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AMERICAN DIABETES ASSOCIATION

STANDARDS OF MEDICAL CARE IN DIABETES—2020

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Standards of Medical Care in Diabetes—2020

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

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Diabetes Care is a journal for the health care practitioner that is intended to increase knowledge, stimulate research, and promote better management of people with diabetes. To achieve these goals, the journal publishes original research on human studies in the following categories: Clinical Care/Education/Nutrition/Psychosocial Research, Epidemiology/Health Services Research, Emerging Technologies and Therapeutics, Pathophysiology/Complications, and Cardiovascular and Metabolic Risk. The journal also publishes ADA statements, consensus reports, clinically relevant review articles, letters to the editor, and health/medical news or points of view. Topics covered are of interest to clinically oriented physicians, researchers, epidemiologists, psychologists, diabetes educators, and other health professionals. More information about the journal can be found online at care.diabetesjournals.org.

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This issue is freely accessible online at care.diabetesjournals.org/content/43/Supplement_1.

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Introduction: *Standards of Medical Care in Diabetes—2020*

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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, payers, 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).

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 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 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 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,

INTRODUCTION

The "Standards of Medical Care in Diabetes" was originally approved in 1988. Most recent review/revision: December 2019.

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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 (4). 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, 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.

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Professional Practice Committee: *Standards of Medical Care in Diabetes—2020*

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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 comprised of physicians, diabetes educators, 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.

The ADA adheres to the National Academy of Medicine Standards for Developing Trustworthy Clinical Practice Guidelines. 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 onset 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—2020*" (https://doi.org/10.2337/dc20-SPPC). The ADA funds development of the Standards of Care out of its general revenues and does not use industry support for this purpose.

For the current revision, PPC members systematically searched MEDLINE for human studies related to each section and published since 15 October 2018. Due to limitations associated with production timelines, evidence published in late 2019 was not incorporated into the initial 2020 Standards of Care release (e.g., Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction [DAPA-HF], Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes [CAROLINA], etc.), but salient new data will be incorporated in a living Standards update in early 2020 (professional.diabetes.org/content-page/living-standards). Recommendations were revised based on new evidence or, in some cases, to clarify the prior recommendation or match the strength of the wording to the strength of the 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 2019 revision of the Standards of Care. Readers who wish to comment on the 2020 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: Nidhi Bansal, MD; Linda A. Barbour, MD, MSPH, FACP; Florence Brown, MD; Thomas Buchanan, MD; Linda A. DiMeglio, MD; Alison B. Evert, MS, RD, CDE; Hermes Flores, MD, PhD; Thomas W. Gardner, MD, MS; Rose Gubitosi-Klug, MD, PhD; William C. Hsu, MD; Sally C. Hughes, BA; Scott Kahan, MD, MPH; Ka Hei Karen Lau, MS, RD, LDN, CDE; Jose Leon, MD; Ingrid Libman, MD, PhD; Sarah K. Lyons, MD; Medha Munshi, MD; Henry Rodriguez, MD; Amy Shah, MD; Connor K. Smith, BS; Andrea Steck, MD; William S. Yancy, MD, MHS; and Ann Zmuda, DPM.

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Summary of Revisions: *Standards of Medical Care in Diabetes—2020*

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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 2020 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/dc20-S001)

Additional information was included on the rising cost of medications, particularly insulin.

A new section "Migrant and Seasonal Agricultural Workers" was added to discuss the challenges of managing type 2 diabetes specific to this group.

Section 2. Classification and Diagnosis of Diabetes

(https://doi.org/10.2337/dc20-S002)

The debate as to whether slowly progressive autoimmune diabetes with an adult onset should be termed latent autoimmune diabetes in adults is now acknowledged.

A new recommendation (2.8) was added regarding testing for prediabetes and/or type 2 diabetes for women with overweight or obesity and/or who have one or more additional risk factors for diabetes who are planning a pregnancy.

Additional considerations were added to the section "Cystic Fibrosis–Related Diabetes" (CFRD) regarding the use of A1C tests to detect CFRD.

The 2020 Standards of Care includes a new section on "Pancreatic Diabetes or Diabetes in the Context of Disease of the Exocrine Pancreas" to describe this form of diabetes and its diverse set of etiologies.

The "Gestational Diabetes Mellitus" (GDM) section was revised, and the two-step approach for screening and diagnosing GDM no longer includes National Diabetes Data Group criteria.

Section 3. Prevention or Delay of Type 2 Diabetes

(https://doi.org/10.2337/dc20-S003)

On the basis of a new consensus report, "Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report" (https://doi.org/10.2337/dci19-0014), published in April 2019, the section "Nutrition" was updated and a new recommendation (3.3) was added to recognize that a variety of eating patterns are acceptable for people with prediabetes.

Additional resources and information were added regarding the National Diabetes Prevention Program, Medicare Diabetes Prevention Programs, and the Centers for Disease Control (CDC) Diabetes Prevention Impact Tool Kit. More information was added on the risk reduction certain groups experienced with metformin use, based on 15-year follow-up data from the Diabetes Prevention Program Outcomes Study.

Section 4. Comprehensive Medical Evaluation and Assessment of Comorbidities

(https://doi.org/10.2337/dc20-S004)

The autoimmune diseases recommendation (4.12) was modified, and a new recommendation was added (4.13) with autoimmune thyroid disease and celiac disease screening guidance differentiated, and more information on the prevalence of and screening for these diseases has been added to the text.

Because infection with hepatitis C virus is associated with a higher prevalence of type 2 diabetes, discussion was added regarding glucose metabolism and eradication of hepatitis C virus infection.

The title of the hearing impairment section was changed to "Sensory Impairment," and new information was added, including content on impairment of smell.

Evidence was updated in the section "Periodontal Disease."

The section "Psychosocial/Emotional Disorders," including anxiety disorders, depression, disordered eating behavior, and serious mental illness, was moved to Section 5 "Facilitating Behavior Change and Well-being to Improve Health Outcomes" (https://doi.org/10.2337/dc20-S005), in order to combine it with existing psychosocial guidance found in that section.

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Section 5. Facilitating Behavior Change and Well-being to Improve Health Outcomes
(https://doi.org/10.2337/dc20-S005)
The title of this section was previously "Lifestyle Management" and was changed to more appropriately emphasize how effective behavior management and psychological well-being are foundational to achieving treatment goals for people with diabetes.

The section "Nutrition Therapy" was updated to include guidance and evidence presented in "Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report" (https://doi.org/10.2337/dci19-0014), published in May 2019.

Because of the emerging evidence from the CDC on deaths related to e-cigarettes, more information was added discouraging their use.

Recommendations and supporting evidence on anxiety disorders, depression, disordered eating behavior, and serious mental illness previously found at the end of Section 4 were moved to Section 5 and are included under "Psychosocial Issues." More information on psychosocial screening for social determinants of health and significant changes in life circumstances was also added.

Section 6. Glycemic Targets
(https://doi.org/10.2337/dc20-S006)
Based on the publication "Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range" (https://doi.org/10.2337/dci19-0028) published in June 2019, new recommendations (6.4 and 6.5) were added on use of the ambulatory glucose profile (AGP) report and time in range (TIR) for assessment of glycemic management. A discussion of AGP reports, time in range, and glucose management indicators follow the new recommendations. An example of an AGP report was also added (**Fig. 6.1**).

Table 6.1 was replaced with a simplified estimated average glucose table.

More discussion on the importance of reducing therapeutic inertia in the management of hyperglycemia and cardiovascular disease was included in the section "A1C and Cardiovascular Disease Outcomes."

Also new to "A1C and Cardiovascular Disease Outcomes" is the strategy to introduce sodium–glucose cotransporter 2 inhibitors or glucagon-like peptide 1 (GLP-1) receptor agonists in patients with cardiovascular disease meeting A1C goals for cardiovascular benefit.

A new recommendation (6.11) on screening patients who are taking medication that can lead to hypoglycemia for hypoglycemia unawareness was introduced.

Intranasal glucagon and glucagon solution for subcutaneous injection were included in the section "Hypoglycemia" due to their recent approval by the U.S. Food and Drug Administration (FDA).

This section was modified to include a new discussion on the use of continuous glucose monitoring technology in hypoglycemia prevention.

Section 7. Diabetes Technology
(https://doi.org/10.2337/dc20-S007)
This section was reorganized into three broad categories titled "Self-Monitoring of Blood Glucose," "Continuous Glucose Monitors," and "Insulin Delivery." Within these revised sections, emphasis has been made on how there is no "one-size-fits-all" approach to technology use in people with diabetes. Due to the rapidly changing field of diabetes technology, the recommendations in each category have been revised, and more evidence has been added to support the recommendations throughout.

Section 8. Obesity Management for the Treatment of Type 2 Diabetes
(https://doi.org/10.2337/dc20-S008)
The body mass index (BMI) calculation recommendation (8.1) was modified to recommend annual BMI calculations rather than at every patient encounter. More discussion was added on how providers measure and record patient weight, including recommendations on how to manage these encounters to maximize patient comfort and engagement. Other considerations—like access to food and individual's motivation level—were added to the section "Lifestyle Interventions."

Section 9. Pharmacologic Approaches to Glycemic Treatment
(https://doi.org/10.2337/dc20-S009)
A discussion was added on access to analog insulins and how there are multiple approaches to insulin treatment, with the goal of keeping patients safe and avoiding diabetic ketoacidosis and significant hypo- or hyperglycemia.

New evidence and a recommendation (9.6) were added on early combination therapy for type 2 diabetes to extend the time to treatment failure based on findings from the VERIFY trial.

FDA approval of oral semaglutide has been included in the discussion of combination therapies.

Figure 9.1 has been revised to include the latest trial findings on GLP-1 receptor agonists and SGLT2 inhibitors. It now suggests that these drugs should be considered for patients when atherosclerotic cardiovascular disease (ASCVD), heart failure, or chronic kidney disease predominates independent of A1C.

Figure 9.2 has been simplified to more easily guide providers through intensification to injectable therapies.

Section 10. Cardiovascular Disease and Risk Management
(https://doi.org/10.2337/dc20-S010)
This section is endorsed for the second consecutive year by the American College of Cardiology.

Blood pressure targets for pregnant patients with pre-existing hypertension have been changed in the interest of reducing the risk for accelerated maternal hypertension and minimizing fetal growth impairment.

Recommendations for statin treatment (primary and secondary prevention, 10.19–10.28) have been revised to minimize ASCVD risk and to align with the "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" (https://doi.org/10.1016/j.jacc.2018.11.002), published in June 2019.

Discussion of REDUCE-IT was added to the section "Treatment of Other Lipoprotein Fractions or Targets," and a new recommendation (10.31) was included on considering icosapent ethyl for reducing cardiovascular risk.

Recommendations for treatment of cardiovascular disease (10.43a, 10.43b, 10.43c) are now individualized based on patients' existing ASCVD, risk of ASCVD, diabetic kidney disease, or heart failure.

Discussion of the trials CANVAS, CANVAS-Renal, CREDENCE, DECLARE-TIMI 58, REWIND, and CARMELINA were added to the section "Glucose-Lowering Therapies and Cardiovascular Outcomes."

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The cardiovascular outcomes trials of available antihyperglycemic medications completed after the issuance of FDA 2008 guidelines table (**Table 10.3**) has been divided into three tables by drug class (**Table 10.3*A*** on DPP-4 Inhibitors; **Table 10.3*B*** on GLP-1 receptor agonists; and **Table 10.3*C*** on SGLT2 inhibitors).

Section 11. Microvascular Complications and Foot Care

(https://doi.org/10.2337/dc20-S011)

The recommendation on screening for chronic kidney disease (11.1) has been modified to include twice-yearly screenings for certain patients. A treatment recommendation (11.3) was modified to provide more detail on use of SGLT2 inhibitors and GLP-1 receptor agonists in patients with type 2 diabetes and diabetic kidney disease. A new recommendation (11.5) was added about avoiding discontinuation of RAS blockade in response to minor increases in serum creatinine in the absence of volume depletion.

Additional information on acute kidney injury was added to the section "Chronic Kidney Disease," with information on increased serum creatinine levels.

More findings were added from the CREDENCE trial.

Screening for diabetic retinopathy recommendations (11.16 and 11.17) and supportive text were revised to include consideration of retinal photograph with remote reading or use of a validated assessment tool as a way to improve screening access.

The section "Foot Care" was updated with more evidence on therapeutic footwear and evaluation for peripheral arterial disease.

Figure 11.1 was introduced (in place of 2019 Table 11.1—CKD Stages and Corresponding Focus of Kidney-Related Care) to show the risk of chronic kidney disease progression, frequency of visits, and referral to nephrology according to estimated glomerular filtration rate and albuminuria.

Section 12. Older Adults

(https://doi.org/10.2337/dc20-S012)

Within the section "Neurocognitive Function," more information was added on the importance of assessment for cognitive decline and impairment.

A new recommendation (12.14) urging providers to consider cost of care and insurance coverage when prescribing medications to older adults to reduce the risk of cost-related nonadherence was added to the section "Pharmacologic Therapy." The GLP-1 receptor agonist and SGLT2 inhibitor discussions were expanded in this section as well.

A new section titled "Special Considerations for Older Adults With Type 1 Diabetes" was added to address the treatment of this growing population.

Section 13. Children and Adolescents

(https://doi.org/10.2337/dc20-S013)

To provide more detail for individualizing targets, new A1C goal recommendations (13.21–13.24) were added to the section "Glycemic Control."

In the section "Management of Cardiovascular Risk Factors," the recommendations for screening and treatment of hypertension (13.31–13.35) have been revised and include new criteria for elevated blood pressure. The dyslipidemia testing recommendation (13.36) was also modified, and more evidence was added to the dyslipidemia screening section.

The retinopathy screening recommendation for type 1 diabetes (13.46) has been revised based on new evidence supporting a lower frequency of eye examinations than previously recommended.

A new recommendation (13.67) was added to the section "Pharmacologic Management" for type 2 diabetes due to new evidence and FDA approval of liraglutide in children 10 years of age or older.

A new recommendation (13.76) on pharmacologic treatment of hypertension in type 2 diabetes was also added.

Section 14. Management of Diabetes in Pregnancy

(https://doi.org/10.2337/dc20-S0014)

Greater emphasis has been placed on preconception care for women with diabetes, and a recommendation (14.5) focusing on nutrition, diabetes education, and screening for diabetes related complications was added. A new table (**Table 14.1**) was also added on preconception education, medical assessment, and screening.

Recommendations (14.9–14.12) on use of continuous glucose monitors and measuring glycemia in pregnancy were added to the section "Glycemic Targets in Pregnancy" to provide more information on their utility.

Further discussion has been added regarding when insulin may not be an option for some women with GDM, and how oral agents may play a role in treatment in certain circumstances.

The section "Postpartum Care" was expanded to include recommendations (14.16–14.22) and supporting evidence on postpartum insulin requirements, management of women with a history of GDM and risks of type 2 diabetes, and psychosocial assessment.

Section 15. Diabetes Care in the Hospital

(https://doi.org/10.2337/dc20-S0015)

Discussion of new studies supporting the use of closed-loop insulin delivery with linked pump/sensor devices to control blood glucose was added to the type 1 diabetes section "Transitioning Intravenous to Subcutaneous Insulin."

New evidence was also added to the section "Preventing Admissions and Readmissions."

Section 16. Diabetes Advocacy

(https://doi.org/10.2337/dc20-S016)

No changes have been made to this section.

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1. Improving Care and Promoting Health in Populations: *Standards of Medical Care in Diabetes—2020*

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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/dc20-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/dc20-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 simultaneous emphasis on 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 system-level and patient-level approaches. With such an integrated approach in 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). Clinical practice recommendations,

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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 remained stagnant in recent years (3). 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 (3). Only 23% met targets for glycemic, blood pressure, and cholesterol measures while also avoiding smoking (3). 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 (3). 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 (4–6). 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 (7). 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 (8).

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 (9). 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% (9). The same study suggested that health care utilization was lower in the CCM group, resulting in health care savings of $7,294 per individual over the study period (10).

Redefining the roles of the health care delivery team and empowering patient self-management are fundamental to the successful implementation of the CCM (11). Collaborative, multidisciplinary teams are best suited to provide care for people with chronic conditions such as diabetes and to facilitate patients' self-management (12–14). There are references to guide the implementation of the CCM into diabetes care delivery, including opportunities and challenges (15).

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 (6,16,17). While many diabetes processes of care have improved nationally in the past decade, the overall quality of care for patients with diabetes remains suboptimal (3). Efforts to increase the quality of diabetes care include providing care that is concordant with evidence-based guidelines (18); expanding the role of teams to implement more intensive disease management strategies (6,19,20); tracking medication-taking behavior at a systems level (21); redesigning the organization of the care process (22); implementing electronic health record tools (23,24); empowering and educating patients (25,26); removing financial barriers and reducing patient out-of-pocket costs for diabetes education, eye exams, diabetes technology, and necessary medications (6); assessing and addressing psychosocial issues (27,28); and identifying, developing, and engaging community resources and public policies that support healthy lifestyles (29). The National Diabetes Education Program maintains an online resource (www.betterdiabetescare.nih.gov) to help health care professionals design and implement more effective health care delivery systems for those with diabetes.

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 (30–32). 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 (33,34); identifying and addressing language, numeracy, or cultural barriers to care (35–37); integrating evidence-based guidelines and clinical information tools into the process of care (18,38,39); soliciting performance feedback, setting reminders, and providing structured care (e.g., guidelines,

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formal case management, and patient education resources) (6); and incorporating care management teams including nurses, dietitians, pharmacists, and other providers (19,40). 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 (41).

Telemedicine

Telemedicine is a growing field that may increase access to care for patients with diabetes. Telemedicine is defined as the use of telecommunications to facilitate remote delivery of health-related services and clinical information (42). A growing body of 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 (43). 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 (44–46). 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. 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 (28). For more information on DSMES, see Section 5 "Facilitating Behavior Change and Well-being to Improve Health Outcomes" (https://doi.org/10.2337/dc20-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 (47). 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. 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 (48).

Access to Care and Quality Improvement

The Affordable Care Act has 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 (49). 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 near universal (50). Patients who have either private or public insurance coverage are more likely to meet quality indicators for diabetes care (51). 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 (52,53). 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 (54,55). Information and guidance specific to quality improvement and practice transformation for diabetes care is available from the National Diabetes Education Program practice transformation website and the National Institute of Diabetes and Digestive and Kidney Diseases report on diabetes care and quality (56,57). 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 (58). 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 (59).

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 (60) and incentives that accommodate personalized care goals (6,61).

TAILORING TREATMENT FOR SOCIAL CONTEXT

Recommendations

1.5 Providers should assess social context, including potential food insecurity, housing stability, and financial barriers, 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 and are heavily influenced by social determinants of health (62–66). Social determinants of health 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 (67). 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 (68). While a comprehensive strategy to reduce diabetes-related health inequities in populations has not been formally studied, general recommendations from other chronic disease models can be drawn upon to inform systems-level strategies in diabetes. For example, the National Academy of Medicine has published a framework for educating health care professionals on the

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importance of social determinants of health (69). 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 (70–72).

Social determinants of health are not always recognized and often go undiscussed in the clinical encounter (65). A study by Piette et al. (73) found that among patients with chronic illnesses, two-thirds of those who reported not taking medications as prescribed due to cost never shared this with their physician. In a study using data from the National Health Interview Survey (NHIS), Patel et al. (65) 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 (74) (see Section 12 "Older Adults," https://doi.org/10.2337/dc20-S012, for a detailed discussion of social considerations in older adults). Creating systems-level mechanisms to screen for social determinants of health may help overcome structural barriers and communication gaps between patients and providers (65,75). In addition, brief, validated screening tools for some social determinants of health 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, and limited English proficiency/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 2005–2014 (76). 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% (77). Additionally, the risk for type 2 diabetes is increased twofold in those with food insecurity (68) 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 (78,79). 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 (80). Risk for food insecurity can be assessed with a validated two-item screening tool (81) 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%.

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, for the treatment options 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 (82).

Homelessness

Homelessness 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 (83). The prevalence of diabetes in the homeless population is estimated to be around 8% (84). 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 (85). Given the potential challenges, providers who care for homeless individuals should be familiar with resources or have access to social workers that can facilitate temporary housing for their patients as a way to improve diabetes care.

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 (85a).

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%) (86).

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

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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 (87). The National CLAS Standards website offers a number of resources and materials that can be used to improve the quality of care delivery to non-English-speaking patients (87).

Community Support

Identification or development of community resources to support healthy lifestyles is a core element of the CCM (8). 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 (88). Community health workers (CHWs) (89), peer supporters (90–92), and lay leaders (93) may assist in the delivery of DSMES services (70,94), 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" (95). 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 (96).

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2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes—2020*

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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 (https://doi.org/10.2337/dc20-SPPC), a multidisciplinary expert committee, 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/dc20-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)
2. Type 2 diabetes (due to a progressive loss of adequate β-cell insulin secretion frequently on the background of insulin resistance)
3. Gestational diabetes mellitus (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)
4. 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)

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 type 1 diabetes may be more variable in adults; they may not present with the classic

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Table 2.1—Staging of type 1 diabetes (8,9)

	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

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 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 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).

Characterization of the underlying pathophysiology is more 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 an almost 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 (8,9). There is debate as to whether slowly progressive autoimmune diabetes with an adult onset should be termed latent autoimmune diabetes in adults (LADA) or whether the clinical priority is awareness that slow autoimmune β-cell destruction means there may be 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.

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. Characterization of subtypes of this heterogeneous disorder have been developed and validated in Scandinavian and Northern European populations but have not been confirmed in other ethnic and racial groups. 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 (8,10,11).

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 (12) (**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 (13,14) 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**). 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 (15).

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 due to hemoglobin variants (i.e., hemoglobinopathies) and consideration of using an assay without interference or plasma blood

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glucose criteria to diagnose diabetes. **B**

2.3 In conditions associated with an altered relationship between A1C and glycemia, such as 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 to diagnose diabetes. **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 or U.S. Food and Drug Administration approved for diagnosis, proficiency testing is not always mandated for performing the test. Therefore, point-of-care assays approved for diagnostic purposes should only be considered in settings licensed to perform moderate-to-high complexity tests. As discussed in Section 6 "Glycemic Targets" (https://doi.org/10.2337/dc20-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, 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 (16).

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 (17,18), 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 epidemiological studies that formed the basis for recommending A1C to diagnose diabetes included only adult populations (16). 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) (19).

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% than those without the trait (20). 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 (21).

Even in the absence of hemoglobin variants, A1C levels may vary with race/ethnicity independently of glycemia (22–24). For example, African Americans may have higher A1C levels than non-Hispanic whites with similar fasting and postglucose load glucose levels (25), and A1C levels may be higher for a given mean glucose concentration when measured with continuous glucose monitoring (26). 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 (27,28). The association of A1C with risk for complications appears to be similar in African Americans and non-Hispanic whites (29,30).

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 the 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.

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 (31,32), hemodialysis, recent blood loss or transfusion, or erythropoietin therapy, only plasma blood glucose criteria should be used to diagnose diabetes (33). A1C is less reliable than blood glucose measurement in other conditions such as the postpartum state (34–36), HIV treated with certain drugs (17), and iron-deficient anemia (37).

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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 from the same sample (38) 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 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.

All the tests have preanalytic and analytic variability, so it is possible that 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 how long a patient has had 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). 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). 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 (3–5,39,40). 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/dc20-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. 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 (41). Patients with

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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 (9). 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 (42). 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 (43–45). 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 (46).

Although there is currently a lack of accepted screening programs, 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.diabetestrialnet.org). Widespread clinical testing of asymptomatic low-risk individuals is not currently recommended due to lack of approved therapeutic interventions. 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 type 1 diabetes in those with evidence of autoimmunity (see www.clinicaltrials.gov).

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 planning pregnancy with overweight or obesity 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. **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. **B**

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.)

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 (29,30). Patients 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 between 100 and 125 mg/dL (between 5.6 and 6.9 mmol/L) (47,56) and IGT as 2-h PG during 75-g OGTT levels between 140 and 199 mg/dL (between 7.8 and 11.0 mmol/L) (48). It should be noted that the

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

1. Testing should be considered in overweight or obese (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) adults 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.

CVD, cardiovascular disease; GDM, gestational diabetes mellitus.

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Table 2.4—Risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting (163)

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, is recommended. Reports of type 2 diabetes before age 10 years exist, and this can be considered with numerous risk factors.

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) (49). 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 (50). 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) (51), and A1C at baseline was a strong predictor of the development of glucose-defined diabetes during the DPP and its follow-up (52). 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/dc20-S003). Similar to glucose measurements, the continuum of risk is curvilinear, so as A1C rises, the diabetes risk rises disproportionately (49). 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.

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.

(**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.

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. 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 or with the use of certain drugs (e.g., corticosteroids, atypical antipsychotics, and sodium–glucose cotransporter 2 inhibitors) (53,54). 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. Nevertheless, even undiagnosed patients are at increased risk of developing macrovascular and microvascular complications.

Whereas patients with type 2 diabetes may have insulin levels that appear normal or elevated, the higher blood glucose levels in these patients would be expected to result in even higher insulin values had their β-cell function been normal. Thus, insulin secretion is defective in these patients and insufficient to compensate for insulin resistance. Insulin resistance

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may improve with weight reduction and/or pharmacologic treatment of hyperglycemia but is seldom restored to normal.

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), in those with hypertension or dyslipidemia, 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. 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 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/dc20-S003) and reduce the risk of diabetes complications (see Section 10 "Cardiovascular Disease and Risk Management," https://doi.org/10.2337/dc20-S010, and Section 11 "Microvascular Complications and Foot Care," https://doi.org/10.2337/dc20-S011).

Approximately one-quarter of people with diabetes in the U.S. and nearly half of Asian and Hispanic Americans with diabetes are undiagnosed (47,56). 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. Employing a probabilistic model, Peterson et al. (57) 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 (55). 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 (48). The 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 (58); 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) (59).

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 ≥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 (60,61). 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 the WHO also suggests that a BMI of ≥23 kg/m^2 should be used to define increased risk in Asian Americans (62). 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 (63,64).

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 (65).

Medications

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

Testing Interval

The appropriate interval between screening tests is not known (67). 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 (67).

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,

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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®

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

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 (68).

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 (69–71), with one study estimating that 30% of patients ≥30 years of age seen in general dental practices had dysglycemia (71). 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 (41). 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 (19). 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/dc20-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 (72). 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 (73). 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 (74,75).

CYSTIC FIBROSIS–RELATED DIABETES

Recommendations

2.14 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**

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

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

2.17 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 (76). 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 lower than 5.4% (5.8% in a second study) would detect more than 90% of cases and reduce patient screening burden (77,78). 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 (77,78). Continuous glucose monitoring or HOMA of β-cell function (79) 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 (80).

CFRD mortality has significantly decreased over time, and the gap in mortality between cystic fibrosis patients with and without diabetes has considerably narrowed (81). 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 (±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 (81). Insulin remains the most widely used therapy for CFRD (82).

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" (83) and in the International Society for Pediatric and Adolescent Diabetes's 2014 clinical practice consensus guidelines (84).

POSTTRANSPLANTATION DIABETES MELLITUS

Recommendations

2.18 Patients should be screened after organ transplantation for hyperglycemia, with a formal diagnosis of posttransplantation

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diabetes mellitus being best made once a patient is stable on an immunosuppressive regimen and in the absence of an acute infection. **E**

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

2.20 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 (85). "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 (86). Another term, "posttransplantation diabetes mellitus" (PTDM) (86,87), 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 (86–89). In most cases, such stress- or steroid-induced hyperglycemia resolves by the time of discharge (89,90). 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 (86). 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 (91). 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 (89–91). The OGTT is considered the gold standard test for the diagnosis of PTDM (86,87,92,93). 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 (91,94,95). Most studies have reported that transplant patients with hyperglycemia and PTDM after transplantation have higher rates of rejection, infection, and rehospitalization (89,91,96).

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 (91). 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 (97), 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 (98,99). Dipeptidyl peptidase 4 inhibitors do not interact with immunosuppressant drugs and have demonstrated safety in small clinical trials (100,101). 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

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

2.22 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**

2.23 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* (102).

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 (103). 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. Correct diagnosis has critical implications because most

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Table 2.6—Most common causes of monogenic diabetes (102)

	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
	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; 2-h PG, 2-h plasma glucose.

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 (104,105). 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 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 (104,105).

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 (104–110). 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 (111). 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 (112), often

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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 (113). 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 (114). 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 (115). 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) (103,116)
- 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 (117), and idiopathic forms (1). 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 (118–122). 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 (123,124). In some cases, this can lead to insulin independence. In others, it may decrease insulin requirements (125).

GESTATIONAL DIABETES MELLITUS

Recommendations

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

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

2.26 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**

2.27 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**

2.28 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 (49), regardless of the degree of hyperglycemia. This definition facilitated a uniform strategy for detection and classification of GDM, but this definition has serious limitations (126). 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 both appropriate diagnostic thresholds and outcomes. 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 (127,128).

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 (129–132). 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 (133) (**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/dc20-S014). The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) GDM

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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 (134) and further work is needed.

GDM is often indicative of underlying β-cell dysfunction (135), which confers marked increased risk for later development of diabetes, generally but not always type 2 diabetes, in the mother after delivery (136,137). As effective prevention interventions are available (138,139), 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 (140).

Diagnosis

GDM carries risks for the mother, fetus, and neonate. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (141), 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 (141a) 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 (142). Many regional studies have investigated the impact of adopting IADPSG criteria on prevalence and have seen a roughly one- to threefold increase (143). 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 (144). The ADA recommends the IADPSG diagnostic criteria with the intent of optimizing gestational outcomes because these criteria were 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 (145,146). 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 (146), 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.

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 [154]):

- 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 (150).

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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 (147,148).

Two-Step Strategy

In 2013, the National Institutes of Health (NIH) convened a consensus development conference to consider diagnostic criteria for diagnosing GDM (149). 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 (150). 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) (151). 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 (152).

Key factors cited by the NIH panel in their decision-making process were the lack of clinical trial data demonstrating 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 (153), 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 (150). 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 (154,155). Each is based on different mathematical conversions of the original recommended thresholds by O'Sullivan (141a), 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 (156) demonstrated that treatment was similarly beneficial in patients meeting only the lower thresholds per Carpenter-Coustan (154) and in those meeting only the higher thresholds per National Diabetes Data Group (155). 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 (157). 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 (158) and IADPSG may be the preferred approach. Data comparing population-wide outcomes with one-step versus two-step approaches have been inconsistent to date (159,160). 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 (161,162). 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.

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3. Prevention or Delay of Type 2 Diabetes: *Standards of Medical Care in Diabetes—2020*

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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/dc20-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/dc20-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/dc20-S002).

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/dc20-S002). Those who are determined to be at high risk for type 2 diabetes, including people with A1C 5.7–6.4% (39–47 mmol/mol), impaired glucose tolerance, or impaired fasting glucose, are ideal candidates for diabetes prevention efforts. 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/dc20-S002) and Section 6 "Glycemic Targets" (https://doi.org/10.2337/dc20-S006) for additional details on the appropriate use of the A1C test.

LIFESTYLE INTERVENTIONS

Recommendations

3.2 Refer patients with prediabetes to an intensive behavioral lifestyle intervention program modeled on the Diabetes Prevention Program (DPP) to achieve and maintain 7% loss of initial body weight and increase moderate-intensity physical activity (such as brisk walking) to at least 150 min/week. **A**

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3.3 A variety of eating patterns are acceptable for persons with prediabetes. **B**

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

3.5 Given the cost-effectiveness of diabetes prevention, such intervention programs should be covered by third-party payers. **B**

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 incidence of 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 rate 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). Notably, in the 30-year follow-up for the Da Qing study, reductions in all-cause mortality, cardiovascular disease–related mortality, and microvascular complications were observed for the lifestyle intervention groups compared with the control group (5).

The two major goals of the DPP intensive, behavioral lifestyle intervention were to achieve and maintain a minimum of 7% weight loss and 150 min of physical activity similar in intensity to brisk walking per week. 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).

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. For further details on the core curriculum sessions, refer to ref. 8.

Nutrition

Structured behavioral weight loss therapy, including a reduced calorie meal plan and physical activity, is of paramount importance for those at high risk for developing type 2 diabetes who have overweight or obesity (1,9). Because weight loss through lifestyle changes alone can be difficult to maintain long term (6), people being treated with weight loss therapy should have access to ongoing support and additional therapeutic options (such as pharmacotherapy) if needed. Based on intervention trials, a variety of eating patterns may be appropriate for patients with prediabetes (10), including Mediterranean (11–13) and low-calorie, low-fat eating patterns (8). An eating pattern represents the totality of all foods and beverages consumed (14). In addition, evidence suggests that the overall quality of food consumed (as measured by the Healthy Eating Index, Alternative Healthy Eating Index, and Dietary Approaches to Stop Hypertension [DASH] score), with an emphasis on whole grains, legumes, nuts, fruits and vegetables and minimal refined and processed foods, is also important (15–18).

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/dc20-S005, for more detailed information) is effective in lowering A1C in individuals diagnosed with prediabetes (19).

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 (20,21). On the basis of these findings, providers are encouraged to promote a DPP-style program, including its 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 (8,22,23). Breaking up prolonged sedentary time may also be encouraged,

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as it is associated with moderately lower postprandial glucose levels (24,25). The preventive effects of exercise appear to extend to the prevention of gestational diabetes mellitus (GDM) (26).

Tobacco Use

Smoking may increase the risk of type 2 diabetes (27); therefore, 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 (27–29) and patients should be monitored for diabetes development and receive evidence-based interventions for diabetes prevention as described in this section. See Section 5 "Facilitating Behavior Change and Well-being to Improve Health Outcomes" (https://doi.org/10.2337/dc20-S005) for more detailed information.

Technology-Assisted Interventions to Deliver Lifestyle Interventions

Technology-assisted interventions may effectively deliver the DPP lifestyle intervention, reducing weight and, therefore, diabetes risk (30–35). Such technology-assisted interventions may deliver content through smartphone and web-based applications and telehealth (30). The Centers for Disease Control and Prevention (CDC) Diabetes Prevention Recognition Program (DPRP) (www.cdc.gov/diabetes/prevention/requirements-recognition.htm) certifies technology-assisted modalities as effective vehicles for DPP-based interventions; 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. The selection of an in-person or virtual program should be based on patient preference.

Cost-effectiveness

A cost-effectiveness model suggested that the lifestyle intervention used in the DPP was cost-effective (36,37). Actual cost data from the DPP and DPPOS confirmed this (38). Group delivery of DPP content in community or primary care settings has the potential to reduce overall program costs while still producing weight loss and diabetes risk reduction (39–42). The use of community health workers to support DPP efforts has been shown to be effective with cost savings (43,44) (see Section 1 "Improving Care and Promoting Health in Populations," https://doi.org/10.2337/dc20-S001, for more information). Given the cost-effectiveness of diabetes prevention, such intervention programs should be covered by third-party payers.

The CDC coordinates the National Diabetes Prevention Program (National DPP), a resource designed to bring 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 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 (45). The CDC has also developed the Diabetes Prevention Impact Tool Kit (available at nccd.cdc.gov/toolkit/diabetesimpact) to help organizations assess the economics of providing or covering the National DPP lifestyle change program (46).

National Policy

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 innovation.cms.gov/initiatives/medicare-diabetes-prevention-program/). The locations of Medicare DPPs are available online at innovation.cms.gov/initiatives/medicare-diabetes-prevention-program/mdpp-map.html. 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.

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 ≥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, and periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy. **B**

Pharmacologic agents including metformin, α-glucosidase inhibitors, glucagon-like peptide 1 receptor agonists, thiazolidinediones, and several agents approved for weight loss have been shown in research studies to decrease the incidence of diabetes to various degrees in those with prediabetes (1,47–53), though none are 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 (54) and demonstrated long-term safety as pharmacologic therapy for diabetes prevention (52). 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 (38). During initial follow up in the DPP, metformin was as effective as lifestyle modification in participants with BMI ≥35 kg/m^2 but not significantly better than placebo in those over 60 years of age (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 (55), and both interventions remained highly effective during a 10-year follow-up period (56). By the time of the 15-year follow-up (DPPOS), exploratory analyses demonstrated that participants with a higher baseline fasting glucose

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(≥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) (57). In the Indian Diabetes Prevention Program (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 (58). 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 (56) (see Section 9 "Pharmacologic Approaches to Glycemic Treatment," https://doi.org/10.2337/dc20-S009, for more details).

PREVENTION OF CARDIOVASCULAR DISEASE

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 (59), and are at increased risk for cardiovascular disease (60,61). Although treatment goals for people with prediabetes are the same as for the general population (62), increased vigilance is warranted to identify and treat these and other cardiovascular risk factors (e.g., smoking).

DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT

Recommendation

3.9 Diabetes self-management education and support programs may be appropriate venues for people with prediabetes to receive education and support to develop and maintain behaviors that can prevent or delay the development of type 2 diabetes. **B**

As for those with established diabetes, the standards for diabetes self-management education and support (see Section 5 "Facilitating Behavior Change and Well-being to Improve Health Outcomes," https://doi.org/10.2337/dc20-S005) can also apply to people with prediabetes. Currently, there are significant barriers to the provision of education and support to those with prediabetes. However, the strategies for supporting successful behavior change and the healthy behaviors recommended for people with prediabetes are comparable to those for people with diabetes. Although reimbursement remains a barrier, studies show that providers of diabetes self-management education and support are particularly well equipped to assist people with prediabetes in developing and maintaining behaviors that can prevent or delay the development of diabetes (19,63).

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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/dc20-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/dc20-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 Diabetes care should be managed by a multidisciplinary team that may draw from primary care physicians, subspecialty physicians, nurse practitioners, physician assistants, 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/dc20-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 an interdisciplinary team that may include 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 management (see Section 5 "Facilitating Behavior Change and Well-being to Improve Health Outcomes," https://doi.org/10.2337/dc20-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

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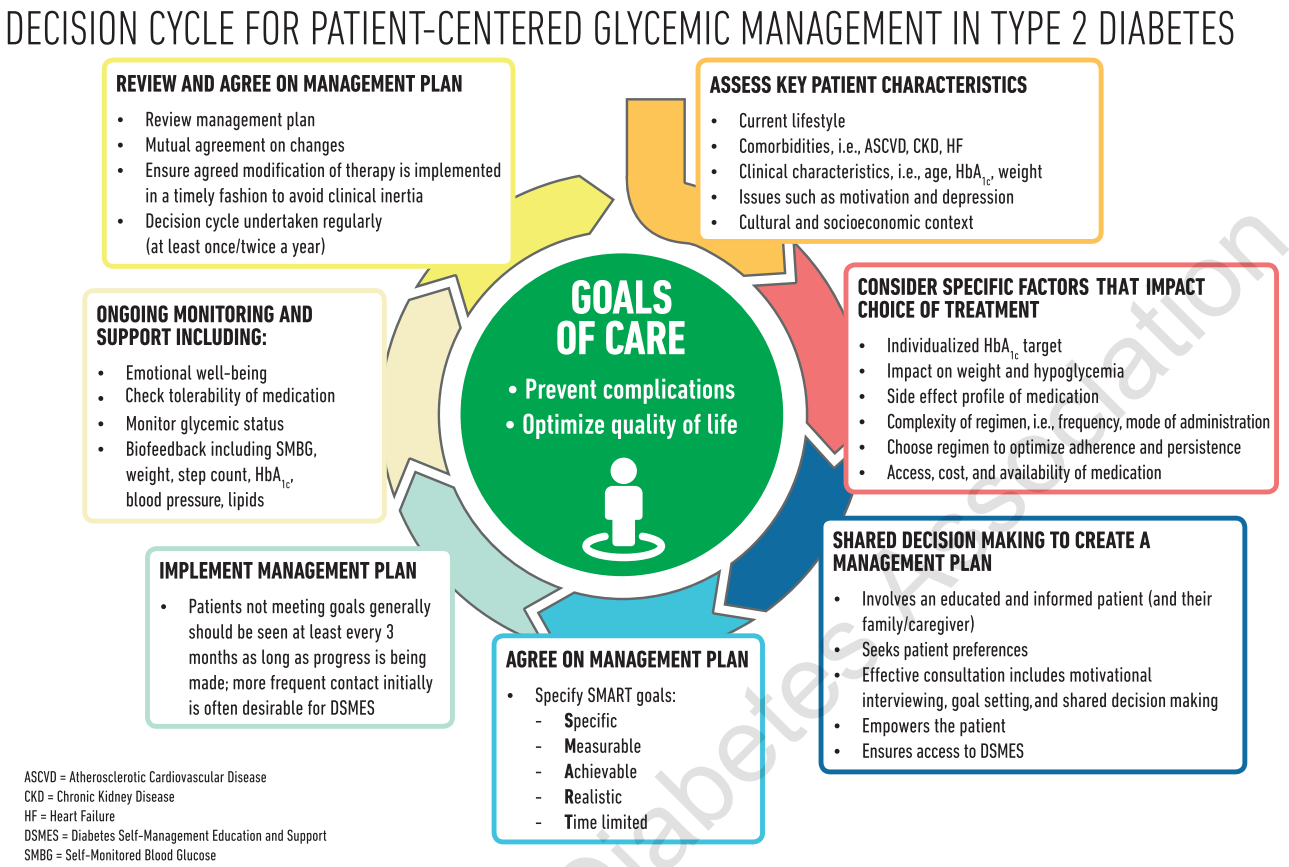

Figure 4.1—Decision cycle for patient-centered glycemic management in type 2 diabetes. Reprinted from Davies et al. (99).

on their individual preferences, values, and goals. The 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 complications and duration of disease, 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 American Association of Diabetes Educators consensus report, "The Use of Language in Diabetes Care and Education," provides the authors' expert opinion regarding the use of language by 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").

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COMPREHENSIVE MEDICAL EVALUATION

Recommendations

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

4.4 A follow-up visit should include most components of the initial comprehensive medical evaluation, including interval medical history, assessment of medication-taking behavior and intolerance/side effects, physical examination, laboratory evaluation as appropriate to assess attainment of A1C and metabolic targets, and assessment of risk for complications, diabetes self-management behaviors, nutrition, psychosocial health, and the need for referrals, immunizations, or other routine health maintenance screening. **B**

4.5 Ongoing management should be guided by the assessment of diabetes complications and shared decision-making to set therapeutic goals. **B**

4.6 The 10-year risk of a first atherosclerotic cardiovascular disease event should be assessed using the race- and sex-specific Pooled Cohort Equations to better stratify atherosclerotic cardiovascular disease risk. **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, and psychosocial health (see Section 5 "Facilitating Behavior Change and Well-being to Improve Health Outcomes," https://doi.org/10.2337/dc20-S005) and give guidance on routine immunizations. The assessment of sleep pattern and duration should be considered; a recent 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 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 (Section 10 "Cardiovascular Disease and Risk Management," https://doi.org/10.2337/dc20-S010), chronic kidney disease staging (Section 11 "Microvascular Complications and Foot Care," https://doi.org/10.2337/dc20-S011), and risk of treatment-associated hypoglycemia (**Table 4.3**) should be used to individualize targets for glycemia (Section 6 "Glycemic Targets," https://doi.org/10.2337/dc20-S006), blood pressure, and lipids and to select specific glucose-lowering medication (Section 9 "Pharmacologic Approaches to Glycemic Treatment," https://doi.org/10.2337/dc20-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

Recommendations

4.7 Provide routinely recommended vaccinations for children and adults with diabetes as indicated by age. **C**

4.8 Annual vaccination against influenza is recommended for all people ≥6 months of age, *especially* those with diabetes. **C**

4.9 Vaccination against pneumococcal disease, including pneumococcal pneumonia, with 13-valent pneumococcal conjugate vaccine (PCV13) is recommended for children before age 2 years. People with diabetes ages 2 through 64 years should also receive 23-valent pneumococcal polysaccharide vaccine (PPSV23). At age ≥65 years, regardless of vaccination history, additional PPSV23 vaccination is necessary. **C**

4.10 Administer a 2- or 3-dose series of hepatitis B vaccine, depending on the vaccine, to unvaccinated adults with diabetes ages 18 through 59 years. **C**

4.11 Consider administering a 3-dose series of hepatitis B vaccine to unvaccinated adults with diabetes ≥60 years of age. **C**

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 at cdc.gov/vaccines/schedules/.

People with diabetes are at higher risk for hepatitis B infection and are more likely to develop complications from influenza and pneumococcal disease. The CDC Advisory Committee on Immunization Practices (ACIP) recommends influenza, pneumococcal, and hepatitis B vaccinations specifically for people with diabetes. Vaccinations against tetanus-diphtheria-pertussis, measles-mumps-rubella, human papillomavirus, and shingles are also important for adults with diabetes, as they are for the general population.

Influenza

Influenza is a common, preventable infectious disease associated with high

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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			
	▪ Macrovascular and microvascular	✓		✓
	▪ Common comorbidities (e.g., obesity, OSA)	✓		✓
	▪ Hypoglycemia: awareness/frequency/causes/timing of episodes	✓	✓	✓
	▪ Presence of hemoglobinopathies or anemias	✓		✓
	▪ High blood pressure or abnormal lipids	✓		✓
	▪ Last dental visit	✓		✓
	▪ Last dilated eye exam	✓		✓
	▪ Visits to specialists	✓	✓	✓
	Interval history			
	▪ Changes in medical/family history since last visit		✓	✓
LIFESTYLE FACTORS	▪ Eating patterns and weight history	✓	✓	✓
	▪ 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	✓	✓	✓
BEHAVIORAL AND DIABETES SELF-MANAGEMENT SKILLS	**Psychosocial conditions**			
	▪ Screen for depression, anxiety, and disordered eating; refer for further assessment or intervention if warranted	✓		✓
	▪ Identify existing social supports	✓		✓
	▪ Consider assessment for cognitive impairment*	✓		✓
	Diabetes self-management education and support			
	▪ History of dietician/diabetes educator visits/classes	✓	✓	✓
	▪ Assess diabetes self-management skills and barriers	✓		✓
	▪ Assess familiarity with carbohydrate counting (type 1 diabetes)	✓		
	Pregnancy planning			
	▪ For women with childbearing capacity, review contraceptive needs and preconception planning	✓	✓	✓

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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	✓		✓
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; 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

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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 influenza and diabetes-related hospital admissions (18).

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% (19). The ADA endorses recommendations from the CDC ACIP that adults age ≥65 years, who are at higher risk for pneumococcal disease, receive an additional 23-valent pneumococcal polysaccharide vaccine (PPSV23), regardless of prior pneumococcal vaccination history. See detailed recommendations at www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/pneumo.html.

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 age <60 years. For adults age ≥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.

ASSESSMENT OF COMORBIDITIES

Besides assessing diabetes-related complications, clinicians and their patients

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 (**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.

need to be aware of common comorbidities that affect people with diabetes and may complicate management (20–24). 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.

Autoimmune Diseases

Recommendations

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

4.13 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 (25). Other associated conditions include autoimmune hepatitis, primary adrenal insufficiency (Addison disease), dermatomyositis, and myasthenia gravis (26–29). Type 1 diabetes may also occur with other autoimmune diseases in the context of specific genetic disorders or polyglandular autoimmune syndromes (30). 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) (31,32). 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 (33). The association may result from shared risk factors between type 2 diabetes and cancer (older age, obesity, and physical inactivity) but may also be due to diabetes-related factors (34), 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 (35). 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

4.14 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 (36,37). 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 (38). 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 (39).

Hyperglycemia

In those with type 2 diabetes, the degree and duration of hyperglycemia are

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)

See references 100–104.

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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

related to dementia. More rapid cognitive decline is associated with both increased A1C and longer duration of diabetes (38). 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 (40). 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 (41).

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 (42). Likewise, the ACCORD trial found that as cognitive function decreased, the risk of severe hypoglycemia increased (43). Tailoring glycemic therapy may help to prevent hypoglycemia in individuals with cognitive dysfunction.

Nutrition

In one study, adherence to the Mediterranean diet correlated with improved cognitive function (44). However, a recent Cochrane review found insufficient evidence to recommend any dietary change for the prevention or treatment of cognitive dysfunction (45).

Statins

A systematic review has reported that data do not support an adverse effect of statins on cognition (46). 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 (46). 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

4.15 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 (47). 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 (48). 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 (49,50). Pioglitazone and vitamin E treatment of biopsy-proven nonalcoholic steatohepatitis have been shown to improve liver histology, but effects on longer-term clinical outcomes are not known (51,52). Treatment with liraglutide and with sodium–glucose cotransporter 2 inhibitors (dapagliflozin and empagliflozin) has also shown some promise in preliminary studies, although benefits may be mediated, at least in part, by weight loss (53–55).

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 (56). 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 (57). 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 (58).

Pancreatitis

Recommendation

4.16 Islet autotransplantation should be considered for patients requiring total pancreatectomy for medically refractory chronic pancreatitis to prevent postsurgical diabetes. **C**

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 (59). People with diabetes are at an approximately twofold higher risk of developing acute pancreatitis (60).

Conversely, prediabetes and/or diabetes has been found to develop in approximately one-third of patients after an episode of acute pancreatitis (61); thus, the relationship is likely bidirectional. Postpancreatitis diabetes may include either new-onset disease or previously unrecognized diabetes (62). 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 (63,64).

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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 (65–69). 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 (70). 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) (71). 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 (72). 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 include vitamin D supplementation. For patients with type 2 diabetes with fracture risk factors, thiazolidinediones (73) and sodium–glucose cotransporter 2 inhibitors (74) should be used with caution.

Sensory Impairment

Hearing impairment, both in high-frequency and low- to mid-frequency ranges, is more common in people with diabetes than in those without, perhaps due to neuropathy and/or vascular disease. 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 (75). Low HDL, 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 (76). 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 (77). Impairment in smell, but not taste, has also been reported in individuals with diabetes (78).

HIV

Recommendation

4.17 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**

Diabetes risk is increased with certain protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (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 (79). 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.

Individuals with HIV are at higher risk for developing prediabetes and diabetes on antiretroviral (ARV) therapies, so a screening protocol is recommended (80). The A1C test may underestimate glycemia in people with HIV; it is not recommended for diagnosis and may present challenges for monitoring (81). 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 similar to that used in patients without HIV is critical to reduce the risks of microvascular and macrovascular complications.

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 (82). 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.

Low Testosterone in Men

Recommendation

4.18 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 (83,84). Treatment in asymptomatic men is controversial. Testosterone replacement in men with symptomatic hypogonadism may have benefits including improved sexual function, well-being, muscle mass and strength, and bone density (85). 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. In men who have total testosterone levels close to the lower limit, it is reasonable to check sex hormone–binding globulin, as it is often low in diabetes and associated with lower testosterone levels. Further testing (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 and, in some studies, an increase in cardiovascular events, which should be considered when assessing the risks and benefits of treatment (86,87).

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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 (88). 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% (89,90). In obese participants enrolled in the Action for Health in Diabetes (Look AHEAD) trial, it exceeded 80% (91). Patients with symptoms suggestive of obstructive sleep apnea (e.g., excessive daytime sleepiness, snoring, witnessed apnea) should be considered for screening (92). 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 (93).

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 (94–96). 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 (24,97). 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 (98).

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5. Facilitating Behavior Change and Well-being to Improve Health Outcomes: *Standards of Medical Care in Diabetes—2020*

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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/dc20-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/dc20-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/dc20-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). Re-evaluation 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

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implementation, medical nutrition therapy, and well-being: at diagnosis, annually, when complicating factors arise, and when transitions in 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**

Diabetes self-management education and support (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/dc20-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 for assessment of education, nutrition, and emotional needs
3. When new complicating factors (health conditions, physical limitations, emotional factors, or basic living needs) arise that influence self-management
4. When transitions in care occur

DSMES focuses on supporting patient empowerment by providing people with diabetes the tools to make informed self-management decisions (13). Diabetes care has shifted to 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 (14,16–18), lower self-reported weight (19,20), improved quality of life (17,21), reduced all-cause mortality risk (22), healthy coping (5,23), and reduced health care costs (24–26). Better outcomes were reported for DSMES interventions that were over 10 h in total duration (18), included ongoing support (12,27), were culturally (28,29) and age appropriate (30,31), were tailored to individual needs and preferences, and addressed psychosocial issues and incorporated behavioral strategies (13,23,32,33). Individual and group approaches are effective (20,34,35), with a slight benefit realized by those who engage in both (18).

Emerging evidence demonstrates the benefit of internet-based DSMES services for diabetes prevention and the management of type 2 diabetes (36–38). 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 (38). Current research supports nurses, dietitians, and pharmacists as providers of DSMES who may also tailor curriculum to the person's needs (39–41). Members of the DSMES team should have specialized clinical knowledge in diabetes and behavior change principles. Certification as a diabetes educator (see www.ncbde.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). Additionally, there is growing evidence for the role of community health workers (42,43), as well as peer (42–46) and lay leaders (47), in providing ongoing support.

DSMES is associated with an increased use of primary care and preventive services (24,48,49) and less frequent use of acute care and inpatient hospital services (19). 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 (25,48). Despite these benefits, reports indicate that only 5–7% of individuals eligible for DSMES through Medicare or a private insurance plan actually receive it (50,51). This low

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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 (52). Thus, in addition to educating referring providers about the benefits of DSMES and the critical times to refer (2), alternative and innovative models of DSMES delivery need to be explored and evaluated.

Reimbursement

Medicare reimburses DSMES when that service meets the national standards (2,11) and is recognized by the American Diabetes Association (ADA) or other approval bodies. 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. 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 (53,54).

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 (41). 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 (41,55). All individuals with diabetes should be referred for individualized MNT provided by a registered dietitian nutritionist (RD/RDN) who is knowledgeable and skilled in providing diabetes-specific MNT (56) at diagnosis and as needed throughout the life span, similar to DSMES. MNT delivered by an RD/RDN is associated with A1C decreases of 1.0–1.9% for people with type 1 diabetes (57) and 0.3–2.0% for people with type 2 diabetes (57). 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 should be integrated with the overall treatment plan (55).

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, Macronutrient Distribution, 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 (41,58,59). It is important that each member of the health care team be knowledgeable about nutrition therapy principles for people with all types of diabetes and be supportive of their implementation. 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 individualized needs and improve overall health. A variety of eating patterns are acceptable for the management of diabetes (41,58,60). 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 (41). 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 (61,62), low-carbohydrate (63–65), and vegetarian or plant-based (66,67) 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. 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 (63–65). As research studies on some 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. This eating pattern is not recommended at this time for women who are pregnant or lactating, people

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Table 5.1—Medical nutrition therapy recommendations

Topic		Recommendation	Evidence rating
Effectiveness of nutrition therapy	**5.6**	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**
	5.7	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**	**B**, **A**, **E**
Energy balance	**5.8**	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	**5.9**	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**
	5.10	A variety of eating patterns are acceptable for the management of type 2 diabetes and prediabetes.	**B**
Carbohydrates	**5.11**	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**
	5.12	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**
	5.13	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.	**A**, **B**
	5.14	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**
	5.15	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**	**B**, **A**
Protein	**5.16**	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	**5.17**	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**
	5.18	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**; however, evidence does not support a beneficial role for the routine use of n-3 dietary supplements. **A**	**B**, **A**
Micronutrients and herbal supplements	**5.19**	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	**5.20**	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**
	5.21	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	**5.22**	As for the general population, people with diabetes and prediabetes should limit sodium consumption to $<$2,300 mg/day.	**B**
Nonnutritive sweeteners	**5.23**	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**

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with or at risk for disordered eating, or people who have renal disease, and it should be used with caution in patients taking sodium–glucose cotransporter 2 inhibitors due to the potential risk of ketoacidosis (68,69). There is inadequate research in type 1 diabetes to support one eating pattern over another at this time.

The diabetes plate method is commonly used for providing basic meal planning guidance (70) and provides a visual guide showing how to portion calories (featuring a 9-inch plate) and carbohydrates (by limiting them to what fits in one-quarter of the plate) and places an emphasis on low-carbohydrate (or nonstarchy) vegetables. Providing a visual/small graphic of the diabetes plate method is preferred, as descriptions of the concept can be confusing when unfamiliar.

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 (41). 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 (58,71,72) (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 (73). In conjunction with lifestyle therapy, 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 (74,75). People with prediabetes at a healthy weight should also be considered for lifestyle intervention involving both aerobic and resistance exercise (73,76,77) and a healthy eating plan, such as a Mediterranean-style eating pattern (78).

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 (79). 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 (80,81). 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 (82–84). Overweight and obesity are also increasingly prevalent in people with type 1 diabetes and present clinical challenges regarding diabetes treatment and CVD risk factors (85,86). Sustaining weight loss can be challenging (79,87) but has long-term benefits; maintaining weight loss for 5 years is associated with sustained improvements in A1C and lipid levels (88). 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 (41). 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 (80,88,89) and the Mediterranean-style eating pattern (78), as well as low-carbohydrate meal plans (90). However, no single approach has been proven to be consistently superior (41,91,92), 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 (92), as well as guidance on achieving the desired energy deficit (93–96). 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 (97,98). The literature concerning glycemic index and glycemic load in individuals with diabetes is complex, often yielding mixed results, though in some studies lowering the glycemic load of consumed carbohydrates has demonstrated A1C reductions of 0.2% to 0.5% (99,100). Studies longer than 12 weeks report no significant influence of glycemic index or glycemic load independent of weight loss on A1C; however, mixed results have been reported for fasting glucose levels and endogenous insulin levels.

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 (41). For people with type 2 diabetes or prediabetes, low-carbohydrate eating plans show potential to improve glycemia and lipid outcomes for up to 1 year (63,65,90,101–104). Part of the challenge in interpreting low-carbohydrate research has been due to the wide range of definitions for a low-carbohydrate eating plan (65,100). 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. Providers should maintain consistent medical oversight and recognize that certain groups are not

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appropriate for low-carbohydrate eating plans, including women who are pregnant or lactating, children, and people who have renal disease or disordered eating behavior, and these plans should be used with caution in those taking sodium–glucose cotransporter 2 inhibitors because of the potential risk of ketoacidosis (68,69). There is inadequate research about dietary patterns for type 1 diabetes to support one eating plan over another at this time.

Most individuals with diabetes report a moderate intake of carbohydrate (44–46% of total calories) (58). Efforts to modify habitual eating patterns are often unsuccessful in the long term; people generally go back to their usual macronutrient distribution (58). Thus, the recommended approach is to individualize meal plans to meet caloric goals with a macronutrient distribution that is more consistent with the individual's 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. The consumption of sugar-sweetened beverages (including fruit juices) and processed food products with high amounts of refined grains and added sugars is strongly discouraged (105–107).

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 (58,97,108–111). 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 differ 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 (41). Checking glucose 3 h after eating may help to determine if additional insulin adjustments are required (112,113). 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 (41).

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 in individuals without diabetic kidney disease, and research is inconclusive regarding the ideal amount of dietary protein to optimize either glycemic management or CVD risk (99,114). 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 (115).

Those with diabetic kidney disease (with albuminuria and/or reduced estimated glomerular filtration rate) should aim to maintain dietary protein at the recommended daily allowance of 0.8 g/kg body wt/day. Reducing the amount of dietary protein below the recommended daily allowance is not recommended because it does not alter glycemic measures, cardiovascular risk measures, or the rate at which glomerular filtration rate declines (116,117).

In individuals with type 2 diabetes, protein intake may enhance or increase the insulin response to dietary carbohydrates (118). 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 (41). 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 (78,105, 119–121). Multiple randomized controlled trials including patients with type 2 diabetes have reported that a Mediterranean-style eating pattern (78, 122–127), rich in polyunsaturated and monounsaturated fats, can improve both glycemic management and blood lipids. However, supplements do not seem to have the same effects as their whole-food counterparts. A systematic review concluded that dietary supplements with n-3 fatty acids did not improve glycemic management in individuals with type 2 diabetes (99). Randomized controlled trials also do not support recommending n-3 supplements for primary or secondary prevention of CVD (128–132). 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 (105). In general, *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 (126).

Sodium

As for the general population, people with diabetes are advised to limit their sodium consumption to <2,300 mg/day (41). Restriction below 1,500 mg, even for those with hypertension, is generally not recommended (133–135). Sodium intake recommendations should take into account palatability, availability, affordability, and the difficulty of achieving low-sodium recommendations in a nutritionally adequate diet (136).

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 (41). Metformin is associated with vitamin B12 deficiency

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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 (137). 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 (138), curcumin, vitamin D (139), aloe vera, or chromium, to improve glycemia in people with diabetes (41,140). 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) (41,140). 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

For some people with diabetes who are accustomed to 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. While use of nonnutritive sweeteners does not appear to have a significant effect on glycemic management (141), they can reduce overall calorie and carbohydrate intake (58). Most systematic reviews and meta-analyses show benefits for nonnutritive sweetener use in weight loss (142,143); however, some research suggests an association with weight gain (144). When use of sugar substitutes is meant to reduce overall caloric and carbohydrate intake, people should be counseled to avoid compensating with intake of additional calories from other food sources (41). Regulatory agencies set acceptable daily intake levels for each nonnutritive sweetener, defined as the amount that can be safely consumed over a person's lifetime (41,145). 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 (146).

PHYSICAL ACTIVITY

Recommendations

5.24 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**

5.25 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.

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

5.27 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**

5.28 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**

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 (147). 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 (148). 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 (149). 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 (150). 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

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(151). 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 (152). 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 (153). Higher levels of exercise intensity are associated with greater improvements in A1C and in fitness (154). Other benefits include slowing the decline in mobility among overweight patients with diabetes (155). 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 recommendation (156). 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 (156).

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 (157). In general, youth with type 1 diabetes benefit from being physically active, and an active lifestyle should be recommended to all (158). Youth with type 1 diabetes who engage in more physical activity may have better health outcomes and health-related quality of life (159, 160).

Frequency and Type of Physical Activity

People with diabetes should perform aerobic and resistance exercise regularly (156). 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 (161,162). 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) (156). Many adults, including most with type 2 diabetes, would 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 (163). Although heavier resistance training with free weights and weight machines may improve glycemic control and strength (164), 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 persons 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 (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 (165,166). Avoiding extended sedentary periods may help prevent type 2 diabetes for those at risk and may also aid in glycemic control for those with diabetes.

A wide range of activities, including yoga, tai chi, and other types, can have significant impacts on A1C, flexibility, muscle strength, and balance (147, 167,168). Flexibility and balance exercises may be particularly important in older adults with diabetes to maintain range of motion, strength, and balance (156).

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 (169) and for an additive benefit of combined aerobic and resistance exercise in adults with type 2 diabetes (170). 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 (169).

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 (171).

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 (156).

Pre-exercise Evaluation

As discussed more fully in Section 10 "Cardiovascular Disease and Risk Management" (https://doi.org/10.2337/dc20-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" (172) 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 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

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patient's age and previous physical activity level should be considered. The provider should customize the exercise regimen to the individual's needs. Those with complications may require a more thorough evaluation prior to beginning an exercise program (171).

Hypoglycemia

In individuals taking insulin and/or insulin secretagogues, physical activity may cause hypoglycemia if the medication dose or carbohydrate consumption is not altered. 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 (156,171). 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 (152). 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/dc20-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 (173). 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 (174). In addition, 150 min/week of moderate exercise was reported to improve outcomes in patients with prediabetic neuropathy (175). 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 (176). Cardiovascular autonomic neuropathy is also an independent risk factor for cardiovascular death and silent myocardial ischemia (177). 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 diabetic kidney disease, and there appears to be no need for specific exercise restrictions for people with diabetic kidney disease in general (173).

SMOKING CESSATION: TOBACCO AND E-CIGARETTES

Recommendations

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

5.30 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**

Results from epidemiological, case-control, and cohort studies provide convincing evidence to support the causal link between cigarette smoking and health risks (178). Recent data show tobacco use is higher among adults with chronic conditions (179) as well as in adolescents and young adults with diabetes (180). Smokers with diabetes (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 nonsmokers (181–183). Smoking may have a role in the development of type 2 diabetes (184–187).

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 (188), and for the patient motivated to quit, the addition of pharmacologic therapy to counseling is more effective than either treatment alone (189). Special considerations should include assessment of level of nicotine dependence, which is associated with difficulty in quitting and relapse (190). Although some patients may gain weight in the period shortly after smoking cessation (191), recent research has demonstrated that this weight gain does not diminish the substantial CVD benefit realized from smoking cessation (192). One study in smokers with 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 (193).

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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 (194,195). However, in light of recent Centers for Disease Control and Prevention evidence (196) 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.

PSYCHOSOCIAL ISSUES

Recommendations

5.31 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**

5.32 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**

5.33 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**

5.34 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 (11).

Emotional well-being is an important part of diabetes care and self-management. Psychological and social problems can impair the individual's (11,197–201) or family's (200) 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 (202, 203). A systematic review and meta-analysis showed that psychosocial interventions modestly but significantly improved A1C (standardized mean difference –0.29%) and mental health outcomes (204). 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 (205), 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 (206).

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 (205). 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

5.35 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 (207–209). 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 (208–210). 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 (208). 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 (210). 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 (207). 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 (5,208,210). DSMES has been shown to reduce diabetes distress (5). It may be helpful to

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provide counseling regarding expected diabetes-related versus generalized psychological distress, at diagnosis and when disease state or treatment changes (211).

Diabetes distress should be routinely monitored (212) 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) (213), 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 (32,207). 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 clinician may not feel qualified to treat psychological problems (214), 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 (215,216). 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 (215). 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

5.36 Consider screening for anxiety in people exhibiting anxiety or worries regarding diabetes complications, insulin administration, and taking 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**

5.37 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 (217). 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 (218). Common diabetes-specific concerns include fears related to hypoglycemia (219,220), not meeting blood glucose targets (217), and insulin

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

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injections or infusion (221). 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 targets may be experiencing symptoms of obsessive compulsive disorder (222).

General anxiety is a predictor of injection-related anxiety and associated with fear of hypoglycemia (220,223). Fear of hypoglycemia and hypoglycemia unawareness often co-occur. Interventions aimed at treating one often benefit both (224). 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 (225,226). 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 (224,227).

Depression

Recommendations

5.38 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**

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

5.40 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 (228–230). Elevated depressive symptoms and depressive disorders affect one in four patients with type 1 or type 2 diabetes (199). 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 (231).

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 (228). Integrating mental and physical health care can improve outcomes. When a patient is in psychological therapy (talk therapy), the mental health provider should be incorporated into the diabetes treatment team (232). As with DSMES, person-centered collaborative care approaches have been shown to improve both depression and medical outcomes (233).

Various randomized controlled trials have shown improvements in diabetes and depression health outcomes when depression is treated (233). 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

5.41 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**

5.42 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 (234–236). For people with type 1 diabetes, insulin omission causing glycosuria in order to lose weight is the most commonly reported disordered eating behavior (237,238); 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 (239). People with diabetes and diagnosable eating disorders have high rates of comorbid psychiatric disorders (240). People with type 1 diabetes and eating disorders have high rates of diabetes distress and fear of hypoglycemia (241).

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 (236,242). Adjunctive medication such as glucagon-like peptide 1 receptor agonists (243) 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

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

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5.44 Annually screen people who are prescribed atypical antipsychotic medications for prediabetes or diabetes. **B**

5.45 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 (244). 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 (245,246). 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 (247).

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6. Glycemic Targets: *Standards of Medical Care in Diabetes—2020*

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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/dc20-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/dc20-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 management is primarily assessed with the A1C test, which was the measure studied in clinical trials demonstrating the benefits of improved glycemic control. Patient self-monitoring of blood glucose (SMBG) may help with self-management and medication adjustment, particularly in individuals taking insulin. Continuous glucose monitoring (CGM) also has an important role in assessing the effectiveness and safety of treatment in many patients with type 1 diabetes, and limited data suggest it may also be helpful in selected patients with type 2 diabetes, such as those on intensive insulin regimens (1).

A1C Testing

Recommendations

6.1 Perform the A1C test *at least* two times a year in patients who are meeting treatment goals (and who have stable glycemic control). **E**

6.2 Perform the A1C test quarterly in patients whose therapy has changed or who are not meeting glycemic goals. **E**

6.3 Point-of-care testing for A1C provides the opportunity for more timely treatment changes. **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 major 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

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use of point-of-care A1C testing may provide an opportunity for more timely treatment changes during encounters between patients and providers. Patients with type 2 diabetes with stable glycemia well within target may do well with A1C testing 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) (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 such variability is less 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. 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 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. 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 meter (or the patient's reported SMBG results) and the adequacy of the SMBG testing schedule.

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 (5). Thus, as suggested, a patient's CGM profile has considerable potential for optimizing his or her glycemic management (5).

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/African American and non-Hispanic white cohorts, with higher A1C values observed in Africans/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

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).

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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 both individualized SMBG and A1C results.

Glucose Assessment

Recommendations

6.4 Standardized, single-page glucose reports with visual cues such as the Ambulatory Glucose Profile (AGP) should be considered as a standard printout for all CGM devices. **E**

6.5 Time in range (TIR) is associated with the risk of microvascular complications and should be an acceptable end point for clinical trials 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. **E**

For many people with diabetes, glucose monitoring is key for the achievement of 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 (16). SMBG is thus an integral component of effective therapy of patients taking insulin. In recent years, CGM has emerged as a complementary method for the assessment of glucose levels. Glucose monitoring allows patients to evaluate their individual response to therapy and assess whether glycemic targets are being safely achieved. The international consensus on time in range provides guidance on standardized CGM metrics (see **Table 6.2**) and considerations for clinical interpretation and care (17). To make these metrics more actionable, standardized reports with visual cues such as the Ambulatory Glucose Profile (see **Fig. 6.1**) are recommended (17) and may help the patient and the provider interpret the data and use it to guide treatment decisions. Integrating SMBG and CGM results into diabetes management can be useful for guiding medical nutrition therapy and physical activity, preventing hypoglycemia, and adjusting medications. As recently reviewed, while A1C is currently the primary measure guiding glucose management and a valuable marker of the risk of developing diabetes complications, the Glucose Management Indicator (GMI) along with the other CGM metrics are suggested to provide for a much more personalized diabetes management plan. The incorporation of these metrics into clinical practice is in evolution, and optimization of CGM terminology will evolve to suit patient and provider needs. The patient's specific needs and goals should dictate SMBG frequency and timing or the consideration of CGM use. Please refer to Section 7 "Diabetes Technology" (https://doi.org/10.2337/dc20-S007) for a fuller discussion of the use of SMBG and CGM.

Glucose Assessment Using Continuous Glucose Monitoring

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 time in range (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 (17). 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 (18,19).

A1C GOALS

For glycemic goals in older adults, please refer to Section 12 "Older Adults" (https://doi.org/10.2337/dc20-S012). For glycemic goals in children, please refer to Section 13 "Children and Adolescents" (https://doi.org/10.2337/dc20-S013). For glycemic goals in pregnant women, please refer to Section 14 "Management of Diabetes in Pregnancy" (https://doi.org/10.2337/dc20-S014).

Recommendations

6.6 An A1C goal for many nonpregnant adults of <7% (53 mmol/mol) is appropriate. **A**

6.7 On the basis of provider judgement and patient preference, achievement of lower A1C levels (such as <6.5%) may be acceptable if this can be achieved safely without significant hypoglycemia or other adverse effects of treatment. **C**

6.8 Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular

Table 6.2—Standardized continuous glucose monitoring (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 (GMI)	
5. Glycemic variability (%CV) target ≤36%*	
6. Time above range (TAR): % of readings and time >250 mg/dL (>13.9 mmol/L)	Level 2
7. Time above range (TAR): % of readings and time 181–250 mg/dL (10.1–13.9 mmol/L)	Level 1
8. Time in range (TIR): % of readings and time 70–180 mg/dL (3.9–10.0 mmol/L)	In range
9. Time below range (TBR): % of readings and time 54–69 mg/dL (3.0–3.8 mmol/L)	Level 1
10. Time below range (TBR): % of readings and time <54 mg/dL (<3.0 mmol/L)	Level 2

CGM, continuous glucose monitoring; CV, coefficient of variation. *Some studies suggest that lower %CV targets (<33%) provide additional protection against hypoglycemia for those receiving insulin or sulfonylureas. Adapted from Battelino et al. (17).

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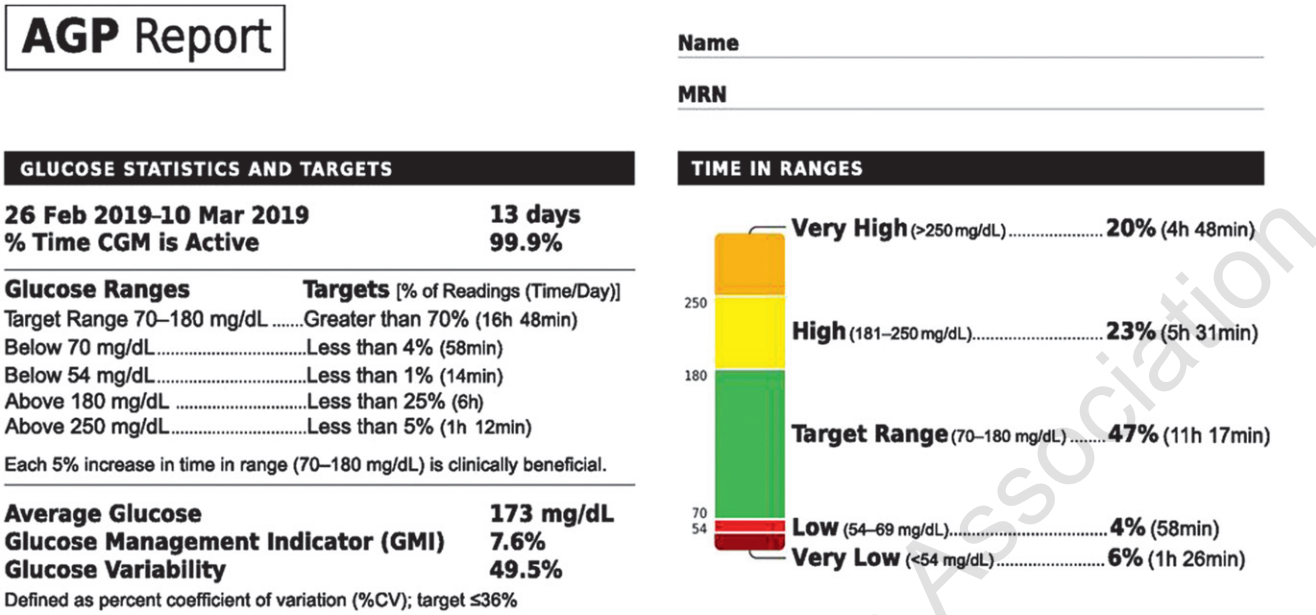

Figure 6.1—Sample Ambulatory Glucose Profile (AGP) report. Adapted from Battelino et al. (17).

complications, extensive comorbid conditions, or long-standing diabetes in whom the goal is difficult to achieve despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. **B**

6.9 Reassess glycemic targets over time based on the criteria in **Fig. 6.2** or, 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) (16), a prospective randomized controlled trial of intensive (mean A1C about 7% [53 mmol/mol]) 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 (20,21) 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 (22) and UK Prospective Diabetes Study (UKPDS) (23,24) 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 (25).

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 (26). Epidemiologic analyses of the DCCT (16) and UKPDS (27) 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.

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 (28–30).

The concerning mortality findings in the ACCORD trial (31), 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. However, on the

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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 it 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 (32). The benefit of intensive glycemic control in this cohort with type 1 diabetes has been shown to persist for several decades (33) and to be associated with a modest reduction in all-cause mortality (34).

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 and 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 (35–37). 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 (37). 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). However, 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) (25).

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 "Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials" (38).

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 (31).

Longer-term follow-up has shown no evidence of cardiovascular benefit or harm in the ADVANCE trial (39). 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 (40) 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 population characteristics (41).

Mortality findings in ACCORD (31) and subgroup analyses of VADT (42) 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 (43,44).

As discussed further below, severe hypoglycemia is a potent marker of high absolute risk of cardiovascular events and mortality (45). 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/dc20-S009), addition of specific sodium–glucose cotransporter 2 inhibitors (SGLT2i) or glucagon-like peptide 1 receptor agonists (GLP-1 RA) that have demonstrated CVD benefit are recommended for use in patients with established CVD or indicators of high risk. As outlined in more detail in Section 9 "Pharmacologic Approaches to Glycemic Treatment" (https://doi.org/10.2337/dc20-S009) and Section 10 "Cardiovascular Disease and Risk Management" (https://doi.org/10.2337/dc20-S010), the cardiovascular benefits of SGLT2i or GLP-1 RA are not dependent upon A1C lowering, so initiation can be considered in people with type 2 diabetes and CVD independent of the current A1C or A1C goal. Based on these considerations, the following two strategies are offered (46):

1. If already on dual therapy or multiple glucose-lowering therapies and not on an SGLT2i or GLP-1 RA, consider switching to one of these agents with proven cardiovascular benefit.
2. Introduce SGLT2i or GLP-1 RA in patients with CVD at A1C goal for cardiovascular benefit.

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

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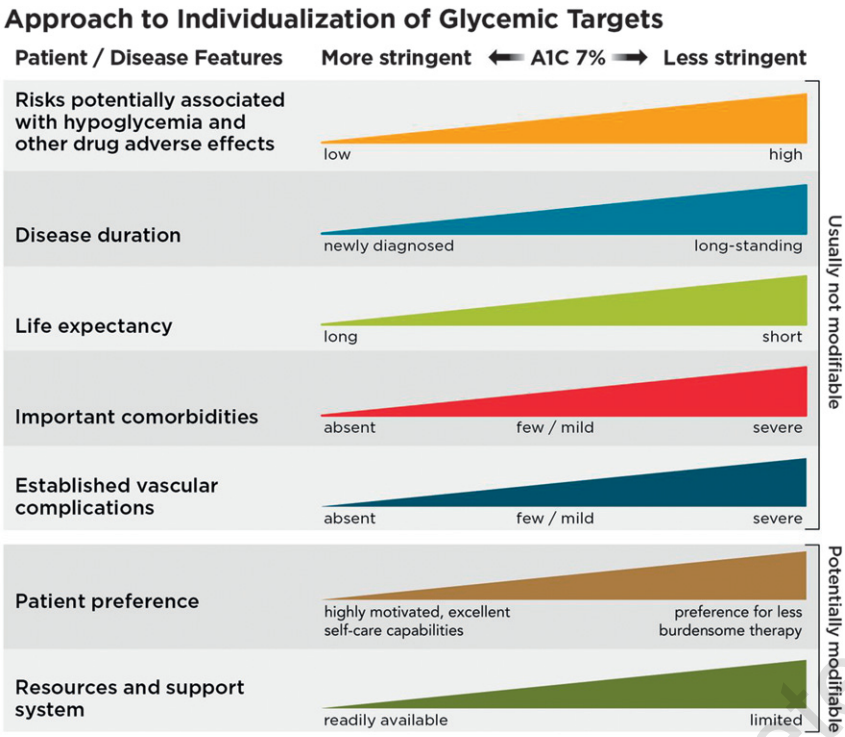

Figure 6.2—Depicted are patient and disease factors used to determine optimal A1C targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. A1C 7% = 53 mmol/mol. Adapted with permission from Inzucchi et al. (47).

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.

The factors to consider in individualizing goals are depicted in **Fig. 6.2**. **Figure 6.2** is not designed to be applied rigidly but to be used as a broad construct to guide clinical decision-making (47) and engage in shared decision-making in both 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 the disease 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 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/dc20-S014).

The issue of preprandial versus postprandial SMBG targets is complex (48). 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, but intervention trials have not shown postprandial glucose to be a cardiovascular risk factor independent of A1C. In subjects 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 (49). Therefore, it is reasonable for postprandial testing to be recommended for individuals who have premeal glucose values within target but have A1C values above target. 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 (7,50). 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)

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but did not affect the definition of hypoglycemia.

HYPOGLYCEMIA

Recommendations

6.10 Individuals at risk for hypoglycemia should be asked about symptomatic and asymptomatic hypoglycemia at each encounter. **C**

6.11 In patients taking medication that can lead to hypoglycemia, investigate, screen, and assess risk for or occurrence of unrecognized hypoglycemia, considering that patients may have hypoglycemia unawareness. **C**

6.12 Glucose (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 SMBG shows continued hypoglycemia, the treatment should be repeated. Once SMBG returns to normal, the individual should consume a meal or snack to prevent recurrence of hypoglycemia. **B**

6.13 Glucagon should be prescribed for all individuals at increased risk of level 2 hypoglycemia, defined as blood glucose <54 mg/dL (3.0 mmol/L), so 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, particularly with the availability of intranasal and stable soluble glucagon available in autoinjector pens. **E**

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

6.15 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**

6.16 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**

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. 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. †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.

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** (51–56). 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, 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. It 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 (52,57–60). 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 (61). Conversely, in a substudy of the ACCORD trial, cognitive impairment at

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

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baseline or decline in cognitive function during the trial was significantly associated with subsequent episodes of level 3 hypoglycemia (62). 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 (63), as discussed in Section 13 "Children and Adolescents" (https://doi.org/10.2337/dc20-S013).

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 (64) yet find high burden of hypoglycemia in adults over 60 years of age in the community (65). African Americans are at substantially increased risk of level 3 hypoglycemia (65,66). 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 (65). 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 (67). An association between self-reported level 3 hypoglycemia and 5-year mortality has also been reported in clinical practice (68)

Young children with type 1 diabetes and the elderly, including those with type 1 and type 2 diabetes (61,69), 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 (70). CGM with automated low glucose suspend has been shown to be effective in reducing hypoglycemia in type 1 diabetes (71). 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 (72,73).

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 (74–76). 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 (77). 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. 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 recently received U.S. Food and Drug Administration approval. 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 (78). 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 (79).

Use of CGM Technology in Hypoglycemia Prevention

With the advent of CGM and CGM-assisted pump therapy, there has been a

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promise of alarm-based prevention of hypoglycemia (80,81). To date, there have been six randomized controlled trials in adults with type 1 diabetes and seven in adults and children with type 1 diabetes using real-time CGM. 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 (81–97). 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. 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 (88). 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 (98), whereas improvements in A1C were observed in most studies (98–104). Overall, real-time CGM appears to be a useful tool for decreasing time spent in hypoglycemia range in people with impaired awareness.

INTERCURRENT ILLNESS

For further information on management of patients with hyperglycemia in the hospital, please refer to Section 15 "Diabetes Care in the Hospital" (https://doi.org/10.2337/dc20-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 the person with diabetes than the person 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" (105).

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7. Diabetes Technology: *Standards of Medical Care in Diabetes—2020*

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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/dc20-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/dc20-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.

OVERALL STATEMENT

Recommendation

7.1 Use of technology should be individualized based on a patient's needs, desires, skill level, and availability of devices. Nonprofit websites can offer advice for providers and patients to determine the suitability of various options. **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 such as DiabetesWise.org (1) and others 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 Most patients using intensive insulin regimens (multiple daily injections or insulin pump therapy) should be encouraged to assess glucose levels using

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self-monitoring of blood glucose (and/or continuous glucose monitoring) prior to meals and snacks, at bedtime, 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. **B**

7.3 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**

7.4 Although self-monitoring of blood glucose in patients on noninsulin therapies has not 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**

7.5 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 from self-monitoring of blood glucose to adjust therapy. **E**

7.6 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**

7.7 Providers should be aware of the differences in accuracy among glucose meters—only U.S. Food and Drug Administration–approved meters should be used with unexpired strips, purchased from a pharmacy or licensed distributor. **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 (2). 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, and 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.

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 (3). Among patients who check their blood glucose at least once daily, many report taking no action when results are high or low (4). Patients should be taught how to use SMBG data to adjust food intake, exercise, or pharmacologic therapy to achieve specific goals. 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 (4–6).

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 testing 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 (–0.2% per additional test per day) and with fewer acute complications (7).

Patients Using Basal Insulin and/or Oral Agents

The evidence is insufficient regarding when to prescribe SMBG and how often testing 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 (8,9).

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 (10–13). 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 (14). 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 (13). Meta-analyses have suggested that SMBG can reduce A1C by 0.25–0.3% at 6 months (15–17), but the effect was attenuated at 12 months in one analysis (15). 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

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structured diabetes therapy adjustment (17). 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 Accuracy

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 (18).

Oxygen. Currently available glucose monitors utilize an enzymatic reaction linked to an electrochemical reaction, either glucose oxidase or glucose dehydrogenase (19). 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 monitors are not sensitive to oxygen.

Temperature. Because the reaction is sensitive to temperature, all monitors have an acceptable temperature range (19). 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 (19). They are listed in **Table 7.1**.

Table 7.1—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)

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 7.2**. 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 (20). The Diabetes Technology Society Blood Glucose Monitoring System Surveillance Program provides information on the performance of devices used for SMBG (diabetestechnology.org/surveillance). In a recent analysis, the program found that only 6 of the top 18 glucose meters met the accuracy standard (21).

Counterfeit Strips. Patients should be advised against purchasing or reselling pre-owned or second-hand test strips, as these may give incorrect results. Only unopened vials of glucose test strips should be used to ensure SMBG accuracy.

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. **E**

7.9 When used properly, real-time continuous glucose monitors in conjunction with insulin therapy are a useful tool to lower A1C levels and/or reduce hypoglycemia in adults with type 1 diabetes who are not meeting glycemic targets, have hypoglycemia unawareness, and/or have episodes of hypoglycemia. **A**

7.10 When used properly, intermittently scanned continuous glucose monitors in conjunction with insulin therapy are useful tools to lower A1C levels and/or reduce hypoglycemia in adults with type 1 diabetes who are not meeting glycemic targets, have hypoglycemia unawareness, and/or have episodes of hypoglycemia. **C**

7.11 When used properly, real-time and intermittently scanned continuous glucose monitors in conjunction with insulin therapy are useful tools to lower A1C and/or reduce hypoglycemia in adults with type 2 diabetes who are not meeting glycemic targets. **B**

7.12 Continuous glucose monitoring (CGM) should be considered in all children and adolescents with type 1 diabetes, whether using injections or continuous subcutaneous insulin infusion, as an additional tool to help improve glucose control. Benefits of CGM correlate with adherence to ongoing use of the device. **B**

7.13 Real-time continuous glucose monitoring (CGM) devices should be used as close to daily as possible for maximal benefit. Intermittently scanned CGM devices should be scanned frequently, at a minimum once every 8 h. **A**

7.14 Real-time continuous glucose monitors may be used effectively to improve A1C levels, time in range, and neonatal outcomes in pregnant women with type 1 diabetes. **B**

7.15 Blinded continuous glucose monitor data, when coupled with diabetes self-management education and medication dose adjustment, can be helpful in identifying and correcting patterns of hyper- and hypoglycemia in people with type 1 diabetes and type 2 diabetes. **E**

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Table 7.2—Comparison of ISO 15197:2013 and FDA blood glucose meter accuracy standards

Setting	FDA (154,155)	ISO 15197:2013 (156)
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 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 (157).

7.16 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). There are two basic types of CGM devices: those that provide unblinded data to the user and those that are blinded with data available to the patient and their health care provider for retrospective analysis. **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 real-time CGM devices that have alarms and alerts. It is difficult to determine how much impact having these notices makes in terms of reacting to glucose levels. There is one small study in patients at risk for hypoglycemia that compares real-time CGM with intermittently scanned CGM (isCGM) (22). The study showed improvement in time spent in hypoglycemia with real-time CGM compared with isCGM.

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 (23). Two CGM devices are approved by the FDA for making treatment decisions without SMBG calibration or confirmation (24,25).

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 (26) and are discussed in Section 6, "Glycemic Targets" (https://doi.org/10.21337/dc20-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 (27).

Table 7.3—Continuous glucose monitoring (CGM) devices

Real-time CGM	CGM systems that measure glucose levels continuously and provide the user automated alarms and alerts at specific glucose levels and/or for changing glucose levels.
Intermittently scanned CGM	CGM systems that measure glucose levels continuously but only display glucose values when swiped by a reader or a smart phone that reveals the glucose levels.
Blinded (professional) CGM	CGM devices that measure glucose levels that are not displayed to the patient in real time. These devices are generally initiated in a clinic, using a reader that is owned by the clinic. They are removed after a period of time (generally 10–14 days) and analyzed by the patient and provider to assess glycemic patterns and trends.
Unblinded CGM	CGM devices that measure glucose levels that are displayed to the patient.

Real-time CGM Device Use in Adults With Type 1 Diabetes

Data exist to support the use of real-time CGM in adults, both those on multiple daily injections (MDI) and continuous subcutaneons insulin infusion (CSII). In terms of RCTs in people with type 1 diabetes, there are four studies in adults with A1C as the primary outcome (28–32), three studies in adults with hypoglycemia as the primary outcome (33–35), four studies in adults and children with A1C as the primary outcome (36–39), and three studies in adults and children with hypoglycemia as a primary outcome (40–42).

Primary Outcome: A1C Reduction

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 real-time CGM in patients on MDI, there were significant reductions in A1C: –0.6% in one (28,29) and –0.43% in the other (30). No reduction in A1C was seen in a small study performed in underserved, less well-educated adults with type 1 diabetes (31). In the adult subset of the JDRF CGM study, there was a significant reduction in A1C of –0.53% (43) in patients who were primarily treated with insulin pump therapy. Better adherence in wearing the real-time CGM device resulted in a greater likelihood of an improvement in glycemic control (32,36).

Primary Outcome: Hypoglycemia

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 (33–35). In one study in patients who were at higher risk for episodes of hypoglycemia (35), there was a reduction in rates of all levels of hypoglycemia (see Section 6 "Glycemic

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Targets," https://doi.org/10.2337/dc20-S006, for hypoglycemia definitions). Real-time CGM 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 (36–38).

Intermittently Scanned CGM Device Use in Adults With Type 1 Diabetes

isCGM does not currently provide alarms and alerts but is an option used by many patients. There is relatively little RCT data proving benefit in people with type 1 diabetes. One study, designed to show a reduction in episodes of hypoglycemia in patients at higher risk for hypoglycemia, showed a significant benefit in terms of time spent in a hypoglycemic range ($P < 0.0001$) (33). Additional observational studies have shown benefit in terms of A1C reduction (44).

There are several published reviews of data available on isCGM (45–47). 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 until January 2017 (45). 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 testing (46). A final review (47) also supported the use of isCGM as a more affordable alternative to real-time CGM systems for individuals with diabetes who are on intensive insulin therapy.

Real-time and Intermittently Scanned CGM Device Use in Adults With 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 (48,49); in one, individuals were on MDI alone (50); and in another, participants were on CSII or MDI (42). The findings in studies with MDI alone (50) and in two studies in people using oral agents with or without insulin (48,49) 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 did not show a reduction in hypoglycemia (50), although it did show a reduction in A1C. Studies in individuals with type 2 diabetes on oral agents with or without insulin did not show reductions in rates of hypoglycemia (48,49).

In one study of isCGM in people with type 2 diabetes on a variety of insulin regimens and an initial A1C of ~8.8%, no reduction in A1C was seen; however, the time spent in a hypoglycemic range was reduced by 43% (51). 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 (52).

Real-time CGM Device Use in Children and Adolescents With Type 1 Diabetes

Data regarding use of real-time CGM in youth consist of findings from RCTs and small observational studies as well as analysis of data collected by registries. Seven RCTs have included both adult and pediatric participants (36–42), while others have only included pediatric participants (53) or limited the analysis of larger studies to just the pediatric participants (36). Given the feasibility problems of performing RCTs in very young children, small observational studies have also provided data on real-time CGM use in the youngest age-groups (54–56). Finally, while limited by the observational nature, registry data provide some evidence of real-world use of the technologies (43,57).

Impact on Glycemic Control

When data from adult and pediatric participants are analyzed together, real-time CGM use in RCTs has been associated with reduction in A1C levels (37–39). 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 real-time CGM adherence (36). 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 (58). One critical component to success with CGM is near-daily wearing of the device (37,59–61).

Though data from small observational studies demonstrate that real-time CGM can be worn by patients <8 years old and the use of real-time CGM provides insight to glycemic patterns (54,55), an RCT in children aged 4–9 years did not demonstrate improvements in glycemic control following 6 months of real-time CGM use (53). 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 (56).

Registry data has also shown an association between real-time CGM use and lower A1C levels (43,57), even when limiting assessment of real-time CGM use to participants on injection therapy (57).

Impact on Hypoglycemia

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 (10,62,63).

Intermittently Scanned CGM Device Use in Children and Adolescents With Type 1 Diabetes

Data on use of isCGM in children come from observational studies. In these reports, isCGM is favorably adopted and is associated with improvements in outcomes (64–67).

Impact of Frequency of CGM Device Use (All Age-groups)

For patients with type 1 diabetes using real-time CGM, an important predictor of A1C lowering for all age-groups was frequency of sensor use (36). 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.

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 (68). Neonatal outcomes were better when the mother used CGM during pregnancy (28). Two studies employing intermittent use of real-time CGM showed no difference in neonatal outcomes in women with type 1 diabetes (69) or gestational diabetes mellitus (70).

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Use of Blinded (Professional) CGM Devices

Blinded CGM devices, which provide retrospective data for analysis, can be used to identify patterns of hypo- and hyperglycemia. While minimal RCT data exist to support their use, in some settings, blinded CGM can be helpful to evaluate patients when either real-time or isCGM is not available to the patient or the patient prefers a blinded analysis. It can be particularly useful to evaluate periods of hypoglycemia in patients on agents that can cause hypoglycemia for making medication dose adjustments. It can also be useful to evaluate for periods of hyperglycemia. Use of blinded 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 has been reported with all devices that attach to the skin (71). 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 (72–74). Patch testing can be done to identify the cause of the contact dermatitis (75).

INSULIN DELIVERY

Insulin Syringes and Pens

Recommendations

7.17 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**

7.18 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**

7.19 Patients using insulin should have an examination of insulin injection/infusion sites on a routine basis—at least annually and if there are clinical issues related to insulin delivery. **E**

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

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

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

Injecting insulin with a syringe or pen is the insulin delivery method used by most people with diabetes (76,77), 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 (78–80), while insulin injection aids are also available to help with these issues. (For a helpful list of injection aids, see main.diabetes.org/dforg/pdfs/2018/2018-cg-injection-aids.pdf.) Inhaled insulin can be useful in people who have an aversion to giving 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 (81).

Insulin pens offer added convenience by combining the vial and syringe into a single device. Insulin pens, allowing pushbutton injections, come as disposable pens with prefilled cartridges or reusable insulin pens with replaceable insulin cartridges. 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. Pens also vary with respect to dosing increment and minimal dose, which can range from half-unit doses to 2-unit dose increments.

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 technique is a requisite to obtain the full benefits of insulin injection therapy, and concerns with technique and using the proper technique are outlined in Section 9 "Pharmacologic Approaches to Glycemic Treatment" (https://doi.org/10.2337/dc20-S009).

Another insulin delivery option is a disposable patch-like 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 (82).

Bolus calculators have been developed to aid in dosing decisions (83–87). 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

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

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

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CSII or insulin pumps have been available in the U.S. for 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 (88). 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 (89). 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 him or her. 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 (90,91) 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 (91,92). Given the additional barriers to optimal diabetes care observed in disadvantaged groups (93), 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 (94,95). 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 [96] 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).

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 (97); lipohypertrophy or, less frequently, lipoatrophy (98,99); and pump site infection (100). Discontinuation of pump therapy is relatively uncommon today; the frequency has decreased over the past few decades, and its causes have changed (100,101). Current reasons for attrition are problems with cost, wearability, disliking the pump, suboptimal glycemic control, or mood disorders (e.g., anxiety or depression) (102).

Insulin Pumps in Pediatric Patients

The safety of insulin pumps in youth has been established for over 15 years (103). 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 (104) 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 (105,106). Observational studies, registry data, and meta-analysis have also suggested an improvement of glycemic control in participants on CSII (107–109). Although hypoglycemia was a major adverse effect of intensified insulin regimen in the Diabetes Control and Complications Trial (DCCT) (110), data suggest that CSII may reduce the rates of severe hypoglycemia compared with MDI (109,111–113).

There is also evidence that CSII may reduce DKA risk (109,114) and diabetes complications, in particular, retinopathy and peripheral neuropathy in youth, compared with MDI (62). Finally, treatment satisfaction and quality-of-life measures improved on CSII compared with MDI (115,116). 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. In particular, pump therapy may be the preferred mode of insulin delivery for children under 7 years of age (63). 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 idea of having a device on the body, therapeutic effectiveness, and financial burden (107,117).

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

Certain patients with insulin deficiency, for instance those with long standing type 2 diabetes, those who have had a pancreatectomy, and/or individuals with cystic fibrosis may benefit from insulin pump therapy. This is an individual decision and must be tailored to fit patient needs and preferences.

Insulin Pumps in Older Adults

Older individuals with type 1 diabetes benefit from ongoing insulin pump therapy. There is no data to suggest that measurement of C-peptide levels or antibodies predicts success with insulin pump therapy (118,119). Additionally, frequency of follow-up does not influence outcomes. Access to insulin pump therapy should be allowed/continued in older adults as it is for younger people.

Combined Insulin Pump and Sensor Systems

Recommendations

7.25 Sensor-augmented pump therapy with automatic low glucose suspend may be considered for adults and children with type 1 diabetes to prevent/mitigate episodes of hypoglycemia. **B**

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

7.27 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 can 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

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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 (39). 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 (120). 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 (121,122).

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. Emerging evidence suggests such systems may lower the risk of exercise-related hypoglycemia (123) and may have psychosocial benefits (124–127).

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, utilizing a variety of systems with varying algorithms, pump, and sensors have been performed in adults and children (128–138). 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 a real-time CGM with a controller and an algorithm designed to automate insulin delivery (139–141). 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 not prescribed by providers, it is important to keep patients who are using these methods for automated insulin delivery safe. 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

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" (142). 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 HIPAA (U.S. Health Insurance Portability and Accountability Act of 1996) compliant. These programs can be useful for monitoring patients, both by the patients themselves as well as their health care team (143). Consumers should read the policy regarding data privacy and sharing before providing data into an application and learn how they can control how 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 (144). 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 (145,146). 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 (147–149). 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 (150,151). 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

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 (152,153). 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.

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

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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 provider 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.

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8. Obesity Management for the Treatment of Type 2 Diabetes: *Standards of Medical Care in Diabetes—2020*

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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/dc20-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/dc20-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 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 to reduce the need for glucose-lowering medications (6–8). Small studies have demonstrated that in patients with type 2 diabetes and obesity, more extreme dietary energy restriction with very low-calorie diets can reduce A1C to <6.5% (48 mmol/mol) and fasting glucose to <126 mg/dL (7.0 mmol/L) in the absence of pharmacologic therapy or ongoing procedures (10,18,19). The goal of this section is to provide evidence-based recommendations for weight-loss therapy, including diet, behavioral, pharmacologic, and surgical interventions, for obesity management as treatment for hyperglycemia in type 2 diabetes.

ASSESSMENT

Recommendations

8.1 Measure height and weight and calculate BMI at annual visits or more frequently. **E**

8.2 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, specifically focused on the association between medication use, food intake, and glycemic status. **E**

8.3 For patients with a high level of weight-related distress, special accommodations should be made to ensure privacy during weighing. **E**

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Height and weight should be measured and used to calculate BMI at annual visits or more frequently when appropriate (20). BMI can be calculated manually as weight divided by the square of height in meters (kg/m^2) or electronically using the electronic medical record or other resources (20). Clinical considerations, such as the presence of comorbid heart failure or unexplained weight change, may warrant more frequent weight measurement and evaluation (21,22). When weighing is questioned or refused, the practitioner should query for concerns, and the need for weight monitoring should be explained as a part of the medical evaluation process that helps to inform treatment decisions (23,24). If patients report or exhibit a high level of weight-related distress, special accommodations should be made to ensure privacy during weighing. Once calculated, BMI should be classified to determine the presence of overweight or obesity, discussed with the patient, and documented in the patient record. In Asian Americans, the BMI cut points to define overweight and obesity are lower than in other populations (**Table 8.1**) (25,26). Providers should advise patients with overweight or obesity that, in general, higher BMIs increase the risk of cardiovascular disease and all-cause mortality, as well as other adverse health and quality of life outcomes. Providers should assess each patient's readiness to engage in behavioral changes for weight loss and jointly determine weight-loss goals and patient-appropriate intervention strategies (27). Strategies may include dietary changes, physical activity, behavioral therapy, pharmacologic therapy, and metabolic surgery (**Table 8.1**). The latter two strategies may be prescribed for carefully selected patients as adjuncts to diet, physical activity, and behavioral therapy.

DIET, PHYSICAL ACTIVITY, AND BEHAVIORAL THERAPY

Recommendations

8.4 Diet, physical activity, and behavioral therapy designed to achieve and maintain ≥5% weight loss is recommended for 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 factors may be gained from even greater weight loss. **B**

8.5 Such interventions should be high intensity (≥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**

8.6 Individual's motivation, life circumstances, and willingness to make lifestyle changes to achieve weight loss should be assessed along with medical status when weight loss interventions are undertaken. **C**

8.7 As all energy-deficit food intake will result in weight loss, eating plans should be individualized to meet the patient's protein, fat, and carbohydrate needs while still promoting weight loss. **A**

8.8 Food availability should be queried, as well as other cultural circumstances that could affect dietary patterns. **C**

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

8.10 To achieve weight loss of >5%, short-term (3-month) interventions that use very low-calorie diets (≤800 kcal/day) and meal replacements may be prescribed for carefully selected patients by trained practitioners in medical care settings with close medical monitoring. To maintain weight loss, such programs must incorporate long-term comprehensive weight-maintenance counseling. **B**

Among patients with both type 2 diabetes and overweight or obesity who also have inadequate glycemic, blood pressure, and lipid control and/or other obesity-related medical conditions, lifestyle changes that result in modest and sustained weight loss produce clinically meaningful reductions in blood glucose, A1C, and triglycerides (6–8). Greater weight loss produces even greater benefits, including reductions in blood pressure, improvements in LDL and HDL cholesterol, and reductions in the need for medications to control blood glucose, blood pressure, and lipids (6–8,28), and may result in achievement of glycemic goals in the absence of glucose-lowering agent use in some patients (29,30). 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/dc20-S005). For a detailed discussion of nutrition interventions please also refer to "Nutrition Therapy for Adults with Diabetes or Prediabetes: A Consensus Report" (https://doi.org/10.2337/dci19-0014).

Look AHEAD Trial

Although the Action for Health in Diabetes (Look AHEAD) trial did not show that an intensive lifestyle intervention reduced cardiovascular events in adults with type 2 diabetes and overweight or obesity (31), it did show the

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.

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feasibility of achieving and maintaining long-term weight loss in patients with type 2 diabetes. In the Look AHEAD intensive lifestyle intervention group, mean weight loss was 4.7% at 8 years (32). 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 (32). Participants randomly assigned to the intensive lifestyle group achieved equivalent risk factor control but 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 other benefits of weight loss in patients with type 2 diabetes, including improvements in mobility, physical and sexual function, and health-related quality of life (23). A post hoc analysis of the Look AHEAD study suggests that heterogeneous treatment effects may have been present. Participants who had moderately or poorly controlled diabetes (A1C ≥6.8% [51 mmol/mol]) as well as those with well-controlled diabetes (A1C <6.8% [51 mmol/mol]) and good self-reported health were found to have significantly reduced cardiovascular events with intensive lifestyle intervention during follow-up (33).

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. Weight loss of 3–5% is the minimum necessary for clinical benefit (20,34). However, weight-loss benefits are progressive; more intensive weight-loss goals (>5%, >7%, >15%, etc.) may be pursued if needed to achieve a healthy weight and/or if the patient is more motivated and more intensive goals can be feasibly and safely attained.

Dietary interventions may differ in the types of foods they restrict (such as high-fat or high-carbohydrate foods) but are effective if they create the necessary energy deficit (20,35–37). 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 (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 (39).

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 (34). 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 (27).

Patients with type 2 diabetes and overweight or obesity who have lost weight during a 6-month intensive behavioral lifestyle intervention should be enrolled in long-term (≥1 year) comprehensive weight-loss maintenance programs that provide at least monthly contact with a trained interventionist 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 consumption of a reduced-calorie diet; and participation in high levels of physical activity (200–300 min/week) (40). Some commercial and proprietary weight-loss programs have shown promising weight-loss results (41).

When provided by trained practitioners in medical care settings with close medical monitoring, short-term (3-month) interventions that use very low-calorie diets (defined as ≤800 kcal/day) and total meal replacements may achieve greater short-term weight loss (10–15%) than intensive behavioral lifestyle interventions that typically achieve 5% weight loss. However, weight regain following the cessation of very low-calorie diets is greater than regain following intensive behavioral lifestyle interventions unless a long-term comprehensive weight-loss maintenance program is provided (42,43).

PHARMACOTHERAPY

Recommendations

8.11 When choosing glucose-lowering medications for patients with type 2 diabetes and overweight or obesity, consider a medication's effect on weight. **B**

8.12 Whenever possible, minimize medications for comorbid conditions that are associated with weight gain. **E**

8.13 Weight-loss medications are effective as adjuncts to diet, physical activity, and behavioral counseling for selected patients with type 2 diabetes and BMI ≥27 kg/m^2. Potential benefits must be weighed against potential risks of medications. **A**

8.14 If a patient's response to weight-loss medications is <5% weight loss after 3 months or if there are significant safety or tolerability issues at any time, the medication should be discontinued and alternative medications or treatment approaches should be considered. **A**

Glucose-Lowering Therapy

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. Unlike these agents, insulin secretagogues, thiazolidinediones, and insulin often cause weight gain (see Section 9 "Pharmacologic Approaches to Glycemic Treatment," https://doi.org/10.2337/dc20-s009).

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 (44).

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,

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olanzapine, risperidone, etc.) and antidepressants (e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors), glucocorticoids, injectable progestins, anticonvulsants including gabapentin, and possibly sedating antihistamines and anticholinergics (45).

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 (46). Phentermine and other older adrenergic agents are indicated as short-term (≤12 weeks) treatment (47). Five weight-loss medications are FDA approved for long-term use (more than a few weeks) by patients with BMI ≥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 (46). Medications approved by the FDA for the treatment of obesity and their key advantages and disadvantages are summarized in **Table 8.2**. The rationale for weight-loss medication use is to help patients to more consistently adhere to low-calorie diets and to reinforce lifestyle changes. 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. Women of reproductive potential must receive counseling regarding the use of reliable methods of contraception.

Assessing Efficacy and Safety

Efficacy and safety should be assessed at least monthly for the first 3 months of treatment. If a patient's response is deemed insufficient (weight loss <5%) after 3 months or if there are significant safety or tolerability issues at any time, the medication should be discontinued and alternative medications or treatment approaches should be considered.

MEDICAL DEVICES FOR WEIGHT LOSS

Several minimally invasive medical devices have been approved by the FDA for short-term weight loss (48,49). 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

8.15 Metabolic surgery should be recommended as an option to treat type 2 diabetes in screened surgical candidates with BMI ≥40 kg/m^2 (BMI ≥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**

8.16 Metabolic surgery may be considered as an option for adults with type 2 diabetes and 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 tested efficacious nonsurgical methods. **A**

8.17 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**

8.18 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**

8.19 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**

8.20 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 (40) 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 (41), 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 (50–61). Cohort studies attempting to match surgical and nonsurgical subjects suggest that the procedure may reduce longer-term mortality (51).

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) (62–69). Randomized controlled trials have documented diabetes remission during postoperative follow-up ranging from 1 to 5 years in 30–63% of patients with Roux-en-Y gastric bypass (RYGB), which generally leads to greater

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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) (108)	National Average Drug Acquisition Cost (30-day supply) (109)	1-Year (52- or 56-week) mean weight loss (% loss from baseline): Treatment arm	1-Year (52- or 56-week) mean weight loss (% loss from baseline): Weight loss (% loss from baseline)	Common side effects (110–115)	Possible safety concerns/considerations (110–115)
Short-term treatment (≤12 weeks)							
Phentermine (116)	8–37.5 mg q.d.*	$5–$56 (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 BP	• Contraindicated for use in combination with monoamine oxidase inhibitors
Long-term treatment (>12 weeks)							
Lipase inhibitor							
Orlistat (3)	60 mg t.i.d. (OTC)	$41–$82	$43	120 mg t.i.d.‡	9.6	Abdominal pain, flatulence, fecal urgency, back pain, headache	• 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
	120 mg t.i.d. (Rx)	$823	$556	PBO	5.6		
Selective serotonin (5-HT) 5-HT_2C receptor agonist							
Lorcaserin (14)**	10 mg b.i.d.	$360	$288	10 mg b.i.d.	4.5	Headache, nausea, dizziness, fatigue, nasopharyngitis, increased BP	• Serotonin syndrome–like and neuroleptic malignant syndrome–like reactions theoretically possible when coadministered with other serotonergic or antidopaminergic agents • Monitor for depression or suicidal thoughts • Avoid in liver and renal failure
Lorcaserin XR	20 mg q.d.	$360	$287	PBO	1.5		
Sympathomimetic amine anorectic/antiepileptic combination							
Phentermine/topiramate ER (117)	7.5 mg/46 mg q.d.§	$223 (7.5 mg/46 mg dose)	$178 (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 BP	• Birth defects • Cognitive impairment • Acute angle-closure glaucoma
Opioid antagonist/antidepressant combination							
Naltrexone/bupropion ER (15)	8 mg/90 mg, 2 tablets b.i.d.	$334	$268	16 mg/180 mg b.i.d. PBO	5.0 1.8	Constipation, nausea, headache, xerostomia, insomnia	• 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
Glucagon-like peptide 1 receptor agonist							
Liraglutide (16)**	3 mg q.d.	$1,497	$1,199	3.0 mg q.d. 1.8 mg q.d. PBO	6.0 4.7 2.0	Gastrointestinal side effects common (nausea, vomiting, diarrhea), injection site reactions	• ?Acute pancreatitis • Caution when initiating or increasing dose due to potential risk of acute kidney injury **Black box warning:** • Risk of thyroid C-cell tumors

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; BP, blood pressure; ER, extended release; MEN 2, multiple endocrine neoplasia syndrome type 2; MTC, medullary thyroid carcinoma; OTC, over the counter; PBO, placebo; q.d., daily; Rx, prescription; t.i.d., three times daily; XR, extended release. *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 (118,119). ‡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.

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degrees and lengths of remission compared with other bariatric surgeries (17,70). Available data suggest an erosion of diabetes remission over time (71): 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 (72,73). 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 (74,75) to 15 years (51,52,73,76–78).

Exceedingly few presurgical predictors of success have been identified, but younger age, shorter duration of diabetes (e.g., <8 years) (79), 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 (51,77,79,80). 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 (81). 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 (82), and enhancements in quality of life (74,79,83).

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 (84).

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 (85,86).

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 (87–91). Morbidity has also dramatically declined with laparoscopic approaches. Major complications rates (e.g., venous thromboembolism, need for operative reintervention) are 2–6%, with other minor complications in up to 15% (87–96), rates which compare favorably with those for other commonly performed elective operations (91). Empirical data suggest that proficiency of the operating surgeon is an important factor for determining mortality, complications, reoperations, and readmissions (97). 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, rarely, severe hypoglycemia (98). 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 (99,100). Postprandial hypoglycemia is most likely to occur with RYGB (100,101). 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 (98). 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 (102–105).

People with diabetes presenting for metabolic surgery also have increased rates of depression and other major psychiatric disorders (106). Candidates for metabolic surgery with histories of alcohol, tobacco, or substance abuse; 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 (107). 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.

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9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes—2020*

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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 be trained 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 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.

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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.

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 (4–6). More recently, two new 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 (7), and faster-acting insulin aspart may reduce prandial excursions better than RAA (8); 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 (9,10). 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, out of diabetic ketoacidosis, and 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 (11). 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 (12). 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 (12–14). The U.S. Food and Drug Administration (FDA) has also approved the first hybrid closed-loop pump system. The safety and efficacy of hybrid closed-loop systems has been supported in the literature in adolescents and adults with type 1 diabetes (15,16), 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 (17). Intensive insulin management using a version of CSII and continuous glucose monitoring should be considered in most patients. See Section 7 "Diabetes Technology" (https://doi.org/10.2337/dc20-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 (18); 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 (19).

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 (20,21). 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 (22).

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 right way. Recommendations have been published elsewhere outlining best practices for insulin injection (23). 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.

Exogenous-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.

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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 obese adults (24).

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. As referenced above, there are now numerous evidence-based insulin delivery recommendations that have been published. 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 (25,26). Similarly, results have been reported for several agents currently approved only for the treatment of type 2 diabetes. The addition of metformin to adults with type 1 diabetes caused small reductions in body weight and lipid levels but did not improve A1C (27,28). The addition of the glucagon-like peptide 1 (GLP-1) receptor agonists (RAs) liraglutide and 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 (29). 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 (30,31); 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 (32). With the advent of improved continuous glucose monitors, closed-loop pump-sensor systems, and devices that offer alternative approaches for patients with hypoglycemia unawareness, the role of pancreas transplantation alone, as well as islet transplant, will need to be reconsidered.

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 cardiovascular comorbidities, hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences (**Table 9.2** and **Figure 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 (**Figure 9.1**). **A**

9.10 In patients with type 2 diabetes who need greater glucose lowering than can be obtained with oral agents, glucagon-like peptide 1 receptor agonists are preferred to insulin when possible. **B**

9.11 Intensification of treatment for patients with type 2 diabetes not meeting treatment goals should not be delayed. **B**

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**

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 (33,34) recommend a patient-centered

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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 m²	▪ 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)	▪ **FDA Black Box:** Risk of amputation (**canagliflozin**) ▪ Risk of bone fractures (canagliflozin) ▪ DKA risk (all agents, rare in T2DM) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol ▪ Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide Benefit: See label indication of reducing CVD events	Neutral	High	SQ; oral (semaglutide)	Benefit: liraglutide	▪ Renal dose adjustment required (exenatide, lixisenatide) ▪ Caution when initiating or increasing dose due to potential risk of acute kidney injury	▪ **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) ▪ Gastrointestinal side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ ?Acute pancreatitis risk
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	▪ Potential risk of acute pancreatitis ▪ 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; 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			

*For agent-specific dosing recommendations, please refer to the manufacturers' prescribing information. †FDA approved for CVD benefit. ‡FDA-approved for heart failure indication; §FDA-approved for CKD indication. CV, cardiovascular; DPP-4, dipeptidyl peptidase 4; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; HF, heart failure; NASH, nonalcoholic steatohepatitis; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2DM, type 2 diabetes.

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approach to choosing appropriate pharmacologic treatment of blood glucose (**Fig. 9.1**). 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 (HF) (see Section 10 "Cardiovascular Disease and Risk Management," https://doi.org/10.2337/dc20-S010, and Section 11 "Microvascular Complications and Foot Care," https://doi.org/10.2337/dc20-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/dc20-S005) should be emphasized along with any pharmacologic therapy. Section 12 "Older Adults" (https://doi.org/10.2337/dc20-S012) and Section 13 "Children and Adolescents" (https://doi.org/10.2337/dc20-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/dc20-S010) and Section 11 "Microvascular Complications and Foot Care" (https://doi.org/10.2337/dc20-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. Metformin is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death (35). 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 (36); 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 (37). A recent randomized trial confirmed previous observations that metformin use is associated with vitamin B12 deficiency and worsening of symptoms of neuropathy (38). This is compatible with a recent report from the Diabetes Prevention Program Outcomes Study (DPPOS) suggesting periodic testing of vitamin B12 (39).

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/dc20-S006, for selecting appropriate targets), many patients will require dual combination therapy to achieve their target A1C level (40). 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 (41).

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 (42); based on these factors, sequential addition of oral agents to metformin has been the standard of care. However, there is data to support initial combination therapy for more rapid attainment of glycemic goals (43,44), and a recent clinical trial has demonstrated that this approach is superior to sequential addition of medications for extending primary and secondary failure (45). 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 compared with metformin alone and to 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.

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, 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% (46,47). 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), established kidney disease, or heart

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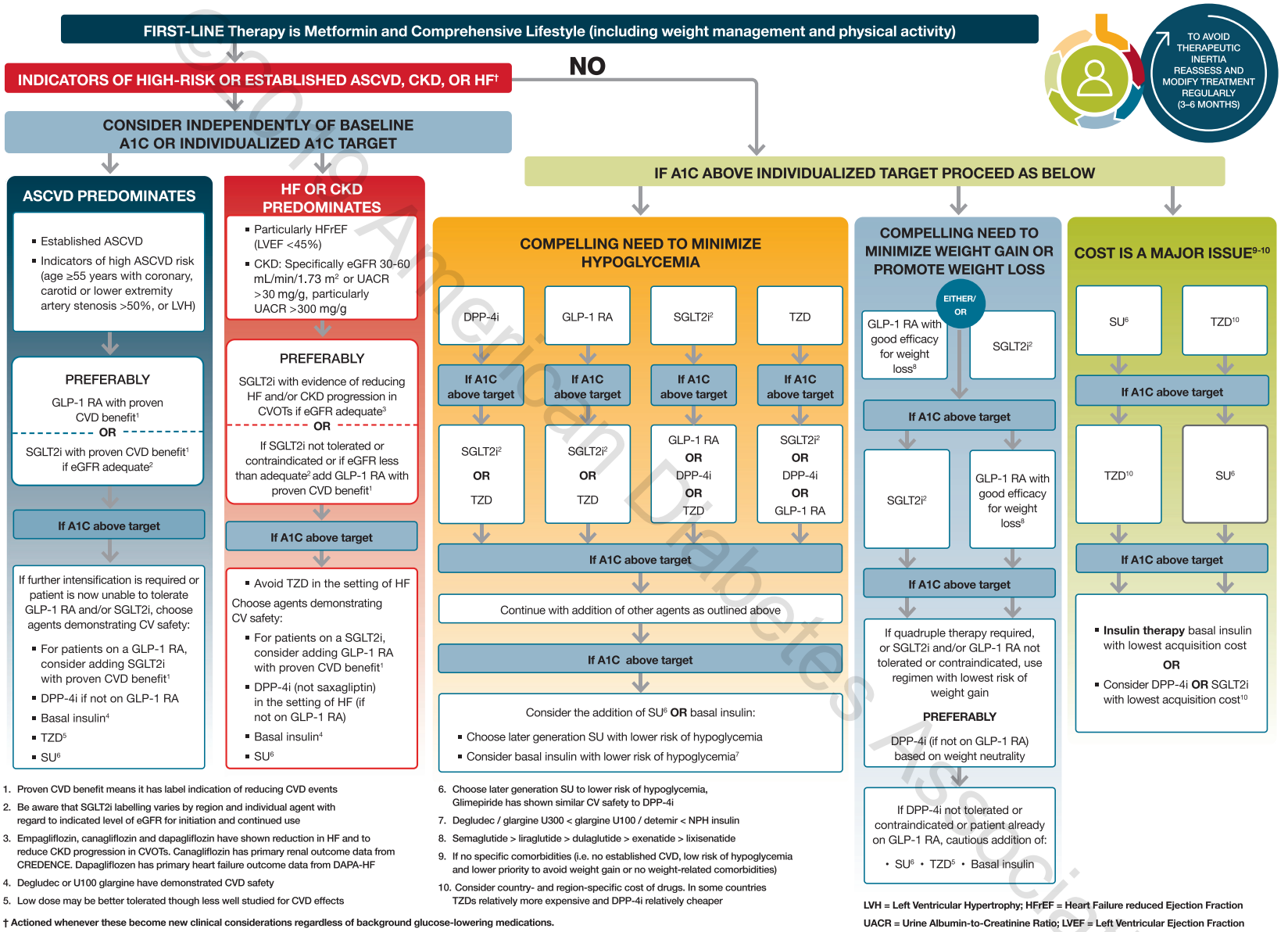

Figure 9.1—Glucose-lowering medication in type 2 diabetes: overall approach. For appropriate context, see **Fig. 4.1**. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. Adapted from Davies and colleagues (33,34).

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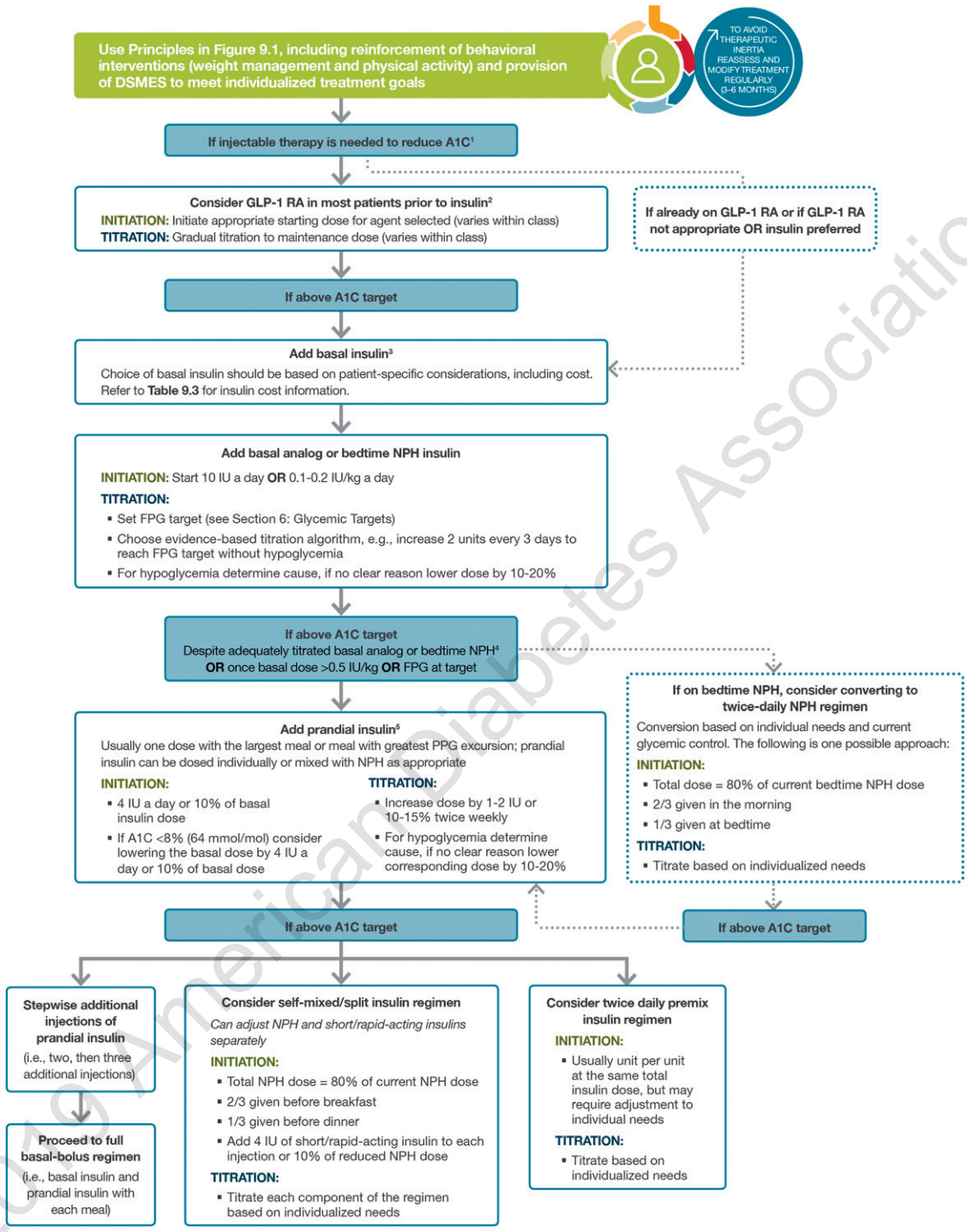

1. Consider insulin as the first injectable if evidence of ongoing catabolism, symptoms of hyperglycemia are present, when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high, or a diagnosis of type 1 diabetes is a possibility.
2. When selecting GLP-1 RA, consider: patient preference, A1C lowering, weight-lowering effect, or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit.
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. (33).

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failure, an SGLT-2 inhibitor or GLP-1 RA with demonstrated CVD 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 (**Figure 9.1**). For patients without established ASCVD, indicators of high ASCVD risk, HF, or CKD, the choice of a second agent to add to metformin is not yet guided by empiric evidence. Rather, drug choice is based on avoidance of side effects, particularly hypoglycemia and weight gain, cost, and patient preferences (48). Similar considerations are applied in patients who require a third agent to achieve glycemic goals; there is very little trial-based evidence to guide this choice. 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/dc20-S012) has a full discussion of treatment considerations in older adults, a setting where changes of glycemic goals and de-escalation of therapy is common.

Although most patients prefer oral medications to drugs that need to be injected, the eventual 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 reaching glycemic targets with use of non-GLP-1 RA oral agent regimens. While most GLP-1 RA products are injectable, an oral formulation of semaglutide is now commercially available (49). In trials comparing the addition of an injectable GLP-1 RAs or insulin in patients needing further glucose lowering, the efficacy of the two treatments was similar (50–52). However, 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 injectable 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 the use of GLP-1 RAs.

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 (53). **Table 9.2** provides cost information for currently approved noninsulin therapies. Of note, prices listed are average wholesale prices (AWP) (54) and National Average Drug Acquisition Costs (NADAC) (55), 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 with medications (56); cost-reducing strategies may improve adherence in some cases (57).

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/dc20-S010) for details. The subjects enrolled in the cardiovascular outcome trials using empagliflozin, canagliflozin, liraglutide, and semaglutide had A1C ≥7%, 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. See Section 11 "Microvascular Complications and Foot Care" (https://doi.org/10.2337/dc20-S011) for a detailed discussion on how CKD may impact treatment choices. Additional large randomized trials of other agents in these classes are ongoing.

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 self-monitoring of blood glucose improves glycemic control in patients with type 2 diabetes initiating insulin (58). 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 (59,60). 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 (61–66), although these advantages are modest and may not persist (67). Longer-acting basal analogs (U-300 glargine or degludec) may convey a lower hypoglycemia risk compared with U-100 glargine when used in combination with oral agents (68–74). 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 (75).

The cost of insulin has been rising steadily over the past two decades, at

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Table 9.2—Median monthly (30-day) cost 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	500 mg (IR)	$84 ($4, $85)	$2	2,000 mg
		850 mg (IR)	$108 ($6, $109)	$3	2,550 mg
		1,000 mg (IR)	$87 ($4, $88)	$2	2,000 mg
		500 mg (ER)	$89 ($87, $7,412)	$5 ($5, $988)	2,000 mg
		750 mg (ER)	$74 ($65, $74)	$4	1,500 mg
		1,000 mg (ER)	$242 ($242, $7,214)	$224 ($224, $910)	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	$15	20 mg (XL)
	• Glyburide	6 mg (micronized)	$50 ($48, $71)	$4	12 mg (micronized)
		5 mg	$93 ($63, $103)	$11	20 mg
Thiazolidinediones	• Pioglitazone	45 mg	$348 ($283, $349)	$4	45 mg
	• Rosiglitazone	4 mg	$407	$330	8 mg
α-Glucosidase inhibitors	• Acarbose	100 mg	$106 ($104, $106)	$23	300 mg
	• Miglitol	100 mg	$241	$311	300 mg
Meglitinides (glinides)	• Nateglinide	120 mg	$155	$39	360 mg
	• Repaglinide	2 mg	$878 ($162, $897)	$39	16 mg
DPP-4 inhibitors	• Alogliptin	25 mg	$234	$168	25 mg
	• Saxagliptin	5 mg	$505	$403	5 mg
	• Linagliptin	5 mg	$523	$419	5 mg
	• Sitagliptin	100 mg	$541	$433	100 mg
SGLT2 inhibitors	• Ertugliflozin	15 mg	$338	$271	15 mg
	• Dapagliflozin	10 mg	$591	$473	10 mg
	• Empagliflozin	25 mg	$591	$473	25 mg
	• Canagliflozin	300 mg	$593	$475	300 mg
GLP-1 RAs	• Exenatide (extended release)	2 mg powder for suspension or pen	$840	$672	2 mg**
	• Exenatide	10 μg pen	$876	$730	20 μg
	• Dulaglutide	1.5/0.5 mL pen	$911	$730	1.5 mg**
	• Semaglutide	1 mg pen	$927	$745	1 mg**
		14 mg (tablet)	$927	N/A	14 mg
	• Liraglutide	18 mg/3 mL pen	$1,106	$886	1.8 mg
	• Lixisenatide	300 μg/3 mL pen	$744	N/A	20 μg
Bile acid sequestrant	• Colesevelam	625 mg tabs	$712 ($674, $712)	$177	3.75 g
		3.75 g suspension	$675	$415	3.75 g
Dopamine-2 agonist	• Bromocriptine	0.8 mg	$906	$729	4.8 mg
Amylin mimetic	• Pramlintide	120 μg pen	$2,623	$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; N/A, data not available; NADAC, National Average Drug Acquisition Cost; SGLT2, sodium–glucose cotransporter 2. †Calculated for 30-day supply (AWP [54] or NADAC [55] 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 μg three times daily.

a pace several fold that of other medical expenditures (76). 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 (76). 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 (75). 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 **Figure 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 (77). 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 (78,79).

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Table 9.3—Median cost of insulin products in the U.S. calculated as AWP (54) and NADAC (55) per 1,000 units of specified dosage form/product

Insulins	Compounds	Dosage form/product	Median AWP (min, max)*	Median NADAC (min, max)*
Rapid-acting	• Lispro follow-on product	U-100 vial	$157	$126
		U-100 prefilled pen	$202	$162
	• Lispro	U-100 vial	$330	$264
		U-100 3 mL cartridges	$408	$327
		U-100 prefilled pen; U-200 prefilled pen	$424	$340
	• Glulisine	U-100 vial	$341	$273
		U-100 prefilled pen	$439	$353
	• Aspart	U-100 vial	$347†	$278†
		U-100 3 mL cartridges	$430	$345
		U-100 prefilled pen	$447†	$358†
	• Inhaled insulin	Inhalation cartridges	$924	$606
Short-acting	• human regular	U-100 vial	$165 ($165, $178)††	$134 ($134, $146)††
Intermediate-acting	• human NPH	U-100 vial	$165 ($165, $178)††	$135 ($135, $146)††
		U-100 prefilled pen	$377	$304
Concentrated human regular insulin	• U-500 human regular insulin	U-500 vial	$178	$144
		U-500 prefilled pen	$230	$184
Long-acting	• Glargine follow-on product	U-100 prefilled pen	$261	$210
	• Glargine	U-100 vial; U-100 prefilled pen	$340	$272
		U-300 prefilled pen	$346	$280
	• Detemir	U-100 vial; U-100 prefilled pen	$370	$295
	• Degludec	U-100 vial; U-100 prefilled pen; U-200 prefilled pen	$407	$326
Premixed insulin products	• NPH/regular 70/30	U-100 vial	$165 ($165, $178)	$134 ($134, $145)
		U-100 prefilled pen	$377	$303
	• Lispro 50/50	U-100 vial	$342	$274
		U-100 prefilled pen	$424	$338
	• Lispro 75/25	U-100 vial	$342	$274
		U-100 prefilled pen	$424	$340
	• Aspart 70/30	U-100 vial	$360	$289
		U-100 prefilled pen	$447	$358
Premixed insulin/GLP-1 RA products	• Glargine/Lixisenatide	100/33 prefilled pen	$565	$454
	• Degludec/Liraglutide	100/3.6 prefilled pen	$832	$668

AWP, average wholesale price; GLP-1, glucagon-like peptide 1; NADAC, National Average Drug Acquisition Cost. *AWP or NADAC calculated as in **Table 9.2**. †Inclusive of both the original and "faster-acting" products. ††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.

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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 (80). 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 (81,82). The FDA has also approved a concentrated formulation of rapid-acting insulin lispro, U-200 (200 units/mL). 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 (a dedicated syringe was approved in July 2016), other concentrated insulins are available only in prefilled pens to minimize the risk of dosing errors.

Inhaled Insulin

Inhaled insulin is available for prandial use with a limited dosing range; studies in people with type 1 diabetes suggest rapid pharmacokinetics (7). 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 (83), 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 (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) 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 (84–86). 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 (87). 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 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/dc20-S012).

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10. Cardiovascular Disease and Risk Management: *Standards of Medical Care in Diabetes—2020*

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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/dc20-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/dc20-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/dc20-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).

For prevention and management of both ASCVD and heart failure, cardiovascular risk factors should be systematically assessed at least annually in all patients

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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.

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 ASCVD risk (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 ≤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

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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 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).

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

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 (174)
HOT (185)	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 (39)	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).

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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 (35). 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 (36).

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 (11,37). 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 (38).

Potential adverse effects of antihypertensive therapy (e.g., hypotension, syncope, falls, acute kidney injury, and electrolyte abnormalities) should also be taken into account (28,39–41). 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. Therefore, current evidence supports controlling blood pressure to these levels, with a target of ≤135/85 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).

During pregnancy, treatment with ACE inhibitors, angiotensin receptor blockers (ARBs), 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/dc20-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 if overweight or obese, 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, restricting sodium intake (<2,300 mg/day), increasing consumption of fruits

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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 (ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers). **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), ARBs (54,55), thiazide-like diuretics (56), or dihydropyridine calcium channel blockers (57). 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 (58). β-Blockers may be used for the treatment of prior MI, active angina, or heart failure but have not been shown to reduce mortality as blood pressure–lowering agents in the absence of these conditions (23,59).

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) (60–62). Titration of and/or addition of further blood pressure medications should be made in a timely fashion to overcome clinical 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 (63). In two subgroup analyses of a single subsequent randomized controlled trial, moving at least one antihypertensive medication to bedtime significantly reduced cardiovascular events, but results were based on a small number of events (64).

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) (65,66). Detection and management of these abnormalities is important because AKI and hyperkalemia each increase the risks of cardiovascular events and death (67). 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 (65,66,68).

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

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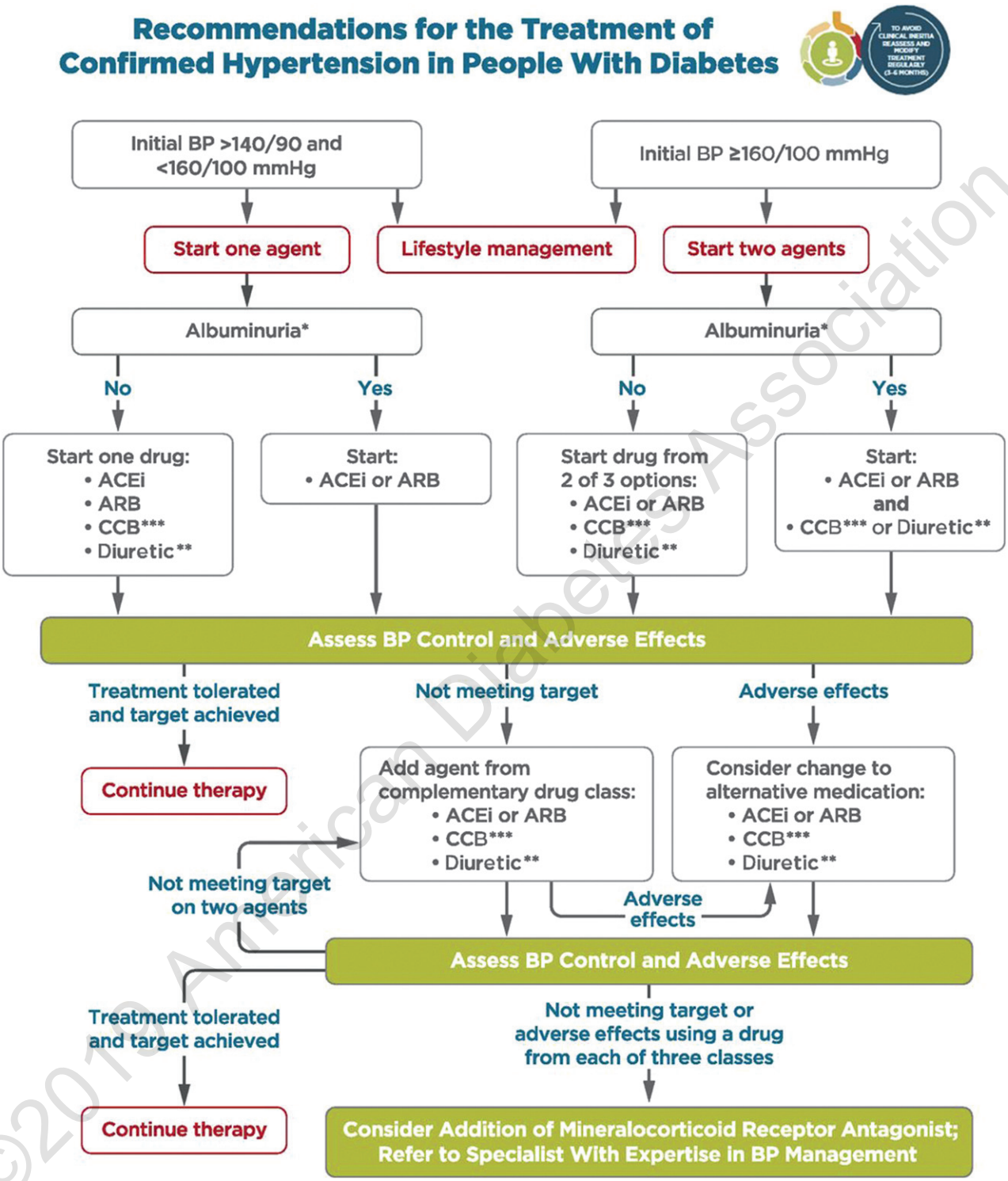

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Figure 10.1—Recommendations for the treatment of confirmed hypertension in people with diabetes. *An ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB) is suggested to treat hypertension for patients with urine albumin-to-creatinine ratio 30–299 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).

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 (69). Mineralocorticoid receptor antagonists also reduce albuminuria and have additional cardiovascular benefits (70–73). 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 (74), 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 (75) 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 (76). 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/dc20-S010) 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 (77). 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 (78).

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**

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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 (79,80). Subgroup analyses of patients with diabetes in larger trials (81–85) and trials in patients with diabetes (86,87) 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 mmol/L (39 mg/dL) reduction in LDL cholesterol (88).

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 (89,90). The *relative* benefit of lipid-lowering therapy has been uniform across most subgroups tested (80,88), 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 (82,89,90), 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 (12,91). 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 (80,87,88), and because older age confers higher risk, the absolute benefits are actually greater (80,92). 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 dose performed as needed. See Section 12 "Older Adults" (https://doi.org/10.2337/dc20-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/dc20-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 (82). 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

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.

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American Diabetes Association" (93) 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 (88,92,94,95). 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 (80,84,94).

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 (92,96) and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (95). 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 (97).

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, 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 (92). 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 (96).

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 (98,99).

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 (95). 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) (100).

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**

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Hypertriglyceridemia should be addressed with dietary and lifestyle changes including weight loss and abstinence from alcohol (101). Severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL and especially >1,000 mg/dL) may warrant pharmacologic therapy (fibric acid derivatives and/or fish oil) 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. 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 (102).

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 (103). In a large trial in patients with diabetes, fenofibrate failed to reduce overall cardiovascular outcomes (104).

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) (105).

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) (106). A prospective trial of a newer fibrate in this specific population of patients is ongoing (107).

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 (108).

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 (109). 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 DP_1 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 (110,111), 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 (112). The absolute

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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) (112). 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 (111).

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 (113). 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 (114–117). In addition, no change in cognitive function has been reported in studies with the addition of ezetimibe (92) or PCSK9 inhibitors (95,118) 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 (119). 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 (119).

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 **A** and may have benefits beyond this period. **B**

10.37 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 (120,121).

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 (122–124).

The Antithrombotic Trialists' Collaboration published an individual patient–level meta-analysis (120) 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 (125). 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]) (126) and in the elderly (ASPREE [Aspirin in Reducing Events in the Elderly]) (127), 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 persons, for the rate of 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 (128).

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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) (129–132). Noninvasive imaging techniques such as coronary calcium scoring may potentially help further tailor aspirin therapy, particularly in those at low risk (133) (134). For patients over the age of 70 years (with or without diabetes), the balance appears to have greater risk than benefit (125,127). 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 (120).

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 (135). 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 (136). 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 (137). "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) (138), but other studies suggest no impairment in aspirin response among patients with diabetes (139). A recent trial suggested that more frequent dosing regimens of aspirin may reduce platelet reactivity in individuals with diabetes (140); 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 (141); however, the ASCEND trial found benefit of low-dose aspirin in those in this weight range, which would thus not validate this suggested hypothesis (125). 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 (142). 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 (143).

CARDIOVASCULAR DISEASE

Screening

Recommendations

10.38 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**

10.39 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

10.40 In patients with known atherosclerotic cardiovascular disease, consider ACE inhibitor or angiotensin receptor blocker therapy to reduce the risk of cardiovascular events. **B**

10.41 In patients with prior myocardial infarction, β-blockers should be continued for at least 2 years after the event. **B**

10.42 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 but should be avoided in unstable or hospitalized patients with heart failure. **B**

10.43 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 glucose-lowering regimen. **A**

10.43a 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

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cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events and heart failure hospitalization. **A**

10.43b 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**

10.43c In patients with type 2 diabetes and established heart failure, a sodium–glucose cotransporter 2 inhibitor may be considered to reduce risk of heart failure hospitalization. **C**

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 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 (144), in part because these high-risk patients should already be receiving intensive medical therapy—an approach that provides similar benefit as invasive revascularization (145,146). There is also some evidence that silent ischemia may reverse over time, adding to the controversy concerning aggressive screening strategies (147). 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 (148–150). However, a randomized observational trial demonstrated no clinical benefit to routine screening of asymptomatic patients with type 2 diabetes and normal ECGs (151). 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 (152,153).

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 (148,154,155), 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 (156), 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 (157). 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. While clear benefit exists for ACE inhibitor or ARB therapy in patients with diabetic kidney disease or hypertension, the benefits in patients with ASCVD in the absence of these conditions are less clear, especially when LDL cholesterol is concomitantly controlled (158,159). In patients with prior MI, active angina, or HFrEF, β-blockers should be used (160).

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 (161). Previously approved diabetes medications were not subject to the guidance. Recently published cardiovascular outcomes trials have provided additional data on cardiovascular 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***). Cardiovascular outcomes trials of dipeptidyl peptidase 4 (DPP-4) inhibitors have all, so far, not shown cardiovascular benefits relative to placebo. 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) trial 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,

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Table 10.3A—Cardiovascular outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: DPP-4 inhibitors

	SAVOR-TIMI 53 (181) (n = 16,492)	EXAMINE (186) (n = 5,380)	TECOS (183) (n = 14,671)	CARMELINA (184,187) (n = 6,979)
Intervention	Saxagliptin/placebo	Alogliptin/placebo	Sitagliptin/placebo	Linagliptin/placebo
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
A1C inclusion criteria (%)	≥6.5	6.5–11.0	6.5–8.0	6.5–10.0
Age (years)††	65.1	61.0	65.4	65.8
Race (% white)	75.2	72.7	67.9	80.2
Sex (% male)	66.9	67.9	70.7	62.9
Diabetes duration (years)††	10.3	7.1	11.6	14.7
Median follow-up (years)	2.1	1.5	3.0	2.2
Statin use (%)	78	91	80	71.8
Metformin use (%)	70	66	82	54.8
Prior CVD/CHF (%)	78/13	100/28	74/18	57/26.8
Mean baseline A1C (%)	8.0	8.0	7.2	7.9
Mean difference in A1C between groups at end of treatment (%)	−0.3^	−0.3^	−0.3^	−0.36^
Year started/reported	2010/2013	2009/2013	2008/2015	2013/2018
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)
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)
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)
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)
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)
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)
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)
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)
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. (188) 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 ($P < 0.05$).

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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 (162). 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 (163). 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

Table 10.3*B*—Cardiovascular outcomes trials of available antihyperglycemic medications completed after the issuance of the FDA 2008 guidelines: GLP-1 receptor agonists

	ELIXA (170) (n = 6,068)	LEADER (165) (n = 9,340)	SUSTAIN-6 (166)* (n = 3,297)	EXSCEL (171) (n = 14,752)	Harmony Outcomes (168) (n = 9,463)	REWIND (169) (n = 9,901)
Intervention	Lixisenatide/ placebo	Liraglutide/ placebo	Semaglutide/ placebo	Exenatide QW/ placebo	Albiglutide/ placebo	Dulaglutide/ 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
A1C inclusion criteria (%)	5.5–11.0	≥7.0	≥7.0	6.5–10.0	≥7.0	≤9.5
Age (years)††	60.3	64.3	64.6	62	64.1	66.2
Race (% white)	75.2	77.5	83.0	75.8	84.8	75.7
Sex (% male)	69.3	64.3	60.7	62	69.4	53.7
Diabetes duration (years)††	9.3	12.8	13.9	12	13.8	10.5
Median follow-up (years)	2.1	3.8	2.1	3.2	1.6	5.4
Statin use (%)	93	72	73	74	84.0	66
Metformin use (%)	66	76	73	77	73.6	81
Prior CVD/CHF (%)	100/22	81/18	60/24	73.1/16.2	100/20.2	32/9
Mean baseline A1C (%)	7.7	8.7	8.7	8.0	8.7	7.4
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^
Year started/ reported	2010/2015	2010/2016	2013/2016	2010/2017	2015/2018	2011/2019
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)
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)
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)
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)
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)
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)
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)

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Table 10.3*B*—Continued

	ELIXA (170) (n = 6,068)	LEADER (165) (n = 9,340)	SUSTAIN-6 (166)* (n = 3,297)	EXSCEL (171) (n = 14,752)	Harmony Outcomes (168) (n = 9,463)	REWIND (169) (n = 9,901)
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)
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. (188) 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. ˆSignificant difference in A1C between groups ($P < 0.05$).

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 (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 (162). The primary outcome was a composite of end-stage kidney disease (ESKD), 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 ESKD 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]) (162).

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 (164). 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.

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; $P = 0.007$) (165). 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.

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Table 10.3C—Cardiovascular 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 (9) (n = 4,330)	CANVAS (9) (n = 5,812)	DECLARE-TIMI 58 (164) (n = 17,160)
Intervention	Empagliflozin/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
A1C inclusion criteria (%)	7.0–10.0	7.0–10.5		≥6.5
Age (years)††	63.1	63.3		64.0
Race (% white)	72.4	78.3		79.6
Sex (% male)	71.5	64.2		62.6
Diabetes duration (years)††	57% >10	13.5		11.0
Median follow-up (years)	3.1	5.7	2.1	4.2
Statin use (%)	77	75		75 (statin or ezetimibe use)
Metformin use (%)	74	77		82
Prior CVD/CHF (%)	99/10	65.6/14.4		40/10
Mean baseline A1C (%)	8.1	8.2		8.3
Mean difference in A1C between groups at end of treatment (%)	−0.3‡	−0.58*		−0.43*
Year started/reported	2010/2015	2009/2017		2013/2018
Primary outcome§	3-point MACE 0.86 (0.74–0.99)	3-point MACE 0.86 (0.75–0.97)§	Progression to albuminuria** 0.73 (0.47–0.77)	3-point MACE 0.93 (0.84–1.03) CV death or HF hospitalization 0.83 (0.73–0.95)
Key secondary outcome§	4-point MACE	All-cause and CV mortality (see below)	40% reduction in composite eGFR, renal replacement, renal death 0.60 (0.47–0.77)	Death from any cause 0.93 (0.82–1.04) Renal composite (≥40% decrease in eGFR rate to <60 mL/min/1.73m^2, new ESRD, or death from renal or CV causes 0.76 (0.67–0.87)
Cardiovascular death§	0.62 (0.49–0.77)	0.96 (0.77–1.18)¶ 0.87 (0.72–1.06)#		0.98 (0.82–1.17)
MI§	0.87 (0.70–1.09)	0.85 (0.65–1.11)	0.85 (0.61–1.19)	0.89 (0.77–1.01)
Stroke§	1.18 (0.89–1.56)	0.97 (0.70–1.35)	0.82 (0.57–1.18)	1.01 (0.84–1.21)
HF hospitalization§	0.65 (0.50–0.85)	0.77 (0.55–1.08)	0.56 (0.38–0.83)	0.73 (0.61–0.88)
Unstable angina hospitalization§	0.99 (0.74–1.34)	—		—
All-cause mortality§	0.68 (0.57–0.82)	0.87 (0.74–1.01)‡‡ 0.90 (0.76–1.07)##		0.93 (0.82–1.04)
Worsening nephropathy§||	0.61 (0.53–0.70)	0.60 (0.47–0.77)		0.53 (0.43–0.66)

—, 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. Data from this table was adapted from Cefalu et al. (188) in the January 2018 issue of *Diabetes Care*. **On the basis of prespecified outcomes, the renal outcomes are not viewed as statistically significant. ††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. ‡AlC 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). ||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 EMPA-REG OUTCOME and as ≥40% decrease in estimated glomerular filtration rate to <60 mL/min/1.73 m^2, ESRD, or death from renal cause in DECLARE-TIMI 58. Worsening nephropathy was a prespecified exploratory adjudicated outcome in DECLARE-TIMI 58 but not in EMPA-REG OUTCOME. ¶Truncated data set (prespecified in treating hierarchy as the principal data set for analysis for superiority of all-cause mortality and cardiovascular death in the CANVAS Program). *Significant difference in A1C between groups ($P < 0.05$). #Nontruncated data set. ‡‡Truncated integrated data set (refers to pooled data from CANVAS after 20 November 2012 plus CANVAS-R; prespecified in treating hierarchy as the principal data set for analysis for superiority of all-cause mortality and cardiovascular death in the CANVAS Program). ##Nontruncated integrated data (refers to pooled data from CANVAS, including before 20 November 2012 plus CANVAS-R).

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Results from a moderate-sized trial of another GLP-1 receptor agonist, semaglutide, were consistent with the LEADER trial (166). 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 initial 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 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 myocardial infarction, or nonfatal stroke (HR 0.79; 95% CI 0.57–1.11; $P <$ 0.001 for noninferiority) (167). 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) (168). 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 (169). Study participants had a mean age of 66 years and a mean duration of diabetes of ~10 years. Approximately 32% of participants had prior history of atherosclerotic cardiovascular events at baseline. After a median follow-up of 5.4 years, the primary composite outcome of nonfatal myocardial infarction, 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 prior 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 (170). 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 (171). 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 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 (172). 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 (173). 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 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

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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 (174). 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 (175–177). 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 (178). 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 (179). 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 (180).

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) (181). However, three other cardiovascular outcomes trials, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) (182), Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) (183), and the Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA) (184) 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 QW, albiglutide, or dulaglutide compared with placebo (**Table 10.3*B***) (165,166,169–171).

Reduced incidence of heart failure has been observed with the use of SGLT2 inhibitors (162,164). 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 (9,164). 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) (162). 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. They also suggest, but do not prove, that SGLT2 inhibitors may be beneficial in patients with established heart failure. This hypothesis is being specifically evaluated in several large outcomes trials in patients with established heart failure, both with and without diabetes, to determine the efficacy of SGLT2 inhibitors in the treatment of heart failure with reduced and preserved ejection fraction.

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11. Microvascular Complications and Foot Care: *Standards of Medical Care in Diabetes—2020*

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For prevention and management of diabetes complications in children and adolescents, please refer to Section 13 "Children and Adolescents" (https://doi.org/10.2337/dc20-S013).

CHRONIC KIDNEY DISEASE

Screening

Recommendations

11.1 At least once a year, assess urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and estimated glomerular filtration rate (eGFR) in patients with type 1 diabetes with duration of ≥5 years and in all patients with type 2 diabetes regardless of treatment. **B** Patients with urinary albumin >30 mg/g creatinine and/or an eGFR <60 mL/min/1.73 m^2 should be monitored twice annually to guide therapy. **C**

Treatment

Recommendations

11.2 Optimize glucose control to reduce the risk or slow the progression of chronic kidney disease. **A**

11.3 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 >30 mg/g creatinine, particularly in those with urinary albumin >300 mg/g creatinine, to reduce risk of chronic kidney disease (CKD) progression, cardiovascular events, or both. **A** In patients with CKD who are at increased risk for cardiovascular events, use of a glucagon-like peptide 1 receptor agonist may reduce risk of progression of albuminuria, cardiovascular events, or both (**Table 9.1**). **C**

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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. **B**

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 will be 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.

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). 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 (1,2,10,11). Exercise within 24 h, infection, fever, congestive heart failure, marked hyperglycemia, menstruation, and marked hypertension may elevate UACR independently of kidney damage (12).

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 (2,13).

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. (3,4,14,15).

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 (16).

Staging of Chronic Kidney Disease

Stages 1–2 CKD have been defined by evidence of high albuminuria with

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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 or 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. (188).

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eGFR ≥60 mL/min/1.73 m^2, while stages 3–5 CKD have been defined by progressively lower ranges of eGFR (17) (**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**) (18,19). The degree of albuminuria may influence choice of antihypertensive (see Section 10 "Cardiovascular Disease and Risk Management," https://doi.org.10.2337/dc20-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 (20).

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 (21,22). People with diabetes are at higher risk of AKI than those without diabetes (23). 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 (24) or high cardiovascular disease risk with normal kidney function (25–27). Timely identification and treatment of AKI is important because AKI is associated with increased risks of progressive CKD and other poor health outcomes (28).

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 (29). 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 (30–32). Moreover, a measure of markers for AKI showed no significant increase of any markers with increased creatinine (32). Accordingly, ACE inhibitors

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 electrolytes
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.

and ARBs should not be discontinued for minor increases in serum creatinine (<30%), in the absense 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 (33–35). 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 achieving 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 ≥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 (36,37).

The prevalence of CKD complications correlates with eGFR (38). 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/dc20-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 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 (39).

Restriction of dietary sodium (to <2,300 mg/day) may be useful to control blood pressure and reduce cardiovascular risk (40,41), and restriction of dietary potassium may be necessary to control serum potassium concentration (23,33–35). 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 (42). 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 (43,44) and type 2 diabetes (1,45–51). 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 (52,53). 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 (49,54,55). Therefore, in some patients with prevalent CKD and substantial comorbidity, target A1C levels may be less intensive (1,56).

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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 (26,57–60). 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 (61–63). 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 (64–67). Renal effects should be considered when selecting antihyperglycemia agents (see Section 9 "Pharmacologic Approaches to Glycemic Treatment," https://doi.org/10.2337/dc20-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 (68,69). 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 (70), 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 <45 mL/min/1.73 m^2; 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.

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) (59,64,67,71). 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 (27,66) and in CANVAS were similar for participants with or without atherosclerotic cardiovascular disease (ASCVD) at baseline (72).

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 End points 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, has a primary composite end point of ESRD, doubling of serum creatinine, or renal or cardiovascular death (24,73). It was stopped early due to positive efficacy and showed a 32% risk reduction for development of ESRD over control (24). 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 (24). 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 (24,74).

In addition to renal effects, some SGLT2 inhibitors and GLP-1 RAs have demonstrated cardiovascular benefits. Namely, in EMPA-REG OUTCOME, CANVAS, and LEADER, empagliflozin, canagliflozin, and liraglutide, 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/dc20-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

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and cardiovascular benefits were still seen down to eGFR levels of 30 mL/min/1.73 m^2 with no significant change in glucose (24,26,43,45,52,56,71). 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 (27).

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 even independent of glucose-lowering effects (75).

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 to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease) trial with injectable semaglutide (76). 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 canagliflozin, 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) (26,27,77). 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 (78). Antihypertensive therapy reduces the risk of albuminuria (79–82), 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 (83–85). Moreover, antihypertensive therapy reduces risks of cardiovascular events (79).

Blood pressure levels <140/90 mmHg are generally recommended to reduce CVD mortality and slow CKD progression among all people with diabetes (82). 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/day 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 (83–86). In general, ACE inhibitors and ARBs are considered to have similar benefits (87,88) 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 (86,89). 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) (90,91).

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 (92). 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 (93). 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 (90) This was further supported by a similar trial in patients with type 2 diabetes (91). *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) (94,95). *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 (96–98). 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 (99). However, other specialists and providers should

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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**

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**

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 ranibizumab 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**

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 (100). 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 (101), nephropathy (102), hypertension (103), and dyslipidemia (104). 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 (46,105–107).

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 (108,109). Laser photocoagulation surgery can minimize the risk of vision loss (109).

Screening

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 (110). 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

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examination (111). Less frequent intervals have been found in simulated modeling to be potentially effective in screening for diabetic retinopathy in patients without diabetic retinopathy (112). 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 (105,106). 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 (113,114). 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 (115). 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 (116).

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 (117,118). 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 (109). 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 (119).

Treatment

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 (120) 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 followup (121). 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 (122) 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 laser (123,124). There are currently three anti-VEGF agents commonly used to treat eyes with central-involved diabetic macular edema—bevacizumab, ranibizumab, and aflibercept (100).

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 (125). 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.

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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 (106). ACE inhibitors and ARBs are both effective treatments in diabetic retinopathy (126). In patients with dyslipidemia, retinopathy progression may be slowed by the addition of fenofibrate, particularly with very mild nonproliferative diabetic retinopathy at baseline (104,127).

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**

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**

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. Numerous treatment options exist for symptomatic diabetic neuropathy.
3. Up to 50% of diabetic peripheral neuropathy (DPN) 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.
4. 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 DPN and cardiac autonomic neuropathy (CAN) in type 1 diabetes (128,129) and may modestly slow their progression in type 2 diabetes (48), 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 (130) 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 (130). 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 (131). See the American Diabetes Association (ADA) position statement "Diabetic Neuropathy" for more details (130).

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 (132,133). 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

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>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 (130). 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 (134). 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

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 (135–138). 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 (48,139). 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 (140).

Neuropathic Pain

Neuropathic pain can be severe and can impact quality of life, limit mobility, and contribute to depression and social dysfunction (141). 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 (142).

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 (143). 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 (144–146).

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 (143,145,147–150). However, not all trials with pregabalin have been positive (143,145,151,152), especially when treating patients with advanced refractory DPN (149). Adverse effects may be more severe in older patients (153) 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 (154).

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 (143,145,150,152). Duloxetine also appeared to improve neuropathy-related quality of life (155). In longer-term studies, a small increase in A1C was reported in people with diabetes treated with duloxetine compared with placebo (156). Adverse events may be more severe in older people but may be attenuated with lower doses and slower titrations 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 (157,158). 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 (143). 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 (130,143,145).

Orthostatic Hypotension

Treating orthostatic hypotension is challenging. The therapeutic goal is to minimize postural symptoms rather than

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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 (159–161). 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 (162–164). In addition, foods with small particle size may improve key symptoms (165). 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 (162,166). 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 (166). Other treatment options include domperidone (available outside of the U.S.) and erythromycin, which is only effective for short-term use due to tachyphylaxis (167,168). 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 (169).

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 sufficient good-quality evidence to support use of appropriate therapeutic footwear with demonstrated pressure relief that is worn by the patient to prevent plantar

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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 (170). 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 (171).

Clinicians are encouraged to review ADA screening recommendations for further details and practical descriptions of how to perform components of the comprehensive foot examination (172).

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 (173,174). 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 peripheral arterial disease 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 (130,175).

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 (176). 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 (173,176).

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 (177). 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 (177).

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 (178–181). 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 (182). 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

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challenges as randomized controlled studies remain few, with a majority being of poor quality (179). Thus, HBOT does not have a significant effect on health-related quality of life in patients with diabetic foot ulcers (183,184). 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 (185). 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 (186). 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 (187), 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 (187).

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12. Older Adults: *Standards of Medical Care in Diabetes—2020*

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/dc20-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/dc20-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 an important health condition for the aging population. Approximately one-quarter of people over the age of 65 years have diabetes and one-half of older adults have prediabetes (1), 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 (2–4). At the same time, older adults with diabetes also are 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 (5). 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/dc20-S004) for comorbidities to consider when caring for older adults with diabetes.

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The comprehensive assessment described above may provide a framework to determine targets and therapeutic approaches (8–10), including whether referral for 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), 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 (15,16).

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 (17). 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 (18–20).

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 (21), 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) (see **Table 4.1** for cognitive screening recommendations). Several simple assessment tools are available to screen for cognitive impairment (22,23), such as the Mini-Mental State Examination (24), Mini-Cog (25), and the Montreal Cognitive Assessment (26), 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 (4,27). 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 (28).

HYPOGLYCEMIA

Recommendation

12.4 Hypoglycemia should be avoided in older adults with diabetes. It should be assessed and managed by adjusting glycemic targets and pharmacologic regimens. **B**

Older adults are at higher risk of hypoglycemia for many reasons, including insulin deficiency necessitating insulin therapy and progressive renal insufficiency (29). 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 (30,31). Therefore, as discussed under 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 should be monitored for hypoglycemia; glycemic targets and pharmacologic regimens may need to be adjusted to minimize the occurrence of hypoglycemic events (2). Of note, it is important to prevent hypoglycemia to reduce the risk of cognitive decline (30) and other major adverse outcomes (32). Intensive glucose control in the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes study (ACCORD-MIND) was not found to benefit brain structure or cognitive function during follow-up (15). In the Diabetes Control and Complications Trial (DCCT), no significant long-term declines in cognitive function were observed, despite participants' relatively high rates of recurrent severe hypoglycemia (33). To achieve the appropriate balance between glycemic control and risk for hypoglycemia, it is important to carefully assess and reassess patients' risk for worsening of glycemic control and functional decline.

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TREATMENT GOALS

Recommendations

12.5 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 <7.5% [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**

12.6 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**

12.7 Screening for diabetes complications should be individualized in older adults. Particular attention should be paid to complications that would lead to functional impairment. **C**

12.8 Treatment of hypertension to individualized target levels is indicated in most older adults. **C**

12.9 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 (34). Some older adults with diabetes have other underlying chronic conditions, substantial diabetes-related comorbidity, limited cognitive or physical functioning, or frailty (35,36). Other older individuals with diabetes have little comorbidity and are active. Life expectancies are highly variable but are often longer than clinicians realize. 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/dc20-S002, for additional details on the limitations of A1C) (37). 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 with functional limitations and can falsely increase or decrease A1C. In these instances, plasma blood glucose and fingerstick 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 (3,28).

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 reduce the burdens and avoid the side effects 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 (38). There is, however, no consensus for the management of type 1 diabetes in this scenario (39). See 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 (40,41), 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.

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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	<7.5% (58 mmol/mol)	90–130 mg/dL (5.0–7.2 mmol/L)	90–150 mg/dL (5.0–8.3 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 dependencies)	Limited remaining life expectancy makes benefit uncertain	<8.5%† (69 mmol/mol)	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 (secondary prevention more so than primary)

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 (54). **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. †A1C of 8.5% (69 mmol/mol) equates to an estimated average glucose of ~200 mg/dL (11.1 mmol/L). Looser A1C targets above 8.5% (69 mmol/mol) are not recommended, as they may expose patients to more frequent higher glucose values and acute risks from glycosuria, dehydration, hyperglycemic hyperosmolar syndrome, and poor wound healing. Adapted from Kirkman et al. (2).

LIFESTYLE MANAGEMENT

Recommendation

12.10 Optimal nutrition and protein intake is recommended for older adults; regular exercise, including aerobic activity and resistance training, should be encouraged in all older adults who can safely engage in such activities. **B**

Diabetes in the aging population is associated with reduced muscle strength, poor muscle quality, and accelerated loss of muscle mass, resulting in sarcopenia (42,43). 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 to clinical, 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 (44,45).

PHARMACOLOGIC THERAPY

Recommendations

12.11 In older adults with type 2 diabetes at increased risk of hypoglycemia, medication classes with low risk of hypoglycemia are preferred. **B**

12.12 Overtreatment of diabetes is common in older adults and should be avoided. **B**

12.13 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**

12.14 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 (46). 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

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agents. Cost may be an important consideration, especially as older adults tend to be on many medications and live on fixed incomes (47). Accordingly, the costs of care and insurance coverage rules should be considered when developing treatment plans to reduce the risk of cost-related nonadherence (48,49). See **Tables 9.2** and **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 testing 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. 6.3**) 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 overtreatment and is associated with an increased risk of hypoglycemia; unfortunately, overtreatment is common in clinical practice (50–54). Deintensification of regimens in patients taking noninsulin glucose-lowering medications can be achieved by either lowering the dose or discontinuing some medications, so long as the individualized glycemic target is 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 (55). 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 (56–58). **Fig. 12.1** depicts an algorithm that can be used to simplify the insulin regimen (56). There are now multiple studies evaluating deintensification protocols; in general, the studies demonstrate that deintensification is safe and possibly beneficial for older adults (59). **Table 12.2** provides examples of and rationale for situations where deintensification and/or insulin regimen simplification may be appropriate in older adults.

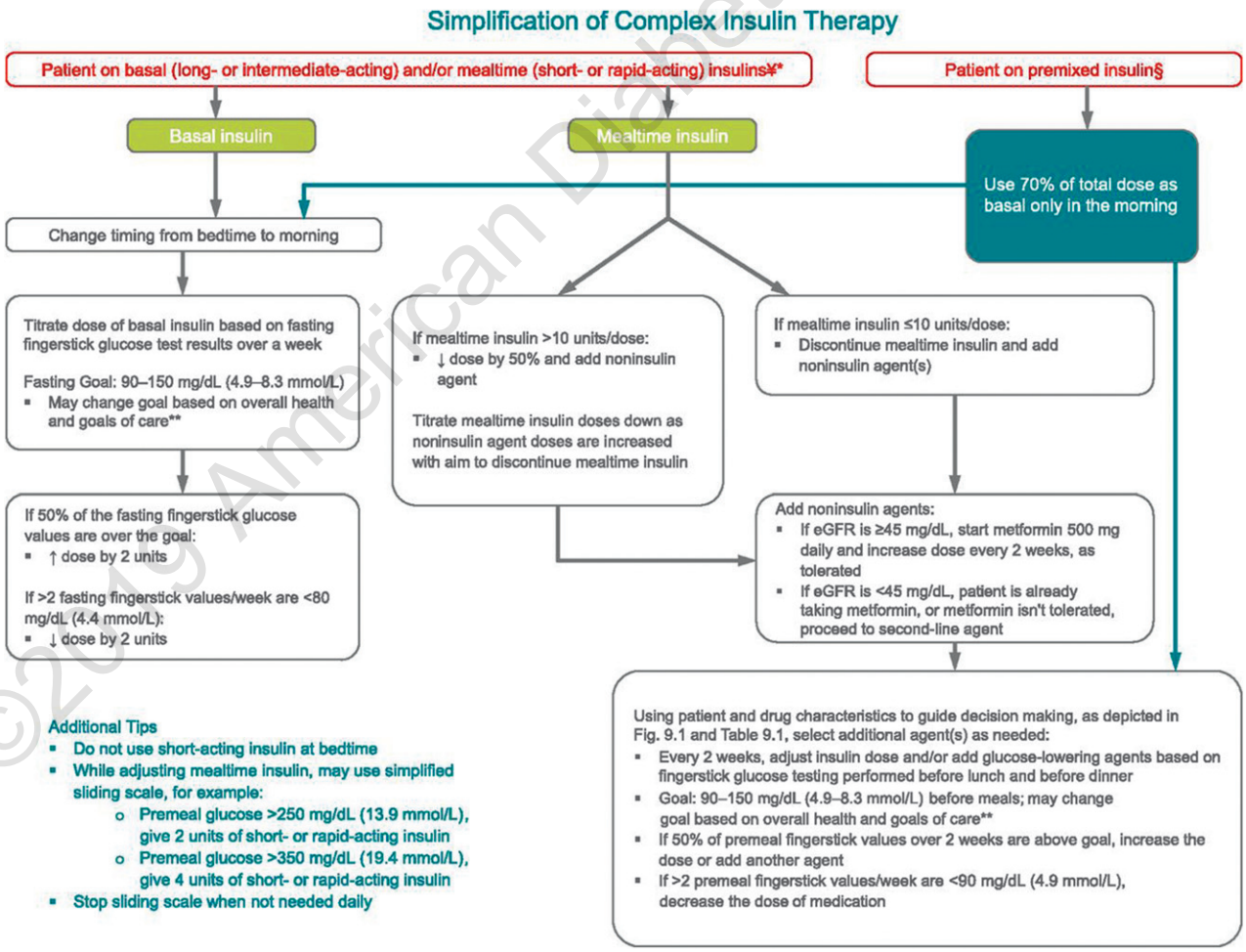

Figure 12.1—Algorithm to simplify insulin regimen for older patients with type 2 diabetes. eGFR, estimated glomerular filtration rate. *Basal insulins: glargine U-100 and U-300, detemir, degludec, and human NPH. **See Table 12.1. ¥Mealtime insulins: short-acting (regular human insulin) or rapid-acting (lispro, aspart, and glulisine). §Premixed insulins: 70/30, 75/25, and 50/50 products. Adapted with permission from Munshi and colleagues (56,82,83).

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Table 12.2—Considerations for treatment regimen simplification and deintensification/deprescribing in older adults with diabetes (56,82)

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 <7.5% (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 dependencies)	A1C <8.5% (69 mmol/)†	• 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
Patients at 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 fingerstick readings, 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. †Consider adjustment of A1C goal if the patient has a condition that may interfere with erythrocyte life span/turnover.

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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 ≥30 mL/min/1.73 m^2 (60). 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 gastrointestinal side effects.

Thiazolidinediones

Thiazolidinediones, if used at all, should be used very cautiously in those with, or at risk for, congestive heart failure, osteoporosis, falls or fractures, and/or macular edema (61,62).

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 (63).

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 (64).

Glucagon-like peptide 1 (GLP-1) receptor agonists have demonstrated cardiovascular benefits among patients with established atherosclerotic cardiovascular disease, and newer trials are expanding our understanding of their benefits in other populations (64). See Section 9 "Pharmacologic Approaches to Glycemic Treatment" (https://doi.org/10.2337/dc20-S009) for a more extensive discussion regarding the specific indications for this class. While the benefits of this class are emerging, these drugs are injectable agents (with the exception of oral semaglutide), 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

Sodium–glucose cotransporter 2 inhibitors are administered orally, which may be convenient for older adults with diabetes. In patients with established atherosclerotic cardiovascular disease, these agents have shown cardiovascular benefits (64). 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/dc20-S009) for a more extensive discussion regarding the indications for this class of agents. 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. **Fig. 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 (65–67). 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 (68). Insulin is an essential life-preserving therapy for patients with type 1 diabetes, unlike for those with type 2 diabetes. In order 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 insulin pump or injections. Continuous glucose monitoring (CGM) is approved for use by Medicare and can play a critical role in improving A1C, reducing glycemic variability, and reducing risk of hypoglycemia (69) (see Section 7 "Diabetes Technology," https://doi.org/10.2337/dc20-S007, and section 9 "Pharmacologic Approaches to Glycemic Treatment," https://doi.org/10.2337/dc20-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

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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 12.15 and 12.16).

TREATMENT IN SKILLED NURSING FACILITIES AND NURSING HOMES

Recommendations

12.15 Consider diabetes education for the staff of long-term care and rehabilitation facilities to improve the management of older adults with diabetes. **E**

12.16 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 (70). 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 (2,71). For more information, see the ADA position statement "Management of Diabetes in Long-term Care and Skilled Nursing Facilities" (70).

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 (72). 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 (73). Oral agents may achieve similar glycemic outcomes in LTC populations as basal insulin (50,74).

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 and 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

12.17 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**

12.18 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 (71,75). 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 has been found to improve quality of life, while similar evidence for glucose and blood pressure control are not yet available (76–78). 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 fingerstick testing (79,80). Glucose targets should aim to prevent hypoglycemia and hyperglycemia. Treatment interventions need to be

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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 (81). 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 (39).

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.

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13. Children and Adolescents: *Standards of Medical Care in Diabetes—2020*

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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/dc20-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/dc20-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 as opposed to type 2 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. **Figure 13.1** provides guidance on managing new-onset diabetes in youth with overweight or obesity before type 1 or type 2 diabetes is diagnosed and so applies to all youth with overweight or obesity. 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 the child with diabetes develops into adulthood. Due to the nature of clinical research in children, 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. Monogenic diabetes (neonatal diabetes and maturity-onset diabetes in the young [MODY]), which often present in youth, are discussed in section 2 "Classification and Diagnosis of Diabetes" (https://doi.org/10.2337/dc20-S002).

TYPE 1 DIABETES

Type 1 diabetes is the most common form of diabetes in youth (4), although recent data suggest that it may account for a large proportion of cases diagnosed in

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adult life (5). 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 young adult.

Diabetes Self-Management Education and Support

Recommendation

13.1 Youth with type 1 diabetes and 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. Health care providers in the diabetes care team who care for children and adolescents 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 day care providers, school nurses, or other school personnel who participate in the care of the child with diabetes (9).

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 (10).

Physical Activity and Exercise

Recommendations

13.5 Exercise is recommended for all youth 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 preexercise glucose level of 90–250 mg/dL (5.0–13.9 mmol/L) and accessible carbohydrates before 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 affects insulin sensitivity, physical fitness, strength building, weight management, social interaction, mood, self-esteem building, and creation of healthful habits for adulthood, but 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 (11–13).

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Overall, it is recommended that youth with type 1 diabetes 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 (14). 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 (10,11).

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 (15). Decreasing basal rates or long-acting insulin doses by ~20% after exercise may reduce delayed exercise-induced hypoglycemia (16). 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 (17). 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 (18–20).

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. (21–25). 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, close communication with and the cooperation of school or day care personnel are essential for optimal diabetes management, safety, and maximal academic opportunities. Refer to the ADA position statements "Diabetes Care in the School Setting" (26) and "Care of Young Children With Diabetes in the Child Care Setting" (27) 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 consider asking youth and their parents about social adjustment (peer relationships) and school performance to determine whether further intervention is needed. **B**

13.13 Assess youth with diabetes for psychosocial and diabetes-related distress, generally starting at 7–8 years of age. **B**

13.14 Offer adolescents time by themselves with their care provider(s) starting at age 12 years, or when developmentally appropriate. **E**

13.15 Starting at puberty, preconception counseling should be incorporated into routine diabetes care for all girls of childbearing potential. **A**

13.16 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 and diabetes distress in the patient and the caregiver during routine diabetes visits (28–34). 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 (35). Consider assessing youth for diabetes distress, generally starting at 7 or 8 years of age (36). Consider screening for depression and disordered eating behaviors using available screening tools (28,37). 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 (33,36). There are validated tools, such as the Problem Areas in Diabetes-Teen (PAID-T) and Parent (P-PAID-Teen) (34), that can be used in assessing diabetes-specific distress in youth starting at age 12 years and in their parent

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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 (38,39). 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 (40). Monitoring of social adjustment (peer relationships) and school performance can facilitate both well-being and academic achievement (41). Suboptimal glycemic control is a risk factor for underperformance at school and increased absenteeism (42).

Shared decision-making with youth regarding the adoption of regimen components and self-management behaviors can improve diabetes self-efficacy, adherence, and metabolic outcomes (22,43). 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 (44).

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 (45). Preconception counseling resources tailored for adolescents are available at no cost through the ADA (46). Refer to the ADA position statement "Psychosocial Care for People With Diabetes" for further details (36).

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 (47) using tools such as the Diabetes Eating Problems Survey-Revised (DEPS-R) to allow for early diagnosis and intervention (37,48–50).

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

13.17 The majority of 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**

13.18 All children and adolescents with type 1 diabetes should self-monitor glucose levels multiple times daily (up to 6–10 times/day), including premeal, prebedtime, and as needed for safety in specific situations such as exercise, driving, or the presence of symptoms of hypoglycemia. **B**

13.19 Continuous glucose monitoring (CGM) should be considered in all children and adolescents with type 1 diabetes, whether using injections or continuous subcutaneous insulin infusion, as an additional tool to help improve glucose control. Benefits of CGM correlate with adherence to ongoing use of the device. **B**

13.20 Automated insulin delivery systems appear to improve glycemic control and reduce hypoglycemia in children and should be considered in children with type 1 diabetes. **B**

13.21 A1C goals must be individualized and reassessed over time. An A1C of <7% (53 mmol/mol) is appropriate for many children. **B**

13.22 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 monitors; cannot check blood glucose regularly; or have nonglycemic factors that increase A1C (e.g., high glycators). **B**

13.23 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 extensive comorbid conditions. **B**

13.24 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**

Current standards for diabetes management reflect the need to lower glucose as safely as possible. This should be done with stepwise goals. When establishing individualized glycemic targets, 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 <6 years, without increased risk of severe hypoglycemia (51,52). Recent data have demonstrated that the use of continuous glucose monitors lowered A1C and increased time in range in adolescents and young adults, and, in children <8 years old, was associated with lower risk of hypoglycemia (53,54). Please refer to Section 7 "Diabetes Technology" (https://doi.org/10.2337/dc20-S007) for more

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information on the use of blood glucose meters, continuous glucose monitors, 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/dc20-S009)."

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 in youth from infancy through adolescence has been associated with more children reaching the blood glucose targets recommended by 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. Furthermore, studies documenting neurocognitive imaging differences related to hyperglycemia in children provide another motivation for lowering glycemic targets (6).

Lower A1C in adolescence and young adulthood is associated with lower risk and rate of microvascular and macrovascular complications, as shown in studies in youth (59–62) and in studies that include youth and adults and demonstrate the effects of metabolic memory (63–66).

In addition, type 1 diabetes can be associated with adverse effects on cognition during childhood and adolescence (6,67,68). DKA has been shown to cause adverse effects on brain development and function. Additional factors (69–72) that contribute to adverse effects on brain development and function include young age, severe hypoglycemia at <6 years of age, and chronic hyperglycemia (73,74). However, meticulous use of new therapeutic modalities such as rapid- and long-acting insulin analogs, technological advances (e.g., continuous glucose monitors, low-glucose suspend insulin pumps, 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 (75–84). Intermittently scanned continuous glucose monitors are not currently approved for use in children and adolescents. A strong relationship exists between frequency of blood glucose monitoring and glycemic stability (77–86). Recent data with newer devices and insulins indicate that the risk of hypoglycemia with lower A1C is less than it was before (52,76,87–94). Some data suggest that there could be a threshold where lower A1C is associated with more hypoglycemia (95,96); however, the confidence intervals were large, suggesting great variability.

In selecting 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. In addition, achieving lower A1C levels is likely facilitated by setting lower A1C targets (51,97). Lower goals may be possible during the "honeymoon" phase of type 1 diabetes.

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

13.25 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 (98–102). 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

13.26 Consider testing children with type 1 diabetes for antithyroid peroxidase and antithyroglobulin antibodies soon after diagnosis. **B**

13.27 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 (99,103,104). At the time of diagnosis, ~25% of children with type 1 diabetes have thyroid autoantibodies (105); their presence is predictive of thyroid dysfunction—most commonly hypothyroidism, although hyperthyroidism occurs in ~0.5% of patients with type 1 diabetes (106,107). For thyroid autoantibodies, a study from Sweden indicated that antithyroid peroxidase antibodies were more predictive than antithyroglobulin antibodies in multivariate analysis (108). 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,

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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 (109) and reduced linear growth rate. Hyperthyroidism alters glucose metabolism and usually causes deterioration of glycemic control.

Celiac Disease

Recommendations

13.28 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**

13.29 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**

13.30 Individuals with biopsy-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) (98,101,102,110–114). 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 (115–118).

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 (112) or if clinical symptoms indicate, such as poor growth or increased hypoglycemia (113,115).

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 (112). Monitoring for symptoms should include assessment of linear growth and weight gain (113,115). A small bowel biopsy in antibody-positive children is recommended to confirm the diagnosis (119). 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 (120). 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 (121).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 (122) and endorsing significant dietary changes. A gluten-free diet was beneficial in asymptomatic adults with positive antibodies confirmed by biopsy (123).

Management of Cardiovascular Risk Factors

Hypertension Screening

Recommendations

13.31 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

13.32 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**

13.33 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**

13.34 ACE inhibitors or angiotensin receptor blockers should be considered for the initial pharmacologic treatment of

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hypertension **E** in children and adolescents, following reproductive counseling due to the potential teratogenic effects of both drug classes. **E**

13.35 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 (124). 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) (125).

Dyslipidemia Testing

Recommendations

13.36 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.

13.37 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

13.38 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**

13.39 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 because of the potential teratogenic effects of statins. **E**

13.40 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 (126–128), and the prevalence of cardiovascular disease (CVD) risk factors increases with age (128) and among racial/ethnic minorities (21), with girls having a higher risk burden than boys (127).

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 (129–131). Studies of carotid intima-media thickness have yielded inconsistent results (124,125).

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 (132). 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 (133). Youth with type 1 diabetes have a high prevalence of lipid abnormalities (126,134).

Even if normal, screening should be repeated within 3 years, as glycemic control and other cardiovascular risk factors can change dramatically during adolescence (135).

Treatment. Pediatric lipid guidelines provide some guidance relevant to children with type 1 diabetes (124,132,136,137); 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 (138); likewise, a lifestyle intervention trial with 6 months of exercise in adolescents demonstrated improvement in lipid levels (139). 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 (135).

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 (137,140). 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 (141).

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 (142,143). 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

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pregnancy; therefore, prevention of unplanned pregnancies is of paramount importance for postpubertal girls (see Section 14 "Management of Diabetes in Pregnancy," https://doi.org/10.2337/dc20-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

13.41 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**

13.42 E-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 (144,145). 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 (132,146). Discouraging cigarette smoking, including e-cigarettes (147,148), is an important part of routine diabetes care. In light of recent Centers for Disease Control and Prevention evidence of deaths related to e-cigarette use (149,150), no persons should be advised to use e-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 if exposed to smokers in childhood.

Microvascular Complications

Nephropathy Screening

Recommendations

13.43 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

Recommendations

13.44 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 (151). An estimation of glomerular filtration rate (GFR), calculated using GFR estimating equations from the serum creatinine, height, age, and sex (152), 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 (152,153). The AdDIT study in adolescents with type 1 diabetes demonstrated safety of ACE inhibitor treatment, but the treatment did not change the albumin-to-creatinine ratio over the course of the study (124).

Retinopathy

Recommendations

13.45 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**

13.46 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 (154). It is currently recognized that there is low risk of development of vision-threatening retinal lesions prior to 12 years of age (155,156). 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 (157,158). 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

13.47 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 (154), although data suggest a prevalence of distal peripheral neuropathy of 7% in 1,734 youth with type 1 diabetes and associated with the presence of CVD risk factors (159,160). 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 (160). Foot inspection can be performed at each visit to educate youth regarding

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the importance of foot care (see Section 11 "Microvascular Complications and Foot Care," https://doi.org/10.2337/dc20-S011).

TYPE 2 DIABETES

For information on testing 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/dc20-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. (161). 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 (162,163).

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 (2,164).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 (22,165–168). Additional risk factors associated with type 2 diabetes in youth include adiposity, family history of diabetes, female sex, and low socioeconomic status (164).

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

13.48 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).

13.49 If tests are normal, repeat testing at a minimum of 3-year intervals **E**, or more frequently if BMI is increasing. **C**

13.50 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**

13.51 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 (132,169). A few recent 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 (170), although fasting glucose alone may overdiagnose diabetes in children (171,172). 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 (173). 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, ADA continues to recommend A1C for diagnosis of type 2 diabetes in this population (174,175).

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 (23), and diabetes-associated autoantibodies and ketosis may be present in pediatric patients with features of type 2 diabetes (including obesity and acanthosis nigricans) (171). The presence of islet autoantibodies has been associated with faster progression to insulin deficiency (171). At onset, DKA occurs in ~6% of youth aged 10–19 years with type 2 diabetes (176). Although uncommon, type 2 diabetes has been observed in prepubertal children under the age of 10, and thus it should be part of the differential in children with suggestive symptoms (177). Finally, obesity (178) contributes to the development of type 1 diabetes in some individuals, 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/dc20-S002). In addition, there are rare and atypical diabetes cases that represent a challenge for clinicians and researchers.

Management

Lifestyle Management

Recommendations

13.52 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 competent. **B**

13.53 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**

13.54 Given the necessity of long-term weight management for children and adolescents with

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type 2 diabetes, lifestyle intervention should be based on a chronic care model and offered in the context of diabetes care. **E**

13.55 Youth with diabetes, like all children, should be encouraged to participate in at least 30–60 min of moderate-to-vigorous physical activity at least 5 days per week (and strength training on at least 3 days/week) **B** and to decrease sedentary behavior. **C**

13.56 Nutrition for youth with 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

13.57 Home self-monitoring of blood glucose regimens should be individualized, taking into consideration the pharmacologic treatment of the patient. **E**

13.58 A1C should be measured every 3 months. **E**

13.59 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**

13.60 Less-stringent A1C goals (such as 7.5% [58 mmol/mol]) may be appropriate if there is increased risk of hypoglycemia. **E**

13.61 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

13.62 Initiate pharmacologic therapy, in addition to lifestyle therapy, at diagnosis of type 2 diabetes. **A**

13.63 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**

13.64 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**

13.65 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**

13.66 In individuals presenting with severe hyperglycemia (blood glucose ≥600 mg/dL [33.3 mmol/L]), consider assessment for hyperglycemic hyperosmolar nonketotic syndrome. **A**

13.67 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**

13.68 Patients treated with basal insulin up to 1.5 units/kg/day who do not meet A1C target should be moved to multiple daily injections with basal and premeal bolus insulins. **E**

13.69 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**

13.70 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 (180). 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.

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 (181–184).

Patients and their families must prioritize lifestyle modifications such as eating a balanced diet, achieving

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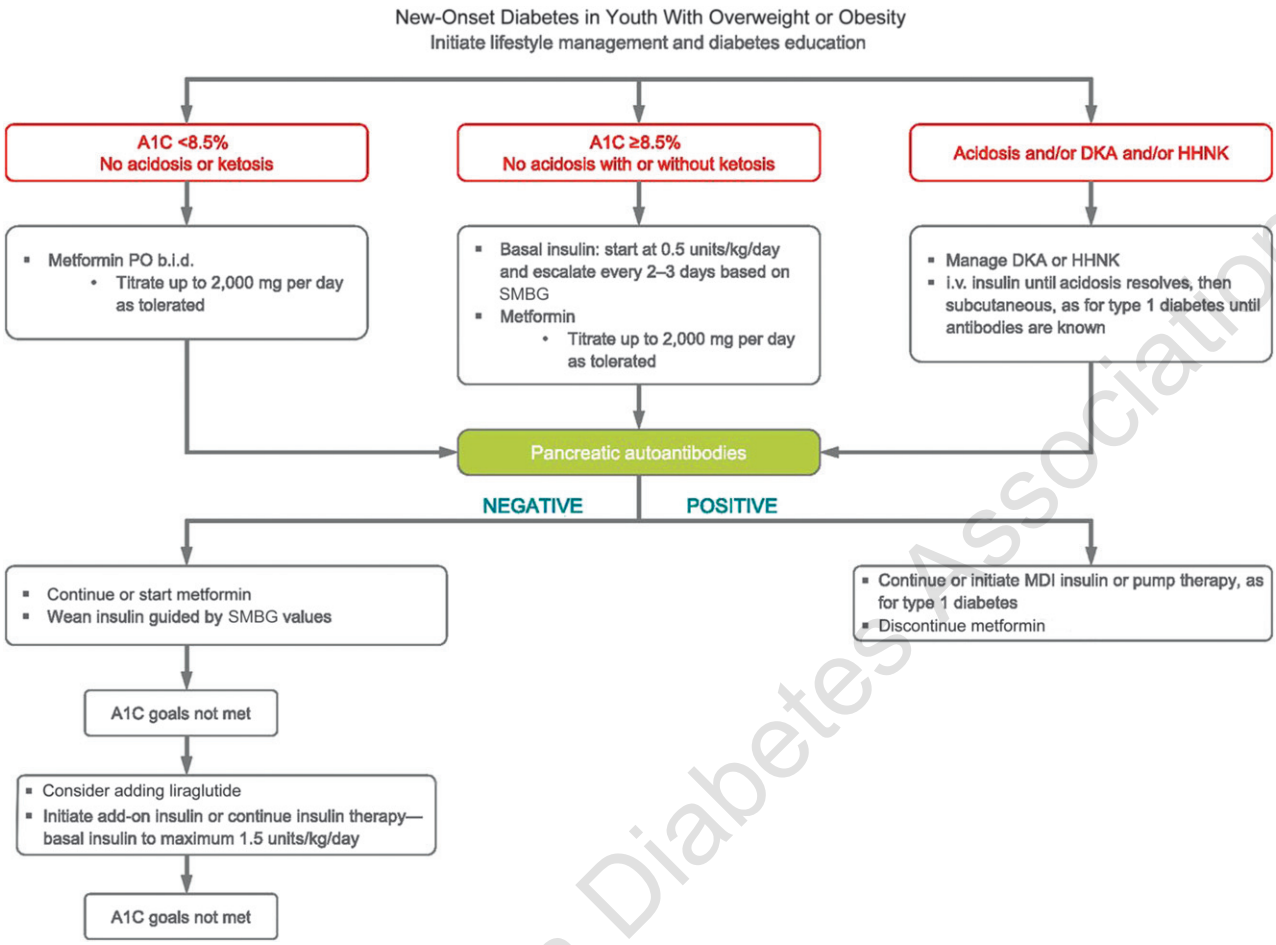

Figure 13.1—Management of new-onset diabetes in youth with overweight or obesity. A1C 8.5% = 69 mmol/mol. Adapted from the ADA position statement "Evaluation and Management of Youth-Onset Type 2 Diabetes" (2). DKA, diabetic ketoacidosis; HHNK, hyperosmolar hyperglycemic nonketotic syndrome; MDI, multiple daily injections.

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and maintaining a healthy weight, and exercising regularly. A family-centered approach to nutrition and lifestyle modification is essential in children with type 2 diabetes, and nutrition recommendations should be culturally appropriate and sensitive to family resources (see Section 5 "Facilitating Behavior Change and Well-being to Improve Health Outcomes," https://doi.org/10.2337/dc20-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 nurse educator, registered dietitian, and psychologist or social worker, is essential. In addition to achieving glycemic targets and self-management education (185–187), 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. 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) (188).

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 (189). 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 (190).

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 (189).

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 (191). In June 2019, the U.S. Food and Drug Administration approved liraglutide injection for treatment of pediatric patients aged 10 years or older with type 2 diabetes (192).

Metabolic Surgery

Recommendations

13.71 Metabolic surgery may be considered for the treatment of adolescents with type 2 diabetes who are markedly obese (BMI >35 kg/m^2) and who have uncontrolled glycemia and/or serious comorbidities despite lifestyle and pharmacologic intervention. **A**

13.72 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, 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 recent prospective multicenter nonrandomized study suggest that bariatric or metabolic surgery may have benefits in obese adolescents with 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 (193). No randomized trials, however, have yet compared the effectiveness and safety of surgery to those of conventional treatment options in adolescents (194). 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 (195–206). A number of groups, including the Pediatric Bariatric Study Group and the Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS) Study, have demonstrated the effectiveness of metabolic surgery in adolescents (199–205).

Prevention and Management of Diabetes Complications

Nephropathy

Recommendations

13.73 Blood pressure should be measured at every visit. **A**

13.74 Blood pressure should be optimized to reduce risk and/or slow the progression of diabetic kidney disease. **A**

13.75 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**

13.76 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**

13.77 Initial therapeutic options include ACE inhibitors or angiotensin receptor blockers. Other blood pressure–lowering agents may be added as needed. **C**

13.78 Protein intake should be at the recommended daily allowance of 0.8 g/kg/day. **E**

13.79 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**

13.80 Estimated glomerular filtration rate should be determined at the time of diagnosis and annually thereafter. **E**

13.81 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**

13.82 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**

13.83 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

13.84 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**

13.85 Prevention should focus on achieving glycemic targets. **C**

Retinopathy

Recommendations

13.86 Screening for retinopathy should be performed by dilated fundoscopy or retinal photography at or soon after diagnosis and annually thereafter. **C**

13.87 Optimizing glycemia is recommended to decrease the risk or slow the progression of retinopathy. **B**

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13.88 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

13.89 Evaluation for nonalcoholic fatty liver disease (by measuring AST and ALT) should be done at diagnosis and annually thereafter. **B**

13.90 Referral to gastroenterology should be considered for persistently elevated or worsening transaminases. **B**

Obstructive Sleep Apnea

Recommendation

13.91 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

13.92 Evaluate for polycystic ovary syndrome in female adolescents with type 2 diabetes, including laboratory studies when indicated. **B**

13.93 Oral contraceptive pills for treatment of polycystic ovary syndrome are not contraindicated for girls with type 2 diabetes. **C**

13.94 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

13.95 Intensive lifestyle interventions focusing on weight loss, dyslipidemia, hypertension, and dysglycemia are important to prevent overt macrovascular disease in early adulthood. **E**

Dyslipidemia

Recommendations

13.96 Lipid testing should be performed when initial glycemic control has been achieved and annually thereafter. **B**

13.97 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**

13.98 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**

13.99 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. **B**

13.100 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

13.101 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 (164,207). 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. Thereafter, screening guidelines and treatment recommendations for hypertension, dyslipidemia, urine albumin excretion, and retinopathy are similar to those for youth with type 1 diabetes. Additional problems 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 those diagnosed later in life (208). 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 (209), and there are high rates of complications (181–184). These diabetes comorbidities also appear to be higher than in youth with type 1 diabetes despite shorter diabetes duration and lower A1C (207). 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 (210).

Psychosocial Factors

Recommendations

13.102 Providers should assess social context, including potential food insecurity, housing stability, and financial barriers, and apply that information to treatment decisions. **E**

13.103 Use patient-appropriate standardized and validated tools to assess for diabetes distress

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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**

13.104 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**

13.105 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**

13.106 Patients should be screened for smoking 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 (22,36,165–168). 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 (211–215), 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 (212,216,217).

Many of the drugs prescribed for diabetes and psychiatric disorders are associated with weight gain and can increase patients' concerns about eating, body shape, and weight (218,219).

The TODAY study documented (220) 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

13.107 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**

13.108 Both pediatric and adult diabetes care providers should provide support and resources for transitioning young adults. **E**

13.109 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 (221), 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 (222–225). 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 (226). Worsening diabetes health outcomes during transition to adult care and early adulthood have been documented (227,228).

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 (222,223,229,230). New technologies and other interventions are being tried to support transition to adult care in young adulthood (231–235) 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" (223).

The Endocrine Society in collaboration with the ADA and other organizations has developed transition tools for clinicians and youth and families (230).

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14. Management of Diabetes in Pregnancy: *Standards of Medical Care in Diabetes—2020*

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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, and other complications. **B**

All women of childbearing age with diabetes should be informed about the importance of achieving and maintaining as near euglycemia as safely possible prior

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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 (3–6).

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 (7). Effective preconception counseling could avert substantial health and associated cost burdens in offspring (8). 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 (9–13).

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 (7). Preconception counseling resources tailored for adolescents are available at no cost through the American Diabetes Association (ADA) (14).

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 educator, 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 (15). 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 (15). Prescription of prenatal vitamins (with at least 400 mg of folic acid and 150 μg of potassium iodide [16]) 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 (15,17). 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 [18], angiotensin receptor blockers [18], and statins [19,20]). 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 (21). The use of aspirin (81–150 mg) can be considered preconception as it is recommended for all pregnant women with diabetes (if no contraindication) by 16 weeks of gestation to reduce the risk of preeclampsia. Please see PREECLAMPSIA AND ASPIRIN for more information.

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 (22–25). One study showed that care of preexisting diabetes in clinics that included diabetes and obstetric specialists improved care (25). 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 (26).

GLYCEMIC TARGETS IN PREGNANCY

Recommendations

14.7 Fasting and postprandial self-monitoring of blood glucose are recommended in both

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Table 14.1—Checklist for preconception care for women with diabetes (15,17)

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/hypoglycemic 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.

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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 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 amounts of carbohydrates to match with insulin dosage and to avoid hyperglycemia or hypoglycemia. Referral to a registered dietitian nutritionist 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 (27). The situation rapidly reverses by approximately 16 weeks as insulin resistance increases exponentially during the second and early third trimesters to 2–3 times the preprandial 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 (28). 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 (29–31). 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 (the same as for GDM; described below) (32), the ADA-recommended targets for women with type 1 or type 2 diabetes are as follows:

- 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)

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 (33). In the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, increasing levels of glycemia were also associated with worsening outcomes (34). 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 (4–6,35). 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 (36,37). 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 (35,38,39), preterm delivery (40), and preeclampsia (1,41). 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

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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 (42). 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 (43). An observational cohort study that evaluated the glycemic variables reported using CGM and their association with large-for-gestational-age births found that mean glucose had a greater association than time in range, time below range, or time above range (44). Using 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 (45).

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 macrosomia and birth complications and an increased risk of maternal type 2 diabetes after pregnancy. The association of macrosomia and birth complications with oral glucose tolerance test (OGTT) results is continuous with no clear inflection points (34). In other words, risks increase with progressive hyperglycemia. Therefore, all women should be tested as outlined in Section 2 "Classification and Diagnosis of Diabetes" (https://doi.org/10.2337/dc20-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 (46–48).

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, and glucose monitoring aiming for the targets recommended by the Fifth International Workshop-Conference on Gestational Diabetes Mellitus (48):

- 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)

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 Diabetes and Pregnancy Study Groups (49) 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 (50,51). 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 (52). 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 not be high in saturated fat. 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 (53). Insulin is the first-line agent recommended for treatment of GDM in the U.S. While individual RCTs support limited efficacy of metformin (54,55) and glyburide (56) 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 (32). Furthermore, glyburide and metformin failed to provide adequate glycemic control in separate randomized controlled trials, failing in 23% and 25–28% of women with GDM, respectively (57,58).

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 (57,58). Glyburide was associated with a higher rate of neonatal hypoglycemia and macrosomia than insulin or metformin in a 2015 meta-analysis and systematic review (59).

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More recently, glyburide failed to be found noninferior to insulin based on a composite outcome of neonatal hypoglycemia, macrosomia, and hyperbilirubinemia (60). Long-term safety data for offspring exposed to glyburide are not available (60).

Metformin

Metformin was associated with a lower risk of neonatal hypoglycemia and less maternal weight gain than insulin in systematic reviews (59,61,62,65). However, metformin readily crosses the placenta, resulting in umbilical cord blood levels of metformin as high or higher than simultaneous maternal levels (66,67). 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 (68). 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 (69,70). 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 (70,71). Metformin is being studied in two ongoing trials in type 2 diabetes (Metformin in Women with Type 2 Diabetes in Pregnancy Trial [MiTY] [72] and Medical Optimization of Management of Type 2 Diabetes Complicating Pregnancy [MOMPOD] [73]), 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 (68,69).

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 (74), and there is no evidence-based need to continue metformin in such patients (75–77).

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, preeclampsia, or at risk for intrauterine growth restriction (78,79).

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 (80).

MANAGEMENT OF PREEXISTING TYPE 1 DIABETES AND TYPE 2 DIABETES IN PREGNANCY

Insulin Use

Recommendations

14.16 Insulin is the preferred agent for management of both type 1 diabetes and 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 (80–86). A recent Cochrane systematic review was not able to recommend any specific insulin regimen over another for the treatment of diabetes in pregnancy (87).

While many providers prefer insulin pumps in pregnancy, it is not clear that they are superior to multiple daily injections (88–90). Closed-loop technology that is U.S. Food and Drug Administration approved outside of pregnancy can only target a glucose of 120 mg/dL at this time, which is likely to be too high for optimal nocturnal control in pregnancy. However, given potential benefits, ongoing work is being done in this area.

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 diabetic ketoacidosis 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. Rapid implementation of euglycemia in the setting of retinopathy is associated with worsening of retinopathy (21).

Type 2 Diabetes

Type 2 diabetes is often associated with obesity. Recommended weight gain during pregnancy for overweight women is 15–25 lb and for obese women is 10–20 lb (52). There is no adequate data on optimal weight gain versus weight maintenance in women with a 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

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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 (91,92).

PREECLAMPSIA AND ASPIRIN

Recommendation

14.18 Women with type 1 or type 2 diabetes should be prescribed low-dose aspirin 60–150 mg/day (usual dose 81 mg/day) by the end of the first trimester in order to lower the risk of preeclampsia. **A**

Diabetes in pregnancy is associated with an increased risk of preeclampsia (93). Based upon the results of clinical trials and meta-analyses (94), 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 (95). A cost-benefit analysis has concluded that this approach would reduce morbidity, save lives, and lower health care costs (96). However, more study is needed to assess the long-term effects of prenatal aspirin exposure on offspring (97).

PREGNANCY AND DRUG CONSIDERATIONS

Recommendations

14.19 In pregnant patients with diabetes and hypertension or significant proteinuria, a consistent blood pressure >135/85 mmHg should be treated in the interest of optimizing long-term maternal health. Blood pressure targets should range no lower than 120/80 mmHg, as lower blood pressure targets may impair fetal growth. **C**

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 <135/85 mmHg is reasonable (98,99). Blood pressure targets lower than 120/80 mmHg may be associated with impaired fetal growth, especially in the setting of placental insufficiency. In a 2015 study targeting diastolic blood pressure of 100 mmHg versus 85 mmHg in pregnant women, only 6% of whom had GDM at enrollment, there was no difference in pregnancy loss, neonatal care, or other neonatal outcomes, although women in the less intensive treatment group had a higher rate of uncontrolled hypertension (100).

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 (18). 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 (101). On the basis of available evidence, statins should also be avoided in pregnancy (102).

See PREGNANCY AND ANTIHYPERTENSIVE MEDICATIONS in Section 10 "Cardiovascular Disease and Risk Management" (https://doi.org/10.2337/dc20-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. **C**

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 at least every 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/dc20-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,

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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 50–70% after 15–25 years (103,104), 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 (103). 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 (105). Adjusting for BMI moderately, but not completely, attenuated this association. Interpregnancy or postpartum weight gain is associated with increased risk of adverse pregnancy outcomes in subsequent pregnancies (106) 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 (107). In these women, lifestyle intervention and metformin reduced progression to diabetes by 35% and 40%, respectively, over 10 years compared with placebo (108). 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 (109,110). 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 (111).

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 (112) and offspring (113) 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.

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15. Diabetes Care in the Hospital: *Standards of Medical Care in Diabetes—2020*

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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/dc20-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/dc20-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Among hospitalized patients, both hyperglycemia and hypoglycemia are associated with adverse outcomes, including death (1–4). 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 (5,6).

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. **C**

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) are inconsistently implemented within hospitals. To correct this, medical centers striving for optimal inpatient diabetes treatment should establish protocols and structured order sets, which include computerized physician order entry (CPOE).

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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 on all patients with diabetes or hyperglycemia admitted to the hospital if the test has not been performed in the previous 3 months (7–10). 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). There is evidence to support preadmission treatment of hyperglycemia in patients scheduled for elective surgery as an effective means of reducing adverse outcomes (11–13).

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 (11,18,19). 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 patients 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) (2,25). 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/dc20-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 (4). 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

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140–180 mg/dL (7.8–10.0 mmol/L) for the majority of critically ill patients (2). 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. On the other hand, glucose concentrations >180 mg/dL (10 mmol/L) may be acceptable in terminally ill patients, in patients with severe comorbidities, and in inpatient care settings where frequent glucose monitoring or close nursing supervision is not feasible. 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 (2).

BEDSIDE BLOOD GLUCOSE MONITORING

In hospitalized patients with diabetes who are eating, glucose monitoring should be performed before meals; in those not eating, glucose monitoring is advised every 4–6 h (2). More frequent 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 (32).

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 (33). 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 (4,34). 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 (34). The balance between analytic requirements (e.g., accuracy, precision, interference) and clinical requirements (rapidity, simplicity, point of care) has not been uniformly resolved (33,35), 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 work flow 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 (36,37). 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. It has theoretical advantages over POC glucose testing in detecting and reducing the incidence of hypoglycemia in the hospital setting that have been borne out in some but not all studies (38,39). Several inpatient studies have shown that CGM use did not improve glucose control but detected a greater number of hypoglycemic events than POC glucose testing (40,41). However, at present, there are insufficient data on clinical outcomes, safety, or cost effectiveness to recommend widespread use of CGM in hospitalized patients (38,40). In particular, more research is needed to support application of CGM for critical care (41). In patients who use CGM in the ambulatory setting for self-management of diabetes, use of CGM for this purpose during hospitalization can be appropriate but requires hospitals to have protocols for guidance, as well as access to specialist care (39). For more information on CGM, see Section 7 "Diabetes Technology" (https://doi.org/10.2337/dc20-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** An insulin regimen with basal, prandial, and correction components is the preferred treatment for noncritically ill hospitalized patients with good nutritional intake. **A**

15.7 Use of only a sliding scale insulin regimen in the inpatient hospital setting is strongly discouraged. **A**

In most instances, insulin is the preferred treatment for hyperglycemia in hospitalized patients (2). However, in certain circumstances, it may be appropriate to continue home regimens including oral glucose-lowering medications (42). 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 (43–45). 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 (46).

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 (2).

Noncritical Care Setting

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 (47). The use of subcutaneous rapid- or short-acting insulin before meals, or every 4–6 h if no

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meals are given or if the patient is receiving continuous enteral/parenteral nutrition, is indicated to correct hyperglycemia (2). 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 (47).

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 pre-emptively) in general surgery patients with type 2 diabetes (48). Prolonged use of sliding scale insulin regimens as the sole treatment of hyperglycemic inpatients is strongly discouraged (2,19).

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.

Transitioning Intravenous to Subcutaneous Insulin

When discontinuing intravenous insulin, a transition protocol is associated with less morbidity and lower costs of care (53) and is therefore recommended. A patient with type 1 or type 2 diabetes being transitioned to an outpatient subcutaneous regimen should receive a dose of subcutaneous basal insulin 2–4 h before the intravenous infusion is discontinued. Converting to basal insulin at 60–80% of the daily infusion dose is an effective approach (2,53,54). 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). New studies support the use of closed-loop insulin delivery with linked pump/sensor devices to control blood glucose in selected groups of hospitalized patients with type 2 diabetes (57,58). The effect of closed-loop treatment on clinical outcomes, the best application of these devices, and cost-effectiveness of this approach are still to be determined.

Noninsulin Therapies

The safety and efficacy of noninsulin glucose-lowering therapies in the hospital setting is an area of active research (59). 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 (60–63). However, an FDA bulletin states that providers should consider discontinuing saxagliptin and alogliptin in people who develop heart failure (64).

Sodium–glucose transporter 2 (SGLT2) inhibitors should be avoided in cases of severe illness, in patients with ketonemia or ketonuria, and during prolonged fasting and surgical procedures (5). Until safety and effectiveness are established, SGLT2 inhibitors are not recommended for routine in-hospital use.

HYPOGLYCEMIA

Recommendations

15.8 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**

15.9 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 (65), 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, because such readings often predict subsequent level 3 hypoglycemia (2). Episodes of hypoglycemia in the hospital should be documented in the medical record and tracked (2).

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 (66,67). 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

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to an unexpected interruption of nutrition. A recent study describes acute kidney injury as an important risk factor for hypoglycemia in the hospital (68), 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% (69,70). 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, 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 (71,72). 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 (73). 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 (74).

Recently, several groups have developed algorithms to predict episodes of hypoglycemia among inpatients (75,76). 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 (77). For enteral nutritional therapy, diabetes-specific formulas appear to be superior to standard formulas in controlling postprandial glucose, A1C, and the insulin response (78).

When the nutritional issues in the hospital are complex, involvement of a registered dietitian nutritionist can contribute to patient care by integrating information about the patient's clinical condition, meal planning, and lifestyle habits and by establishing realistic treatment goals after discharge. 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.

SELF-MANAGEMENT IN THE HOSPITAL

Diabetes self-management in the hospital may be appropriate for specific patients (79,80). 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 (39,81).

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. It is particularly important that patients with type 1 diabetes continue to receive basal insulin even if feedings are discontinued. A reasonable estimate of basal needs can be made from the preadmission dose of long-acting or intermediate insulin or a percentage of the total daily requirements established in the hospital (usually 30–50% of the total daily dose of insulin). In the absence of previous insulin dosing, a reasonable starting point is to use 5 units of NPH/detemir insulin subcutaneously every 12 h or 10 units of insulin glargine every 24 h (82).

For patients receiving continuous tube feedings, the total daily nutritional component may be calculated as 1 unit of insulin for every 10–15 g carbohydrate per day or as a percentage of the total daily dose of insulin when the patient is being fed (usually 50–70% of the total daily dose of insulin). Correctional insulin should also be administered subcutaneously every 6 h using human regular insulin or every 4 h using a rapid-acting insulin such as lispro, aspart, or glulisine.

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.

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 (83), and should be adjusted daily in the solution. Correctional insulin should be administered subcutaneously. For full enteral/parenteral feeding guidance, the reader is encouraged to consult review articles detailing this topic (2,84).

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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 (85). Glucocorticoid type and duration of action must be considered in determining insulin treatment regimens. Daily ingestion of short-acting glucocorticoids such as prednisone reach peak plasma levels in 4–6 h (86) 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 (85). In subjects on once-daily steroids, prandial insulin dosing, often with intermediate-acting (NPH) insulin, is a standard approach. For long-acting glucocorticoids such as dexamethasone and multidose or continuous glucocorticoid use, long-acting insulin may be required to control fasting blood glucose (42,84). For higher doses of glucocorticoids, increasing doses of prandial and correctional insulin, sometimes in extraordinary amounts, are often needed in addition to basal insulin (87). 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 (88) 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. Withhold any other oral glucose-lowering agents the morning of surgery or procedure and give half of NPH dose or 60–80% doses of long-acting analog or pump basal insulin.
5. Monitor blood glucose at least every 4–6 h while patient is taking nothing by mouth and dose with short- or rapid-acting insulin as needed.

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 (89); 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 (90).

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) (48,91).

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 (92–95).

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 (95). 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 (96). Patients with uncomplicated DKA may sometimes be treated with subcutaneous insulin in the emergency department or step-down units (97), an approach that may be safer and more cost-effective than treatment with intravenous insulin (98). 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 (99). For further information regarding treatment, refer to recent in-depth reviews (5).

TRANSITION FROM THE HOSPITAL TO THE AMBULATORY SETTING

Recommendation

15.10 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 (100). 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/dc20-S012) for more information.

An outpatient follow-up visit with the primary care provider, endocrinologist, or diabetes educator 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

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guide treatment decisions and significantly improved A1C after discharge (8). 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 (101):

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 (102,103). 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 (104). 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 (102,103). While there is no standard to prevent readmissions, several successful strategies have been reported (103). These include targeting ketosis-prone patients with type 1 diabetes (105), insulin treatment of patients with admission A1C >9% (75 mmol/mol) (106), and use of a transitional care model (107). For people with diabetic kidney disease, collaborative patient-centered medical homes may decrease risk-adjusted readmission rates (108). A recently published algorithm based on patient demographic and clinical characteristics had only moderate predictive power but identifies a promising future strategy (109).

Age is also an important risk factor in hospitalization and readmission among patients with diabetes. Insulin-treated patients 80 years of age or older are more than twice as likely as those 45–64 years of age to visit the emergency department and nearly five times as likely to be admitted for insulin-related hypoglycemia (110). One approach to reducing insulin-related morbidity in older adults with type 2 diabetes is to substitute oral agents for insulin in patients in whom these drugs are effective. Among elderly patients in long-term care facilities, there was no significant difference in glycemic control between those taking basal insulin and those on oral glucose-lowering medications (111). In addition, many older adults with diabetes are overtreated (112), with half of those maintaining an A1C <7% (53 mmol/mol) being treated with insulin or a sulfonylurea, which are associated with hypoglycemia. To further lower the risk of hypoglycemia-related admissions in older adults, providers should consider relaxing A1C targets to 8% (64 mmol/mol) or 8.5% (69 mmol/mol) in patients with shortened life expectancies and significant comorbidities (refer to Section 12 "Older Adults," https://doi.org/10.2337/dc20-S012, for detailed criteria).

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16. Diabetes Advocacy: *Standards of Medical Care in Diabetes—2019*

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/dc20-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/dc20-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, 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)

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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)

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DISCLOSURES

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*≥$10,000 per year from company to individual. #Grant or contract is to university or other employer. William T. Cefalu, MD, joined the Professional Practice Committee in August 2019 subsequent to his resignation as Chief Scientific, Medical, and Mission Officer of ADA. Kenneth P. Moritsugu, MD, MPH, FACPM, is currently the Interim Chief Scientific and Medical Officer of ADA and continues his work with First Samurai Consulting, LLC. Prior to joining ADA in September 2019, Malaika I. Hill, MA, was the principal of MD Writing & Editing Solutions, LLC. Jane Reusch, MD, joined the Professional Practice Committee in April 2019. Christine Lee, MD, joined the Professional Practice Committee in June 2019.

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