocardial infarction; UL, upper limit. Data from this table was adapted from Cefalu et al. (203) in the January 2018 issue of *Diabetes Care*. ††Age was reported as means in all trials except EXAMINE, which reported medians; diabetes duration was reported as means in all trials except SAVOR-TIMI 53 and EXAMINE, which reported medians. §Outcomes reported as hazard ratio (95% CI). ‖Worsening nephropathy is defined as as doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dL (530 mmol/L) in SAVOR-TIMI 53. Worsening nephropathy was a prespecified exploratory adjudicated outcome in SAVOR-TIMI 53.^Significant difference in A1C between groups ($P < 0.05$).

CARDIAC TESTING

Candidates for advanced or invasive cardiac testing include those with *1*) typical or atypical cardiac symptoms and *2*) an abnormal resting electrocardiogram (ECG). Exercise ECG testing without or with echocardiography may be used as the initial test. In adults with diabetes ≥40 years of age, measurement of coronary artery calcium is also reasonable for cardiovascular risk assessment. Pharmacologic stress echocardiography or nuclear imaging should be considered in individuals with diabetes in whom resting ECG abnormalities preclude exercise stress testing (e.g., left bundle branch block or ST-T abnormalities). In addition, individuals who require stress

Table 10.3*B*—Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: GLP-1 receptor agonists

	ELIXA (183) (n = 6,068)	LEADER (178) (n = 9,340)	SUSTAIN-6 (179)* (n = 3,297)	EXSCEL (184) (n = 14,752)	Harmony Outcomes (181) (n = 9,463)	REWIND (182) (n = 9,901)	PIONEER-6 (180) (n = 3,183)
Intervention	Lixisenatide/placebo	Liraglutide/placebo	Semaglutide s.c. injection/placebo	Exenatide QW/ placebo	Albiglutide/placebo	Dulaglutide/ placebo	Semaglutide oral/ placebo
Main inclusion criteria	Type 2 diabetes and history of ACS (<180 days)	Type 2 diabetes and preexisting CVD, CKD, or HF at ≥50 years of age or CV risk at ≥60 years of age	Type 2 diabetes and preexisting CVD, HF, or CKD at ≥50 years of age or CV risk at ≥60 years of age	Type 2 diabetes with or without preexisting CVD	Type 2 diabetes with preexisting CVD	Type 2 diabetes and prior ASCVD event or risk factors for ASCVD	Type 2 diabetes and high CV risk (age of ≥50 years with established CVD or CKD, or age of ≥60 years with CV risk factors only)
A1C inclusion criteria (%)	5.5–11.0	≥7.0	≥7.0	6.5–10.0	≥7.0	≤9.5	None
Age (years)††	60.3	64.3	64.6	62	64.1	66.2	66
Race (% White)	75.2	77.5	83.0	75.8	84.8	75.7	72.3
Sex (% male)	69.3	64.3	60.7	62	69.4	53.7	68.4
Diabetes duration (years)††	9.3	12.8	13.9	12	13.8	10.5	14.9
Median follow-up (years)	2.1	3.8	2.1	3.2	1.6	5.4	1.3
Statin use (%)	93	72	73	74	84.0	66	85.2 (all lipid-lowering)
Metformin use (%)	66	76	73	77	73.6	81	77.4
Prior CVD/CHF (%)	100/22	81/18	60/24	73.1/16.2	100/20.2	32/9	84.7/12.2
Mean baseline A1C (%)	7.7	8.7	8.7	8.0	8.7	7.4	8.2
Mean difference in A1C between groups at end of treatment (%)	−0.3‡	−0.4‡	−0.7 or −1.0††	−0.53‡	−0.52‡	−0.61‡	−0.7
Year started/reported	2010/2015	2010/2016	2013/2016	2010/2017	2015/2018	2011/2019	2017/2019
Primary outcome§	4-point MACE 1.02 (0.89–1.17)	3-point MACE 0.87 (0.78–0.97)	3-point MACE 0.74 (0.58–0.95)	3-point MACE 0.91 (0.83–1.00)	3-point MACE 0.78 (0.68–0.90)	3-point MACE 0.88 (0.79–0.99)	3-point MACE 0.79 (0.57–1.11)

Continued on p. S140

Table 10.3*B*—Continued

	ELIXA (183) (n = 6,068)	LEADER (178) (n = 9,340)	SUSTAIN-6 (179)* (n = 3,297)	EXSCEL (184) (n = 14,752)	Harmony Outcomes (181) (n = 9,463)	REWIND (182) (n = 9,901)	PIONEER-6 (180) (n = 3,183)
Key secondary outcome§	Expanded MACE (0.90–1.11)	Expanded MACE 0.88 (0.81–0.96)	Expanded MACE 0.74 (0.62–0.89)	Individual components of MACE (see below)	Expanded MACE (with urgent revascularization for unstable angina) 0.78 (0.69–0.90) CV death or HF hospitalization 0.85 (0.70–1.04) Individual components of MACE (see below)	Composite microvascular outcome (eye or renal outcome) 0.87 (0.79–0.95)	Expanded MACE or HF hospitalization 0.82 (0.61–1.10)
Cardiovascular death§	0.98 (0.78–1.22)	0.78 (0.66–0.93)	0.98 (0.65–1.48)	0.88 (0.76–1.02)	0.93 (0.73–1.19)	0.91 (0.78–1.06)	0.49 (0.27–0.92)
MI§	1.03 (0.87–1.22)	0.86 (0.73–1.00)	0.74 (0.51–1.08)	0.97 (0.85–1.10)	0.75 (0.61–0.90)	0.96 (0.79–1.15)	1.18 (0.73–1.90)
Stroke§	1.12 (0.79–1.58)	0.86 (0.71–1.06)	0.61 (0.38–0.99)	0.85 (0.70–1.03)	0.86 (0.66–1.14)	0.76 (0.61–0.95)	0.74 (0.35–1.57)
HF hospitalization§	0.96 (0.75–1.23)	0.87 (0.73–1.05)	1.11 (0.77–1.61)	0.94 (0.78–1.13)	—	0.93 (0.77–1.12)	0.86 (0.48–1.55)
Unstable angina hospitalization§	1.11 (0.47–2.62)	0.98 (0.76–1.26)	0.82 (0.47–1.44)	1.05 (0.94–1.18)	—	1.14 (0.84–1.54)	1.56 (0.60–4.01)
All-cause mortality§	0.94 (0.78–1.13)	0.85 (0.74–0.97)	1.05 (0.74–1.50)	0.86 (0.77–0.97)	0.95 (0.79–1.16)	0.90 (0.80–1.01)	0.51 (0.31–0.84)
Worsening nephropathy§‖	—	0.78 (0.67–0.92)	0.64 (0.46–0.88)	—	—	0.85 (0.77–0.93)	—

—, not assessed/reported; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CHF, congestive heart failure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; GLP-1, glucagon-like peptide 1; HF, heart failure; MACE, major adverse cardiac event; MI, myocardial infarction. Data from this table was adapted from Cefalu et al. (203) in the January 2018 issue of *Diabetes Care*. *Powered to rule out a hazard ratio of 1.8; superiority hypothesis not prespecified. ††Age was reported as means in all trials; diabetes duration was reported as means in all trials except EXSCEL, which reported medians. †A1C change of 0.66% with 0.5 mg and 1.05% with 1 mg dose of semaglutide. §Outcomes reported as hazard ratio (95% CI). ‖Worsening nephropathy is defined as the new onset of urine albumin-to-creatinine ratio >300 mg/g creatinine or a doubling of the serum creatinine level and an estimated glomerular filtration rate of <45 mL/min/1.73 m^2, the need for continuous renal replacement therapy, or death from renal disease in LEADER and SUSTAIN-6 and as new macroalbuminuria, a sustained decline in estimated glomerular filtration rate of 30% or more from baseline, or chronic renal replacement therapy in REWIND. Worsening nephropathy was a prespecified exploratory adjudicated outcome in LEADER, SUSTAIN-6, and REWIND. ¶Significant difference in A1C between groups ($P < 0.05$).

Table 10.3C—Cardiovascular and cardiorenal outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: SGLT2 inhibitors

	EMPA-REG OUTCOME (8) (n = 7,020)	CANVAS Program (9) (n = 10,142)	DECLARE-TIMI 58 (176) (n = 17,160)	CREDENCE (174) (n = 4,401)	DAPA-HF (177) (n = 4,744; 1,983 with diabetes)
Intervention	Empagliflozin/placebo	Canagliflozin/placebo	Dapagliflozin/placebo	Canagliflozin/placebo	Dapagliflozin/placebo
Main inclusion criteria	Type 2 diabetes and preexisting CVD	Type 2 diabetes and preexisting CVD at ≥30 years of age or >2 CV risk factors at ≥50 years of age	Type 2 diabetes and established ASCVD or multiple risk factors for ASCVD	Type 2 diabetes and albuminuric kidney disease	NYHA class II, III, or IV heart failure and an ejection fraction ≤40%, with or without diabetes
A1C inclusion criteria (%)	7.0–10.0	7.0–10.5	≥6.5	6.5–12	—
Age (years)††	63.1	63.3	64.0	63	66
Race (% White)	72.4	78.3	79.6	66.6	70.3
Sex (% male)	71.5	64.2	62.6	66.1	76.6
Diabetes duration (years)††	57% >10	13.5	11.0	15.8	N/A
Median follow-up (years)	3.1	3.6	4.2	2.6	1.5
Statin use (%)	77	75	75 (statin or ezetimibe use)	69	—
Metformin use (%)	74	77	82	57.8	51.2% (of patients with diabetes)
Prior CVD/CHF (%)	99/10	65.6/14.4	40/10	50.4/14.8	100% with CHF
Mean baseline A1C (%)	8.1	8.2	8.3	8.3	—
Mean difference in A1C between groups at end of treatment (%)	−0.3^‡	−0.58^	−0.43^	−0.31	N/A
Year started/ reported	2010/2015	2009/2017	2013/2018	2017/2019	2017/2019
Primary outcome§	3-point MACE 0.86 (0.74–0.99)	3-point MACE 0.86 (0.75–0.97)§	3-point MACE 0.93 (0.84–1.03) CV death or HF hospitalization 0.83 (0.73–0.95)	ESRD, doubling of creatinine, or death from renal or CV cause 0.70 (0.59–0.82)	Worsening heart failure or death from CV causes 0.74 (0.65–0.85) Results did not differ by diabetes status
Key secondary outcome§	4-point MACE 0.89 (0.78–1.01)	All-cause and CV mortality (see below)	Death from any cause 0.93 (0.82–1.04) Renal composite (≥40% decrease in eGFR rate to <60 mL/min/1.73 m^2, new ESRD, or death from renal or CV causes 0.76 (0.67–0.87)	CV death or HF hospitalization 0.69 (0.57–0.83) 3-point MACE 0.80 (0.67–0.95)	CV death or HF hospitalization 0.75 (0.65–0.85)
Cardiovascular death§	0.62 (0.49–0.77)	0.87 (0.72–1.06)	0.98 (0.82–1.17)	0.78 (0.61–1.00)	0.82 (0.69–0.98)
MI§	0.87 (0.70–1.09)	0.89 (0.73–1.09)	0.89 (0.77–1.01)	—	—
Stroke§	1.18 (0.89–1.56)	0.87 (0.69–1.09)	1.01 (0.84–1.21)	—	—
HF hospitalization§	0.65 (0.50–0.85)	0.67 (0.52–0.87)	0.73 (0.61–0.88)	0.61 (0.47–0.80)	0.70 (0.59–0.83)
Unstable angina hospitalization§	0.99 (0.74–1.34)	—	—	—	—
All-cause mortality§	0.68 (0.57–0.82)	0.87 (0.74–1.01)	0.93 (0.82–1.04)	0.83 (0.68–1.02)	0.83 (0.71–0.97)
Worsening nephropathy§‖	0.61 (0.53–0.70)	0.60 (0.47–0.77)	0.53 (0.43–0.66)	(See primary outcome)	0.71 (0.44–1.16)

—, not assessed/reported; CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; MACE, major adverse cardiac event; MI, myocardial infarction; SGLT2, sodium–glucose cotransporter 2; NYHA, New York Heart Association. Data from this table was adapted from Cefalu et al. (203) in the January 2018 issue of *Diabetes Care.* ††Age was reported as means in all trials; diabetes duration was reported as means in all trials except EMPA-REG OUTCOME, which reported as percentage of population with diabetes duration >10 years, and DECLARE-TIMI 58, which reported median. ‡A1C change of 0.30 in EMPA-REG OUTCOME is based on pooled results for both doses (i.e., 0.24% for 10 mg and 0.36% for 25 mg of empagliflozin). §Outcomes reported as hazard ratio (95% CI). ‖Definitions of worsening nephropathy differed between trials. ^Significant difference in A1C between groups ($P < 0.05$).

testing and are unable to exercise should undergo pharmacologic stress echocardiography or nuclear imaging.

SCREENING ASYMPTOMATIC PATIENTS

The screening of asymptomatic patients with high ASCVD risk is not recommended (155), in part because these high-risk patients should already be receiving intensive medical therapy—an approach that provides similar benefit as invasive revascularization (156,157). There is also some evidence that silent ischemia may reverse over time, adding to the controversy concerning aggressive screening strategies (158). In prospective studies, coronary artery calcium has been established as an independent predictor of future ASCVD events in patients with diabetes and is consistently superior to both the UK Prospective Diabetes Study (UKPDS) risk engine and the Framingham Risk Score in predicting risk in this population (159–161). However, a randomized observational trial demonstrated no clinical benefit to routine screening of asymptomatic patients with type 2 diabetes and normal ECGs (162). Despite abnormal myocardial perfusion imaging in more than one in five patients, cardiac outcomes were essentially equal (and very low) in screened versus unscreened patients. Accordingly, indiscriminate screening is not considered cost-effective. Studies have found that a risk factor–based approach to the initial diagnostic evaluation and subsequent follow-up for coronary artery disease fails to identify which patients with type 2 diabetes will have silent ischemia on screening tests (163,164).

Any benefit of newer noninvasive coronary artery disease screening methods, such as computed tomography calcium scoring and computed tomography angiography, to identify patient subgroups for different treatment strategies remains unproven in asymptomatic patients with diabetes, though research is ongoing. Although asymptomatic patients with diabetes with higher coronary disease burden have more future cardiac events (159,165,166), the role of these tests beyond risk stratification is not clear.

While coronary artery screening methods, such as calcium scoring, may improve cardiovascular risk assessment in people with type 2 diabetes (167), their routine use leads to radiation exposure and may result in unnecessary invasive testing such as coronary angiography and revascularization procedures. The ultimate balance of benefit, cost, and risks of such an approach in asymptomatic patients remains controversial, particularly in the modern setting of aggressive ASCVD risk factor control.

LIFESTYLE AND PHARMACOLOGIC INTERVENTIONS

Intensive lifestyle intervention focusing on weight loss through decreased caloric intake and increased physical activity as performed in the Action for Health in Diabetes (Look AHEAD) trial may be considered for improving glucose control, fitness, and some ASCVD risk factors (168). Patients at increased ASCVD risk should receive statin, ACE inhibitor, or ARB therapy if the patient has hypertension, and possibly aspirin, unless there are contraindications to a particular drug class. Clear benefit exists for ACE inhibitor or ARB therapy in patients with diabetic kidney disease or hypertension, and these agents are recommended for hypertension management in patients with known ASCVD (particularly coronary artery disease) (59,60,169). β-Blockers should be used in patients with active angina or HFrEF and for 3 years after MI in patients with preserved left ventricular function (170,171).

GLUCOSE-LOWERING THERAPIES AND CARDIOVASCULAR OUTCOMES

In 2008, the FDA issued a guidance for industry to perform cardiovascular outcomes trials for all new medications for the treatment for type 2 diabetes amid concerns of increased cardiovascular risk (172). Previously approved diabetes medications were not subject to the guidance. Recently published cardiovascular outcomes trials have provided additional data on cardiovascular and renal outcomes in patients with type 2 diabetes with cardiovascular disease or at high risk for cardiovascular disease (see **Table 10.3*A***, **Table 10.3*B***, and **Table 10.3*C***). An expanded review of the effects of glucose-lowering therapy in patients with chronic kidney disease is included in Section 11 "Microvascular Complications and Foot Care" (https://doi.org/10.2337/dc21-S011).

Cardiovascular outcomes trials of dipeptidyl peptidase 4 (DPP-4) inhibitors have all, so far, not shown cardiovascular benefits relative to placebo. In addition, the CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Type 2 Diabetes) study demonstrated noninferiority between a DPP-4 inhibitor, linagliptin, and a sulfonylurea, glimepiride, on cardiovascular outcomes despite lower rates of hypoglycemia in the linagliptin treatment group (173). However, results from other new agents have provided a mix of results.

SGLT2 Inhibitor Trials

The BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) was a randomized, double-blind trial that assessed the effect of empagliflozin, an SGLT2 inhibitor, versus placebo on cardiovascular outcomes in 7,020 patients with type 2 diabetes and existing cardiovascular disease. Study participants had a mean age of 63 years, 57% had diabetes for more than 10 years, and 99% had established cardiovascular disease. EMPA-REG OUTCOME showed that over a median follow-up of 3.1 years, treatment reduced the composite outcome of MI, stroke, and cardiovascular death by 14% (absolute rate 10.5% vs. 12.1% in the placebo group, HR in the empagliflozin group 0.86 [95% CI 0.74–0.99]; $P = 0.04$ for superiority) and cardiovascular death by 38% (absolute rate 3.7% vs. 5.9%, HR 0.62 [95% CI 0.49–0.77]; $P < 0.001$) (8). The FDA added an indication for empagliflozin to reduce the risk of major adverse cardiovascular death in adults with type 2 diabetes and cardiovascular disease.

Two large outcomes trials of the SGLT2 inhibitor canagliflozin that separately assessed *1*) the cardiovascular effects of treatment in patients at high risk for major adverse cardiovascular events, and *2*) the impact of canagliflozin therapy on cardiorenal outcomes in patients with diabetes-related chronic kidney disease have been conducted (174). First, the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program integrated data from two trials. The CANVAS trial that started in 2009 was partially unblinded prior to completion because of the need to file interim cardiovascular outcomes

data for regulatory approval of the drug (175). Thereafter, the postapproval CANVAS-Renal (CANVAS-R) trial was started in 2014. Combining both of these trials, 10,142 participants with type 2 diabetes were randomized to canagliflozin or placebo and were followed for an average 3.6 years. The mean age of patients was 63 years, and 66% had a history of cardiovascular disease. The combined analysis of the two trials found that canagliflozin significantly reduced the composite outcome of cardiovascular death, MI, or stroke versus placebo (occurring in 26.9 vs. 31.5 participants per 1,000 patient-years; HR 0.86 [95% CI 0.75–0.97]). The specific estimates for canagliflozin versus placebo on the primary composite cardiovascular outcome were HR 0.88 (95% CI 0.75–1.03) for the CANVAS trial and 0.82 (0.66–1.01) for CANVAS-R, with no heterogeneity found between trials. Of note, there was an increased risk of lower-limb amputation with canagliflozin (6.3 vs. 3.4 participants per 1,000 patient-years; HR 1.97 [95% CI 1.41–2.75]) (9). Second, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial randomized 4,401 patients with type 2 diabetes and chronic diabetes-related kidney disease (UACR >300 mg/g and estimated glomerular filtration rate 30 to <90 mL/min/1.73 m^2) to canagliflozin 100 mg daily or placebo (174). The primary outcome was a composite of end-stage kidney disease, doubling of serum creatinine, or death from renal or cardiovascular causes. The trial was stopped early due to conclusive evidence of efficacy identified during a prespecified interim analysis with no unexpected safety signals. The risk of the primary composite outcome was 30% lower with canagliflozin treatment when compared with placebo (HR 0.70 [95% CI 0.59–0.82]). Moreover, it reduced the prespecified end point of end-stage kidney disease alone by 32% (HR 0.68 [95% CI 0.54–0.86]). Canagliflozin was additionally found to have a lower risk of the composite of cardiovascular death, myocardial infarction, or stroke (HR 0.80 [95% CI 0.67–0.95]), as well as lower risk of hospitalizations for heart failure (HR 0.61 [95% CI 0.47–0.80]), and of the composite of cardiovascular death or hospitalization for heart failure (HR 0.69 [95% CI 0.57–0.83]). In terms of safety, no significant increase in lower-limb amputations, fractures, acute kidney injury, or hyperkalemia was noted for canagliflozin relative to placebo in CREDENCE. An increased risk for diabetic ketoacidosis was noted, however, with 2.2 and 0.2 events per 1,000 patient-years noted in the canagliflozin and placebo groups, respectively (HR 10.80 [95% CI 1.39–83.65]) (174).

The Dapagliflozin Effect on Cardiovascular Events–Thrombosis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial was another randomized, double-blind trial that assessed the effects of dapagliflozin versus placebo on cardiovascular and renal outcomes in 17,160 patients with type 2 diabetes and established ASCVD or multiple risk factors for atherosclerotic cardiovascular disease (176). Study participants had a mean age of 64 years, with ~40% of study participants having established ASCVD at baseline—a characteristic of this trial that differs from other large cardiovascular trials where a majority of participants had established cardiovascular disease. DECLARE-TIMI 58 met the prespecified criteria for noninferiority to placebo with respect to MACE but did not show a lower rate of MACE when compared with placebo (8.8% in the dapagliflozin group and 9.4% in the placebo group; HR 0.93 [95% CI 0.84–1.03]; $P = 0.17$). A lower rate of cardiovascular death or hospitalization for heart failure was noted (4.9% vs. 5.8%; HR 0.83 [95% CI 0.73–0.95]; $P = 0.005$), which reflected a lower rate of hospitalization for heart failure (HR 0.73 [95% CI 0.61–0.88]). No difference was seen in cardiovascular death between groups. Results of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, which assessed the effects of dapagliflozin in patients with established heart failure (177), are described in the GLUCOSE-LOWERING THERAPIES AND HEART FAILURE section.

GLP-1 Receptor Agonist Trials

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial was a randomized, double-blind trial that assessed the effect of liraglutide, a glucagon-like peptide 1 (GLP-1) receptor agonist, versus placebo on cardiovascular outcomes in 9,340 patients with type 2 diabetes at high risk for cardiovascular disease or with cardiovascular disease. Study participants had a mean age of 64 years and a mean duration of diabetes of nearly 13 years. Over 80% of study participants had established cardiovascular disease. After a median follow-up of 3.8 years, LEADER showed that the primary composite outcome (MI, stroke, or cardiovascular death) occurred in fewer participants in the treatment group (13.0%) when compared with the placebo group (14.9%) (HR 0.87 [95% CI 0.78–0.97]; $P < 0.001$ for noninferiority; $P = 0.01$ for superiority). Deaths from cardiovascular causes were significantly reduced in the liraglutide group (4.7%) compared with the placebo group (6.0%) (HR 0.78 [95% CI 0.66–0.93]; $P = 0.007$) (178). The FDA approved the use of liraglutide to reduce the risk of major adverse cardiovascular events, including heart attack, stroke, and cardiovascular death, in adults with type 2 diabetes and established cardiovascular disease.

Results from a moderate-sized trial of another GLP-1 receptor agonist, semaglutide, were consistent with the LEADER trial (179). Semaglutide is a once-weekly GLP-1 receptor agonist approved by the FDA for the treatment of type 2 diabetes. The Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) was the initial randomized trial powered to test noninferiority of semaglutide for the purpose of regulatory approval. In this study, 3,297 patients with type 2 diabetes were randomized to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 2 years. The primary outcome (the first occurrence of cardiovascular death, nonfatal MI, or nonfatal stroke) occurred in 108 patients (6.6%) in the semaglutide group vs. 146 patients (8.9%) in the placebo group (HR 0.74 [95% CI 0.58–0.95]; $P < 0.001$). More patients discontinued treatment in the semaglutide group because of adverse events, mainly gastrointestinal. The cardiovascular effects of the oral formulation of semaglutide compared with placebo have been assessed in Peptide Innovation for Early Diabetes Treatment (PIONEER) 6, a preapproval trial designed to rule out an unacceptable increase in cardiovascular risk. In this trial of 3,183 patients with type 2 diabetes and high cardiovascular risk followed for a median of 15.9 months, oral semaglutide was noninferior to placebo for the primary composite outcome of cardiovascular death, nonfatal MI, or nonfatal stroke (HR 0.79 [95% CI

0.57–1.11]; $P < 0.001$ for noninferiority) (180). The cardiovascular effects of this formulation of semaglutide will be further tested in a large, longer-term outcomes trial.

The Harmony Outcomes trial randomized 9,463 patients with type 2 diabetes and cardiovascular disease to once-weekly subcutaneous albiglutide or matching placebo, in addition to their standard care. Over a median duration of 1.6 years, the GLP-1 receptor agonist reduced the risk of cardiovascular death, MI, or stroke to an incidence rate of 4.6 events per 100 person-years in the albiglutide group vs. 5.9 events in the placebo group (HR ratio 0.78, $P = 0.0006$ for superiority) (181). This agent is not currently available for clinical use.

The Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) trial was a randomized, double-blind, placebo-controlled trial that assessed the effect of the once-weekly GLP-1 receptor agonist dulaglutide versus placebo on MACE in ~9,990 patients with type 2 diabetes at risk for cardiovascular events or with a history of cardiovascular disease (182). Study participants had a mean age of 66 years and a mean duration of diabetes of ~10 years. Approximately 32% of participants had history of atherosclerotic cardiovascular events at baseline. After a median follow-up of 5.4 years, the primary composite outcome of nonfatal MI, nonfatal stroke, or death from cardiovascular causes occurred in 12.0% and 13.4% of participants in the dulaglutide and placebo treatment groups, respectively (HR 0.88 [95% CI 0.79–0.99]; $P = 0.026$). These findings equated to incidence rates of 2.4 and 2.7 events per 100 person-years, respectively. The results were consistent across the subgroups of patients with and without history of CV events. All-cause mortality did not differ between groups ($P = 0.067$).

The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial studied the once-daily GLP-1 receptor agonist lixisenatide on cardiovascular outcomes in patients with type 2 diabetes who had had a recent acute coronary event (183). A total of 6,068 patients with type 2 diabetes with a recent hospitalization for MI or unstable angina within the previous 180 days were randomized to receive lixisenatide or placebo in addition to standard care and were followed for a median of ~2.1 years. The primary outcome of cardiovascular death, MI, stroke, or hospitalization for unstable angina occurred in 406 patients (13.4%) in the lixisenatide group vs. 399 (13.2%) in the placebo group (HR 1.2 [95% CI 0.89–1.17]), which demonstrated the noninferiority of lixisenatide to placebo ($P < 0.001$) but did not show superiority ($P = 0.81$).

The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial also reported results with the once-weekly GLP-1 receptor agonist extended-release exenatide and found that major adverse cardiovascular events were numerically lower with use of extended-release exenatide compared with placebo, although this difference was not statistically significant (184). A total of 14,752 patients with type 2 diabetes (of whom 10,782 [73.1%] had previous cardiovascular disease) were randomized to receive extended-release exenatide 2 mg or placebo and followed for a median of 3.2 years. The primary end point of cardiovascular death, MI, or stroke occurred in 839 patients (11.4%; 3.7 events per 100 person-years) in the exenatide group and in 905 patients (12.2%; 4.0 events per 100 person-years) in the placebo group (HR 0.91 [95% CI 0.83–1.00]; $P < 0.001$ for noninferiority), but exenatide was not superior to placebo with respect to the primary end point ($P = 0.06$ for superiority). However, all-cause mortality was lower in the exenatide group (HR 0.86 [95% CI 0.77–0.97]). The incidence of acute pancreatitis, pancreatic cancer, medullary thyroid carcinoma, and serious adverse events did not differ significantly between the two groups.

In summary, there are now numerous large randomized controlled trials reporting statistically significant reductions in cardiovascular events for three of the FDA-approved SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) and four FDA-approved GLP-1 receptor agonists (liraglutide, albiglutide [although that agent was removed from the market for business reasons], semaglutide [lower risk of cardiovascular events in a moderate-sized clinical trial but one not powered as a cardiovascular outcomes trial], and dulaglutide). Meta-analyses of the trials reported to date suggest that GLP-1 receptor agonists and SGLT2 inhibitors reduce risk of atherosclerotic major adverse cardiovascular events to a comparable degree in patients with type 2 diabetes and established ASCVD (185). SGLT2 inhibitors also appear to reduce risk of heart failure hospitalization and progression of kidney disease in patients with established ASCVD, multiple risk factors for ASCVD, or diabetic kidney disease (186). In patients with type 2 diabetes and established ASCVD, multiple ASCVD risk factors, or diabetic kidney disease, an SGLT2 inhibitor with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events and/or heart failure hospitalization. In patients with type 2 diabetes and established ASCVD or multiple risk factors for ASCVD, a glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events. For many patients, use of either an SGLT2 inhibitor or a GLP-1 receptor agonist to reduce cardiovascular risk is appropriate. It is unknown whether use of both classes of drugs will provide an additive cardiovascular outcomes benefit.

Glucose-Lowering Therapies and Heart Failure

As many as 50% of patients with type 2 diabetes may develop heart failure (187). Data on the effects of glucose-lowering agents on heart failure outcomes have demonstrated that thiazolidinediones have a strong and consistent relationship with increased risk of heart failure (188–190). Therefore, thiazolidinedione use should be avoided in patients with symptomatic heart failure. Restrictions to use of metformin in patients with medically treated heart failure were removed by the FDA in 2006 (191). In fact, observational studies of patients with type 2 diabetes and heart failure suggest that metformin users have better outcomes than patients treated with other antihyperglycemic agents (192). Metformin may be used for the management of hyperglycemia in patients with stable heart failure as long as kidney function remains within the recommended range for use (193).

Recent studies examining the relationship between DPP-4 inhibitors and heart failure have had mixed results. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) study

showed that patients treated with the DPP-4 inhibitor saxagliptin were more likely to be hospitalized for heart failure than those given placebo (3.5% vs. 2.8%, respectively) (194). However, three other cardiovascular outcomes trials—Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) (195), Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) (196), and the Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA) (197)—did not find a significant increase in risk of heart failure hospitalization with DPP-4 inhibitor use compared with placebo. No increased risk of heart failure hospitalization has been identified in the cardiovascular outcomes trials of the GLP-1 receptor agonists lixisenatide, liraglutide, semaglutide, exenatide once-weekly, albiglutide, or dulaglutide compared with placebo (**Table 10.3*B***) (178,179,182–184).

Reduced incidence of heart failure has been observed with the use of SGLT2 inhibitors (174,176). In EMPA-REG OUTCOME, the addition of empagliflozin to standard care led to a significant 35% reduction in hospitalization for heart failure compared with placebo (8). Although the majority of patients in the study did not have heart failure at baseline, this benefit was consistent in patients with and without a history of heart failure (10). Similarly, in CANVAS and DECLARE-TIMI 58, there were 33% and 27% reductions in hospitalization for heart failure, respectively, with SGLT2 inhibitor use versus placebo (9,176). Additional data from the CREDENCE trial with canagliflozin showed a 39% reduction in hospitalization for heart failure, and 31% reduction in the composite of cardiovascular death or hospitalization for heart failure, in a diabetic kidney disease population with albuminuria (UACR of >300 to 5,000 mg/g) (174). These combined findings from four large outcomes trials of three different SGLT2 inhibitors are highly consistent and clearly indicate robust benefits of SGLT2 inhibitors in the prevention of heart failure hospitalizations. The EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, and CREDENCE trials suggested, but did not prove, that SGLT2 inhibitors would be beneficial in the treatment of patients with established heart failure. More recently, the placebo-controlled DAPA-HF trial evaluated the effects of dapagliflozin on the primary outcome of a composite of worsening heart failure or cardiovascular death in patients with New York Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less. Of the 4,744 trial participants, 45% had a history of type 2 diabetes. Over a median of 18.2 months, the group assigned to dapagliflozin treatment had a lower risk of the primary outcome (HR 0.74 [95% CI 0.65–0.85]), lower risk of first worsening heart failure event (HR 0.70 [95% CI 0.59–0.83]), and lower risk of cardiovascular death (HR 0.82 [95% CI 0.69–0.98]) compared with placebo. The effect of dapagliflozin on the primary outcome was consistent regardless of the presence or absence of type 2 diabetes (177). Therefore, in patients with type 2 diabetes and established HFrEF, an SGLT2 inhibitor with proven benefit in this patient population is recommended to reduce the risk of worsening heart failure and cardiovascular death. The benefits seen in this patient population may represent a class effect. Ongoing trials are assessing the effects of several SGLT2 inhibitors in heart failure patients with both reduced and preserved ejection fraction.

References

1. American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. Diabetes Care 2018;41:917–928
2. Ali MK, Bullard KM, Saaddine JB, Cowie CC, Imperatore G, Gregg EW. Achievement of goals in U.S. diabetes care, 1999-2010. N Engl J Med 2013;368:1613–1624
3. Buse JB, Ginsberg HN, Bakris GL, et al.; American Heart Association; American Diabetes Association. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care 2007;30:162–172
4. Gaede P, Lund-Andersen H, Parving H-H, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008;358:580–591
5. Cavender MA, Steg PG, Smith SC Jr, et al.; REACH Registry Investigators. Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death: outcomes at 4 years from the Reduction of Atherothrombosis for Continued Health (REACH) Registry. Circulation 2015;132:923–931
6. McAllister DA, Read SH, Kerssens J, et al. Incidence of hospitalization for heart failure and case-fatality among 3.25 million people with and without diabetes mellitus. Circulation 2018;138:2774–2786
7. Lam CSP, Voors AA, de Boer RA, Solomon SD, van Veldhuisen DJ. Heart failure with preserved ejection fraction: from mechanisms to therapies. Eur Heart J 2018;39:2780–2792
8. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128
9. Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–657
10. Fitchett D, Butler J, van de Borne P, et al.; EMPA-REG OUTCOME® trial investigators. Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME® trial. Eur Heart J 2018;39:363–370
11. Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. Lancet 2014;384:591–598
12. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73:3168–3209
13. Muntner P, Colantonio LD, Cushman M, et al. Validation of the atherosclerotic cardiovascular disease Pooled Cohort risk equations. JAMA 2014;311:1406–1415
14. DeFilippis AP, Young R, McEvoy JW, et al. Risk score overestimation: the impact of individual cardiovascular risk factors and preventive therapies on the performance of the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score in a modern multi-ethnic cohort. Eur Heart J 2017;38:598–608
15. Bohula EA, Morrow DA, Giugliano RP, et al. Atherothrombotic risk stratification and ezetimibe for secondary prevention. J Am Coll Cardiol 2017;69:911–921
16. Bohula EA, Bonaca MP, Braunwald E, et al. Atherothrombotic risk stratification and the efficacy and safety of vorapaxar in patients with stable ischemic heart disease and previous myocardial infarction. Circulation 2016;134:304–313
17. de Boer IH, Bangalore S, Benetos A, et al. Diabetes and hypertension: a position statement by the American Diabetes Association. Diabetes Care 2017;40:1273–1284
18. Bobrie G, Genès N, Vaur L, et al. Is "isolated home" hypertension as opposed to "isolated office" hypertension a sign of greater cardiovascular risk? Arch Intern Med 2001;161:2205–2211
19. Sega R, Facchetti R, Bombelli M, et al. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. Circulation 2005;111:1777–1783
20. Omboni S, Gazzola T, Carabelli G, Parati G. Clinical usefulness and cost effectiveness of home blood pressure telemonitoring: meta-analysis of randomized controlled studies. J Hypertens 2013;31:455–467; discussion 467–468
21. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA 2015;313:603–615

22. Arguedas JA, Leiva V, Wright JM. Blood pressure targets for hypertension in people with diabetes mellitus. Cochrane Database Syst Rev 2013;10:CD008277
23. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016;387:957–967
24. Brunström M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. BMJ 2016;352:i717
25. Bangalore S, Kumar S, Lobach I, Messerli FH. Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: observations from traditional and Bayesian random-effects meta-analyses of randomized trials. Circulation 2011;123:2799–2810
26. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10 - Should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials. J Hypertens 2017;35:922–944
27. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet 2016;387:435–443
28. Cushman WC, Evans GW, Byington RP, et al.; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575–1585
29. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007;370:829–840
30. Bakris GL. The implications of blood pressure measurement methods on treatment targets for blood pressure. Circulation 2016;134:904–905
31. Margolis KL, O'Connor PJ, Morgan TM, et al. Outcomes of combined cardiovascular risk factor management strategies in type 2 diabetes: the ACCORD randomized trial. Diabetes Care 2014;37:1721–1728
32. Buckley LF, Dixon DL, Wohlford GF 4th, Wijesinghe DS, Baker WL, Van Tassell BW. Intensive versus standard blood pressure control in SPRINT-eligible participants of ACCORD-BP. Diabetes Care 2017;40:1733–1738
33. Brouwer TF, Vehmeijer JT, Kalkman DN, et al. Intensive blood pressure lowering in patients with and patients without type 2 diabetes: a pooled analysis from two randomized trials. Diabetes Care 2018;41:1142–1148
34. Lamprea-Montealegre JA, de Boer IH. Reevaluating the evidence for blood pressure targets in type 2 diabetes. Diabetes Care 2018;41:1132–1133
35. Beddhu S, Greene T, Boucher R, et al. Intensive systolic blood pressure control and incident chronic kidney disease in people with and without diabetes mellitus: secondary analyses of two randomised controlled trials. Lancet Diabetes Endocrinol 2018;6:555–563
36. de Boer IH, Bakris G, Cannon CP. Individualizing blood pressure targets for people with diabetes and hypertension: comparing the ADA and the ACC/AHA recommendations. JAMA 2018;319:1319–1320
37. Basu S, Sussman JB, Rigdon J, Steimle L, Denton BT, Hayward RA. Benefit and harm of intensive blood pressure treatment: derivation and validation of risk models using data from the SPRINT and ACCORD trials. PLoS Med 2017;14:e1002410
38. Phillips RA, Xu J, Peterson LE, Arnold RM, Diamond JA, Schussheim AE. Impact of cardiovascular risk on the relative benefit and harm of intensive treatment of hypertension. J Am Coll Cardiol 2018;71:1601–1610
39. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018;71:e127–e248
40. Wright JT Jr, Williamson JD, Whelton PK, et al.; SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103–2116
41. Sink KM, Evans GW, Shorr RI, et al. Syncope, hypotension, and falls in the treatment of hypertension: results from the randomized clinical systolic blood pressure intervention trial. J Am Geriatr Soc 2018;66:679–686
42. Abalos E, Duley L, Steyn DW. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev 2014;2:CD002252
43. Magee LA, von Dadelszen P, Rey E, et al. Less-tight versus tight control of hypertension in pregnancy. N Engl J Med 2015;372:407–417
44. Brown MA, Magee LA, Kenny LC, et al.; International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. Hypertension 2018;72:24–43
45. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013;122:1122–1131
46. Al-Balas M, Bozzo P, Einarson A. Use of diuretics during pregnancy. Can Fam Physician 2009;55:44–45
47. Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. BMJ 2001;323:1213–1217
48. Sacks FM, Svetkey LP, Vollmer WM, et al.; DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. N Engl J Med 2001;344:3–10
49. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507–520
50. Bakris GL, Weir MR; Study of Hypertension and the Efficacy of Lotrel in Diabetes (SHIELD) Investigators. Achieving goal blood pressure in patients with type 2 diabetes: conventional versus fixed-dose combination approaches. J Clin Hypertens (Greenwich) 2003;5:202–209
51. Feldman RD, Zou GY, Vandervoort MK, Wong CJ, Nelson SAE, Feagan BG. A simplified approach to the treatment of uncomplicated hypertension: a cluster randomized, controlled trial. Hypertension 2009;53:646–653
52. Webster R, Salam A, de Silva HA, Selak V, Stepien S, Rajapakse S, et al. Fixed low-dose triple combination antihypertensive medication vs usual care for blood pressure control in patients with mild to moderate hypertension in Sri Lanka: a randomized clinical trial. JAMA 2018;320:566–579
53. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. Am J Med 2007;120:713–719
54. Catalá-López F, Macías Saint-Gerons D, González-Bermejo D, et al. Cardiovascular and renal outcomes of renin-angiotensin system blockade in adult patients with diabetes mellitus: a systematic review with network meta-analyses. PLoS Med 2016;13:e1001971
55. Palmer SC, Mavridis D, Navarese E, et al. Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. Lancet 2015;385:2047–2056
56. Barzilay JI, Davis BR, Bettencourt J, et al.; ALLHAT Collaborative Research Group. Cardiovascular outcomes using doxazosin vs. chlorthalidone for the treatment of hypertension in older adults with and without glucose disorders: a report from the ALLHAT study. J Clin Hypertens (Greenwich) 2004;6:116–125
57. Weber MA, Bakris GL, Jamerson K, et al.; ACCOMPLISH Investigators. Cardiovascular events during differing hypertension therapies in patients with diabetes. J Am Coll Cardiol 2010;56:77–85
58. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000;355:253–259
59. Arnold SV, Bhatt DL, Barsness GW, et al.; American Heart Association Council on Lifestyle and Cardiometabolic Health and Council on Clinical Cardiology. Clinical management of stable coronary artery disease in patients with type 2 diabetes mellitus: a scientific statement from the American Heart Association. Circulation 2020;141:e779–e806
60. Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators, Yusuf S, Teo K, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet 2008;372:1174–1183
61. Bangalore S, Fakheri R, Toklu B, Messerli FH. Diabetes mellitus as a compelling indication for use of renin angiotensin system blockers: systematic review and meta-analysis of randomized trials. BMJ 2016;352:i438
62. Carlberg B, Samuelsson O, Lindholm LH. Atenolol in hypertension: is it a wise choice? Lancet 2004;364:1684–1689
63. Murphy SP, Ibrahim NE, Januzzi JL Jr. Heart failure with reduced ejection fraction: a review. JAMA 2020;324:488–504

64. Yusuf S, Teo KK, Pogue J, et al.; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547–1559
65. Fried LF, Emanuele N, Zhang JH, et al.; VA NEPHRON-D Investigators. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med 2013;369:1892–1903
66. Makani H, Bangalore S, Desouza KA, Shah A, Messerli FH. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials. BMJ 2013;346:f360
67. Zhao P, Xu P, Wan C, Wang Z. Evening versus morning dosing regimen drug therapy for hypertension. Cochrane Database Syst Rev 2011; 10:CD004184
68. Hermida RC, Ayala DE, Mojón A, Fernández JR. Influence of time of day of blood pressure-lowering treatment on cardiovascular risk in hypertensive patients with type 2 diabetes. Diabetes Care 2011;34:1270–1276
69. Nilsson E, Gasparini A, Ärnlöv J, et al. Incidence and determinants of hyperkalemia and hypokalemia in a large healthcare system. Int J Cardiol 2017;245:277–284
70. Bandak G, Sang Y, Gasparini A, et al. Hyperkalemia after initiating renin-angiotensin system blockade: the Stockholm Creatinine Measurements (SCREAM) project. J Am Heart Assoc 2017; 6:e005428
71. Hughes-Austin JM, Rifkin DE, Beben T, et al. The relation of serum potassium concentration with cardiovascular events and mortality in community-living individuals. Clin J Am Soc Nephrol 2017;12:245–252
72. James MT, Grams ME, Woodward M, et al.; CKD Prognosis Consortium. A meta-analysis of the association of estimated GFR, albuminuria, diabetes mellitus, and hypertension with acute kidney injury. Am J Kidney Dis 2015;66:602–612
73. Iliescu R, Lohmeier TE, Tudorancea I, Laffin L, Bakris GL. Renal denervation for the treatment of resistant hypertension: review and clinical perspective. Am J Physiol Renal Physiol 2015;309: F583–F594
74. Bakris GL, Agarwal R, Chan JC, et al.; Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy (ARTS-DN) Study Group. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. JAMA 2015;314:884–894
75. Williams B, MacDonald TM, Morant S, et al.; British Hypertension Society's PATHWAY Studies Group. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet 2015;386:2059–2068
76. Filippatos G, Anker SD, Böhm M, et al. A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. Eur Heart J 2016;37: 2105–2114
77. Bomback AS, Klemmer PJ. Mineralocorticoid receptor blockade in chronic kidney disease. Blood Purif 2012;33:119–124
78. Jensen MD, Ryan DH, Apovian CM, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Obesity Society. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. J Am Coll Cardiol 2014;63(25 Pt B):2985–3023
79. Estruch R, Ros E, Salas-Salvadó J, et al.; PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med 2018;378:e34
80. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2013;129:S76–S99
81. Chasman DI, Posada D, Subrahmanyan L, Cook NR, Stanton VP Jr, Ridker PM. Pharmacogenetic study of statin therapy and cholesterol reduction. JAMA 2004;291:2821–2827
82. Meek C, Wierzbicki AS, Jewkes C, et al. Daily and intermittent rosuvastatin 5 mg therapy in statin intolerant patients: an observational study. Curr Med Res Opin 2012;28:371–378
83. Mihaylova B, Emberson J, Blackwell L, et al.; Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012; 380:581–590
84. Baigent C, Keech A, Kearney PM, et al.; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267–1278
85. Pyörälä K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). Diabetes Care 1997;20:614–620
86. Collins R, Armitage J, Parish S, Sleigh P, Peto R; Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003;361:2005–2016
87. Goldberg RB, Mellies MJ, Sacks FM, et al.; The Care Investigators. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the Cholesterol and Recurrent Events (CARE) trial. Circulation 1998;98:2513–2519
88. Shepherd J, Barter P, Carmena R, et al. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. Diabetes Care 2006;29:1220–1226
89. Sever PS, Poulter NR, Dahlöf B, et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial–lipid-lowering arm (ASCOT-LLA). Diabetes Care 2005;28:1151–1157
90. Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN). Diabetes Care 2006;29:1478–1485
91. Colhoun HM, Betteridge DJ, Durrington PN, et al.; CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364:685–696
92. Kearney PM, Blackwell L, Collins R, et al.; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008; 371:117–125
93. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013; 1:CD004816
94. Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. Risk of incident diabetes among patients treated with statins: population based study [published correction appears in BMJ 2013;347:f4356]. BMJ 2013;346:f2610
95. Baigent C, Blackwell L, Emberson J, et al.; Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670–1681
96. Cannon CP, Blazing MA, Giugliano RP, et al.; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372:2387–2397
97. de Ferranti SD, de Boer IH, Fonseca V, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Circulation 2014;130:1110–1130
98. Cannon CP, Braunwald E, McCabe CH, et al.; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350: 1495–1504
99. Sabatine MS, Giugliano RP, Keech AC, et al.; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017; 376:1713–1722
100. Giugliano RP, Cannon CP, Blazing MA, et al.; IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) Investigators. Benefit of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus: results from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). Circulation 2018;137:1571–1582
101. Das SR, Everett BM, Birtcher KK, et al. 2018 ACC expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes and atherosclerotic cardiovascular disease: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol 2018;72:3200–3223
102. Moriarty PM, Jacobson TA, Bruckert E, et al. Efficacy and safety of alirocumab, a monoclonal

antibody to PCSK9, in statin-intolerant patients: design and rationale of ODYSSEY ALTERNATIVE, a randomized phase 3 trial. J Clin Lipidol 2014; 8:554–561
103. Zhang X-L, Zhu Q-Q, Zhu L, et al. Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials. BMC Med 2015;13:123
104. Sabatine MS, Leiter LA, Wiviott SD, et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. Lancet Diabetes Endocrinol 2017;5:941–950
105. Schwartz GG, Steg PG, Szarek M, et al.; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379:2097–2107
106. Ray KK, Colhoun HM, Szarek M, et al.; ODYSSEY OUTCOMES Committees and Investigators. Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial. Lancet Diabetes Endocrinol 2019;7:618–628
107. Berglund L, Brunzell JD, Goldberg AC, et al.; Endocrine Society. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2012;97:2969–2989
108. Bhatt DL, Steg PG, Miller M, et al.; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med 2019;380:11–22
109. Singh IM, Shishehbor MH, Ansell BJ. High-density lipoprotein as a therapeutic target: a systematic review. JAMA 2007;298:786–798
110. Keech A, Simes RJ, Barter P, et al.; FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005;366:1849–1861
111. Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. Am J Cardiol 2005;95: 120–122
112. Ginsberg HN, Elam MB, Lovato LC, et al.; ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010;362:1563–1574
113. Kowa Research Institute, Inc. Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabeTes (PROMINENT) In: ClinicalTrials.gov [Internet]. Bethesda, MD, National Library of Medicine. NLM Identifier: NCT03071692. Accessed 3 November 2020. Available from https://clinicaltrials.gov/ct2/show/NCT03071692
114. Boden WE, Probstfield JL, Anderson T, et al.; AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 2011;365:2255–2267
115. Landray MJ, Haynes R, Hopewell JC, et al.; HPS2-THRIVE Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med 2014;371: 203–212
116. Rajpathak SN, Kumbhani DJ, Crandall J, Barzilai N, Alderman M, Ridker PM. Statin therapy and risk of developing type 2 diabetes: a meta-analysis. Diabetes Care 2009;32:1924–1929
117. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010;375:735–742
118. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet 2012;380: 565–571
119. Mach F, Ray KK, Wiklund O, et al.; European Atherosclerosis Society Consensus Panel. Adverse effects of statin therapy: perception vs. the evidence - focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. Eur Heart J 2018;39: 2526–2539
120. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7–22
121. Shepherd J, Blauw GJ, Murphy MB, et al.; PROSPER study group. PROspective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360:1623–1630
122. Trompet S, van Vliet P, de Craen AJM, et al. Pravastatin and cognitive function in the elderly. Results of the PROSPER study. J Neurol 2010; 257:85–90
123. Yusuf S, Bosch J, Dagenais G, et al.; HOPE-3 Investigators. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med 2016;374:2021–2031
124. Giugliano RP, Mach F, Zavitz K, et al.; EBBINGHAUS Investigators. Cognitive function in a randomized trial of evolocumab. N Engl J Med 2017;377:633–643
125. Richardson K, Schoen M, French B, et al. Statins and cognitive function: a systematic review. Ann Intern Med 2013;159:688–697
126. Baigent C, Blackwell L, Collins R, et al.; Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849–1860
127. Perk J, De Backer G, Gohlke H, et al.; European Association for Cardiovascular Prevention & Rehabilitation (EACPR); ESC Committee for Practice Guidelines (CPG). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J 2012;33:1635–1701
128. Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ 2008;337:a1840
129. Zhang C, Sun A, Zhang P, et al. Aspirin for primary prevention of cardiovascular events in patients with diabetes: a meta-analysis. Diabetes Res Clin Pract 2010;87:211–218
130. De Berardis G, Sacco M, Strippoli GFM, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. BMJ 2009;339: b4531
131. ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med 2018;379:1529–1539
132. Gaziano JM, Brotons C, Coppolecchia R, et al.; ARRIVE Executive Committee. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. Lancet 2018;392:1036–1046
133. McNeil JJ, Wolfe R, Woods RL, et al.; ASPREE Investigator Group. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med 2018;379:1509–1518
134. Pignone M, Earnshaw S, Tice JA, Pletcher MJ. Aspirin, statins, or both drugs for the primary prevention of coronary heart disease events in men: a cost-utility analysis. Ann Intern Med 2006; 144:326–336
135. Huxley RR, Peters SAE, Mishra GD, Woodward M. Risk of all-cause mortality and vascular events in women versus men with type 1 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2015;3:198–206
136. Peters SAE, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. Diabetologia 2014;57:1542–1551
137. Kalyani RR, Lazo M, Ouyang P, et al. Sex differences in diabetes and risk of incident coronary artery disease in healthy young and middle-aged adults. Diabetes Care 2014;37:830–838
138. Peters SAE, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. Lancet 2014;383: 1973–1980
139. Miedema MD, Duprez DA, Misialek JR, et al. Use of coronary artery calcium testing to guide aspirin utilization for primary prevention: estimates from the multi-ethnic study of atherosclerosis. Circ Cardiovasc Qual Outcomes 2014;7: 453–460
140. Dimitriu-Leen AC, Scholte AJHA, van Rosendael AR, et al. Value of coronary computed tomography angiography in tailoring aspirin therapy for primary prevention of atherosclerotic events in patients at high risk with diabetes mellitus. Am J Cardiol 2016;117:887–893
141. Mora S, Ames JM, Manson JE. Low-dose aspirin in the primary prevention of cardiovascular disease: shared decision making in clinical practice. JAMA 2016;316:709–710
142. Campbell CL, Smyth S, Montalescot G, Steinhubl SR. Aspirin dose for the prevention

of cardiovascular disease: a systematic review. JAMA 2007;297:2018–2024
143. Davì G, Patrono C. Platelet activation and atherothrombosis. N Engl J Med 2007;357:2482–2494
144. Larsen SB, Grove EL, Neergaard-Petersen S, Würtz M, Hvas A-M, Kristensen SD. Determinants of reduced antiplatelet effect of aspirin in patients with stable coronary artery disease. PLoS One 2015;10:e0126767
145. Zaccardi F, Rizzi A, Petrucci G, et al. In vivo platelet activation and aspirin responsiveness in type 1 diabetes. Diabetes 2016;65:503–509
146. Bethel MA, Harrison P, Sourij H, et al. Randomized controlled trial comparing impact on platelet reactivity of twice-daily with once-daily aspirin in people with type 2 diabetes. Diabet Med 2016;33:224–230
147. Rothwell PM, Cook NR, Gaziano JM, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. Lancet 2018;392:387–399
148. Vandvik PO, Lincoff AM, Gore JM, et al. Primary and secondary prevention of cardiovascular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [published correction appears in Chest 2012;141:1129]. Chest 2012;141(Suppl.): e637S–e668S
149. Bhatt DL, Bonaca MP, Bansilal S, et al. Reduction in ischemic events with ticagrelor in diabetic patients with prior myocardial infarction in PEGASUS-TIMI 54. J Am Coll Cardiol 2016;67:2732–2740
150. Steg PG, Bhatt DL, Simon T, et al.; THEMIS Steering Committee and Investigators. Ticagrelor in patients with stable coronary disease and diabetes. N Engl J Med 2019;381:1309–1320
151. Bhatt DL, Steg PG, Mehta SR, et al.; THEMIS Steering Committee and Investigators. Ticagrelor in patients with diabetes and stable coronary artery disease with a history of previous percutaneous coronary intervention (THEMIS-PCI): a phase 3, placebo-controlled, randomised trial. Lancet 2019;394:1169–1180
152. Bhatt DL, Eikelboom JW, Connolly SJ, et al.; COMPASS Steering Committee and Investigators. Role of combination antiplatelet and anticoagulation therapy in diabetes mellitus and cardiovascular disease: insights from the COMPASS trial. Circulation 2020;141:1841–1854
153. Connolly SJ, Eikelboom JW, Bosch J, et al.; COMPASS investigators. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet 2018;391:205–218
154. Bonaca MP, Bauersachs RM, Anand SS, et al. Rivaroxaban in peripheral artery disease after revascularization. N Engl J Med 2020;382:1994–2004
155. Bax JJ, Young LH, Frye RL, Bonow RO, Steinberg HO, Barrett EJ. Screening for coronary artery disease in patients with diabetes. Diabetes Care 2007;30:2729–2736
156. Boden WE, O'Rourke RA, Teo KK, et al.; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503–1516
157. BARI 2D Study Group, Frye RL, August P, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med 2009;360:2503–2015
158. Wackers FJT, Chyun DA, Young LH, et al.; Detection of Ischemia in Asymptomatic Diabetics (DIAD) Investigators. Resolution of asymptomatic myocardial ischemia in patients with type 2 diabetes in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study. Diabetes Care 2007;30:2892–2898
159. Elkeles RS, Godsland IF, Feher MD, et al.; PREDICT Study Group. Coronary calcium measurement improves prediction of cardiovascular events in asymptomatic patients with type 2 diabetes: the PREDICT study. Eur Heart J 2008;29:2244–2251
160. Raggi P, Shaw LJ, Berman DS, Callister TQ. Prognostic value of coronary artery calcium screening in subjects with and without diabetes. J Am Coll Cardiol 2004;43:1663–1669
161. Anand DV, Lim E, Hopkins D, et al. Risk stratification in uncomplicated type 2 diabetes: prospective evaluation of the combined use of coronary artery calcium imaging and selective myocardial perfusion scintigraphy. Eur Heart J 2006;27:713–721
162. Young LH, Wackers FJT, Chyun DA, et al.; DIAD Investigators. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. JAMA 2009;301:1547–1555
163. Wackers FJT, Young LH, Inzucchi SE, et al.; Detection of Ischemia in Asymptomatic Diabetics Investigators. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. Diabetes Care 2004;27:1954–1961
164. Scognamiglio R, Negut C, Ramondo A, Tiengo A, Avogaro A. Detection of coronary artery disease in asymptomatic patients with type 2 diabetes mellitus. J Am Coll Cardiol 2006;47:65–71
165. Hadamitzky M, Hein F, Meyer T, et al. Prognostic value of coronary computed tomographic angiography in diabetic patients without known coronary artery disease. Diabetes Care 2010;33:1358–1363
166. Choi E-K, Chun EJ, Choi S-I, et al. Assessment of subclinical coronary atherosclerosis in asymptomatic patients with type 2 diabetes mellitus with single photon emission computed tomography and coronary computed tomography angiography. Am J Cardiol 2009;104:890–896
167. Malik S, Zhao Y, Budoff M, et al. Coronary artery calcium score for long-term risk classification in individuals with type 2 diabetes and metabolic syndrome from the Multi-Ethnic Study of Atherosclerosis. JAMA Cardiol 2017;2:1332–1340
168. Wing RR, Bolin P, Brancati FL, et al.; Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369:145–154
169. Braunwald E, Domanski MJ, Fowler SE, et al.; PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. N Engl J Med 2004;351:2058–2068
170. Kezerashvili A, Marzo K, De Leon J. Beta blocker use after acute myocardial infarction in the patient with normal systolic function: when is it "ok" to discontinue? Curr Cardiol Rev 2012;8:77–84
171. Fihn SD, Gardin JM, Abrams J, et al.; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; American College of Physicians; American Association for Thoracic Surgery; Preventive Cardiovascular Nurses Association; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2012;60:e44–e164
172. U.S. Food and Drug Administration. Guidance for industry on diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Silver Spring, MD, 2008. Accessed 3 November 2020. Available from https://www.federalregister.gov/documents/2008/12/19/E8-30086/guidance-for-industry-on-diabetes-mellitus-evaluating-cardiovascular-risk-in-new-antidiabetic
173. Rosenstock J, Perkovic V, Johansen OE, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. JAMA 2019;321:69–79
174. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295–2306
175. Neal B, Perkovic V, Matthews DR, et al.; CANVAS-R Trial Collaborative Group. Rationale, design and baseline characteristics of the CANagliflozin cardioVascular Assessment Study-Renal (CANVAS-R): a randomized, placebo-controlled trial. Diabetes Obes Metab 2017;19:387–393
176. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347–357
177. McMurray JJV, Solomon SD, Inzucchi SE, et al.; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995–2008
178. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–322
179. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–1844
180. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2019;381:841–851

181. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet 2018; 392:1519–1529
182. Gerstein HC, Colhoun HM, Dagenais GR, et al.; REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019;394: 121–130
183. Pfeffer MA, Claggett B, Diaz R, et al.; ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015;373:2247–2257
184. Holman RR, Bethel MA, Mentz RJ, et al.; EXSCEL Study Group. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2017;377:1228–1239
185. Zelniker TA, Wiviott SD, Raz I, et al. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus. Circulation 2019;139:2022–2031
186. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;393:31–39
187. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol 1974;34:29–34
188. Dormandy JA, Charbonnel B, Eckland DJA, et al.; PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279–1289
189. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. JAMA 2007;298:1189–1195
190. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA 2007;298: 1180–1188
191. Inzucchi SE, Masoudi FA, McGuire DK. Metformin in heart failure. Diabetes Care 2007;30: e129–e129
192. Eurich DT, Majumdar SR, McAlister FA, Tsuyuki RT, Johnson JA. Improved clinical outcomes associated with metformin in patients with diabetes and heart failure. Diabetes Care 2005;28:2345–2351
193. U.S. Food and Drug Administration. FDA drug safety communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function, 2016. Accessed 3 November 2020. Available from http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm
194. Scirica BM, Bhatt DL, Braunwald E, et al.; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317–1326
195. Zannad F, Cannon CP, Cushman WC, et al.; EXAMINE Investigators. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. Lancet 2015; 385:2067–2076
196. Green JB, Bethel MA, Armstrong PW, et al.; TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;373:232–242
197. Rosenstock J, Perkovic V, Johansen OE, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. JAMA 2019;321:69–79
198. Zoungas S, Chalmers J, Neal B, et al.; ADVANCE-ON Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. N Engl J Med 2014;371:1392–1406
199. Hansson L, Zanchetti A, Carruthers SG, et al.; HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998;351:1755–1762
200. White WB, Cannon CP, Heller SR, et al.; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327–1335
201. Rosenstock J, Perkovic V, Alexander JH, et al. Rationale, design, and baseline characteristics of the CArdiovascular safety and Renal Microvascular outcomE study with LINAgliptin (CARMELINA): a randomized, double-blind, placebo-controlled clinical trial in patients with type 2 diabetes and high cardio-renal risk. Cardiovasc Diabetol 2018;17:30
202. Marx N, Rosenstock J, Kahn SE, et al. Design and baseline characteristics of the CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes (CAROLINA®). Diab Vasc Dis Res 2015;12:164–174
203. Cefalu WT, Kaul S, Gerstein HC, et al. Cardiovascular outcomes trials in type 2 diabetes: where do we go from here? Reflections from a *Diabetes Care* Editors' Expert Forum. Diabetes Care 2018;41:14–31

11. Microvascular Complications and Foot Care: *Standards of Medical Care in Diabetes—2021*

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The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc21-SPPC), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc21-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

*For prevention and management of diabetes complications in children and adolescents, please refer to Section 13 "Children and Adolescents" (*https://doi.org/10.2337/dc21-S013*).*

CHRONIC KIDNEY DISEASE

Screening

Recommendations

11.1a At least annually, urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate should be assessed in patients with type 1 diabetes with duration of ≥5 years and in all patients with type 2 diabetes regardless of treatment. **B**

11.1b Patients with diabetes and urinary albumin >300 mg/g creatinine and/or an estimated glomerular filtration rate 30–60 mL/min/1.73 m^2 should be monitored twice annually to guide therapy. **B**

Treatment

Recommendations

11.2 Optimize glucose control to reduce the risk or slow the progression of chronic kidney disease. **A**

11.3a For patients with type 2 diabetes and diabetic kidney disease, consider use of a sodium–glucose cotransporter 2 inhibitor in patients with an estimated glomerular filtration rate ≥30 mL/min/1.73 m^2 and urinary albumin >300 mg/g creatinine. **A**

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11.3b In patients with type 2 diabetes and diabetic kidney disease, consider use of sodium–glucose cotransporter 2 inhibitors additionally for cardiovascular risk reduction when estimated glomerular filtration rate and urinary albumin creatinine are ≥30 mL/min/1.73 m^2 or >300 mg/g, respectively. **A**

11.3c In patients with chronic kidney disease who are at increased risk for cardiovascular events, use of a glucagon-like peptide 1 receptor agonist reduces renal end point, primarily albuminuria, progression of albuminuria, and cardiovascular events (**Table 9.1**). **A**

11.4 Optimize blood pressure control to reduce the risk or slow the progression of chronic kidney disease. **A**

11.5 Do not discontinue renin-angiotensin system blockade for minor increases in serum creatinine (<30%) in the absence of volume depletion. **A**

11.6 For people with nondialysis-dependent chronic kidney disease, dietary protein intake should be approximately 0.8 g/kg body weight per day (the recommended daily allowance). **A** For patients on dialysis, higher levels of dietary protein intake should be considered, since malnutrition is a major problem in some dialysis patients. **B**

11.7 In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin-to-creatinine ratio (30–299 mg/g creatinine) **B** and is strongly recommended for those with urinary albumin-to-creatinine ratio ≥300 mg/g creatinine and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2. **A**

11.8 Periodically monitor serum creatinine and potassium levels for the development of increased creatinine or changes in potassium when ACE inhibitors, angiotensin receptor blockers, or diuretics are used. **B**

11.9 An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of chronic kidney disease in patients with diabetes who have normal blood pressure, normal urinary albumin-to-creatinine ratio (<30 mg/g creatinine), and normal estimated glomerular filtration rate. **A**

11.10 Patients should be referred for evaluation by a nephrologist if they have an estimated glomerular filtration rate <30 mL/min/1.73 m^2. **A**

11.11 Promptly refer to a physician experienced in the care of kidney disease for uncertainty about the etiology of kidney disease, difficult management issues, and rapidly progressing kidney disease. **A**

Epidemiology of Diabetes and Chronic Kidney Disease

Chronic kidney disease (CKD) is diagnosed by the persistent presence of elevated urinary albumin excretion (albuminuria), low estimated glomerular filtration rate (eGFR), or other manifestations of kidney damage (1,2). In this section, the focus is on CKD attributed to diabetes (diabetic kidney disease), which occurs in 20–40% of patients with diabetes (1,3–5). CKD typically develops after diabetes duration of 10 years in type 1 diabetes but may be present at diagnosis of type 2 diabetes. CKD can progress to end-stage renal disease (ESRD) requiring dialysis or kidney transplantation and is the leading cause of ESRD in the U.S. (6). In addition, among people with type 1 or 2 diabetes, the presence of CKD markedly increases cardiovascular risk and health care costs (7).

Assessment of Albuminuria and Estimated Glomerular Filtration Rate

Screening for albuminuria can be most easily performed by urinary albumin-to-creatinine ratio (UACR) in a random spot urine collection (1,2). Timed or 24-h collections are more burdensome and add little to prediction or accuracy. Measurement of a spot urine sample for albumin alone (whether by immunoassay or by using a sensitive dipstick test specific for albuminuria) without simultaneously measuring urine creatinine (Cr) is less expensive but susceptible to false-negative and false-positive determinations as a result of variation in urine concentration due to hydration (8).

Normal UACR is defined as <30 mg/g Cr, and high urinary albumin excretion is defined as ≥30 mg/g Cr. However, UACR is a continuous measurement, and differences within the normal and abnormal ranges are associated with renal and cardiovascular outcomes (7,9,10). Furthermore, because of high biological variability of >20% between measurements in urinary albumin excretion, two of three specimens of UACR collected within a 3- to 6-month period should be abnormal before considering a patient to have high or very high albuminuria (1,2,11,12). Exercise within 24 h, infection, fever, congestive heart failure, marked hyperglycemia, menstruation, and marked hypertension may elevate UACR independently of kidney damage (13).

eGFR should be calculated from serum creatinine using a validated formula. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is generally preferred (2). eGFR is routinely reported by laboratories with serum creatinine, and eGFR calculators are available online at nkdep.nih.gov. An eGFR persistently <60 mL/min/1.73 m^2 is considered abnormal, though optimal thresholds for clinical diagnosis are debated in older adults (2,14).

Diagnosis of Diabetic Kidney Disease

Diabetic kidney disease is usually a clinical diagnosis made based on the presence of albuminuria and/or reduced eGFR in the absence of signs or symptoms of other primary causes of kidney damage. The typical presentation of diabetic kidney disease is considered to include a long-standing duration of diabetes, retinopathy, albuminuria without gross hematuria, and gradually progressive loss of eGFR. However, signs of CKD may be present at diagnosis or without retinopathy in type 2 diabetes, and reduced eGFR without albuminuria has been frequently reported in type 1 and type 2 diabetes and is becoming more common over time as the prevalence of diabetes increases in the U.S. (3,4,15,16).

An active urinary sediment (containing red or white blood cells or cellular casts), rapidly increasing albuminuria or nephrotic syndrome, rapidly decreasing eGFR, or the absence of retinopathy (in type 1 diabetes) suggests alternative or additional causes of kidney disease.

For patients with these features, referral to a nephrologist for further diagnosis, including the possibility of kidney biopsy, should be considered. It is rare for patients with type 1 diabetes to develop kidney disease without retinopathy. In type 2 diabetes, retinopathy is only moderately sensitive and specific for CKD caused by diabetes, as confirmed by kidney biopsy (17).

Staging of Chronic Kidney Disease

Stages 1–2 CKD have been defined by evidence of high albuminuria with eGFR $\geq$60 mL/min/1.73 m^2, while stages 3–5 CKD have been defined by progressively lower ranges of eGFR (18) (**Fig. 11.1**). At any eGFR, the degree of albuminuria is associated with risk of cardiovascular disease (CVD), CKD progression, and mortality (7). Therefore, Kidney Disease: Improving Global Outcomes (KDIGO) recommends a more comprehensive CKD staging that incorporates albuminuria at all stages of eGFR; this system is more closely associated with risk but is also more complex and does not translate directly to treatment decisions (2). Thus, based on the current classification system, both eGFR and albuminuria must be quantified to guide treatment decisions. This is also important since eGFR levels are essential to modify drug dosage or restrictions of use (**Fig. 11.1**) (19,20). The degree of albuminuria may influence choice of antihypertensive (see Section 10 "Cardiovascular Disease and Risk Management," https://doi.org/10.2337/dc21-S010) or glucose-lowering medications (see below). Observed history of eGFR loss (which is also associated with risk of CKD progression and other adverse health outcomes) and cause of kidney damage (including possible causes other than diabetes) may also affect these decisions (21).

Acute Kidney Injury

Acute kidney injury (AKI) is diagnosed by a 50% or greater sustained increase in serum creatinine over a short period of time, which is also reflected as a rapid decrease in eGFR (23,24). People with diabetes are at higher risk of AKI than those without diabetes (25). Other risk factors for AKI include preexisting CKD, the use of medications that cause kidney injury (e.g., nonsteroidal anti-inflammatory drugs), and the use of medications that alter renal blood flow and intrarenal hemodynamics. In particular, many antihypertensive medications (e.g., diuretics, ACE inhibitors, and angiotensin receptor blockers [ARBs]) can reduce intravascular volume, renal blood flow, and/or glomerular filtration. There was concern that sodium–glucose cotransporter 2 (SGLT2) inhibitors may promote AKI through volume depletion, particularly when combined with diuretics or other medications that reduce glomerular filtration; however, this has not been found to be true in randomized clinical outcome trials of advanced kidney disease (26) or high cardiovascular disease risk with normal kidney function (27–29). Timely identification and treatment of AKI is important because AKI is associated with increased risks of progressive CKD and other poor health outcomes (30).

Small elevations in serum creatinine (up to 30% from baseline) with renin-angiotensin system blockers (such as ACE inhibitors and ARBs) must not be confused with AKI (31). An analysis of the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial demonstrates that those randomized to intensive blood pressure lowering with up to a 30% increase in serum creatinine did not have any increase in mortality or progressive kidney disease (32–36). Moreover, a measure of markers for AKI showed no significant increase of any markers with increased creatinine (34). Accordingly, ACE inhibitors and ARBs should not be discontinued for minor increases in serum creatinine ($<$30%), in the absence of volume depletion.

Surveillance

Albuminuria and eGFR should be monitored regularly to enable timely diagnosis of CKD, monitor progression of CKD, detect superimposed kidney diseases including AKI, assess risk of CKD complications, dose drugs appropriately, and determine whether nephrology referral is needed. Among people with existing kidney disease, albuminuria and eGFR may change due to progression of CKD, development of a separate superimposed cause of kidney disease, AKI, or other effects of medications, as noted above. Serum potassium should also be monitored for patients treated with ACE inhibitors, ARBs, and diuretics because these medications can cause hyperkalemia or hypokalemia, which are associated with cardiovascular risk and mortality (37–39). For patients with eGFR $<$60 mL/min/1.73 m^2, appropriate medication dosing should be verified, exposure to nephrotoxins (e.g., nonsteroidal anti-inflammatory drugs and iodinated contrast) should be minimized, and potential CKD complications should be evaluated (**Table 11.1**).

The need for annual quantitative assessment of albumin excretion after diagnosis of albuminuria, institution of ACE inhibitors or ARB therapy, and achievement of blood pressure control is a subject of debate. Continued surveillance can assess both response to therapy and disease progression and may aid in assessing adherence to ACE inhibitor or ARB therapy. In addition, in clinical trials of ACE inhibitors or ARB therapy in type 2 diabetes, reducing albuminuria from levels $\geq$300 mg/g Cr has been associated with improved renal and cardiovascular outcomes, leading some to suggest that medications should be titrated to minimize UACR. However, this approach has not been formally evaluated in prospective trials. In type 1 diabetes, remission of albuminuria may occur spontaneously, and cohort studies evaluating associations of change in albuminuria with clinical outcomes have reported inconsistent results (40,41).

The prevalence of CKD complications correlates with eGFR (42). When eGFR is $<$60 mL/min/1.73 m^2, screening for complications of CKD is indicated (**Table 11.1**). Early vaccination against hepatitis B virus is indicated in patients likely to progress to ESRD (see Section 4 "Comprehensive Medical Evaluation and Assessment of Comorbidities," https://doi.org/10.2337/dc21-S004, for further information on immunization).

Interventions

Nutrition

For people with nondialysis-dependent CKD, dietary protein intake should be ~0.8 g/kg body weight per day (the recommended daily allowance) (1). Compared with higher levels of dietary protein intake, this level slowed GFR decline with evidence of a greater effect over time. Higher levels of dietary protein intake ($>$20% of daily calories from protein or $>$1.3 g/kg/day) have been associated with increased albuminuria, more rapid kidney function loss, and CVD mortality and therefore should be avoided. Reducing the amount of dietary protein

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73m^2) Description and range	G1	Normal to high	≥90	1 if CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 if CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

Figure 11.1—Risk of chronic kidney disease (CKD) progression, frequency of visits, and referral to nephrology according to glomerular filtration rate (GFR) and albuminuria. The GFR and albuminuria grid depicts the risk of progression, morbidity, and mortality by color, from best to worst (green, yellow, orange, red, dark red). The numbers in the boxes are a guide to the frequency of visits (number of times per year). Green can reflect CKD with normal eGFR and albumin-to-creatinine ratio only in the presence of other markers of kidney damage, such as imaging showing polycystic kidney disease or kidney biopsy abnormalities, with follow-up measurements annually; yellow requires caution and measurements at least once per year; orange requires measurements twice per year; red requires measurements three times per year; and dark red requires measurements four times per year. These are general parameters only, based on expert opinion, and underlying comorbid conditions and disease state as well as the likelihood of impacting a change in management for any individual patient must be taken into account. "Refer" indicates that nephrology services are recommended. *Referring clinicians may wish to discuss with their nephrology service, depending on local arrangements regarding treating or referring. Reprinted with permission from Vassalotti et al. (22).

below the recommended daily allowance of 0.8 g/kg/day is not recommended because it does not alter glycemic measures, cardiovascular risk measures, or the course of GFR decline (43).

Restriction of dietary sodium (to <2,300 mg/day) may be useful to control blood pressure and reduce cardiovascular risk (44,45), and restriction of dietary potassium may be necessary to control serum potassium concentration (25,37–39). These interventions may be most important for patients with reduced eGFR, for whom urinary excretion of sodium and potassium may be impaired. For patients on dialysis, higher levels of dietary protein intake should be considered, since malnutrition is a major problem in some dialysis patients (46). Recommendations for dietary sodium and potassium intake should be individualized on the basis of comorbid conditions, medication use, blood pressure, and laboratory data.

Glycemic Targets

Intensive glycemic control with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to delay the onset and progression of albuminuria and reduced eGFR in patients with type 1 diabetes (47,48) and type 2 diabetes (1,49–55). Insulin alone was used to lower blood glucose in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study of type 1 diabetes, while a variety of agents were used in clinical trials of type 2 diabetes, supporting the conclusion that glycemic control itself helps prevent CKD and its progression. The effects of glucose-lowering therapies on CKD have helped define A1C targets (see **Table 6.2**).

The presence of CKD affects the risks and benefits of intensive glycemic control and a number of specific glucose-lowering medications. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial of type 2 diabetes, adverse effects of intensive glycemic control (hypoglycemia and mortality) were increased among patients with kidney disease at baseline (56,57). Moreover, there is a lag time of at least 2 years in type 2 diabetes to over 10 years in type 1 diabetes for the effects of intensive glucose control to manifest as improved eGFR outcomes (53,58,59). Therefore, in some patients with prevalent CKD and substantial comorbidity, target A1C levels may be less intensive (1,60).

Direct Renal Effects of Glucose-Lowering Medications

Some glucose-lowering medications also have effects on the kidney that are direct, i.e., not mediated through glycemia. For example, SGLT2 inhibitors reduce renal tubular glucose reabsorption, weight, systemic blood pressure, intraglomerular pressure, and albuminuria and slow GFR loss through mechanisms that appear independent of glycemia (28,61–64). Moreover, recent data support the notion that SGLT2 inhibitors reduce oxidative stress in the kidney by >50% and blunt increases in angiotensinogen as well as reduce NLRP3 inflammasome activity (65–67). Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) also have direct effects on the kidney and have been reported to improve renal outcomes compared with placebo (68–71). Renal effects should be considered when selecting antihyperglycemia agents (see Section 9 "Pharmacologic Approaches to

Table 11.1—Selected complications of chronic kidney disease

Complication	Medical and laboratory evaluation
Elevated blood pressure >140/90 mmHg	Blood pressure, weight
Volume overload	History, physical examination, weight
Electrolyte abnormalities	Serum electrolyte
Metabolic acidosis	Serum electrolytes
Anemia	Hemoglobin; iron testing if indicated
Metabolic bone disease	Serum calcium, phosphate, PTH, vitamin 25(OH)D

Complications of chronic kidney disease (CKD) generally become prevalent when estimated glomerular filtration rate falls below 60 mL/min/1.73 m^2 (stage 3 CKD or greater) and become more common and severe as CKD progresses. Evaluation of elevated blood pressure and volume overload should occur at every clinical contact possible; laboratory evaluations are generally indicated every 6–12 months for stage 3 CKD, every 3–5 months for stage 4 CKD, and every 1–3 months for stage 5 CKD, or as indicated to evaluate symptoms or changes in therapy. PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D.

Glycemic Treatment," https://doi.org/10.2337/dc21-S009).

Selection of Glucose-Lowering Medications for Patients With Chronic Kidney Disease

For patients with type 2 diabetes and established CKD, special considerations for the selection of glucose-lowering medications include limitations to available medications when eGFR is diminished and a desire to mitigate high risks of CKD progression, CVD, and hypoglycemia (72,73). Drug dosing may require modification with eGFR <60 mL/min/1.73 m^2 (1).

The U.S. Food and Drug Administration (FDA) revised its guidance for the use of metformin in CKD in 2016 (74), recommending use of eGFR instead of serum creatinine to guide treatment and expanding the pool of patients with kidney disease for whom metformin treatment should be considered. The revised FDA guidance states that metformin is contraindicated in patients with an eGFR <30 mL/min/1.73 m^2; eGFR should be monitored while taking metformin; the benefits and risks of continuing treatment should be reassessed when eGFR falls to <45 mL/min/1.73 m^2 (75,76); metformin should not be initiated for patients with an eGFR <45 mL/min/1.73 m^2; and metformin should be temporarily discontinued at the time of or before iodinated contrast imaging procedures in patients with eGFR 30–60 mL/min/1.73 m^2. Within these constraints, metformin should be considered the first-line treatment for all patients with type 2 diabetes, including those with CKD.

SGLT2 inhibitors and GLP-1 RAs should be considered for patients with type 2 diabetes and CKD who require another drug added to metformin to attain target A1C or cannot use or tolerate metformin. SGLT2 inhibitors reduce risks of CKD progression, CVD events, and hypoglycemia. GLP-1 RAs are suggested because they reduce risks of CVD events and hypoglycemia and appear to possibly slow CKD progression (77).

A number of large cardiovascular outcomes trials in patients with type 2 diabetes at high risk for CVD or with existing CVD examined kidney effects as secondary outcomes. These trials include EMPA-REG OUTCOME [BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients], CANVAS (Canagliflozin Cardiovascular Assessment Study), LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), and SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) (63,68,71,78). Specifically, compared with placebo, empagliflozin reduced the risk of incident or worsening nephropathy (a composite of progression to UACR >300 mg/g Cr, doubling of serum creatinine, ESRD, or death from ESRD) by 39% and the risk of doubling of serum creatinine accompanied by eGFR ≤45 mL/min/1.73 m^2 by 44%; canagliflozin reduced the risk of progression of albuminuria by 27% and the risk of reduction in eGFR, ESRD, or death from ESRD by 40%; liraglutide reduced the risk of new or worsening nephropathy (a composite of persistent macroalbuminuria, doubling of serum creatinine, ESRD, or death from ESRD) by 22%; and semaglutide reduced the risk of new or worsening nephropathy (a composite of persistent UACR >300 mg/g Cr, doubling of serum creatinine, or ESRD) by 36% (each $P < 0.01$).

These analyses were limited by evaluation of study populations not selected primarily for CKD and examination of renal effects as secondary outcomes. However, all of these trials included large numbers of people with stage 3a (eGFR 45–59 mL/min/1.73 m^2) kidney disease. In addition, subgroup analyses of CANVAS and LEADER suggested that the renal benefits of canagliflozin and liraglutide were as great or greater for participants with CKD at baseline (29,70) and in CANVAS were similar for participants with or without atherosclerotic cardiovascular disease (ASCVD) at baseline (79).

Several large clinical trials of SGLT2 inhibitors focused on patients with advanced CKD, and assessment of primary renal outcomes are completed or ongoing. Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE), a placebo-controlled trial of canagliflozin among 4,401 adults with type 2 diabetes, UACR ≥300 mg/g Cr, and mean eGFR 56 mL/min/1.73 m^2 with a mean albuminuria level of over 900 mg/day, had a primary composite end point of ESRD, doubling of serum creatinine, or renal or cardiovascular death (26,80). It was stopped early due to positive efficacy and showed a 32% risk reduction for development of ESRD over control (26). Additionally, the development of the primary end point, which included chronic dialysis for ≥30 days, kidney transplantation or eGFR <15 mL/min/1.73 m^2 sustained for ≥30 days by central laboratory assessment, doubling from the baseline serum creatinine average sustained for ≥30 days by central laboratory assessment, or renal death or cardiovascular death, was reduced by 30%. This benefit was on background ACE inhibitor or ARB therapy in >99% of the patients (26). Moreover, in this advanced CKD group, there were clear benefits on cardiovascular outcomes demonstrating a 31% reduction in cardiovascular death or heart failure hospitalization and a 20% reduction in cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (26,81,82).

In addition to renal effects, some SGLT2 inhibitors and GLP-1 RAs have demonstrated cardiovascular benefits. Namely, in EMPA-REG OUTCOME, CANVAS, LEADER, and SUSTAIN-6, empagliflozin, canagliflozin, liraglutide, and semaglutide, respectively, each reduced cardiovascular

events, evaluated as primary outcomes, compared with placebo (see Section 10 "Cardiovascular Disease and Risk Management," https://doi.org/10.2337/dc21-S010 for further discussion). While the glucose-lowering effects of SGLT2 inhibitors are blunted with eGFR <45 mL/min/1.73 m^2, the renal and cardiovascular benefits were still seen down to eGFR levels of 30 mL/min/1.73 m^2 with no significant change in glucose (26,28,47, 49,56,60,71,78). Most participants with CKD in these trials also had diagnosed ASCVD at baseline, though ~28% of CANVAS participants with CKD did not have diagnosed ASCVD (29).

Based on evidence from the CREDENCE trial and secondary analyses of cardiovascular outcomes trials with SGLT2 inhibitors, cardiovascular and renal events are reduced with SGLT2 inhibitor use in patients down to an eGFR of 30 mL/min/1.73 m^2, independent of glucose-lowering effects (81,82).

While there is clear cardiovascular risk reduction associated with GLP-1 RA use in patients with type 2 diabetes and CKD, the proof of benefit on renal outcome will come with the results of the ongoing FLOW (A Research Study to See How Semaglutide Works Compared with Placebo in People With Type 2 Diabetes and Chronic Kidney Disease) trial with injectable semaglutide (83). As noted above, published data address a limited group of CKD patients, mostly with coexisting ASCVD. Renal events have been examined, however, as both primary and secondary outcomes in published large trials. Also, adverse event profiles of these agents must be considered. Please refer to **Table 9.1** for drug-specific factors, including adverse event information, for these agents. Additional clinical trials focusing on CKD and cardiovascular outcomes in CKD patients are ongoing and will be reported in the next few years.

For patients with type 2 diabetes and CKD, the selection of specific agents may depend on comorbidity and CKD stage. SGLT2 inhibitors may be more useful for patients at high risk of CKD progression (i.e., with albuminuria or a history of documented eGFR loss) (**Fig. 9.1**) because they appear to have large beneficial effects on CKD incidence. The SGLT2 inhibitors empagliflozin and dapagliflozin are approved by the FDA for use with eGFR ≥45 mL/min/1.73 m^2 (though pivotal trials for each included participants with eGFR ≥30 mL/min/1.73 m^2 and demonstrated benefit in subgroups with low eGFR) (28,29,84). Canagliflozin was recently approved to be started down to eGFR levels of 30 mL/min/1.73 m^2. Some GLP-1 RAs may be used with lower eGFR, but most require dose adjustment.

Cardiovascular Disease and Blood Pressure

Hypertension is a strong risk factor for the development and progression of CKD (85). Antihypertensive therapy reduces the risk of albuminuria (86–89), and among patients with type 1 or 2 diabetes with established CKD (eGFR <60 mL/min/1.73 m^2 and UACR ≥300 mg/g Cr), ACE inhibitor or ARB therapy reduces the risk of progression to ESRD (90–92). Moreover, antihypertensive therapy reduces risks of cardiovascular events (86).

Blood pressure levels <140/90 mmHg are generally recommended to reduce CVD mortality and slow CKD progression among all people with diabetes (89). Lower blood pressure targets (e.g., <130/80 mmHg) should be considered for patients based on individual anticipated benefits and risks. Patients with CKD are at increased risk of CKD progression (particularly those with albuminuria) and CVD and therefore may be suitable in some cases for lower blood pressure targets, especially in those with ≥300 mg/g Cr albuminuria.

ACE inhibitors or ARBs are the preferred first-line agent for blood pressure treatment among patients with diabetes, hypertension, eGFR <60 mL/min/1.73 m^2, and UACR ≥300 mg/g Cr because of their proven benefits for prevention of CKD progression (90–93). In general, ACE inhibitors and ARBs are considered to have similar benefits (94,95) and risks. In the setting of lower levels of albuminuria (30–299 mg/g Cr), ACE inhibitor or ARB therapy has been demonstrated to reduce progression to more advanced albuminuria (≥300 mg/g Cr) and cardiovascular events but not progression to ESRD (93,96). While ACE inhibitors or ARBs are often prescribed for high albuminuria without hypertension, outcome trials have not been performed in this setting to determine whether this improves renal outcomes. Moreover, two long-term, double-blind studies demonstrate no renoprotective effect of either ACE inhibitors or ARBs in type 1 and type 2 diabetes among those who were normotensive with or without high albuminuria (formerly microalbuminuria) (97,98).

Absent kidney disease, ACE inhibitors or ARBs are useful to control blood pressure but have not proven superior to alternative classes of antihypertensive therapy, including thiazide-like diuretics and dihydropyridine calcium channel blockers (99). In a trial of people with type 2 diabetes and normal urine albumin excretion, an ARB reduced or suppressed the development of albuminuria but increased the rate of cardiovascular events (100). In a trial of people with type 1 diabetes exhibiting neither albuminuria nor hypertension, ACE inhibitors or ARBs did not prevent the development of diabetic glomerulopathy assessed by kidney biopsy (97). This was further supported by a similar trial in patients with type 2 diabetes (98). *Therefore, ACE inhibitors or ARBs are not recommended for patients without hypertension to prevent the development of CKD.*

Two clinical trials studied the combinations of ACE inhibitors and ARBs and found no benefits on CVD or CKD, and the drug combination had higher adverse event rates (hyperkalemia and/or AKI) (101,102). *Therefore, the combined use of ACE inhibitors and ARBs should be avoided.*

Mineralocorticoid receptor antagonists (spironolactone, eplerenone, and finerenone) in combination with ACE inhibitors or ARBs remain an area of great interest. Mineralocorticoid receptor antagonists are effective for management of resistant hypertension, have been shown to reduce albuminuria in short-term studies of CKD, and may have additional cardiovascular benefits (103–105). There has been, however, an increase in hyperkalemic episodes in those on dual therapy, and larger, longer trials with clinical outcomes are needed before recommending such therapy.

Referral to a Nephrologist

Consider referral to a physician experienced in the care of kidney disease when there is uncertainty about the etiology of kidney disease, for difficult management issues (anemia, secondary hyperparathyroidism, metabolic bone disease, resistant hypertension, or electrolyte disturbances), or when there is advanced kidney disease (eGFR <30 mL/min/1.73 m^2) requiring discussion of renal

replacement therapy for ESRD (2). The threshold for referral may vary depending on the frequency with which a provider encounters patients with diabetes and kidney disease. Consultation with a nephrologist when stage 4 CKD develops (eGFR <30 mL/min/1.73 m^2) has been found to reduce cost, improve quality of care, and delay dialysis (106). However, other specialists and providers should also educate their patients about the progressive nature of CKD, the kidney preservation benefits of proactive treatment of blood pressure and blood glucose, and the potential need for renal replacement therapy.

DIABETIC RETINOPATHY

Recommendations

11.12 Optimize glycemic control to reduce the risk or slow the progression of diabetic retinopathy. **A**

11.13 Optimize blood pressure and serum lipid control to reduce the risk or slow the progression of diabetic retinopathy. **A**

Diabetic retinopathy is a highly specific vascular complication of both type 1 and type 2 diabetes, with prevalence strongly related to both the duration of diabetes and the level of glycemic control (107). Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20–74 years in developed countries. Glaucoma, cataracts, and other disorders of the eye occur earlier and more frequently in people with diabetes.

In addition to diabetes duration, factors that increase the risk of, or are associated with, retinopathy include chronic hyperglycemia (108), nephropathy (109), hypertension (110), and dyslipidemia (111). Intensive diabetes management with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to prevent and/or delay the onset and progression of diabetic retinopathy and potentially improve patient reported visual function (50,112–114).

Several case series and a controlled prospective study suggest that pregnancy in patients with type 1 diabetes may aggravate retinopathy and threaten vision, especially when glycemic control is poor at the time of conception (115,116). Laser photocoagulation surgery can minimize the risk of vision loss (116). However, intervention is not appropriate during pregnancy. This problem often resolves after pregnancy and so does not require treatment.

Screening

Recommendations

11.14 Adults with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes. **B**

11.15 Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of the diabetes diagnosis. **B**

11.16 If there is no evidence of retinopathy for one or more annual eye exams and glycemia is well controlled, then screening every 1–2 years may be considered. If any level of diabetic retinopathy is present, subsequent dilated retinal examinations should be repeated at least annually by an ophthalmologist or optometrist. If retinopathy is progressing or sight-threatening, then examinations will be required more frequently. **B**

11.17 Programs that use retinal photography (with remote reading or use of a validated assessment tool) to improve access to diabetic retinopathy screening can be appropriate screening strategies for diabetic retinopathy. Such programs need to provide pathways for timely referral for a comprehensive eye examination when indicated. **B**

11.18 Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who are pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. **B**

11.19 Eye examinations should occur before pregnancy or in the first trimester in patients with preexisting type 1 or type 2 diabetes, and then patients should be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy. **B**

The preventive effects of therapy and the fact that patients with proliferative diabetic retinopathy (PDR) or macular edema may be asymptomatic provide strong support for screening to detect diabetic retinopathy.

Diabetic retinopathy screening should be performed using validated approaches and methodologies. Youth with type 1 or type 2 diabetes are also at risk for complications and need to be screened for diabetic retinopathy (117). If diabetic retinopathy is evident on screening, prompt referral to an ophthalmologist is recommended. Subsequent examinations for patients with type 1 or type 2 diabetes are generally repeated annually for patients with minimal to no retinopathy. Exams every 1–2 years may be cost-effective after one or more normal eye exams, and in a population with well controlled type 2 diabetes, there was essentially no risk of development of significant retinopathy with a 3-year interval after a normal examination (118). Less frequent intervals have been found in simulated modeling to be potentially effective in screening for diabetic retinopathy in patients without diabetic retinopathy (119). More frequent examinations by the ophthalmologist will be required if retinopathy is progressing.

Retinal photography with remote reading by experts has great potential to provide screening services in areas where qualified eye care professionals are not readily available (112,113). High-quality fundus photographs can detect most clinically significant diabetic retinopathy. Interpretation of the images should be performed by a trained eye care provider. Retinal photography may also enhance efficiency and reduce costs when the expertise of ophthalmologists can be used for more complex examinations and for therapy (120,121). In-person exams are still necessary when the retinal photos are of unacceptable quality and for follow-up if abnormalities are detected. Retinal photos are not a substitute for comprehensive eye exams, which should be performed at least initially and at intervals thereafter as recommended by an eye care professional. Artificial intelligence systems that detect more than

mild diabetic retinopathy and diabetic macular edema authorized for use by the FDA represent an alternative to traditional screening approaches (122). However, the benefits and optimal utilization of this type of screening have yet to be fully determined. Artificial intelligence systems should not be used for patients with known retinopathy, prior retinopathy treatment, or symptoms of vision impairment. Results of eye examinations should be documented and transmitted to the referring health care professional.

Type 1 Diabetes

Because retinopathy is estimated to take at least 5 years to develop after the onset of hyperglycemia, patients with type 1 diabetes should have an initial dilated and comprehensive eye examination within 5 years after the diagnosis of diabetes (123).

Type 2 Diabetes

Patients with type 2 diabetes who may have had years of undiagnosed diabetes and have a significant risk of prevalent diabetic retinopathy at the time of diagnosis should have an initial dilated and comprehensive eye examination at the time of diagnosis.

Pregnancy

Pregnancy is associated with a rapid progression of diabetic retinopathy (124,125). Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. In addition, rapid implementation of intensive glycemic management in the setting of retinopathy is associated with early worsening of retinopathy (116). Women who develop gestational diabetes mellitus do not require eye examinations during pregnancy and do not appear to be at increased risk of developing diabetic retinopathy during pregnancy (126).

Treatment

Recommendations

11.20 Promptly refer patients with any level of macular edema, severe nonproliferative diabetic retinopathy (a precursor of proliferative diabetic retinopathy), or any proliferative diabetic retinopathy to an ophthalmologist who is knowledgeable and experienced in the management of diabetic retinopathy. **A**

11.21 The traditional standard treatment, panretinal laser photocoagulation therapy, is indicated to reduce the risk of vision loss in patients with high-risk proliferative diabetic retinopathy and, in some cases, severe nonproliferative diabetic retinopathy. **A**

11.22 Intravitreous injections of anti–vascular endothelial growth factor are not inferior to traditional panretinal laser photocoagulation and are also indicated to reduce the risk of vision loss in patients with proliferative diabetic retinopathy. **A**

11.23 Intravitreous injections of anti–vascular endothelial growth factor are indicated for central involved diabetic macular edema, which occurs beneath the foveal center and may threaten reading vision. **A**

11.24 The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as aspirin does not increase the risk of retinal hemorrhage. **A**

Two of the main motivations for screening for diabetic retinopathy are to prevent loss of vision and to intervene with treatment when vision loss can be prevented or reversed.

Photocoagulation Surgery

Two large trials, the Diabetic Retinopathy Study (DRS) in patients with PDR and the Early Treatment Diabetic Retinopathy Study (ETDRS) in patients with macular edema, provide the strongest support for the therapeutic benefits of photocoagulation surgery. The DRS (127) showed in 1978 that panretinal photocoagulation surgery reduced the risk of severe vision loss from PDR from 15.9% in untreated eyes to 6.4% in treated eyes with the greatest benefit ratio in those with more advanced baseline disease (disc neovascularization or vitreous hemorrhage). In 1985, the ETDRS also verified the benefits of panretinal photocoagulation for high-risk PDR and in older-onset patients with severe nonproliferative diabetic retinopathy or less-than-high-risk PDR. Panretinal laser photocoagulation is still commonly used to manage complications of diabetic retinopathy that involve retinal neovascularization and its complications.

Anti–Vascular Endothelial Growth Factor Treatment

Recent data from the Diabetic Retinopathy Clinical Research Network and others demonstrate that intravitreal injections of anti–vascular endothelial growth factor (anti-VEGF) agent, specifically ranibizumab, resulted in visual acuity outcomes that were not inferior to those observed in patients treated with panretinal laser at 2 years of follow-up (128). In addition, it was observed that patients treated with ranibizumab tended to have less peripheral visual field loss, fewer vitrectomy surgeries for secondary complications from their proliferative disease, and a lower risk of developing diabetic macular edema. However, a potential drawback in using anti-VEGF therapy to manage proliferative disease is that patients were required to have a greater number of visits and received a greater number of treatments than is typically required for management with panretinal laser, which may not be optimal for some patients. Other emerging therapies for retinopathy that may use sustained intravitreal delivery of pharmacologic agents are currently under investigation. The FDA approved ranibizumab for the treatment of diabetic retinopathy in 2017.

While the ETDRS (129) established the benefit of focal laser photocoagulation surgery in eyes with clinically significant macular edema (defined as retinal edema located at or within 500 μm of the center of the macula), current data from well-designed clinical trials demonstrate that intravitreal anti-VEGF agents provide a more effective treatment regimen for central-involved diabetic macular edema than monotherapy or even combination therapy with a laser (130,131). There are currently three anti-VEGF agents commonly used to treat eyes with central-involved diabetic macular edema—bevacizumab, ranibizumab, and aflibercept (107).

In both the DRS and the ETDRS, laser photocoagulation surgery was beneficial in reducing the risk of further visual loss in affected patients but generally not beneficial in reversing already diminished acuity. Anti-VEGF therapy improves vision and has replaced the need for laser photocoagulation in the vast majority of patients

with diabetic macular edema (132). Most patients require near-monthly administration of intravitreal therapy with anti-VEGF agents during the first 12 months of treatment, with fewer injections needed in subsequent years to maintain remission from central-involved diabetic macular edema.

Adjunctive Therapy

Lowering blood pressure has been shown to decrease retinopathy progression, although tight targets (systolic blood pressure <120 mmHg) do not impart additional benefit (113). ACE inhibitors and ARBs are both effective treatments in diabetic retinopathy (133). In patients with dyslipidemia, retinopathy progression may be slowed by the addition of fenofibrate, particularly with very mild nonproliferative diabetic retinopathy at baseline (111,134).

NEUROPATHY

Screening

Recommendations

11.25 All patients should be assessed for diabetic peripheral neuropathy starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter. **B**

11.26 Assessment for distal symmetric polyneuropathy should include a careful history and assessment of either temperature or pinprick sensation (small fiber function) and vibration sensation using a 128-Hz tuning fork (for large-fiber function). All patients should have annual 10-g monofilament testing to identify feet at risk for ulceration and amputation. **B**

11.27 Symptoms and signs of autonomic neuropathy should be assessed in patients with microvascular complications. **E**

The diabetic neuropathies are a heterogeneous group of disorders with diverse clinical manifestations. The early recognition and appropriate management of neuropathy in the patient with diabetes is important.

1. Diabetic neuropathy is a diagnosis of exclusion. Nondiabetic neuropathies may be present in patients with diabetes and may be treatable.
2. Up to 50% of diabetic peripheral neuropathy may be a symptomatic. If not recognized and if preventive foot care is not implemented, patients are at risk for injuries to their insensate feet.
3. Recognition and treatment of autonomic neuropathy may improve symptoms, reduce sequelae, and improve quality of life.

Specific treatment for the underlying nerve damage, other than improved glycemic control, is currently not available. Glycemic control can effectively prevent diabetic peripheral neuropathy (DPN) and cardiac autonomic neuropathy (CAN) in type 1 diabetes (135,136) and may modestly slow their progression in type 2 diabetes (52), but it does not reverse neuronal loss. Therapeutic strategies (pharmacologic and nonpharmacologic) for the relief of painful DPN and symptoms of autonomic neuropathy can potentially reduce pain (137) and improve quality of life.

Diagnosis

Diabetic Peripheral Neuropathy

Patients with type 1 diabetes for 5 or more years and all patients with type 2 diabetes should be assessed annually for DPN using the medical history and simple clinical tests (137). Symptoms vary according to the class of sensory fibers involved. The most common early symptoms are induced by the involvement of small fibers and include pain and dysesthesia (unpleasant sensations of burning and tingling). The involvement of large fibers may cause numbness and loss of protective sensation (LOPS). LOPS indicates the presence of distal sensorimotor polyneuropathy and is a risk factor for diabetic foot ulceration. The following clinical tests may be used to assess small- and large-fiber function and protective sensation:

1. Small-fiber function: pinprick and temperature sensation
2. Large-fiber function: vibration perception and 10-g monofilament
3. Protective sensation: 10-g monofilament

These tests not only screen for the presence of dysfunction but also predict future risk of complications. Electrophysiological testing or referral to a neurologist is rarely needed, except in situations where the clinical features are atypical or the diagnosis is unclear.

In all patients with diabetes and DPN, causes of neuropathy other than diabetes should be considered, including toxins (e.g., alcohol), neurotoxic medications (e.g., chemotherapy), vitamin B12 deficiency, hypothyroidism, renal disease, malignancies (e.g., multiple myeloma, bronchogenic carcinoma), infections (e.g., HIV), chronic inflammatory demyelinating neuropathy, inherited neuropathies, and vasculitis (138). See the American Diabetes Association (ADA) position statement "Diabetic Neuropathy" for more details (137).

Diabetic Autonomic Neuropathy

The symptoms and signs of autonomic neuropathy should be elicited carefully during the history and physical examination. Major clinical manifestations of diabetic autonomic neuropathy include hypoglycemia unawareness, resting tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, neurogenic bladder, and sudomotor dysfunction with either increased or decreased sweating.

Cardiac Autonomic Neuropathy. CAN is associated with mortality independently of other cardiovascular risk factors (139,140). In its early stages, CAN may be completely asymptomatic and detected only by decreased heart rate variability with deep breathing. Advanced disease may be associated with resting tachycardia (>100 bpm) and orthostatic hypotension (a fall in systolic or diastolic blood pressure by >20 mmHg or >10 mmHg, respectively, upon standing without an appropriate increase in heart rate). CAN treatment is generally focused on alleviating symptoms.

Gastrointestinal Neuropathies. Gastrointestinal neuropathies may involve any portion of the gastrointestinal tract with manifestations including esophageal dysmotility, gastroparesis, constipation, diarrhea, and fecal incontinence. Gastroparesis should be suspected in individuals with erratic glycemic control or with upper gastrointestinal symptoms without another identified cause. Exclusion of organic causes of gastric outlet obstruction or peptic ulcer disease (with esophagogastroduodenoscopy or a barium study of the stomach) is needed before considering a diagnosis of or specialized testing for gastroparesis. The diagnostic

gold standard for gastroparesis is the measurement of gastric emptying with scintigraphy of digestible solids at 15-min intervals for 4 h after food intake. The use of ^{13}C octanoic acid breath test is emerging as a viable alternative.

Genitourinary Disturbances. Diabetic autonomic neuropathy may also cause genitourinary disturbances, including sexual dysfunction and bladder dysfunction. In men, diabetic autonomic neuropathy may cause erectile dysfunction and/or retrograde ejaculation (137). Female sexual dysfunction occurs more frequently in those with diabetes and presents as decreased sexual desire, increased pain during intercourse, decreased sexual arousal, and inadequate lubrication (141). Lower urinary tract symptoms manifest as urinary incontinence and bladder dysfunction (nocturia, frequent urination, urination urgency, and weak urinary stream). Evaluation of bladder function should be performed for individuals with diabetes who have recurrent urinary tract infections, pyelonephritis, incontinence, or a palpable bladder.

Treatment

Recommendations

11.28 Optimize glucose control to prevent or delay the development of neuropathy in patients with type 1 diabetes **A** and to slow the progression of neuropathy in patients with type 2 diabetes. **B**

11.29 Assess and treat patients to reduce pain related to diabetic peripheral neuropathy **B** and symptoms of autonomic neuropathy and to improve quality of life. **E**

11.30 Pregabalin, duloxetine, or gabapentin are recommended as initial pharmacologic treatments for neuropathic pain in diabetes. **A**

Glycemic Control

Near-normal glycemic control, implemented early in the course of diabetes, has been shown to effectively delay or prevent the development of DPN and CAN in patients with type 1 diabetes (142–145). Although the evidence for the benefit of near-normal glycemic control is not as strong for type 2 diabetes, some studies have demonstrated a modest slowing of progression without reversal of neuronal loss (52,146). Specific glucose-lowering strategies may have different effects. In a post hoc analysis, participants, particularly men, in the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial treated with insulin sensitizers had a lower incidence of distal symmetric polyneuropathy over 4 years than those treated with insulin/sulfonylurea (147).

Neuropathic Pain

Neuropathic pain can be severe and can impact quality of life, limit mobility, and contribute to depression and social dysfunction (148). No compelling evidence exists in support of glycemic control or lifestyle management as therapies for neuropathic pain in diabetes or prediabetes, which leaves only pharmaceutical interventions (149).

Pregabalin and duloxetine have received regulatory approval by the FDA, Health Canada, and the European Medicines Agency for the treatment of neuropathic pain in diabetes. The opioid tapentadol has regulatory approval in the U.S. and Canada, but the evidence of its use is weaker (150). Comparative effectiveness studies and trials that include quality-of-life outcomes are rare, so treatment decisions must consider each patient's presentation and comorbidities and often follow a trial-and-error approach. Given the range of partially effective treatment options, a tailored and stepwise pharmacologic strategy with careful attention to relative symptom improvement, medication adherence, and medication side effects is recommended to achieve pain reduction and improve quality of life (151–153).

Pregabalin, a calcium channel α2-δ subunit ligand, is the most extensively studied drug for DPN. The majority of studies testing pregabalin have reported favorable effects on the proportion of participants with at least 30–50% improvement in pain (150,152,154–157). However, not all trials with pregabalin have been positive (150,152,158,159), especially when treating patients with advanced refractory DPN (156). Adverse effects may be more severe in older patients (160) and may be attenuated by lower starting doses and more gradual titration. The related drug, *gabapentin,* has also shown efficacy for pain control in diabetic neuropathy and may be less expensive, although it is not FDA approved for this indication (161).

Duloxetine is a selective norepinephrine and serotonin reuptake inhibitor. Doses of 60 and 120 mg/day showed efficacy in the treatment of pain associated with DPN in multicenter randomized trials, although some of these had high drop-out rates (150,152,157,159). Duloxetine also appeared to improve neuropathy-related quality of life (162). In longer-term studies, a small increase in A1C was reported in people with diabetes treated with duloxetine compared with placebo (163). Adverse events may be more severe in older people but may be attenuated with lower doses and slower titration of duloxetine.

Tapentadol is a centrally acting opioid analgesic that exerts its analgesic effects through both μ-opioid receptor agonism and noradrenaline reuptake inhibition. Extended-release tapentadol was approved by the FDA for the treatment of neuropathic pain associated with diabetes based on data from two multicenter clinical trials in which participants titrated to an optimal dose of tapentadol were randomly assigned to continue that dose or switch to placebo (164,165). However, both used a design enriched for patients who responded to tapentadol and therefore their results are not generalizable. A recent systematic review and meta-analysis by the Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain found the evidence supporting the effectiveness of tapentadol in reducing neuropathic pain to be inconclusive (150). Therefore, given the high risk for addiction and safety concerns compared with the relatively modest pain reduction, the use of extended-release tapentadol is not generally recommended as a first-or second-line therapy. The use of any opioids for management of chronic neuropathic pain carries the risk of addiction and should be avoided.

Tricyclic antidepressants, venlafaxine, carbamazepine, and topical capsaicin, although not approved for the treatment of painful DPN, may be effective and considered for the treatment of painful DPN (137,150,152).

Orthostatic Hypotension

Treating orthostatic hypotension is challenging. The therapeutic goal is to minimize postural symptoms rather than to restore normotension. Most patients require both nonpharmacologic measures

(e.g., ensuring adequate salt intake, avoiding medications that aggravate hypotension, or using compressive garments over the legs and abdomen) and pharmacologic measures. Physical activity and exercise should be encouraged to avoid deconditioning, which is known to exacerbate orthostatic intolerance, and volume repletion with fluids and salt is critical. There have been clinical studies that assessed the impact of an approach incorporating the aforementioned nonpharmacologic measures. Additionally, supine blood pressure tends to be much higher in these patients, often requiring treatment of blood pressure at bedtime with shorter-acting drugs that also affect baroreceptor activity such as guanfacine or clonidine, shorter-acting calcium blockers (e.g., isradipine), or shorter-acting β-blockers such as atenolol or metoprolol tartrate. Alternatives can include enalapril if patients are unable to tolerate preferred agents (166–168). Midodrine and droxidopa are approved by the FDA for the treatment of orthostatic hypotension.

Gastroparesis

Treatment for diabetic gastroparesis may be very challenging. A low-fiber, low-fat eating plan provided in small frequent meals with a greater proportion of liquid calories may be useful (169–171). In addition, foods with small particle size may improve key symptoms (172). Withdrawing drugs with adverse effects on gastrointestinal motility, including opioids, anticholinergics, tricyclic antidepressants, GLP-1 RAs, pramlintide, and possibly dipeptidyl peptidase 4 inhibitors, may also improve intestinal motility (169,173). In cases of severe gastroparesis, pharmacologic interventions are needed. Only metoclopramide, a prokinetic agent, is approved by the FDA for the treatment of gastroparesis. However, the level of evidence regarding the benefits of metoclopramide for the management of gastroparesis is weak, and given the risk for serious adverse effects (extrapyramidal signs such as acute dystonic reactions, drug-induced parkinsonism, akathisia, and tardive dyskinesia), its use in the treatment of gastroparesis beyond 12 weeks is no longer recommended by the FDA or the European Medicines Agency. It should be reserved for severe cases that are unresponsive to other therapies (173). Other treatment options include domperidone (available outside of the U.S.) and erythromycin, which is only effective for short-term use due to tachyphylaxis (174,175). Gastric electrical stimulation using a surgically implantable device has received approval from the FDA, although its efficacy is variable and use is limited to patients with severe symptoms that are refractory to other treatments (176).

Erectile Dysfunction

In addition to treatment of hypogonadism if present, treatments for erectile dysfunction may include phosphodiesterase type 5 inhibitors, intracorporeal or intraurethral prostaglandins, vacuum devices, or penile prostheses. As with DPN treatments, these interventions do not change the underlying pathology and natural history of the disease process but may improve the patient's quality of life.

FOOT CARE

Recommendations

11.31 Perform a comprehensive foot evaluation at least annually to identify risk factors for ulcers and amputations. **B**

11.32 Patients with evidence of sensory loss or prior ulceration or amputation should have their feet inspected at every visit. **B**

11.33 Obtain a prior history of ulceration, amputation, Charcot foot, angioplasty or vascular surgery, cigarette smoking, retinopathy, and renal disease and assess current symptoms of neuropathy (pain, burning, numbness) and vascular disease (leg fatigue, claudication). **B**

11.34 The examination should include inspection of the skin, assessment of foot deformities, neurological assessment (10-g monofilament testing with at least one other assessment: pinprick, temperature, vibration), and vascular assessment including pulses in the legs and feet. **B**

11.35 Patients with symptoms of claudication or decreased or absent pedal pulses should be referred for ankle-brachial index and for further vascular assessment as appropriate. **C**

11.36 A multidisciplinary approach is recommended for individuals with foot ulcers and high-risk feet (e.g., dialysis patients and those with Charcot foot or prior ulcers or amputation). **B**

11.37 Refer patients who smoke or who have histories of prior lower-extremity complications, loss of protective sensation, structural abnormalities, or peripheral arterial disease to foot care specialists for ongoing preventive care and lifelong surveillance. **C**

11.38 Provide general preventive foot self-care education to all patients with diabetes. **B**

11.39 The use of specialized therapeutic footwear is recommended for high-risk patients with diabetes including those with severe neuropathy, foot deformities, ulcers, callous formation, poor peripheral circulation, or history of amputation. **B**

Foot ulcers and amputation, which are consequences of diabetic neuropathy and/or peripheral arterial disease (PAD), are common and represent major causes of morbidity and mortality in people with diabetes.

Early recognition and treatment of patients with diabetes and feet at risk for ulcers and amputations can delay or prevent adverse outcomes.

The risk of ulcers or amputations is increased in people who have the following risk factors:

- Poor glycemic control
- Peripheral neuropathy with LOPS
- Cigarette smoking
- Foot deformities
- Preulcerative callus or corn
- PAD
- History of foot ulcer
- Amputation
- Visual impairment
- CKD (especially patients on dialysis)

Moreover, there is good-quality evidence to support use of appropriate therapeutic footwear with demonstrated pressure relief that is worn by the patient to prevent plantar foot ulcer recurrence or worsening. However, there is very little evidence for the use of interventions to prevent a first foot ulcer or heal ischemic, infected, nonplantar, or proximal foot

ulcers (177). Studies on specific types of footwear demonstrated that shape and barefoot plantar pressure–based orthoses were more effective in reducing submetatarsal head plantar ulcer recurrence than current standard-of-care orthoses (178).

Clinicians are encouraged to review ADA screening recommendations for further details and practical descriptions of how to perform components of the comprehensive foot examination (179).

Evaluation for Loss of Protective Sensation

All adults with diabetes should undergo a comprehensive foot evaluation at least annually. Detailed foot assessments may occur more frequently in patients with histories of ulcers or amputations, foot deformities, insensate feet, and PAD (180,181). To assess risk, clinicians should ask about history of foot ulcers or amputation, neuropathic and peripheral vascular symptoms, impaired vision, renal disease, tobacco use, and foot care practices. A general inspection of skin integrity and musculoskeletal deformities should be performed. Vascular assessment should include inspection and palpation of pedal pulses.

The neurological exam performed as part of the foot examination is designed to identify LOPS rather than early neuropathy. The 10-g monofilament is the most useful test to diagnose LOPS. Ideally, the 10-g monofilament test should be performed with at least one other assessment (pinprick, temperature or vibration sensation using a 128-Hz tuning fork, or ankle reflexes). Absent monofilament sensation suggests LOPS, while at least two normal tests (and no abnormal test) rules out LOPS.

Evaluation for Peripheral Arterial Disease

Initial screening for PAD should include a history of decreased walking speed, leg fatigue, claudication, and an assessment of the pedal pulses. Ankle-brachial index testing should be performed in patients with symptoms or signs of PAD. Additionally, at least one of the following tests in a patient with a diabetic foot ulcer and PAD should be performed: skin perfusion pressure ($\geq$40 mmHg), toe pressure ($\geq$30 mmHg), or transcutaneous oxygen pressure ($TcPO_2$ $\geq$25 mmHg). Urgent vascular imaging and revascularization should be considered in a patient with a diabetic foot ulcer and an ankle pressure (ankle-brachial index) $<$50 mmHg, toe pressure $<$30 mmHg, or a $TcPO_2$ $<$25 mmHg (137,182).

Patient Education

All patients with diabetes and particularly those with high-risk foot conditions (history of ulcer or amputation, deformity, LOPS, or PAD) and their families should be provided general education about risk factors and appropriate management (183). Patients at risk should understand the implications of foot deformities, LOPS, and PAD; the proper care of the foot, including nail and skin care; and the importance of foot monitoring on a daily basis. Patients with LOPS should be educated on ways to substitute other sensory modalities (palpation or visual inspection using an unbreakable mirror) for surveillance of early foot problems.

The selection of appropriate footwear and footwear behaviors at home should also be discussed. Patients' understanding of these issues and their physical ability to conduct proper foot surveillance and care should be assessed. Patients with visual difficulties, physical constraints preventing movement, or cognitive problems that impair their ability to assess the condition of the foot and to institute appropriate responses will need other people, such as family members, to assist with their care.

Treatment

People with neuropathy or evidence of increased plantar pressures (e.g., erythema, warmth, or calluses) may be adequately managed with well-fitted walking shoes or athletic shoes that cushion the feet and redistribute pressure. People with bony deformities (e.g., hammertoes, prominent metatarsal heads, bunions) may need extra wide or deep shoes. People with bony deformities, including Charcot foot, who cannot be accommodated with commercial therapeutic footwear, will require custom-molded shoes. Special consideration and a thorough workup should be performed when patients with neuropathy present with the acute onset of a red, hot, swollen foot or ankle, and Charcot neuroarthropathy should be excluded. Early diagnosis and treatment of Charcot neuroarthropathy is the best way to prevent deformities that increase the risk of ulceration and amputation. The routine prescription of therapeutic footwear is not generally recommended. However, patients should be provided adequate information to aid in selection of appropriate footwear. General footwear recommendations include a broad and square toe box, laces with three or four eyes per side, padded tongue, quality lightweight materials, and sufficient size to accommodate a cushioned insole. Use of custom therapeutic footwear can help reduce the risk of future foot ulcers in high-risk patients (180,183).

Most diabetic foot infections are polymicrobial, with aerobic gram-positive cocci. Staphylococci and streptococci are the most common causative organisms. Wounds without evidence of soft tissue or bone infection do not require antibiotic therapy. Empiric antibiotic therapy can be narrowly targeted at gram-positive cocci in many patients with acute infections, but those at risk for infection with antibiotic-resistant organisms or with chronic, previously treated, or severe infections require broader-spectrum regimens and should be referred to specialized care centers (184). Foot ulcers and wound care may require care by a podiatrist, orthopedic or vascular surgeon, or rehabilitation specialist experienced in the management of individuals with diabetes (184).

Hyperbaric oxygen therapy (HBOT) in patients with diabetic foot ulcers has mixed evidence supporting its use as an adjunctive treatment to enhance wound healing and prevent amputation (185–188). A well-conducted randomized controlled study performed in 103 patients found that HBOT did not reduce the indication for amputation or facilitate wound healing compared with comprehensive wound care in patients with chronic diabetic foot ulcers (189). Moreover, a systematic review by the International Working Group on the Diabetic Foot of interventions to improve the healing of chronic diabetic foot ulcers concluded that analysis of the evidence continues to present methodological challenges as randomized controlled studies remain few, with a majority being of poor quality (186). Thus, HBOT does not have a significant effect on health-related quality of life in patients with diabetic foot ulcers (190,191). A recent review concluded that the evidence to date remains inconclusive regarding the clinical and cost-effectiveness of HBOT as an adjunctive

treatment to standard wound care for diabetic foot ulcers (192). Results from the Dutch DAMOCLES (Does Applying More Oxygen Cure Lower Extremity Sores?) trial demonstrated that HBOT in patients with diabetes and ischemic wounds did not significantly improve complete wound healing and limb salvage (193). While the Centers for Medicare & Medicaid Services currently covers HBOT for diabetic foot ulcers that have failed a standard course of wound therapy when there are no measurable signs of healing for at least 30 consecutive days (194), given the data not supporting an effect, such an approach is not currently warranted. HBOT should be a topic of shared decision-making before treatment is considered for selected patients with diabetic foot ulcers (194).

References

1. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Diabetes Care 2014; 37:2864–2883
2. National Kidney Foundation. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int suppl 2013;3:1–150
3. Afkarian M, Zelnick LR, Hall YN, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. JAMA 2016; 316:602–610
4. de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. JAMA 2011;305:2532–2539
5. de Boer IH; DCCT/EDIC Research Group. Kidney disease and related findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. Diabetes Care 2014;37:24–30
6. United States Renal Data System. *Annual Data Report: Epidemiology of Kidney Disease in the United States*. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2016
7. Fox CS, Matsushita K, Woodward M, et al.; Chronic Kidney Disease Prognosis Consortium. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet 2012;380:1662–1673
8. Yarnoff BO, Hoerger TJ, Simpson SK, et al.; Centers for Disease Control and Prevention CKD Initiative. The cost-effectiveness of using chronic kidney disease risk scores to screen for early-stage chronic kidney disease. BMC Nephrol 2017; 18:85
9. Afkarian M, Sachs MC, Kestenbaum B, et al. Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol 2013;24:302–308
10. Groop P-H, Thomas MC, Moran JL, et al.; FinnDiane Study Group. The presence and severity of chronic kidney disease predicts all-cause mortality in type 1 diabetes. Diabetes 2009;58: 1651–1658
11. Gomes MB, Gonçalves MF. Is there a physiological variability for albumin excretion rate? Study in patients with diabetes type 1 and non-diabetic individuals. Clin Chim Acta 2001;304: 117–123
12. Naresh CN, Hayen A, Weening A, Craig JC, Chadban SJ. Day-to-day variability in spot urine albumin-creatinine ratio. Am J Kidney Dis 2013; 62:1095–1101
13. Tankeu AT, Kaze FF, Noubiap JJ, Chelo D, Dehayem MY, Sobngwi E. Exercise-induced albuminuria and circadian blood pressure abnormalities in type 2 diabetes. World J Nephrol 2017; 6:209–216
14. Delanaye P, Glassock RJ, Pottel H, Rule AD. An age-calibrated definition of chronic kidney disease: rationale and benefits. Clin Biochem Rev 2016;37:17–26
15. Kramer HJ, Nguyen QD, Curhan G, Hsu C-Y. Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. JAMA 2003;289:3273–3277
16. Molitch ME, Steffes M, Sun W, et al.; Epidemiology of Diabetes Interventions and Complications Study Group. Development and progression of renal insufficiency with and without albuminuria in adults with type 1 diabetes in the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications Study. Diabetes Care 2010;33: 1536–1543
17. He F, Xia X, Wu XF, Yu XQ, Huang FX. Diabetic retinopathy in predicting diabetic nephropathy in patients with type 2 diabetes and renal disease: a meta-analysis. Diabetologia 2013; 56:457–466
18. Levey AS, Coresh J, Balk E, et al.; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med 2003;139:137–147
19. Flynn C, Bakris GL. Noninsulin glucose-lowering agents for the treatment of patients on dialysis. Nat Rev Nephrol 2013;9:147–153
20. Matzke GR, Aronoff GR, Atkinson AJ Jr, et al. Drug dosing consideration in patients with acute and chronic kidney disease-a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2011;80:1122–1137
21. Coresh J, Turin TC, Matsushita K, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA 2014;311:2518–2531
22. Vassalotti JA, Centor R, Turner BJ, Greer RC, Choi M, Sequist TD; National Kidney Foundation Kidney Disease Outcomes Quality Initiative. Practical approach to detection and management of chronic kidney disease for the primary care clinician. Am J Med 2016;129:153–162.e7
23. Zhou J, Liu Y, Tang Y, et al. A comparison of RIFLE, AKIN, KDIGO, and Cys-C criteria for the definition of acute kidney injury in critically ill patients. Int Urol Nephrol 2016;48:125–132
24. Hoste EAJ, Kellum JA, Selby NM, et al. Global epidemiology and outcomes of acute kidney injury. Nat Rev Nephrol 2018;14:607–625
25. James MT, Grams ME, Woodward M, et al.; CKD Prognosis Consortium. A meta-analysis of the association of estimated GFR, albuminuria, diabetes mellitus, and hypertension with acute kidney injury. Am J Kidney Dis 2015;66: 602–612
26. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380: 2295–2306
27. Nadkarni GN, Ferrandino R, Chang A, et al. Acute kidney injury in patients on SGLT2 inhibitors: a propensity-matched analysis. Diabetes Care 2017;40:1479–1485
28. Wanner C, Inzucchi SE, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323–334
29. Neuen BL, Ohkuma T, Neal B, et al. Cardiovascular and renal outcomes with canagliflozin according to baseline kidney function: data from the CANVAS Program. Circulation 2018;138: 1537–1550
30. Thakar CV, Christianson A, Himmelfarb J, Leonard AC. Acute kidney injury episodes and chronic kidney disease risk in diabetes mellitus. Clin J Am Soc Nephrol 2011;6:2567–2572
31. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med 2000;160:685–693
32. Beddhu S, Greene T, Boucher R, et al. Intensive systolic blood pressure control and incident chronic kidney disease in people with and without diabetes mellitus: secondary analyses of two randomised controlled trials. Lancet Diabetes Endocrinol 2018;6:555–563
33. Collard D, Brouwer TF, Peters RJG, Vogt L, van den Born BH. Creatinine rise during blood pressure therapy and the risk of adverse clinical outcomes in patients with type 2 diabetes mellitus. Hypertension 2018;72:1337–1344
34. Malhotra R, Craven T, Ambrosius WT, et al.; SPRINT Research Group. Effects of intensive blood pressure lowering on kidney tubule injury in CKD: a longitudinal subgroup analysis in SPRINT. Am J Kidney Dis 2019;73:21–30
35. Qiao Y, Shin J-I, Chen TK, et al. Association between renin-angiotensin system blockade discontinuation and all-cause mortality among persons with low estimated glomerular filtration rate. JAMA Intern Med 2020;180:718–726
36. Collard D, Brouwer TF, Olde Engberink RHG, Zwinderman AH, Vogt L, van den Born BH. Initial estimated glomerular filtration rate decline and long-term renal function during intensive antihypertensive therapy: a post hoc analysis of the SPRINT and ACCORD-BP randomized controlled trials. Hypertension 2020;75:1205–1212
37. Hughes-Austin JM, Rifkin DE, Beben T, et al. The relation of serum potassium concentration with cardiovascular events and mortality in community-living individuals. Clin J Am Soc Nephrol 2017;12:245–252
38. Bandak G, Sang Y, Gasparini A, et al. Hyperkalemia after initiating renin-angiotensin system blockade: the Stockholm Creatinine Measurements (SCREAM) project. J Am Heart Assoc 2017; 6:e005428
39. Nilsson E, Gasparini A, Ärnlöv J, et al. Incidence and determinants of hyperkalemia and hypokalemia in a large healthcare system. Int J Cardiol 2017;245:277–284
40. de Boer IH, Gao X, Cleary PA, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications

(DCCT/EDIC) Research Group. Albuminuria changes and cardiovascular and renal outcomes in type 1 diabetes: the DCCT/EDIC study. Clin J Am Soc Nephrol 2016;11:1969–1977
41. Sumida K, Molnar MZ, Potukuchi PK, et al. Changes in albuminuria and subsequent risk of incident kidney disease. Clin J Am Soc Nephrol 2017;12:1941–1949
42. Inker LA, Grams ME, Levey AS, et al.; CKD Prognosis Consortium. Relationship of estimated GFR and albuminuria to concurrent laboratory abnormalities: an individual participant data meta-analysis in a global consortium. Am J Kidney Dis 2019;73:206–217
43. Klahr S, Levey AS, Beck GJ, et al.; Modification of Diet in Renal Disease Study Group. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. N Engl J Med 1994;330:877–884
44. Mills KT, Chen J, Yang W, et al.; Chronic Renal Insufficiency Cohort (CRIC) Study Investigators. Sodium excretion and the risk of cardiovascular disease in patients with chronic kidney disease. JAMA 2016;315:2200–2210
45. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2018;71:1269–1324
46. Murray DP, Young L, Waller J, et al. Is dietary protein intake predictive of 1-year mortality in dialysis patients? Am J Med Sci 2018;356:234–243
47. DCCT/EDIC research group. Effect of intensive diabetes treatment on albuminuria in type 1 diabetes: long-term follow-up of the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications study. Lancet Diabetes Endocrinol 2014;2:793–800
48. de Boer IH, Sun W, Cleary PA, et al.; DCCT/EDIC Research Group. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. N Engl J Med 2011;365:2366–2376
49. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854–865
50. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853
51. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572
52. Ismail-Beigi F, Craven T, Banerji MA, et al.; ACCORD trial group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010;376:419–430
53. Zoungas S, Chalmers J, Neal B, et al.; ADVANCE-ON Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. N Engl J Med 2014;371:1392–1406
54. Zoungas S, Arima H, Gerstein HC, et al.; Collaborators on Trials of Lowering Glucose (CONTROL) group. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. Lancet Diabetes Endocrinol 2017;5:431–437
55. Agrawal L, Azad N, Bahn GD, et al.; VADT Study Group. Long-term follow-up of intensive glycaemic control on renal outcomes in the Veterans Affairs Diabetes Trial (VADT). Diabetologia 2018;61:295–299
56. Miller ME, Bonds DE, Gerstein HC, et al.; ACCORD Investigators. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. BMJ 2010;340:b5444
57. Papademetriou V, Lovato L, Doumas M, et al.; ACCORD Study Group. Chronic kidney disease and intensive glycemic control increase cardiovascular risk in patients with type 2 diabetes. Kidney Int 2015;87:649–659
58. Perkovic V, Heerspink HL, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive glucose control improves kidney outcomes in patients with type 2 diabetes. Kidney Int 2013;83:517–523
59. Wong MG, Perkovic V, Chalmers J, et al.; ADVANCE-ON Collaborative Group. Long-term benefits of intensive glucose control for preventing end-stage kidney disease: ADVANCE-ON. Diabetes Care 2016;39:694–700
60. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. Am J Kidney Dis 2012;60:850–886
61. Cherney DZI, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation 2014;129:587–597
62. Heerspink HJL, Desai M, Jardine M, Balis D, Meininger G, Perkovic V. Canagliflozin slows progression of renal function decline independently of glycemic effects. J Am Soc Nephrol 2017;28:368–375
63. Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–657
64. Zelniker TA, Braunwald E. Cardiac and renal effects of sodium-glucose co-transporter 2 inhibitors in diabetes: JACC state-of-the-art review. J Am Coll Cardiol 2018;72:1845–1855
65. Woods TC, Satou R, Miyata K, et al. Canagliflozin prevents intrarenal angiotensinogen augmentation and mitigates kidney injury and hypertension in mouse model of type 2 diabetes mellitus. Am J Nephrol 2019;49:331–342
66. Heerspink HJL, Perco P, Mulder S, et al. Canagliflozin reduces inflammation and fibrosis biomarkers: a potential mechanism of action for beneficial effects of SGLT2 inhibitors in diabetic kidney disease. Diabetologia 2019;62:1154–1166
67. Yaribeygi H, Butler AE, Atkin SL, Katsiki N, Sahebkar A. Sodium-glucose cotransporter 2 inhibitors and inflammation in chronic kidney disease: possible molecular pathways. J Cell Physiol 2018;234:223–230
68. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–322
69. Cooper ME, Perkovic V, McGill JB, et al. Kidney disease end points in a pooled analysis of individual patient-level data from a large clinical trials program of the dipeptidyl peptidase 4 inhibitor linagliptin in type 2 diabetes. Am J Kidney Dis 2015;66:441–449
70. Mann JFE, Ørsted DD, Brown-Frandsen K, et al.; LEADER Steering Committee and Investigators. Liraglutide and renal outcomes in type 2 diabetes. N Engl J Med 2017;377:839–848
71. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–1844
72. Karter AJ, Warton EM, Lipska KJ, et al. Development and validation of a tool to identify patients with type 2 diabetes at high risk of hypoglycemia-related emergency department or hospital use. JAMA Intern Med 2017;177:1461–1470
73. Moen MF, Zhan M, Hsu VD, et al. Frequency of hypoglycemia and its significance in chronic kidney disease. Clin J Am Soc Nephrol 2009;4:1121–1127
74. U.S. Food and Drug Administration. FDA drug safety communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function, 2016. Accessed 11 August 2020. Available from http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm
75. Lalau J-D, Kajbaf F, Bennis Y, Hurtel-Lemaire A-S, Belpaire F, De Broe ME. Metformin treatment in patients with type 2 diabetes and chronic kidney disease stages 3A, 3B, or 4. Diabetes Care 2018;41:547–553
76. Chu PY, Hackstadt AJ, Chipman J, et al. Hospitalization for lactic acidosis among patients with reduced kidney function treated with metformin or sulfonylureas. Diabetes Care 2020;43:1462–1470
77. Zelniker TA, Wiviott SD, Raz I, et al. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus. Circulation 2019;139:2022–2031
78. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128
79. Mahaffey KW, Neal B, Perkovic V, et al.; CANVAS Program Collaborative Group. Canagliflozin for primary and secondary prevention of cardiovascular events: results from the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). Circulation 2018;137:323–334
80. Jardine MJ, Mahaffey KW, Neal B, et al.; CREDENCE study investigators. The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study rationale, design, and baseline characteristics. Am J Nephrol 2017;46:462–472

81. Mahaffey KW, Jardine MJ, Bompoint S, et al. Canagliflozin and cardiovascular and renal outcomes in type 2 diabetes mellitus and chronic kidney disease in primary and secondary cardiovascular prevention groups. Circulation 2019; 140:739–750
82. Bakris GL. Major advancements in slowing diabetic kidney disease progression: focus on SGLT2 inhibitors. Am J Kidney Dis 2019;74:573–575
83. Novo Nordisk A/S. A research study to see how semaglutide works compared to placebo in people with type 2 diabetes and chronic kidney disease (FLOW). In: ClinicalTrials.gov. Bethesda, MD, National Library of Medicine, 2019. Accessed 11 August 2020. Available from https://clinicaltrials.gov/ct2/show/NCT03819153
84. Franki, L. FDA approves label extension for dapagliflozin. Accessed 11 August 2020. Available from https://www.mdedge.com/endocrinology/article/195314/diabetes/fda-approves-label-extension-dapagliflozin
85. Leehey DJ, Zhang JH, Emanuele NV, et al.; VA NEPHRON-D Study Group. BP and renal outcomes in diabetic kidney disease: the Veterans Affairs Nephropathy in Diabetes Trial. Clin J Am Soc Nephrol 2015;10:2159–2169
86. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA 2015;313:603–615
87. Cushman WC, Evans GW, Byington RP, et al.; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575–1585
88. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703–713
89. de Boer IH, Bangalore S, Benetos A, et al. Diabetes and hypertension: a position statement by the American Diabetes Association. Diabetes Care 2017;40:1273–1284
90. Brenner BM, Cooper ME, de Zeeuw D, et al.; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861–869
91. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD; The Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med 1993; 329:1456–1462
92. Lewis EJ, Hunsicker LG, Clarke WR, et al.; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851–860
93. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000; 355:253–259
94. Barnett AH, Bain SC, Bouter P, et al.; Diabetics Exposed to Telmisartan and Enalapril Study Group. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J Med 2004; 351:1952–1961
95. Wu H-Y, Peng C-L, Chen P-C, et al. Comparative effectiveness of angiotensin-converting enzyme inhibitors versus angiotensin II receptor blockers for major renal outcomes in patients with diabetes: a 15-year cohort study. PLoS One 2017;12:e0177654
96. Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P; Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870–878
97. Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. N Engl J Med 2009;361:40–51
98. Weil EJ, Fufaa G, Jones LI, et al. Effect of losartan on prevention and progression of early diabetic nephropathy in American Indians with type 2 diabetes. Diabetes 2013;62:3224–3231
99. Bangalore S, Fakheri R, Toklu B, Messerli FH. Diabetes mellitus as a compelling indication for use of renin angiotensin system blockers: systematic review and meta-analysis of randomized trials. BMJ 2016;352:i438
100. Haller H, Ito S, Izzo JL Jr, et al.; ROADMAP Trial Investigators. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med 2011;364:907–917
101. Yusuf S, Teo KK, Pogue J, et al.; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547–1559
102. Fried LF, Emanuele N, Zhang JH, et al.; VA NEPHRON-D Investigators. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med 2013;369:1892–1903
103. Bakris GL, Agarwal R, Chan JC, et al.; Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy (ARTS-DN) Study Group. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. JAMA 2015;314:884–894
104. Williams B, MacDonald TM, Morant S, et al.; British Hypertension Society's PATHWAY Studies Group. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet 2015;386:2059–2068
105. Filippatos G, Anker SD, Böhm M, et al. A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. Eur Heart J 2016;37: 2105–2114
106. Smart NA, Dieberg G, Ladhani M, Titus T. Early referral to specialist nephrology services for preventing the progression to end-stage kidney disease. Cochrane Database Syst Rev 2014;6: CD007333
107. Solomon SD, Chew E, Duh EJ, et al. Diabetic retinopathy: a position statement by the American Diabetes Association. Diabetes Care 2017; 40:412–418
108. Klein R. Hyperglycemia and microvascular and macrovascular disease in diabetes. Diabetes Care 1995;18:258–268
109. Estacio RO, McFarling E, Biggerstaff S, Jeffers BW, Johnson D, Schrier RW. Overt albuminuria predicts diabetic retinopathy in Hispanics with NIDDM. Am J Kidney Dis 1998;31: 947–953
110. Leske MC, Wu S-Y, Hennis A, et al.; Barbados Eye Study Group. Hyperglycemia, blood pressure, and the 9-year incidence of diabetic retinopathy: the Barbados Eye Studies. Ophthalmology 2005;112:799–805
111. Chew EY, Davis MD, Danis RP, et al.; Action to Control Cardiovascular Risk in Diabetes Eye Study Research Group. The effects of medical management on the progression of diabetic retinopathy in persons with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study. Ophthalmology 2014;121:2443–2451
112. Nathan DM, Genuth S, Lachin J, et al.; Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
113. Chew EY, Ambrosius WT, Davis MD, et al.; ACCORD Study Group; ACCORD Eye Study Group. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med 2010; 363:233–244
114. Gubitosi-Klug RA, Sun W, Cleary PA, et al.; Writing Team for the DCCT/EDIC Research Group. Effects of prior intensive insulin therapy and risk factors on patient-reported visual function outcomes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort. JAMA Ophthalmol 2016;134:137–145
115. Fong DS, Aiello LP, Ferris FL 3rd, Klein R. Diabetic retinopathy. Diabetes Care 2004;27: 2540–2553
116. Diabetes Control and Complications Trial Research Group. Effect of pregnancy on microvascular complications in the diabetes control and complications trial. Diabetes Care 2000;23: 1084–1091
117. Dabelea D, Stafford JM, Mayer-Davis EJ, et al.; SEARCH for Diabetes in Youth Research Group. Association of type 1 diabetes vs type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood. JAMA 2017;317: 825–835
118. Agardh E, Tababat-Khani P. Adopting 3-year screening intervals for sight-threatening retinal vascular lesions in type 2 diabetic subjects without retinopathy. Diabetes Care 2011;34:1318–1319
119. Nathan DM, Bebu I, Hainsworth D, et al.; DCCT/EDIC Research Group. Frequency of evidence-based screening for retinopathy in type 1 diabetes. N Engl J Med 2017;376:1507–1516
120. Daskivich LP, Vasquez C, Martinez C Jr, Tseng C-H, Mangione CM. Implementation and evaluation of a large-scale teleretinal diabetic retinopathy screening program in the Los Angeles County Department of Health Services. JAMA Intern Med 2017;177:642–649
121. Sim DA, Mitry D, Alexander P, et al. The evolution of teleophthalmology programs in the United Kingdom: beyond diabetic retinopathy screening. J Diabetes Sci Technol 2016;10: 308–317
122. Abràmoff MD, Lavin PT, Birch M, Shah N, Folk JC. Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. npj Digital Med 2018;1:39

123. Hooper P, Boucher MC, Cruess A, et al. Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of diabetic retinopathy. Can J Ophthalmol 2012; 47(Suppl. 1):S1–S30
124. Axer-Siegel R, Hod M, Fink-Cohen S, et al. Diabetic retinopathy during pregnancy. Ophthalmology 1996;103:1815–1819
125. Best RM, Chakravarthy U. Diabetic retinopathy in pregnancy. Br J Ophthalmol 1997;81:249–251
126. Gunderson EP, Lewis CE, Tsai A-L, et al. A 20-year prospective study of childbearing and incidence of diabetes in young women, controlling for glycemia before conception: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Diabetes 2007;56:2990–2996
127. The Diabetic Retinopathy Study Research Group. Preliminary report on effects of photocoagulation therapy. Am J Ophthalmol 1976;81: 383–396
128. Gross JG, Glassman AR, Jampol LM, et al.; Writing Committee for the Diabetic Retinopathy Clinical Research Network. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. JAMA 2015;314:2137–2146
129. Early Treatment Diabetic Retinopathy Study research group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol 1985;103:1796–1806
130. Elman MJ, Bressler NM, Qin H, et al.; Diabetic Retinopathy Clinical Research Network. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2011;118:609–614
131. Mitchell P, Bandello F, Schmidt-Erfurth U, et al.; RESTORE study group. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology 2011;118:615–625
132. Nguyen QD, Brown DM, Marcus DM, et al.; RISE and RIDE Research Group. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology 2012;119:789–801
133. Shih C-J, Chen H-T, Kuo S-C, et al. Comparative effectiveness of angiotensin-converting-enzyme inhibitors and angiotensin II receptor blockers in patients with type 2 diabetes and retinopathy. CMAJ 2016;188:E148–E157
134. Shi R, Zhao L, Wang F, et al. Effects of lipid-lowering agents on diabetic retinopathy: a meta-analysis and systematic review. Int J Ophthalmol 2018;11:287–295
135. Ang L, Jaiswal M, Martin C, Pop-Busui R. Glucose control and diabetic neuropathy: lessons from recent large clinical trials. Curr Diab Rep 2014;14:528
136. Martin CL, Albers JW, Pop-Busui R; DCCT/EDIC Research Group. Neuropathy and related findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. Diabetes Care 2014;37:31–38
137. Pop-Busui R, Boulton AJM, Feldman EL, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. Diabetes Care 2017;40:136–154
138. Freeman R. Not all neuropathy in diabetes is of diabetic etiology: differential diagnosis of diabetic neuropathy. Curr Diab Rep 2009;9:423–431
139. Pop-Busui R, Evans GW, Gerstein HC, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care 2010;33:1578–1584
140. Pop-Busui R, Cleary PA, Braffett BH, et al.; DCCT/EDIC Research Group. Association between cardiovascular autonomic neuropathy and left ventricular dysfunction: DCCT/EDIC study (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications). J Am Coll Cardiol 2013;61:447–454
141. Smith AG, Lessard M, Reyna S, Doudova M, Singleton JR. The diagnostic utility of Sudoscan for distal symmetric peripheral neuropathy. J Diabetes Complications 2014;28:511–516
142. Diabetes Control and Complications Trial (DCCT) Research Group. Effect of intensive diabetes treatment on nerve conduction in the Diabetes Control and Complications Trial. Ann Neurol 1995;38:869–880
143. CDC Study Group. The effect of intensive diabetes therapy on measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT). Diabetologia 1998;41:416–423
144. Albers JW, Herman WH, Pop-Busui R, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of prior intensive insulin treatment during the Diabetes Control and Complications Trial (DCCT) on peripheral neuropathy in type 1 diabetes during the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. Diabetes Care 2010;33: 1090–1096
145. Pop-Busui R, Low PA, Waberski BH, et al.; DCCT/EDIC Research Group. Effects of prior intensive insulin therapy on cardiac autonomic nervous system function in type 1 diabetes mellitus: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study (DCCT/EDIC). Circulation 2009;119:2886–2893
146. Callaghan BC, Little AA, Feldman EL, Hughes RAC. Enhanced glucose control for preventing and treating diabetic neuropathy. Cochrane Database Syst Rev 2012;6:CD007543
147. Pop-Busui R, Lu J, Brooks MM, et al.; BARI 2D Study Group. Impact of glycemic control strategies on the progression of diabetic peripheral neuropathy in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Cohort. Diabetes Care 2013;36:3208–3215
148. Sadosky A, Schaefer C, Mann R, et al. Burden of illness associated with painful diabetic peripheral neuropathy among adults seeking treatment in the US: results from a retrospective chart review and cross-sectional survey. Diabetes Metab Syndr Obes 2013;6:79–92
149. Waldfogel JM, Nesbit SA, Dy SM, et al. Pharmacotherapy for diabetic peripheral neuropathy pain and quality of life: a systematic review. Neurology 2017;88:1958–1967
150. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015;14:162–173
151. Bril V, England J, Franklin GM, et al.; American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation [published correction appears in Neurology 2011;77:603]. Neurology 2011;76:1758–1765
152. Griebeler ML, Morey-Vargas OL, Brito JP, et al. Pharmacologic interventions for painful diabetic neuropathy: an umbrella systematic review and comparative effectiveness network meta-analysis. Ann Intern Med 2014;161:639–649
153. Ziegler D, Fonseca V. From guideline to patient: a review of recent recommendations for pharmacotherapy of painful diabetic neuropathy. J Diabetes Complications 2015;29:146–156
154. Freeman R, Durso-Decruz E, Emir B. Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: findings from seven randomized, controlled trials across a range of doses. Diabetes Care 2008;31: 1448–1454
155. Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. Cochrane Database Syst Rev 2009; 3:CD007076
156. Raskin P, Huffman C, Toth C, et al. Pregabalin in patients with inadequately treated painful diabetic peripheral neuropathy: a randomized withdrawal trial. Clin J Pain 2014;30: 379–390
157. Tesfaye S, Wilhelm S, Lledo A, et al. Duloxetine and pregabalin: high-dose monotherapy or their combination? The "COMBO-DN study"–a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. Pain 2013;154:2616–2625
158. Ziegler D, Duan WR, An G, Thomas JW, Nothaft W. A randomized double-blind, placebo-, and active-controlled study of T-type calcium channel blocker ABT-639 in patients with diabetic peripheral neuropathic pain. Pain 2015;156: 2013–2020
159. Quilici S, Chancellor J, Löthgren M, et al. Meta-analysis of duloxetine vs. pregabalin and gabapentin in the treatment of diabetic peripheral neuropathic pain. BMC Neurol 2009;9:6
160. Dworkin RH, Jensen MP, Gammaitoni AR, Olaleye DO, Galer BS. Symptom profiles differ in patients with neuropathic versus non-neuropathic pain. J Pain 2007;8:118–126
161. Wiffen PJ, Derry S, Bell RF, et al. Gabapentin for chronic neuropathic pain in adults. Cochrane Database Syst Rev 2017;6:CD007938
162. Wernicke JF, Pritchett YL, D'Souza DN, et al. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology 2006;67:1411–1420
163. Hardy T, Sachson R, Shen S, Armbruster M, Boulton AJM. Does treatment with duloxetine for neuropathic pain impact glycemic control? Diabetes Care 2007;30:21–26
164. Schwartz S, Etropolski M, Shapiro DY, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results

of a randomized-withdrawal, placebo-controlled trial. Curr Med Res Opin 2011;27:151–162
165. Vinik AI, Shapiro DY, Rauschkolb C, et al. A randomized withdrawal, placebo-controlled study evaluating the efficacy and tolerability of tapentadol extended release in patients with chronic painful diabetic peripheral neuropathy. Diabetes Care 2014;37:2302–2309
166. Briasoulis A, Silver A, Yano Y, Bakris GL. Orthostatic hypotension associated with baroreceptor dysfunction: treatment approaches. J Clin Hypertens (Greenwich) 2014;16:141–148
167. Figueroa JJ, Basford JR, Low PA. Preventing and treating orthostatic hypotension: as easy as A, B, C. Cleve Clin J Med 2010;77:298–306
168. Jordan J, Fanciulli A, Tank J, et al. Management of supine hypertension in patients with neurogenic orthostatic hypotension: scientific statement of the American Autonomic Society, European Federation of Autonomic Societies, and the European Society of Hypertension. J Hypertens 2019;37:1541–1546
169. Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L; American College of Gastroenterology. Clinical guideline: management of gastroparesis. Am J Gastroenterol 2013;108:18–37; quiz 38
170. Parrish CR, Pastors JG. Nutritional management of gastroparesis in people with diabetes. Diabetes Spectr 2007;20:231–234
171. Parkman HP, Yates KP, Hasler WL, et al.; NIDDK Gastroparesis Clinical Research Consortium. Dietary intake and nutritional deficiencies in patients with diabetic or idiopathic gastroparesis. Gastroenterology 2011;141:486–498, 498.e1–498.e7
172. Olausson EA, Störsrud S, Grundin H, Isaksson M, Attvall S, Simrén M. A small particle size diet reduces upper gastrointestinal symptoms in patients with diabetic gastroparesis: a randomized controlled trial. Am J Gastroenterol 2014;109:375–385
173. Umpierrez GE, Ed. *Therapy for Diabetes Mellitus and Related Disorders.* 6th ed. Alexandria, VA, American Diabetes Association, 2014
174. Sugumar A, Singh A, Pasricha PJ. A systematic review of the efficacy of domperidone for the treatment of diabetic gastroparesis. Clin Gastroenterol Hepatol 2008;6:726–733
175. Maganti K, Onyemere K, Jones MP. Oral erythromycin and symptomatic relief of gastroparesis: a systematic review. Am J Gastroenterol 2003;98:259–263
176. McCallum RW, Snape W, Brody F, Wo J, Parkman HP, Nowak T. Gastric electrical stimulation with Enterra therapy improves symptoms from diabetic gastroparesis in a prospective study. Clin Gastroenterol Hepatol 2010;8:947–954; quiz e116
177. Bus SA, van Deursen RW, Armstrong DG, Lewis JE, Caravaggi CF, Cavanagh PR; International Working Group on the Diabetic Foot. Footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in patients with diabetes: a systematic review. Diabetes Metab Res Rev 2016;32(Suppl. 1):99–118
178. Ulbrecht JS, Hurley T, Mauger DT, Cavanaugh PR. Prevention of recurrent foot ulcers with plantar pressure–based in-shoe orthoses: the CareFUL Prevention multicenter randomized controlled trial. Diabetes Care 2014;37:1982–1989
179. Boulton AJM, Armstrong DG, Albert SF, et al.; American Diabetes Association; American Association of Clinical Endocrinologists. Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. Diabetes Care 2008;31:1679–1685
180. Hingorani A, LaMuraglia GM, Henke P, et al. The management of diabetic foot: a clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. J Vasc Surg 2016;63(Suppl.):3S–21S
181. Litzelman DK, Slemenda CW, Langefeld CD, et al. Reduction of lower extremity clinical abnormalities in patients with non-insulin-dependent diabetes mellitus. A randomized, controlled trial. Ann Intern Med 1993;119:36–41
182. IWGDF. IWGDF Guidelines on the prevention and management of diabetic foot disease. Accessed 11 August 2020. Available from https://iwgdfguidelines.org/wp-content/uploads/2019/05/IWGDF-Guidelines-2019.pdf
183. Bonner T, Foster M, Spears-Lanoix E. Type 2 diabetes-related foot care knowledge and foot self-care practice interventions in the United States: a systematic review of the literature. Diabet Foot Ankle 2016;7:29758
184. Lipsky BA, Berendt AR, Cornia PB, et al.; Infectious Diseases Society of America. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2012;54:e132–e173
185. Elraiyah T, Tsapas A, Prutsky G, et al. A systematic review and meta-analysis of adjunctive therapies in diabetic foot ulcers. J Vasc Surg 2016;63(2 Suppl.):46S–58S .e1–e2
186. Game FL, Apelqvist J, Attinger C, et al.; International Working Group on the Diabetic Foot. Effectiveness of interventions to enhance healing of chronic ulcers of the foot in diabetes: a systematic review. Diabetes Metab Res Rev 2016;32(Suppl. 1):154–168
187. Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE, Weibel S. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database Syst Rev 2015 (6):CD004123
188. Löndahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. Diabetes Care 2010;33:998–1003
189. Fedorko L, Bowen JM, Jones W, et al. Hyperbaric oxygen therapy does not reduce indications for amputation in patients with diabetes with nonhealing ulcers of the lower limb: a prospective, double-blind, randomized controlled clinical trial. Diabetes Care 2016;39:392–399
190. Li G, Hopkins RB, Levine MAH, et al. Relationship between hyperbaric oxygen therapy and quality of life in participants with chronic diabetic foot ulcers: data from a randomized controlled trial. Acta Diabetol 2017;54:823–831
191. Boulton AJM. The Diabetic Foot, 2000. South Dartmouth, MA, MDText.com, Inc. Accessed 11 August 2020. Available from http://www.ncbi.nlm.nih.gov/books/NBK409609/
192. Health Quality Ontario. Hyperbaric oxygen therapy for the treatment of diabetic foot ulcers: a health technology assessment. Ont Health Technol Assess Ser 2017;17:1–142
193. Stoekenbroek RM, Santema TB, Koelemay MJ, et al. Is additional hyperbaric oxygen therapy cost-effective for treating ischemic diabetic ulcers? Study protocol for the Dutch DAMOCLES multicenter randomized clinical trial? J Diabetes 2015;7:125–132
194. Huang ET, Mansouri J, Murad MH, et al.; UHMS CPG Oversight Committee. A clinical practice guideline for the use of hyperbaric oxygen therapy in the treatment of diabetic foot ulcers. Undersea Hyperb Med 2015;42:205–247

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The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc21-SPPC), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc21-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Recommendations

12.1 Consider the assessment of medical, psychological, functional (self-management abilities), and social geriatric domains in older adults to provide a framework to determine targets and therapeutic approaches for diabetes management. **B**

12.2 Screen for geriatric syndromes (i.e., polypharmacy, cognitive impairment, depression, urinary incontinence, falls, and persistent pain) in older adults, as they may affect diabetes self-management and diminish quality of life. **B**

Diabetes is a highly prevalent health condition in the aging population. Over one-quarter of people over the age of 65 years have diabetes and one-half of older adults have prediabetes (1,2), and the number of older adults living with these conditions is expected to increase rapidly in the coming decades. Diabetes management in older adults requires regular assessment of medical, psychological, functional, and social domains. Older adults with diabetes have higher rates of premature death, functional disability, accelerated muscle loss, and coexisting illnesses, such as hypertension, coronary heart disease, and stroke, than those without diabetes. Screening for diabetes complications in older adults should be individualized and periodically revisited, as the results of screening tests may impact targets and therapeutic approaches (3–5). At the same time, older adults with diabetes are also at greater risk than other older adults for several common geriatric syndromes, such as polypharmacy, cognitive impairment, depression, urinary incontinence, injurious falls, and persistent pain (1). These conditions may impact older adults' diabetes self-management abilities and quality of life if left unaddressed (2,6,7). See Section 4 "Comprehensive Medical Evaluation and Assessment of Comorbidities" (https://doi.org/10.2337/dc21-S004), for the full range of issues to consider when caring for older adults with diabetes.

The comprehensive assessment described above may provide a framework to determine targets and therapeutic approaches (8–10), including whether referral for

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diabetes self-management education is appropriate (when complicating factors arise or when transitions in care occur) or whether the current regimen is too complex for the patient's self-management ability or the caregivers providing care. Particular attention should be paid to complications that can develop over short periods of time and/or would significantly impair functional status, such as visual and lower-extremity complications. Please refer to the American Diabetes Association (ADA) consensus report "Diabetes in Older Adults" for details (2).

NEUROCOGNITIVE FUNCTION

Recommendation

12.3 Screening for early detection of mild cognitive impairment or dementia should be performed for adults 65 years of age or older at the initial visit and annually as appropriate. **B**

Older adults with diabetes are at higher risk of cognitive decline and institutionalization (11,12). The presentation of cognitive impairment ranges from subtle executive dysfunction to memory loss and overt dementia. People with diabetes have higher incidences of all-cause dementia, Alzheimer disease, and vascular dementia than people with normal glucose tolerance (13). The effects of hyperglycemia and hyperinsulinemia on the brain are areas of intense research. Poor glycemic control is associated with a decline in cognitive function (14,15), and longer duration of diabetes is associated with worsening cognitive function. There are ongoing studies evaluating whether preventing or delaying diabetes onset may help to maintain cognitive function in older adults. However, studies examining the effects of intensive glycemic and blood pressure control to achieve specific targets have not demonstrated a reduction in brain function decline (16,17).

Clinical trials of specific interventions—including cholinesterase inhibitors and glutamatergic antagonists—have not shown positive therapeutic benefit in maintaining or significantly improving cognitive function or in preventing cognitive decline (18). Pilot studies in patients with mild cognitive impairment evaluating the potential benefits of intranasal insulin therapy and metformin therapy provide insights for future clinical trials and mechanistic studies (19–21).

Despite the paucity of therapies to prevent or remedy cognitive decline, identifying cognitive impairment early has important implications for diabetes care. The presence of cognitive impairment can make it challenging for clinicians to help their patients reach individualized glycemic, blood pressure, and lipid targets. Cognitive dysfunction makes it difficult for patients to perform complex self-care tasks (22), such as monitoring glucose and adjusting insulin doses. It also hinders their ability to appropriately maintain the timing of meals and content of diet. When clinicians are managing patients with cognitive dysfunction, it is critical to simplify drug regimens and to facilitate and engage the appropriate support structure to assist the patient in all aspects of care.

Older adults with diabetes should be carefully screened and monitored for cognitive impairment (2). Several simple assessment tools are available to screen for cognitive impairment (23,24), such as the Mini Mental State Examination (25), Mini-Cog (26), and the Montreal Cognitive Assessment (27), which may help to identify patients requiring neuropsychological evaluation, particularly those in whom dementia is suspected (i.e., experiencing memory loss and decline in their basic and instrumental activities of daily living). Annual screening is indicated for adults 65 years of age or older for early detection of mild cognitive impairment or dementia (4,28). Screening for cognitive impairment should additionally be considered when a patient presents with a significant decline in clinical status due to increased problems with self-care activities, such as errors in calculating insulin dose, difficulty counting carbohydrates, skipped meals, skipped insulin doses, and difficulty recognizing, preventing, or treating hypoglycemia. People who screen positive for cognitive impairment should receive diagnostic assessment as appropriate, including referral to a behavioral health provider for formal cognitive/neuropsychological evaluation (29).

HYPOGLYCEMIA

Recommendations

12.4 Because older adults with diabetes have a greater risk of hypoglycemia than younger adults, episodes of hypoglycemia should be ascertained and addressed at routine visits. **B**

12.5 For older adults with type 1 diabetes, continuous glucose monitoring should be considered to reduce hypoglycemia. **A**

Older adults are at higher risk of hypoglycemia for many reasons, including insulin deficiency necessitating insulin therapy and progressive renal insufficiency (30). As described above, older adults have higher rates of unidentified cognitive impairment and dementia, leading to difficulties in adhering to complex self-care activities (e.g., glucose monitoring, insulin dose adjustment, etc.). Cognitive decline has been associated with increased risk of hypoglycemia, and conversely, severe hypoglycemia has been linked to increased risk of dementia (31,32). Therefore, as discussed in Recommendation 12.3, it is important to routinely screen older adults for cognitive impairment and dementia and discuss findings with the patients and their caregivers.

Patients and their caregivers should be routinely queried about hypoglycemia (e.g., selected questions from the Diabetes Care Profile) (33) and hypoglycemia unawareness (34). Older patients can also be stratified for future risk for hypoglycemia with validated risk calculators (e.g., Kaiser Hypoglycemia Model) (35). An important step to mitigating hypoglycemia risk is to determine whether the patient is skipping meals or inadvertently repeating doses of their medications. Glycemic targets and pharmacologic regimens may need to be adjusted to minimize the occurrence of hypoglycemic events (2). This recommendation is supported by observations from multiple randomized controlled trials, such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study and the Veterans Affairs Diabetes Trial (VADT), which showed that intensive treatment protocols targeting A1C $<6.0\%$ with complex drug regimens significantly increased the risk for hypoglycemia requiring assistance compared with standard treatment (36,37). However, these intensive treatment regimens included extensive use of insulin and minimal use of glucagon-like peptide 1 (GLP-1) receptor agonists, and they preceded the availability of sodium–glucose cotransporter 2 (SGLT2) inhibitors.

For older patients with type 1 diabetes, continuous glucose monitoring (CGM) may be another approach to reducing the risk of hypoglycemia. In the Wireless Innovation in Seniors with Diabetes Mellitus (WISDM) trial, patients over 60 years of age with type 1 diabetes were randomized to CGM or standard blood glucose monitoring (BGM). Over 6 months, use of CGM resulted in a small but statistically significant reduction in time spent with hypoglycemia (glucose level <70 mg/dL) compared with routine fingerstick monitoring using standard BGM (adjusted treatment difference, −1.9% [−27 min per day]; 95% CI −2.8% to −1.1% [−40 to −16 min per day]; $P < 0.001$) (38,39). While the current evidence base for older adults is primarily in type 1 diabetes, CGM may be an option for older patients with type 2 diabetes using multiple daily injections of insulin (see Section 7 "Diabetes Technology," https://doi.org/10.2337/dc21-S007).

TREATMENT GOALS

Recommendations

12.6 Older adults who are otherwise healthy with few coexisting chronic illnesses and intact cognitive function and functional status should have lower glycemic goals (such as A1C <7.0–7.5% [53–58 mmol/mol]), while those with multiple coexisting chronic illnesses, cognitive impairment, or functional dependence should have less stringent glycemic goals (such as A1C <8.0–8.5% [64–69 mmol/mol]). **C**

12.7 Glycemic goals for some older adults might reasonably be relaxed as part of individualized care, but hyperglycemia leading to symptoms or risk of acute hyperglycemia complications should be avoided in all patients. **C**

12.8 Screening for diabetes complications should be individualized in older adults. Particular attention should be paid to complications that would lead to functional impairment. **C**

12.9 Treatment of hypertension to individualized target levels is indicated in most older adults. **C**

12.10 Treatment of other cardiovascular risk factors should be individualized in older adults considering the time frame of benefit. Lipid-lowering therapy and aspirin therapy may benefit those with life expectancies at least equal to the time frame of primary prevention or secondary intervention trials. **E**

The care of older adults with diabetes is complicated by their clinical, cognitive, and functional heterogeneity. Some older individuals may have developed diabetes years earlier and have significant complications, others are newly diagnosed and may have had years of undiagnosed diabetes with resultant complications, and still other older adults may have truly recent-onset disease with few or no complications (40). Some older adults with diabetes have other underlying chronic conditions, substantial diabetes-related comorbidity, limited cognitive or physical functioning, or frailty (41,42). Other older individuals with diabetes have little comorbidity and are active. Life expectancies are highly variable but are often longer than clinicians realize. Multiple prognostic tools for life expectancy for older adults are available (43), including tools specifically designed for older adults with diabetes (44). Providers caring for older adults with diabetes must take this heterogeneity into consideration when setting and prioritizing treatment goals (9,10) (**Table 12.1**). In addition, older adults with diabetes should be assessed for disease treatment and self-management knowledge, health literacy, and mathematical literacy (numeracy) at the onset of treatment. See **Fig. 6.2** for patient- and disease-related factors to consider when determining individualized glycemic targets.

A1C is used as the standard biomarker for glycemic control in all patients with diabetes but may have limitations in patients who have medical conditions that impact red blood cell turnover (see Section 2 "Classification and Diagnosis of Diabetes," https://doi.org/10.2337/dc21-S002, for additional details on the limitations of A1C) (45). Many conditions associated with increased red blood cell turnover, such as hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, are commonly seen in older adults and can falsely increase or decrease A1C. In these instances, plasma blood glucose fingerstick and sensor glucose readings should be used for goal setting (**Table 12.1**).

Healthy Patients With Good Functional Status

There are few long-term studies in older adults demonstrating the benefits of intensive glycemic, blood pressure, and lipid control. Patients who can be expected to live long enough to reap the benefits of long-term intensive diabetes management, who have good cognitive and physical function, and who choose to do so via shared decision-making may be treated using therapeutic interventions and goals similar to those for younger adults with diabetes (**Table 12.1**).

As with all patients with diabetes, diabetes self-management education and ongoing diabetes self-management support are vital components of diabetes care for older adults and their caregivers. Self-management knowledge and skills should be reassessed when regimen changes are made or an individual's functional abilities diminish. In addition, declining or impaired ability to perform diabetes self-care behaviors may be an indication that a patient needs a referral for cognitive and physical functional assessment, using age-normalized evaluation tools, as well as help establishing a support structure for diabetes care (3,29).

Patients With Complications and Reduced Functionality

For patients with advanced diabetes complications, life-limiting comorbid illnesses, or substantial cognitive or functional impairments, it is reasonable to set less-intensive glycemic goals (**Table 12.1**). Factors to consider in individualizing glycemic goals are outlined in **Fig. 6.2**. These patients are less likely to benefit from reducing the risk of microvascular complications and more likely to suffer serious adverse effects from hypoglycemia. However, patients with poorly controlled diabetes may be subject to acute complications of diabetes, including dehydration, poor wound healing, and hyperglycemic hyperosmolar coma. Glycemic goals should, at a minimum, avoid these consequences.

Vulnerable Patients at the End of Life

For patients receiving palliative care and end-of-life care, the focus should be to avoid hypoglycemia and symptomatic

Table 12.1—Framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes

Patient characteristics/ health status	Rationale	Reasonable A1C goal‡	Fasting or preprandial glucose	Bedtime glucose	Blood pressure	Lipids
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.0–7.5% (53–58 mmol/mol)	80–130 mg/dL (4.4–7.2 mmol/L)	80–180 mg/dL (4.4–10.0 mmol/L)	<140/90 mmHg	Statin unless contraindicated or not tolerated
Complex/ intermediate (multiple coexisting chronic illnesses* or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0% (64 mmol/mol)	90–150 mg/dL (5.0–8.3 mmol/L)	100–180 mg/dL (5.6–10.0 mmol/L)	<140/90 mmHg	Statin unless contraindicated or not tolerated
Very complex/poor health (LTC or end-stage chronic illnesses** or moderate-to-severe cognitive impairment or 2+ ADL impairments)	Limited remaining life expectancy makes benefit uncertain	Avoid reliance on A1C; glucose control decisions should be based on avoiding hypoglycemia and symptomatic hyperglycemia	100–180 mg/dL (5.6–10.0 mmol/L)	110–200 mg/dL (6.1–11.1 mmol/L)	<150/90 mmHg	Consider likelihood of benefit with statin

This table represents a consensus framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes. The patient characteristic categories are general concepts. Not every patient will clearly fall into a particular category. Consideration of patient and caregiver preferences is an important aspect of treatment individualization. Additionally, a patient's health status and preferences may change over time. ADL, activities of daily living; LTC, long-term care. ‡A lower A1C goal may be set for an individual if achievable without recurrent or severe hypoglycemia or undue treatment burden. *Coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke. "Multiple" means at least three, but many patients may have five or more (50). **The presence of a single end-stage chronic illness, such as stage 3–4 congestive heart failure or oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer, may cause significant symptoms or impairment of functional status and significantly reduce life expectancy. Adapted from Kirkman et al. (3).

hyperglycemia while reducing the burdens of glycemic management. Thus, when organ failure develops, several agents will have to be deintensified or discontinued. For the dying patient, most agents for type 2 diabetes may be removed (46). There is, however, no consensus for the management of type 1 diabetes in this scenario (47). See the section END-OF-LIFE CARE below, for additional information.

Beyond Glycemic Control

Although hyperglycemia control may be important in older individuals with diabetes, greater reductions in morbidity and mortality are likely to result from control of other cardiovascular risk factors rather than from tight glycemic control alone. There is strong evidence from clinical trials of the value of treating hypertension in older adults (48,49), with treatment of hypertension to individualized target levels indicated in most. There is less evidence for lipid-lowering therapy and aspirin therapy, although the benefits of these interventions for primary prevention and secondary intervention are likely to apply to older adults whose life expectancies equal or exceed the time frames of the clinical trials.

LIFESTYLE MANAGEMENT

Recommendations

12.11 Optimal nutrition and protein intake is recommended for older adults; regular exercise, including aerobic activity, weight-bearing exercise, and/or resistance training, should be encouraged in all older adults who can safely engage in such activities. **B**

12.12 For older adults with type 2 diabetes, overweight/obesity, and capacity to safely exercise, an intensive lifestyle intervention focused on dietary changes, physical activity, and modest weight loss (e.g., 5–7%) should be considered for its benefits on quality of life, mobility and physical functioning, and cardiometabolic risk factor control. **A**

Diabetes in the aging population is associated with reduced muscle strength, poor muscle quality, and accelerated loss of muscle mass, which may result in sarcopenia and/or osteopenia (51,52). Diabetes is also recognized as an independent risk factor for frailty. Frailty is characterized by decline in physical performance and an increased risk of poor health outcomes due to physiologic vulnerability and functional or psychosocial stressors. Inadequate nutritional intake, particularly inadequate protein intake, can increase the risk of sarcopenia and frailty in older adults. Management of frailty in diabetes includes optimal nutrition with adequate protein intake

combined with an exercise program that includes aerobic and resistance training (53,54).

Many older adults with type 2 diabetes also have overweight or obesity and will benefit from an intensive lifestyle intervention. The Look Action for Health in Diabetes (Look AHEAD) trial is described in Section 8 "Obesity Management for the Treatment of Type 2 Diabetes" (https://doi.org/10.2337/dc21-S008). The trial enrolled patients between 45 and 74 years of age and required that patients be able perform a maximal exercise test (55,56). While the Look AHEAD trial did not achieve its primary outcome of reducing cardiovascular events, the intensive lifestyle intervention had multiple clinical benefits that are important to the quality of life of older patients. Benefits included weight loss, improved physical fitness, increased HDL cholesterol, lowered systolic blood pressure, reduced A1C levels, and reduced waist circumference (57). Additionally, several subgroups, including participants who lost at least 10% of baseline body weight at year 1, had improved cardiovascular outcomes (58). Risk factor control was improved with reduced utilization of antihypertensive medications, statins, and insulin (59). In age-stratified analyses, older patients in the trial (60 to early 70s) had similar benefits compared with younger patients (60,61). In addition, lifestyle intervention produced benefits on aging-relevant outcomes like better physical function and quality of life (62–65).

PHARMACOLOGIC THERAPY

Recommendations

12.13 In older adults with type 2 diabetes at increased risk of hypoglycemia, medication classes with low risk of hypoglycemia are preferred. **B**

12.14 Overtreatment of diabetes is common in older adults and should be avoided. **B**

12.15 Deintensification (or simplification) of complex regimens is recommended to reduce the risk of hypoglycemia and polypharmacy, if it can be achieved within the individualized A1C target. **B**

12.16 Consider costs of care and insurance coverage rules when developing treatment plans in order to reduce risk of cost-related nonadherence. **B**

Special care is required in prescribing and monitoring pharmacologic therapies in older adults (66). See **Fig. 9.1** for general recommendations regarding glucose-lowering treatment for adults with type 2 diabetes and **Table 9.1** for patient- and drug-specific factors to consider when selecting glucose-lowering agents. Cost may be an important consideration, especially as older adults tend to be on many medications and live on fixed incomes (67). Accordingly, the costs of care and insurance coverage rules should be considered when developing treatment plans to reduce the risk of cost-related nonadherence (68,69). See **Table 9.2** and **Table 9.3** for median monthly cost in the U.S. of noninsulin glucose-lowering agents and insulin, respectively. It is important to match complexity of the treatment regimen to the self-management ability of older patients and their available social and medical support. Many older adults with diabetes struggle to maintain the frequent blood glucose monitoring and insulin injection regimens they previously followed, perhaps for many decades, as they develop medical conditions that may impair their ability to follow their regimen safely. Individualized glycemic goals should be established (**Fig. 6.2**) and periodically adjusted based on coexisting chronic illnesses, cognitive function, and functional status (2). Tight glycemic control in older adults with multiple medical conditions is considered over treatment and is associated with an increased risk of hypoglycemia; overtreatment is unfortunately common in clinical practice (50,70–73). Deintensification of regimens in patients taking noninsulin glucose-lowering medications can be achieved by either lowering the dose or discontinuing some medications, as long as the individualized glycemic targets are maintained. When patients are found to have an insulin regimen with complexity beyond their self-management abilities, lowering the dose of insulin may not be adequate (74). Simplification of the insulin regimen to match an individual's self-management abilities and their available social and medical support in these situations has been shown to reduce hypoglycemia and disease-related distress without worsening glycemic control (75–77). **Figure 12.1** depicts an algorithm that can be used to simplify the insulin regimen (75). There are now multiple studies evaluating deintensification protocols that, in general, demonstrate that deintensification is safe and possibly beneficial for older adults (78). **Table 12.2** provides examples of and rationale for situations where deintensification and/or insulin regimen simplification may be appropriate in older adults.

Metformin

Metformin is the first-line agent for older adults with type 2 diabetes. Recent studies have indicated that it may be used safely in patients with estimated glomerular filtration rate $\geq$30 mL/min/1.73 m^2 (81). However, it is contraindicated in patients with advanced renal insufficiency and should be used with caution in patients with impaired hepatic function or congestive heart failure because of the increased risk of lactic acidosis. Metformin may be temporarily discontinued before procedures, during hospitalizations, and when acute illness may compromise renal or liver function. Additionally, metformin can cause gastrointestinal side effects and a reduction in appetite that can be problematic for some older adults. Reduction or elimination of metformin may be necessary for patients experiencing persistent gastrointestinal side effects.

Thiazolidinediones

Thiazolidinediones, if used at all, should be used very cautiously in those patients on insulin therapy as well as those patients with or at risk for congestive heart failure, osteoporosis, falls or fractures, and/or macular edema (82,83).

Insulin Secretagogues

Sulfonylureas and other insulin secretagogues are associated with hypoglycemia and should be used with caution. If used, sulfonylureas with a shorter duration of action, such as glipizide or glimepiride, are preferred. Glyburide is a longer-acting sulfonylurea and should be avoided in older adults (84).

Incretin-Based Therapies

Oral dipeptidyl peptidase 4 (DPP-4) inhibitors have few side effects and minimal

risk of hypoglycemia, but their cost may be a barrier to some older patients. DPP-4 inhibitors do not increase major adverse cardiovascular outcomes (85). Across the trials of this drug class, there appears to be no interaction by age-group (86–88). A challenge of interpreting the age-stratified analyses of this drug class and other cardiovascular outcomes trials is that while most of these analyses were prespecified, they were not powered to detect differences.

GLP-1 receptor agonists have demonstrated cardiovascular benefits among patients with established atherosclerotic cardiovascular disease (CVD), and newer trials are expanding our understanding of their benefits in other populations (85). See Section 9 "Pharmacologic Approaches to Glycemic Treatment" (https://doi.org/10.2337/dc21-S009) and Section 10 "Cardiovascular Disease and Risk Management" (https://doi.org/10.2337/dc21-S010) for a more extensive discussion regarding the specific indications for this class. The stratified analyses of several of the trials of this drug class indicate a complex interaction with age. In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial with liraglutide, those aged ≥50 years with CVD at baseline had a reduction in primary outcome (n = 7,598; hazard ratio [HR] 0.83), whereas those aged ≥60 years with no established CVD had a significantly adverse outcome (n = 1,742; HR 1.20, P = 0.04), except in a small subgroup of those aged ≥75 years (89,90). A similar trend was seen in the Harmony Outcomes trial with albiglutide, comparing participants aged <65 years to those aged 65–75 years and a smaller group aged ≥75 years (91). While the evidence for this class for older patients continues to grow, there are a number of practical issues that should be considered for older patients. These drugs are injectable agents (with the exception of oral semaglutide) (92), which require visual, motor, and cognitive skills for appropriate administration. They may also be associated with nausea, vomiting, and diarrhea. Given the gastrointestinal side-effects of this class, GLP-1 receptor agonists may not be preferred in older patients who are experiencing unexplained weight loss.

Sodium–Glucose Cotransporter 2 Inhibitors

SGLT2 inhibitors are administered orally, which may be convenient for older

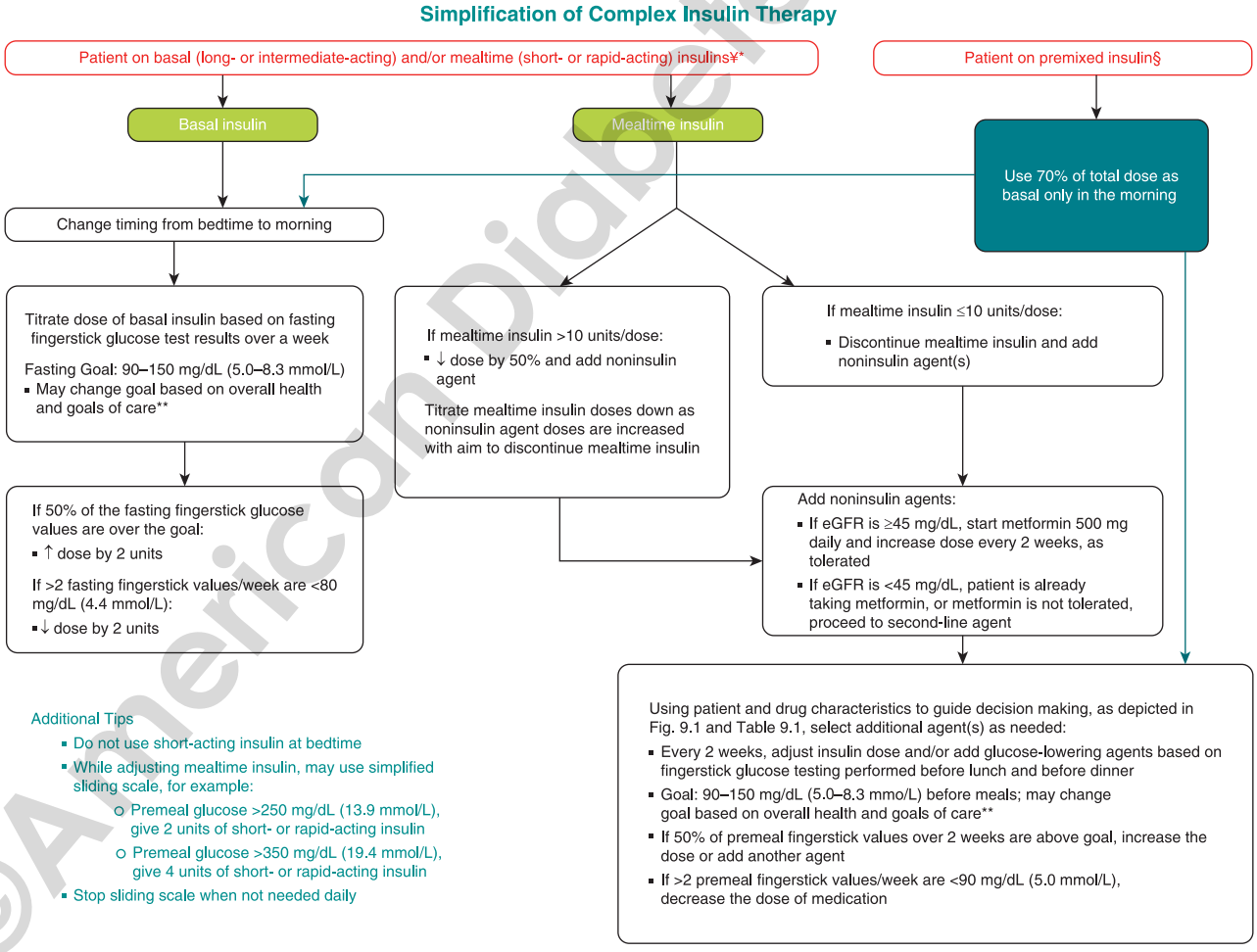

Figure 12.1—Algorithm to simplify insulin regimen for older patients with type 2 diabetes. eGFR, estimated glomerular filtration rate. *Basal insulins: glargine U-100 and U-300, detemir, degludec, and human NPH. **See **Table 12.1**. ¥Mealtime insulins: short-acting (regular human insulin) or rapid-acting (lispro, aspart, and glulisine). §Premixed insulins: 70/30, 75/25, and 50/50 products. Adapted with permission from Munshi and colleagues (75,79,80).

Table 12.2—Considerations for treatment regimen simplification and deintensification/deprescribing in older adults with diabetes (75,79)

Patient characteristics/ health status	Reasonable A1C/ treatment goal	Rationale/considerations	When may regimen simplification be required?	When may treatment deintensification/ deprescribing be required?
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	A1C <7.0–7.5% (53–58 mmol/mol)	• Patients can generally perform complex tasks to maintain good glycemic control when health is stable • During acute illness, patients may be more at risk for administration or dosing errors that can result in hypoglycemia, falls, fractures, etc.	• If severe or recurrent hypoglycemia occurs in patients on insulin therapy (even if A1C is appropriate) • If wide glucose excursions are observed • If cognitive or functional decline occurs following acute illness	• If severe or recurrent hypoglycemia occurs in patients on noninsulin therapies with high risk of hypoglycemia (even if A1C is appropriate) • If wide glucose excursions are observed • In the presence of polypharmacy
Complex/intermediate (multiple coexisting chronic illnesses or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)	A1C <8.0% (64 mmol/mol)	• Comorbidities may affect self-management abilities and capacity to avoid hypoglycemia • Long-acting medication formulations may decrease pill burden and complexity of medication regimen	• If severe or recurrent hypoglycemia occurs in patients on insulin therapy (even if A1C is appropriate) • If unable to manage complexity of an insulin regimen • If there is a significant change in social circumstances, such as loss of caregiver, change in living situation, or financial difficulties	• If severe or recurrent hypoglycemia occurs in patients on noninsulin therapies with high risk of hypoglycemia (even if A1C is appropriate) • If wide glucose excursions are observed • In the presence of polypharmacy
Community-dwelling patients receiving care in a skilled nursing facility for short-term rehabilitation	Avoid reliance on A1C Glucose target: 100–200 mg/dL (5.55–11.1 mmol/L)	• Glycemic control is important for recovery, wound healing, hydration, and avoidance of infections • Patients recovering from illness may not have returned to baseline cognitive function at the time of discharge • Consider the type of support the patient will receive at home	• If treatment regimen increased in complexity during hospitalization, it is reasonable, in many cases, to reinstate the prehospitalization medication regimen during the rehabilitation	• If the hospitalization for acute illness resulted in weight loss, anorexia, short-term cognitive decline, and/or loss of physical functioning
Very complex/poor health (long-term care or end-stage chronic illnesses or moderate-to-severe cognitive impairment or 2+ ADL impairments)	Avoid reliance on A1C. Avoid hypoglycemia and symptomatic hyperglycemia	• No benefits of tight glycemic control in this population • Hypoglycemia should be avoided • Most important outcomes are maintenance of cognitive and functional status	• If on an insulin regimen and the patient would like to decrease the number of injections and fingerstick blood glucose monitoring events each day • If the patient has an inconsistent eating pattern	• If on noninsulin agents with a high hypoglycemia risk in the context of cognitive dysfunction, depression, anorexia, or inconsistent eating pattern • If taking any medications without clear benefits
At the end of life	Avoid hypoglycemia and symptomatic hyperglycemia	• Goal is to provide comfort and avoid tasks or interventions that cause pain or discomfort • Caregivers are important in providing medical care and maintaining quality of life	• If there is pain or discomfort caused by treatment (e.g., injections or fingersticks) • If there is excessive caregiver stress due to treatment complexity	• If taking any medications without clear benefits in improving symptoms and/or comfort

Treatment regimen simplification refers to changing strategy to decrease the complexity of a medication regimen, e.g., fewer administration times, fewer blood glucose checks, and decreasing the need for calculations (such as sliding scale insulin calculations or insulin-carbohydrate ratio calculations). Deintensification/deprescribing refers to decreasing the dose or frequency of administration of a treatment or discontinuing a treatment altogether. ADL, activities of daily living.

adults with diabetes. In patients with established atherosclerotic CVD, these agents have shown cardiovascular benefits (85). This class of agents has also been found to be beneficial for patients with heart failure and to slow the progression of chronic kidney disease. See Section 9 "Pharmacologic Approaches to Glycemic Treatment" (https://doi.org/10.2337/dc21-S009) and Section 10 "Cardiovascular Disease and Risk Management" (https://doi.org/10.2337/dc21-S010) for a more extensive discussion regarding the indications for this class of agents. The stratified analyses of the trials of this drug class indicate that older patients have similar or greater benefits than younger patients (93–95). While understanding of the clinical benefits of this class is evolving, side effects such as volume depletion may be more common among older patients.

Insulin Therapy

The use of insulin therapy requires that patients or their caregivers have good visual and motor skills and cognitive ability. Insulin therapy relies on the ability of the older patient to administer insulin on their own or with the assistance of a caregiver. Insulin doses should be titrated to meet individualized glycemic targets and to avoid hypoglycemia.

Once-daily basal insulin injection therapy is associated with minimal side effects and may be a reasonable option in many older patients. Multiple daily injections of insulin may be too complex for the older patient with advanced diabetes complications, life-limiting coexisting chronic illnesses, or limited functional status. **Figure 12.1** provides a potential approach to insulin regimen simplification.

Other Factors to Consider

The needs of older adults with diabetes and their caregivers should be evaluated to construct a tailored care plan. Impaired social functioning may reduce these patients' quality of life and increase the risk of functional dependency (7). The patient's living situation must be considered as it may affect diabetes management and support needs. Social and instrumental support networks (e.g., adult children, caretakers) that provide instrumental or emotional support for older adults with diabetes should be included in diabetes management discussions and shared decision-making.

Older adults in assisted living facilities may not have support to administer their own medications, whereas those living in a nursing home (community living centers) may rely completely on the care plan and nursing support. Those receiving palliative care (with or without hospice) may require an approach that emphasizes comfort and symptom management, while de-emphasizing strict metabolic and blood pressure control.

SPECIAL CONSIDERATIONS FOR OLDER ADULTS WITH TYPE 1 DIABETES

Due in part to the success of modern diabetes management, patients with type 1 diabetes are living longer, and the population of these patients over 65 years of age is growing (96–99). Many of the recommendations in this section regarding a comprehensive geriatric assessment and personalization of goals and treatments are directly applicable to older adults with type 1 diabetes; however, this population has unique challenges and requires distinct treatment considerations (100). Insulin is an essential life-preserving therapy for patients with type 1 diabetes, unlike for those with type 2 diabetes. To avoid diabetic ketoacidosis, older adults with type 1 diabetes need some form of basal insulin even when they are unable to ingest meals. Insulin may be delivered through an insulin pump or injections. CGM is approved for use by Medicare and can play a critical role in improving A1C, reducing glycemic variability, and reducing risk of hypoglycemia (101) (see Section 7 "Diabetes Technology," https://doi.org/10.2337/dc21-S007, and Section 9 "Pharmacologic Approaches to Glycemic Treatment," https://doi.org/10.2337/dc21-S009). In the older patient with type 1 diabetes, administration of insulin may become more difficult as complications, cognitive impairment, and functional impairment arise. This increases the importance of caregivers in the lives of these patients. Many older patients with type 1 diabetes require placement in long-term care (LTC) settings (i.e., nursing homes and skilled nursing facilities), and unfortunately these patients encounter providers that are unfamiliar with insulin pumps or CGM. Some providers may be unaware of the distinction between type 1 and type 2 diabetes. In these instances, the patient or the patient's family may be more familiar with diabetes management than the providers. Education of relevant support staff and providers in rehabilitation and LTC settings regarding insulin dosing and use of pumps and CGM is recommended as part of general diabetes education (see Recommendations 12.17 and 12.18).

TREATMENT IN SKILLED NURSING FACILITIES AND NURSING HOMES

Recommendations

12.17 Consider diabetes education for the staff of long-term care and rehabilitation facilities to improve the management of older adults with diabetes. **E**

12.18 Patients with diabetes residing in long-term care facilities need careful assessment to establish individualized glycemic goals and to make appropriate choices of glucose-lowering agents based on their clinical and functional status. **E**

Management of diabetes in the LTC setting is unique. Individualization of health care is important in all patients; however, practical guidance is needed for medical providers as well as the LTC staff and caregivers (102). Training should include diabetes detection and institutional quality assessment. LTC facilities should develop their own policies and procedures for prevention and management of hypoglycemia.

Resources

Staff of LTC facilities should receive appropriate diabetes education to improve the management of older adults with diabetes. Treatments for each patient should be individualized. Special management considerations include the need to avoid both hypoglycemia and the complications of hyperglycemia (2,103). For more information, see the ADA position statement "Management of Diabetes in Long-term Care and Skilled Nursing Facilities" (102).

Nutritional Considerations

An older adult residing in an LTC facility may have irregular and unpredictable meal consumption, undernutrition, anorexia, and impaired swallowing. Furthermore, therapeutic diets may inadvertently lead to decreased food intake and contribute to unintentional weight loss and undernutrition. Diets tailored

to a patient's culture, preferences, and personal goals may increase quality of life, satisfaction with meals, and nutrition status (104). It may be helpful to give insulin after meals to ensure that the dose is appropriate for the amount of carbohydrate the patient consumed in the meal.

Hypoglycemia

Older adults with diabetes in LTC are especially vulnerable to hypoglycemia. They have a disproportionately high number of clinical complications and comorbidities that can increase hypoglycemia risk: impaired cognitive and renal function, slowed hormonal regulation and counterregulation, suboptimal hydration, variable appetite and nutritional intake, polypharmacy, and slowed intestinal absorption (105). Oral agents may achieve glycemic outcomes in LTC populations similar to basal insulin (70,106).

Another consideration for the LTC setting is that, unlike in the hospital setting, medical providers are not required to evaluate the patients daily. According to federal guidelines, assessments should be done at least every 30 days for the first 90 days after admission and then at least once every 60 days. Although in practice the patients may actually be seen more frequently, the concern is that patients may have uncontrolled glucose levels or wide excursions without the practitioner being notified. Providers may make adjustments to treatment regimens by telephone, fax, or in person directly at the LTC facilities provided they are given timely notification of blood glucose management issues from a standardized alert system.

The following alert strategy could be considered:

1. **Call provider immediately** in cases of low blood glucose levels (<70 mg/dL [3.9 mmol/L]).
2. **Call as soon as possible when**
   a) glucose values are 70–100 mg/dL (3.9–5.6 mmol/L) (regimen may need to be adjusted),
   b) glucose values are >250 mg/dL (13.9 mmol/L) within a 24-h period,
   c) glucose values are >300 mg/dL (16.7 mmol/L) over 2 consecutive days,
   d) any reading is too high for the glucometer, or
   e) the patient is sick, with vomiting, symptomatic hyperglycemia, or poor oral intake.

END-OF-LIFE CARE

Recommendations

12.19 When palliative care is needed in older adults with diabetes, providers should initiate conversations regarding the goals and intensity of care. Strict glucose and blood pressure control may not be necessary **E**, and reduction of therapy may be appropriate. Similarly, the intensity of lipid management can be relaxed, and withdrawal of lipid-lowering therapy may be appropriate. **A**

12.20 Overall comfort, prevention of distressing symptoms, and preservation of quality of life and dignity are primary goals for diabetes management at the end of life. **C**

The management of the older adult at the end of life receiving palliative medicine or hospice care is a unique situation. Overall, palliative medicine promotes comfort, symptom control and prevention (pain, hypoglycemia, hyperglycemia, and dehydration), and preservation of dignity and quality of life in patients with limited life expectancy (103,107). In the setting of palliative care, providers should initiate conversations regarding the goals and intensity of diabetes care; strict glucose and blood pressure control may not be consistent with achieving comfort and quality of life. In a multicenter trial, withdrawal of statins among patients in palliative care was found to improve quality of life, while similar evidence for glucose and blood pressure control are not yet available (108–110). A patient has the right to refuse testing and treatment, whereas providers may consider withdrawing treatment and limiting diagnostic testing, including a reduction in the frequency of blood glucose monitoring (111,112). Glucose targets should aim to prevent hypoglycemia and hyperglycemia. Treatment interventions need to be mindful of quality of life. Careful monitoring of oral intake is warranted. The decision process may need to involve the patient, family, and caregivers, leading to a care plan that is both convenient and effective for the goals of care (113). The pharmacologic therapy may include oral agents as first line, followed by a simplified insulin regimen. If needed, basal insulin can be implemented, accompanied by oral agents and without rapid-acting insulin. Agents that can cause gastrointestinal symptoms such as nausea or excess weight loss may not be good choices in this setting. As symptoms progress, some agents may be slowly tapered and discontinued.

Different patient categories have been proposed for diabetes management in those with advanced disease (47).

1. A stable patient: Continue with the patient's previous regimen, with a focus on the prevention of hypoglycemia and the management of hyperglycemia using blood glucose testing, keeping levels below the renal threshold of glucose. There is very little role for A1C monitoring and lowering.
2. A patient with organ failure: Preventing hypoglycemia is of greater significance. Dehydration must be prevented and treated. In people with type 1 diabetes, insulin administration may be reduced as the oral intake of food decreases but should not be stopped. For those with type 2 diabetes, agents that may cause hypoglycemia should be reduced in dose. The main goal is to avoid hypoglycemia, allowing for glucose values in the upper level of the desired target range.
3. A dying patient: For patients with type 2 diabetes, the discontinuation of all medications may be a reasonable approach, as patients are unlikely to have any oral intake. In patients with type 1 diabetes, there is no consensus, but a small amount of basal insulin may maintain glucose levels and prevent acute hyperglycemic complications.

References

1. Laiteerapong N, Huang E. Diabetes in older adults. In *Diabetes in America*. 3rd ed. Cowie C, Casagrande S, Menke A, et al., Eds. Bethesda, MD, National Institutes of Health, 2017, pp. 16.11–16.26 (NIH publ. no. 17-1468)
2. Centers for Disease Control and Prevention. National Diabetes Statistics Report: estimates of diabetes and its burden in the United States, 2020. Accessed 9 October 2020. Available from https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf
3. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. Diabetes Care 2012;35:2650–2664
4. Young-Hyman D, de Groot M, Hill-Briggs F, Gonzalez JS, Hood K, Peyrot M. Psychosocial care

for people with diabetes: a position statement of the American Diabetes Association. Diabetes Care 2016;39:2126–2140
5. Institute of Medicine of the National Academies. Cognitive Aging: Progress in Understanding and Opportunities for Action, 2015. Accessed 9 October 2020. Available from http://nationalacademies.org/hmd/Reports/2015/Cognitive-Aging.aspx
6. Sudore RL, Karter AJ, Huang ES, et al. Symptom burden of adults with type 2 diabetes across the disease course: diabetes & aging study. J Gen Intern Med 2012;27:1674–1681
7. Laiteerapong N, Karter AJ, Liu JY, et al. Correlates of quality of life in older adults with diabetes: the diabetes & aging study. Diabetes Care 2011;34:1749–1753
8. McClintock MK, Dale W, Laumann EO, Waite L. Empirical redefinition of comprehensive health and well-being in the older adults of the United States. Proc Natl Acad Sci U S A 2016;113:E3071–E3080
9. Laiteerapong N, Iveniuk J, John PM, Laumann EO, Huang ES. Classification of older adults who have diabetes by comorbid conditions, United States, 2005-2006. Prev Chronic Dis 2012;9:E100
10. Blaum C, Cigolle CT, Boyd C, et al. Clinical complexity in middle-aged and older adults with diabetes: the Health and Retirement Study. Med Care 2010;48:327–334
11. Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes–systematic overview of prospective observational studies. Diabetologia 2005;48:2460–2469
12. Roberts RO, Knopman DS, Przybelski SA, et al. Association of type 2 diabetes with brain atrophy and cognitive impairment. Neurology 2014;82:1132–1141
13. Xu WL, von Strauss E, Qiu CX, Winblad B, Fratiglioni L. Uncontrolled diabetes increases the risk of Alzheimer's disease: a population-based cohort study. Diabetologia 2009;52:1031–1039
14. Yaffe K, Falvey C, Hamilton N, et al. Diabetes, glucose control, and 9-year cognitive decline among older adults without dementia. Arch Neurol 2012;69:1170–1175
15. Rawlings AM, Sharrett AR, Schneider ALC, et al. Diabetes in midlife and cognitive change over 20 years: a cohort study. Ann Intern Med 2014;161:785–793
16. Launer LJ, Miller ME, Williamson JD, et al.; ACCORD MIND investigators. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. Lancet Neurol 2011;10:969–977
17. Murray AM, Hsu F-C, Williamson JD, et al.; Action to Control Cardiovascular Risk in Diabetes Follow-On Memory in Diabetes (ACCORDION MIND) Investigators. ACCORDION MIND: results of the observational extension of the ACCORD MIND randomised trial. Diabetologia 2017;60:69–80
18. Ghezzi L, Scarpini E, Galimberti D. Disease-modifying drugs in Alzheimer's disease. Drug Des Devel Ther 2013;7:1471–1478
19. Craft S, Baker LD, Montine TJ, et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Arch Neurol 2012;69:29–38
20. Freiherr J, Hallschmid M, Frey WH 2nd, et al. Intranasal insulin as a treatment for Alzheimer's disease: a review of basic research and clinical evidence. CNS Drugs 2013;27:505–514
21. Alagiakrishnan K, Sankaralingam S, Ghosh M, Mereu L, Senior P. Antidiabetic drugs and their potential role in treating mild cognitive impairment and Alzheimer's disease. Discov Med 2013;16:277–286
22. Tomlin A, Sinclair A. The influence of cognition on self-management of type 2 diabetes in older people. Psychol Res Behav Manag 2016;9:7–20
23. National Institute on Aging. Assessing cognitive impairment in older patients. Accessed 9 October 2020. Available from https://www.nia.nih.gov/health/assessing-cognitive-impairment-older-patients
24. Alzheimer's Association. Cognitive Assessment: Alzheimer's Disease and Dementia. Accessed 9 October 2020. Available from: https://alz.org/professionals/healthcare-professionals/cognitive-assessment
25. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198
26. Borson S, Scanlan JM, Chen P, Ganguli M. The Mini-Cog as a screen for dementia: validation in a population-based sample. J Am Geriatr Soc 2003;51:1451–1454
27. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695–699
28. Moreno G, Mangione CM, Kimbro L, Vaisberg E; American Geriatrics Society Expert Panel on Care of Older Adults with Diabetes Mellitus. Guidelines abstracted from the American Geriatrics Society Guidelines for Improving the Care of Older Adults with Diabetes Mellitus: 2013 update. J Am Geriatr Soc 2013;61:2020–2026
29. American Psychological Association. Guidelines for the evaluation of dementia and age-related cognitive change. Accessed 9 October 2020. Available from http://www.apa.org/practice/guidelines/dementia.aspx
30. Lee AK, Lee CJ, Huang ES, Sharrett AR, Coresh J, Selvin E. Risk factors for severe hypoglycemia in black and white adults with diabetes: the Atherosclerosis Risk in Communities (ARIC) study. Diabetes Care 2017;40:1661–1667
31. Feinkohl I, Aung PP, Keller M, et al.; Edinburgh Type 2 Diabetes Study (ET2DS) Investigators. Severe hypoglycemia and cognitive decline in older people with type 2 diabetes: the Edinburgh type 2 diabetes study. Diabetes Care 2014;37:507–515
32. Lee AK, Rawlings AM, Lee CJ, et al. Severe hypoglycaemia, mild cognitive impairment, dementia and brain volumes in older adults with type 2 diabetes: the Atherosclerosis Risk in Communities (ARIC) cohort study. Diabetologia 2018;61:1956–1965
33. Fitzgerald JT, Davis WK, Connell CM, Hess GE, Funnell MM, Hiss RG. Development and validation of the Diabetes Care Profile. Eval Health Prof 1996;19:208–230
34. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM: a prospective study of hypoglycemic frequency and associated symptoms. Diabetes Care 1995;18:517–522
35. Karter AJ, Warton EM, Lipska KJ, et al. Development and validation of a tool to identify patients with type 2 diabetes at high risk of hypoglycemia-related emergency department or hospital use. JAMA Intern Med 2017;177:1461–1470
36. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
37. Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–139
38. Carlson AL, Kanapka LG, Miller KM, et al.; WISDM Study Group. Hypoglycemia and glycemic control in older adults with type 1 diabetes: baseline results from the WISDM study. J Diabetes Sci Technol 21 December 2019 [Epub ahead of print]. DOI: 1932296819894974
39. Pratley RE, Kanapka LG, Rickels MR, et al.; Wireless Innovation for Seniors With Diabetes Mellitus (WISDM) Study Group. Effect of continuous glucose monitoring on hypoglycemia in older adults with type 1 diabetes: a randomized clinical trial. JAMA 2020;323:2397–2406
40. Selvin E, Coresh J, Brancati FL. The burden and treatment of diabetes in elderly individuals in the U.S. Diabetes Care 2006;29:2415–2419
41. Bandeen-Roche K, Seplaki CL, Huang J, et al. Frailty in older adults: a nationally representative profile in the United States. J Gerontol A Biol Sci Med Sci 2015;70:1427–1434
42. Kalyani RR, Tian J, Xue Q-L, et al. Hyperglycemia and incidence of frailty and lower extremity mobility limitations in older women. J Am Geriatr Soc 2012;60:1701–1707
43. Pilla SJ, Schoenborn NL, Maruthur NM, Huang ES. Approaches to risk assessment among older patients with diabetes. Curr Diab Rep 2019;19:59
44. Griffith KN, Prentice JC, Mohr DC, Conlin PR. Predicting 5- and 10-year mortality risk in older adults with diabetes. Diabetes Care 2020;43:1724–1731
45. NGSP. Factors that interfere with HbA1c test results. Accessed 9 October 2020. Available from http://www.ngsp.org/factors.asp
46. Sinclair A, Dunning T, Colagiuri S. *IDF Global Guideline For Managing Older People With Type 2 Diabetes*. Brussels, Belgium, International Diabetes Federation, 2013
47. Angelo M, Ruchalski C, Sproge BJ. An approach to diabetes mellitus in hospice and palliative medicine. J Palliat Med 2011;14:83–87
48. Beckett NS, Peters R, Fletcher AE, et al.; HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008;358:1887–1898
49. de Boer IH, Bangalore S, Benetos A, et al. Diabetes and hypertension: a position statement by the American Diabetes Association. Diabetes Care 2017;40:1273–1284
50. Arnold SV, Lipska KJ, Wang J, Seman L, Mehta SN, Kosiborod M. Use of intensive glycemic management in older adults with diabetes mellitus. J Am Geriatr Soc 2018;66:1190–1194

51. Park SW, Goodpaster BH, Strotmeyer ES, et al. Decreased muscle strength and quality in older adults with type 2 diabetes: the health, aging, and body composition study. Diabetes 2006;55:1813–1818
52. Park SW, Goodpaster BH, Strotmeyer ES, et al.; Health, Aging, and Body Composition Study. Accelerated loss of skeletal muscle strength in older adults with type 2 diabetes: the health, aging, and body composition study. Diabetes Care 2007;30:1507–1512
53. Villareal DT, Chode S, Parimi N, et al. Weight loss, exercise, or both and physical function in obese older adults. N Engl J Med 2011;364:1218–1229
54. Villareal DT, Aguirre L, Gurney AB, et al. Aerobic or resistance exercise, or both, in dieting obese older adults. N Engl J Med 2017;376:1943–1955
55. Curtis JM, Horton ES, Bahnson J, et al.; Look AHEAD Research Group. Prevalence and predictors of abnormal cardiovascular responses to exercise testing among individuals with type 2 diabetes: the Look AHEAD (Action for Health in Diabetes) study. Diabetes Care 2010;33:901–907
56. Bray G, Gregg E, Haffner S, et al.; Look Ahead Research Group. Baseline characteristics of the randomised cohort from the Look AHEAD (Action for Health in Diabetes) study. Diab Vasc Dis Res 2006;3:202–215
57. Wing RR, Bolin P, Brancati FL, et al.; Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369:145–154
58. Gregg EW, Jakicic JM, Blackburn G, et al.; Look AHEAD Research Group. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. Lancet Diabetes Endocrinol 2016;4:913–921
59. Gregg EW, Chen H, Wagenknecht LE, et al.; Look AHEAD Research Group. Association of an intensive lifestyle intervention with remission of type 2 diabetes. JAMA 2012;308:2489–2496
60. Rejeski WJ, Bray GA, Chen S-H, et al.; Look AHEAD Research Group. Aging and physical function in type 2 diabetes: 8 years of an intensive lifestyle intervention. J Gerontol A Biol Sci Med Sci 2015;70:345–353
61. Espeland MA, Rejeski WJ, West DS, et al.; Action for Health in Diabetes Research Group. Intensive weight loss intervention in older individuals: results from the Action for Health in Diabetes Type 2 diabetes mellitus trial. J Am Geriatr Soc 2013;61:912–922
62. Houston DK, Neiberg RH, Miller ME, et al. Physical function following a long-term lifestyle intervention among middle aged and older adults with type 2 diabetes: the Look AHEAD study. J Gerontol A Biol Sci Med Sci 2018;73:1552–1559
63. Simpson FR, Pajewski NM, Nicklas B, et al.; Indices for Accelerated Aging in Obesity and Diabetes Ancillary Study of the Action for Health in Diabetes (Look AHEAD) Trial. Impact of multidomain lifestyle intervention on frailty through the lens of deficit accumulation in adults with type 2 diabetes mellitus. J Gerontol A Biol Sci Med Sci 2020;75:1921–1927
64. Espeland MA, Gaussoin SA, Bahnson J, et al. Impact of an 8-year intensive lifestyle intervention on an index of multimorbidity. J Am Geriatr Soc 2020;68:2249–2256
65. Gregg EW, Lin J, Bardenheier B, et al.; Look AHEAD Study Group. Impact of intensive lifestyle intervention on disability-free life expectancy: the Look AHEAD study. Diabetes Care 2018;41:1040–1048
66. Valencia WM, Florez H. Pharmacological treatment of diabetes in older people. Diabetes Obes Metab 2014;16:1192–1203
67. Zhang JX, Bhaumik D, Huang ES, Meltzer DO. Change in insurance status and cost-related medication non-adherence among older U.S. adults with diabetes from 2010 to 2014. J Health Med Econ 2018;4:7
68. Schmittdiel JA, Steers N, Duru OK, et al. Patient-provider communication regarding drug costs in Medicare Part D beneficiaries with diabetes: a TRIAD study. BMC Health Serv Res 2010;10:164
69. Patel MR, Resnicow K, Lang I, Kraus K, Heisler M. Solutions to address diabetes-related financial burden and cost-related nonadherence: results from a pilot study. Health Educ Behav 2018;45:101–111
70. Andreassen LM, Sandberg S, Kristensen GBB, Sølvik UØ, Kjome RLS. Nursing home patients with diabetes: prevalence, drug treatment and glycemic control. Diabetes Res Clin Pract 2014;105:102–109
71. Lipska KJ, Ross JS, Miao Y, Shah ND, Lee SJ, Steinman MA. Potential overtreatment of diabetes mellitus in older adults with tight glycemic control. JAMA Intern Med 2015;175:356–362
72. Thorpe CT, Gellad WF, Good CB, et al. Tight glycemic control and use of hypoglycemic medications in older veterans with type 2 diabetes and comorbid dementia. Diabetes Care 2015;38:588–595
73. McAlister FA, Youngson E, Eurich DT. Treatment deintensification is uncommon in adults with type 2 diabetes mellitus: a retrospective cohort study. Circ Cardiovasc Qual Outcomes 2017;10:e003514
74. Weiner JZ, Gopalan A, Mishra P, et al. Use and discontinuation of insulin treatment among adults aged 75 to 79 years with type 2 diabetes. JAMA Intern Med 2019;179:1633-1641
75. Munshi MN, Slyne C, Segal AR, Saul N, Lyons C, Weinger K. Simplification of insulin regimen in older adults and risk of hypoglycemia. JAMA Intern Med 2016;176:1023–1025
76. Sussman JB, Kerr EA, Saini SD, et al. Rates of deintensification of blood pressure and glycemic medication treatment based on levels of control and life expectancy in older patients with diabetes mellitus. JAMA Intern Med 2015;175:1942–1949
77. Abdelhafiz AH, Sinclair AJ. Deintensification of hypoglycaemic medications-use of a systematic review approach to highlight safety concerns in older people with type 2 diabetes. J Diabetes Complications 2018;32:444–450
78. Seidu S, Kunutsor SK, Topsever P, Hambling CE, Cos FX, Khunti K. Deintensification in older patients with type 2 diabetes: a systematic review of approaches, rates and outcomes. Diabetes Obes Metab 2019;21:1668–1679
79. Munshi MN, Slyne C, Segal AR, Saul N, Lyons C, Weinger K. Liberating A1C goals in older adults may not protect against the risk of hypoglycemia. J Diabetes Complications 2017;31:1197–1199
80. Leung E, Wongrakpanich S, Munshi MN. Diabetes management in the elderly. Diabetes Spectr 2018;31:245–253
81. Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. JAMA 2014;312:2668–2675
82. Schwartz AV, Chen H, Ambrosius WT, et al. Effects of TZD use and discontinuation on fracture rates in ACCORD Bone Study. J Clin Endocrinol Metab 2015;100:4059–4066
83. Billington EO, Grey A, Bolland MJ. The effect of thiazolidinediones on bone mineral density and bone turnover: systematic review and meta-analysis. Diabetologia 2015;58:2238–2246
84. American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2015;63:2227–2246
85. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018: a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669–2701
86. Leiter LA, Teoh H, Braunwald E, et al.; SAVOR-TIMI 53 Steering Committee and Investigators. Efficacy and safety of saxagliptin in older participants in the SAVOR-TIMI 53 trial. Diabetes Care 2015;38:1145–1153
87. Green JB, Bethel MA, Armstrong PW, et al.; TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;373:232–242
88. White WB, Cannon CP, Heller SR, et al.; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327–1335
89. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–322
90. Gilbert MP, Bain SC, Franek E, Jodar-Gimeno E, Nauck MA, Pratley R, et al. Effect of liraglutide on cardiovascular outcomes in elderly patients: a post hoc analysis of a randomized controlled trial. Ann Intern Med. 2019;170:423–426
91. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. The Lancet 2018;392:1519–1529
92. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2019;381:841-51
93. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128
94. Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in

type 2 diabetes. N Engl J Med 2017;377:644–657
95. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380:347–357
96. Livingstone SJ, Levin D, Looker HC, et al.; Scottish Diabetes Research Network epidemiology group; Scottish Renal Registry. Estimated life expectancy in a Scottish cohort with type 1 diabetes, 2008-2010. JAMA 2015;313:37–44
97. Miller RG, Secrest AM, Sharma RK, Songer TJ, Orchard TJ. Improvements in the life expectancy of type 1 diabetes: the Pittsburgh Epidemiology of Diabetes Complications study cohort. Diabetes 2012;61:2987–2992
98. Bullard KM. Prevalence of diagnosed diabetes in adults by diabetes type—United States, 2016. MMWR 30 March 2018;67;359–361
99. Chiang JL, Kirkman MS, Laffel LMB, Peters AL. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. Diabetes Care 2014;37:2034–2054
100. Heise T, Nosek L, Rønn BB, et al. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. Diabetes 2004; 53:1614–1620
101. Ruedy KJ, Parkin CG, Riddlesworth TD, Graham C; DIAMOND Study Group. Continuous glucose monitoring in older adults with type 1 and type 2 diabetes using multiple daily injections of insulin: results from the DIAMOND trial. J Diabetes Sci Technol 2017;11: 1138–1146
102. Munshi MN, Florez H, Huang ES, et al. Management of diabetes in long-term care and skilled nursing facilities: a position statement of the American Diabetes Association. Diabetes Care 2016;39:308–318
103. Sinclair A, Morley JE, Rodriguez-Mañas L, et al. Diabetes mellitus in older people: position statement on behalf of the International Association of Gerontology and Geriatrics (IAGG), the European Diabetes Working Party for Older People (EDWPOP), and the International Task Force of Experts in Diabetes. J Am Med Dir Assoc 2012;13:497–502
104. Dorner B, Friedrich EK, Posthauer ME. Practice paper of the American Dietetic Association: Individualized nutrition approaches for older adults in health care communities. J Am Diet Assoc 2010;110:1554–1563
105. Migdal A, Yarandi SS, Smiley D, Umpierrez GE. Update on diabetes in the elderly and in nursing home residents. J Am Med Dir Assoc 2011;12:627–632.e2
106. Pasquel FJ, Powell W, Peng L, et al. A randomized controlled trial comparing treatment with oral agents and basal insulin in elderly patients with type 2 diabetes in long-term care facilities. BMJ Open Diabetes Res Care 2015;3: e000104
107. Quinn K, Hudson P, Dunning T. Diabetes management in patients receiving palliative care. J Pain Symptom Manage 2006;32:275–286
108. Kutner JS, Blatchford PJ, Taylor DH Jr, et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. JAMA Intern Med 2015;175: 691–700
109. Dunning T, Martin P. Palliative and end of life care of people with diabetes: issues, challenges and strategies. Diabetes Res Clin Pract 2018;143:454–463
110. Bouça-Machado R, Rosário M, Alarcão J, Correia-Guedes L, Abreu D, Ferreira JJ. Clinical trials in palliative care: a systematic review of their methodological characteristics and of the quality of their reporting. BMC Palliat Care 2017; 16:10
111. Ford-Dunn S, Smith A, Quin J. Management of diabetes during the last days of life: attitudes of consultant diabetologists and consultant palliative care physicians in the UK. Palliat Med 2006;20:197–203
112. Petrillo LA, Gan S, Jing B, Lang-Brown S, Boscardin WJ, Lee SJ. Hypoglycemia in hospice patients with type 2 diabetes in a national sample of nursing homes. JAMA Intern Med 2018;178: 713–715
113. Mallery LH, Ransom T, Steeves B, Cook B, Dunbar P, Moorhouse P. Evidence-informed guidelines for treating frail older adults with type 2 diabetes: from the Diabetes Care Program of Nova Scotia (DCPNS) and the Palliative and Therapeutic Harmonization (PATH) program. J Am Med Dir Assoc 2013; 14:801–808

13. Children and Adolescents: *Standards of Medical Care in Diabetes—2021*

American Diabetes Association

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The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc21-SPPC), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc21-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

The management of diabetes in children and adolescents cannot simply be derived from care routinely provided to adults with diabetes. The epidemiology, pathophysiology, developmental considerations, and response to therapy in pediatric-onset diabetes are different from adult diabetes. There are also differences in recommended care for children and adolescents with type 1 diabetes, type 2 diabetes, and other forms of pediatric diabetes. This section first addresses care for children and adolescents with type 1 diabetes and next addresses care for children and adolescents with type 2 diabetes. Monogenic diabetes (neonatal diabetes and maturity-onset diabetes in the young [MODY]) and cystic fibrosis–related diabetes, which often present in youth, are discussed in Section 2 "Classification and Diagnosis of Diabetes" (https://doi.org/10.2337/dc21-S002). Lastly, guidance is provided in this section on transition of care from pediatric to adult providers to ensure that the continuum of care is appropriate as an adolescent with diabetes becomes an adult. Due to the nature of clinical pediatric research, the recommendations for children and adolescents with diabetes are less likely to be based on clinical trial evidence. However, expert opinion and a review of available and relevant experimental data are summarized in the American Diabetes Association (ADA) position statements "Type 1 Diabetes in Children and Adolescents" (1) and "Evaluation and Management of Youth-Onset Type 2 Diabetes" (2). The ADA consensus report "Youth-Onset Type 2 Diabetes Consensus Report: Current Status, Challenges, and Priorities" (3) characterizes type 2 diabetes in children and evaluates treatment options but also discusses knowledge gaps and recruitment challenges in clinical and translational research in youth-onset type 2 diabetes.

TYPE 1 DIABETES

Type 1 diabetes is the most common form of diabetes in youth (4), although data suggest that it may account for a large proportion of cases diagnosed in adult life (5).

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The provider must consider the unique aspects of care and management of children and adolescents with type 1 diabetes, such as changes in insulin sensitivity related to physical growth and sexual maturation, ability to provide self-care, supervision in the childcare and school environment, neurological vulnerability to hypoglycemia and hyperglycemia in young children, and possible adverse neurocognitive effects of diabetic ketoacidosis (DKA) (6,7). Attention to family dynamics, developmental stages, and physiologic differences related to sexual maturity is essential in developing and implementing an optimal diabetes treatment plan (8).

A multidisciplinary team of specialists trained in pediatric diabetes management and sensitive to the challenges of children and adolescents with type 1 diabetes and their families should provide care for this population. It is essential that diabetes self-management education and support, medical nutrition therapy, and psychosocial support be provided at diagnosis and regularly thereafter in a developmentally appropriate format that builds on prior knowledge by individuals experienced with the biological, educational, nutritional, behavioral, and emotional needs of the growing child and family. The appropriate balance between adult supervision and independent self-care should be defined at the first interaction and reevaluated at subsequent visits, with the expectation that it will evolve as the adolescent gradually becomes an emerging adult.

Diabetes Self-Management Education and Support

Recommendation

13.1 Youth with type 1 diabetes and their parents/caregivers (for patients aged <18 years) should receive culturally sensitive and developmentally appropriate individualized diabetes self-management education and support according to national standards at diagnosis and routinely thereafter. **B**

No matter how sound the medical regimen, it can only be effective if the family and/or affected individuals are able to implement it. Family involvement is a vital component of optimal diabetes management throughout childhood and adolescence. The pediatric diabetes care team must be capable of evaluating the educational, behavioral, emotional, and psychosocial factors that impact implementation of a treatment plan and must work with the individual and family to overcome barriers or redefine goals as appropriate. Diabetes self-management education and support requires periodic reassessment, especially as the youth grows, develops, and acquires the need for greater independent self-care skills. In addition, it is necessary to assess the educational needs and skills of, and provide training to, day care workers, school nurses, and school personnel who are responsible for the care and supervision of the child with diabetes (9–11).

Nutrition Therapy

Recommendations

13.2 Individualized medical nutrition therapy is recommended for children and adolescents with type 1 diabetes as an essential component of the overall treatment plan. **A**

13.3 Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, is key to achieving optimal glycemic control. **B**

13.4 Comprehensive nutrition education at diagnosis, with annual updates, by an experienced registered dietitian nutritionist is recommended to assess caloric and nutrition intake in relation to weight status and cardiovascular disease risk factors and to inform macronutrient choices. **E**

Dietary management should be individualized: family habits, food preferences, religious or cultural needs, finances, schedules, physical activity, and the patient's and family's abilities in numeracy, literacy, and self-management should be considered. Visits with a registered dietitian nutritionist should include assessment for changes in food preferences over time, access to food, growth and development, weight status, cardiovascular risk, and potential for eating disorders. Dietary adherence is associated with better glycemic control in youth with type 1 diabetes (12).

Physical Activity and Exercise

Recommendations

13.5 Exercise is recommended for all children and adolescents with type 1 diabetes with the goal of 60 min of moderate- to vigorous-intensity aerobic activity daily, with vigorous muscle-strengthening and bone-strengthening activities at least 3 days per week. **C**

13.6 Education about frequent patterns of glycemia during and after exercise, which may include initial transient hyperglycemia followed by hypoglycemia, is essential. Families should also receive education on prevention and management of hypoglycemia during and after exercise, including ensuring patients have a pre-exercise glucose level of 90–250 mg/dL (5.0–13.9 mmol/L) and accessible carbohydrates before, during, and after engaging in activity, individualized according to the type/intensity of the planned physical activity. **E**

13.7 Patients should be educated on strategies to prevent hypoglycemia during exercise, after exercise, and overnight following exercise, which may include reducing prandial insulin dosing for the meal/snack preceding (and, if needed, following) exercise, reducing basal insulin doses, increasing carbohydrate intake, eating bedtime snacks, and/or using continuous glucose monitoring. **C**

13.8 Frequent glucose monitoring before, during, and after exercise, with or without use of continuous glucose monitoring, is important to prevent, detect, and treat hypoglycemia and hyperglycemia with exercise. **C**

Exercise positively impacts metabolic and psychological health in children with type 1 diabetes (13). While it affects insulin sensitivity, physical fitness, strength building, weight management, social interaction, mood, self-esteem building, and creation of healthful habits for adulthood, it also has the potential to cause both hypoglycemia and hyperglycemia.

See below for strategies to mitigate hypoglycemia risk and minimize hyperglycemia with exercise. For an in-depth discussion, see recently published reviews and guidelines (14–16).

Overall, it is recommended that youth participate in 60 min of moderate- (e.g., brisk walking, dancing) to vigorous- (e.g., running, jumping rope) intensity aerobic activity daily, including resistance and flexibility training (17). Although uncommon in the pediatric population, patients should be medically evaluated for comorbid conditions or diabetes complications that may restrict participation in an exercise program. As hyperglycemia can occur before, during, and after physical activity, it is important to ensure that the elevated glucose level is not related to insulin deficiency that would lead to worsening hyperglycemia with exercise and ketosis risk. Intense activity should be postponed with marked hyperglycemia (glucose ≥350 mg/dL [19.4 mmol/L]), moderate to large urine ketones, and/or β-hydroxybutyrate (B-OHB) >1.5 mmol/L. Caution may be needed when B-OHB levels are ≥0.6 mmol/L (12,14).

The prevention and treatment of hypoglycemia associated with physical activity include decreasing the prandial insulin for the meal/snack before exercise and/or increasing food intake. Patients on insulin pumps can lower basal rates by ~10–50% or more or suspend for 1–2 h during exercise (18). Decreasing basal rates or long-acting insulin doses by ~20% after exercise may reduce delayed exercise-induced hypoglycemia (19). Accessible rapid-acting carbohydrates and frequent blood glucose monitoring before, during, and after exercise, with or without continuous glucose monitoring, maximize safety with exercise.

Blood glucose targets prior to exercise should be 90–250 mg/dL (5.0–13.9 mmol/L). Consider additional carbohydrate intake during and/or after exercise, depending on the duration and intensity of physical activity, to prevent hypoglycemia. For low-to-moderate intensity aerobic activities (30–60 min), and if the patient is fasting, 10–15 g of carbohydrate may prevent hypoglycemia (20). After insulin boluses (relative hyperinsulinemia), consider 0.5–1.0 g of carbohydrates/kg per hour of exercise (~30–60 g), which is similar to carbohydrate requirements to optimize performance in athletes without type 1 diabetes (21–23).

In addition, obesity is as common in children and adolescents with type 1 diabetes as in those without diabetes. It is associated with higher frequency of cardiovascular risk factors, and it disproportionately affects racial/ethnic minorities in the U.S. (24–28). Therefore, diabetes care providers should monitor weight status and encourage a healthy diet, exercise, and healthy weight as key components of pediatric type 1 diabetes care.

School and Child Care

As a large portion of a child's day is spent in school and/or day care, training of school or day care personnel to provide care in accordance with the child's individualized diabetes medical management plan is essential for optimal diabetes management and safe access to all school or day care sponsored opportunities (10,11,29). In addition, federal and state laws require schools, day care facilities, and other entities to provide needed diabetes care to enable the child to safely access the school or day care environment. Refer to the ADA position statements "Diabetes Care in the School Setting" (10) and "Care of Young Children With Diabetes in the Child Care Setting" (11) and ADA's Safe at School website (https://www.diabetes.org/resources/know-your-rights/safe-at-school-state-laws) for additional details.

Psychosocial Issues

Recommendations

13.9 At diagnosis and during routine follow-up care, assess psychosocial issues and family stresses that could impact diabetes management and provide appropriate referrals to trained mental health professionals, preferably experienced in childhood diabetes. **E**

13.10 Mental health professionals should be considered integral members of the pediatric diabetes multidisciplinary team. **E**

13.11 Encourage developmentally appropriate family involvement in diabetes management tasks for children and adolescents, recognizing that premature transfer of diabetes care to the child can result in diabetes burnout, nonadherence, and deterioration in glycemic control. **A**

13.12 Providers should assess food security, housing stability/homelessness, health literacy, financial barriers, and social/community support and apply that information to treatment decisions. **E**

13.13 Providers should consider asking youth and their parents about social adjustment (peer relationships) and school performance to determine whether further intervention is needed. **B**

13.14 Assess youth with diabetes for psychosocial and diabetes-related distress, generally starting at 7–8 years of age. **B**

13.15 Offer adolescents time by themselves with their care provider(s) starting at age 12 years, or when developmentally appropriate. **E**

13.16 Starting at puberty, preconception counseling should be incorporated into routine diabetes care for all girls of childbearing potential. **A**

13.17 Begin screening youth with type 1 diabetes for eating disorders between 10 and 12 years of age. The Diabetes Eating Problems Survey-Revised (DEPS-R) is a reliable, valid, and brief screening tool for identifying disturbed eating behavior. **B**

Rapid and dynamic cognitive, developmental, and emotional changes occur during childhood, adolescence, and emerging adulthood. Diabetes management during childhood and adolescence places substantial burdens on the youth and family, necessitating ongoing assessment of psychosocial status, social determinants of health, and diabetes distress in the patient and the caregiver during routine diabetes visits (30–38). It is important to consider the impact of diabetes on quality of life as well as the development of mental health problems related to diabetes distress, fear of hypoglycemia (and hyperglycemia), symptoms of anxiety, disordered eating behaviors and eating disorders, and symptoms of depression (39). Consider assessing youth for diabetes distress, generally starting at 7 or 8 years of age (40). Consider screening for depression and disordered eating behaviors using available screening tools (30,41). Early detection of depression, anxiety, eating disorders, and learning disabilities can facilitate effective treatment options and help minimize adverse effects on diabetes management and disease outcomes (35,40). There are

validated tools, such as the Problem Areas in Diabetes-Teen (PAID-T) and Parent (P-PAID-T) (36), that can be used in assessing diabetes-specific distress in youth starting at age 12 years and in their parent caregivers. Furthermore, the complexities of diabetes management require ongoing parental involvement in care throughout childhood with developmentally appropriate family teamwork between the growing child/teen and parent in order to maintain adherence and to prevent deterioration in glycemic control (42,43). As diabetes-specific family conflict is related to poorer adherence and glycemic control, it is appropriate to inquire about such conflict during visits and to either help to negotiate a plan for resolution or refer to an appropriate mental health specialist (44). Monitoring of social adjustment (peer relationships) and school performance can facilitate both well-being and academic achievement (45). Suboptimal glycemic control is a risk factor for underperformance at school and increased absenteeism (46).

Shared decision-making with youth regarding the adoption of regimen components and self-management behaviors can improve diabetes self-efficacy, adherence, and metabolic outcomes (25,47). Although cognitive abilities vary, the ethical position often adopted is the "mature minor rule," whereby children after age 12 or 13 years who appear to be "mature" have the right to consent or withhold consent to general medical treatment, except in cases in which refusal would significantly endanger health (48).

Beginning at the onset of puberty or at diagnosis of diabetes, all adolescent girls and women with childbearing potential should receive education about the risks of malformations associated with poor metabolic control and the use of effective contraception to prevent unplanned pregnancy. Preconception counseling using developmentally appropriate educational tools enables adolescent girls to make well-informed decisions (49). Preconception counseling resources tailored for adolescents are available at no cost through the ADA (50). Refer to the ADA position statement "Psychosocial Care for People With Diabetes" for further details (40).

Youth with type 1 diabetes have an increased risk of disordered eating behavior as well as clinical eating disorders with serious short-term and long-term negative effects on diabetes outcomes and health in general. It is important to recognize the unique and dangerous disordered eating behavior of insulin omission for weight control in type 1 diabetes (51) using tools such as the Diabetes Eating Problems Survey-Revised (DEPS-R) to allow for early diagnosis and intervention (41,52–54).

The presence of a mental health professional on pediatric multidisciplinary teams highlights the importance of attending to the psychosocial issues of diabetes. These psychosocial factors are significantly related to self-management difficulties, suboptimal glycemic control, reduced quality of life, and higher rates of acute and chronic diabetes complications.

Glycemic Control

Recommendations

13.18 Whenever possible, children and adolescents with type 1 diabetes should be treated with intensive insulin regimens, either via multiple daily injections or continuous subcutaneous insulin infusion. **A**

13.19 All children and adolescents with type 1 diabetes should self-monitor glucose levels multiple times daily (up to 6–10 times/day by glucose meter or continuous glucose monitoring), including prior to meals and snacks, at bedtime, and as needed for safety in specific situations such as exercise, driving, or the presence of symptoms of hypoglycemia. **B**

13.20 When used properly, real-time continuous glucose monitoring in conjunction with insulin therapy is a useful tool to lower and/or maintain A1C levels and/or reduce hypoglycemia. **A**

13.21 When used properly, intermittently scanned continuous glucose monitoring in conjunction with insulin therapy can be useful to replace self-monitoring of blood glucose. **B**

13.22 Automated insulin delivery systems may be considered to improve glycemic control. **A**

13.23 A1C goals must be individualized and reassessed over time. An A1C of <7% (53 mmol/mol) is appropriate for many children. **B**

13.24 Less stringent A1C goals (such as <7.5% [58 mmol/mol]) may be appropriate for patients who cannot articulate symptoms of hypoglycemia; have hypoglycemia unawareness; lack access to analog insulins, advanced insulin delivery technology, and/or continuous glucose monitoring; cannot check blood glucose regularly; or have nonglycemic factors that increase A1C (e.g., high glycators). **B**

13.25 Even less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, or where the harms of treatment are greater than the benefits. **B**

13.26 Providers may reasonably suggest more stringent A1C goals (such as <6.5% [48 mmol/mol]) for selected individual patients if they can be achieved without significant hypoglycemia, negative impacts on well-being, or undue burden of care, or in those who have nonglycemic factors that decrease A1C (e.g., lower erythrocyte life span). Lower targets may also be appropriate during the honeymoon phase. **B**

13.27 Continuous glucose monitoring (CGM) metrics derived from CGM use over the most recent 14 days (or longer for patients with more glycemic variability), including time in ranges (within target, below target, and above target), are recommended to be used in conjunction with A1C whenever possible. **E**

Current standards for diabetes management reflect the need to minimize hyperglycemia as safely as possible. The Diabetes Control and Complications Trial (DCCT), which did not enroll children <13 years of age, demonstrated that near normalization of blood glucose levels was more difficult to achieve in adolescents than in adults. Nevertheless, the increased use of basal-bolus regimens, insulin pumps, frequent blood glucose monitoring, goal setting, and improved patient education has been associated

with more children and adolescents reaching the blood glucose targets recommended by the ADA (55–58), particularly in patients of families in which both the parents and the child with diabetes participate jointly to perform the required diabetes-related tasks.

Lower A1C in adolescence and young adulthood is associated with lower risk and rate of microvascular and macrovascular complications (59–63) and demonstrates the effects of metabolic memory (64–67).

In addition, type 1 diabetes can be associated with adverse effects on cognition during childhood and adolescence (6,68,69), and neurocognitive imaging differences related to hyperglycemia in children provide another motivation for lowering glycemic targets (6). DKA has been shown to cause adverse effects on brain development and function. Additional factors (70–73) that contribute to adverse effects on brain development and function include young age, severe hypoglycemia at <6 years of age, and chronic hyperglycemia (74,75). However, meticulous use of new therapeutic modalities such as rapid- and long-acting insulin analogs, technological advances (e.g., continuous glucose monitoring [CGM], sensor-augmented pump therapy with automatic low glucose suspend, and automated insulin delivery systems), and intensive self-management education now make it more feasible to achieve excellent glycemic control while reducing the incidence of severe hypoglycemia (76–86).

In selecting individualized glycemic targets, the long-term health benefits of achieving a lower A1C should be balanced against the risks of hypoglycemia and the developmental burdens of intensive regimens in children and youth. Recent data with newer devices and insulins indicate that the risk of hypoglycemia with lower A1C is less than it was before (77,87–95). Some data suggest that there could be a threshold where lower A1C is associated with more hypoglycemia (96,97); however, the confidence intervals were large, suggesting great variability. In addition, achieving lower A1C levels is likely facilitated by setting lower A1C targets (98,99). Lower goals may be possible during the "honeymoon" phase of type 1 diabetes. Special consideration should be given to the risk of hypoglycemia in young children (aged <6 years) who are often unable to recognize, articulate, and/or manage hypoglycemia. However, registry data indicate that A1C targets can be achieved in children, including those aged <6 years, without increased risk of severe hypoglycemia (87,98). Recent data have demonstrated that the use of real-time CGM lowered A1C and increased time in range in adolescents and young adults and, in children aged <8 years old, was associated with lower risk of hypoglycemia (100,101).

A strong relationship exists between frequency of blood glucose monitoring and glycemic control (78–85,102,103). All children and adolescents with type 1 diabetes should self-monitor glucose levels multiple times daily by glucose meter or CGM. In the U.S., real-time CGM is approved for nonadjunctive use in children aged 2 years and older, and intermittently scanned CGM is approved for nonadjunctive use in children aged 4 years and older. Metrics derived from CGM include percent time in target range, below target range, and above target range (104). While studies indicate a relation between time in range and A1C (105,106), it is still uncertain what the ideal target time in range should be for children, and further studies are needed. Please refer to Section 7 "Diabetes Technology" (https://doi.org/10.2337/dc21-S007) for more information on the use of blood glucose meters, CGM, and insulin pumps. More information on insulin injection technique can be found in Section 9 "Pharmacologic Approaches to Glycemic Treatment" (https://doi.org/10.2337/dc21-S009).

Key Concepts in Setting Glycemic Targets

- Targets should be individualized, and lower targets may be reasonable based on a benefit-risk assessment.
- Blood glucose targets should be modified in children with frequent hypoglycemia or hypoglycemia unawareness.
- Postprandial blood glucose values should be measured when there is a discrepancy between preprandial blood glucose values and A1C levels and to assess preprandial insulin doses in those on basal-bolus or pump regimens.

Autoimmune Conditions

Recommendation

13.28 Assess for additional autoimmune conditions soon after the diagnosis of type 1 diabetes and if symptoms develop. **B**

Because of the increased frequency of other autoimmune diseases in type 1 diabetes, screening for thyroid dysfunction and celiac disease should be considered (107–111). Periodic screening in asymptomatic individuals has been recommended, but the optimal frequency of screening is unclear.

Although much less common than thyroid dysfunction and celiac disease, other autoimmune conditions, such as Addison disease (primary adrenal insufficiency), autoimmune hepatitis, autoimmune gastritis, dermatomyositis, and myasthenia gravis, occur more commonly in the population with type 1 diabetes than in the general pediatric population and should be assessed and monitored as clinically indicated. In addition, relatives of patients should be offered testing for islet autoantibodies through research studies (e.g., TrialNet) for early diagnosis of preclinical type 1 diabetes (stages 1 and 2).

Thyroid Disease

Recommendations

13.29 Consider testing children with type 1 diabetes for antithyroid peroxidase and antithyroglobulin antibodies soon after diagnosis. **B**

13.30 Measure thyroid-stimulating hormone concentrations at diagnosis when clinically stable or soon after glycemic control has been established. If normal, suggest rechecking every 1–2 years or sooner if the patient has positive thyroid antibodies or develops symptoms or signs suggestive of thyroid dysfunction, thyromegaly, an abnormal growth rate, or unexplained glycemic variability. **B**

Autoimmune thyroid disease is the most common autoimmune disorder associated with diabetes, occurring in 17–30% of patients with type 1 diabetes (108,112,113). At the time of diagnosis, ~25% of children with type 1 diabetes have thyroid autoantibodies (114), the presence of which is predictive of thyroid dysfunction—most commonly hypothyroidism, although hyperthyroidism occurs in ~0.5% of patients with type 1 diabetes (115,116). For

thyroid autoantibodies, a study from Sweden indicated that antithyroid peroxidase antibodies were more predictive than antithyroglobulin antibodies in multivariate analysis (117). Thyroid function tests may be misleading (euthyroid sick syndrome) if performed at the time of diagnosis owing to the effect of previous hyperglycemia, ketosis or ketoacidosis, weight loss, etc. Therefore, if performed at diagnosis and slightly abnormal, thyroid function tests should be repeated soon after a period of metabolic stability and achievement of glycemic targets. Subclinical hypothyroidism may be associated with increased risk of symptomatic hypoglycemia (118) and reduced linear growth rate. Hyperthyroidism alters glucose metabolism and usually causes deterioration of glycemic control.

Celiac Disease

Recommendations

13.31 Screen children with type 1 diabetes for celiac disease by measuring IgA tissue transglutaminase (tTG) antibodies, with documentation of normal total serum IgA levels, soon after the diagnosis of diabetes, or IgG to tTG and deamidated gliadin antibodies if IgA deficient. **B**

13.32 Repeat screening within 2 years of diabetes diagnosis and then again after 5 years and consider more frequent screening in children who have symptoms or a first-degree relative with celiac disease. **B**

13.33 Individuals with confirmed celiac disease should be placed on a gluten-free diet for treatment and to avoid complications; they should also have a consultation with a dietitian experienced in managing both diabetes and celiac disease. **B**

Celiac disease is an immune-mediated disorder that occurs with increased frequency in patients with type 1 diabetes (1.6–16.4% of individuals compared with 0.3–1% in the general population) (107,110,111,119–123). Screening patients with type 1 diabetes for celiac disease is further justified by its association with osteoporosis, iron deficiency, growth failure, and potential increased risk of retinopathy and albuminuria (124–127).

Screening for celiac disease includes measuring serum levels of IgA and tissue transglutaminase antibodies, or, with IgA deficiency, screening can include measuring IgG tissue transglutaminase antibodies or IgG deamidated gliadin peptide antibodies. Because most cases of celiac disease are diagnosed within the first 5 years after the diagnosis of type 1 diabetes, screening should be considered at the time of diagnosis and repeated at 2 and then 5 years (121) or if clinical symptoms indicate, such as poor growth or increased hypoglycemia (122,124).

Although celiac disease can be diagnosed more than 10 years after diabetes diagnosis, there are insufficient data after 5 years to determine the optimal screening frequency. Measurement of tissue transglutaminase antibody should be considered at other times in patients with symptoms suggestive of celiac disease (121). Monitoring for symptoms should include assessment of linear growth and weight gain (122,124). A small bowel biopsy in antibody-positive children is recommended to confirm the diagnosis (128). European guidelines on screening for celiac disease in children (not specific to children with type 1 diabetes) suggest that biopsy may not be necessary in symptomatic children with high antibody titers (i.e., greater than 10 times the upper limit of normal) provided that further testing is performed (verification of endomysial antibody positivity on a separate blood sample). Whether this approach may be appropriate for asymptomatic children in high-risk groups remains an open question, though evidence is emerging (129). It is also advisable to check for celiac disease–associated HLA types in patients who are diagnosed without a small intestinal biopsy. In symptomatic children with type 1 diabetes and confirmed celiac disease, gluten-free diets reduce symptoms and rates of hypoglycemia (130). The challenging dietary restrictions associated with having both type 1 diabetes and celiac disease place a significant burden on individuals. Therefore, a biopsy to confirm the diagnosis of celiac disease is recommended, especially in asymptomatic children, before establishing a diagnosis of celiac disease (131) and endorsing significant dietary changes. A gluten-free diet was beneficial in asymptomatic adults with positive antibodies confirmed by biopsy (132).

Management of Cardiovascular Risk Factors

Hypertension Screening

Recommendation

13.34 Blood pressure should be measured at each routine visit. Children found to have elevated blood pressure (systolic blood pressure or diastolic blood pressure ≥90th percentile for age, sex, and height or, in adolescents ≥13 years, systolic blood pressure 120–129 mmHg with diastolic blood pressure <80 mmHg) or hypertension (systolic blood pressure or diastolic blood pressure ≥95th percentile for age, sex, and height or, in adolescents ≥13 years, systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg) should have elevated blood pressure confirmed on three separate days. **B**

Hypertension Treatment

Recommendations

13.35 Initial treatment of elevated blood pressure (systolic blood pressure or diastolic blood pressure consistently ≥90th percentile for age, sex, and height or ≥120/80 mmHg in adolescents ≥13 years) includes dietary modification and increased exercise, if appropriate, aimed at weight control. If target blood pressure is not reached within 3–6 months of initiating lifestyle intervention, pharmacologic treatment should be considered. **E**

13.36 In addition to lifestyle modification, pharmacologic treatment of hypertension (systolic blood pressure or diastolic blood pressure consistently ≥95th percentile for age, sex, and height or ≥140/90 mmHg in adolescents ≥13 years) should be considered as soon as hypertension is confirmed. **E**

13.37 ACE inhibitors or angiotensin receptor blockers should be considered for the initial pharmacologic treatment of hypertension **E** in children and adolescents, following reproductive counseling due to the potential teratogenic effects of both drug classes. **E**

13.38 The goal of treatment is blood pressure consistently <90th percentile for age, sex, and height or <120/<80 mmHg in children ≥13 years. **E**

Blood pressure measurements should be performed using the appropriate size cuff with the child seated and relaxed. Hypertension should be confirmed on at least three separate days. Evaluation should proceed as clinically indicated (133). Treatment is generally initiated with an ACE inhibitor, but an angiotensin receptor blocker can be used if the ACE inhibitor is not tolerated (e.g., due to cough) (134).

Dyslipidemia Testing

Recommendations

13.39 Initial lipid testing should be performed when initial glycemic control has been achieved and age is ≥2 years. If initial LDL cholesterol is ≤100 mg/dL (2.6 mmol/L), subsequent testing should be performed at 9–11 years of age. **B** Initial testing may be done with a nonfasting non-HDL cholesterol level with confirmatory testing with a fasting lipid panel.

13.40 If LDL cholesterol values are within the accepted risk level (<100 mg/dL [2.6 mmol/L]), a lipid profile repeated every 3 years is reasonable. **E**

Dyslipidemia Treatment

Recommendations

13.41 If lipids are abnormal, initial therapy should consist of optimizing glucose control and medical nutrition therapy to limit the amount of calories from fat to 25–30%, saturated fat to <7%, cholesterol <200 mg/day, avoidance of *trans* fats, and aim for ~10% calories from monounsaturated fats. **A**

13.42 After the age of 10 years, addition of a statin may be considered in patients who, despite medical nutrition therapy and lifestyle changes, continue to have LDL cholesterol >160 mg/dL (4.1 mmol/L) or LDL cholesterol >130 mg/dL (3.4 mmol/L) and one or more cardiovascular disease risk factors, following reproductive counseling for females because of the potential teratogenic effects of statins. **E**

13.43 The goal of therapy is an LDL cholesterol value <100 mg/dL (2.6 mmol/L). **E**

Population-based studies estimate that 14–45% of children with type 1 diabetes have two or more atherosclerotic cardiovascular disease (ASCVD) risk factors (135–137), and the prevalence of cardiovascular disease (CVD) risk factors increases with age (137) and among racial/ethnic minorities (24), with girls having a higher risk burden than boys (136).

Pathophysiology. The atherosclerotic process begins in childhood, and although ASCVD events are not expected to occur during childhood, observations using a variety of methodologies show that youth with type 1 diabetes may have subclinical CVD within the first decade of diagnosis (138–140). Studies of carotid intima-media thickness have yielded inconsistent results (133,134).

Screening. Diabetes predisposes to development of accelerated arteriosclerosis. Lipid evaluation for these patients contributes to risk assessment and identifies an important proportion of those with dyslipidemia. Therefore, initial screening should be done soon after diagnosis. If the initial screen is normal, subsequent screening may be done at 9–11 years of age, which is a stable time for lipid assessment in children (141). Children with a primary lipid disorder (e.g., familial hyperlipidemia) should be referred to a lipid specialist. Non-HDL cholesterol level has been identified as a significant predictor of the presence of atherosclerosis—as powerful as any other lipoprotein cholesterol measure in children and adolescents. For both children and adults, non-HDL cholesterol level seems to be more predictive of persistent dyslipidemia and, therefore, atherosclerosis and future events than total cholesterol, LDL cholesterol, or HDL cholesterol levels alone. A major advantage of non-HDL cholesterol is that it can be accurately calculated in a nonfasting state and is therefore practical to obtain in clinical practice as a screening test (142). Youth with type 1 diabetes have a high prevalence of lipid abnormalities (135,143).

Even if normal, screening should be repeated within 3 years, as glycemic control and other cardiovascular risk factors can change dramatically during adolescence (144).

Treatment. Pediatric lipid guidelines provide some guidance relevant to children with type 1 diabetes and secondary dyslipidemia (133,141,145,146); however, there are few studies on modifying lipid levels in children with type 1 diabetes. A 6-month trial of dietary counseling produced a significant improvement in lipid levels (147); likewise, a lifestyle intervention trial with 6 months of exercise in adolescents demonstrated improvement in lipid levels (148). Data from the SEARCH for Diabetes in Youth (SEARCH) study show that improved glucose over a 2-year period is associated with a more favorable lipid profile; however, improved glycemia alone will not normalize lipids in youth with type 1 diabetes and dyslipidemia (144).

Although intervention data are sparse, the American Heart Association categorizes children with type 1 diabetes in the highest tier for cardiovascular risk and recommends both lifestyle and pharmacologic treatment for those with elevated LDL cholesterol levels (146,149). Initial therapy should be with a nutrition plan that restricts saturated fat to 7% of total calories and dietary cholesterol to 200 mg/day. Data from randomized clinical trials in children as young as 7 months of age indicate that this diet is safe and does not interfere with normal growth and development (150).

Neither long-term safety nor cardiovascular outcome efficacy of statin therapy has been established for children; however, studies have shown short-term safety equivalent to that seen in adults and efficacy in lowering LDL cholesterol levels in familial hypercholesterolemia or severe hyperlipidemia, improving endothelial function and causing regression of carotid intimal thickening (151,152). Statins are not approved for patients aged <10 years, and statin treatment should generally not be used in children with type 1 diabetes before this age.

Statins are contraindicated in pregnancy; therefore, prevention of unplanned pregnancies is of paramount importance. Statins should be avoided in females of childbearing age who are sexually active and not using reliable contraception (see Section 14 "Management of Diabetes in Pregnancy," https://doi.org/10.2337/dc21-S014, for more information). The multicenter, randomized, placebo-controlled Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT) provides safety data on pharmacologic treatment with an ACE inhibitor and statin in adolescents with type 1 diabetes.

Smoking

Recommendations

13.44 Elicit a smoking history at initial and follow-up diabetes visits; discourage smoking in youth who do not smoke and encourage smoking cessation in those who do smoke. **A**

13.45 Electronic cigarette use should be discouraged. **A**

The adverse health effects of smoking are well recognized with respect to future cancer and CVD risk. Despite this, smoking rates are significantly higher among youth with diabetes than among youth without diabetes (153,154). In youth with diabetes, it is important to avoid additional CVD risk factors. Smoking increases the risk of onset of albuminuria; therefore, smoking avoidance is important to prevent both microvascular and macrovascular complications (141,155). Discouraging cigarette smoking, including electronic cigarettes (156,157), is an important part of routine diabetes care. In light of recent Centers for Disease Control and Prevention evidence of deaths related to electronic cigarette use (158,159), no persons should be advised to use electronic cigarettes, either as a way to stop smoking tobacco or as a recreational drug. In younger children, it is important to assess exposure to cigarette smoke in the home because of the adverse effects of secondhand smoke and to discourage youth from ever smoking.

Microvascular Complications

Nephropathy Screening

Recommendation

13.46 Annual screening for albuminuria with a random (morning sample preferred to avoid effects of exercise) spot urine sample for albumin-to-creatinine ratio should be considered at puberty or at age >10 years, whichever is earlier, once the child has had diabetes for 5 years. **B**

Nephropathy Treatment

Recommendation

13.47 An ACE inhibitor or an angiotensin receptor blocker, titrated to normalization of albumin excretion, may be considered when elevated urinary albumin-to-creatinine ratio (>30 mg/g) is documented (two of three urine samples obtained over a 6-month interval following efforts to improve glycemic control and normalize blood pressure). **E**

Data from 7,549 participants <20 years of age in the T1D Exchange clinic registry emphasize the importance of good glycemic and blood pressure control, particularly as diabetes duration increases, in order to reduce the risk of diabetic kidney disease. The data also underscore the importance of routine screening to ensure early diagnosis and timely treatment of albuminuria (160). An estimation of glomerular filtration rate (GFR), calculated using GFR estimating equations from the serum creatinine, height, age, and sex (161), should be considered at baseline and repeated as indicated based on clinical status, age, diabetes duration, and therapies. Improved methods are needed to screen for early GFR loss, since estimated GFR is inaccurate at GFR >60 mL/min/1.73 m^2 (161,162). The AdDIT study in adolescents with type 1 diabetes demonstrated the safety of ACE inhibitor treatment, but the treatment did not change the albumin-to-creatinine ratio over the course of the study (133).

Retinopathy

Recommendations

13.48 An initial dilated and comprehensive eye examination is recommended once youth have had type 1 diabetes for 3–5 years, provided they are aged ≥11 years or puberty has started, whichever is earlier. **B**

13.49 After the initial examination, repeat dilated and comprehensive eye examination every 2 years. Less frequent examinations, every 4 years, may be acceptable on the advice of an eye care professional and based on risk factor assessment, including a history of glycemic control with A1C <8%. **B**

Retinopathy (like albuminuria) most commonly occurs after the onset of puberty and after 5–10 years of diabetes duration (163). It is currently recognized that there is low risk of development of vision-threatening retinal lesions prior to 12 years of age (164,165). A 2019 publication based on the follow-up of the DCCT adolescent cohort supports lower frequency of eye examinations than previously recommended, in particular in adolescents with A1C closer to the target range (166,167). Referrals should be made to eye care professionals with expertise in diabetic retinopathy and experience in counseling pediatric patients and families on the importance of prevention, early detection, and intervention.

Neuropathy

Recommendation

13.50 Consider an annual comprehensive foot exam at the start of puberty or at age ≥10 years, whichever is earlier, once the youth has had type 1 diabetes for 5 years. **B**

Diabetic neuropathy rarely occurs in prepubertal children or after only 1–2 years of diabetes (163), although data suggest a prevalence of distal peripheral neuropathy of 7% in 1,734 youth with type 1 diabetes and association with the presence of CVD risk factors (168,169). A comprehensive foot exam, including inspection, palpation of dorsalis pedis and posterior tibial pulses, and determination of proprioception, vibration, and monofilament sensation, should be performed annually along with an assessment of symptoms of neuropathic pain (169). Foot inspection can be performed at each visit to educate youth regarding the importance of foot care (see Section 11 "Microvascular Complications and Foot Care," https://doi.org/10.2337/dc21-S011).

TYPE 2 DIABETES

For information on risk-based screening for type 2 diabetes and prediabetes in children and adolescents, please refer to Section 2 "Classification and Diagnosis of Diabetes" (https://doi.org/10.2337/dc21-S002). For additional support for these recommendations, see the ADA position statement "Evaluation and Management of Youth-Onset Type 2 Diabetes" (2).

Type 2 diabetes in youth has increased over the past 20 years, and recent estimates suggest an incidence of ~5,000 new cases per year in the U.S. (170). The Centers for Disease Control and Prevention published projections for type 2 diabetes prevalence using the SEARCH database; assuming a 2.3% annual increase, the prevalence in those under 20 years of age will quadruple in 40 years (171,172).

Evidence suggests that type 2 diabetes in youth is different not only from type 1 diabetes but also from type 2 diabetes in adults and has unique features, such as a more rapidly progressive decline in β-cell function and accelerated development of diabetes complications (2,173).Type 2 diabetes disproportionately impacts youth of ethnic and racial minorities and can occur in complex psychosocial and cultural environments, which may make it difficult to sustain healthy lifestyle changes and self-management behaviors (25,174–177). Additional risk factors associated with type 2 diabetes in youth include adiposity, family history of diabetes, female sex, and low socioeconomic status (173).

As with type 1 diabetes, youth with type 2 diabetes spend much of the day in school. Therefore, close communication with and the cooperation of school personnel are essential for optimal diabetes management, safety, and maximal academic opportunities.

Screening and Diagnosis

Recommendations

13.51 Risk-based screening for prediabetes and/or type 2 diabetes should be considered in children and adolescents after the onset of puberty or ≥10 years of age, whichever occurs earlier, with overweight (BMI ≥85th percentile) or obesity (BMI ≥95th percentile) and who have one or more additional risk factors for diabetes (see **Table 2.4** for evidence grading of other risk factors).

13.52 If tests are normal, repeat testing at a minimum of 3-year intervals **E**, or more frequently if BMI is increasing. **C**

13.53 Fasting plasma glucose, 2-h plasma glucose during a 75-g oral glucose tolerance test, and A1C can be used to test for prediabetes or diabetes in children and adolescents. **B**

13.54 Children and adolescents with overweight or obesity in whom the diagnosis of type 2 diabetes is being considered should have a panel of pancreatic autoantibodies tested to exclude the possibility of autoimmune type 1 diabetes. **B**

In the last decade, the incidence and prevalence of type 2 diabetes in adolescents has increased dramatically, especially in racial and ethnic minority populations (141,178). A few studies suggest oral glucose tolerance tests or fasting plasma glucose values as more suitable diagnostic tests than A1C in the pediatric population, especially among certain ethnicities (179), although fasting glucose alone may overdiagnose diabetes in children (180,181). In addition, many of these studies do not recognize that diabetes diagnostic criteria are based on long-term health outcomes, and validations are not currently available in the pediatric population (182). A recent analysis of National Health and Nutrition Examination Survey (NHANES) data suggests using A1C for screening of high-risk youth (183).

The ADA acknowledges the limited data supporting A1C for diagnosing type 2 diabetes in children and adolescents. Although A1C is not recommended for diagnosis of diabetes in children with cystic fibrosis or symptoms suggestive of acute onset of type 1 diabetes, and only A1C assays without interference are appropriate for children with hemoglobinopathies, the ADA continues to recommend A1C for diagnosis of type 2 diabetes in this population (184,185).

Diagnostic Challenges

Given the current obesity epidemic, distinguishing between type 1 and type 2 diabetes in children can be difficult. Overweight and obesity are common in children with type 1 diabetes (26), and diabetes-associated autoantibodies and ketosis may be present in pediatric patients with features of type 2 diabetes (including obesity and acanthosis nigricans) (180). The presence of islet autoantibodies has been associated with faster progression to insulin deficiency (180). At onset, DKA occurs in ~6% of youth aged 10–19 years with type 2 diabetes (186). Although uncommon, type 2 diabetes has been observed in prepubertal children under the age of 10 years, and thus it should be part of the differential in children with suggestive symptoms (187). Finally, obesity contributes to the development of type 1 diabetes in some individuals (188), which further blurs the lines between diabetes types. However, accurate diagnosis is critical, as treatment regimens, educational approaches, dietary advice, and outcomes differ markedly between patients with the two diagnoses. The significant diagnostic difficulties posed by MODY are discussed in Section 2 "Classification and Diagnosis of Diabetes" (https://doi.org/10.2337/dc21-S002). In addition, there are rare and atypical diabetes cases that represent a challenge for clinicians and researchers.

Management

Lifestyle Management

Recommendations

13.55 All youth with type 2 diabetes and their families should receive comprehensive diabetes self-management education and support that is specific to youth with type 2 diabetes and is culturally appropriate. **B**

13.56 Youth with overweight/obesity and type 2 diabetes and their families should be provided with developmentally and culturally appropriate comprehensive lifestyle programs that are integrated with diabetes management to achieve 7–10% decrease in excess weight. **C**

13.57 Given the necessity of long-term weight management for children and adolescents with type 2 diabetes, lifestyle intervention should be based on a chronic care model and offered in the context of diabetes care. **E**

13.58 Youth with prediabetes and type 2 diabetes, like all children and adolescents, should be encouraged to participate in at least 60 min of moderate to vigorous physical activity daily (with muscle and bone strength training at least 3 days/week) **B** and to decrease sedentary behavior. **C**

13.59 Nutrition for youth with prediabetes and type 2 diabetes, like for all children, should focus on healthy eating patterns that emphasize consumption of nutrient-dense, high-quality foods and decreased consumption of calorie-dense, nutrient-poor foods, particularly sugar-added beverages. **B**

Glycemic Targets

Recommendations

13.60 Home self-monitoring of blood glucose regimens should be individualized, taking into consideration the pharmacologic treatment of the patient. **E**

13.61 Glycemic status should be assessed every 3 months. **E**

13.62 A reasonable A1C target for most children and adolescents with type 2 diabetes treated with oral agents alone is <7% (53 mmol/mol). More stringent A1C targets (such as <6.5% [48 mmol/mol]) may be appropriate for selected individual patients if they can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate patients might include those with short duration of diabetes and lesser degrees of β-cell dysfunction and patients treated with lifestyle or metformin only who achieve significant weight improvement. **E**

13.63 Less stringent A1C goals (such as 7.5% [58 mmol/mol]) may be appropriate if there is increased risk of hypoglycemia. **E**

13.64 A1C targets for patients on insulin should be individualized, taking into account the relatively low rates of hypoglycemia in youth-onset type 2 diabetes. **E**

Pharmacologic Management

Recommendations

13.65 Initiate pharmacologic therapy, in addition to behavioral counseling for healthful nutrition and physical activity changes, at diagnosis of type 2 diabetes. **A**

13.66 In incidentally diagnosed or metabolically stable patients (A1C <8.5% [69 mmol/mol] and asymptomatic), metformin is the initial pharmacologic treatment of choice if renal function is normal. **A**

13.67 Youth with marked hyperglycemia (blood glucose ≥250 mg/dL [13.9 mmol/L], A1C ≥8.5% [69 mmol/mol]) without acidosis at diagnosis who are symptomatic with polyuria, polydipsia, nocturia, and/or weight loss should be treated initially with basal insulin while metformin is initiated and titrated. **B**

13.68 In patients with ketosis/ketoacidosis, treatment with subcutaneous or intravenous insulin should be initiated to rapidly correct the hyperglycemia and the metabolic derangement. Once acidosis is resolved, metformin should be initiated while subcutaneous insulin therapy is continued. **A**

13.69 In individuals presenting with severe hyperglycemia (blood glucose ≥600 mg/dL [33.3 mmol/L]), consider assessment for hyperglycemic hyperosmolar nonketotic syndrome. **A**

13.70 If glycemic targets are no longer met with metformin (with or without basal insulin), liraglutide (a glucagon-like peptide 1 receptor agonist) therapy should be considered in children 10 years of age or older if they have no past medical history or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2. **A**

13.71 Patients treated with basal insulin who do not meet glycemic target should be moved to multiple daily injections with basal and premeal bolus insulins. **E**

13.72 In patients initially treated with insulin and metformin who are meeting glucose targets based on home blood glucose monitoring, insulin can be tapered over 2–6 weeks by decreasing the insulin dose 10–30% every few days. **B**

13.73 Use of medications not approved by the U.S. Food and Drug Administration for youth with type 2 diabetes is not recommended outside of research trials. **B**

Treatment of youth-onset type 2 diabetes should include lifestyle management, diabetes self-management education, and pharmacologic treatment. Initial treatment of youth with obesity and diabetes must take into account that diabetes type is often uncertain in the first few weeks of treatment, due to overlap in presentation, and that a substantial percentage of youth with type 2 diabetes will present with clinically significant ketoacidosis (189). Therefore, initial therapy should address the hyperglycemia and associated metabolic derangements irrespective of ultimate diabetes type, with adjustment of therapy once metabolic compensation has been established and subsequent information, such as islet autoantibody results, becomes available. **Figure 13.1** provides an approach to initial treatment of new-onset diabetes in youth with overweight or obesity with clinical suspicion of type 2 diabetes.

Glycemic targets should be individualized, taking into consideration long-term health benefits of more stringent targets and risk for adverse effects, such as hypoglycemia. A lower target A1C in youth with type 2 diabetes when compared with those recommended in type 1 diabetes is justified by lower risk of hypoglycemia and higher risk of complications (190–193).

Patients and their families should receive counseling for healthful nutrition and physical activity changes such as eating a balanced diet, achieving and maintaining a healthy weight, and exercising regularly. Physical activity should include aerobic, muscle-strengthening, and bone-strengthening activities (17). A family-centered approach to nutrition and lifestyle modification is essential in children and adolescents with type 2 diabetes, and nutrition recommendations should be culturally appropriate and

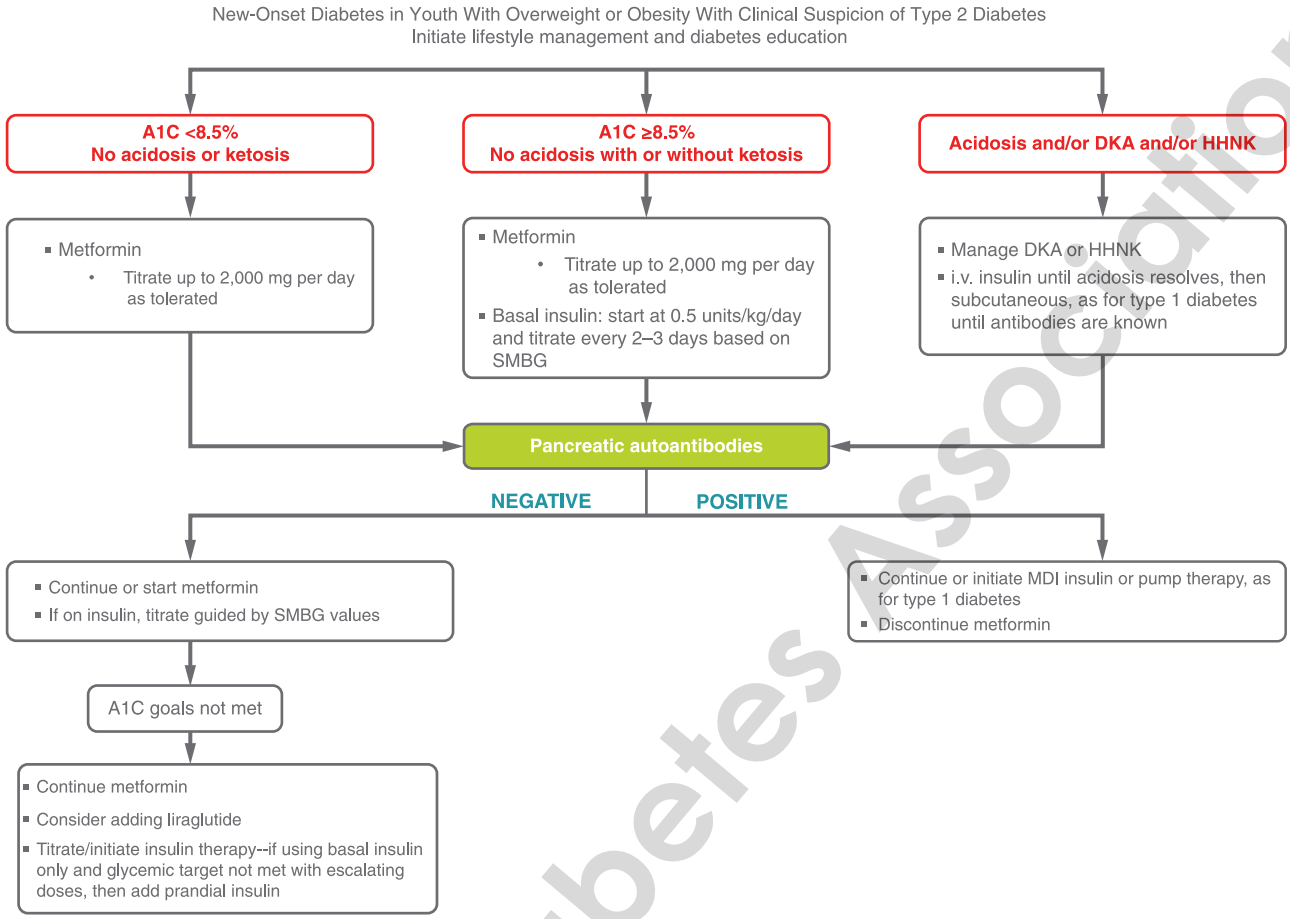

Figure 13.1—Management of new-onset diabetes in youth with overweight or obesity with clinical suspicion of type 2 diabetes. A1C 8.5% = 69 mmol/mol. Adapted from the ADA position statement "Evaluation and Management of Youth-Onset Type 2 Diabetes" (2). DKA, diabetic ketoacidosis; HHNK, hyperosmolar hyperglycemic nonketotic syndrome; MDI, multiple daily injections; SMBG; self-monitoring of blood glucose.

sensitive to family resources (see Section 5 "Facilitating Behavior Change and Well-being to Improve Health Outcomes," https://doi.org/10.2337/dc21-S005). Given the complex social and environmental context surrounding youth with type 2 diabetes, individual-level lifestyle interventions may not be sufficient to target the complex interplay of family dynamics, mental health, community readiness, and the broader environmental system (2).

A multidisciplinary diabetes team, including a physician, diabetes care and education specialist, registered dietitian nutritionist, and psychologist or social worker, is essential. In addition to achieving glycemic targets and self-management education (194–196), initial treatment must include management of comorbidities such as obesity, dyslipidemia, hypertension, and microvascular complications.

Current pharmacologic treatment options for youth-onset type 2 diabetes are limited to three approved drugs—insulin, metformin, and liraglutide (2). Presentation with ketoacidosis or marked ketosis requires a period of insulin therapy until fasting and postprandial glycemia have been restored to normal or near-normal levels. Insulin pump therapy may be considered as an option for those on long-term multiple daily injections who are able to safely manage the device. Metformin therapy may be used as an adjunct after resolution of ketosis/ketoacidosis. Initial treatment should also be with insulin when the distinction between type 1 diabetes and type 2 diabetes is unclear and in patients who have random blood glucose concentrations ≥250 mg/dL (13.9 mmol/L) and/or A1C ≥8.5% (69 mmol/mol) (197).

When insulin treatment is not required, initiation of metformin is recommended. The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study found that metformin alone provided durable glycemic control (A1C ≤8% [64 mmol/mol] for 6 months) in approximately half of the subjects (198). The RISE Consortium study did not demonstrate differences in measures of glucose or β-cell function preservation between metformin and insulin, but there was more weight gain with insulin (199).

To date, the TODAY study is the only trial combining lifestyle and metformin therapy in youth with type 2 diabetes; the combination did not perform better than metformin alone in achieving durable glycemic control (198).

A recent randomized clinical trial in children aged 10–17 years with type 2 diabetes demonstrated the addition of subcutaneous liraglutide (up to 1.8 mg daily) to metformin (with or without basal insulin) as safe and effective to decrease A1C (estimated decrease of 1.06 percentage points at 26 weeks and 1.30 at 52 weeks), although it did increase the frequency of gastrointestinal side effects (200). Liraglutide is approved

for treatment of type 2 diabetes in youth aged 10 years or older (201).

Home self-monitoring of blood glucose regimens should be individualized, taking into consideration the pharmacologic treatment of the patient. Although data on CGM in youth with type 2 diabetes is sparse (202), CGM could be considered in individuals requiring frequent blood glucose monitoring for diabetes management.

Metabolic Surgery

Recommendations

13.74 Metabolic surgery may be considered for the treatment of adolescents with type 2 diabetes who have severe obesity (BMI >35 kg/m^2) and who have uncontrolled glycemia and/or serious comorbidities despite lifestyle and pharmacologic intervention. **A**

13.75 Metabolic surgery should be performed only by an experienced surgeon working as part of a well-organized and engaged multidisciplinary team including a surgeon, endocrinologist, dietitian nutritionist, behavioral health specialist, and nurse. **A**

The results of weight-loss and lifestyle interventions for obesity in children and adolescents have been disappointing, and no effective and safe pharmacologic intervention is available or approved by the U.S. Food and Drug Administration in youth. Over the last decade, weight-loss surgery has been increasingly performed in adolescents with obesity. Small retrospective analyses and a prospective multicenter nonrandomized study suggest that bariatric or metabolic surgery may have benefits in adolescents with obesity and type 2 diabetes similar to those observed in adults. Teenagers experience similar degrees of weight loss, diabetes remission, and improvement of cardiometabolic risk factors for at least 3 years after surgery (203). A secondary data analysis from the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) and TODAY studies suggests surgical treatment of adolescents with severe obesity and type 2 diabetes is associated with improved glycemic control (204); however, no randomized trials have yet compared the effectiveness and safety of surgery to those of conventional treatment options in adolescents (205). The guidelines used as an indication for metabolic surgery in adolescents generally include BMI >35 kg/m^2 with comorbidities or BMI >40 kg/m^2 with or without comorbidities (206–217). A number of groups, including the Pediatric Bariatric Study Group and Teen-LABS study, have demonstrated the effectiveness of metabolic surgery in adolescents (210–216).

Prevention and Management of Diabetes Complications

Nephropathy

Recommendations

13.76 Blood pressure should be measured at every visit. **A**

13.77 Blood pressure should be optimized to reduce risk and/or slow the progression of diabetic kidney disease. **A**

13.78 If blood pressure is ≥90th percentile for age, sex, and height or, in adolescents ≥13 years, blood pressure is ≥120/80 mmHg, increased emphasis should be placed on lifestyle management to promote weight loss. If blood pressure remains above the 90th percentile or, in adolescents ≥13 years, blood pressure is ≥120/80 after 6 months, antihypertensive therapy should be initiated. **C**

13.79 In addition to lifestyle modification, pharmacologic treatment of hypertension (systolic blood pressure or diastolic blood pressure consistently ≥95th percentile for age, sex, and height or ≥140/90 mmHg in adolescents ≥13 years) should be considered as soon as hypertension is confirmed. **E**

13.80 Initial therapeutic options include ACE inhibitors or angiotensin receptor blockers. Other blood pressure–lowering agents may be added as needed. **C**

13.81 Protein intake should be at the recommended daily allowance of 0.8 g/kg/day. **E**

13.82 Urine albumin-to-creatinine ratio should be obtained at the time of diagnosis and annually thereafter. An elevated urine albumin-to-creatinine ratio (>30 mg/g creatinine) should be confirmed on two of three samples. **B**

13.83 Estimated glomerular filtration rate should be determined at the time of diagnosis and annually thereafter. **E**

13.84 In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated urinary albumin-to-creatinine ratio (30–299 mg/g creatinine) and is strongly recommended for those with urinary albumin-to-creatinine ratio >300 mg/g creatinine and/or estimated glomerular filtration rate <60 mL/min/1.73 m^2. **E**

13.85 For those with nephropathy, continued monitoring (yearly urinary albumin-to-creatinine ratio, estimated glomerular filtration rate, and serum potassium) may aid in assessing adherence and detecting progression of disease. **E**

13.86 Referral to nephrology is recommended in case of uncertainty of etiology, worsening urinary albumin-to-creatinine ratio, or decrease in estimated glomerular filtration rate. **E**

Neuropathy

Recommendations

13.87 Youth with type 2 diabetes should be screened for the presence of neuropathy by foot examination at diagnosis and annually. The examination should include inspection, assessment of foot pulses, pinprick and 10-g monofilament sensation tests, testing of vibration sensation using a 128-Hz tuning fork, and ankle reflex tests. **C**

13.88 Prevention should focus on achieving glycemic targets. **C**

Retinopathy

Recommendations

13.89 Screening for retinopathy should be performed by dilated fundoscopy or retinal

photography at or soon after diagnosis and annually thereafter. C

13.90 Optimizing glycemia is recommended to decrease the risk or slow the progression of retinopathy. B

13.91 Less frequent examination (every 2 years) may be considered if there is adequate glycemic control and a normal eye exam. C

Nonalcoholic Fatty Liver Disease

Recommendations

13.92 Evaluation for nonalcoholic fatty liver disease (by measuring AST and ALT) should be done at diagnosis and annually thereafter. B

13.93 Referral to gastroenterology should be considered for persistently elevated or worsening transaminases. B

Obstructive Sleep Apnea

Recommendation

13.94 Screening for symptoms of sleep apnea should be done at each visit, and referral to a pediatric sleep specialist for evaluation and a polysomnogram, if indicated, is recommended. Obstructive sleep apnea should be treated when documented. B

Polycystic Ovary Syndrome

Recommendations

13.95 Evaluate for polycystic ovary syndrome in female adolescents with type 2 diabetes, including laboratory studies when indicated. B

13.96 Oral contraceptive pills for treatment of polycystic ovary syndrome are not contraindicated for girls with type 2 diabetes. C

13.97 Metformin in addition to lifestyle modification is likely to improve the menstrual cyclicity and hyperandrogenism in girls with type 2 diabetes. E

Cardiovascular Disease

Recommendation

13.98 Intensive lifestyle interventions focusing on weight loss, dyslipidemia, hypertension, and dysglycemia are important to prevent overt macrovascular disease in early adulthood. E

Dyslipidemia

Recommendations

13.99 Lipid testing should be performed when initial glycemic control has been achieved and annually thereafter. B

13.100 Optimal goals are LDL cholesterol <100 mg/dL (2.6 mmol/L), HDL cholesterol >35 mg/dL (0.91 mmol/L), and triglycerides <150 mg/dL (1.7 mmol/L). E

13.101 If lipids are abnormal, initial therapy should consist of optimizing glucose control and medical nutritional therapy to limit the amount of calories from fat to 25–30%, saturated fat to <7%, cholesterol <200 mg/day, avoid *trans* fats, and aim for ~10% calories from monounsaturated fats for elevated LDL. For elevated triglycerides, medical nutrition therapy should also focus on decreasing simple sugar intake and increasing dietary n-3 fatty acids in addition to the above changes. A

13.102 If LDL cholesterol remains >130 mg/dL after 6 months of dietary intervention, initiate therapy with statin, with a goal of LDL <100 mg/dL, following reproductive counseling for females because of the potential teratogenic effects of statins. B

13.103 If triglycerides are >400 mg/dL (4.7 mmol/L) fasting or >1,000 mg/dL (11.6 mmol/L) nonfasting, optimize glycemia and begin fibrate, with a goal of <400 mg/dL (4.7 mmol/L) fasting (to reduce risk for pancreatitis). C

Cardiac Function Testing

Recommendation

13.104 Routine screening for heart disease with electrocardiogram, echocardiogram, or stress testing is not recommended in asymptomatic youth with type 2 diabetes. B

Comorbidities may already be present at the time of diagnosis of type 2 diabetes in youth (173,218). Therefore, blood pressure measurement, a fasting lipid panel, assessment of random urine albumin-to-creatinine ratio, and a dilated eye examination should be performed at diagnosis. Additional medical conditions that may need to be addressed include polycystic ovary disease and other comorbidities associated with pediatric obesity, such as sleep apnea, hepatic steatosis, orthopedic complications, and psychosocial concerns. The ADA position statement "Evaluation and Management of Youth-Onset Type 2 Diabetes" (2) provides guidance on the prevention, screening, and treatment of type 2 diabetes and its comorbidities in children and adolescents.

Youth-onset type 2 diabetes is associated with significant microvascular and macrovascular risk burden and a substantial increase in the risk of cardiovascular morbidity and mortality at an earlier age than in those diagnosed later in life (219). The higher complication risk in earlier-onset type 2 diabetes is likely related to prolonged lifetime exposure to hyperglycemia and other atherogenic risk factors, including insulin resistance, dyslipidemia, hypertension, and chronic inflammation. There is low risk of hypoglycemia in youth with type 2 diabetes, even if they are being treated with insulin (220), and there are high rates of complications (190–193). These diabetes comorbidities also appear to be higher than in youth with type 1 diabetes despite shorter diabetes duration and lower A1C (218). In addition, the progression of vascular abnormalities appears to be more pronounced in youth-onset type 2 diabetes compared with type 1 diabetes of similar duration, including ischemic heart disease and stroke (221).

Psychosocial Factors

Recommendations

13.105 Providers should assess food security, housing stability/homelessness, health literacy, financial barriers, and social/community support and apply that information to treatment decisions. E

13.106 Use patient-appropriate standardized and validated tools to assess for diabetes distress and mental/behavioral health

in youth with type 2 diabetes, with attention to symptoms of depression and eating disorders, and refer to specialty care when indicated. **B**

13.107 When choosing glucose-lowering or other medications for youth with overweight or obesity and type 2 diabetes, consider medication-taking behavior and their effect on weight. **E**

13.108 Starting at puberty, preconception counseling should be incorporated into routine diabetes clinic visits for all females of childbearing potential because of the adverse pregnancy outcomes in this population. **A**

13.109 Patients should be screened for tobacco, electronic cigarettes, and alcohol use at diagnosis and regularly thereafter. **C**

Most youth with type 2 diabetes come from racial/ethnic minority groups, have low socioeconomic status, and often experience multiple psychosocial stressors (25,40,174–177). Consideration of the sociocultural context and efforts to personalize diabetes management are of critical importance to minimize barriers to care, enhance adherence, and maximize response to treatment.

Evidence about psychiatric disorders and symptoms in youth with type 2 diabetes is limited (222–226), but given the sociocultural context for many youth and the medical burden and obesity associated with type 2 diabetes, ongoing surveillance of mental health/behavioral health is indicated. Symptoms of depression and disordered eating are common and associated with poorer glycemic control (223,227,228).

Many of the medications prescribed for diabetes and psychiatric disorders are associated with weight gain and can increase patients' concerns about eating, body shape, and weight (229,230).

The TODAY study documented (231) that despite disease- and age-specific counseling, 10.2% of the females in the cohort became pregnant over an average of 3.8 years of study participation. Of note, 26.4% of pregnancies ended in a miscarriage, stillbirth, or intrauterine death, and 20.5% of the liveborn infants had a major congenital anomaly.

TRANSITION FROM PEDIATRIC TO ADULT CARE

Recommendations

13.110 Pediatric diabetes providers should begin to prepare youth for transition to adult health care in early adolescence and, at the latest, at least 1 year before the transition. **E**

13.111 Both pediatric and adult diabetes care providers should provide support and resources for transitioning young adults. **E**

13.112 Youth with type 2 diabetes should be transferred to an adult-oriented diabetes specialist when deemed appropriate by the patient and provider. **E**

Care and close supervision of diabetes management are increasingly shifted from parents and other adults to the youth with type 1 or type 2 diabetes throughout childhood and adolescence. The shift from pediatric to adult health care providers, however, often occurs abruptly as the older teen enters the next developmental stage, referred to as emerging adulthood (232), which is a critical period for young people who have diabetes. During this period of major life transitions, youth begin to move out of their parents' homes and must become fully responsible for their diabetes care. Their new responsibilities include self-management of their diabetes, making medical appointments, and financing health care, once they are no longer covered by their parents' health insurance plans (ongoing coverage until age 26 years is currently available under provisions of the U.S. Affordable Care Act). In addition to lapses in health care, this is also a period associated with deterioration in glycemic stability; increased occurrence of acute complications; psychosocial, emotional, and behavioral challenges; and the emergence of chronic complications (233–236). The transition period from pediatric to adult care is prone to fragmentation in health care delivery, which may adversely impact health care quality, cost, and outcomes (237). Worsening diabetes health outcomes during transition to adult care and early adulthood have been documented (238,239).

Although scientific evidence is limited, it is clear that comprehensive and coordinated planning that begins in early adolescence is necessary to facilitate a seamless transition from pediatric to adult health care (233,234,240,241). New technologies and other interventions are being tried to support transition to adult care in young adulthood (242–246). A comprehensive discussion regarding the challenges faced during this period, including specific recommendations, is found in the ADA position statement "Diabetes Care for Emerging Adults: Recommendations for Transition From Pediatric to Adult Diabetes Care Systems" (234).

The Endocrine Society in collaboration with the ADA and other organizations has developed transition tools for clinicians and youth and families (241).

References

1. Chiang JL, Maahs DM, Garvey KC, et al. Type 1 diabetes in children and adolescents: a position statement by the American Diabetes Association. Diabetes Care 2018;41:2026–2044
2. Arslanian S, Bacha F, Grey M, Marcus MD, White NH, Zeitler P. Evaluation and management of youth-onset type 2 diabetes: a position statement by the American Diabetes Association. Diabetes Care 2018;41:2648–2668
3. Nadeau KJ, Anderson BJ, Berg EG, et al. Youth-onset type 2 diabetes consensus report: current status, challenges, and priorities. Diabetes Care 2016;39:1635–1642
4. Mayer-Davis EJ, Lawrence JM, Dabelea D, et al.; SEARCH for Diabetes in Youth Study. Incidence trends of type 1 and type 2 diabetes among youths, 2002-2012. N Engl J Med 2017; 376:1419–1429
5. Thomas NJ, Jones SE, Weedon MN, Shields BM, Oram RA, Hattersley AT. Frequency and phenotype of type 1 diabetes in the first six decades of life: a cross-sectional, genetically stratified survival analysis from UK Biobank. Lancet Diabetes Endocrinol 2018;6:122–129
6. Barnea-Goraly N, Raman M, Mazaika P, et al.; Diabetes Research in Children Network (DirecNet). Alterations in white matter structure in young children with type 1 diabetes. Diabetes Care 2014;37:332–340
7. Cameron FJ, Scratch SE, Nadebaum C, et al.; DKA Brain Injury Study Group. Neurological consequences of diabetic ketoacidosis at initial presentation of type 1 diabetes in a prospective cohort study of children. Diabetes Care 2014;37: 1554–1562
8. Markowitz JT, Garvey KC, Laffel LMB. Developmental changes in the roles of patients and families in type 1 diabetes management. Curr Diabetes Rev 2015;11:231–238
9. Driscoll KA, Volkening LK, Haro H, et al. Are children with type 1 diabetes safe at school?

Examining parent perceptions. Pediatr Diabetes 2015;16:613–620
10. Jackson CC, Albanese-O'Neill A, Butler KL, et al. Diabetes care in the school setting: a position statement of the American Diabetes Association. Diabetes Care 2015;38:1958–1963
11. Siminerio LM, Albanese-O'Neill A, Chiang JL, et al.; American Diabetes Association. Care of young children with diabetes in the child care setting: a position statement of the American Diabetes Association. Diabetes Care 2014;37:2834–2842
12. Mehta SN, Volkening LK, Anderson BJ, et al.; Family Management of Childhood Diabetes Study Steering Committee. Dietary behaviors predict glycemic control in youth with type 1 diabetes. Diabetes Care 2008;31:1318–1320
13. Absil H, Baudet L, Robert A, Lysy PA. Benefits of physical activity in children and adolescents with type 1 diabetes: a systematic review. Diabetes Res Clin Pract 2019;156:107810
14. Riddell MC, Gallen IW, Smart CE, et al. Exercise management in type 1 diabetes: a consensus statement. Lancet Diabetes Endocrinol 2017;5:377–390
15. Colberg SR, Sigal RJ, Yardley JE, et al. Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. Diabetes Care 2016;39:2065–2079
16. Robertson K, Adolfsson P, Scheiner G, Hanas R, Riddell MC. Exercise in children and adolescents with diabetes. Pediatr Diabetes 2009;10(Suppl. 12):154–168
17. U.S. Department of Health and Human Services. Physical activity guidelines for Americans, 2nd ed., 2018. Accessed 28 October 2020. Available from https://health.gov/our-work/physical-activity/current-guidelines
18. Tsalikian E, Kollman C, Tamborlane WB, et al.; Diabetes Research in Children Network (DirecNet) Study Group. Prevention of hypoglycemia during exercise in children with type 1 diabetes by suspending basal insulin. Diabetes Care 2006;29:2200–2204
19. Taplin CE, Cobry E, Messer L, McFann K, Chase HP, Fiallo-Scharer R. Preventing post-exercise nocturnal hypoglycemia in children with type 1 diabetes. J Pediatr 2010;157:784–788.e1
20. Riddell MC, Milliken J. Preventing exercise-induced hypoglycemia in type 1 diabetes using real-time continuous glucose monitoring and a new carbohydrate intake algorithm: an observational field study. Diabetes Technol Ther 2011;13:819–825
21. Francescato MP, Stel G, Stenner E, Geat M. Prolonged exercise in type 1 diabetes: performance of a customizable algorithm to estimate the carbohydrate supplements to minimize glycemic imbalances. PLoS One 2015;10:e0125220
22. Adolfsson P, Mattsson S, Jendle J. Evaluation of glucose control when a new strategy of increased carbohydrate supply is implemented during prolonged physical exercise in type 1 diabetes. Eur J Appl Physiol 2015;115:2599–2607
23. Baker LB, Rollo I, Stein KW, Jeukendrup AE. Acute effects of carbohydrate supplementation on intermittent sports performance. Nutrients 2015;7:5733–5763
24. Redondo MJ, Libman I, Cheng P, et al.; Pediatric Diabetes Consortium. Racial/ethnic minority youth with recent-onset type 1 diabetes have poor prognostic factors. Diabetes Care 2018;41:1017–1024
25. Liu LL, Lawrence JM, Davis C, et al.; SEARCH for Diabetes in Youth Study Group. Prevalence of overweight and obesity in youth with diabetes in USA: the SEARCH for Diabetes in Youth study. Pediatr Diabetes 2010;11:4–11
26. DuBose SN, Hermann JM, Tamborlane WV, et al.; Type 1 Diabetes Exchange Clinic Network and Diabetes Prospective Follow-up Registry. Obesity in youth with type 1 diabetes in Germany, Austria, and the United States. J Pediatr 2015;167:627–32.e1, 4
27. Corbin KD, Driscoll KA, Pratley RE, Smith SR, Maahs DM, Mayer-Davis EJ; Advancing Care for Type 1 Diabetes and Obesity Network (ACT1ON). Obesity in type 1 diabetes: pathophysiology, clinical impact, and mechanisms. Endocr Rev 2018;39:629–663
28. Redondo MJ, Foster NC, Libman IM, et al. Prevalence of cardiovascular risk factors in youth with type 1 diabetes and elevated body mass index. Acta Diabetol 2016;53:271–277
29. American Association of Diabetes Educators. Management of children with diabetes in the school setting. Diabetes Educ 2019;45:54–59
30. Corathers SD, Kichler J, Jones N-HY, et al. Improving depression screening for adolescents with type 1 diabetes. Pediatrics 2013;132:e1395–e1402
31. Hood KK, Beavers DP, Yi-Frazier J, et al. Psychosocial burden and glycemic control during the first 6 years of diabetes: results from the SEARCH for Diabetes in Youth study. J Adolesc Health 2014;55:498–504
32. Ducat L, Philipson LH, Anderson BJ. The mental health comorbidities of diabetes. JAMA 2014;312:691–692
33. Hagger V, Hendrieckx C, Sturt J, Skinner TC, Speight J. Diabetes distress among adolescents with type 1 diabetes: a systematic review. Curr Diab Rep 2016;16:9
34. Anderson BJ, Laffel LM, Domenger C, et al. Factors associated with diabetes-specific health-related quality of life in youth with type 1 diabetes: the global TEENs study [published correction appears in Diabetes Care 2018;41:640]. Diabetes Care 2017;40:1002–1009
35. Hilliard ME, De Wit M, Wasserman RM, et al. Screening and support for emotional burdens of youth with type 1 diabetes: strategies for diabetes care providers. Pediatr Diabetes 2018;19:534–543
36. Shapiro JB, Vesco AT, Weil LEG, Evans MA, Hood KK, Weissberg-Benchell J. Psychometric properties of the problem areas in diabetes: teen and parent of teen versions. J Pediatr Psychol 2018;43:561–571
37. Iturralde E, Rausch JR, Weissberg-Benchell J, Hood KK. Diabetes-related emotional distress over time. Pediatrics 2019;143:e20183011
38. Hill-Briggs F, Adler NE, Berkowitz SA, et al. Social determinants of health and diabetes: a scientific review. Diabetes Care. 2 November 2020 [Epub ahead of print]. DOI: 10.2337/dci20-0053
39. Lawrence JM, Yi-Frazier JP, Black MH, et al.; SEARCH for Diabetes in Youth Study Group. Demographic and clinical correlates of diabetes-related quality of life among youth with type 1 diabetes. J Pediatr 2012;161:201–207.e2
40. Young-Hyman D, de Groot M, Hill-Briggs F, Gonzalez JS, Hood K, Peyrot M. Psychosocial care for people with diabetes: a position statement of the American Diabetes Association. Diabetes Care 2016;39:2126–2140
41. Markowitz JT, Butler DA, Volkening LK, Antisdel JE, Anderson BJ, Laffel LMB. Brief screening tool for disordered eating in diabetes: internal consistency and external validity in a contemporary sample of pediatric patients with type 1 diabetes. Diabetes Care 2010;33:495–500
42. Katz ML, Volkening LK, Butler DA, Anderson BJ, Laffel LM. Family-based psychoeducation and Care Ambassador intervention to improve glycemic control in youth with type 1 diabetes: a randomized trial. Pediatr Diabetes 2014;15:142–150
43. Laffel LMB, Vangsness L, Connell A, Goebel-Fabbri A, Butler D, Anderson BJ. Impact of ambulatory, family-focused teamwork intervention on glycemic control in youth with type 1 diabetes. J Pediatr 2003;142:409–416
44. Anderson BJ, Vangsness L, Connell A, Butler D, Goebel-Fabbri A, Laffel LMB. Family conflict, adherence, and glycaemic control in youth with short duration type 1 diabetes. Diabet Med 2002;19:635–642
45. Helgeson VS, Palladino DK. Implications of psychosocial factors for diabetes outcomes among children with type 1 diabetes: a review. Soc Personal Psychol Compass 2012;6:228–242
46. McCarthy AM, Lindgren S, Mengeling MA, Tsalikian E, Engvall J. Factors associated with academic achievement in children with type 1 diabetes. Diabetes Care 2003;26:112–117
47. Kuther TL. Medical decision-making and minors: issues of consent and assent. Adolescence 2003;38:343–358
48. Coleman DL, Rosoff PM. The legal authority of mature minors to consent to general medical treatment. Pediatrics 2013;131:786–793
49. Charron-Prochownik D, Sereika SM, Becker D, et al. Long-term effects of the booster-enhanced READY-Girls preconception counseling program on intentions and behaviors for family planning in teens with diabetes. Diabetes Care 2013;36:3870–3874
50. Charron-Prochownik D, Downs J. *Diabetes and Reproductive Health for Girls*. Alexandria, VA, American Diabetes Association, 2016
51. Wisting L, Frøisland DH, Skrivarhaug T, Dahl-Jørgensen K, Rø O. Disturbed eating behavior and omission of insulin in adolescents receiving intensified insulin treatment: a nationwide population-based study. Diabetes Care 2013;36:3382–3387
52. Goebel-Fabbri AE. Disturbed eating behaviors and eating disorders in type 1 diabetes: clinical significance and treatment recommendations. Curr Diab Rep 2009;9:133–139
53. Atik Altınok Y, Özgür S, Meseri R, Özen S, Darcan Ş, Gökşen D. Reliability and validity of the diabetes eating problem survey in Turkish children and adolescents with type 1 diabetes mellitus. J Clin Res Pediatr Endocrinol 2017;9:323–328
54. Saßmann H, Albrecht C, Busse-Widmann P, et al. Psychometric properties of the German version of the Diabetes Eating Problem Survey-Revised: additional benefit of disease-specific screening in adolescents with type 1 diabetes. Diabet Med 2015;32:1641–1647
55. Rosenbauer J, Dost A, Karges B, et al.; DPV Initiative and the German BMBF Competence

Network Diabetes Mellitus. Improved metabolic control in children and adolescents with type 1 diabetes: a trend analysis using prospective multicenter data from Germany and Austria. Diabetes Care 2012;35:80–86
56. Cameron FJ, de Beaufort C, Aanstoot HJ, et al.; Hvidoere International Study Group. Lessons from the Hvidoere International Study Group on childhood diabetes: be dogmatic about outcome and flexible in approach. Pediatr Diabetes 2013;14:473–480
57. Nimri R, Weintrob N, Benzaquen H, Ofan R, Fayman G, Phillip M. Insulin pump therapy in youth with type 1 diabetes: a retrospective paired study. Pediatrics 2006;117:2126–2131
58. Doyle EA, Weinzimer SA, Steffen AT, Ahern JAH, Vincent M, Tamborlane WVA. A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine. Diabetes Care 2004;27:1554–1558
59. Diabetes Control and Complications Trial Research Group. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. J Pediatr 1994;125:177–188
60. White NH, Cleary PA, Dahms W, Goldstein D, Malone J, Tamborlane WV; Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Beneficial effects of intensive therapy of diabetes during adolescence: outcomes after the conclusion of the Diabetes Control and Complications Trial (DCCT). J Pediatr 2001;139:804–812
61. Samuelsson U, Steineck I, Gubbjornsdottir S. A high mean-HbA1c value 3-15 months after diagnosis of type 1 diabetes in childhood is related to metabolic control, macroalbuminuria, and retinopathy in early adulthood–a pilot study using two nation-wide population based quality registries. Pediatr Diabetes 2014;15:229–235
62. Carlsen S, Skrivarhaug T, Thue G, et al. Glycemic control and complications in patients with type 1 diabetes - a registry-based longitudinal study of adolescents and young adults. Pediatr Diabetes 2017;18:188–195
63. Lind M, Pivodic A, Svensson A-M, Ólafsdóttir AF, Wedel H, Ludvigsson J. HbA_{1c} level as a risk factor for retinopathy and nephropathy in children and adults with type 1 diabetes: Swedish population based cohort study. BMJ 2019;366:l4894
64. Genuth SM, Backlund J-YC, Bayless M, et al.; DCCT/EDIC Research Group. Effects of prior intensive versus conventional therapy and history of glycemia on cardiac function in type 1 diabetes in the DCCT/EDIC. Diabetes 2013;62:3561–3569
65. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. JAMA 2003;290:2159–2167
66. Writing Team for the DCCT/EDIC Research Group, Gubitosi-Klug RA, Sun W, et al. Effects of prior intensive insulin therapy and risk factors on patient-reported visual function outcomes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort. JAMA Ophthalmol 2016;134:137–145
67. Orchard TJ, Nathan DM, Zinman B, et al.; Writing Group for the DCCT/EDIC Research Group. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. JAMA 2015;313:45–53
68. Foland-Ross LC, Reiss AL, Mazaika PK, et al.; Diabetes Research in Children Network (DirecNet). Longitudinal assessment of hippocampus structure in children with type 1 diabetes. Pediatr Diabetes 2018;19:1116–1123
69. Mauras N, Mazaika P, Buckingham B, et al.; Diabetes Research in Children Network (DirecNet). Longitudinal assessment of neuroanatomical and cognitive differences in young children with type 1 diabetes: association with hyperglycemia. Diabetes 2015;64:1770–1779
70. Pourabbasi A, Tehrani-Doost M, Qavam SE, Arzaghi SM, Larijani B. Association of diabetes mellitus and structural changes in the central nervous system in children and adolescents: a systematic review. J Diabetes Metab Disord 2017;16:10
71. Perantie DC, Wu J, Koller JM, et al. Regional brain volume differences associated with hyperglycemia and severe hypoglycemia in youth with type 1 diabetes. Diabetes Care 2007;30:2331–2337
72. Arbelaez AM, Semenkovich K, Hershey T. Glycemic extremes in youth with T1DM: the structural and functional integrity of the developing brain. Pediatr Diabetes 2013;14:541–553
73. Broadley MM, White MJ, Andrew B. A systematic review and meta-analysis of executive function performance in type 1 diabetes mellitus. Psychosom Med 2017;79:684–696
74. Ryan CM. Why is cognitive dysfunction associated with the development of diabetes early in life? The diathesis hypothesis. Pediatr Diabetes 2006;7:289–297
75. Cameron FJ. The impact of diabetes on brain function in childhood and adolescence. Pediatr Clin North Am 2015;62:911–927
76. Campbell MS, Schatz DA, Chen V, et al.; T1D Exchange Clinic Network. A contrast between children and adolescents with excellent and poor control: the T1D Exchange clinic registry experience. Pediatr Diabetes 2014;15:110–117
77. Cooper MN, O'Connell SM, Davis EA, Jones TW. A population-based study of risk factors for severe hypoglycaemia in a contemporary cohort of childhood-onset type 1 diabetes. Diabetologia 2013;56:2164–2170
78. Bergenstal RM, Klonoff DC, Garg SK, et al.; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med 2013;369:224–232
79. Abraham MB, Davey R, O'Grady MJ, et al. Effectiveness of a predictive algorithm in the prevention of exercise-induced hypoglycemia in type 1 diabetes. Diabetes Technol Ther 2016;18:543–550
80. Buckingham BA, Bailey TS, Christiansen M, et al. Evaluation of a predictive low-glucose management system in-clinic. Diabetes Technol Ther 2017;19:288–292
81. Nimri R, Muller I, Atlas E, et al. MD-Logic overnight control for 6 weeks of home use in patients with type 1 diabetes: randomized crossover trial. Diabetes Care 2014;37:3025–3032
82. Thabit H, Tauschmann M, Allen JM, et al. Home use of an artificial beta cell in type 1 diabetes. N Engl J Med 2015;373:2129–2140
83. Bergenstal RM, Garg S, Weinzimer SA, et al. Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. JAMA 2016;316:1407–1408
84. Kovatchev B, Cheng P, Anderson SM, et al. Feasibility of long-term closed-loop control: a multicenter 6-month trial of 24/7 automated insulin delivery. Diabetes Technol Ther 2017;19:18–24
85. El-Khatib FH, Balliro C, Hillard MA, et al. Home use of a bihormonal bionic pancreas versus insulin pump therapy in adults with type 1 diabetes: a multicentre randomised crossover trial. Lancet 2017;389:369–380
86. Brown SA, Kovatchev BP, Raghinaru D, et al.; iDCL Trial Research Group. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. N Engl J Med 2019;381:1707–1717
87. Haynes A, Hermann JM, Miller KM, et al.; T1D Exchange, WACDD and DPV registries. Severe hypoglycemia rates are not associated with HbA1c: a cross-sectional analysis of 3 contemporary pediatric diabetes registry databases. Pediatr Diabetes 2017;18:643–650
88. Haynes A, Hermann JM, Clapin H, et al.; WACDD and DPV registries. Decreasing trends in mean HbA_{1c} are not associated with increasing rates of severe hypoglycemia in children: a longitudinal analysis of two contemporary population-based pediatric type 1 diabetes registries from Australia and Germany/Austria between 1995 and 2016. Diabetes Care 2019;42:1630–1636
89. Fredheim S, Johansen A, Thorsen SU, et al.; Danish Society for Diabetes in Childhood and Adolescence. Nationwide reduction in the frequency of severe hypoglycemia by half. Acta Diabetol 2015;52:591–599
90. Birkebaek NH, Drivvoll AK, Aakeson K, et al. Incidence of severe hypoglycemia in children with type 1 diabetes in the Nordic countries in the period 2008-2012: association with hemoglobin A_{1c} and treatment modality. BMJ Open Diabetes Res Care 2017;5:e000377
91. Ly TT, Nicholas JA, Retterath A, Lim EM, Davis EA, Jones TW. Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. JAMA 2013;310:1240–1247
92. Downie E, Craig ME, Hing S, Cusumano J, Chan AKF, Donaghue KC. Continued reduction in the prevalence of retinopathy in adolescents with type 1 diabetes: role of insulin therapy and glycemic control. Diabetes Care 2011;34:2368–2373
93. Karges B, Rosenbauer J, Kapellen T, et al. Hemoglobin A1c levels and risk of severe hypoglycemia in children and young adults with type 1 diabetes from Germany and Austria: a trend analysis in a cohort of 37,539 patients between 1995 and 2012. PloS Med 2014;11:e1001742
94. Johnson SR, Cooper MN, Jones TW, Davis EA. Long-term outcome of insulin pump therapy in

children with type 1 diabetes assessed in a large population-based case-control study. Diabetologia 2013;56:2392–2400
95. Karges B, Kapellen T, Wagner VM, et al.; DPV Initiative. Glycated hemoglobin A1c as a risk factor for severe hypoglycemia in pediatric type 1 diabetes. Pediatr Diabetes 2017;18:51–58
96. Saydah S, Imperatore G, Divers J, et al. Occurrence of severe hypoglycaemic events among US youth and young adults with type 1 or type 2 diabetes. Endocrinol Diabetes Metab 2019;2:e00057
97. Ishtiak-Ahmed K, Carstensen B, Pedersen-Bjergaard U, Jørgensen ME. Incidence trends and predictors of hospitalization for hypoglycemia in 17,230 adult patients with type 1 diabetes: a Danish Register linkage cohort study. Diabetes Care 2017;40:226–232
98. Maahs DM, Hermann JM, DuBose SN, et al.; DPV Initiative; T1D Exchange Clinic Network. Contrasting the clinical care and outcomes of 2,622 children with type 1 diabetes less than 6 years of age in the United States T1D Exchange and German/Austrian DPV registries. Diabetologia 2014;57:1578–1585
99. Swift PGF, Skinner TC, de Beaufort CE, et al.; Hvidoere Study Group on Childhood Diabetes. Target setting in intensive insulin management is associated with metabolic control: the Hvidoere Childhood Diabetes Study Group Centre Differences Study 2005. Pediatr Diabetes 2010;11:271–278
100. Laffel LM, Kanapka LG, Beck RW, et al.; CGM Intervention in Teens and Young Adults with T1D (CITY) Study Group; CDE10. Effect of continuous glucose monitoring on glycemic control in adolescents and young adults with type 1 diabetes: a randomized clinical trial. JAMA 2020;323:2388–2396
101. Jaeb Center for Health Research. Strategies to Enhance New CGM Use in Early Childhood (SENCE). In: ClinicalTrials.gov. Accessed 30 October 2020. Available from https://clinicaltrials.gov/ct2/show/NCT02912728
102. Levine BS, Anderson BJ, Butler DA, Antisdel JE, Brackett J, Laffel LM. Predictors of glycemic control and short-term adverse outcomes in youth with type 1 diabetes. J Pediatr 2001;139:197–203
103. Miller KM, Beck RW, Bergenstal RM, et al.; T1D Exchange Clinic Network. Evidence of a strong association between frequency of self-monitoring of blood glucose and hemoglobin A_{1c} levels in T1D Exchange clinic registry participants. Diabetes Care 2013;36:2009–2014
104. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care 2019;42:1593–1603
105. Vigersky RA, McMahon C. The relationship of hemoglobin A1C to time-in-range in patients with diabetes. Diabetes Technol Ther 2019;21:81–85
106. Petersson J, Åkesson K, Sundberg F, Särnblad S. Translating glycated hemoglobin A1c into time spent in glucose target range: a multicenter study. Pediatr Diabetes 2019;20:339–344
107. Warncke K, Fröhlich-Reiterer EE, Thon A, Hofer SE, Wiemann D, Holl RW; DPV Initiative of the German Working Group for Pediatric Diabetology; German BMBF Competence Network for Diabetes Mellitus. Polyendocrinopathy in children, adolescents, and young adults with type 1 diabetes: a multicenter analysis of 28,671 patients from the German/Austrian DPV-Wiss database. Diabetes Care 2010;33:2010–2012
108. Nederstigt C, Uitbeijerse BS, Janssen LGM, Corssmit EPM, de Koning EJP, Dekkers OM. Associated auto-immune disease in type 1 diabetes patients: a systematic review and meta-analysis. Eur J Endocrinol 2019;180:135–144
109. Kozhakhmetova A, Wyatt RC, Caygill C, et al. A quarter of patients with type 1 diabetes have co-existing non-islet autoimmunity: the findings of a UK population-based family study. Clin Exp Immunol 2018;192:251–258
110. Hughes JW, Riddlesworth TD, DiMeglio LA, Miller KM, Rickels MR, McGill JB; T1D Exchange Clinic Network. Autoimmune diseases in children and adults with type 1 diabetes from the T1D Exchange Clinic Registry. J Clin Endocrinol Metab 2016;101:4931–4937
111. Kahaly GJ, Hansen MP. Type 1 diabetes associated autoimmunity. Autoimmun Rev 2016;15:644–648
112. Roldán MB, Alonso M, Barrio R. Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus. Diabetes Nutr Metab 1999;12:27–31
113. Shun CB, Donaghue KC, Phelan H, Twigg SM, Craig ME. Thyroid autoimmunity in type 1 diabetes: systematic review and meta-analysis. Diabet Med 2014;31:126–135
114. Triolo TM, Armstrong TK, McFann K, et al. Additional autoimmune disease found in 33% of patients at type 1 diabetes onset. Diabetes Care 2011;34:1211–1213
115. Kordonouri O, Deiss D, Danne T, Dorow A, Bassir C, Grüters-Kieslich A. Predictivity of thyroid autoantibodies for the development of thyroid disorders in children and adolescents with Type 1 diabetes. Diabet Med 2002;19:518–521
116. Dost A, Rohrer TR, Fröhlich-Reiterer E, et al.; DPV Initiative and the German Competence Network Diabetes Mellitus. Hyperthyroidism in 276 children and adolescents with type 1 diabetes from Germany and Austria. Horm Res Paediatr 2015;84:190–198
117. Jonsdottir B, Larsson C, Carlsson A, et al.; Better Diabetes Diagnosis Study Group. Thyroid and islet autoantibodies predict autoimmune thyroid disease at type 1 diabetes diagnosis. J Clin Endocrinol Metab 2017;102:1277–1285
118. Mohn A, Di Michele S, Di Luzio R, Tumini S, Chiarelli F. The effect of subclinical hypothyroidism on metabolic control in children and adolescents with type 1 diabetes mellitus. Diabet Med 2002;19:70–73
119. Holmes GKT. Screening for coeliac disease in type 1 diabetes. Arch Dis Child 2002;87:495–498
120. Rewers M, Liu E, Simmons J, Redondo MJ, Hoffenberg EJ. Celiac disease associated with type 1 diabetes mellitus. Endocrinol Metab Clin North Am 2004;33:197–214, xi
121. Pham-Short A, Donaghue KC, Ambler G, Phelan H, Twigg S, Craig ME. Screening for celiac disease in type 1 diabetes: a systematic review. Pediatrics 2015;136:e170–e176
122. Craig ME, Prinz N, Boyle CT, et al.; Australasian Diabetes Data Network (ADDN); T1D Exchange Clinic Network (T1DX); National Paediatric Diabetes Audit (NPDA) and the Royal College of Paediatrics and Child Health; Prospective Diabetes Follow-up Registry (DPV) initiative. Prevalence of celiac disease in 52,721 youth with type 1 diabetes: international comparison across three continents. Diabetes Care 2017;40:1034–1040
123. Cerutti F, Bruno G, Chiarelli F, Lorini R, Meschi F, Sacchetti C; Diabetes Study Group of the Italian Society of Pediatric Endocrinology and Diabetology. Younger age at onset and sex predict celiac disease in children and adolescents with type 1 diabetes: an Italian multicenter study. Diabetes Care 2004;27:1294–1298
124. Simmons JH, Foster NC, Riddlesworth TD, et al.; T1D Exchange Clinic Network. Sex- and age-dependent effects of celiac disease on growth and weight gain in children with type 1 diabetes: analysis of the Type 1 Diabetes Exchange Clinic Registry. Pediatr Diabetes 2018;19:741–748F
125. Margoni D, Chouliaras G, Duscas G, et al. Bone health in children with celiac disease assessed by dual x-ray absorptiometry: effect of gluten-free diet and predictive value of serum biochemical indices. J Pediatr Gastroenterol Nutr 2012;54:680–684
126. Rohrer TR, Wolf J, Liptay S, et al.; DPV Initiative and the German BMBF Competence Network Diabetes Mellitus. Microvascular complications in childhood-onset type 1 diabetes and celiac disease: a multicenter longitudinal analysis of 56,514 patients from the German-Austrian DPV database. Diabetes Care 2015;38:801–807
127. Mollazadegan K, Kugelberg M, Montgomery SM, Sanders DS, Ludvigsson J, Ludvigsson JF. A population-based study of the risk of diabetic retinopathy in patients with type 1 diabetes and celiac disease. Diabetes Care 2013;36:316–321
128. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA; American College of Gastroenterology. ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol 2013;108:656–676; quiz 677
129. Paul SP, Sandhu BK, Spray CH, Basude D, Ramani P. Evidence supporting serology-based pathway for diagnosing celiac disease in asymptomatic children from high-risk groups. J Pediatr Gastroenterol Nutr 2018;66:641–644
130. Abid N, McGlone O, Cardwell C, McCallion W, Carson D. Clinical and metabolic effects of gluten free diet in children with type 1 diabetes and coeliac disease. Pediatr Diabetes 2011;12:322–325
131. Husby S, Koletzko S, Korponay-Szabó IR, et al.; ESPGHAN Working Group on Coeliac Disease Diagnosis; ESPGHAN Gastroenterology Committee; European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr 2012;54:136–160
132. Kurppa K, Paavola A, Collin P, et al. Benefits of a gluten-free diet for asymptomatic patients with serologic markers of celiac disease. Gastroenterology 2014;147:610–617.e1
133. Marcovecchio ML, Chiesa ST, Bond S, et al.; AdDIT Study Group. ACE inhibitors and statins in adolescents with type 1 diabetes. N Engl J Med 2017;377:1733–1745

134. de Ferranti SD, de Boer IH, Fonseca V, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Circulation 2014;130:1110–1130
135. Rodriguez BL, Fujimoto WY, Mayer-Davis EJ, et al. Prevalence of cardiovascular disease risk factors in U.S. children and adolescents with diabetes: the SEARCH for Diabetes in Youth study. Diabetes Care 2006;29:1891–1896
136. Margeirsdottir HD, Larsen JR, Brunborg C, Overby NC, Dahl-Jørgensen K; Norwegian Study Group for Childhood Diabetes. High prevalence of cardiovascular risk factors in children and adolescents with type 1 diabetes: a population-based study. Diabetologia 2008;51:554–561
137. Schwab KO, Doerfer J, Hecker W, et al.; DPV Initiative of the German Working Group for Pediatric Diabetology. Spectrum and prevalence of atherogenic risk factors in 27,358 children, adolescents, and young adults with type 1 diabetes: cross-sectional data from the German diabetes documentation and quality management system (DPV). Diabetes Care 2006;29:218–225
138. Singh TP, Groehn H, Kazmers A. Vascular function and carotid intimal-medial thickness in children with insulin-dependent diabetes mellitus. J Am Coll Cardiol 2003;41:661–665
139. Haller MJ, Stein J, Shuster J, et al. Peripheral artery tonometry demonstrates altered endothelial function in children with type 1 diabetes. Pediatr Diabetes 2007;8:193–198
140. Urbina EM, Wadwa RP, Davis C, et al. Prevalence of increased arterial stiffness in children with type 1 diabetes mellitus differs by measurement site and sex: the SEARCH for Diabetes in Youth Study. J Pediatr 2010;156:731–737, 737.e1
141. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics 2011;128(Suppl. 5): S213–S256
142. Blaha MJ, Blumenthal RS, Brinton EA, Jacobson TA; National Lipid Association Taskforce on Non-HDL Cholesterol. The importance of non-HDL cholesterol reporting in lipid management. J Clin Lipidol 2008;2:267–273
143. Kershnar AK, Daniels SR, Imperatore G, et al. Lipid abnormalities are prevalent in youth with type 1 and type 2 diabetes: the SEARCH for Diabetes in Youth Study. J Pediatr 2006;149:314–319
144. Maahs DM, Dabelea D, D'Agostino RB Jr, et al.; SEARCH for Diabetes in Youth Study. Glucose control predicts 2-year change in lipid profile in youth with type 1 diabetes. J Pediatr 2013;162:101–107.e1
145. Daniels SR, Greer FR; Committee on Nutrition. Lipid screening and cardiovascular health in childhood. Pediatrics 2008;122:198–208
146. Kavey R-EW, Allada V, Daniels SR, et al.; American Heart Association Expert Panel on Population and Prevention Science; American Heart Association Council on Cardiovascular Disease in the Young; American Heart Association Council on Epidemiology and Prevention; American Heart Association Council on Nutrition, Physical Activity and Metabolism; American Heart Association Council on High Blood Pressure Research; American Heart Association Council on Cardiovascular Nursing; American Heart Association Council on the Kidney in Heart Disease; Interdisciplinary Working Group on Quality of Care and Outcomes Research. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. Circulation 2006;114: 2710–2738
147. Cadario F, Prodam F, Pasqualicchio S, et al. Lipid profile and nutritional intake in children and adolescents with type 1 diabetes improve after a structured dietician training to a Mediterranean-style diet. J Endocrinol Invest 2012;35:160–168
148. Salem MA, AboElAsrar MA, Elbarbary NS, ElHilaly RA, Refaat YM. Is exercise a therapeutic tool for improvement of cardiovascular risk factors in adolescents with type 1 diabetes mellitus? A randomised controlled trial. Diabetol Metab Syndr 2010;2:47
149. McCrindle BW, Urbina EM, Dennison BA, et al.; American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee; American Heart Association Council of Cardiovascular Disease in the Young; American Heart Association Council on Cardiovascular Nursing. Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. Circulation 2007;115:1948–1967
150. Salo P, Viikari J, Hämäläinen M, et al. Serum cholesterol ester fatty acids in 7- and 13-month-old children in a prospective randomized trial of a low-saturated fat, low-cholesterol diet: the STRIP baby project. Acta Paediatr 1999;88: 505–512
151. McCrindle BW, Ose L, Marais AD. Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. J Pediatr 2003;143: 74–80
152. Wiegman A, Hutten BA, de Groot E, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. JAMA 2004; 292:331–337
153. Karter AJ, Stevens MR, Gregg EW, et al. Educational disparities in rates of smoking among diabetic adults: the translating research into action for diabetes study. Am J Public Health 2008;98:365–370
154. Reynolds K, Liese AD, Anderson AM, et al. Prevalence of tobacco use and association between cardiometabolic risk factors and cigarette smoking in youth with type 1 or type 2 diabetes mellitus. J Pediatr 2011;158:594–601.e1
155. Scott LJ, Warram JH, Hanna LS, Laffel LM, Ryan L, Krolewski AS. A nonlinear effect of hyperglycemia and current cigarette smoking are major determinants of the onset of microalbuminuria in type 1 diabetes. Diabetes 2001; 50:2842–2849
156. Chaffee BW, Watkins SL, Glantz SA. Electronic cigarette use and progression from experimentation to established smoking. Pediatrics 2018;141:e20173594
157. Audrain-McGovern J, Stone MD, Barrington-Trimis J, Unger JB, Leventhal AM. Adolescent e-cigarette, hookah, and conventional cigarette use and subsequent marijuana use. Pediatrics 2018;142:e20173616
158. Centers for Disease Control and Prevention. Outbreak of lung injury associated with e-cigarette use, or vaping. Accessed 30 October 2020. Available from https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html
159. Miech R, Johnston L, O'Malley PM, Bachman JG, Patrick ME. Trends in adolescent vaping, 2017-2019. N Engl J Med 2019;381:1490–1491
160. Daniels M, DuBose SN, Maahs DM, et al.; T1D Exchange Clinic Network. Factors associated with microalbuminuria in 7,549 children and adolescents with type 1 diabetes in the T1D Exchange clinic registry. Diabetes Care 2013;36: 2639–2645
161. Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. Clin J Am Soc Nephrol 2009;4:1832–1843
162. Inker LA, Schmid CH, Tighiouart H, et al.; CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367:20–29
163. Cho YH, Craig ME, Hing S, et al. Microvascular complications assessment in adolescents with 2- to 5-yr duration of type 1 diabetes from 1990 to 2006. Pediatr Diabetes 2011;12:682–689
164. Scanlon PH, Stratton IM, Bachmann MO, Jones C, Leese GP; Four Nations Diabetic Retinopathy Screening Study Group. Risk of diabetic retinopathy at first screen in children at 12 and 13 years of age. Diabet Med 2016;33:1655–1658
165. Beauchamp G, Boyle CT, Tamborlane WV, et al.; T1D Exchange Clinic Network. Treatable diabetic retinopathy is extremely rare among pediatric T1D Exchange clinic registry participants. Diabetes Care 2016;39:e218–e219
166. Nathan DM, Bebu I, Hainsworth D, et al.; DCCT/EDIC Research Group. Frequency of evidence-based screening for retinopathy in type 1 diabetes. N Engl J Med 2017;376:1507–1516
167. Gubitosi-Klug RA, Bebu I, White NH, et al.; Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group*. Screening eye exams in youth with type 1 diabetes under 18 years of age: once may be enough? Pediatr Diabetes 2019;20:743–749
168. Jaiswal M, Divers J, Dabelea D, et al. Prevalence of and risk factors for diabetic peripheral neuropathy in youth with type 1 and type 2 diabetes: SEARCH for Diabetes in Youth Study. Diabetes Care 2017;40:1226–1232
169. Pop-Busui R, Boulton AJM, Feldman EL, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. Diabetes Care 2017;40:136–154

170. Lawrence JM, Imperatore G, Pettitt DJ, et al. Incidence of diabetes in United States youth by diabetes type, race/ethnicity, and age, 2008–2009 (Abstract). Diabetes 2014;63(Suppl. 1): A407
171. Imperatore G, Boyle JP, Thompson TJ, et al.; SEARCH for Diabetes in Youth Study Group. Projections of type 1 and type 2 diabetes burden in the U.S. population aged <20 years through 2050: dynamic modeling of incidence, mortality, and population growth. Diabetes Care 2012;35: 2515–2520
172. Pettitt DJ, Talton J, Dabelea D, et al.; SEARCH for Diabetes in Youth Study Group. Prevalence of diabetes in U.S. youth in 2009: the SEARCH for Diabetes in Youth Study. Diabetes Care 2014;37:402–408
173. Copeland KC, Zeitler P, Geffner M, et al.; TODAY Study Group. Characteristics of adolescents and youth with recent-onset type 2 diabetes: the TODAY cohort at baseline. J Clin Endocrinol Metab 2011;96:159–167
174. Arslanian SA. Metabolic differences between Caucasian and African-American children and the relationship to type 2 diabetes mellitus. J Pediatr Endocrinol Metab 2002;15(Suppl. 1): 509–517
175. Naughton MJ, Ruggiero AM, Lawrence JM, et al.; SEARCH for Diabetes in Youth Study Group. Health-related quality of life of children and adolescents with type 1 or type 2 diabetes mellitus: SEARCH for Diabetes in Youth Study. Arch Pediatr Adolesc Med 2008;162:649–657
176. Wadden TA, Webb VL, Moran CH, Bailer BA. Lifestyle modification for obesity: new developments in diet, physical activity, and behavior therapy. Circulation 2012;125:1157–1170
177. Whalen DJ, Belden AC, Tillman R, Barch DM, Luby JL. Early adversity, psychopathology, and latent class profiles of global physical health from preschool through early adolescence. Psychosom Med 2016;78:1008–1018
178. Dabelea D, Mayer-Davis EJ, Saydah S, et al.; SEARCH for Diabetes in Youth Study. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. JAMA 2014;311: 1778–1786
179. Buse JB, Kaufman FR, Linder B, Hirst K, El Ghormli L, Willi S; HEALTHY Study Group. Diabetes screening with hemoglobin A_{1c} versus fasting plasma glucose in a multiethnic middle-school cohort. Diabetes Care 2013;36:429–435
180. Klingensmith GJ, Pyle L, Arslanian S, et al.; TODAY Study Group. The presence of GAD and IA-2 antibodies in youth with a type 2 diabetes phenotype: results from the TODAY study. Diabetes Care 2010;33:1970–1975
181. Hannon TS, Arslanian SA. The changing face of diabetes in youth: lessons learned from studies of type 2 diabetes. Ann N Y Acad Sci 2015;1353: 113–137
182. Kapadia C, Zeitler P; Drugs and Therapeutics Committee of the Pediatric Endocrine Society. Hemoglobin A1c measurement for the diagnosis of type 2 diabetes in children. Int J Pediatr Endocrinol 2012;2012:31
183. Wallace AS, Wang D, Shin J-I, Selvin E. Screening and diagnosis of prediabetes and diabetes in US children and adolescents. Pediatrics 2020;146:e20200265
184. Kester LM, Hey H, Hannon TS. Using hemoglobin A1c for prediabetes and diabetes diagnosis in adolescents: can adult recommendations be upheld for pediatric use? J Adolesc Health 2012;50:321–323
185. Wu E-L, Kazzi NG, Lee JM. Cost-effectiveness of screening strategies for identifying pediatric diabetes mellitus and dysglycemia. JAMA Pediatr 2013;167:32–39
186. Dabelea D, Rewers A, Stafford JM, et al.; SEARCH for Diabetes in Youth Study Group. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for Diabetes in Youth Study. Pediatrics 2014;133:e938–e945
187. Hutchins J, Barajas RA, Hale D, Escaname E, Lynch J. Type 2 diabetes in a 5-year-old and single center experience of type 2 diabetes in youth under 10. Pediatr Diabetes 2017;18:674–677
188. Ferrara CT, Geyer SM, Liu Y-F, et al.; Type 1 Diabetes TrialNet Study Group. Excess BMI in childhood: a modifiable risk factor for type 1 diabetes development? Diabetes Care 2017;40: 698–701
189. Pinhas-Hamiel O, Dolan LM, Zeitler PS. Diabetic ketoacidosis among obese African-American adolescents with NIDDM. Diabetes Care 1997;20:484–486
190. TODAY Study Group. Safety and tolerability of the treatment of youth-onset type 2 diabetes: the TODAY experience. Diabetes Care 2013;36: 1765–1771
191. Group TS; TODAY Study Group. Retinopathy in youth with type 2 diabetes participating in the TODAY clinical trial. Diabetes Care 2013;36: 1772–1774
192. Group TS; TODAY Study Group. Lipid and inflammatory cardiovascular risk worsens over 3 years in youth with type 2 diabetes: the TODAY clinical trial. Diabetes Care 2013;36:1758–1764
193. Group TS; TODAY Study Group. Rapid rise in hypertension and nephropathy in youth with type 2 diabetes: the TODAY clinical trial. Diabetes Care 2013;36:1735–1741
194. Grey M, Schreiner B, Pyle L. Development of a diabetes education program for youth with type 2 diabetes. Diabetes Educ 2009;35:108–116
195. American Diabetes Association. Be Healthy Today; Be Healthy For Life. Accessed 30 October 2020. Available from http://main.diabetes.org/dorg/PDFs/Type-2-Diabetes-in-Youth/Type-2-Diabetes-in-Youth.pdf
196. Atkinson A, Radjenovic D. Meeting quality standards for self-management education in pediatric type 2 diabetes. Diabetes Spectr 2007;20:40–46
197. Copeland KC, Silverstein J, Moore KR, et al.; American Academy of Pediatrics. Management of newly diagnosed type 2 diabetes mellitus (T2DM) in children and adolescents. Pediatrics 2013;131:364–382
198. Zeitler P, Hirst K, Pyle L, et al.; TODAY Study Group. A clinical trial to maintain glycemic control in youth with type 2 diabetes. N Engl J Med 2012;366:2247–2256
199. RISE Consortium. Impact of insulin and metformin versus metformin alone on β-cell function in youth with impaired glucose tolerance or recently diagnosed type 2 diabetes. Diabetes Care 2018;41:1717–1725
200. Tamborlane WV, Barrientos-Pérez M, Fainberg U, et al.; Ellipse Trial Investigators. Liraglutide in children and adolescents with type 2 Diabetes. N Engl J Med 2019;381:637–646
201. U.S. Food and Drug Administration. FDA approves new treatment for pediatric patients with type 2 diabetes. Accessed 30 October 2020. Available from http://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-pediatric-patients-type-2-diabetes
202. Chan CL. Use of continuous glucose monitoring in youth-onset type 2 diabetes. Curr Diab Rep 2017;17:66
203. Inge TH, Courcoulas AP, Jenkins TM, et al.; Teen-LABS Consortium. Weight loss and health status 3 years after bariatric surgery in adolescents. N Engl J Med 2016;374:113–123
204. Inge TH, Laffel LM, Jenkins TM, et al.; Teen–Longitudinal Assessment of Bariatric Surgery (Teen-LABS) and Treatment Options of Type 2 Diabetes in Adolescents and Youth (TODAY) Consortia. Comparison of surgical and medical therapy for type 2 diabetes in severely obese adolescents. JAMA Pediatr 2018;172:452–460
205. Rubino F, Nathan DM, Eckel RH, et al.; Delegates of the 2nd Diabetes Surgery Summit. Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by international diabetes organizations. Diabetes Care 2016;39:861–877
206. Pratt JSA, Lenders CM, Dionne EA, et al. Best practice updates for pediatric/adolescent weight loss surgery. Obesity (Silver Spring) 2009; 17:901–910
207. Dolan K, Creighton L, Hopkins G, Fielding G. Laparoscopic gastric banding in morbidly obese adolescents. Obes Surg 2003;13:101–104
208. Sugerman HJ, Sugerman EL, DeMaria EJ, et al. Bariatric surgery for severely obese adolescents. J Gastrointest Surg 2003;7:102–108
209. Inge TH, Garcia V, Daniels S, et al. A multidisciplinary approach to the adolescent bariatric surgical patient. J Pediatr Surg 2004; 39:442–447; discussion 446–447
210. Lawson ML, Kirk S, Mitchell T, et al.; Pediatric Bariatric Study Group. One-year outcomes of Roux-en-Y gastric bypass for morbidly obese adolescents: a multicenter study from the Pediatric Bariatric Study Group. J Pediatr Surg 2006; 41:137–143; discussion 137–143
211. Inge TH, Zeller M, Harmon C, et al. Teen-Longitudinal Assessment of Bariatric Surgery: methodological features of the first prospective multicenter study of adolescent bariatric surgery. J Pediatr Surg 2007;42:1969–1971
212. Ells LJ, Mead E, Atkinson G, et al. Surgery for the treatment of obesity in children and adolescents. Cochrane Database Syst Rev 2015;6: CD011740
213. Michalsky MP, Inge TH, Simmons M, et al.; Teen-LABS Consortium. Cardiovascular risk factors in severely obese adolescents: the Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS) Study. JAMA Pediatr 2015;169: 438–444
214. Zeinoddini A, Heidari R, Talebpour M. Laparoscopic gastric plication in morbidly obese adolescents: a prospective study. Surg Obes Relat Dis 2014;10:1135–1139
215. Göthberg G, Gronowitz E, Flodmark C-E, et al. Laparoscopic Roux-en-Y gastric bypass in adolescents with morbid obesity–surgical aspects and clinical outcome. Semin Pediatr Surg 2014;23:11–16

216. Inge TH, Prigeon RL, Elder DA, et al. Insulin sensitivity and β-cell function improve after gastric bypass in severely obese adolescents. J Pediatr 2015;167:1042–1048.e1
217. Styne DM, Arslanian SA, Connor EL, et al. Pediatric obesity-assessment, treatment, and prevention: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2017;102:709–757
218. Eppens MC, Craig ME, Cusumano J, et al. Prevalence of diabetes complications in adolescents with type 2 compared with type 1 diabetes. Diabetes Care 2006;29:1300–1306
219. Song SH, Hardisty CA. Early onset type 2 diabetes mellitus: a harbinger for complications in later years–clinical observation from a secondary care cohort. QJM 2009;102:799–806
220. Zeitler P, Fu J, Tandon N, et al.; International Society for Pediatric and Adolescent Diabetes. ISPAD Clinical Practice Consensus Guidelines 2014. Type 2 diabetes in the child and adolescent. Pediatr Diabetes 2014;15(Suppl. 20):26–46
221. Song SH. Complication characteristics between young-onset type 2 versus type 1 diabetes in a UK population. BMJ Open Diabetes Res Care 2015;3:e000044
222. Cefalu WT. "TODAY" reflects on the changing "faces" of type 2 diabetes. Diabetes Care 2013;36:1732–1734
223. Lawrence JM, Standiford DA, Loots B, et al.; SEARCH for Diabetes in Youth Study. Prevalence and correlates of depressed mood among youth with diabetes: the SEARCH for Diabetes in Youth study. Pediatrics 2006;117:1348–1358
224. Levitt Katz LE, Swami S, Abraham M, et al. Neuropsychiatric disorders at the presentation of type 2 diabetes mellitus in children. Pediatr Diabetes 2005;6:84–89
225. Lewis-Fernández R, Rotheram-Borus MJ, Betts VT, et al. Rethinking funding priorities in mental health research. Br J Psychiatry 2016;208:507–509
226. Reinehr T. Type 2 diabetes mellitus in children and adolescents. World J Diabetes 2013;4:270–281
227. Pinhas-Hamiel O, Hamiel U, Levy-Shraga Y. Eating disorders in adolescents with type 1 diabetes: challenges in diagnosis and treatment. World J Diabetes 2015;6:517–526
228. Wilfley D, Berkowitz R, Goebel-Fabbri A, et al.; TODAY Study Group. Binge eating, mood, and quality of life in youth with type 2 diabetes: baseline data from the today study. Diabetes Care 2011;34:858–860
229. Shelton RC. Depression, antidepressants, and weight gain in children. Obesity (Silver Spring) 2016;24:2450
230. Baeza I, Vigo L, de la Serna E, et al. The effects of antipsychotics on weight gain, weight-related hormones and homocysteine in children and adolescents: a 1-year follow-up study. Eur Child Adolesc Psychiatry 2017;26:35–46
231. Klingensmith GJ, Pyle L, Nadeau KJ, et al.; TODAY Study Group. Pregnancy outcomes in youth with type 2 diabetes: the TODAY study experience. Diabetes Care 2016;39:122–129
232. Arnett JJ. Emerging adulthood: a theory of development from the late teens through the twenties. Am Psychol 2000;55:469–480
233. Weissberg-Benchell J, Wolpert H, Anderson BJ. Transitioning from pediatric to adult care: a new approach to the post-adolescent young person with type 1 diabetes. Diabetes Care 2007;30:2441–2446
234. Peters A, Laffel L; American Diabetes Association Transitions Working Group. Diabetes care for emerging adults: recommendations for transition from pediatric to adult diabetes care systems: a position statement of the American Diabetes Association, with representation by the American College of Osteopathic Family Physicians, the American Academy of Pediatrics, the American Association of Clinical Endocrinologists, the American Osteopathic Association, the Centers for Disease Control and Prevention, Children with Diabetes, The Endocrine Society, the International Society for Pediatric and Adolescent Diabetes, Juvenile Diabetes Research Foundation International, the National Diabetes Education Program, and the Pediatric Endocrine Society (formerly Lawson Wilkins Pediatric Endocrine Society). Diabetes Care 2011;34:2477–2485
235. Bryden KS, Peveler RC, Stein A, Neil A, Mayou RA, Dunger DB. Clinical and psychological course of diabetes from adolescence to young adulthood: a longitudinal cohort study. Diabetes Care 2001;24:1536–1540
236. Laing SP, Jones ME, Swerdlow AJ, Burden AC, Gatling W. Psychosocial and socioeconomic risk factors for premature death in young people with type 1 diabetes. Diabetes Care 2005;28:1618–1623
237. Mays JA, Jackson KL, Derby TA, et al. An evaluation of recurrent diabetic ketoacidosis, fragmentation of care, and mortality across Chicago, Illinois. Diabetes Care 2016;39:1671–1676
238. Lotstein DS, Seid M, Klingensmith G, et al.; SEARCH for Diabetes in Youth Study Group. Transition from pediatric to adult care for youth diagnosed with type 1 diabetes in adolescence. Pediatrics 2013;131:e1062–e1070
239. Lyons SK, Becker DJ, Helgeson VS. Transfer from pediatric to adult health care: effects on diabetes outcomes. Pediatr Diabetes 2014;15:10–17
240. Garvey KC, Foster NC, Agarwal S, et al. Health care transition preparation and experiences in a U.S. national sample of young adults with type 1 diabetes. Diabetes Care 2017;40:317–324
241. The Endocrine Society. Transitions of care: a successful approach to managing pediatric to adult transitions of care. Accessed 30 October 2020. Available from https://www.endocrine.org/improving-practice/patient-resources/transitions
242. Reid MW, Krishnan S, Berget C, et al. CoYoT1 Clinic: home telemedicine increases young adult engagement in diabetes care. Diabetes Technol Ther 2018;20:370–379
243. Spaic T, Robinson T, Goldbloom E, et al.; JDRF Canadian Clinical Trial CCTN1102 Study Group. Closing the gap: results of the multicenter Canadian randomized controlled trial of structured transition in young adults with type 1 diabetes. Diabetes Care 2019;42:1018–1026
244. White M, O'Connell MA, Cameron FJ. Clinic attendance and disengagement of young adults with type 1 diabetes after transition of care from paediatric to adult services (TrACeD): a randomised, open-label, controlled trial. Lancet Child Adolesc Health 2017;1:274–283
245. Schultz AT, Smaldone A. Components of interventions that improve transitions to adult care for adolescents with type 1 diabetes. J Adolesc Health 2017;60:133–146
246. Sequeira PA, Pyatak EA, Weigensberg MJ, et al. Let's Empower and Prepare (LEAP): evaluation of a structured transition program for young adults with type 1 diabetes. Diabetes Care 2015;38:1412–1419

14. Management of Diabetes in Pregnancy: *Standards of Medical Care in Diabetes—2021*

American Diabetes Association

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The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc21-SPPC), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc21-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

DIABETES IN PREGNANCY

The prevalence of diabetes in pregnancy has been increasing in the U.S. in parallel with the worldwide epidemic of obesity. Not only is the prevalence of type 1 diabetes and type 2 diabetes increasing in women of reproductive age, but there is also a dramatic increase in the reported rates of gestational diabetes mellitus. Diabetes confers significantly greater maternal and fetal risk largely related to the degree of hyperglycemia but also related to chronic complications and comorbidities of diabetes. In general, specific risks of diabetes in pregnancy include spontaneous abortion, fetal anomalies, preeclampsia, fetal demise, macrosomia, neonatal hypoglycemia, hyperbilirubinemia, and neonatal respiratory distress syndrome, among others. In addition, diabetes in pregnancy may increase the risk of obesity, hypertension, and type 2 diabetes in offspring later in life (1,2).

PRECONCEPTION COUNSELING

Recommendations

14.1 Starting at puberty and continuing in all women with diabetes and reproductive potential, preconception counseling should be incorporated into routine diabetes care. **A**

14.2 Family planning should be discussed, and effective contraception (with consideration of long-acting, reversible contraception) should be prescribed and used until a woman's treatment regimen and A1C are optimized for pregnancy. **A**

14.3 Preconception counseling should address the importance of achieving glucose levels as close to normal as is safely possible, ideally A1C $<6.5\%$ (48 mmol/mol), to reduce the risk of congenital anomalies, preeclampsia, macrosomia, preterm birth, and other complications. **B**

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All women of childbearing age with diabetes should be informed about the importance of achieving and maintaining as near euglycemia as safely possible prior to conception and throughout pregnancy. Observational studies show an increased risk of diabetic embryopathy, especially anencephaly, microcephaly, congenital heart disease, renal anomalies, and caudal regression, directly proportional to elevations in A1C during the first 10 weeks of pregnancy (3). Although observational studies are confounded by the association between elevated periconceptional A1C and other poor self-care behavior, the quantity and consistency of data are convincing and support the recommendation to optimize glycemia prior to conception, given that organogenesis occurs primarily at 5–8 weeks of gestation, with an A1C <6.5% (48 mmol/mol) being associated with the lowest risk of congenital anomalies, preeclampsia, and preterm birth (3–7).

There are opportunities to educate all women and adolescents of reproductive age with diabetes about the risks of unplanned pregnancies and about improved maternal and fetal outcomes with pregnancy planning (8). Effective preconception counseling could avert substantial health and associated cost burdens in offspring (9). Family planning should be discussed, including the benefits of long-acting, reversable contraception, and effective contraception should be prescribed and used until a woman is prepared and ready to become pregnant (10–14).

To minimize the occurrence of complications, beginning at the onset of puberty or at diagnosis, all girls and women with diabetes of childbearing potential should receive education about *1*) the risks of malformations associated with unplanned pregnancies and even mild hyperglycemia and *2*) the use of effective contraception at all times when preventing a pregnancy. Preconception counseling using developmentally appropriate educational tools enables adolescent girls to make well-informed decisions (8). Preconception counseling resources tailored for adolescents are available at no cost through the American Diabetes Association (ADA) (15).

Preconception Care

Recommendations

14.4 Women with preexisting diabetes who are planning a pregnancy should ideally be managed beginning in preconception in a multidisciplinary clinic including an endocrinologist, maternal-fetal medicine specialist, registered dietitian nutritionist, and diabetes care and education specialist, when available. **B**

14.5 In addition to focused attention on achieving glycemic targets **A**, standard preconception care should be augmented with extra focus on nutrition, diabetes education, and screening for diabetes comorbidities and complications. **E**

14.6 Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. Dilated eye examinations should occur ideally before pregnancy or in the first trimester, and then patients should be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy and as recommended by the eye care provider. **B**

The importance of preconception care for all women is highlighted by the American College of Obstetricians and Gynecologists (ACOG) Committee Opinion 762, Prepregnancy Counseling (16). A key point is the need to incorporate a question about a woman's plans for pregnancy into routine primary and gynecologic care. The preconception care of women with diabetes should include the standard screenings and care recommended for all women planning pregnancy (16). Prescription of prenatal vitamins (with at least 400 μg of folic acid and 150 μg of potassium iodide [17]) is recommended prior to conception. Review and counseling on the use of nicotine products, alcohol, and recreational drugs, including marijuana, is important. Standard care includes screening for sexually transmitted diseases and thyroid disease, recommended vaccinations, routine genetic screening, a careful review of all prescription and nonprescription medications and supplements used, and a review of travel history and plans with special attention to areas known to have Zika virus, as outlined by ACOG. See **Table 14.1** for additional details on elements of preconception care (16,18). Counseling on the specific risks of obesity in pregnancy and lifestyle interventions to prevent and treat obesity, including referral to a registered dietitian nutritionist (RD/RDN), is recommended when indicated.

Diabetes-specific counseling should include an explanation of the risks to mother and fetus related to pregnancy and the ways to reduce risk including glycemic goal setting, lifestyle management, and medical nutrition therapy. The most important diabetes-specific component of preconception care is the attainment of glycemic goals prior to conception. Diabetes-specific testing should include A1C, creatinine, and urinary albumin-to-creatinine ratio. Special attention should be paid to the review of the medication list for potentially harmful drugs (i.e., ACE inhibitors [19,20], angiotensin receptor blockers [19], and statins [21,22]). A referral for a comprehensive eye exam is recommended. Women with preexisting diabetic retinopathy will need close monitoring during pregnancy to assess for progression of retinopathy and provide treatment if indicated (23).

Several studies have shown improved diabetes and pregnancy outcomes when care has been delivered from preconception through pregnancy by a multidisciplinary group focused on improved glycemic control (24–27). One study showed that care of preexisting diabetes in clinics that included diabetes and obstetric specialists improved care (27). However, there is no consensus on the structure of multidisciplinary team care for diabetes and pregnancy, and there is a lack of evidence on the impact on outcomes of various methods of health care delivery (28).

GLYCEMIC TARGETS IN PREGNANCY

Recommendations

14.7 Fasting and postprandial self-monitoring of blood glucose are recommended in both gestational diabetes mellitus and preexisting diabetes in pregnancy to achieve optimal glucose levels. Glucose targets are fasting plasma glucose <95 mg/dL (5.3 mmol/L) and either 1-h postprandial glucose <140 mg/dL (7.8 mmol/L) or 2-h postprandial

glucose <120 mg/dL (6.7 mmol/L). Some women with preexisting diabetes should also test blood glucose preprandially. **B**

14.8 Due to increased red blood cell turnover, A1C is slightly lower in normal pregnancy than in normal nonpregnant women. Ideally, the A1C target in pregnancy is <6% (42 mmol/mol) if this can be achieved without significant hypoglycemia, but the target may be relaxed to <7% (53 mmol/mol) if necessary to prevent hypoglycemia. **B**

14.9 When used in addition to pre- and postprandial self-monitoring of blood glucose, continuous glucose monitoring can help to achieve A1C targets in diabetes and pregnancy. **B**

14.10 When used in addition to self-monitoring of blood glucose targeting traditional pre- and postprandial targets, continuous glucose monitoring can reduce macrosomia and neonatal hypoglycemia in pregnancy complicated by type 1 diabetes. **B**

14.11 Continuous glucose monitoring metrics may be used as an adjunct but should not be used as a substitute for self-monitoring of blood glucose to achieve optimal pre- and postprandial glycemic targets. **E**

14.12 Commonly used estimated A1C and glucose management indicator calculations should not be used in pregnancy as estimates of A1C. **C**

Pregnancy in women with normal glucose metabolism is characterized by fasting levels of blood glucose that are lower than in the nonpregnant state due to insulin-independent glucose uptake by the fetus and placenta and by mild postprandial hyperglycemia and carbohydrate intolerance as a result of diabetogenic placental hormones. In patients with preexisting diabetes, glycemic targets are usually achieved through a combination of insulin administration and medical nutrition therapy. Because glycemic targets in pregnancy are stricter than in nonpregnant individuals, it is important that women with diabetes eat consistent

Table 14.1—Checklist for preconception care for women with diabetes (16,18)

Preconception education should include:
- ☐ Comprehensive nutrition assessment and recommendations for:
  - Overweight/obesity or underweight
  - Meal planning
  - Correction of dietary nutritional deficiencies
  - Caffeine intake
  - Safe food preparation technique
- ☐ Lifestyle recommendations for:
  - Regular moderate exercise
  - Avoidance of hyperthermia (hot tubs)
  - Adequate sleep
- ☐ Comprehensive diabetes self-management education
- ☐ Counseling on diabetes in pregnancy per current standards, including: natural history of insulin resistance in pregnancy and postpartum; preconception glycemic targets; avoidance of DKA/severe hyperglycemia; avoidance of severe hypoglycemia; progression of retinopathy; PCOS (if applicable); fertility in patients with diabetes; genetics of diabetes; risks to pregnancy including miscarriage, still birth, congenital malformations, macrosomia, preterm labor and delivery, hypertensive disorders in pregnancy, etc.
- ☐ Supplementation
  - Folic acid supplement (400 μg routine)
  - Appropriate use of over-the-counter medications and supplements

Medical assessment and plan should include:
- ☐ General evaluation of overall health
- ☐ Evaluation of diabetes and its comorbidities and complications, including: DKA/severe hyperglycemia; severe hypoglycemia/hypoglycemia unawareness; barriers to care; comorbidities such as hyperlipidemia, hypertension, NAFLD, PCOS, and thyroid dysfunction; complications such as macrovascular disease, nephropathy, neuropathy (including autonomic bowel and bladder dysfunction), and retinopathy
- ☐ Evaluation of obstetric/gynecologic history, including history of: cesarean section, congenital malformations or fetal loss, current methods of contraception, hypertensive disorders of pregnancy, postpartum hemorrhage, preterm delivery, previous macrosomia, Rh incompatibility, and thrombotic events (DVT/PE)
- ☐ Review of current medications and appropriateness during pregnancy

Screening should include:
- ☐ Diabetes complications and comorbidities, including: comprehensive foot exam; comprehensive ophthalmologic exam; ECG in women starting at age 35 years who have cardiac signs/symptoms or risk factors, and if abnormal, further evaluation; lipid panel; serum creatinine; TSH; and urine protein-to-creatinine ratio
- ☐ Anemia
- ☐ Genetic carrier status (based on history):
  - Cystic fibrosis
  - Sickle cell anemia
  - Tay-Sachs disease
  - Thalassemia
  - Others if indicated
- ☐ Infectious disease
  - *Neisseria gonorrhea/Chlamydia trachomatis*
  - Hepatitis C
  - HIV
  - Pap smear
  - Syphilis

Immunizations should include:
- ☐ Rubella
- ☐ Varicella
- ☐ Hepatitis B
- ☐ Influenza
- ☐ Others if indicated

Preconception plan should include:
- ☐ Nutrition and medication plan to achieve glycemic targets prior to conception, including appropriate implementation of monitoring, continuous glucose monitoring, and pump technology
- ☐ Contraceptive plan to prevent pregnancy until glycemic targets are achieved
- ☐ Management plan for general health, gynecologic concerns, comorbid conditions, or complications, if present, including: hypertension, nephropathy, retinopathy; Rh incompatibility; and thyroid dysfunction

DKA, diabetic ketoacidosis; DVT/PE, deep vein thrombosis/pulmonary embolism; ECG, electrocardiogram; NAFLD, nonalcoholic fatty liver disease; PCOS, polycystic ovary syndrome; TSH, thyroid-stimulating hormone.

amounts of carbohydrates to match with insulin dosage and to avoid hyperglycemia or hypoglycemia. Referral to an RD/RDN is important in order to establish a food plan and insulin-to-carbohydrate ratio and to determine weight gain goals.

Insulin Physiology

Given that early pregnancy is a time of enhanced insulin sensitivity and lower glucose levels, many women with type 1 diabetes will have lower insulin requirements and increased risk for hypoglycemia (29). Around 16 weeks, insulin resistance begins to increase, and total daily insulin doses increase linearly ~5% per week through week 36. This usually results in a doubling of daily insulin dose compared with the prepregnancy requirement. The insulin requirement levels off toward the end of the third trimester with placental aging. A rapid reduction in insulin requirements can indicate the development of placental insufficiency (30). In women with normal pancreatic function, insulin production is sufficient to meet the challenge of this physiological insulin resistance and to maintain normal glucose levels. However, in women with diabetes, hyperglycemia occurs if treatment is not adjusted appropriately.

Glucose Monitoring

Reflecting this physiology, fasting and postprandial monitoring of blood glucose is recommended to achieve metabolic control in pregnant women with diabetes. Preprandial testing is also recommended when using insulin pumps or basal-bolus therapy so that premeal rapid-acting insulin dosage can be adjusted. Postprandial monitoring is associated with better glycemic control and lower risk of preeclampsia (31–33). There are no adequately powered randomized trials comparing different fasting and postmeal glycemic targets in diabetes in pregnancy.

Similar to the targets recommended by ACOG (upper limits are the same as for gestational diabetes mellitus [GDM], described below) (34), the ADA-recommended targets for women with type 1 or type 2 diabetes are as follows:

- Fasting glucose 70–95 mg/dL (3.9–5.3 mmol/L) and either
- One-hour postprandial glucose 110–140 mg/dL (6.1–7.8 mmol/L) or
- Two-hour postprandial glucose 100–120 mg/dL (5.6–6.7 mmol/L)

Lower limits are based on the mean of normal blood glucoses in pregnancy (35). Lower limits do not apply to diet-controlled type 2 diabetes. Hypoglycemia in pregnancy is as defined and treated in Recommendations 6.9–6.14 (Section 6 "Glycemic Targets," https://doi.org/10.2337/dc21-S006). These values represent optimal control if they can be achieved safely. In practice, it may be challenging for women with type 1 diabetes to achieve these targets without hypoglycemia, particularly women with a history of recurrent hypoglycemia or hypoglycemia unawareness. If women cannot achieve these targets without significant hypoglycemia, the ADA suggests less stringent targets based on clinical experience and individualization of care.

A1C in Pregnancy

In studies of women without preexisting diabetes, increasing A1C levels within the normal range are associated with adverse outcomes (36). In the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, increasing levels of glycemia were also associated with worsening outcomes (37). Observational studies in preexisting diabetes and pregnancy show the lowest rates of adverse fetal outcomes in association with A1C <6–6.5% (42–48 mmol/mol) early in gestation (4–6,38). Clinical trials have not evaluated the risks and benefits of achieving these targets, and treatment goals should account for the risk of maternal hypoglycemia in setting an individualized target of <6% (42 mmol/mol) to <7% (53 mmol/mol). Due to physiological increases in red blood cell turnover, A1C levels fall during normal pregnancy (39,40). Additionally, as A1C represents an integrated measure of glucose, it may not fully capture postprandial hyperglycemia, which drives macrosomia. Thus, although A1C may be useful, it should be used as a secondary measure of glycemic control in pregnancy, after self-monitoring of blood glucose.

In the second and third trimesters, A1C <6% (42 mmol/mol) has the lowest risk of large-for-gestational-age infants (38,41,42), preterm delivery (43), and preeclampsia (1,44). Taking all of this into account, a target of <6% (42 mmol/mol) is optimal during pregnancy if it can be achieved without significant hypoglycemia. The A1C target in a given patient should be achieved without hypoglycemia, which, in addition to the usual adverse sequelae, may increase the risk of low birth weight (45). Given the alteration in red blood cell kinetics during pregnancy and physiological changes in glycemic parameters, A1C levels may need to be monitored more frequently than usual (e.g., monthly).

Continuous Glucose Monitoring in Pregnancy

CONCEPTT (Continuous Glucose Monitoring in Pregnant Women With Type 1 Diabetes Trial) was a randomized controlled trial of continuous glucose monitoring (CGM) in addition to standard care, including optimization of pre- and postprandial glucose targets versus standard care for pregnant women with type 1 diabetes. It demonstrated the value of CGM in pregnancy complicated by type 1 diabetes by showing a mild improvement in A1C without an increase in hypoglycemia and reductions in large-for-gestational-age births, length of stay, and neonatal hypoglycemia (46). An observational cohort study that evaluated the glycemic variables reported using CGM found that lower mean glucose, lower standard deviation, and a higher percentage of time in target range were associated with lower risk of large-for-gestational-age births and other adverse neonatal outcomes (47). Use of the CGM-reported mean glucose is superior to the use of estimated A1C, glucose management indicator, and other calculations to estimate A1C given the changes to A1C that occur in pregnancy (48). CGM time in range (TIR) can be used for assessment of glycemic control in patients with type 1 diabetes, but it does not provide actionable data to address fasting and postprandial hypoglycemia or hyperglycemia. There are no data to support the use of TIR in women with type 2 diabetes or GDM.

The international consensus on time in range (49) endorses pregnancy target ranges and goals for TIR for patients with type 1 diabetes using CGM as reported on the ambulatory glucose profile.

- Target range 63–140 mg/dL (3.5–7.8 mmol/L): TIR, goal >70%
- Time below range (<63 mg/dL [3.5 mmol/L]), goal <4%
- Time below range (<54 mg/dL [3.0 mmol/L]), goal <1%

- Time above range (>140 mg/dL [7.8 mmol/L]), goal <25%.

MANAGEMENT OF GESTATIONAL DIABETES MELLITUS

Recommendations

14.13 Lifestyle behavior change is an essential component of management of gestational diabetes mellitus and may suffice for the treatment of many women. Insulin should be added if needed to achieve glycemic targets. **A**

14.14 Insulin is the preferred medication for treating hyperglycemia in gestational diabetes mellitus. Metformin and glyburide should not be used as first-line agents, as both cross the placenta to the fetus. **A** Other oral and noninsulin injectable glucose-lowering medications lack long-term safety data.

14.15 Metformin, when used to treat polycystic ovary syndrome and induce ovulation, should be discontinued by the end of the first trimester. **A**

GDM is characterized by increased risk of large-for-gestational-age birth weight and neonatal and pregnancy complications and an increased risk of long-term maternal type 2 diabetes and offspring abnormal glucose metabolism in childhood. These associations with maternal oral glucose tolerance test (OGTT) results are continuous with no clear inflection points (37,50). Offspring with exposure to untreated GDM have reduced insulin sensitivity and β-cell compensation and are more likely to have impaired glucose tolerance in childhood (51). In other words, short-term and long-term risks increase with progressive maternal hyperglycemia. Therefore, all women should be tested as outlined in Section 2 "Classification and Diagnosis of Diabetes" (https://doi.org/10.2337/dc21-S002). Although there is some heterogeneity, many randomized controlled trials (RCTs) suggest that the risk of GDM may be reduced by diet, exercise, and lifestyle counseling, particularly when interventions are started during the first or early in the second trimester (52–54). There are no intervention trials in offspring of mothers with GDM.

Lifestyle Management

After diagnosis, treatment starts with medical nutrition therapy, physical activity, and weight management, depending on pregestational weight, as outlined in the section below on preexisting type 2 diabetes, as well as glucose monitoring aiming for the targets recommended by the Fifth International Workshop-Conference on Gestational Diabetes Mellitus (54):

- Fasting glucose <95 mg/dL (5.3 mmol/L) and either
- One-hour postprandial glucose <140 mg/dL (7.8 mmol/L) or
- Two-hour postprandial glucose <120 mg/dL (6.7 mmol/L)

Glycemic target lower limits defined above for preexisting diabetes apply for GDM that is treated with insulin. Depending on the population, studies suggest that 70–85% of women diagnosed with GDM under Carpenter-Coustan can control GDM with lifestyle modification alone; it is anticipated that this proportion will be even higher if the lower International Association of the Diabetes and Pregnancy Study Groups (55) diagnostic thresholds are used.

Medical Nutrition Therapy

Medical nutrition therapy for GDM is an individualized nutrition plan developed between the woman and an RD/RDN familiar with the management of GDM (56,57). The food plan should provide adequate calorie intake to promote fetal/neonatal and maternal health, achieve glycemic goals, and promote weight gain according to 2009 Institute of Medicine recommendations (58). There is no definitive research that identifies a specific optimal calorie intake for women with GDM or suggests that their calorie needs are different from those of pregnant women without GDM. The food plan should be based on a nutrition assessment with guidance from the Dietary Reference Intakes (DRI). The DRI for all pregnant women recommends a minimum of 175 g of carbohydrate, a minimum of 71 g of protein, and 28 g of fiber. The diet should emphasize monounsaturated and polyunsaturated fats while limiting saturated fats and avoiding *trans* fats. As is true for all nutrition therapy in patients with diabetes, the amount and type of carbohydrate will impact glucose levels. Simple carbohydrates will result in higher postmeal excursions.

Pharmacologic Therapy

Treatment of GDM with lifestyle and insulin has been demonstrated to improve perinatal outcomes in two large randomized studies as summarized in a U.S. Preventive Services Task Force review (59). Insulin is the first-line agent recommended for treatment of GDM in the U.S. While individual RCTs support limited efficacy of metformin (60,61) and glyburide (62) in reducing glucose levels for the treatment of GDM, these agents are not recommended as first-line treatment for GDM because they are known to cross the placenta and data on long-term safety for offspring is of some concern (34). Furthermore, glyburide and metformin failed to provide adequate glycemic control in separate RCTs in 23% and 25–28% of women with GDM, respectively (63,64).

Sulfonylureas

Sulfonylureas are known to cross the placenta and have been associated with increased neonatal hypoglycemia. Concentrations of glyburide in umbilical cord plasma are approximately 50–70% of maternal levels (63,64). Glyburide was associated with a higher rate of neonatal hypoglycemia and macrosomia than insulin or metformin in a 2015 meta-analysis and systematic review (65).

More recently, glyburide failed to be found noninferior to insulin based on a composite outcome of neonatal hypoglycemia, macrosomia, and hyperbilirubinemia (66). Long-term safety data for offspring exposed to glyburide are not available (66).

Metformin

Metformin was associated with a lower risk of neonatal hypoglycemia and less maternal weight gain than insulin in systematic reviews (65,67–69). However, metformin readily crosses the placenta, resulting in umbilical cord blood levels of metformin as high or higher than simultaneous maternal levels (70,71). In the Metformin in Gestational Diabetes: The Offspring Follow-Up (MiG TOFU) study's analyses of 7- to 9-year-old offspring, the 9-year-old offspring exposed to metformin in the Auckland cohort for the treatment of GDM were heavier and had a higher waist-to-height ratio and waist circumference than those exposed to insulin (72). This was not found in the Adelaide cohort. In two RCTs of metformin use in pregnancy for polycystic ovary

syndrome, follow-up of 4-year-old offspring demonstrated higher BMI and increased obesity in the offspring exposed to metformin (73,74). A follow-up study at 5–10 years showed that the offspring had higher BMI, weight-to-height ratios, waist circumferences, and a borderline increase in fat mass (74,75). Metformin is being studied in two ongoing trials in type 2 diabetes (Metformin in Women with Type 2 Diabetes in Pregnancy Trial [MiTY] [76] and Medical Optimization of Management of Type 2 Diabetes Complicating Pregnancy [MOMPOD] [77]), but long-term offspring data will not be available for some time. A recent meta-analysis concluded that metformin exposure resulted in smaller neonates with acceleration of postnatal growth resulting in higher BMI in childhood (74).

Randomized, double-blind, controlled trials comparing metformin with other therapies for ovulation induction in women with polycystic ovary syndrome have not demonstrated benefit in preventing spontaneous abortion or GDM (78), and there is no evidence-based need to continue metformin in such patients (79–81).

There are some women with GDM requiring medical therapy who, due to cost, language barriers, comprehension, or cultural influences, may not be able to use insulin safely or effectively in pregnancy. Oral agents may be an alternative in these women after a discussion of the known risks and the need for more long-term safety data in offspring. However, due to the potential for growth restriction or acidosis in the setting of placental insufficiency, metformin should not be used in women with hypertension or preeclampsia or at risk for intrauterine growth restriction (82,83).

Insulin

Insulin use should follow the guidelines below. Both multiple daily insulin injections and continuous subcutaneous insulin infusion are reasonable delivery strategies, and neither has been shown to be superior to the other during pregnancy (84).

MANAGEMENT OF PREEXISTING TYPE 1 DIABETES AND TYPE 2 DIABETES IN PREGNANCY

Insulin Use

Recommendations

14.16 Insulin should be used for management of type 1 diabetes in pregnancy. **A** Insulin is the preferred agent for the management of type 2 diabetes in pregnancy. **E**

14.17 Either multiple daily injections or insulin pump technology can be used in pregnancy complicated by type 1 diabetes. **C**

The physiology of pregnancy necessitates frequent titration of insulin to match changing requirements and underscores the importance of daily and frequent self-monitoring of blood glucose. Due to the complexity of insulin management in pregnancy, referral to a specialized center offering team-based care (with team members including maternal-fetal medicine specialist, endocrinologist or other provider experienced in managing pregnancy in women with preexisting diabetes, dietitian, nurse, and social worker, as needed) is recommended if this resource is available.

None of the currently available human insulin preparations have been demonstrated to cross the placenta (84–89). A recent Cochrane systematic review was not able to recommend any specific insulin regimen over another for the treatment of diabetes in pregnancy (90).

While many providers prefer insulin pumps in pregnancy, it is not clear that they are superior to multiple daily injections (91,92). Hybrid closed-loop insulin pumps that allow for the achievement of pregnancy fasting and postprandial glycemic targets may reduce hypoglycemia and allow for more aggressive prandial dosing to achieve targets. Not all hybrid closed-loop pumps are able to achieve the pregnancy targets.

Type 1 Diabetes

Women with type 1 diabetes have an increased risk of hypoglycemia in the first trimester and, like all women, have altered counterregulatory response in pregnancy that may decrease hypoglycemia awareness. Education for patients and family members about the prevention, recognition, and treatment of hypoglycemia is important before, during, and after pregnancy to help to prevent and manage the risks of hypoglycemia. Insulin resistance drops rapidly with delivery of the placenta.

Pregnancy is a ketogenic state, and women with type 1 diabetes, and to a lesser extent those with type 2 diabetes, are at risk for diabetic ketoacidosis (DKA) at lower blood glucose levels than in the nonpregnant state. Women with type 1 diabetes should be prescribed ketone strips and receive education on DKA prevention and detection. DKA carries a high risk of stillbirth. Women in DKA who are unable to eat often require 10% dextrose with an insulin drip to adequately meet the higher carbohydrate demands of the placenta and fetus in the third trimester in order to resolve their ketosis.

Retinopathy is a special concern in pregnancy. The necessary rapid implementation of euglycemia in the setting of retinopathy is associated with worsening of retinopathy (23).

Type 2 Diabetes

Type 2 diabetes is often associated with obesity. Recommended weight gain during pregnancy for women with overweight is 15–25 lb and for women with obesity is 10–20 lb (58). There are no adequate data on optimal weight gain versus weight maintenance in women with BMI >35 kg/m^2.

Glycemic control is often easier to achieve in women with type 2 diabetes than in those with type 1 diabetes but can require much higher doses of insulin, sometimes necessitating concentrated insulin formulations. As in type 1 diabetes, insulin requirements drop dramatically after delivery.

The risk for associated hypertension and other comorbidities may be as high or higher with type 2 diabetes as with type 1 diabetes, even if diabetes is better controlled and of shorter apparent duration, with pregnancy loss appearing to be more prevalent in the third trimester in women with type 2 diabetes compared with the first trimester in women with type 1 diabetes (93,94).

PREECLAMPSIA AND ASPIRIN

Recommendation

14.18 Women with type 1 or type 2 diabetes should be prescribed low-dose aspirin 100–150 mg/day starting at 12 to 16 weeks of gestation to lower the risk of preeclampsia. **E** A dosage of 162 mg/day may be acceptable; currently in the U.S., low-dose aspirin is available in 81-mg tablets. **E**

Diabetes in pregnancy is associated with an increased risk of preeclampsia (95). The U.S. Preventive Services Task Force recommends the use of low-dose aspirin (81 mg/day) as a preventive medication at 12 weeks of gestation in women who are at high risk for preeclampsia (96). However, a meta-analysis and an additional trial demonstrate that low-dose aspirin <100 mg is not effective in reducing preeclampsia. Low-dose aspirin >100 mg is required (97–99). A cost-benefit analysis has concluded that this approach would reduce morbidity, save lives, and lower health care costs (100). However, there is insufficient data regarding the benefits of aspirin in women with preexisting diabetes (98). More studies are needed to assess the long-term effects of prenatal aspirin exposure on offspring (101).

PREGNANCY AND DRUG CONSIDERATIONS

Recommendations

14.19 In pregnant patients with diabetes and chronic hypertension, a blood pressure target of 110–135/85 mmHg is suggested in the interest of reducing the risk for accelerated maternal hypertension **A** and minimizing impaired fetal growth. **E**

14.20 Potentially harmful medications in pregnancy (i.e., ACE inhibitors, angiotensin receptor blockers, statins) should be stopped at conception and avoided in sexually active women of childbearing age who are not using reliable contraception. **B**

In normal pregnancy, blood pressure is lower than in the nonpregnant state. In a pregnancy complicated by diabetes and chronic hypertension, a target goal blood pressure of 110–135/85 mmHg is suggested to reduce the risk of uncontrolled maternal hypertension and minimize impaired fetal growth (102–104). The 2015 study (104) excluded pregnancies complicated by preexisting diabetes and only 6% had GDM at enrollment. There was no difference in pregnancy loss, neonatal care, or other neonatal outcomes between the groups with tighter versus less tight control of hypertension (104).

During pregnancy, treatment with ACE inhibitors and angiotensin receptor blockers is contraindicated because they may cause fetal renal dysplasia, oligohydramnios, pulmonary hypoplasia, and intrauterine growth restriction (19).

A large study found that after adjusting for confounders, first trimester ACE inhibitor exposure does not appear to be associated with congenital malformations (20). However, ACE inhibitors and angiotensin receptor blockers should be stopped as soon as possible in the first trimester to avoid second and third trimester fetopathy (20). Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, nifedipine, labetalol, diltiazem, clonidine, and prazosin. Atenolol is not recommended, but other β-blockers may be used, if necessary. Chronic diuretic use during pregnancy is not recommended as it has been associated with restricted maternal plasma volume, which may reduce uteroplacental perfusion (105). On the basis of available evidence, statins should also be avoided in pregnancy (106).

See PREGNANCY AND ANTIHYPERTENSIVE MEDICATIONS in Section 10 "Cardiovascular Disease and Risk Management" (https://doi.org/10.2337/dc21-S010) for more information on managing blood pressure in pregnancy.

POSTPARTUM CARE

Recommendations

14.21 Insulin resistance decreases dramatically immediately postpartum, and insulin requirements need to be evaluated and adjusted as they are often roughly half the prepregnancy requirements for the initial few days postpartum. **C**

14.22 A contraceptive plan should be discussed and implemented with all women with diabetes of reproductive potential. **A**

14.23 Screen women with a recent history of gestational diabetes mellitus at 4–12 weeks postpartum, using the 75-g oral glucose tolerance test and clinically appropriate nonpregnancy diagnostic criteria. **B**

14.24 Women with a history of gestational diabetes mellitus found to have prediabetes should receive intensive lifestyle interventions and/or metformin to prevent diabetes. **A**

14.25 Women with a history of gestational diabetes mellitus should have lifelong screening for the development of type 2 diabetes or prediabetes every 1–3 years. **B**

14.26 Women with a history of gestational diabetes mellitus should seek preconception screening for diabetes and preconception care to identify and treat hyperglycemia and prevent congenital malformations. **E**

14.27 Postpartum care should include psychosocial assessment and support for self-care. **E**

Gestational Diabetes Mellitus

Initial Testing

Because GDM often represents previously undiagnosed prediabetes, type 2 diabetes, maturity-onset diabetes of the young, or even developing type 1 diabetes, women with GDM should be tested for persistent diabetes or prediabetes at 4–12 weeks postpartum with a 75-g OGTT using nonpregnancy criteria as outlined in Section 2 "Classification and Diagnosis of Diabetes" (https://doi.org/10.2334/dc21-S002).

Postpartum Follow-up

The OGTT is recommended over A1C at 4–12 weeks postpartum because A1C may be persistently impacted (lowered) by the increased red blood cell turnover related to pregnancy, by blood loss at delivery, or by the preceding 3-month glucose profile. The OGTT is more sensitive at detecting glucose intolerance, including both prediabetes and diabetes. Women of reproductive age with prediabetes may develop type 2 diabetes by the time of their next pregnancy and will need preconception evaluation. Because GDM is associated with an increased lifetime maternal risk for diabetes estimated at 50–60% (107,108), women should also be tested every 1–3 years thereafter if the 4–12 weeks postpartum 75-g OGTT is normal. Ongoing evaluation may be performed with any recommended glycemic test (e.g., annual A1C, annual fasting plasma glucose, or triennial 75-g OGTT using nonpregnant thresholds).

Gestational Diabetes Mellitus and Type 2 Diabetes

Women with a history of GDM have a greatly increased risk of conversion to

type 2 diabetes over time (108). Women with GDM have a 10-fold increased risk of developing type 2 diabetes compared with women without GDM (107). Absolute risk increases linearly through a woman's lifetime, being approximately 20% at 10 years, 30% at 20 years, 40% at 30 years, 50% at 40 years, and 60% at 50 years (108). In the prospective Nurses' Health Study II (NHS II), subsequent diabetes risk after a history of GDM was significantly lower in women who followed healthy eating patterns (109). Adjusting for BMI attenuated this association moderately, but not completely. Interpregnancy or postpartum weight gain is associated with increased risk of adverse pregnancy outcomes in subsequent pregnancies (110) and earlier progression to type 2 diabetes.

Both metformin and intensive lifestyle intervention prevent or delay progression to diabetes in women with prediabetes and a history of GDM. Of women with a history of GDM and prediabetes, only 5–6 women need to be treated with either intervention to prevent one case of diabetes over 3 years (111). In these women, lifestyle intervention and metformin reduced progression to diabetes by 35% and 40%, respectively, over 10 years compared with placebo (112). If the pregnancy has motivated the adoption of a healthier diet, building on these gains to support weight loss is recommended in the postpartum period.

Preexisting Type 1 and Type 2 Diabetes

Insulin sensitivity increases dramatically with delivery of the placenta. In one study, insulin requirements in the immediate postpartum period are roughly 34% lower than prepregnancy insulin requirements (113,114). Insulin sensitivity then returns to prepregnancy levels over the following 1–2 weeks. In women taking insulin, particular attention should be directed to hypoglycemia prevention in the setting of breastfeeding and erratic sleep and eating schedules (115).

Lactation

In light of the immediate nutritional and immunological benefits of breastfeeding for the baby, all women including those with diabetes should be supported in attempts to breastfeed. Breastfeeding may also confer longer-term metabolic benefits to both mother (116) and offspring (117). However, lactation can increase the risk of overnight hypoglycemia, and insulin dosing may need to be adjusted.

Contraception

A major barrier to effective preconception care is the fact that the majority of pregnancies are unplanned. Planning pregnancy is critical in women with preexisting diabetes due to the need for preconception glycemic control to prevent congenital malformations and reduce the risk of other complications. Therefore, all women with diabetes of childbearing potential should have family planning options reviewed at regular intervals to make sure that effective contraception is implemented and maintained. This applies to women in the immediate postpartum period. Women with diabetes have the same contraception options and recommendations as those without diabetes. Long-acting, reversable contraception may be ideal for many women. The risk of an unplanned pregnancy outweighs the risk of any given contraception option.

References

1. Dabelea D, Hanson RL, Lindsay RS, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. Diabetes 2000;49:2208–2211
2. Holmes VA, Young IS, Patterson CC, et al.; Diabetes and Pre-eclampsia Intervention Trial Study Group. Optimal glycemic control, pre-eclampsia, and gestational hypertension in women with type 1 diabetes in the diabetes and pre-eclampsia intervention trial. Diabetes Care 2011;34:1683–1688
3. Guerin A, Nisenbaum R, Ray JG. Use of maternal GHb concentration to estimate the risk of congenital anomalies in the offspring of women with prepregnancy diabetes. Diabetes Care 2007;30:1920–1925
4. Jensen DM, Korsholm L, Ovesen P, et al. Periconceptional A1C and risk of serious adverse pregnancy outcome in 933 women with type 1 diabetes. Diabetes Care 2009;32:1046–1048
5. Nielsen GL, Møller M, Sørensen HT. HbA_{1c} in early diabetic pregnancy and pregnancy outcomes: a Danish population-based cohort study of 573 pregnancies in women with type 1 diabetes. Diabetes Care 2006;29:2612–2616
6. Suhonen L, Hiilesmaa V, Teramo K. Glycaemic control during early pregnancy and fetal malformations in women with type I diabetes mellitus. Diabetologia 2000;43:79–82
7. Ludvigsson JF, Neovius M, Söderling J, et al. Maternal glycemic control in type 1 diabetes and the risk for preterm birth: a population-based cohort study. Ann Intern Med 2019;170:691–701
8. Charron-Prochownik D, Sereika SM, Becker D, et al. Long-term effects of the booster-enhanced READY-Girls preconception counseling program on intentions and behaviors for family planning in teens with diabetes. Diabetes Care 2013;36:3870–3874
9. Peterson C, Grosse SD, Li R, et al. Preventable health and cost burden of adverse birth outcomes associated with pregestational diabetes in the United States. Am J Obstet Gynecol 2015;212:74.e1–74.e9
10. Britton LE, Hussey JM, Berry DC, Crandell JL, Brooks JL, Bryant AG. Contraceptive use among women with prediabetes and diabetes in a US national sample. J Midwifery Womens Health 2019;64:36–45
11. Morris JR, Tepper NK. Description and comparison of postpartum use of effective contraception among women with and without diabetes. Contraception 2019;100:474–479
12. Goldstuck ND, Steyn PS. The intrauterine device in women with diabetes mellitus type I and II: a systematic review. ISRN Obstet Gynecol 2013;2013:814062
13. Wu JP, Moniz MH, Ursu AN. Long-acting reversible contraception—highly efficacious, safe, and underutilized. JAMA 2018;320:397–398
14. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 201: Pregestational Diabetes Mellitus. Obstet Gynecol 2018;132:e228–e248
15. Charron-Prochownik D, Downs J. *Diabetes and Reproductive Health for Girls*. Alexandria, VA, American Diabetes Association, 2016
16. ACOG Committee Opinion No. 762: Prepregnancy Counseling. Obstet Gynecol 2019;133:e78–e89
17. Alexander EK, Pearce EN, Brent GA, et al. 2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid 2017;27:315–389
18. Ramos DE. Preconception health: changing the paradigm on well-woman health. Obstet Gynecol Clin North Am 2019;46:399–408
19. Bullo M, Tschumi S, Bucher BS, Bianchetti MG, Simonetti GD. Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists: a systematic review. Hypertension 2012;60:444–450
20. Bateman BT, Patorno E, Desai RJ, et al. Angiotensin-converting enzyme inhibitors and the risk of congenital malformations. Obstet Gynecol 2017;129:174–184
21. Taguchi N, Rubin ET, Hosokawa A, et al. Prenatal exposure to HMG-CoA reductase inhibitors: effects on fetal and neonatal outcomes. Reprod Toxicol 2008;26:175–177
22. Bateman BT, Hernandez-Diaz S, Fischer MA, et al. Statins and congenital malformations: cohort study. BMJ 2015;350:h1035
23. Chew EY, Mills JL, Metzger BE, et al.; National Institute of Child Health and Human Development Diabetes in Early Pregnancy Study. Metabolic control and progression of retinopathy. The Diabetes in Early Pregnancy Study. Diabetes Care 1995;18:631–637
24. McElvy SS, Miodovnik M, Rosenn B, et al. A focused preconceptional and early pregnancy program in women with type 1 diabetes reduces perinatal mortality and malformation rates to general population levels. J Matern Fetal Med 2000;9:14–20

25. Murphy HR, Roland JM, Skinner TC, et al. Effectiveness of a regional prepregnancy care program in women with type 1 and type 2 diabetes: benefits beyond glycemic control. Diabetes Care 2010;33:2514–2520
26. Elixhauser A, Weschler JM, Kitzmiller JL, et al. Cost-benefit analysis of preconception care for women with established diabetes mellitus. Diabetes Care 1993;16:1146–1157
27. Owens LA, Avalos G, Kirwan B, Carmody L, Dunne F. ATLANTIC DIP: closing the loop: a change in clinical practice can improve outcomes for women with pregestational diabetes. Diabetes Care 2012;35:1669–1671
28. Taylor C, McCance DR, Chappell L, et al. Implementation of guidelines for multidisciplinary team management of pregnancy in women with pre-existing diabetes or cardiac conditions: results from a UK national survey. BMC Pregnancy Childbirth 2017;17:434
29. García-Patterson A, Gich I, Amini SB, Catalano PM, de Leiva A, Corcoy R. Insulin requirements throughout pregnancy in women with type 1 diabetes mellitus: three changes of direction. Diabetologia 2010;53:446–451
30. Padmanabhan S, Lee VW, Mclean M, et al. The association of falling insulin requirements with maternal biomarkers and placental dysfunction: a prospective study of women with preexisting diabetes in pregnancy. Diabetes Care 2017;40:1323–1330
31. Manderson JG, Patterson CC, Hadden DR, Traub AI, Ennis C, McCance DR. Preprandial versus postprandial blood glucose monitoring in type 1 diabetic pregnancy: a randomized controlled clinical trial. Am J Obstet Gynecol 2003;189:507–512
32. de Veciana M, Major CA, Morgan MA, et al. Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. N Engl J Med 1995;333:1237–1241
33. Jovanovic-Peterson L, Peterson CM, Reed GF, et al.; National Institute of Child Health and Human Development—Diabetes in Early Pregnancy Study. Maternal postprandial glucose levels and infant birth weight: the Diabetes in Early Pregnancy Study. Am J Obstet Gynecol 1991;164:103–111
34. Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstet Gynecol 2018;131:e49–e64
35. Hernandez TL, Friedman JE, Van Pelt RE, Barbour LA. Patterns of glycemia in normal pregnancy: should the current therapeutic targets be challenged? Diabetes Care 2011;34:1660–1668
36. Ho Y-R, Wang P, Lu M-C, Tseng S-T, Yang C-P, Yan Y-H. Associations of mid-pregnancy HbA1c with gestational diabetes and risk of adverse pregnancy outcomes in high-risk Taiwanese women. PLoS One 2017;12:e0177563
37. HAPO Study Cooperative Research Group; Metzger BE, Lowe LP, Dyer AR, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991–2002
38. Maresh MJA, Holmes VA, Patterson CC, et al.; Diabetes and Pre-eclampsia Intervention Trial Study Group. Glycemic targets in the second and third trimester of pregnancy for women with type 1 diabetes. Diabetes Care 2015;38:34–42
39. Nielsen LR, Ekbom P, Damm P, et al. HbA_{1c} levels are significantly lower in early and late pregnancy. Diabetes Care 2004;27:1200–1201
40. Mosca A, Paleari R, Dalfrà MG, et al. Reference intervals for hemoglobin A1c in pregnant women: data from an Italian multicenter study. Clin Chem 2006;52:1138–1143
41. Hummel M, Marienfeld S, Huppmann M, et al. Fetal growth is increased by maternal type 1 diabetes and HLA DR4-related gene interactions. Diabetologia 2007;50:850–858
42. Cyganek K, Skupien J, Katra B, et al. Risk of macrosomia remains glucose-dependent in a cohort of women with pregestational type 1 diabetes and good glycemic control. Endocrine 2017;55:447–455
43. Abell SK, Boyle JA, de Courten B, et al. Impact of type 2 diabetes, obesity and glycaemic control on pregnancy outcomes. Aust N Z J Obstet Gynaecol 2017;57:308–314
44. Temple RC, Aldridge V, Stanley K, Murphy HR. Glycaemic control throughout pregnancy and risk of pre-eclampsia in women with type I diabetes. BJOG 2006;113:1329–1332
45. Combs CA, Gunderson E, Kitzmiller JL, Gavin LA, Main EK. Relationship of fetal macrosomia to maternal postprandial glucose control during pregnancy. Diabetes Care 1992;15:1251–1257
46. Feig DS, Donovan LE, Corcoy R, et al.; CONCEPTT Collaborative Group. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. Lancet 2017;390:2347–2359
47. Kristensen K, Ögge LE, Sengpiel V, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes: an observational cohort study of 186 pregnancies. Diabetologia 2019;62:1143–1153
48. Law GR, Gilthorpe MS, Secher AL, et al. Translating HbA_{1c} measurements into estimated average glucose values in pregnant women with diabetes. Diabetologia 2017;60:618–624
49. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care 2019;42:1593–1603
50. Scholtens DM, Kuang A, Lowe LP, et al.; HAPO Follow-up Study Cooperative Research Group; HAPO Follow-Up Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): maternal glycemia and childhood glucose metabolism. Diabetes Care 2019;42:381–392
51. Lowe WL Jr, Scholtens DM, Kuang A, et al.; HAPO Follow-up Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): maternal gestational diabetes mellitus and childhood glucose metabolism. Diabetes Care 2019;42:372–380
52. Koivusalo SB, Rönö K, Klemetti MM, et al. Gestational diabetes mellitus can be prevented by lifestyle intervention: the Finnish Gestational Diabetes Prevention Study (RADIEL): a randomized controlled trial. Diabetes Care 2016;39:24–30
53. Wang C, Wei Y, Zhang X, et al. A randomized clinical trial of exercise during pregnancy to prevent gestational diabetes mellitus and improve pregnancy outcome in overweight and obese pregnant women. Am J Obstet Gynecol 2017;216:340–351
54. Metzger BE, Buchanan TA, Coustan DR, et al. Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. Diabetes Care 2007;30(Suppl. 2):S251–S260
55. Mayo K, Melamed N, Vandenberghe H, Berger H. The impact of adoption of the International Association of Diabetes In Pregnancy Study Group criteria for the screening and diagnosis of gestational diabetes. Am J Obstet Gynecol 2015;212:224.e1–224.e9
56. Han S, Crowther CA, Middleton P, Heatley E. Different types of dietary advice for women with gestational diabetes mellitus. Cochrane Database Syst Rev 20133:CD009275
57. Viana LV, Gross JL, Azevedo MJ. Dietary intervention in patients with gestational diabetes mellitus: a systematic review and meta-analysis of randomized clinical trials on maternal and newborn outcomes. Diabetes Care 2014;37:3345–3355
58. Institute of Medicine and National Research Council. *Weight Gain During Pregnancy: Reexamining the Guidelines*. Washington, D.C., National Academies Press, 2009
59. Hartling L, Dryden DM, Guthrie A, Muise M, Vandermeer B, Donovan L. Benefits and harms of treating gestational diabetes mellitus: a systematic review and meta-analysis for the U.S. Preventive Services Task Force and the National Institutes of Health Office of Medical Applications of Research. Ann Intern Med 2013;159:123–129
60. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP; MiG Trial Investigators. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med 2008;358:2003–2015
61. Gui J, Liu Q, Feng L. Metformin vs insulin in the management of gestational diabetes: a meta-analysis. PLoS One 2013;8:e64585
62. Langer O, Conway DL, Berkus MD, Xenakis EM-J, Gonzales O. A comparison of glyburide and insulin in women with gestational diabetes mellitus. N Engl J Med 2000;343:1134–1138
63. Hebert MF, Ma X, Naraharisetti SB, et al.; Obstetric-Fetal Pharmacology Research Unit Network. Are we optimizing gestational diabetes treatment with glyburide? The pharmacologic basis for better clinical practice. Clin Pharmacol Ther 2009;85:607–614
64. Malek R, Davis SN. Pharmacokinetics, efficacy and safety of glyburide for treatment of gestational diabetes mellitus. Expert Opin Drug Metab Toxicol 2016;12:691–699
65. Balsells M, García-Patterson A, Solà I, Roqué M, Gich I, Corcoy R. Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. BMJ 2015;350:h102
66. Sénat M-V, Affres H, Letourneau A, et al.; Groupe de Recherche en Obstétrique et Gynécologie (GROG). Effect of glyburide vs subcutaneous insulin on perinatal complications among women with gestational diabetes: a randomized clinical trial. JAMA 2018;319:1773–1780
67. Silva JC, Pacheco C, Bizato J, de Souza BV, Ribeiro TE, Bertini AM. Metformin compared with glyburide for the management of gestational diabetes. Int J Gynaecol Obstet 2010;111:37–40

68. Nachum Z, Zafran N, Salim R, et al. Glyburide versus metformin and their combination for the treatment of gestational diabetes mellitus: a randomized controlled study. Diabetes Care 2017; 40:332–337
69. Jiang Y-F, Chen X-Y, Ding T, Wang X-F, Zhu Z-N, Su S-W. Comparative efficacy and safety of OADs in management of GDM: network meta-analysis of randomized controlled trials. J Clin Endocrinol Metab 2015;100:2071–2080
70. Vanky E, Zahlsen K, Spigset O, Carlsen SM. Placental passage of metformin in women with polycystic ovary syndrome. Fertil Steril 2005;83: 1575–1578
71. Charles B, Norris R, Xiao X, Hague W. Population pharmacokinetics of metformin in late pregnancy. Ther Drug Monit 2006;28:67–72
72. Rowan JA, Rush EC, Plank LD, et al. Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): body composition and metabolic outcomes at 7-9 years of age. BMJ Open Diabetes Res Care 2018;6:e000456
73. Hanem LGE, Stridsklev S, Júlíusson PB, et al. Metformin use in PCOS pregnancies increases the risk of offspring overweight at 4 years of age: follow-up of two RCTs. J Clin Endocrinol Metab 2018;103:1612–1621
74. Tarry-Adkins JL, Aiken CE, Ozanne SE. Neonatal, infant, and childhood growth following metformin versus insulin treatment for gestational diabetes: a systematic review and meta-analysis. PLoS Med 2019;16:e1002848
75. Hanem LGE, Salvesen Ø, Juliusson PB, et al. Intrauterine metformin exposure and offspring cardiometabolic risk factors (PedMet study): a 5-10 year follow-up of the PregMet randomised controlled trial. Lancet Child Adolesc Health 2019;3:166–174
76. Mount Sinai Hospital, Canada. Metformin in Women With Type 2 Diabetes in Pregnancy Trial (MiTy). Bethesda, MD, National Library of Medicine, ClinicalTrials.gov. Accessed 3 October 2019. Available from https://clinicaltrials.gov/ct2/show/NCT01353391
77. University of North Carolina, Chapel Hill. Medical Optimization of Management of Type 2 Diabetes Complicating Pregnancy (MOMPOD). Bethesda, MD, National Library of Medicine, ClinicalTrials.gov. Accessed 3 October 2019. Available from https://clinicaltrials.gov/ct2/show/NCT02932475
78. Vanky E, Stridsklev S, Heimstad R, et al. Metformin versus placebo from first trimester to delivery in polycystic ovary syndrome: a randomized, controlled multicenter study. J Clin Endocrinol Metab 2010;95:E448–E455
79. Legro RS, Barnhart HX, Schlaff WD, et al.; Cooperative Multicenter Reproductive Medicine Network. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. N Engl J Med 2007;356:551–566
80. Palomba S, Orio F Jr, Falbo A, et al. Prospective parallel randomized, double-blind, double-dummy controlled clinical trial comparing clomiphene citrate and metformin as the first-line treatment for ovulation induction in nonobese anovulatory women with polycystic ovary syndrome. J Clin Endocrinol Metab 2005;90:4068–4074
81. Palomba S, Orio F Jr, Nardo LG, et al. Metformin administration versus laparoscopic ovarian diathermy in clomiphene citrate-resistant women with polycystic ovary syndrome: a prospective parallel randomized double-blind placebo-controlled trial. J Clin Endocrinol Metab 2004;89:4801–4809
82. Barbour LA, Scifres C, Valent AM, et al. A cautionary response to SMFM statement: pharmacological treatment of gestational diabetes. Am J Obstet Gynecol 2018;219:367.e1–367.e7
83. Barbour LA, Feig DS. Metformin for gestational diabetes mellitus: progeny, perspective, and a personalized approach. Diabetes Care 2019;42:396–399
84. Farrar D, Tuffnell DJ, West J, West HM. Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes. Cochrane Database Syst Rev 20166:CD005542
85. Pollex EK, Feig DS, Lubetsky A, Yip PM, Koren G. Insulin glargine safety in pregnancy: a transplacental transfer study. Diabetes Care 2010;33: 29–33
86. Holcberg G, Tsadkin-Tamir M, Sapir O, et al. Transfer of insulin lispro across the human placenta. Eur J Obstet Gynecol Reprod Biol 2004;115:117–118
87. Boskovic R, Feig DS, Derewlany L, Knie B, Portnoi G, Koren G. Transfer of insulin lispro across the human placenta: in vitro perfusion studies. Diabetes Care 2003;26:1390–1394
88. McCance DR, Damm P, Mathiesen ER, et al. Evaluation of insulin antibodies and placental transfer of insulin aspart in pregnant women with type 1 diabetes mellitus. Diabetologia 2008;51: 2141–2143
89. Suffecool K, Rosenn B, Niederkofler EE, et al. Insulin detemir does not cross the human placenta. Diabetes Care 2015;38:e20–e21
90. O'Neill SM, Kenny LC, Khashan AS, West HM, Smyth RM, Kearney PM. Different insulin types and regimens for pregnant women with pre-existing diabetes. Cochrane Database Syst Rev 2017;2:CD011880
91. Carta Q, Meriggi E, Trossarelli GF, et al. Continuous subcutaneous insulin infusion versus intensive conventional insulin therapy in type I and type II diabetic pregnancy. Diabete Metab 1986;12:121–129
92. Kernaghan D, Farrell T, Hammond P, Owen P. Fetal growth in women managed with insulin pump therapy compared to conventional insulin. Eur J Obstet Gynecol Reprod Biol 2008;137:47–49
93. Clausen TD, Mathiesen E, Ekbom P, Hellmuth E, Mandrup-Poulsen T, Damm P. Poor pregnancy outcome in women with type 2 diabetes. Diabetes Care 2005;28:323–328
94. Cundy T, Gamble G, Neale L, et al. Differing causes of pregnancy loss in type 1 and type 2 diabetes. Diabetes Care 2007;30:2603–2607
95. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ 2005;330:565
96. Henderson JT, Whitlock EP, O'Conner E, Senger CA, Thompson JH, Rowland MG. Low-Dose Aspirin for the Prevention of Morbidity and Mortality From Preeclampsia: A Systematic Evidence Review for the U.S. Preventive Services Task Force. Rockville, MD, Agency for Healthcare Research and Quality, 2014 (Evidence Syntheses, No. 112). Accessed 21 June 2020. Available from https://www.ncbi.nlm.nih.gov/books/NBK196392/
97. Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. Am J Obstet Gynecol 2018;218:287–293.e1
98. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. N Engl J Med 2017;377: 613–622
99. Hoffman MK, Goudar SS, Kodkany BS, et al.; ASPIRIN Study Group. Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (ASPIRIN): a randomised, double-blind, placebo-controlled trial. Lancet 2020;395:285–293
100. Werner EF, Hauspurg AK, Rouse DJ. A cost-benefit analysis of low-dose aspirin prophylaxis for the prevention of preeclampsia in the United States. Obstet Gynecol 2015;126:1242–1250
101. Voutetakis A, Pervanidou P, Kanaka-Gantenbein C. Aspirin for the prevention of preeclampsia and potential consequences for fetal brain development. JAMA Pediatr 2019; 173:619–620
102. Brown MA, Magee LA, Kenny LC, et al.; International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. Hypertension 2018;72:24–43
103. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 203: Chronic Hypertension in Pregnancy. Obstet Gynecol 2019;133:e26–e50
104. Magee LA, von Dadelszen P, Rey E, et al. Less-tight versus tight control of hypertension in pregnancy. N Engl J Med 2015;372:407–417
105. Sibai BM. Treatment of hypertension in pregnant women. N Engl J Med 1996;335:257–265
106. Kazmin A, Garcia-Bournissen F, Koren G. Risks of statin use during pregnancy: a systematic review. J Obstet Gynaecol Can 2007;29:906–908
107. Vounzoulaki E, Khunti K, Abner SC, Tan BK, Davies MJ, Gillies CL. Progression to type 2 diabetes in women with a known history of gestational diabetes: systematic review and meta-analysis. BMJ 2020;369:m1361
108. Li Z, Cheng Y, Wang D, et al. Incidence rate of type 2 diabetes mellitus after gestational diabetes mellitus: a systematic review and meta-analysis of 170,139 women. J Diabetes Res 2020; 2020:3076463
109. Tobias DK, Hu FB, Chavarro J, Rosner B, Mozaffarian D, Zhang C. Healthful dietary patterns and type 2 diabetes mellitus risk among women with a history of gestational diabetes mellitus. Arch Intern Med 2012;172:1566–1572
110. Villamor E, Cnattingius S. Interpregnancy weight change and risk of adverse pregnancy outcomes: a population-based study. Lancet 2006; 368:1164–1170
111. Ratner RE, Christophi CA, Metzger BE, et al.; Diabetes Prevention Program Research Group. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. J Clin Endocrinol Metab 2008;93:4774–4779
112. Aroda VR, Christophi CA, Edelstein SL, et al.; Diabetes Prevention Program Research Group. The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the Diabetes Prevention Program outcomes study 10-year follow-up. J Clin Endocrinol Metab 2015;100:1646–1653
113. Achong N, Duncan EL, McIntyre HD, Callaway L. Peripartum management of glycemia

in women with type 1 diabetes. Diabetes Care 2014;37:364–371
114. Roeder HA, Moore TR, Ramos GA. Changes in postpartum insulin requirements for patients with well-controlled type 1 diabetes. Am J Perinatol 2016;33:683–687
115. Riviello C, Mello G, Jovanovic LG. Breastfeeding and the basal insulin requirement in type 1 diabetic women. Endocr Pract 2009;15:187–193
116. Stuebe AM, Rich-Edwards JW, Willett WC, Manson JE, Michels KB. Duration of lactation and incidence of type 2 diabetes. JAMA 2005;294:2601–2610
117. Pereira PF, Alfenas RdeCG, Araújo RMA. Does breastfeeding influence the risk of developing diabetes mellitus in children? A review of current evidence. J Pediatr (Rio J) 2014;90:7–15

15. Diabetes Care in the Hospital: *Standards of Medical Care in Diabetes—2021*

American Diabetes Association

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The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc21-SPPC), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc21-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Among hospitalized patients, hyperglycemia, hypoglycemia, and glucose variability are associated with adverse outcomes, including death (1–3). Therefore, careful management of inpatients with diabetes has direct and immediate benefits. Hospital management of diabetes is facilitated by preadmission treatment of hyperglycemia in patients having elective procedures, a dedicated inpatient diabetes service applying well-developed standards, and careful transition out of the hospital to prearranged outpatient management. These steps can shorten hospital stays and reduce the need for readmission as well as improve patient outcomes. Some in-depth reviews of hospital care for patients with diabetes have been published (3–5). For older hospitalized patients or for patients in the long-term care facilities, please see Section 12 "Older Adults" (https://doi.org/10.2337/dc21-S012).

HOSPITAL CARE DELIVERY STANDARDS

Recommendations

15.1 Perform an A1C test on all patients with diabetes or hyperglycemia (blood glucose >140 mg/dL [7.8 mmol/L]) admitted to the hospital if not performed in the prior 3 months. **B**

15.2 Insulin should be administered using validated written or computerized protocols that allow for predefined adjustments in the insulin dosage based on glycemic fluctuations. **B**

Considerations on Admission

High-quality hospital care for diabetes requires standards for care delivery, which are best implemented using structured order sets, and quality assurance for process improvement. Unfortunately, "best practice" protocols, reviews, and guidelines (2–4) are inconsistently implemented within hospitals. To correct this, medical centers

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striving for optimal inpatient diabetes treatment should establish protocols and structured order sets, which include computerized physician order entry (CPOE).

Initial orders should state the type of diabetes (i.e., type 1, type 2, gestational diabetes mellitus, pancreatic diabetes) when it is known. Because inpatient treatment and discharge planning are more effective if based on preadmission glycemia, an A1C should be measured for all patients with diabetes or hyperglycemia admitted to the hospital if the test has not been performed in the previous 3 months (6–9). In addition, diabetes self-management knowledge and behaviors should be assessed on admission and diabetes self-management education provided, if appropriate. Diabetes self-management education should include appropriate skills needed after discharge, such as medication dosing and administration, glucose monitoring, and recognition and treatment of hypoglycemia (2,3). There is evidence to support preadmission treatment of hyperglycemia in patients scheduled for elective surgery as an effective means of reducing adverse outcomes (10–13).

The National Academy of Medicine recommends CPOE to prevent medication-related errors and to increase efficiency in medication administration (14). A Cochrane review of randomized controlled trials using computerized advice to improve glucose control in the hospital found significant improvement in the percentage of time patients spent in the target glucose range, lower mean blood glucose levels, and no increase in hypoglycemia (15). Thus, where feasible, there should be structured order sets that provide computerized advice for glucose control. Electronic insulin order templates also improve mean glucose levels without increasing hypoglycemia in patients with type 2 diabetes, so structured insulin order sets should be incorporated into the CPOE (16,17).

Diabetes Care Providers in the Hospital

Recommendation

15.3 When caring for hospitalized patients with diabetes, consult with a specialized diabetes or glucose management team when possible. **C**

Appropriately trained specialists or specialty teams may reduce length of stay, improve glycemic control, and improve outcomes (10,18,19). In addition, the greater risk of 30-day readmission following hospitalization that has been attributed to diabetes can be reduced, and costs saved, when inpatient care is provided by a specialized diabetes management team (20,21). In a cross-sectional comparison of usual care to management by specialists who reviewed cases and made recommendations solely through the electronic medical record, rates of both hyper- and hypoglycemia were reduced 30–40% by electronic "virtual care" (22). Details of team formation are available in The Joint Commission Standards for programs and from the Society of Hospital Medicine (23,24).

Even the best orders may not be carried out in a way that improves quality, nor are they automatically updated when new evidence arises. To this end, the Joint Commission has an accreditation program for the hospital care of diabetes (23), and the Society of Hospital Medicine has a workbook for program development (24).

GLYCEMIC TARGETS IN HOSPITALIZED PATIENTS

Recommendations

15.4 Insulin therapy should be initiated for treatment of persistent hyperglycemia starting at a threshold ≥180 mg/dL (10.0 mmol/L). Once insulin therapy is started, a target glucose range of 140–180 mg/dL (7.8–10.0 mmol/L) is recommended for the majority of critically ill and noncritically ill patients. **A**

15.5 More stringent goals, such as 110–140 mg/dL (6.1–7.8 mmol/L), may be appropriate for selected patients if they can be achieved without significant hypoglycemia. **C**

Standard Definitions of Glucose Abnormalities

Hyperglycemia in hospitalized patients is defined as blood glucose levels >140 mg/dL (7.8 mmol/L) (2,3,25). Blood glucose levels persistently above this level should prompt conservative interventions, such as alterations in diet or changes to medications that cause hyperglycemia. An admission A1C value ≥6.5% (48 mmol/mol) suggests that the onset of diabetes preceded hospitalization (see Section 2 "Classification and Diagnosis of Diabetes," https://doi.org/10.2337/dc21-S002) (2,25). Hypoglycemia in hospitalized patients is categorized by blood glucose concentration and clinical correlates (**Table 6.4**) (26): Level 1 hypoglycemia is a glucose concentration 54–70 mg/dL (3.0–3.9 mmol/L). Level 2 hypoglycemia is a blood glucose concentration <54 mg/dL (3.0 mmol/L), which is typically the threshold for neuroglycopenic symptoms. Level 3 hypoglycemia is a clinical event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery. Levels 2 and 3 require immediate correction of low blood glucose.

Glycemic Targets

In a landmark clinical trial, Van den Berghe et al. (27) demonstrated that an intensive intravenous insulin regimen to reach a target glycemic range of 80–110 mg/dL (4.4–6.1 mmol/L) reduced mortality by 40% compared with a standard approach targeting blood glucose of 180–215 mg/dL (10–12 mmol/L) in critically ill patients with recent surgery. This study provided robust evidence that active treatment to lower blood glucose in hospitalized patients had immediate benefits. However, a large, multicenter follow-up study, the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial (28), led to a reconsideration of the optimal target range for glucose lowering in critical illness. In this trial, critically ill patients randomized to intensive glycemic control (80–110 mg/dL) derived no significant treatment advantage compared with a group with more moderate glycemic targets (140–180 mg/dL [7.8–10.0 mmol/L]) and in fact had slightly but significantly higher mortality (27.5% vs. 25%). The intensively treated group had 10- to 15-fold greater rates of hypoglycemia, which may have contributed to the adverse outcomes noted. The findings from NICE-SUGAR are supported by several meta-analyses, some of which suggest that tight glycemic control increases mortality compared with more moderate glycemic targets and generally causes higher rates

of hypoglycemia (29–31). Based on these results, insulin therapy should be initiated for treatment of persistent hyperglycemia ≥180 mg/dL (10.0 mmol/L) and targeted to a glucose range of 140–180 mg/dL (7.8–10.0 mmol/L) for the majority of critically ill patients. Although not as well supported by data from randomized controlled trials, these recommendations have been extended to hospitalized patients without critical illness. More stringent goals, such as 110–140 mg/dL (6.1–7.8 mmol/L), may be appropriate for selected patients (e.g., critically ill postsurgical patients or patients with cardiac surgery), as long as they can be achieved without significant hypoglycemia (32,33). On the other hand, glucose concentrations between 180 mg/dL and 250 mg/dL (10–13.9 mmol/L) may be acceptable in patients with severe comorbidities, and in inpatient care settings where frequent glucose monitoring or close nursing supervision is not feasible. Glycemic levels above 250 mg/dL (13.9 mmol/L) may be acceptable in terminally ill patients with short life expectancy. In these patients, less aggressive insulin regimens to minimize glucosuria, dehydration, and electrolyte disturbances are often more appropriate. Clinical judgment combined with ongoing assessment of clinical status, including changes in the trajectory of glucose measures, illness severity, nutritional status, or concomitant medications that might affect glucose levels (e.g., glucocorticoids), should be incorporated into the day-to-day decisions regarding insulin dosing (34).

BEDSIDE BLOOD GLUCOSE MONITORING

In hospitalized patients with diabetes who are eating, bedside glucose monitoring should be performed before meals; in those not eating, glucose monitoring is advised every 4–6 h (2). More frequent bedside blood glucose testing ranging from every 30 min to every 2 h is the required standard for safe use of intravenous insulin. Safety standards for blood glucose monitoring that prohibit the sharing of lancets, other testing materials, and needles are mandatory (35).

The vast majority of hospital glucose monitoring is performed using standard glucose monitors and capillary blood taken from fingersticks, similar to the process used by outpatients for home glucose monitoring (36). Point-of-care (POC) meters are not as accurate or as precise as laboratory glucose analyzers, and capillary blood glucose readings are subject to artifact due to perfusion, edema, anemia/erythrocytosis, and several medications commonly used in the hospital (37). The U.S. Food and Drug Administration (FDA) has established standards for capillary (fingerstick) blood glucose meters used in the ambulatory setting as well as standards to be applied for POC measures in the hospital (37). The balance between analytic requirements (e.g., accuracy, precision, interference) and clinical requirements (rapidity, simplicity, point of care) has not been uniformly resolved (36,38), and most hospitals/medical centers have arrived at their own policies to balance these parameters. It is critically important that devices selected for in-hospital use, and the workflow through which they are applied, have careful analysis of performance and reliability and ongoing quality assessments. Recent studies indicate that POC measures provide adequate information for usual practice, with only rare instances where care has been compromised (39,40). Good practice dictates that any glucose result that does not correlate with the patient's clinical status should be confirmed through measurement of a serum sample in the clinical laboratory.

Continuous Glucose Monitoring

Real-time continuous glucose monitoring (CGM) provides frequent measurements of interstitial glucose levels as well as direction and magnitude of glucose trends. Even though CGM has theoretical advantages over POC glucose testing in detecting and reducing the incidence of hypoglycemia, it has not been approved by the FDA for inpatient use. Some hospitals with established glucose management teams allow the use of CGM in selected patients on an individual basis, provided both the patients and the glucose management team are well educated in the use of this technology. CGM is not approved for intensive care unit use. For more information on CGM, see Section 7 "Diabetes Technology" (https://doi.org/10.2337/dc21-S007).

GLUCOSE-LOWERING TREATMENT IN HOSPITALIZED PATIENTS

Recommendations

15.6 Basal insulin or a basal plus bolus correction insulin regimen is the preferred treatment for noncritically ill hospitalized patients with poor oral intake or those who are taking nothing by mouth. **A**

15.7 An insulin regimen with basal, prandial, and correction components is the preferred treatment for noncritically ill hospitalized patients with good nutritional intake. **A**

15.8 Use of only a sliding scale insulin regimen in the inpatient hospital setting is strongly discouraged. **A**

Insulin Therapy

Critical Care Setting

In the critical care setting, continuous intravenous insulin infusion is the most effective method for achieving glycemic targets. Intravenous insulin infusions should be administered based on validated written or computerized protocols that allow for predefined adjustments in the infusion rate, accounting for glycemic fluctuations and insulin dose (3).

Noncritical Care Setting

In most instances, insulin is the preferred treatment for hyperglycemia in hospitalized patients. However, in certain circumstances, it may be appropriate to continue home regimens including oral glucose-lowering medications (41). If oral medications are held in the hospital, there should be a protocol for resuming them 1–2 days before discharge. For patients using insulin, recent reports indicate that inpatient use of insulin pens is safe and may be associated with improved nurse satisfaction compared with the use of insulin vials and syringes (42–44). Insulin pens have been the subject of an FDA warning because of potential blood-borne diseases; the warning "For single patient use only" should be rigorously followed (45).

Outside of critical care units, scheduled insulin regimens are recommended to manage hyperglycemia in patients with diabetes. Regimens using insulin analogs and human insulin result in similar glycemic control in the hospital setting (46). The use of subcutaneous rapid- or short-acting insulin before meals, or every 4–6 h if no meals are given or if

the patient is receiving continuous enteral/parenteral nutrition, is indicated to correct hyperglycemia. Basal insulin, or a basal plus bolus correction regimen, is the preferred treatment for noncritically ill hospitalized patients with poor oral intake or those who are restricted from oral intake. An insulin regimen with basal, prandial, and correction components is the preferred treatment for noncritically ill hospitalized patients with good nutritional intake.

For patients who are eating, insulin injections should align with meals. In such instances, POC glucose testing should be performed immediately before meals. If oral intake is poor, a safer procedure is to administer prandial insulin immediately after the patient eats, with the dose adjusted to be appropriate for the amount ingested (46).

A randomized controlled trial has shown that basal-bolus treatment improved glycemic control and reduced hospital complications compared with reactive, or sliding scale, insulin regimens (i.e., dosing given in response to elevated glucose rather than preemptively) in general surgery patients with type 2 diabetes (47). Prolonged use of sliding scale insulin regimens as the sole treatment of hyperglycemic inpatients is strongly discouraged (19,48).

While there is evidence for using premixed insulin formulations in the outpatient setting (49), a recent inpatient study of 70/30 NPH/regular insulin versus basal-bolus therapy showed comparable glycemic control but significantly increased hypoglycemia in the group receiving premixed insulin (50). Therefore, premixed insulin regimens are not routinely recommended for in-hospital use.

Type 1 Diabetes

For patients with type 1 diabetes, dosing insulin based solely on premeal glucose levels does not account for basal insulin requirements or caloric intake, increasing the risk of both hypoglycemia and hyperglycemia. Typically, basal insulin dosing schemes are based on body weight, with some evidence that patients with renal insufficiency should be treated with lower doses (51,52). An insulin regimen with basal and correction components is necessary for all hospitalized patients with type 1 diabetes, with the addition of prandial insulin if the patient is eating. Most importantly, patients with type 1 diabetes should always be treated with insulin.

Transitioning Intravenous to Subcutaneous Insulin

When discontinuing intravenous insulin, a transition protocol is associated with less morbidity and lower costs of care (53,54) and is therefore recommended. A patient with type 1 or type 2 diabetes being transitioned to a subcutaneous regimen should receive a dose of subcutaneous basal insulin 2 h before the intravenous infusion is discontinued. The dose of basal insulin is best calculated on the basis of the insulin infusion rate during the last 6 h when stable glycemic goals were achieved (55). For patients transitioning to regimens with concentrated insulin (U-200, U-300, or U-500) in the inpatient setting, it is important to ensure correct dosing by utilizing an individual pen and cartridge for each patient and by meticulous supervision of the dose administered (55,56).

Noninsulin Therapies

The safety and efficacy of noninsulin glucose-lowering therapies in the hospital setting is an area of active research (57,58). Several recent randomized trials have demonstrated the potential effectiveness of glucagon-like peptide 1 receptor agonists and dipeptidyl peptidase 4 inhibitors in specific groups of hospitalized patients (59–62). However, an FDA bulletin states that providers should consider discontinuing saxagliptin and alogliptin in people who develop heart failure (63).

Sodium–glucose cotransporter 2 (SGLT2) inhibitors should be avoided in cases of severe illness, in patients with ketonemia or ketonuria, and during prolonged fasting and surgical procedures (4). Until safety and effectiveness are established, SGLT2 inhibitors are not recommended for routine in-hospital use. Furthermore, the FDA has recently warned that SGLT2 inhibitors should be stopped 3 days before scheduled surgeries (4 days in the case of ertugliflozin).

HYPOGLYCEMIA

Recommendations

15.9 A hypoglycemia management protocol should be adopted and implemented by each hospital or hospital system. A plan for preventing and treating hypoglycemia should be established for each patient. Episodes of hypoglycemia in the hospital should be documented in the medical record and tracked. **E**

15.10 The treatment regimen should be reviewed and changed as necessary to prevent further hypoglycemia when a blood glucose value of <70 mg/dL (3.9 mmol/L) is documented. **C**

Patients with or without diabetes may experience hypoglycemia in the hospital setting. While hypoglycemia is associated with increased mortality (64), in many cases it is a marker of underlying disease rather than the cause of fatality. However, hypoglycemia is a severe consequence of dysregulated metabolism and/or diabetes treatment, and it is imperative that it be minimized in hospitalized patients. Many episodes of hypoglycemia among inpatients are preventable. Therefore, a hypoglycemia prevention and management protocol should be adopted and implemented by each hospital or hospital system. A standardized hospital-wide, nurse-initiated hypoglycemia treatment protocol should be in place to immediately address blood glucose levels of <70 mg/dL (3.9 mmol/L). In addition, individualized plans for preventing and treating hypoglycemia for each patient should also be developed. An American Diabetes Association (ADA) consensus statement recommends that a patient's treatment regimen be reviewed any time a blood glucose value of <70 mg/dL (3.9 mmol/L) occurs, as such readings often predict subsequent level 3 hypoglycemia (2). Episodes of hypoglycemia in the hospital should be documented in the medical record and tracked (3).

Triggering Events and Prevention of Hypoglycemia

Insulin is one of the most common drugs causing adverse events in hospitalized patients, and errors in insulin dosing and/or administration occur relatively frequently (64–66). Beyond insulin dosing errors, common preventable sources of iatrogenic hypoglycemia are improper prescribing of other glucose-lowering medications, inappropriate management of the first episode of hypoglycemia, and nutrition-insulin mismatch, often related to an unexpected interruption of nutrition.

A recent study describes acute kidney injury as an important risk factor for hypoglycemia in the hospital (67), possibly as a result of decreased insulin clearance. Studies of "bundled" preventive therapies, including proactive surveillance of glycemic outliers and an interdisciplinary data-driven approach to glycemic management, showed that hypoglycemic episodes in the hospital could be prevented. Compared with baseline, two such studies found that hypoglycemic events fell by 56–80% (68,69). The Joint Commission recommends that all hypoglycemic episodes be evaluated for a root cause and the episodes be aggregated and reviewed to address systemic issues (23).

In addition to errors with insulin treatment, iatrogenic hypoglycemia may be induced by a sudden reduction of corticosteroid dose, reduced oral intake, emesis, inappropriate timing of short- or rapid-acting insulin in relation to meals, reduced infusion rate of intravenous dextrose, unexpected interruption of enteral or parenteral feedings, delayed or missed blood glucose checks, and altered ability of the patient to report symptoms (5).

Predictors of Hypoglycemia

In ambulatory patients with diabetes, it is well established that an episode of severe hypoglycemia increases the risk for a subsequent event, in part because of impaired counterregulation (70,71). This relationship also holds for inpatients. For example, in a study of hospitalized patients treated for hyperglycemia, 84% who had an episode of "severe hypoglycemia" (defined as <40 mg/dL [2.2 mmol/L]) had a preceding episode of hypoglycemia (<70 mg/dL [3.9 mmol/L]) during the same admission (72). In another study of hypoglycemic episodes (defined as <50 mg/dL [2.8 mmol/L]), 78% of patients were using basal insulin, with the incidence of hypoglycemia peaking between midnight and 6:00 A.M. Despite recognition of hypoglycemia, 75% of patients did not have their dose of basal insulin changed before the next insulin administration (73).

Recently, several groups have developed algorithms to predict episodes of hypoglycemia among inpatients (74,75). Models such as these are potentially important and, once validated for general use, could provide a valuable tool to reduce rates of hypoglycemia in hospitalized patients.

MEDICAL NUTRITION THERAPY IN THE HOSPITAL

The goals of medical nutrition therapy in the hospital are to provide adequate calories to meet metabolic demands, optimize glycemic control, address personal food preferences, and facilitate creation of a discharge plan. The ADA does not endorse any single meal plan or specified percentages of macronutrients. Current nutrition recommendations advise individualization based on treatment goals, physiological parameters, and medication use. Consistent carbohydrate meal plans are preferred by many hospitals as they facilitate matching the prandial insulin dose to the amount of carbohydrate consumed (76).

Orders should also indicate that the meal delivery and nutritional insulin coverage should be coordinated, as their variability often creates the possibility of hyperglycemic and hypoglycemic events.

Many hospitals offer "meals on demand," allowing patients to order meals from the menu at any time of the day. This option improves patient satisfaction but complicates meal–insulin coordination. Finally, if carbohydrate counting is provided by the hospital kitchen, this option should be used in patients counting carbohydrates at home (77).

SELF-MANAGEMENT IN THE HOSPITAL

Diabetes self-management in the hospital may be appropriate for specific patients (78,79). Candidates include both adolescent and adult patients who successfully conduct self-management of diabetes at home, and whose cognitive and physical skills needed to successfully self-administer insulin and perform self-monitoring of blood glucose are not compromised. In addition, they should have adequate oral intake, be proficient in carbohydrate estimation, use multiple daily insulin injections or continuous subcutaneous insulin infusion (CSII), have stable insulin requirements, and understand sick-day management. If self-management is to be used, a protocol should include a requirement that the patient, nursing staff, and physician agree that patient self-management is appropriate. If CSII or CGM is to be used, hospital policy and procedures delineating guidelines for CSII therapy, including the changing of infusion sites, are advised (80,81). As outlined in Recommendation 7.27, patients using diabetes devices should be allowed to use them in an inpatient setting when proper supervision is available.

STANDARDS FOR SPECIAL SITUATIONS

Enteral/Parenteral Feedings

For patients receiving enteral or parenteral feedings who require insulin, the regimen should include coverage of basal, prandial, and correctional needs (82,83). It is particularly important that patients with type 1 diabetes continue to receive basal insulin even if feedings are discontinued.

Most patients receiving basal insulin should continue with their basal dose while the dose of insulin for the total daily nutritional component may be calculated as 1 unit of insulin for every 10–15 g carbohydrate in the formula. Commercially available cans of enteral nutrition contain variable amounts of carbohydrate and may be infused at different rates. All of this must be taken into consideration while calculating insulin doses to cover the nutritional component of enteral nutrition (77). Most specialists recommend using NPH insulin twice or three times daily (every 8 or 12 h) to cover patient needs. Adjustments in insulin doses must be made frequently. Correctional insulin should also be administered subcutaneously every 6 h using human regular insulin or every 4 h using a rapid-acting insulin. If enteral nutrition is interrupted, a 10% dextrose infusion must be started immediately to prevent hypoglycemia and to allow time to select more appropriate insulin doses.

For patients receiving enteral bolus feedings, approximately 1 unit of regular human insulin or rapid-acting insulin per 10–15 g carbohydrate should be given subcutaneously before each feeding. Correctional insulin coverage should be added as needed before each feeding.

In patients receiving nocturnal tube feeding, NPH insulin administered with the initiation of feeding represents a reasonable approach to cover this nutritional load.

For patients receiving continuous peripheral or central parenteral nutrition, human regular insulin may be added to the solution, particularly if >20 units of correctional insulin have been required

in the past 24 h. A starting dose of 1 unit of human regular insulin for every 10 g dextrose has been recommended (84) and should be adjusted daily in the solution. Adding insulin to the parenteral nutrition bag is the safest way to prevent hypoglycemia if the parenteral nutrition is stopped or interrupted. Correctional insulin should be administered subcutaneously. For full enteral/parenteral feeding guidance, please refer to review articles detailing this topic (82,85).

Because continuous enteral or parenteral nutrition results in a continuous postprandial state, any attempt to bring blood glucose levels to below 140 mg/dL (7.8 mmol/L) substantially increases the risk of hypoglycemia in these patients.

Glucocorticoid Therapy

The prevalence of glucocorticoid therapy in hospitalized patients can approach 10%, and these medications can induce hyperglycemia in patients with and without antecedent diabetes (86). Glucocorticoid type and duration of action must be considered in determining insulin treatment regimens. Daily-ingested short-acting glucocorticoids such as prednisone reach peak plasma levels in 4–6 h (87) but have pharmacologic actions that last through the day. Patients on morning steroid regimens have disproportionate hyperglycemia during the day, but they frequently reach normal blood glucose levels overnight regardless of treatment (86). In subjects on once- or twice-daily steroids, administration of intermediate-acting (NPH) insulin is a standard approach. NPH is usually administered in addition to daily basal-bolus insulin or in addition to oral antidiabetes medications. Because NPH action peaks at 4–6 h after administration, it is best to give it concomitantly with steroids (88). For long-acting glucocorticoids such as dexamethasone and multidose or continuous glucocorticoid use, long-acting insulin may be required to control fasting blood glucose (41,89). For higher doses of glucocorticoids, increasing doses of prandial and correctional insulin, sometimes in extraordinary amounts, are often needed in addition to basal insulin (90,91). Whatever orders are started, adjustments based on anticipated changes in glucocorticoid dosing and POC glucose test results are critical.

Perioperative Care

Many standards for perioperative care lack a robust evidence base. However, the following approach (92–94) may be considered:

1. The target range for blood glucose in the perioperative period should be 80–180 mg/dL (4.4–10.0 mmol/L).
2. A preoperative risk assessment should be performed for patients with diabetes who are at high risk for ischemic heart disease and those with autonomic neuropathy or renal failure.
3. Metformin should be withheld on the day of surgery.
4. SGLT2 inhibitors must be discontinued 3–4 days before surgery.
5. Withhold any other oral glucose-lowering agents the morning of surgery or procedure and give half of NPH dose or 75–80% doses of long-acting analog or pump basal insulin.
6. Monitor blood glucose at least every 2–4 h while patient is taking nothing by mouth and dose with short- or rapid-acting insulin as needed.
7. There are no data on the use and/or influence of glucagon-like peptide 1 receptor agonists or ultra-long-acting insulin analogs upon glycemia in perioperative care.

A recent review concluded that perioperative glycemic control tighter than 80–180 mg/dL (4.4–10.0 mmol/L) did not improve outcomes and was associated with more hypoglycemia (95); therefore, in general, tighter glycemic targets are not advised. Evidence from a recent study indicates that compared with usual dosing, a reduction of insulin given the evening before surgery by ~25% was more likely to achieve perioperative blood glucose levels in the target range with lower risk for hypoglycemia (96).

In noncardiac general surgery patients, basal insulin plus premeal short- or rapid-acting insulin (basal-bolus) coverage has been associated with improved glycemic control and lower rates of perioperative complications compared with the reactive, sliding scale regimens (short- or rapid-acting insulin coverage only with no basal insulin dosing) (47,97).

Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

There is considerable variability in the presentation of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic states, ranging from euglycemia or mild hyperglycemia and acidosis to severe hyperglycemia, dehydration, and coma; therefore, individualization of treatment based on a careful clinical and laboratory assessment is needed (98–101).

Management goals include restoration of circulatory volume and tissue perfusion, resolution of hyperglycemia, and correction of electrolyte imbalance and acidosis. It is also important to treat any correctable underlying cause of DKA such as sepsis, myocardial infarction, or stroke. In critically ill and mentally obtunded patients with DKA or hyperosmolar hyperglycemia, continuous intravenous insulin is the standard of care. Successful transition of patients from intravenous to subcutaneous insulin requires administration of basal insulin 2–4 h prior to the intravenous insulin being stopped to prevent recurrence of ketoacidosis and rebound hyperglycemia (100). There is no significant difference in outcomes for intravenous human regular insulin versus subcutaneous rapid-acting analogs when combined with aggressive fluid management for treating mild or moderate DKA (102). Patients with uncomplicated DKA may sometimes be treated with subcutaneous insulin in the emergency department or step-down units (103), an approach that may be safer and more cost-effective than treatment with intravenous insulin. If subcutaneous insulin administration is used, it is important to provide adequate fluid replacement, frequent bedside testing, appropriate treatment of any concurrent infections, and appropriate follow-up to avoid recurrent DKA. Several studies have shown that the use of bicarbonate in patients with DKA made no difference in resolution of acidosis or time to discharge, and its use is generally not recommended. For further information regarding treatment, refer to recent in-depth reviews (4).

TRANSITION FROM THE HOSPITAL TO THE AMBULATORY SETTING

Recommendation

15.11 There should be a structured discharge plan tailored to the individual patient with diabetes. **B**

A structured discharge plan tailored to the individual patient may reduce length of hospital stay and readmission rates and increase patient satisfaction (104). Discharge planning should begin at admission and be updated as patient needs change.

Transition from the acute care setting presents risks for all patients. Inpatients may be discharged to varied settings, including home (with or without visiting nurse services), assisted living, rehabilitation, or skilled nursing facilities. For the patient who is discharged to home or to assisted living, the optimal program will need to consider diabetes type and severity, effects of the patient's illness on blood glucose levels, and the patient's capacities and preferences. See Section 12 "Older Adults" (https://doi.org/10.2337/dc21-S012) for more information.

An outpatient follow-up visit with the primary care provider, endocrinologist, or diabetes care and education specialist within 1 month of discharge is advised for all patients experiencing hyperglycemia in the hospital. If glycemic medications are changed or glucose control is not optimal at discharge, an earlier appointment (in 1–2 weeks) is preferred, and frequent contact may be needed to avoid hyperglycemia and hypoglycemia. A recently described discharge algorithm for glycemic medication adjustment based on admission A1C was found useful to guide treatment decisions and significantly improved A1C after discharge (7). Therefore, if an A1C from the prior 3 months is unavailable, measuring the A1C in all patients with diabetes or hyperglycemia admitted to the hospital is recommended.

Clear communication with outpatient providers either directly or via hospital discharge summaries facilitates safe transitions to outpatient care. Providing information regarding the cause of hyperglycemia (or the plan for determining the cause), related complications and comorbidities, and recommended treatments can assist outpatient providers as they assume ongoing care.

The Agency for Healthcare Research and Quality (AHRQ) recommends that, at a minimum, discharge plans include the following (105):

Medication Reconciliation

- The patient's medications must be cross-checked to ensure that no chronic medications were stopped and to ensure the safety of new prescriptions.
- Prescriptions for new or changed medication should be filled and reviewed with the patient and family at or before discharge.

Structured Discharge Communication

- Information on medication changes, pending tests and studies, and follow-up needs must be accurately and promptly communicated to outpatient physicians.
- Discharge summaries should be transmitted to the primary care provider as soon as possible after discharge.
- Scheduling follow-up appointments prior to discharge increases the likelihood that patients will attend.

It is recommended that the following areas of knowledge be reviewed and addressed prior to hospital discharge:

- Identification of the health care provider who will provide diabetes care after discharge.
- Level of understanding related to the diabetes diagnosis, self-monitoring of blood glucose, home blood glucose goals, and when to call the provider.
- Definition, recognition, treatment, and prevention of hyperglycemia and hypoglycemia.
- Information on making healthy food choices at home and referral to an outpatient registered dietitian nutritionist to guide individualization of meal plan, if needed.
- If relevant, when and how to take blood glucose–lowering medications, including insulin administration.
- Sick-day management.
- Proper use and disposal of needles and syringes.

It is important that patients be provided with appropriate durable medical equipment, medications, supplies (e.g., blood glucose test strips), and prescriptions along with appropriate education at the time of discharge in order to avoid a potentially dangerous hiatus in care.

PREVENTING ADMISSIONS AND READMISSIONS

In patients with diabetes, the hospital readmission rate is between 14% and 20%, nearly twice that in patients without diabetes (106,107). This reflects increased disease burden for patients and has important financial implications. Of patients with diabetes who are hospitalized, 30% have two or more hospital stays, and these admissions account for over 50% of inpatient costs for diabetes (108). Factors contributing to readmission include male sex, longer duration of prior hospitalization, number of previous hospitalizations, number and severity of comorbidities, and lower socioeconomic and/or educational status; scheduled home health visits and timely outpatient follow-up reduce rates of readmission (106,107). While there is no standard to prevent readmissions, several successful strategies have been reported (107). These include targeting ketosis-prone patients with type 1 diabetes (109), insulin treatment of patients with admission A1C >9% (75 mmol/mol) (110), and use of a transitional care model (111). For people with diabetic kidney disease, collaborative patient-centered medical homes may decrease risk-adjusted readmission rates (112). A recently published algorithm based on patient demographic and clinical characteristics had only moderate predictive power but identifies a promising future strategy (113).

Age is also an important risk factor in hospitalization and readmission among patients with diabetes (refer to Section 12 "Older Adults," https://doi.org/10.2337/dc21-S012, for detailed criteria).

References

1. Clement S, Braithwaite SS, Magee MF, et al.; American Diabetes Association Diabetes in Hospitals Writing Committee. Management of diabetes and hyperglycemia in hospitals. Diabetes Care 2004;27:553–591 [published corrections appear in Diabetes Care 2004;27:856 and Diabetes Care 2004;27:1255]
2. Moghissi ES, Korytkowski MT, DiNardo M, et al.; American Association of Clinical Endocrinologists; American Diabetes Association. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Diabetes Care 2009;32:1119–1131
3. Bogun M, Inzucchi SE. Inpatient management of diabetes and hyperglycemia. Clin Ther 2013;35:724–733
4. Moghissi E, Inzucchi S. The evolution of glycemic control in the hospital setting. In *Managing Diabetes and Hyperglycemia in the Hospital Setting*. Draznin B, Ed. Alexandria, VA, American Diabetes Association, 2016, pp. 1–10
5. Umpierrez G, Korytkowski M. Diabetic emergencies - ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. Nat Rev Endocrinol 2016;12:222–232
6. Pasquel FJ, Gomez-Huelgas R, Anzola I, et al. Predictive value of admission hemoglobin A_{1c} on inpatient glycemic control and response to

insulin therapy in medicine and surgery patients with type 2 diabetes. Diabetes Care 2015;38:e202–e203
7. Umpierrez GE, Reyes D, Smiley D, et al. Hospital discharge algorithm based on admission HbA_{1c} for the management of patients with type 2 diabetes. Diabetes Care 2014;37:2934–2939
8. Carpenter DL, Gregg SR, Xu K, Buchman TG, Coopersmith CM. Prevalence and impact of unknown diabetes in the ICU. Crit Care Med 2015;43:e541–e550
9. Rhee MK, Safo SE, Jackson SL, et al. Inpatient glucose values: determining the nondiabetic range and use in identifying patients at high risk for diabetes. Am J Med 2018;131:443.e11–443.e24
10. Garg R, Schuman B, Bader A, et al. Effect of preoperative diabetes management on glycemic control and clinical outcomes after elective surgery. Ann Surg 2018;267:858–862
11. van den Boom W, Schroeder RA, Manning MW, Setji TL, Fiestan G-O, Dunson DB. Effect of A1C and glucose on postoperative mortality in noncardiac and cardiac surgeries. Diabetes Care 2018;41:782–788
12. Setji T, Hopkins TJ, Jimenez M, et al. Rationalization, development, and implementation of a preoperative diabetes optimization program designed to improve perioperative outcomes and reduce cost. Diabetes Spectr 2017;30:217–223
13. Okabayashi T, Shima Y, Sumiyoshi T, et al. Intensive versus intermediate glucose control in surgical intensive care unit patients. Diabetes Care 2014;37:1516–1524
14. Institute of Medicine. *Preventing Medication Errors*. Aspden P, Wolcott J, Bootman JL, Cronenwett LR, Eds. Washington, DC, National Academies Press, 2007
15. Gillaizeau F, Chan E, Trinquart L, et al. Computerized advice on drug dosage to improve prescribing practice. Cochrane Database Syst Rev 2013;11:CD002894
16. Wexler DJ, Shrader P, Burns SM, Cagliero E. Effectiveness of a computerized insulin order template in general medical inpatients with type 2 diabetes: a cluster randomized trial. Diabetes Care 2010;33:2181–2183
17. Schnipper JL, Liang CL, Ndumele CD, Pendergrass ML. Effects of a computerized order set on the inpatient management of hyperglycemia: a cluster-randomized controlled trial. Endocr Pract 2010;16:209–218
18. Wang YJ, Seggelke S, Hawkins RM, et al. Impact of glucose management team on outcomes of hospitalization in patients with type 2 diabetes admitted to the medical service. Endocr Pract 2016;22:1401–1405
19. Draznin B, Gilden J, Golden SH, et al.; PRIDE investigators. Pathways to quality inpatient management of hyperglycemia and diabetes: a call to action. Diabetes Care 2013;36:1807–1814
20. Bansal V, Mottalib A, Pawar TK, et al. Inpatient diabetes management by specialized diabetes team versus primary service team in non-critical care units: impact on 30-day readmission rate and hospital cost. BMJ Open Diabetes Res Care 2018;6:e000460
21. Ostling S, Wyckoff J, Ciarkowski SL, et al. The relationship between diabetes mellitus and 30-day readmission rates. Clin Diabetes Endocrinol 2017;3:3
22. Rushakoff RJ, Sullivan MM, MacMaster HW, et al. Association between a virtual glucose management service and glycemic control in hospitalized adult patients: an observational study. Ann Intern Med 2017;166:621–627
23. Arnold P, Scheurer D, Dake AW, et al. Hospital guidelines for diabetes management and the Joint Commission-American Diabetes Association inpatient diabetes certification. Am J Med Sci 2016;351:333–341
24. Society of Hospital Medicine. Glycemic control for hospitalists. Accessed 30 October 2020. Available from https://www.hospitalmedicine.org/clinical-topics/glycemic-control/
25. Umpierrez GE, Hellman R, Korytkowski MT, et al.; Endocrine Society. Management of hyperglycemia in hospitalized patients in non-critical care setting: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2012;97:16–38
26. Agiostratidou G, Anhalt H, Ball D, et al. Standardizing clinically meaningful outcome measures beyond HbA_{1c} for type 1 diabetes: a consensus report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. Diabetes Care 2017;40:1622–1630
27. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359–1367
28. Finfer S, Chittock DR, Su SY, et al.; NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283–1297
29. Kansagara D, Fu R, Freeman M, Wolf F, Helfand M. Intensive insulin therapy in hospitalized patients: a systematic review. Ann Intern Med 2011;154:268–282
30. Sathya B, Davis R, Taveira T, Whitlatch H, Wu WC. Intensity of peri-operative glycemic control and postoperative outcomes in patients with diabetes: a meta-analysis. Diabetes Res Clin Pract 2013;102:8–15
31. Umpierrez G, Cardona S, Pasquel F, et al. Randomized controlled trial of intensive versus conservative glucose control in patients undergoing coronary artery bypass graft surgery: GLUCO-CABG trial. Diabetes Care 2015;38:1665–1672
32. Duncan AE, Abd-Elsayed A, Maheshwari A, Xu M, Soltesz E, Koch CG. Role of intraoperative and postoperative blood glucose concentrations in predicting outcomes after cardiac surgery. Anesthesiology 2010;112:860–871
33. Furnary AP, Wu Y, Bookin SO. Effect of hyperglycemia and continuous intravenous insulin infusions on outcomes of cardiac surgical procedures: the Portland Diabetic Project. Endocr Pract 2004;10(Suppl. 2):21–33
34. Wang CCL, Draznin B. Practical approach to management inpatient hyperglycemia in selected populations. Hosp Pract 2013;41:45–53
35. Cobaugh DJ, Maynard G, Cooper L, et al. Enhancing insulin-use safety in hospitals: practical recommendations from an ASHP Foundation expert consensus panel. Am J Health Syst Pharm 2013;70:1404–1413
36. Rice MJ, Coursin DB. Glucose meters: here today, gone tomorrow? Crit Care Med 2016;44:e97–e100
37. Rice MJ, Smith JL, Coursin DB. Glucose measurement in the ICU: regulatory intersects reality. Crit Care Med 2017;45:741–743
38. Klonoff DC, Draznin B, Drincic A, et al. PRIDE statement on the need for a moratorium on the CMS plan to cite hospitals for performing point-of-care capillary blood glucose monitoring on critically ill patients. J Clin Endocrinol Metab 2015;100:3607–3612
39. DuBois JA, Slingerland RJ, Fokkert M, et al. Bedside glucose monitoring—is it safe? A new, regulatory-compliant risk assessment evaluation protocol in critically ill patient care settings. Crit Care Med 2017;45:567–574
40. Zhang R, Isakow W, Kollef MH, Scott MG. Performance of a modern glucose meter in ICU and general hospital inpatients: 3 years of real-world paired meter and central laboratory results. Crit Care Med 2017;45:1509–1514
41. Maynard G, Wesorick DH, O'Malley C, Inzucchi SE; Society of Hospital Medicine Glycemic Control Task Force. Subcutaneous insulin order sets and protocols: effective design and implementation strategies. J Hosp Med 2008;3(Suppl.):29–41
42. Brown KE, Hertig JB. Determining current insulin pen use practices and errors in the inpatient setting. Jt Comm J Qual Patient Saf 2016;42:568–AP7
43. Horne J, Bond R, Sarangarm P. Comparison of inpatient glycemic control with insulin vials versus insulin pens in general medicine patients. Hosp Pharm 2015;50:514–521
44. Veronesi G, Poerio CS, Braus A, et al. Determinants of nurse satisfaction using insulin pen devices with safety needles: an exploratory factor analysis. Clin Diabetes Endocrinol 2015;1:15
45. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA requires label warnings to prohibit sharing of multi-dose diabetes pen devices among patients. Accessed 30 October 2020. Available from https://www.fda.gov/Drugs/DrugSafety/ucm435271.htm
46. Bueno E, Benitez A, Rufinelli JV, et al. Basal-bolus regimen with insulin analogues versus human insulin in medical patients with type 2 diabetes: a randomized controlled trial in Latin America. Endocr Pract 2015;21:807–813
47. Umpierrez GE, Smiley D, Jacobs S, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). Diabetes Care 2011;34:256–261
48. Colunga-Lozano LE, Gonzalez Torres FJ, Delgado-Figueroa N, et al. Sliding scale insulin for non-critically ill hospitalized adults with diabetes mellitus. Cochrane Database Syst Rev 2018;11:CD011296.pub2
49. Giugliano D, Chiodini P, Maiorino MI, Bellastella G, Esposito K. Intensification of insulin therapy with basal-bolus or premixed insulin regimens in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Endocrine 2016;51:417–428
50. Bellido V, Suarez L, Rodriguez MG, et al. Comparison of basal-bolus and premixed insulin regimens in hospitalized patients with type 2 diabetes. Diabetes Care 2015;38:2211–2216

51. Baldwin D, Zander J, Munoz C, et al. A randomized trial of two weight-based doses of insulin glargine and glulisine in hospitalized subjects with type 2 diabetes and renal insufficiency. Diabetes Care 2012;35:1970–1974
52. Iyengar R, Franzese J, Gianchandani R. Inpatient glycemic management in the setting of renal insufficiency/failure/dialysis. Curr Diab Rep 2018;18:75
53. Shomali ME, Herr DL, Hill PC, Pehlivanova M, Sharretts JM, Magee MF. Conversion from intravenous insulin to subcutaneous insulin after cardiovascular surgery: transition to target study. Diabetes Technol Ther 2011;13:121–126
54. Lien LF, Low Wang CC, Kreider KE, Baldwin D. Transitioning from intravenous to subcutaneous insilun. In *Managing Diabetes and Hyperglycemia in the Hospital Setting*. Draznin B, Ed. Alexandria, VA, American Diabetes Association, 2016, pp. 115–128
55. Tripathy PR, Lansang MC. U-500 regular insulin use in hospitalized patients. Endocr Pract 2015;21:54–58
56. Lansang MC, Umpierrez GE. Inpatient hyperglycemia management: a practical review for primary medical and surgical teams. Cleve Clin J Med 2016;83(Suppl. 1):S34–S43
57. Umpierrez GE, Gianchandani R, Smiley D, et al. Safety and efficacy of sitagliptin therapy for the inpatient management of general medicine and surgery patients with type 2 diabetes: a pilot, randomized, controlled study. Diabetes Care 2013;36:3430–3435
58. Pasquel FJ, Fayfman M, Umpierrez GE. Debate on insulin vs non-insulin use in the hospital setting—is it time to revise the guidelines for the management of inpatient diabetes? Curr Diab Rep 2019;19:65
59. Fushimi N, Shibuya T, Yoshida Y, Ito S, Hachiya H, Mori A. Dulaglutide-combined basal plus correction insulin therapy contributes to ideal glycemic control in non-critical hospitalized patients. J Diabetes Investig 2020;11:125–131
60. Fayfman M, Galindo RJ, Rubin DJ, et al. A randomized controlled trial on the safety and efficacy of exenatide therapy for the inpatient management of general medicine and surgery patients with type 2 diabetes. Diabetes Care 2019;42:450–456
61. Pérez-Belmonte LM, Osuna-Sánchez J, Millán-Gómez M, et al. Glycaemic efficacy and safety of linagliptin for the management of non-cardiac surgery patients with type 2 diabetes in a real-world setting: Lina-Surg study. Ann Med 2019;51:252–261
62. Vellanki P, Rasouli N, Baldwin D, et al. Linagliptin Inpatient Research Group. Glycaemic efficacy and safety of linagliptin compared to basal-bolus insulin regimen in patients with type 2 diabetes undergoing non-cardiac surgery: a multicenter randomized clinical trial. Diabetes Obes Metab 2019;21:837–843
63. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin. Accessed 30 October 2020. Available from http://www.fda.gov/Drugs/DrugSafety/ucm486096.htm
64. Akirov A, Grossman A, Shochat T, Shimon I. Mortality among hospitalized patients with hypoglycemia: insulin related and noninsulin related. J Clin Endocrinol Metab 2017;102:416–424
65. Amori RE, Pittas AG, Siegel RD, et al. Inpatient medical errors involving glucose-lowering medications and their impact on patients: review of 2,598 incidents from a voluntary electronic error-reporting database. Endocr Pract 2008;14:535–542
66. Alwan D, Chipps E, Yen P-Y, Dungan K. Evaluation of the timing and coordination of prandial insulin administration in the hospital. Diabetes Res Clin Pract 2017;131:18–32
67. Hung AM, Siew ED, Wilson OD, et al. Risk of hypoglycemia following hospital discharge in patients with diabetes and acute kidney injury. Diabetes Care 2018;41:503–512
68. Maynard G, Kulasa K, Ramos P, et al. Impact of a hypoglycemia reduction bundle and a systems approach to inpatient glycemic management. Endocr Pract 2015;21:355–367
69. Milligan PE, Bocox MC, Pratt E, Hoehner CM, Krettek JE, Dunagan WC. Multifaceted approach to reducing occurrence of severe hypoglycemia in a large healthcare system. Am J Health Syst Pharm 2015;72:1631–1641
70. Dagogo-Jack S. Hypoglycemia in type 1 diabetes mellitus: pathophysiology and prevention. Treat Endocrinol 2004;3:91–103
71. Rickels MR. Hypoglycemia-associated autonomic failure, counterregulatory responses, and therapeutic options in type 1 diabetes. Ann N Y Acad Sci 2019;1454:68–79
72. Dendy JA, Chockalingam V, Tirumalasetty NN, et al. Identifying risk factors for severe hypoglycemia in hospitalized patients with diabetes. Endocr Pract 2014;20:1051–1056
73. Ulmer BJ, Kara A, Mariash CN. Temporal occurrences and recurrence patterns of hypoglycemia during hospitalization. Endocr Pract 2015;21:501–507
74. Shah BR, Walji S, Kiss A, James JE, Lowe JM. Derivation and validation of a risk-prediction tool for hypoglycemia in hospitalized adults with diabetes: the Hypoglycemia During Hospitalization (HyDHo) score. Can J Diabetes 2019;43:278–282.e1
75. Mathioudakis NN, Everett E, Routh S, et al. Development and validation of a prediction model for insulin-associated hypoglycemia in non-critically ill hospitalized adults. BMJ Open Diabetes Res Care 2018;6:e000499
76. Curll M, Dinardo M, Noschese M, Korytkowski MT. Menu selection, glycaemic control and satisfaction with standard and patient-controlled consistent carbohydrate meal plans in hospitalised patients with diabetes. Qual Saf Health Care 2010;19:355–359
77. Korytkowski M, Draznin B, Drincic A. Food, fasting, insulin, and glycemic control in the hospital. In *Managing Diabetes and Hyperglycemia in the Hospital Setting*. Draznin B, Ed. Alexandria, VA, American Diabetes Association, 2016, pp. 70–83
78. Mabrey ME, Setji TL. Patient self-management of diabetes care in the inpatient setting: pro. J Diabetes Sci Technol 2015;9:1152–1154
79. Shah AD, Rushakoff RJ. Patient self-management of diabetes care in the inpatient setting: con. J Diabetes Sci Technol 2015;9:1155–1157
80. Umpierrez GE, Klonoff DC. Diabetes technology update:use of insulin pumps and continuous glucose monitoring in the hospital. Diabetes Care 2018;41:1579–1589
81. Houlden RL, Moore S. In-hospital management of adults using insulin pump therapy. Can J Diabetes 2014;38:126–133
82. Korytkowski MT, Salata RJ, Koerbel GL, et al. Insulin therapy and glycemic control in hospitalized patients with diabetes during enteral nutrition therapy: a randomized controlled clinical trial. Diabetes Care 2009;32:594–596
83. Hsia E, Seggelke SA, Gibbs J, Rasouli N, Draznin B. Comparison of 70/30 biphasic insulin with glargine/lispro regimen in non-critically ill diabetic patients on continuous enteral nutrition therapy. Nutr Clin Pract 2011;26:714–717
84. Drincic AT, Knezevich JT, Akkireddy P. Nutrition and hyperglycemia management in the inpatient setting (meal on demand, parenteral, or enteral nutrition). Curr Diab Rep 2017;17:59–71
85. Low Wang CC, Hawkins RM, Gianchandani R, Dungan K. Glycemic control in the setting of parenteral or enteral nutrition via tube feeding. In *Managing Diabetes and Hyperglycemia in the Hospital Setting*. Draznin B, Ed. Alexandria, VA, American Diabetes Association, 2016, pp. 84–98
86. Pichardo-Lowden AR, Fan CY, Gabbay RA. Management of hyperglycemia in the non-intensive care patient: featuring subcutaneous insulin protocols. Endocr Pract 2011;17:249–260
87. Roberts A, James J, Dhatariya K; Joint British Diabetes Societies (JBDS) for Inpatient Care. Management of hyperglycaemia and steroid (glucocorticoid) therapy: a guideline from the Joint British Diabetes Societies (JBDS) for Inpatient Care group. Diabet Med 2018;35:1011–1017
88. Kwon S, Hermayer KL, Hermayer K. Glucocorticoid-induced hyperglycemia. Am J Med Sci 2013;345:274–277
89. Seggelke SA, Gibbs J, Draznin B. Pilot study of using NPH insulin to counteract the effect of methylprednisolone in hospitalized patients with diabetes. J Hosp Med 2011;6:175–176
90. Mathioudakis N, Dungan K, Baldwin D, Korytkpwski M, Reider J. Steroid-associated hyperglycemia. In *Managing Diabetes and Hyperglycemia in the Hospital Setting*. Draznin B, Ed. Alexandria, VA, American Diabetes Association, 2016, pp. 99–114
91. Brady V, Thosani S, Zhou S, Bassett R, Busaidy NL, Lavis V. Safe and effective dosing of basal-bolus insulin in patients receiving high-dose steroids for hyper-cyclophosphamide, doxorubicin, vincristine, and dexamethasone chemotherapy. Diabetes Technol Ther 2014;16:874–879
92. Smiley DD, Umpierrez GE. Perioperative glucose control in the diabetic or nondiabetic patient. South Med J 2006;99:580–589; quiz 590–591
93. Buchleitner AM, Martínez-Alonso M, Hernández M, Solà I, Mauricio D. Perioperative glycaemic control for diabetic patients undergoing surgery. Cochrane Database Syst Rev 2012;9:CD007315
94. Gianchandani R, Dubois E, Alexanian S, Rushakoff R. Preoperative, intraoperative, and postoperative glucose management. In *Managing Diabetes and Hyperglycemia in the Hospital Setting*. Draznin B, Ed. Alexandria, VA, American Diabetes Association, 2016, pp. 129–144
95. Buchleitner AM, Martínez-Alonso M, Hernández M, Solà I, Mauricio D. Perioperative glycaemic control for diabetic patients undergoing surgery. Cochrane Database Syst Rev 2012;9:CD007315

96. Demma LJ, Carlson KT, Duggan EW, Morrow JG 3rd, Umpierrez G. Effect of basal insulin dosage on blood glucose concentration in ambulatory surgery patients with type 2 diabetes. J Clin Anesth 2017;36:184–188
97. Umpierrez GE, Smiley D, Hermayer K, et al. Randomized study comparing a basal-bolus with a basal plus correction insulin regimen for the hospital management of medical and surgical patients with type 2 diabetes: basal plus trial. Diabetes Care 2013;36:2169–2174
98. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009;32:1335–1343
99. Vellanki P, Umpierrez GE. Diabetic ketoacidosis: a common debut of diabetes among African Americans with type 2 diabetes. Endocr Pract 2017;23:971–978
100. Harrison VS, Rustico S, Palladino AA, Ferrara C, Hawkes CP. Glargine co-administration with intravenous insulin in pediatric diabetic ketoacidosis is safe and facilitates transition to a subcutaneous regimen. Pediatr Diabetes 2017;18:742–748
101. Hsia E, Seggelke S, Gibbs J, et al. Subcutaneous administration of glargine to diabetic patients receiving insulin infusion prevents rebound hyperglycemia. J Clin Endocrinol Metab 2012;97:3132–3137
102. Andrade-Castellanos CA, Colunga-Lozano LE, Delgado-Figueroa N, Gonzalez-Padilla DA. Subcutaneous rapid-acting insulin analogues for diabetic ketoacidosis. Cochrane Database Syst Rev 2016;1:CD011281
103. Kitabchi AE, Umpierrez GE, Fisher JN, Murphy MB, Stentz FB. Thirty years of personal experience in hyperglycemic crises: diabetic ketoacidosis and hyperglycemic hyperosmolar state. J Clin Endocrinol Metab 2008;93:1541–1552
104. Shepperd S, Lannin NA, Clemson LM, McCluskey A, Cameron ID, Barras SL. Discharge planning from hospital to home. Cochrane Database Syst Rev 1996;1:CD000313
105. Agency for Healthcare Research and Quality. Readmissions and adverse events after discharge. Accessed 30 October 2020. Available from https://psnet.ahrq.gov/primers/primer/11
106. Rubin DJ. Hospital readmission of patients with diabetes. Curr Diab Rep 2015;15:17
107. Gregory NS, Seley JJ, Dargar SK, Galla N, Gerber LM, Lee JI. Strategies to prevent readmission in high-risk patients with diabetes: the importance of an interdisciplinary approach. Curr Diab Rep 2018;18:54
108. Jiang HJ, Stryer D, Friedman B, Andrews R. Multiple hospitalizations for patients with diabetes. Diabetes Care 2003;26:1421–1426
109. Maldonado MR, D'Amico S, Rodriguez L, Iyer D, Balasubramanyam A. Improved outcomes in indigent patients with ketosis-prone diabetes: effect of a dedicated diabetes treatment unit. Endocr Pract 2003;9:26–32
110. Wu EQ, Zhou S, Yu A, et al. Outcomes associated with post-discharge insulin continuity in US patients with type 2 diabetes mellitus initiating insulin in the hospital. Hosp Pract (1995) 2012;40:40–48
111. Hirschman KB, Bixby MB. Transitions in care from the hospital to home for patients with diabetes. Diabetes Spectr 2014;27:192–195
112. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Diabetes Care 2014;37:2864–2883
113. Rubin DJ, Recco D, Turchin A, Zhao H, Golden SH. External validation of the Diabetes Early Re-admission Risk Indicator (DERRI). Endocr Pract 2018;24:527–541

16. Diabetes Advocacy: *Standards of Medical Care in Diabetes—2021*

American Diabetes Association

Diabetes Care 2021;44(Suppl. 1):S221–S222 | https://doi.org/10.2337/dc21-S016

The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc21-SPPC), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc21-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Managing the daily health demands of diabetes can be challenging. People living with diabetes should not have to face discrimination due to diabetes. By advocating for the rights of those with diabetes at all levels, the ADA can help to ensure that they live a healthy and productive life. A strategic goal of the ADA is for more children and adults with diabetes to live free from the burden of discrimination. The ADA is also focused on making sure cost is not a barrier to successful diabetes management.

One tactic for achieving these goals has been to implement the ADA Standards of Care through advocacy-oriented position statements. The ADA publishes evidence-based, peer-reviewed statements on topics such as diabetes and employment, diabetes and driving, insulin access and affordability, and diabetes management in certain settings such as schools, childcare programs, and correctional institutions. In addition to the ADA's clinical documents, these advocacy statements are important tools in educating schools, employers, licensing agencies, policy makers, and others about the intersection of diabetes medicine and the law and for providing scientifically supported policy recommendations.

ADVOCACY STATEMENTS

The following is a partial list of advocacy statements ordered by publication date, with the most recent statement appearing first.

Insulin Access and Affordability

The ADA's Insulin Access and Affordability Working Group compiled public information and convened a series of meetings with stakeholders throughout the insulin supply chain to learn how each entity affects the cost of insulin for the consumer. Their conclusions and recommendations are published in the following ADA statement.

Cefalu WT, Dawes DE, Gavlak G, et al.; Insulin Access and Affordability Working Group. Insulin Access and Affordability Working Group: conclusions and recommendations. Diabetes Care 2018;41:1299–1311 [published correction appears in Diabetes Care 2018;41:1831]; https://doi.org/10.2337/dci18-0019 (first publication 2018)

Diabetes Care in the School Setting

A sizable portion of a child's day is spent in school, so close communication with and cooperation of school personnel are essential to optimize diabetes management, safety, and academic opportunities. See the following ADA position statement for diabetes management information for students with diabetes in the elementary and secondary school settings.

Jackson CC, Albanese-O'Neill A, Butler KL, et al.; American Diabetes Association. Diabetes care in the school setting: a position statement of the American Diabetes Association. Diabetes Care 2015;38:1958–1963; https://doi.org/10.2337/dc15-1418 (first publication 1998; latest revision 2015)

Care of Young Children With Diabetes in the ChildCare Setting

Very young children with diabetes have legal protections and can be safely cared for by childcare providers with appropriate training, access to resources, and a system of communication with parents and the child's diabetes provider. See the following ADA position statement for information on young children aged <6 years in settings such as day care centers, preschools, camps, and other programs.

Siminerio LM, Albanese-O'Neill A, Chiang JL, et al.; American Diabetes Association. Care of young children with diabetes in the childcare setting: a position statement of the American Diabetes Association. Diabetes Care 2014;37:2834–2842; https://doi.org/10.2337/dc14-1676 (first publication 2014)

Suggested citation: American Diabetes Association. 16. Diabetes advocacy: Standards of Medical Care in Diabetes—2021. *Diabetes Care 2021; 44(Suppl. 1):S221–S222*

Diabetes and Driving

People with diabetes who wish to operate motor vehicles are subject to a great variety of licensing requirements applied by both state and federal jurisdictions. For an overview of existing licensing rules for people with diabetes, factors that impact driving for this population, and general guidelines for assessing driver fitness and determining appropriate licensing restrictions, see the following ADA position statement.

Editor's note: Federal commercial driving rules for individuals with insulin-related diabetes changed on 19 November 2018. These changes will be reflected in a future updated ADA statement.

Lorber D, Anderson J, Arent S, et al.; American Diabetes Association. Diabetes and driving. Diabetes Care 2014;37-(Suppl. 1):S97–S103; https://doi.org/10.2337/dc14-S097 (first publication 2012)

Diabetes and Employment

Any person with diabetes, whether insulin treated or noninsulin treated, should be eligible for any employment for which he or she is otherwise qualified. Employment decisions should never be based on generalizations or stereotypes regarding the effects of diabetes. For a general set of guidelines for evaluating individuals with diabetes for employment, including how an assessment should be performed and what changes (accommodations) in the workplace may be needed for an individual with diabetes, see the following ADA position statement.

Anderson JE, Greene MA, Griffin JW Jr, et al.; American Diabetes Association. Diabetes and employment. Diabetes Care 2014;37(Suppl. 1):S112–S117; https://doi.org/10.2337/dc14-S112 (first publication 1984; latest revision 2009)

Diabetes Care in Correctional Institutions

People with diabetes in correctional facilities should receive care that meets national standards. Correctional institutions should have written policies and procedures for the management of diabetes and for the training of medical and correctional staff in diabetes care practices. For a general set of guidelines for diabetes care in correction institutions, see the following ADA position statement.

American Diabetes Association. Diabetes management in correctional institutions. Diabetes Care 2014;37(Suppl. 1):S104–S111; https://doi.org/10.2337/dc14-S104 (first publication 1989; latest revision 2008)

Disclosures: *Standards of Medical Care in Diabetes—2021*

Diabetes Care 2021;44(Suppl. 1):S223–S225 | https://doi.org/10.2337/dc21-SDIS

Committee members disclosed the following financial or other conflicts of interest (COI) covering the period 12 months before December 2020

Member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Ownership interest	Consultant/ advisory board	Other
Professional Practice Committee							
Boris Draznin, MD, PhD (Chair)	University of Colorado Denver, School of Medicine	None	None	None	None	None	eDoctate (unpaid professional education)
Vanita R. Aroda, MD	Brigham and Women's Hospital; Faculty, Harvard Medical School	Applied Therapeutics#, Premier/Fractyl#, Novo Nordisk#, Sanofi#	None	None	Merck (spouse employee benefits), Janssen (spouse employee benefits)	Applied Therapeutics#, Duke, Novo Nordisk#*, Pfizer, Sanofi	Merck Research Laboratories (spouse employee) 2017–2020 Janssen Pharmaceutical Companies of Johnson & Johnson (spouse Sandip Datta, MD, Senior Medical Director, Early Development, Infectious Diseases, May 2020 to present)
George Bakris, MD	University of Chicago	Bayer: principal investigator—clinical trial#	None	None	None	Merck, Relypsa/Vifor, KBP, Biosciences, Ionis, Alnylam, AstraZeneca	Steering committee member of clinical outcome trials for Vascular Dynamics and Novo Nordisk
Gretchen Benson, RDN, LD, CDCES	Minneapolis Heart Institute Foundation	None	None	None	None	None	None
Florence M. Brown, MD	Joslin Diabetes Center, Inc.	None	None	None	None	None	None
RaShaye Freeman, DNP, FNP-BC, CDCES, ADM-BC	HCA Healthcare	None	None	None	None	None	None
Jennifer Green, MD	Duke University Medical Center	Boehringer Ingelheim*#, Merck#, Sanofi Lexicon*#	None	None	None	AstraZeneca, Boehringer Ingelheim*, Novo Nordisk*, Pfizer, Hawthorne Effect	None
Elbert Huang, MD, MPH, FACP	University of Chicago	None	None	None	Merck, Pfizer—stockholder	None	Medical Research Analytics and Informatics Alliance—BOD The Institute for Clinical and Economic Review—Midwest Comparative Effectiveness Public Advisory Council
Diana Isaacs, PharmD, BCPS, BC-ADM, CDCES	Cleveland Clinic	None	None	Abbott, Dexcom, Xeris Pharmaceuticals, Novo Nordisk, Companion Medical	None	Association of Diabetes Care and Education Specialists, Eli Lilly, Insulet, LifeScan	None

Member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Ownership interest	Consultant/ advisory board	Other
Scott Kahan, MD, MPH	George Washington University, Milken Institute, National Center for Weight and Wellness	None	None	None	None	Vivus*, Gelesis, Pfizer	(All without compensation) The Obesity Society—BOD American Board of Obesity Medicine—BOD National Diabetes Education Program—author/editor National Academy of Science/ IOM—Committee on Obesity Solutions Obesity Action Coalition—BOD Obesity Treatment Foundation—BOD Endocrine Society—Advocacy and Public Outreach Core Committee True Health Initiative—BOD Global Liver Institute/NASH Council—Advisory Board Endocrine Today—Editorial Board Medscape—Diabetes & Endocrinology Advisory Board Medscape—Obesity Advisory Board Strategies to Overcome and Prevent (STOP) Obesity Alliance
Christine Lee, MD, MS	National Institute of Diabetes and Digestive and Kidney Diseases	None	None	None	None	None	None
Jose Leon, MD, MPH	National Center for Health in Public Housing	None	None	None	None	None	None
Sarah K. Lyons, MD	Baylor College of Medicine/Texas Children's Hospital	None	None	None	None	None	None
Anne L. Peters, MD	Keck School of Medicine of USC	Dexcom#, vTv Therapeutics#	None	None	Stock options	Abbott Diabetes Care, Bio-Rad, Eli Lilly, MannKind, Merck, Novo Nordisk, Zealand	Medscape Endocrinology Advisory Board/video blogger*
Jane E.B. Reusch, MD	University of Colorado	None	None	None	None	Medtronic#	None
Deborah Young-Hyman, PhD, CDCES	Behavioral Health & Social Science Research, National Institutes of Health	None	None	None	None	None	None
American College of Cardiology Designated Representatives (Section 10 "Cardiovascular Disease and Risk Management")							
Sandeep Das, MD, MPH, FACC	University of Texas Southwestern Medical Center	None	None	Associate Editor	None	None	None
Mikhail Kosiborod, MD, FACC	Saint Luke's Mid America Heart Institute	AstraZeneca#, Boehringer-Ingelheim#	AstraZeneca#	None	None	Amgen*, Applied Therapeutics#, AstraZeneca*#, Bayer*, Boehringer Ingelheim*, Eli Lilly, Janssen#, Merck Diabetes*, Novo Nordisk*#, Sanofi*, Vifor Pharma*#	None
American Diabetes Association Staff							
Mindy Saraco, MHA	American Diabetes Association	None	None	None	None	None	None
Malaika I. Hill, MA	American Diabetes Association	None	None	None	None	None	None
Matthew P. Petersen	American Diabetes Association	None	None	None	None	None	None
Shamera Robinson, MPH, RDN	American Diabetes Association	None	None	None	None	None	None

Member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Ownership interest	Consultant/ advisory board	Other
Jo Mandelson, MS, RDN	American Diabetes Association	None	None	None	None	None	None
Robert A. Gabbay, MD, PhD	American Diabetes Association (Joslin Diabetes Center)	None	None	None	None	Onduo*, Health Reveal, Form Health, Lark*, Vida Health*	Spouse Christi Gabbay, CHSE, Managing Director, Major Gifts and Philanthropy at American Diabetes Association
Kenneth P. Moritsugu, MD, MPH	American Diabetes Association, First Samurai Consulting, LLC	None	None	None	First Samurai Consulting, LLC	None	None

BOD, board of directors; IOM, Institute of Medicine; NASH, nonalcoholic steatohepatitis. *≥$10,000 per year from company to individual. #Grant or contract is to university or other employer. Kenneth P. Moritsugu, MD, MPH, worked as the Interim Chief Scientific and Medical Officer of the American Diabetes Association (ADA) until July 2020. Prior to joining ADA in July 2020, Robert Gabbay, MD, PhD, was employed by Joslin Diabetes Center.

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