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1

AMERICAN DIABETES ASSOCIATION

STANDARDS OF MEDICAL CARE IN DIABETES—2015



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American Diabetes Association
**Standards of
Medical Care in
Diabetes—2015**



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[T]he simple word *Care* may suffice to express [the journal's] philosophical mission. The new journal is designed to promote better patient care by serving the expanded needs of all health professionals committed to the care of patients with diabetes. As such, the American Diabetes Association views *Diabetes Care* as a reaffirmation of Francis Weld Peabody's contention that "the secret of the care of the patient is in caring for the patient."

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

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Introduction

Diabetes Care 2015;38(Suppl. 1):S1–S2 | DOI: 10.2337/dc15-S001

Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control. Ongoing patient 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's (ADA's) "Standards of Medical Care in Diabetes" 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 management of diabetes, please refer to *Medical Management of Type 1 Diabetes* (1) and *Medical Management of Type 2 Diabetes* (2).

The recommendations 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 them as the most authoritative and current guidelines for diabetes care.

ADA STANDARDS, STATEMENTS, AND REPORTS

The ADA has been actively involved in the development and dissemination of diabetes care standards, guidelines, and related documents for over 20 years. ADA's clinical practice recommendations are viewed as important resources for health care professionals who care for people with diabetes. ADA's "Standards of Medical Care in Diabetes," position statements, and scientific statements undergo a formal review process by ADA's Professional Practice Committee (PPC) and the Executive Committee of the Board of Directors. The Standards and all ADA position statements, scientific statements, and consensus reports are available on the Association's Web site at <http://professional.diabetes.org/adastatements>.

"Standards of Medical Care in Diabetes" Standards of Care: *ADA position statement that provides key clinical practice recommendations.* The PPC performs an extensive literature search and updates the Standards annually based on the quality of new evidence.

ADA Position Statement

A position statement is an official ADA point of view or belief that contains clinical or research recommendations. Position statements are issued on scientific or medical issues related to diabetes. They are published in ADA journals and other scientific/medical publications. ADA position statements are typically based on a systematic review or other review of published literature. Position statements undergo a formal review process. They are updated annually or as needed.

ADA Scientific Statement

A scientific statement is an official ADA point of view or belief that may or may not contain clinical or research recommendations. Scientific statements contain scholarly synopsis of a topic related to diabetes. Workgroup reports fall into this category. Scientific statements are published in the ADA journals and other scientific/medical publications, as appropriate. Scientific statements also undergo a formal review process.

Consensus Report

A consensus report contains a comprehensive examination by an expert panel (i.e., consensus panel) of a scientific or medical issue related to diabetes. A consensus report is not an ADA position and represents expert opinion only. The category may also include task force and expert committee reports. The need for a consensus report arises when clinicians or scientists desire guidance on a subject for which the evidence is contradictory or incomplete. A consensus report is typically developed immediately following a consensus conference where the controversial issue is extensively discussed. The report represents the panel's collective analysis, evaluation, and opinion at that point in time based in part on the conference proceedings. A consensus report does not undergo a formal ADA review process.

GRADING OF SCIENTIFIC EVIDENCE

Since the ADA first began publishing practice guidelines, there has been considerable evolution in the evaluation of scientific evidence and in the development of evidence-based guidelines. In 2002, we developed a classification

"Standards of Medical Care in Diabetes" was originally approved in 1988. Most recent review/revision: October 2014.

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

Level of evidence	Description
A	<p>Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, including</p> <ul style="list-style-type: none"> • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis <p>Compelling nonexperimental evidence; i.e., “all or none” rule developed by the Centre for Evidence-Based Medicine at the University of Oxford</p> <p>Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including</p> <ul style="list-style-type: none"> • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporated quality ratings in the analysis
B	<p>Supportive evidence from well-conducted cohort studies</p> <ul style="list-style-type: none"> • Evidence from a well-conducted prospective cohort study or registry • Evidence from a well-conducted meta-analysis of cohort studies <p>Supportive evidence from a well-conducted case-control study</p>
C	<p>Supportive evidence from poorly controlled or uncontrolled studies</p> <ul style="list-style-type: none"> • 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 <p>Conflicting evidence with the weight of evidence supporting the recommendation</p>
E	Expert consensus or clinical experience

system to grade the quality of scientific evidence supporting ADA recommendations for all new and revised ADA position statements. A recent analysis of the evidence cited in the Standards of Care found steady improvement in quality over the past 10 years, with last year’s Standards for the first time having the majority of bulleted recommendations supported by **A-** or **B-**level evidence (4). A grading system (**Table 1**) developed by 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 evidence. Expert opinion **E** is a separate category for recommendations in which there is no evidence from clinical trials, in which clinical trials may be impractical, or in which there is conflicting evidence. Recommendations with an **A** rating 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 to 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. Also, conventional evidence hierarchies, such as the one adapted by the ADA, may miss nuances important in diabetes care. For example, although there is excellent evidence from clinical trials supporting the importance of achieving multiple risk factor control, the optimal way to achieve this result is less clear. It is difficult to assess each component of such a complex intervention.

References

1. Kaufman FR (Ed.). *Medical Management of Type 1 Diabetes*, 6th ed. Alexandria, VA, American Diabetes Association, 2012
2. Burant CF (Ed.). *Medical Management of Type 2 Diabetes*, 7th ed. Alexandria, VA, American Diabetes Association, 2012
3. Li R, Zhang P, Barker LE, Chowdhury FM, Zhang X. Cost-effectiveness of interventions to prevent and control diabetes mellitus: a systematic review. *Diabetes Care* 2010;33:1872–1894
4. Grant RW, Kirkman MS. Trends in the evidence level for the American Diabetes Association’s “Standards of Medical Care in Diabetes” from 2005 to 2014. *Diabetes Care* 2015;38:6–8

Professional Practice Committee

Diabetes Care 2015;38(Suppl. 1):S3 | DOI: 10.2337/dc15-S002

The Professional Practice Committee (PPC) of the American Diabetes Association (ADA) is responsible for the “Standards of Medical Care in Diabetes” position statement, referred to as the “Standards of Care.” The PPC is a multidisciplinary expert committee comprised of physicians, diabetes educators, registered dietitians, and others who have expertise in a range of areas, including adult and pediatric endocrinology, epidemiology, public health, lipid research, hypertension, and preconception and pregnancy care. Appointment to the PPC is based on excellence in clinical practice and/or research. While the primary role of the PPC is to review and update the Standards of Care, it is also responsible for overseeing the review and revisions of ADA’s position statements and scientific statements.

All members of the PPC are required to disclose potential conflicts of interest with industry and/or other relevant organizations. These disclosures are discussed at the onset of each Standards of Care revision meeting. Members of the committee, their employer, and their disclosed conflicts of interest are listed in the “Professional Practice Committee for the *Standards of Medical Care in Diabetes—2015*” table (see p. S88).

For the current revision, PPC members systematically searched MEDLINE

for human studies related to each section and published since 1 January 2014. 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 at <http://professional.diabetes.org/SOC>. As for all position statements, the Standards of Care position statement was reviewed and approved by the Executive Committee of ADA’s Board of Directors, which includes health care professionals, scientists, and lay people.

Feedback from the larger clinical community was valuable for the 2015 revision of the Standards of Care. Readers who wish to comment on the *Standards of Medical Care in Diabetes—2015* are invited to do so at <http://professional.diabetes.org/SOC>.

The ADA funds development of the Standards of Care and all ADA position statements out of its general revenues and does not use industry support for these purposes.

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Standards of Medical Care in Diabetes—2015: Summary of Revisions

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GENERAL CHANGES

Diabetes Care Supplement 1 was previously called *Clinical Practice Recommendations* and included the “Standards of Medical Care in Diabetes” and key American Diabetes Association (ADA) position statements. The supplement has been renamed *Standards of Medical Care in Diabetes* (“Standards”) and contains a single ADA position statement that provides evidence-based clinical practice recommendations for diabetes care.

Whereas the “Standards of Medical Care in Diabetes—2015” should still be viewed as a single document, it has been divided into 14 sections, each individually referenced, to highlight important topic areas and to facilitate navigation.

The supplement now includes an index to help readers find information on particular topics.

SECTION CHANGES

Although the levels of evidence for several recommendations have been updated, these changes are not included below as the clinical recommendations have remained the same. Changes in evidence level from, for example, **C** to **E** are not noted below. The “Standards of Medical Care in Diabetes—2015” contains, in addition to many minor changes that clarify recommendations or reflect new evidence, the following more substantive revisions.

Section 2. Classification and Diagnosis of Diabetes

The BMI cut point for screening overweight or obese Asian Americans for prediabetes and type 2 diabetes was changed to 23 kg/m² (vs. 25 kg/m²) to reflect the evidence that this population is at an increased risk for diabetes at lower BMI levels relative to the general population.

Section 4. Foundations of Care: Education, Nutrition, Physical Activity, Smoking Cessation, Psychosocial Care, and Immunization

The physical activity section was revised to reflect evidence that all individuals, including those with diabetes, should be encouraged to limit the amount of time they spend being sedentary by breaking up extended amounts of time (>90 min) spent sitting.

Due to the increasing use of e-cigarettes, the Standards were updated to make clear that e-cigarettes are not supported as an alternative to smoking or to facilitate smoking cessation.

Immunization recommendations were revised to reflect recent Centers for Disease Control and Prevention guidelines regarding PCV13 and PPSV23 vaccinations in older adults.

Section 6. Glycemic Targets

The ADA now recommends a premeal blood glucose target of 80–130 mg/dL, rather than 70–130 mg/dL, to better reflect new data comparing actual average glucose levels with A1C targets.

To provide additional guidance on the successful implementation of continuous glucose monitoring (CGM), the Standards include new recommendations on assessing a patient’s readiness for CGM and on providing ongoing CGM support.

Section 7. Approaches to Glycemic Treatment

The type 2 diabetes management algorithm was updated to reflect all of the currently available therapies for diabetes management.

Section 8. Cardiovascular Disease and Risk Management

The recommended goal for diastolic blood pressure was changed from 80 mmHg to 90 mmHg for most people with diabetes and hypertension to better

reflect evidence from randomized clinical trials. Lower diastolic targets may still be appropriate for certain individuals.

Recommendations for statin treatment and lipid monitoring were revised after consideration of 2013 American College of Cardiology/American Heart Association guidelines on the treatment of blood cholesterol. Treatment initiation (and initial statin dose) is now driven primarily by risk status rather than LDL cholesterol level.

With consideration for the new statin treatment recommendations, the Standards now provide the following lipid monitoring guidance: a screening lipid profile is reasonable at diabetes diagnosis, at an initial medical evaluation and/or at age 40 years, and periodically thereafter.

Section 9. Microvascular Complications and Foot Care

To better target those at high risk for foot complications, the Standards emphasize that all patients with insensate feet, foot deformities, or a history of foot ulcers have their feet examined at every visit.

Section 11. Children and Adolescents

To reflect new evidence regarding the risks and benefits of tight glycemic control in children and adolescents with diabetes, the Standards now recommend a target A1C of <7.5% for all pediatric age-groups; however, individualization is still encouraged.

Section 12. Management of Diabetes in Pregnancy

This new section was added to the Standards to provide recommendations related to pregnancy and diabetes, including recommendations regarding preconception counseling, medications, blood glucose targets, and monitoring.

1. Strategies for Improving Care

American Diabetes Association

Diabetes Care 2015;38(Suppl. 1):S5–S7 | DOI: 10.2337/dc15-S004

Recommendations

- A patient-centered communication style that incorporates patient preferences, assesses literacy and numeracy, and addresses cultural barriers to care should be used. **B**
- Treatment decisions should be timely and founded on evidence-based guidelines that are tailored to individual patient preferences, prognoses, and comorbidities. **B**
- Care should be aligned with components of the Chronic Care Model (CCM) to ensure productive interactions between a prepared proactive practice team and an informed activated patient. **A**
- When feasible, care systems should support team-based care, community involvement, patient registries, and decision support tools to meet patient needs. **B**

DIABETES CARE CONCEPTS

In the following sections, different components of the clinical management of patients with (or at risk for) diabetes are reviewed. We highlight the following three themes that are woven throughout these sections that clinicians, policymakers, and advocates should keep in mind:

1. **Patient-Centeredness:** Practice recommendations, whether based on evidence or expert opinion, are intended to guide an overall approach to care. The science and art of medicine come together when the clinician is faced with making treatment recommendations for a patient who would not have met eligibility criteria for the studies on which guidelines were based. Recognizing that one size does not fit all, these Standards provide guidance for when and how to adapt recommendations (e.g., see Section 10. Older Adults and Fig. 6.1. Approach to the Management of Hyperglycemia). Because patients with diabetes are also at greatly increased risk of cardiovascular disease, a patient-centered approach should include a comprehensive plan to reduce cardiovascular risk by addressing blood pressure and lipid control, smoking cessation, weight management, and healthy lifestyle changes that include adequate physical activity.
2. **Diabetes Across the Life Span:** An increasing proportion of patients with type 1 diabetes are adults. Conversely, and for less salutary reasons, the incidence of type 2 diabetes is increasing in children and young adults. Finally, patients both with type 1 diabetes and with type 2 diabetes are living well into older age, a stage of life for which there is little evidence from clinical trials to guide therapy. All these demographic changes highlight another challenge to high-quality diabetes care, which is the need to improve coordination between clinical teams as patients pass through different stages of the life span or the stages of pregnancy (preconception, pregnancy, and postpartum).
3. **Advocacy for Patients With Diabetes:** Advocacy can be defined as active support and engagement to advance a cause or policy. Advocacy in the cause of improving the lives of patients with (or at risk for) diabetes is an ongoing need. Given the tremendous toll that lifestyle factors such as obesity, physical inactivity, and smoking have on the health of patients with diabetes, ongoing and energetic efforts are needed to address and change the societal determinants at the root of these problems. Within the more narrow domain of clinical practice guidelines, the application of evidence level grading to practice recommendations can help identify areas that require more research investment (1). This topic is explored in more depth in Section 14. Diabetes Advocacy.

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CARE DELIVERY SYSTEMS

There has been steady improvement in the proportion of diabetic patients achieving recommended levels of A1C, blood pressure, and LDL cholesterol in the last 10 years (2). The mean A1C nationally has declined from 7.6% in 1999–2002 to 7.2% in 2007–2010 based on the National Health and Nutrition Examination Survey (NHANES) data (E.W. Gregg, Centers for Disease Control and Prevention, personal communication). This has been accompanied by improvements in lipids and blood pressure control and has led to substantial reductions in end-stage microvascular complications in patients with diabetes. Nevertheless, between 33 and 49% of patients still do not meet targets for glyce-mic, blood pressure, or cholesterol control, and only 14% meet targets for all three measures and nonsmoking status (2). Evidence also suggests that progress in cardiovascular risk factor control (particularly tobacco use) may be slowing (2,3). Certain patient groups, such as young adults and patients with complex comorbidities, financial or other social hardships, and/or limited English proficiency, may present particular challenges to goal-based care (4–6). Persistent variation in quality of diabetes care across providers and across practice settings even after adjusting for patient factors indicates that there remains potential for substantial system-level improvements in diabetes care.

Chronic Care Model

Although numerous interventions to improve adherence to the recommended standards have been implemented, a major barrier to optimal care is a delivery system that too often is fragmented, lacks clinical information capabilities, duplicates services, and is poorly designed for the coordinated delivery of chronic care. The CCM has been shown to be an effective framework for improving the quality of diabetes care (7). The CCM includes six core elements for the provision of optimal 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), and 6) health systems (to create a quality-oriented culture). Redefining the roles of the clinic staff and promoting self-management on the part of the patient are fundamental to the successful implementation of the CCM (8). Collaborative, multidisciplinary teams are best suited to provide care for people with chronic conditions such as diabetes and to facilitate patients' self-management (9–12).

Key Objectives

The National Diabetes Education Program (NDEP) 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. Three specific objectives, with references to literature that outlines practical strategies to achieve each, are delineated below.

Objective 1: Optimize Provider and Team Behavior

The care team should prioritize timely and appropriate intensification of lifestyle and/or pharmaceutical therapy for patients who have not achieved beneficial levels of blood pressure, lipid, or glucose control (13). Strategies such as explicit goal setting with patients (14); identifying and addressing language, numeracy, or cultural barriers to care (15–18); integrating evidence-based guidelines and clinical information tools into the process of care (19–21); and incorporating care management teams including nurses, pharmacists, and other providers (22–24) have each been shown to optimize provider and team behavior and thereby catalyze reductions in A1C, blood pressure, and LDL cholesterol.

Objective 2: Support Patient Behavior Change

Successful diabetes care requires a systematic approach to supporting patients' behavior change efforts, including 1) healthy lifestyle changes (physical activity, healthy eating, tobacco cessation, weight management, and effective coping), 2) disease self-management (taking and managing medication and, when clinically appropriate, self-monitoring of glucose and blood pressure), and 3) prevention of diabetes complications (self-monitoring of foot health; active participation in screening for eye, foot, and renal complications; and immunizations). High-quality

diabetes self-management education (DSME) has been shown to improve patient self-management, satisfaction, and glucose control (25,26), as has delivery of ongoing diabetes self-management support (DSMS), so that gains achieved during DSME are sustained (27–29). National DSME standards call for an integrated approach that includes clinical content and skills, behavioral strategies (goal setting, problem solving), and engagement with emotional concerns in each needed curriculum content area.

Objective 3: Change the Care System

An institutional priority in most successful care systems is providing a high quality of care (30). Changes that have been shown to increase quality of diabetes care include basing care on evidence-based guidelines (19); expanding the role of teams and staff and implementing more intensive disease management strategies (6,22,31); redesigning the care process (32); implementing electronic health record tools (33,34); activating and educating patients (35,36); removing financial barriers and reducing patient out-of-pocket costs for diabetes education, eye exams, self-monitoring of blood glucose, and necessary medications (6); and identifying/developing/engaging community resources and public policy that support healthy lifestyles (37). Recent initiatives such as the Patient-Centered Medical Home show promise for improving outcomes through coordinated primary care and offer new opportunities for team-based chronic disease care (38). Additional strategies to improve diabetes care include reimbursement structures that, in contrast to visit-based billing, reward the provision of appropriate and high-quality care (39), and incentives that accommodate personalized care goals (6,40).

It is clear that 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).

WHEN TREATMENT GOALS ARE NOT MET

Some patients and their health care providers may not achieve the desired treatment goals. Reassessing the treatment regimen may require evaluation of

barriers such as income, health literacy, diabetes-related distress, depression, poverty, and competing demands, including those related to family responsibilities and dynamics. Other strategies may include culturally appropriate and enhanced DSME and DSMS, comanagement with a diabetes team, referral to a medical social worker for assistance with insurance coverage, medication-taking behavior assessment, or change in pharmacological therapy. Initiation of or increase in self-monitoring of blood glucose, continuous glucose monitoring, frequent patient contact, or referral to a mental health professional or physician with special expertise in diabetes may be useful.

References

- Grant RW, Kirkman MS. Trends in the evidence level for the American Diabetes Association's "Standards of Medical Care in Diabetes" from 2005 to 2014. *Diabetes Care* 2015;38:6–8
- Ali MK, Bullard KM, Saaddine JB, Cowie CC, Imperatore G, Gregg EW. Achievement of goals in U.S. diabetes care, 1999–2010. *N Engl J Med* 2013;368:1613–1624
- Wang J, Geiss LS, Cheng YJ, et al. Long-term and recent progress in blood pressure levels among U.S. adults with diagnosed diabetes, 1988–2008. *Diabetes Care* 2011;34:1579–1581
- Kerr EA, Heisler M, Krein SL, et al. Beyond comorbidity counts: how do comorbidity type and severity influence diabetes patients' treatment priorities and self-management? *J Gen Intern Med* 2007;22:1635–1640
- Fernandez A, Schillinger D, Warton EM, et al. Language barriers, physician-patient language concordance, and glycemic control among insured Latinos with diabetes: the Diabetes Study of Northern California (DISTANCE). *J Gen Intern Med* 2011;26:170–176
- TRIAD Study Group. Health systems, patients factors, and quality of care for diabetes: a synthesis of findings from the TRIAD study. *Diabetes Care* 2010;33:940–947
- Stellefson M, Dipnarine K, Stopka C. The chronic care model and diabetes management in US primary care settings: a systematic review. *Prev Chronic Dis* 2013;10:E26
- Coleman K, Austin BT, Brach C, Wagner EH. Evidence on the Chronic Care Model in the new millennium. *Health Aff (Millwood)* 2009;28:75–85
- Piatt GA, Anderson RM, Brooks MM, et al. 3-year follow-up of clinical and behavioral improvements following a multifaceted diabetes care intervention: results of a randomized controlled trial. *Diabetes Educ* 2010;36:301–309
- Renders CM, Valk GD, Griffin SJ, Wagner EH, Eijk Van JT, Assendelft WJ. Interventions to improve the management of diabetes in primary care, outpatient, and community settings: a systematic review. *Diabetes Care* 2001;24:1821–1833
- Katon WJ, Lin EHB, Von Korff M, et al. Collaborative care for patients with depression and chronic illnesses. *N Engl J Med* 2010;363:2611–2620
- Parchman ML, Zeber JE, Romero RR, Pugh JA. Risk of coronary artery disease in type 2 diabetes and the delivery of care consistent with the chronic care model in primary care settings: a STARNet study. *Med Care* 2007;45:1129–1134
- Davidson MB. How our current medical care system fails people with diabetes: lack of timely, appropriate clinical decisions. *Diabetes Care* 2009;32:370–372
- Grant RW, Pabon-Nau L, Ross KM, Youatt EJ, Pandiscio JC, Park ER. Diabetes oral medication initiation and intensification: patient views compared with current treatment guidelines. *Diabetes Educ* 2011;37:78–84
- Schillinger D, Piette J, Grumbach K, et al. Closing the loop: physician communication with diabetic patients who have low health literacy. *Arch Intern Med* 2003;163:83–90
- Rosal MC, Ockene IS, Restrepo A, et al. Randomized trial of a literacy-sensitive, culturally tailored diabetes self-management intervention for low-income Latinos: Latinos en Control. *Diabetes Care* 2011;34:838–844
- Osborn CY, Cavanaugh K, Wallston KA, et al. Health literacy explains racial disparities in diabetes medication adherence. *J Health Commun* 2011;16(Suppl. 3):268–278
- Rothman R, Malone R, Bryant B, Horlen C, DeWalt D, Pignone M. The relationship between literacy and glycemic control in a diabetes disease-management program. *Diabetes Educ* 2004;30:263–273
- O'Connor PJ, Bodkin NL, Fradkin J, et al. Diabetes performance measures: current status and future directions. *Diabetes Care* 2011;34:1651–1659
- Garg AX, Adhikari NK, McDonald H, et al. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. *JAMA* 2005;293:1223–1238
- Smith SA, Shah ND, Bryant SC, et al.; Evdencs Research Group. Chronic care model and shared care in diabetes: randomized trial of an electronic decision support system. *Mayo Clin Proc* 2008;83:747–757
- Jaffe MG, Lee GA, Young JD, Sidney S, Go AS. Improved blood pressure control associated with a large-scale hypertension program. *JAMA* 2013;310:699–705
- Davidson MB, Ansari A, Karlan VJ. Effect of a nurse-directed diabetes disease management program on urgent care/emergency room visits and hospitalizations in a minority population. *Diabetes Care* 2007;30:224–227
- Stone RA, Rao RH, Sevic MA, et al. Active care management supported by home telemonitoring in veterans with type 2 diabetes: the DiaTel randomized controlled trial. *Diabetes Care* 2010;33:478–484
- Duncan I, Birkmeyer C, Coughlin S, Li QE, Sherr D, Boren S. Assessing the value of diabetes education. *Diabetes Educ* 2009;35:752–760
- Berikai P, Meyer PM, Kazlauskaitė R, Savoy B, Kozik K, Fogelfeld L. Gain in patients' knowledge of diabetes management targets is associated with better glycemic control. *Diabetes Care* 2007;30:1587–1589
- Funnell MM, Brown TL, Childs BP, et al. National standards for diabetes self-management education. *Diabetes Care* 2007;30:1630–1637
- Klein S, Sheard NF, Pi-Sunyer X, et al. Weight management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies: a statement of the American Diabetes Association, the North American Association for the Study of Obesity, and the American Society for Clinical Nutrition. *Diabetes Care* 2004;27:2067–2073
- Norris SL, Zhang X, Avenell A, et al. Efficacy of pharmacotherapy for weight loss in adults with type 2 diabetes mellitus: a meta-analysis. *Arch Intern Med* 2004;164:1395–1404
- Tricco AC, Ivers NM, Grimshaw JM, et al. Effectiveness of quality improvement strategies on the management of diabetes: a systematic review and meta-analysis. *Lancet* 2012;379:2252–2261
- Peikes D, Chen A, Schore J, Brown R. Effects of care coordination on hospitalization, quality of care, and health care expenditures among Medicare beneficiaries: 15 randomized trials. *JAMA* 2009;301:603–618
- Feifer C, Nemeth L, Nietert PJ, et al. Different paths to high-quality care: three archetypes of top-performing practice sites. *Ann Fam Med* 2007;5:233–241
- Reed M, Huang J, Graetz I, et al. Outpatient electronic health records and the clinical care and outcomes of patients with diabetes mellitus. *Ann Intern Med* 2012;157:482–489
- Cebul RD, Love TE, Jain AK, Hebert CJ. Electronic health records and quality of diabetes care. *N Engl J Med* 2011;365:825–833
- Battersby M, Von Korff M, Schaefer J, et al. Twelve evidence-based principles for implementing self-management support in primary care. *Jt Comm J Qual Patient Saf* 2010;36:561–570
- Grant RW, Wald JS, Schnipper JL, et al. Practice-linked online personal health records for type 2 diabetes mellitus: a randomized controlled trial. *Arch Intern Med* 2008;168:1776–1782
- Pullen-Smith B, Carter-Edwards L, Leathers KH. Community health ambassadors: a model for engaging community leaders to promote better health in North Carolina. *J Public Health Manag Pract* 2008;14(Suppl.):S73–S81
- Bojadzievski T, Gabbay RA. Patient-centered medical home and diabetes. *Diabetes Care* 2011;34:1047–1053
- Rosenthal MB, Cutler DM, Feder J. The ACO rules—striking the balance between participation and transformative potential. *N Engl J Med* 2011;365:e6
- Washington AE, Lipstein SH. The Patient-Centered Outcomes Research Institute—promoting better information, decisions, and health. *N Engl J Med* 2011;365:e31

2. Classification and Diagnosis of Diabetes

American Diabetes Association

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CLASSIFICATION

Diabetes can be classified into the following general categories:

1. Type 1 diabetes (due to β -cell destruction, usually leading to absolute insulin deficiency)
2. Type 2 diabetes (due to a progressive insulin secretory defect on the background of insulin resistance)
3. Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes)
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 [MODY]), diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced diabetes (such as 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).

Assigning a type of diabetes to an individual often depends on the circumstances present at the time of diagnosis, with individuals not necessarily fitting clearly into a single category. For example, some patients cannot be clearly classified as having type 1 or type 2 diabetes. Clinical presentation and disease progression may vary considerably in both types of diabetes.

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 cohorts. Occasionally, patients with type 2 diabetes may present with diabetic ketoacidosis (DKA). Children with type 1 diabetes typically present with the hallmark symptoms of polyuria/polydipsia and occasionally with DKA. The onset of type 1 diabetes may be variable in adults and may not present with the classic symptoms seen in children. However, difficulties in diagnosis may occur in children, adolescents, and adults, with the true diagnosis becoming more obvious over time.

DIAGNOSTIC TESTS FOR DIABETES

Diabetes may be diagnosed based on A1C criteria or plasma glucose criteria, either the fasting plasma glucose (FPG) or the 2-h plasma glucose (2-h PG) value after a 75-g oral glucose tolerance test (OGTT) (1,2) (**Table 2.1**).

The same tests are used to both screen for and diagnose diabetes. Diabetes may be identified anywhere along the spectrum of clinical scenarios: in seemingly low-risk individuals who happen to have glucose testing, in symptomatic patients, and in higher-risk individuals whom the provider tests because of a suspicion of diabetes. The same tests will also detect individuals with prediabetes.

A1C

The A1C test should be performed using a method that is certified by the NGSP and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. Although point-of-care (POC) A1C assays may be NGSP certified, proficiency testing is not mandated for performing the test, so use of POC assays for diagnostic purposes may be problematic and is not recommended.

The A1C has several advantages to the FPG and OGTT, including greater convenience (fasting not required), greater preanalytical stability, and less day-to-day perturbations during stress and illness. These advantages must be balanced by

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Table 2.1—Criteria for the diagnosis of diabetes

A1C $\geq 6.5\%$. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

OR

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 an 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

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

greater cost, the limited availability of A1C testing in certain regions of the developing world, and the incomplete correlation between A1C and average glucose in certain individuals.

It is important to take age, race/ethnicity, and anemia/hemoglobinopathies into consideration when using the A1C to diagnose diabetes.

Age

The epidemiological studies that formed the framework for recommending A1C to diagnose diabetes only included adult populations. Therefore, it remains unclear if A1C and the same A1C cut point should be used to diagnose diabetes in children and adolescents (3–5).

Race/Ethnicity

A1C levels may vary with patients' race/ethnicity (6,7). For example, African Americans may have higher A1C levels than non-Hispanic whites despite similar fasting and postglucose load glucose levels. A recent epidemiological study found that, when matched for FPG, African Americans (with and without diabetes) had higher A1C levels than non-Hispanic whites, but also had higher levels of fructosamine and glycated albumin and lower levels of 1,5-anhydroglucitol, suggesting that their glycemic burden (particularly postprandially) may be higher (8).

Hemoglobinopathies/Anemias

Interpreting A1C levels in the presence of certain hemoglobinopathies and anemia may be problematic. For patients with an abnormal hemoglobin but normal red cell turnover, such as those with the sickle cell trait, an A1C assay without interference from abnormal hemoglobins should be used. An updated list of interferences is available at www.ngsp.org/interf.asp. In conditions associated with increased red cell turnover, such as pregnancy (second and third trimesters), recent blood loss or transfusion, erythropoietin therapy, or hemolysis, only blood glucose criteria should be used to diagnose diabetes.

Fasting and 2-Hour Plasma Glucose

In addition to the A1C test, the FPG and 2-h PG may also be used to diagnose diabetes (Table 2.1). The concordance between the FPG and 2-h PG tests is imperfect, as is the concordance between A1C and either glucose-based test. National Health and Nutrition Examination Survey (NHANES) data indicate that an A1C cut point of $\geq 6.5\%$ identifies one-third fewer cases of undiagnosed diabetes than a fasting glucose cut point of ≥ 126 mg/dL (7.0 mmol/L) (9). Numerous studies have confirmed that, compared with these A1C and FPG cut points, the 2-h PG value diagnoses more people with diabetes. Of note, the lower sensitivity of A1C at the designated cut point may be offset by the test's ease of use and facilitation of more widespread testing.

Unless there is a clear clinical diagnosis (e.g., a patient in a hyperglycemic crisis or with classic symptoms of hyperglycemia and a random plasma glucose ≥ 200 mg/dL), it is recommended that the same test be repeated immediately using a new blood sample for confirmation because there will be a greater likelihood of concurrence. For example, if the A1C is 7.0% and a repeat result is 6.8%, the diagnosis of diabetes is confirmed. If two different tests (such as A1C and FPG) are both above the diagnostic threshold, 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. 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 $\geq 6.5\%$), but not

FPG (<126 mg/dL [7.0 mmol/L]), that person should nevertheless be considered to have diabetes.

Since all the tests have preanalytic and analytic variability, 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 least likely for A1C, more likely for FPG, and most likely for the 2-h PG, especially if the glucose samples are collected at room temperature and not centrifuged promptly. Barring laboratory error, such patients will likely have test results near the margins of the diagnostic threshold. The health care professional should follow the patient closely and repeat the test in 3–6 months.

CATEGORIES OF INCREASED RISK FOR DIABETES (PREDIABETES)

Recommendations

- Testing to assess risk for future diabetes in asymptomatic people should be considered in adults of any age who are overweight or obese (BMI ≥ 25 kg/m² or ≥ 23 kg/m² in Asian Americans) and who have one or more additional risk factors for diabetes. For all patients, particularly those who are overweight or obese, testing should begin at age 45 years. **B**
- If tests are normal, repeat testing carried out at a minimum of 3-year intervals is reasonable. **C**
- To test for prediabetes, the A1C, FPG, and 2-h PG after 75-g OGTT are appropriate. **B**
- In patients with prediabetes, identify and, if appropriate, treat other cardiovascular disease (CVD) risk factors. **B**
- Testing to detect prediabetes should be considered in children and adolescents who are overweight or obese and who have two or more additional risk factors for diabetes. **E**

Description

In 1997 and 2003, the Expert Committee on Diagnosis and Classification of Diabetes Mellitus (10,11) recognized a group of individuals whose glucose levels did not meet the criteria for diabetes but were too high to be considered

Table 2.2—Criteria for testing for diabetes or prediabetes in asymptomatic adults

- Testing should be considered in all adults who are overweight (BMI ≥ 25 kg/m² or ≥ 23 kg/m² in Asian Americans) and have additional risk factors:
 - physical inactivity
 - first-degree relative with diabetes
 - high-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
 - women who delivered a baby weighing >9 lb or were diagnosed with GDM
 - hypertension ($\geq 140/90$ 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
 - A1C $\geq 5.7\%$, IGT, or IFG on previous testing
 - other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
 - history of CVD
- For all patients, particularly those who are overweight or obese, testing should begin at age 45 years.
- 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 (e.g., those with prediabetes should be tested yearly) and risk status.

normal. “Prediabetes” is the term used for individuals with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) and indicates an increased risk for the future development of diabetes. IFG and IGT should not be viewed as clinical entities in their own right but rather risk factors for diabetes (Table 2.2) and CVD. IFG and IGT are associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension.

Diagnosis

In 1997 and 2003, the Expert Committee on Diagnosis and Classification of Diabetes Mellitus (10,11) defined IFG as FPG levels 100–125 mg/dL (5.6–6.9 mmol/L) and IGT as 2-h PG after 75-g OGTT levels 140–199 mg/dL (7.8–11.0 mmol/L). It should be noted that the World Health Organization (WHO) and numerous 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 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 an A1C between 5.5–6.0% had a substantially increased risk of diabetes (5-year incidence from

9 to 25%). An A1C range of 6.0–6.5% had a 5-year risk of developing diabetes between 25–50% and a relative risk 20 times higher compared with an A1C of 5.0% (12). 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 (13). Other analyses suggest that an A1C of 5.7% is associated with a diabetes risk similar to that of the high-risk participants in the Diabetes Prevention Program (DPP) (14).

Hence, it is reasonable to consider an A1C range of 5.7–6.4% as identifying individuals with prediabetes. As with those with IFG and/or IGT, individuals with an A1C of 5.7–6.4% should be informed of their increased risk for diabetes and CVD and counseled about effective strategies to lower their risks (see Section 5. Prevention or Delay of Type 2 Diabetes). Similar to glucose measurements, the continuum of risk is curvilinear, so as A1C rises, the diabetes risk rises disproportionately (12). Aggressive interventions and vigilant follow-up should be pursued for those considered at very high risk (e.g., those with A1C $>6.0\%$).

Table 2.3 summarizes the categories of prediabetes. For recommendations regarding risk factors and screening for prediabetes, see p. S12 (“Testing for Type 2 Diabetes and Prediabetes in Asymptomatic Adults” and “Testing for Type 2 Diabetes and Prediabetes in Children and Adolescents”).

TYPE 1 DIABETES

Recommendation

- Inform the relatives of patients with type 1 diabetes of the opportunity to be tested for type 1 diabetes risk, but only in the setting of a clinical research study. **E**

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, autoantibodies to insulin, autoantibodies to GAD (GAD65), autoantibodies to the tyrosine phosphatases IA-2 and IA-2 β , and autoantibodies to zinc transporter 8 (ZnT8). Type 1 diabetes is defined by the presence of one 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.

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 ketoacidosis as the first manifestation of the disease. Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or ketoacidosis with infection or other stress. Adults may retain sufficient β -cell function to prevent ketoacidosis for many years; such individuals eventually become dependent on insulin for survival and are at risk for ketoacidosis. 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

Table 2.3—Categories of increased risk for diabetes (prediabetes)*

FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)

OR

2-h PG in the 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%

*For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.

commonly occurs 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 should not preclude the diagnosis. These patients are also prone to other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, celiac disease, autoimmune hepatitis, myasthenia gravis, and pernicious anemia.

Idiopathic Diabetes

Some forms of type 1 diabetes have no known etiologies. These patients have permanent insulinopenia and are prone to ketoacidosis, but have no evidence of autoimmunity. Although only a minority of patients with type 1 diabetes fall into this category, of those who do, most are of African or Asian ancestry. Individuals with this form of diabetes suffer from episodic ketoacidosis and exhibit varying degrees of insulin deficiency between episodes. This form of diabetes is strongly inherited, lacks immunological evidence for β -cell autoimmunity, and is not HLA associated. An absolute requirement for insulin replacement therapy in affected patients may come and go.

Testing for Type 1 Diabetes

The incidence and prevalence of type 1 diabetes is increasing (15). Type 1 diabetic patients often present with acute symptoms of diabetes and markedly elevated blood glucose levels, and some are diagnosed with life-threatening ketoacidosis. Several studies suggest that measuring islet autoantibodies in relatives of those with type 1 diabetes may identify individuals who are at risk for developing type 1 diabetes. Such testing, coupled with education about diabetes symptoms and close follow-up in an observational clinical study, may enable earlier identification of type 1 diabetes onset. There is evidence to suggest that early diagnosis may limit acute complications (16) and extend long-term endogenous insulin production (17).

A recent 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 (16,18). 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 genetic cases of type 1 diabetes.

While there is currently a lack of accepted screening programs, one should consider referring relatives of those with type 1 diabetes for antibody testing for risk assessment in the setting of a clinical research study (<http://www2.diabetestrialnet.org>). Widespread clinical testing of asymptomatic low-risk individuals is not currently recommended due to lack of approved therapeutic interventions. Higher-risk individuals may be tested, but only in the context of a clinical research setting. Individuals who test positive will 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 (www.clinicaltrials.gov).

TYPE 2 DIABETES

Recommendations

- Testing to detect type 2 diabetes in asymptomatic people should be considered in adults of any age who are overweight or obese ($\text{BMI} \geq 25 \text{ kg/m}^2$ or $\geq 23 \text{ kg/m}^2$ in Asian Americans) and who have one or more additional risk factors for diabetes. For all patients, particularly those who are overweight or obese, testing should begin at age 45 years. **B**
- If tests are normal, repeat testing carried out at a minimum of 3-year intervals is reasonable. **C**
- To test for diabetes, the A1C, FPG, and 2-h PG after 75-g OGTT are appropriate. **B**
- In patients with diabetes, identify and, if appropriate, treat other CVD risk factors. **B**

- Testing to detect type 2 diabetes should be considered in children and adolescents who are overweight or obese and who have two or more additional risk factors for diabetes. **E**

Description

This form, previously referred to as "non-insulin-dependent diabetes" or "adult-onset diabetes," accounts for ~90–95% of all diabetes. Type 2 diabetes encompasses individuals who have insulin resistance and usually relative (rather than absolute) insulin deficiency. 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 are obese. Obesity itself causes some degree of insulin resistance. Patients who are not obese by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region.

Ketoacidosis seldom occurs spontaneously in type 2 diabetes; when seen, it usually arises in association with the stress of another illness such as infection. 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, such patients are at an 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 may improve with weight reduction and/or pharmacological 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 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, more so than type 1 diabetes. However, the genetics of type 2 diabetes is poorly understood.

Testing for Type 2 Diabetes and Prediabetes in Asymptomatic Adults

Prediabetes and 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 5. Prevention or Delay of Type 2 Diabetes) and reduce the risk of diabetes complications (see Section 8. Cardiovascular Disease and Risk Management and Section 9. Microvascular Complications and Foot Care).

Approximately one-quarter of people with diabetes in the U.S. are undiagnosed. 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. A large European randomized controlled trial compared the impact of screening for diabetes and intensive multifactorial intervention with that of screening and routine care (19). General practice patients between the ages of 40–69 years were screened for diabetes and randomized 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 (19). The excellent care provided to patients in the routine care group and the lack of an unscreened control arm limit our ability to prove that screening and early intensive treatment impact outcomes. Mathematical modeling studies suggest that 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) (20).

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

Age

Testing recommendations for diabetes in asymptomatic adults are listed in **Table 2.2**. Age is a major risk factor for diabetes. Testing should begin at age 45 years for all patients, particularly those who are overweight or obese.

BMI and Ethnicity

Testing should be considered in adults of any age with BMI ≥ 25 kg/m² and one or more additional risk factors for diabetes. However, recent data (21) and evidence from the ADA position statement “BMI Cut Points to Identify At-Risk Asian Americans for Type 2 Diabetes Screening” (22) suggest that the BMI cut point should be lower for the Asian American population. For diabetes screening purposes, the BMI cut points fall consistently between 23–24 kg/m² (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/m² practical. In determining a single BMI cut point, it is important to balance sensitivity and specificity so as to provide a valuable screening tool without numerous false positives. An argument can be made to push the BMI cut point to lower than 23 kg/m² in favor of increased sensitivity; however, this would lead to an unacceptably low specificity (13.1%). Data from the WHO also suggest that a BMI ≥ 23 kg/m² should be used to define increased risk in Asian Americans (23).

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/m² in non-Hispanic whites was equivalent to a BMI of 26 kg/m² in African Americans (24).

Medications

Certain medications, such as glucocorticoids, thiazide diuretics, and atypical antipsychotics (25), are known to increase the risk of diabetes and should be considered when ascertaining a diagnosis.

Diagnostic Tests

The A1C, FPG, and 2-h PG after 75-g OGTT are appropriate for testing. 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 (26–32) has primarily been demonstrated among individuals with IGT, not for individuals with isolated IFG or for those with prediabetes defined by A1C criteria.

Testing Interval

The appropriate interval between tests is not known (33). 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 (33).

Community Screening

Ideally, testing should be carried out within a health care setting because of the need for follow-up and treatment. Community testing outside a health care setting is not recommended because people with positive tests may not seek, or have access to, appropriate follow-up testing and care. 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.

Testing for Type 2 Diabetes and Prediabetes in Children and Adolescents

In the last decade, the incidence and prevalence of type 2 diabetes in adolescents has increased dramatically, especially in ethnic populations (15). Recent studies question the validity of A1C in the pediatric population, especially among certain ethnicities, and suggest OGTT or FPG as more suitable diagnostic tests (34). 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 (35). The ADA acknowledges the limited data supporting A1C for diagnosing diabetes in children and adolescents. However, aside from rare instances, such as cystic fibrosis and hemoglobinopathies, the ADA continues to recommend A1C in this cohort (36,37). The modified recommendations of the ADA consensus report “Type 2 Diabetes in Children and Adolescents” are summarized in **Table 2.4**.

Table 2.4—Testing for type 2 diabetes or prediabetes in asymptomatic children*

Criteria

- Overweight (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)

Plus any two of the following risk factors:

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

Age of initiation: age 10 years or at onset of puberty, if puberty occurs at a younger age

Frequency: every 3 years

*Persons aged ≤18 years.

GESTATIONAL DIABETES MELLITUS**Recommendations**

- Test for undiagnosed type 2 diabetes at the first prenatal visit in those with risk factors, using standard diagnostic criteria. **B**
- Test for GDM at 24–28 weeks of gestation in pregnant women not previously known to have diabetes. **A**
- Screen women with GDM for persistent diabetes at 6–12 weeks postpartum, using the OGTT and clinically appropriate nonpregnancy diagnostic criteria. **E**
- Women with a history of GDM should have lifelong screening for the development of diabetes or prediabetes at least every 3 years. **B**
- Women with a history of GDM found to have prediabetes should receive lifestyle interventions 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 (10), regardless of whether the condition may have predated the pregnancy or persisted after the pregnancy. This definition facilitated a uniform strategy for detection and classification of GDM, but it was limited by imprecision.

The ongoing epidemic of obesity and diabetes has led to more type 2 diabetes in women of childbearing age, resulting in an increase in the number of pregnant women with undiagnosed type 2 diabetes (38). 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 (**Table 2.2**) at their initial prenatal visit, using standard diagnostic criteria (**Table 2.1**). Women with diabetes in the first trimester would be classified as having type 2 diabetes. GDM is diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes.

Diagnosis

GDM carries risks for the mother and neonate. Not all adverse outcomes are of equal clinical importance. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (39), a large-scale (~25,000 pregnant women) multinational cohort study, demonstrated that risk of adverse maternal, fetal, and neonatal outcomes continuously increased as a function of maternal glycemia at 24–28 weeks, 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 2.5**) can be accomplished with either of two strategies:

1. “One-step” 75-g OGTT or
2. “Two-step” approach with a 50-g (nonfasting) screen followed by a 100-g OGTT for those who screen positive

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

In the 2011 Standards of Care (40), the ADA for the first time recommended that all pregnant women not known to have prior diabetes undergo a 75-g OGTT at 24–28 weeks of gestation, based on a recommendation of the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) (41). The IADPSG defined diagnostic cut

points for GDM as the average glucose values (fasting, 1-h, and 2-h PG) in the HAPO study at which odds for adverse outcomes reached 1.75 times the estimated odds of these outcomes at the mean glucose 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. The ADA recognized that the anticipated increase in the incidence of GDM would have significant impact on the costs, medical infrastructure capacity, and potential for increased “medicalization” of pregnancies previously categorized as normal, but recommended these diagnostic criteria changes in the context of worrisome worldwide increases in obesity and diabetes rates with the intent of optimizing gestational outcomes for women and their offspring.

The expected benefits to these pregnancies and offspring are inferred from intervention trials that focused on women with lower levels of hyperglycemia than identified using older GDM diagnostic criteria and that found modest benefits including reduced rates of large-for-gestational-age births and preeclampsia (42,43). It is important to note that 80–90% of women being treated for mild GDM in two randomized controlled trials (whose glucose values overlapped with the thresholds recommended by the IADPSG) could be managed with lifestyle therapy alone. Data are lacking on how the treatment of lower levels of hyperglycemia affects a mother's risk for the development of type 2 diabetes in the future and her offspring's risk for obesity, diabetes, and other metabolic dysfunction. 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.

Two-Step Strategy

In 2013, the National Institutes of Health (NIH) convened a consensus development conference on diagnosing GDM. The 15-member panel had representatives from obstetrics/gynecology, maternal-fetal medicine, pediatrics, diabetes research, biostatistics, and other related fields to consider diagnostic criteria (44). The panel recommended the two-step approach of screening with a 1-h 50-g

Table 2.5—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 overt 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 overt diabetes.

If the plasma glucose level measured 1 h after the load is ≥ 140 mg/dL* (7.8 mmol/L), 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 if at least two of the following four plasma glucose levels (measured fasting and 1 h, 2 h, 3 h after the OGTT) are met or exceeded:

	Carpenter/Coustan (56)	or	NDDG (57)
● Fasting	95 mg/dL (5.3 mmol/L)		105 mg/dL (5.8 mmol/L)
● 1 h	180 mg/dL (10.0 mmol/L)		190 mg/dL (10.6 mmol/L)
● 2 h	155 mg/dL (8.6 mmol/L)		165 mg/dL (9.2 mmol/L)
● 3 h	140 mg/dL (7.8 mmol/L)		145 mg/dL (8.0 mmol/L)

NDDG, National Diabetes Data Group.

*The ACOG recommends a lower threshold of 135 mg/dL (7.5 mmol/L) in high-risk ethnic populations with higher prevalence of GDM; some experts also recommend 130 mg/dL (7.2 mmol/L).

glucose load test (GLT) followed by a 3-h 100-g OGTT for those who screen positive, a strategy commonly used in the U.S.

Key factors reported in the NIH panel's decision-making process were the lack of clinical trial interventions demonstrating the benefits of the one-step strategy and the potential negative consequences of identifying a large new group of women with GDM, including medicalization of pregnancy with increased interventions 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, and shoulder dystocia, without increasing small-for-gestational-age births (45). The American College of Obstetricians and Gynecologists (ACOG) updated its guidelines in 2013 and supported the two-step approach (46).

Future Considerations

The conflicting recommendations from expert groups underscore the fact that there are data to support each strategy. 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., cost-benefit estimation, willingness to change practice based on correlation studies rather than clinical intervention trial results, relative role of cost considerations, and available infrastructure locally, nationally, and internationally).

As the IADPSG criteria have been adopted internationally, further evidence has emerged to support improved pregnancy outcomes with cost savings (47) and may be the preferred approach. In addition, pregnancies complicated by GDM per IADPSG criteria, but not recognized as such, have comparable outcomes to pregnancies diagnosed as GDM by the more stringent two-step criteria (48). There remains strong consensus that establishing a uniform approach to diagnosing GDM will benefit patients, caregivers, and policymakers. Longer-term outcome studies are currently underway.

MONOGENIC DIABETES SYNDROMES

Monogenic defects that cause β -cell dysfunction, such as neonatal diabetes and MODY, represent a small fraction of patients with diabetes (<5%). These forms

of diabetes are frequently characterized by onset of hyperglycemia at an early age (generally before age 25 years).

Neonatal Diabetes

Diabetes diagnosed in the first 6 months of life has been shown not to be typical autoimmune type 1 diabetes. This so-called neonatal diabetes can either be transient or permanent. The most common genetic defect causing transient disease is a defect on ZAC/HYAMI imprinting, whereas permanent neonatal diabetes is most commonly a defect in the gene encoding the Kir6.2 subunit of the β -cell K_{ATP} channel. Diagnosing the latter has implications, since such children can be well managed with sulfonylureas.

Maturity-Onset Diabetes of the Young

MODY is characterized by impaired insulin secretion with minimal or no defects in insulin action. It is inherited in an autosomal dominant pattern. Abnormalities at six genetic loci on different chromosomes have been identified to date. The most common form is associated with mutations on chromosome 12 in a hepatic transcription factor referred to as hepatocyte nuclear factor (HNF)-1 α . A second form is associated with mutations in the glucokinase gene on chromosome 7p and results in a defective glucokinase molecule. Glucokinase converts glucose to glucose-6-phosphate, the metabolism of which, in turn, stimulates insulin secretion by the β -cell. The less common forms of MODY result from mutations in other transcription factors, including HNF-4 α , HNF-1 β , insulin promoter factor (IPF)-1, and NeuroD1.

Diagnosis

Readily available commercial genetic testing now enables a true genetic diagnosis. It is important to correctly diagnose one of the monogenic forms of diabetes because these children may be incorrectly diagnosed with type 1 or type 2 diabetes, leading to suboptimal treatment regimens and delays in diagnosing other family members (49).

The diagnosis of monogenic diabetes should be considered in children with the following findings:

- Diabetes diagnosed within the first 6 months of life
- Strong family history of diabetes but without typical features of type 2 diabetes (nonobese, low-risk ethnic group)

- Mild fasting hyperglycemia (100–150 mg/dL [5.5–8.5 mmol/L]), especially if young and nonobese
- Diabetes with negative autoantibodies and without signs of obesity or insulin resistance

CYSTIC FIBROSIS–RELATED DIABETES

Recommendations

- Annual screening for cystic fibrosis–related diabetes (CFRD) with OGTT should begin by age 10 years in all patients with cystic fibrosis who do not have CFRD. **B** A1C as a screening test for CFRD is not recommended. **B**
- Patients with CFRD should be treated with insulin to attain individualized glycemic goals. **A**
- In patients with cystic fibrosis and IGT without confirmed diabetes, prandial insulin therapy should be considered to maintain weight. **B**
- Annual monitoring for complications of diabetes is recommended, beginning 5 years after the diagnosis of CFRD. **E**

CFRD is the most common comorbidity in people with cystic fibrosis, occurring in about 20% of adolescents and 40–50% of adults. Diabetes in this population is associated with worse nutritional status, more severe inflammatory lung disease, and greater mortality from respiratory failure. Insulin insufficiency related to partial fibrotic destruction of the islet mass is the primary defect in CFRD. Genetically determined function of the remaining β -cells and insulin resistance associated with infection and inflammation may also play a role. While screening for diabetes before the age of 10 years can identify risk for progression to CFRD in those with abnormal glucose tolerance, there appears to be no benefit with respect to weight, height, BMI, or lung function compared with those with normal glucose tolerance <10 years of age. The use of continuous glucose monitoring may be more sensitive than OGTT to detect risk for progression to CFRD, but this likely needs more evidence.

Encouraging data suggest that improved screening (50,51) and aggressive insulin therapy have narrowed the gap in mortality between cystic fibrosis patients

with and without diabetes and have eliminated the sex difference in mortality (52). Recent trials comparing insulin with oral repaglinide showed no significant difference between the groups. However, another study compared three different groups: premeal insulin aspart, repaglinide, or oral placebo in cystic fibrosis patients with abnormal glucose tolerance. Patients all had weight loss; however, in the insulin-treated group, this pattern was reversed, and they gained 0.39 (\pm 0.21) BMI units ($P = 0.02$). Patients in the repaglinide-treated group had initial weight gain, but this was not sustained by 6 months. The placebo group continued to lose weight (53). Insulin remains the most widely used therapy for CFRD (54).

Recommendations for the clinical management of CFRD can be found in the ADA 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” (55).

References

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2014;37(Suppl. 1):S81–S90
2. The International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care* 2009;32:1327–1334
3. Nowicka P, Santoro N, Liu H, et al. Utility of hemoglobin A_{1c} for diagnosing prediabetes and diabetes in obese children and adolescents. *Diabetes Care* 2011;34:1306–1311
4. García de Guadiana Romualdo L, González Morales M, Albaladejo Otón MD, et al. [The value of hemoglobin A1c for diagnosis of diabetes mellitus and other changes in carbohydrate metabolism in women with recent gestational diabetes mellitus] *Endocrinol Nutr* 2012;59:362–366 [in Spanish]
5. Cowie CC, Rust KF, Byrd-Holt DD, et al. Prevalence of diabetes and high risk for diabetes using A1C criteria in the U.S. population in 1988–2006. *Diabetes Care* 2010;33:562–568
6. Ziemer DC, Kolm P, Weintraub WS, et al. Glucose-independent, black-white differences in hemoglobin A1c levels: a cross-sectional analysis of 2 studies. *Ann Intern Med* 2010;152:770–777
7. Kumar PR, Bhansali A, Ravikiran M, et al. Utility of glycosylated hemoglobin in diagnosing type 2 diabetes mellitus: a community-based study. *J Clin Endocrinol Metab* 2010;95:2832–2835
8. Selvin E, Steffes MW, Ballantyne CM, Hoogeveen RC, Coresh J, Brancati FL. Racial differences in glycemic markers: a cross-sectional analysis of community-based data. *Ann Intern Med* 2011;154:303–309
9. Picón MJ, Murri M, Muñoz A, Fernández-García JC, Gomez-Huelgas R, Tinahones FJ.

Hemoglobin A1c versus oral glucose tolerance test in postpartum diabetes screening. *Diabetes Care* 2012;35:1648–1653

10. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997;20:1183–1197

11. Genuth S, Alberti KG, Bennett P, et al.; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003;26:3160–3167

12. Zhang X, Gregg EW, Williamson DF, et al. A1C level and future risk of diabetes: a systematic review. *Diabetes Care* 2010;33:1665–1673

13. Selvin E, Steffes MW, Zhu H, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med* 2010;362:800–811

14. Ackermann RT, Cheng YJ, Williamson DF, Gregg EW. Identifying adults at high risk for diabetes and cardiovascular disease using hemoglobin A1c National Health and Nutrition Examination Survey 2005–2006. *Am J Prev Med* 2011;40:11–17

15. Dabelea D, Mayer-Davis EJ, Saydah S, et al.; SEARCH for Diabetes in Youth Study. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. *JAMA* 2014;311:1778–1786

16. Ziegler AG, Rewers M, Simell O, et al. Seroprevalence to multiple islet autoantibodies and risk of progression to diabetes in children. *JAMA* 2013;309:2473–2479

17. Sorensen JS, Johannesen J, Pociot F, et al. Residual β -cell function 3–6 years after onset of type 1 diabetes reduces risk of severe hypoglycemia in children and adolescents. *Diabetes Care* 2013;36:3454–3459

18. Sosenko JM, Skyler JS, Palmer JP, et al.; Type 1 Diabetes TrialNet Study Group; Diabetes Prevention Trial-Type 1 Study Group. The prediction of type 1 diabetes by multiple autoantibody levels and their incorporation into an autoantibody risk score in relatives of type 1 diabetic patients. *Diabetes Care* 2013;36:2615–2620

19. Griffin SJ, Borch-Johnsen K, Davies MJ, et al. Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. *Lancet* 2011;378:156–167

20. Kahn R, Alperin P, Eddy D, et al. Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effectiveness analysis. *Lancet* 2010;375:1365–1374

21. Araneta MR, Gandinetti A, Chang HK. Optimum BMI cut points to screen Asian Americans for type 2 diabetes: the UCSD Filipino Health Study and the North Kohala Study. *Diabetes* 2014;63(Suppl. 1):A20

22. Hsu WC, Araneta MR, Kanaya AM, Chiang JL, Fujimoto W. BMI cut points to identify at-risk Asian Americans for type 2 diabetes screening. *Diabetes Care* 2015;38:150–158

23. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004;363:157–163

24. Chiu M, Austin PC, Manuel DG, Shah BR, Tu JV. Deriving ethnic-specific BMI cutoff points for

- assessing diabetes risk. *Diabetes Care* 2011;34:1741–1748
25. Erickson SC, Le L, Zakharyan A, et al. New-onset treatment-dependent diabetes mellitus and hyperlipidemia associated with atypical antipsychotic use in older adults without schizophrenia or bipolar disorder. *J Am Geriatr Soc* 2012;60:474–479
26. Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393–403
27. Tuomilehto J, Lindström J, Eriksson JG, et al.; Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001;344:1343–1350
28. Pan X-R, Li G-W, Hu Y-H, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and Diabetes Study. *Diabetes Care* 1997;20:537–544
29. Buchanan TA, Xiang AH, Peters RK, et al. Preservation of pancreatic β -cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes* 2002;51:2796–2803
30. Chiasson J-L, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trial Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002;359:2072–2077
31. Gerstein HC, Yusuf S, Bosch J, et al.; DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 2006;368:1096–1105
32. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V; Indian Diabetes Prevention Programme (IDPP). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia* 2006;49:289–297
33. Johnson SL, Tabaei BP, Herman WH. The efficacy and cost of alternative strategies for systematic screening for type 2 diabetes in the U.S. population 45–74 years of age. *Diabetes Care* 2005;28:307–311
34. Buse JB, Kaufman FR, Linder B, Hirst K, El Ghormli L, Willi S; HEALTHY Study Group. Diabetes screening with hemoglobin A(1c) versus fasting plasma glucose in a multiethnic middle-school cohort. *Diabetes Care* 2013;36:429–435
35. Kapadia C, Zeitler P; Drugs and Therapeutics Committee of the Pediatric Endocrine Society. Hemoglobin A1c measurement for the diagnosis of type 2 diabetes in children. *Int J Pediatr Endocrinol* 2012;2012:31
36. Kester LM, Hey H, Hannon TS. Using hemoglobin A1c for prediabetes and diabetes diagnosis in adolescents: can adult recommendations be upheld for pediatric use? *J Adolesc Health* 2012;50:321–323
37. Wu E-L, Kazzi NG, Lee JM. Cost-effectiveness of screening strategies for identifying pediatric diabetes mellitus and dysglycemia. *JAMA Pediatr* 2013;167:32–39
38. Lawrence JM, Contreras R, Chen W, Sacks DA. Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women, 1999–2005. *Diabetes Care* 2008;31:899–904
39. Metzger BE, Lowe LP, Dyer AR, et al.; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008;358:1991–2002
40. American Diabetes Association. Standards of medical care in diabetes—2011. *Diabetes Care* 2011;34(Suppl. 1):S11–S61
41. Metzger BE, Gabbe SG, Persson B, et al.; International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010;33:676–682
42. Landon MB, Spong CY, Thom E, et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med* 2009;361:1339–1348
43. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS; Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* 2005;352:2477–2486
44. Vandersten JP, Dodson WC, Espeland MA, et al. NIH consensus development conference: diagnosing gestational diabetes mellitus. *NIH Consens State Sci Statements* 2013;29:1–31
45. Horvath K, Koch K, Jeitler K, et al. Effects of treatment in women with gestational diabetes mellitus: systematic review and meta-analysis. *BMJ* 2010;340:c1395
46. Committee on Practice Bulletins—Obstetrics. Practice Bulletin No. 137: gestational diabetes mellitus. *Obstet Gynecol* 2013;122:406–416
47. Duran A, Sáenz S, Torrejón MJ, et al. Introduction of IADPSG criteria for the screening and diagnosis of gestational diabetes mellitus results in improved pregnancy outcomes at a lower cost in a large cohort of pregnant women: the St. Carlos Gestational Diabetes Study. *Diabetes Care* 2014;37:2442–2450
48. Ethridge JK Jr, Catalano PM, Waters TP. Perinatal outcomes associated with the diagnosis of gestational diabetes made by the International Association of the Diabetes and Pregnancy Study Groups criteria. *Obstet Gynecol* 2014;124:571–578
49. Hattersley A, Bruining J, Shield J, Njolstad P, Donaghue KC. The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes* 2009;10(Suppl. 12):33–42
50. Kern AS, Prestridge AL. Improving screening for cystic fibrosis-related diabetes at a pediatric cystic fibrosis program. *Pediatrics* 2013;132:e512–e518
51. Waugh N, Royle P, Craigie I, et al. Screening for cystic fibrosis-related diabetes: a systematic review. *Health Technol Assess* 2012;16:iii–iv, 1–179
52. Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W. Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. *Diabetes Care* 2009;32:1626–1631
53. Moran A, Pekow P, Grover P, et al.; Cystic Fibrosis Related Diabetes Therapy Study Group. Insulin therapy to improve BMI in cystic fibrosis-related diabetes without fasting hyperglycemia: results of the cystic fibrosis related diabetes therapy trial. *Diabetes Care* 2009;32:1783–1788
54. Onady GM, Stolfi A. Insulin and oral agents for managing cystic fibrosis-related diabetes. *Cochrane Database Syst Rev* 2013;7:CD004730
55. Moran A, Brunzell C, Cohen RC, et al.; CFRD Guidelines Committee. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. *Diabetes Care* 2010;33:2697–2708
56. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol* 1982;144:768–773
57. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 1979;28:1039–1057

3. Initial Evaluation and Diabetes Management Planning

American Diabetes Association

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MEDICAL EVALUATION

Recommendation

- Consider screening those with type 1 diabetes for autoimmune diseases (e.g., thyroid dysfunction, celiac disease) as appropriate. **E**

A complete medical evaluation should be performed at the initial visit to

1. Classify diabetes
2. Detect diabetes complications
3. Review previous treatment and risk factor control in patients with established diabetes
4. Assist in formulating a management plan
5. Provide a basis for continuing care

Laboratory tests appropriate to the evaluation of each patient's medical condition should be completed. A focus on the components of comprehensive care (**Table 3.1**) will enable the health care team to optimally manage the patient with diabetes. Adults who develop type 1 diabetes can develop additional autoimmune disorders, although their risk is lower than that in children and adolescents with type 1 diabetes. For additional details on autoimmune conditions, see Section 11. Children and Adolescents.

MANAGEMENT PLAN

People with diabetes should receive medical care from a collaborative, integrated team with expertise in diabetes. This team may include physicians, nurse practitioners, physician's assistants, nurses, dietitians, pharmacists, and mental health professionals. Individuals with diabetes must also assume an active role in their care.

The management plan should be written with input from the patient and family, the physician, and other members of the health care team. Diabetes self-management education (DSME) and ongoing diabetes support should be integral components of the management plan. Various strategies and techniques should be used to enable patients to self-manage diabetes, including providing education on problem-solving skills for all aspects of diabetes management. Treatment goals and plans should be individualized and take patient preferences into account. In developing the plan, consideration should be given to the patient's age, school/work schedule and conditions, physical activity, eating patterns, social situation, cultural factors, presence of diabetes complications, health priorities, and other medical conditions.

COMMON COMORBID CONDITIONS

Recommendation

- Consider assessing for and addressing common comorbid conditions (e.g., depression, obstructive sleep apnea) that may complicate diabetes management. **B**

Improved disease prevention and treatment efficacy means that patients with diabetes are living longer, often with multiple comorbidities requiring complicated medical regimens (1). Obesity, hypertension, and dyslipidemia are the most commonly appreciated comorbidities. However, concurrent conditions, such as heart

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Table 3.1—Components of the comprehensive diabetes evaluation**Medical history**

- Age and characteristics of onset of diabetes (e.g., DKA, asymptomatic laboratory finding)
- Eating patterns, physical activity habits, nutritional status, and weight history; growth and development in children and adolescents
- Presence of common comorbidities, psychosocial problems, and dental disease
- Diabetes education history
- Review of previous treatment regimens and response to therapy (A1C records)
- Current treatment of diabetes, including medications, medication adherence and barriers thereto, meal plan, physical activity patterns, and readiness for behavior change
- Results of glucose monitoring and patient's use of data
- DKA frequency, severity, and cause
- Hypoglycemic episodes
 - Hypoglycemia awareness
 - Any severe hypoglycemia: frequency and cause
- History of diabetes-related complications
 - Microvascular: retinopathy, nephropathy, neuropathy (sensory, including history of foot lesions; autonomic, including sexual dysfunction and gastroparesis)
 - Macrovascular: coronary heart disease, cerebrovascular disease, and peripheral arterial disease

Physical examination

- Height, weight, BMI
- Blood pressure determination, including orthostatic measurements when indicated
- Fundoscopic examination
- Thyroid palpation
- Skin examination (for acanthosis nigricans and insulin injection sites)
- Comprehensive foot examination
 - Inspection
 - Palpation of dorsalis pedis and posterior tibial pulses
 - Presence/absence of patellar and Achilles reflexes
 - Determination of proprioception, vibration, and monofilament sensation

Laboratory evaluation

- A1C, if results not available within past 3 months
- If not performed/available within past year
 - Fasting lipid profile, including total, LDL, and HDL cholesterol and triglycerides, as needed
 - Liver function tests
 - Test for urine albumin excretion with spot urine albumin-to-creatinine ratio
 - Serum creatinine and calculated glomerular filtration rate
 - TSH in type 1 diabetes, dyslipidemia, or women over age 50 years

Referrals

- Eye care professional for annual dilated eye exam
- Family planning for women of reproductive age
- Registered dietitian for medical nutrition therapy
- DSME/DSMS
- Dentist for comprehensive periodontal examination
- Mental health professional, if needed

DKA, diabetic ketoacidosis; DSMS, diabetes self-management support; TSH, thyroid-stimulating hormone.

failure, depression, anxiety, and arthritis, are found at higher rates in people with diabetes than in age-matched people without diabetes and often complicate diabetes management. These concurrent conditions present clinical challenges related to polypharmacy, prevalent symptoms, and complexity of care (2–5).

Depression

As discussed in Section 4. Foundations of Care, depression, anxiety, and other mental health symptoms are highly prevalent in people with diabetes and are associated with worse outcomes.

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, in men and women (6). The prevalence in general populations with type 2 diabetes may be up to 23% (7) and in obese participants enrolled in the Look AHEAD trial exceeded 80% (8). Treatment of sleep apnea significantly improves quality of life and blood pressure control. The evidence for a treatment effect on glycemic control is mixed (9).

Fatty Liver Disease

Unexplained elevations of hepatic transaminase concentrations are significantly associated with higher BMI, waist circumference, triglycerides, and fasting insulin and with lower HDL cholesterol. In a prospective analysis, diabetes was significantly associated with incident nonalcoholic chronic liver disease and with hepatocellular carcinoma (10). 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 (11).

Cancer

Diabetes (possibly only type 2 diabetes) is associated with increased risk of cancers of the liver, pancreas, endometrium, colon/rectum, breast, and bladder (12). The association may result from shared risk factors between type 2 diabetes and cancer (obesity, older age, and physical inactivity), but may also be due to hyperinsulinemia or hyperglycemia (13). Patients with diabetes should be encouraged to undergo recommended age- and sex-appropriate cancer screenings and to reduce their modifiable cancer risk factors (obesity, smoking, and physical inactivity).

Fractures

Age-matched hip fracture risk is significantly increased in both type 1 (summary relative risk [RR] 6.3) and type 2 diabetes (summary RR 1.7) in both sexes (14). 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) (15). In three large observational studies of older adults, femoral neck BMD T score and the WHO Fracture Risk Algorithm (FRAX) score were associated with hip and nonspine fracture, although 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 (16). It is appropriate to assess fracture history and risk factors in older patients with diabetes and recommend BMD testing if appropriate for the patient's age and sex. Prevention strategies are the same as for the general population. For type 2 diabetic patients with fracture risk factors, avoiding thiazolidinediones is warranted.

Cognitive Impairment

Diabetes is associated with a significantly increased risk, and rate, of cognitive decline and with increased risk of dementia (17,18). In a 15-year prospective study of community-dwelling people over the age of 60 years, the presence of diabetes at baseline significantly increased the age- and sex-adjusted incidence of all-cause dementia, Alzheimer disease, and vascular dementia compared with rates in those with normal glucose tolerance (19). In a substudy of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) clinical trial, there were no differences in cognitive outcomes between intensive and standard glycemic control, although there was significantly less of a decrement in total brain volume, as measured by MRI, in participants in the intensive arm (20). The effects of hyperglycemia and insulin on the brain are areas of intense research interest.

Low Testosterone in Men

Mean levels of testosterone are lower in men with diabetes compared with age-matched men without diabetes, but obesity is a major confounder (21). Treatment in asymptomatic men is controversial. The evidence that testosterone replacement affects outcomes is mixed, and recent guidelines suggest that testing and treating men without symptoms are not recommended (22).

Periodontal Disease

Periodontal disease is more severe, but not necessarily more prevalent, in patients with diabetes than in those without (23). Current evidence suggests that periodontal disease adversely affects diabetes outcomes, although evidence for treatment benefits remains controversial (5).

Hearing Impairment

Hearing impairment, both in high frequency and low/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 (24).

References

1. Selvin E, Coresh J, Brancati FL. The burden and treatment of diabetes in elderly individuals in the U.S. *Diabetes Care* 2006;29:2415–2419
2. Grant RW, Ashburner JM, Hong CS, Chang Y, Barry MJ, Atlas SJ. Defining patient complexity from the primary care physician's perspective: a cohort study. *Ann Intern Med* 2011;155:797–804
3. Tinetti ME, Fried TR, Boyd CM. Designing health care for the most common chronic condition—multimorbidity. *JAMA* 2012;307:2493–2494
4. Sudore RL, Karter AJ, Huang ES, et al. Symptom burden of adults with type 2 diabetes across the disease course: *Diabetes & Aging Study*. *J Gen Intern Med* 2012;27:1674–1681
5. Borgnakke WS, Ylöstalo PV, Taylor GW, Genco RJ. Effect of periodontal disease on diabetes: systematic review of epidemiologic observational evidence. *J Periodontol* 2013;84(Suppl.):S135–S152
6. Li C, Ford ES, Zhao G, Croft JB, Balluz LS, Mokdad AH. Prevalence of self-reported clinically diagnosed sleep apnea according to obesity status in men and women: National Health and Nutrition Examination Survey, 2005–2006. *Prev Med* 2010;51:18–23
7. West SD, Nicoll DJ, Stradling JR. Prevalence of obstructive sleep apnoea in men with type 2 diabetes. *Thorax* 2006;61:945–950
8. Foster GD, Sanders MH, Millman R, et al.; Sleep AHEAD Research Group. Obstructive sleep apnea among obese patients with type 2 diabetes. *Diabetes Care* 2009;32:1017–1019
9. Shaw JE, Punjabi NM, Wilding JP, Alberti KGMM, Zimmet PZ; International Diabetes Federation Taskforce on Epidemiology and Prevention. Sleep-disordered breathing and type 2 diabetes: a report from the International Diabetes Federation Taskforce on Epidemiology and Prevention. *Diabetes Res Clin Pract* 2008;81:2–12
10. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology* 2004;126:460–468
11. American Gastroenterological Association. American Gastroenterological Association medical position statement: nonalcoholic fatty liver disease. *Gastroenterology* 2002;123:1702–1704
12. Suh S, Kim KW. Diabetes and cancer: is diabetes causally related to cancer? *Diabetes Metab J* 2011;35:193–198
13. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. *Diabetes Care* 2010;33:1674–1685
14. Janghorbani M, Van Dam RM, Willett WC, Hu FB. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. *Am J Epidemiol* 2007;166:495–505
15. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes—a meta-analysis. *Osteoporos Int* 2007;18:427–444
16. Schwartz AV, Vittinghoff E, Bauer DC, et al.; Study of Osteoporotic Fractures (SOF) Research Group; Osteoporotic Fractures in Men (MrOS) Research Group; Health, Aging, and Body Composition (Health ABC) Research Group. Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes. *JAMA* 2011;305:2184–2192
17. Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes—systematic overview of prospective observational studies. *Diabetologia* 2005;48:2460–2469
18. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol* 2006;5:64–74
19. Ohara T, Doi Y, Ninomiya T, et al. Glucose tolerance status and risk of dementia in the community: the Hisayama study. *Neurology* 2011;77:1126–1134
20. Launer LJ, Miller ME, Williamson JD, et al.; ACCORD MIND investigators. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. *Lancet Neurol* 2011;10:969–977
21. Dhindsa S, Miller MG, McWhirter CL, et al. Testosterone concentrations in diabetic and nondiabetic obese men. *Diabetes Care* 2010;33:1186–1192
22. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010;95:2536–2559
23. Khader YS, Dauod AS, El-Qaderi SS, Alkafajei A, Batayha WQ. Periodontal status of diabetics compared with nondiabetics: a meta-analysis. *J Diabetes Complications* 2006;20:59–68
24. Bainbridge KE, Hoffman HJ, Cowie CC. Diabetes and hearing impairment in the United States: audiometric evidence from the National Health and Nutrition Examination Survey, 1999 to 2004. *Ann Intern Med* 2008;149:1–10

4. Foundations of Care: Education, Nutrition, Physical Activity, Smoking Cessation, Psychosocial Care, and Immunization

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DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT

Recommendations

- People with diabetes should receive diabetes self-management education (DSME) and diabetes self-management support (DSMS) according to the national standards for DSME and DSMS when their diabetes is diagnosed and as needed thereafter. **B**
- Effective self-management and quality of life are the key outcomes of DSME and DSMS and should be measured and monitored as part of care. **C**
- DSME and DSMS should address psychosocial issues, as emotional well-being is associated with positive diabetes outcomes. **C**
- DSME and DSMS programs are appropriate venues for people with prediabetes to receive education and support to develop and maintain behaviors that can prevent or delay the onset of diabetes. **C**
- Because DSME and DSMS can result in cost-savings and improved outcomes **B**, DSME and DSMS should be adequately reimbursed by third-party payers. **E**

DSME and DSMS are the ongoing processes of facilitating the knowledge, skill, and ability necessary for diabetes self-care. This process incorporates the needs, goals, and life experiences of the person with diabetes. The overall objectives of DSME and DSMS are to support informed decision making, self-care behaviors, problem solving, and active collaboration with the health care team to improve clinical outcomes, health status, and quality of life in a cost-effective manner (1).

DSME and DSMS are essential elements of diabetes care (2,3), and the current national standards for DSME and DSMS (1) are based on evidence of their benefits. Education helps people with diabetes initiate effective self-management and cope with diabetes when they are first diagnosed. Ongoing DSME and DSMS also help people with diabetes maintain effective self-management throughout a lifetime of diabetes as they face new challenges and as treatment advances become available. DSME enables patients (including youth) to optimize metabolic control, prevent and manage complications, and maximize quality of life in a cost-effective manner (2,4).

Current best practice of DSME is a skill-based approach that focuses on helping those with diabetes make informed self-management choices (1,2). DSME has changed from a didactic approach focusing on providing information to empowerment models that focus on helping those with diabetes make informed self-management decisions (2). Diabetes care has shifted to an approach that is more patient centered and places the person with diabetes and his or her family 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 and ensures that patient values guide all decision making (5).

Evidence for the Benefits

Multiple studies have found that DSME is associated with improved diabetes knowledge, improved self-care behavior (1), improved clinical outcomes, such as lower

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A1C (3,6–8), lower self-reported weight (9,10), improved quality of life (8,11), healthy coping (12,13), and lower costs (14,15). Better outcomes were reported for DSME interventions that were longer and included follow-up support (DSMS) (16–18), that were culturally (19,20) and age appropriate (21,22), that were tailored to individual needs and preferences, and that addressed psychosocial issues and incorporated behavioral strategies (2,12,23,24). Both individual and group approaches have been found effective (10,25). There is growing evidence for the role of community health workers (26), as well as peer (27–30) and lay leaders (31), in delivering DSME and DSMS (32).

Diabetes education is associated with increased use of primary and preventive services (14,33,34) and lower use of acute, inpatient hospital services (14). Patients who participate in diabetes education are more likely to follow best practice treatment recommendations, particularly among the Medicare population, and have lower Medicare and insurance claim costs (15,33).

National Standards

The national standards for DSME and DSMS are designed to define quality and to assist diabetes educators in a variety of settings to provide evidence-based education and self-management support (1). The standards are reviewed and updated every 5 years by a task force representing key organizations involved in diabetes education and care.

Reimbursement

DSME, when provided by a program that meets national standards for DSME and is recognized by the American Diabetes Association (ADA) or other approval bodies, is reimbursed as part of the Medicare program as overseen by the Centers for Medicare & Medicaid Services. DSME is also covered by most health insurance plans. Although DSMS has been shown to be instrumental for improving outcomes and can be provided via phone calls and telehealth, it currently has limited reimbursement as in-person follow-up to DSME.

MEDICAL NUTRITION THERAPY

For many individuals with diabetes, the most challenging part of the treatment

plan is determining what to eat. It is the position of the ADA that there is not a one-size-fits-all eating pattern for individuals with diabetes. The ADA also recognizes the integral role of nutrition therapy in overall diabetes management and recommends that each person with diabetes be actively engaged in self-management, education, and treatment planning with his or her health care provider, which includes the collaborative development of an individualized eating plan (35,36). Therefore, it is important that all members of the health care team be knowledgeable about diabetes nutrition therapy and support its implementation. See **Table 4.1** for specific nutrition recommendations.

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, in order to improve overall health and specifically to
 - Attain individualized glycemic, blood pressure, and lipid goals
 - Achieve and maintain body weight goals
 - Delay or prevent complications of diabetes
2. To address individual nutrition needs based on personal and cultural preferences, health literacy and numeracy, access to healthful food choices, willingness and ability to make behavioral changes, and barriers to change.
3. To maintain the pleasure of eating by providing positive messages about food choices while limiting food choices only when indicated by scientific evidence.
4. To provide the individual with diabetes with practical tools for day-to-day meal planning rather than focusing on individual macronutrients, micronutrients, or single foods.

Nutrition therapy is an integral component of diabetes prevention, management, and self-management education. All individuals with diabetes should receive individualized medical nutrition therapy (MNT), preferably provided by a registered dietitian who is knowledgeable and skilled in providing diabetes MNT. Comprehensive group diabetes education

programs including nutrition therapy or individualized education sessions have reported A1C decreases of 0.3–1% for type 1 diabetes (37–41) and 0.5–2% for type 2 diabetes (42–49).

Carbohydrate Management

Individuals with type 1 diabetes should be offered intensive insulin therapy education using the carbohydrate-counting meal planning approach (37,39,40,43,50), which has been shown to improve glycemic control (50,51). Consistent carbohydrate intake with respect to time and amount can result in improved glycemic control for individuals using fixed daily insulin doses (36). A simple diabetes meal planning approach, such as portion control or healthful food choices, may be better suited for individuals with health literacy and numeracy concerns (36–40,42).

Weight Loss

Intensive lifestyle programs with frequent follow-up are required to achieve significant reductions in excess body weight and improve clinical indicators (52,53). Weight loss of 2–8 kg may provide clinical benefits in those with type 2 diabetes, especially early in the disease process (52,53). Although several studies resulted in improvements in A1C at 1 year (52,54–56), not all weight-loss interventions led to 1-year A1C improvements (45,57–60). The most consistently identified changes in cardiovascular risk factors were an increase in HDL cholesterol (52,54,56,59,61), decrease in triglycerides (52,61–63), and decrease in blood pressure (52,54,57,59,61).

Weight-loss studies have used a variety of energy-restricted eating patterns, with no clear evidence that one eating pattern or optimal macronutrient distribution was ideal, suggesting that macronutrient proportions should be individualized (64). Studies show that people with diabetes eat on average about 45% of their calories from carbohydrates, ~36–40% of calories from fat, and ~16–18% from protein (57–59). A variety of eating patterns have been shown to be effective in managing diabetes, including Mediterranean-style (53,65), Dietary Approaches to Stop Hypertension (DASH)-style (66), and plant-based (vegan or vegetarian) (67), lower-fat (68), and lower-carbohydrate patterns (68).

Table 4.1—Nutrition therapy recommendations

Topic	Recommendations	Evidence rating
Effectiveness of nutrition therapy	● Nutrition therapy is recommended for all people with type 1 and type 2 diabetes as an effective component of the overall treatment plan.	A
	● Individuals who have diabetes should receive individualized MNT to achieve treatment goals, preferably provided by a registered dietitian familiar with the components of diabetes MNT.	A
	● For individuals with type 1 diabetes, participation in an intensive, flexible insulin therapy education program using the carbohydrate-counting meal planning approach can result in improved glycemic control.	A
	● For individuals using fixed daily insulin doses, consistent carbohydrate intake with respect to time and amount can result in improved glycemic control and reduce hypoglycemia risk.	B
	● A simple diabetes meal planning approach, such as portion control or healthful food choices, may be better suited to individuals with type 2 diabetes with health and numeracy literacy concerns. This strategy also may be effective for older adults.	C
	● Because diabetes nutrition therapy can result in cost savings B and improved outcomes (e.g., A1C reduction) A , MNT should be adequately reimbursed by insurance and other payers. E	B, A, E
Energy balance	● For overweight or obese adults with type 2 diabetes or at risk for diabetes, reducing energy intake while maintaining a healthful eating pattern is recommended to promote weight loss.	A
	● Modest weight loss may provide clinical benefits in some individuals with diabetes, especially those early in the disease process. To achieve modest weight loss, intensive lifestyle interventions with ongoing support are recommended.	A
Eating patterns and macronutrient distribution	● Evidence suggests that there is not an ideal percentage of calories from carbohydrate, protein, and fat for all people with diabetes B ; therefore, macronutrient distribution should be based on individualized assessment of current eating patterns, preferences, and metabolic goals. E	B, E
	● Carbohydrate amount and available insulin may be the most important factors influencing glycemic response after eating and should be considered when developing the eating plan.	A
	● Monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, remains critical in achieving glycemic control.	B
	● Carbohydrate intake from vegetables, fruits, whole grains, legumes, and dairy products should be advised over intake from other carbohydrate sources, especially those that contain added fats, sugars, or sodium.	B
	● Substituting low glycemic-load foods for higher glycemic-load foods may modestly improve glycemic control.	C
	● Individuals at high risk for type 2 diabetes should be encouraged to achieve the U.S. Department of Agriculture recommendation for dietary fiber (14 g fiber/1,000 kcal) and to consume foods containing whole grains (one-half of grain intake).	B
	● While substituting sucrose-containing foods for isocaloric amounts of other carbohydrates may have similar blood glucose effects, consumption should be minimized to avoid displacing nutrient-dense food choices.	A
	● People with diabetes and those at risk should limit or avoid intake of sugar-sweetened beverages to reduce risk for weight gain and worsening of cardiometabolic risk profile.	B
Protein	● 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 not be used to treat or prevent hypoglycemia.	B
	● Evidence is inconclusive regarding an ideal amount of total fat for people with diabetes; therefore, goals should be individualized. C Fat quality appears to be far more important than quantity. B	C, B
	● A Mediterranean-style eating pattern, rich in monounsaturated fatty acids, may benefit glycemic control and CVD risk factors and can therefore be recommended as an effective alternative to a lower-fat, higher-carbohydrate eating pattern.	B

Continued on p. S23

Table 4.1—Continued

Topic	Recommendations	Evidence rating
Dietary fat	<ul style="list-style-type: none"> Increased consumption of foods containing long-chain omega-3 fatty acids (EPA and DHA), such as fatty fish, and omega-3 linolenic acid (ALA) is recommended. 	B
	<ul style="list-style-type: none"> The consumption of fish (particularly fatty fish) at least two times (two servings) per week is recommended. 	B
	<ul style="list-style-type: none"> The amount of dietary saturated fat, cholesterol, and <i>trans</i> fat recommended for people with diabetes is the same as that recommended for the general population. 	C
	<ul style="list-style-type: none"> Evidence does not support recommending omega-3 supplements for people with diabetes for the prevention or treatment of cardiovascular events. 	A
Micronutrients and herbal supplements	<ul style="list-style-type: none"> There is no clear evidence of benefit from vitamin or mineral supplementation in people with diabetes who do not have underlying deficiencies. 	C
	<ul style="list-style-type: none"> Routine supplementation with antioxidants, such as vitamins E and C and carotene, is not advised due to insufficient evidence of efficacy and concerns related to long-term safety. 	C
	<ul style="list-style-type: none"> There is insufficient evidence to support the routine use of micronutrients such as chromium, magnesium, and vitamin D to improve glycemic control in people with diabetes. 	C
	<ul style="list-style-type: none"> There is insufficient evidence to support the use of cinnamon or other herbs/supplements for the treatment of diabetes. 	E
	<ul style="list-style-type: none"> It is recommended that individualized meal planning include optimization of food choices to meet recommended dietary allowance/dietary reference intake for all micronutrients. 	E
Alcohol	<ul style="list-style-type: none"> If adults with diabetes choose to drink alcohol, they should be advised to 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
	<ul style="list-style-type: none"> Alcohol consumption may place people with diabetes at an increased risk for delayed hypoglycemia, especially if taking insulin or insulin secretagogues. Education and awareness regarding the recognition and management of delayed hypoglycemia are warranted. 	B
Sodium	<ul style="list-style-type: none"> The recommendation for the general population to reduce sodium to less than 2,300 mg/day is also appropriate for people with diabetes. 	B
	<ul style="list-style-type: none"> For individuals with both diabetes and hypertension, further reduction in sodium intake should be individualized. 	B

Macronutrients

Carbohydrates

Studies examining the ideal amount of carbohydrate intake for people with diabetes are inconclusive, although monitoring carbohydrate intake and considering the available insulin are key strategies for improving postprandial glucose control (37,69). The literature concerning glycemic index and glycemic load in individuals with diabetes is complex, although reductions in A1C of -0.2% to -0.5% have been demonstrated in some studies (64,70). A systematic review (64) found consumption of whole grains was not associated with improvements in glycemic control in people with type 2 diabetes, although it may reduce systemic inflammation. One study did find a potential benefit of whole-grain intake in reducing mortality and cardiovascular disease (CVD) (71).

Proteins

For people with diabetes and no evidence of diabetic kidney disease, the evidence is inconclusive about recommending an ideal amount of protein for optimizing glycemic control or for improving one or more CVD risk measures (64). Therefore, these goals should be individualized. For people with diabetes and diabetic kidney disease (with albuminuria), reducing the amount of dietary protein below usual intake is not recommended because it does not alter glycemic measures, cardiovascular risk measures, or the course of glomerular filtration rate decline (72,73). In individuals with type 2 diabetes, ingested protein appears to increase insulin response without increasing plasma glucose concentrations (74). Therefore, carbohydrate sources high in protein should not be used to treat or prevent hypoglycemia.

Protein's effect on blood glucose levels in type 1 diabetes is less clear.

Fats

Limited research exists concerning the ideal amount of fat for individuals with diabetes. The Institute of Medicine has defined an acceptable macronutrient distribution range for all adults for total fat of 20–35% of energy with no tolerable upper intake level defined (75). The type of fatty acids consumed is more important than total amount of fat when looking at metabolic goals and risk of CVD (53,76,77). Multiple randomized controlled trials including patients with type 2 diabetes have reported improved glycemic control and/or blood lipids when a Mediterranean-style eating pattern, rich in monounsaturated fatty acid, was consumed (53,57,78,79). A systematic review (64) concluded that

supplementation with omega-3 fatty acids did not improve glycemic control but that higher dose supplementation decreased triglycerides in individuals with type 2 diabetes. Randomized controlled trials also do not support recommending omega-3 supplements for primary or secondary prevention of CVD (80–85). 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 (86).

Sodium

A review found that decreasing sodium intake reduces blood pressure in those with diabetes (87). Incrementally lowering sodium intake (i.e., to 1,500 mg/day) has shown beneficial effects on blood pressure (87–89). The American Heart Association recommends 1,500 mg/day for African Americans, people diagnosed with hypertension, diabetes, or chronic kidney disease, and those over 51 years of age (90). However, other studies (88,89) have warranted caution for universal sodium restriction to 1,500 mg in this population. For individuals with diabetes and hypertension, setting a sodium intake goal of <2,300 mg/day should be considered on an individual basis. Sodium intake recommendations should take into account palatability, availability, additional cost of specialty low-sodium products, and the difficulty of achieving both low-sodium recommendations and a nutritionally adequate diet (86).

For complete discussion and references of all recommendations, see the ADA position statement “Nutrition Therapy Recommendations for the Management of Adults With Diabetes” (36).

PHYSICAL ACTIVITY

Recommendations

- Children with diabetes or prediabetes should be encouraged to engage in at least 60 min of physical activity each day. **B**
- Adults with diabetes should be advised to perform at least 150 min/week of moderate-intensity aerobic physical activity (50–70% of maximum heart rate), spread over at least 3 days/week with no more than 2 consecutive days without exercise. **A**

- Evidence supports that all individuals, including those with diabetes, should be encouraged to reduce sedentary time, particularly by breaking up extended amounts of time (>90 min) spent sitting. **B**
- In the absence of contraindications, adults with type 2 diabetes should be encouraged to perform resistance training at least twice per week. **A**

Exercise is an important part of the diabetes management plan. Regular exercise has been shown to improve blood glucose control, reduce cardiovascular risk factors, contribute to weight loss, and improve well-being. Furthermore, regular exercise may prevent type 2 diabetes in high-risk individuals (91–93). 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 with no significant change in BMI (94). There are considerable data for the health benefits (e.g., increased cardiovascular fitness, muscle strength, improved insulin sensitivity, etc.) of regular physical activity for those with type 1 diabetes (95). Higher levels of exercise intensity are associated with greater improvements in A1C and in fitness (96). Other benefits include slowing the decline in mobility among overweight patients with diabetes (97). “Exercise and Type 2 Diabetes: The American College of Sports Medicine and the American Diabetes Association: Joint Position Statement Executive Summary” reviews the evidence for the benefits of exercise in people with type 2 diabetes (98).

Exercise and Children

As is recommended for all children, children with diabetes or prediabetes should be encouraged to engage in at least 60 min of physical activity each day. Included in the 60 min each day, children should engage in vigorous-intensity aerobic activity, muscle-strengthening activities, and bone-strengthening activities at least 3 of those days (99).

Frequency and Type of Exercise

The U.S. Department of Health and Human Services' physical activity guidelines for Americans (100) suggest that adults over age 18 years do 150 min/week of moderate-intensity or 75

min/week of vigorous-intensity aerobic physical activity, or an equivalent combination of the two. In addition, the guidelines suggest that adults also do muscle-strengthening activities that involve all major muscle groups 2 or more days/week. The guidelines suggest that adults over age 65 years, or those with disabilities, follow the adult guidelines if possible or, if this is not possible, be as physically active as they are able.

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 TV) particularly by breaking up extended amounts of time (>90 min) spent sitting (101).

Exercise and Glycemic Control

Based on physical activity studies that include people with diabetes, it seems reasonable to recommend that people with diabetes follow the physical activity guidelines as for the general population. For example, studies included in the meta-analysis of effects of exercise interventions on glycemic control (94) had a mean of 3.4 sessions/week, with a mean of 49 min/session. Also, the Diabetes Prevention Program (DPP) lifestyle intervention included 150 min/week of moderate-intensity exercise and showed beneficial effect on glycemia in those with prediabetes (91).

Clinical trials have provided strong evidence for the A1C-lowering value of resistance training in older adults with type 2 diabetes (98) and for an additive benefit of combined aerobic and resistance exercise in adults with type 2 diabetes (102,103). 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 of five or more different resistance exercises involving the large muscle groups (98).

Pre-exercise Evaluation

As discussed more fully in Section 8. Cardiovascular Disease and Risk Management, the best protocol for screening asymptomatic diabetic patients for coronary artery disease (CAD) remains unclear. The ADA consensus report “Screening for Coronary Artery Disease in Patients With Diabetes” (104) on this issue concluded that routine screening is not recommended. Providers should use clinical judgment in

this area. Certainly, high-risk patients should be encouraged to start with short periods of low-intensity exercise and slowly increase the intensity and duration. Providers should assess patients for conditions that might contraindicate certain types of exercise or predispose to injury, such as uncontrolled hypertension, severe autonomic neuropathy, severe peripheral neuropathy, a history of foot lesions, and unstable proliferative retinopathy. The patient's age and previous physical activity level should be considered. For type 1 diabetic patients, the provider should customize the exercise regimen to the individual's needs. Those with complications may require a more thorough evaluation (95).

Exercise in the Presence of Nonoptimal Glycemic Control

Hyperglycemia

When individuals with type 1 diabetes are deprived of insulin for 12–48 h and are ketotic, exercise can worsen hyperglycemia and ketosis (105); therefore, vigorous activity should be avoided with ketosis. However, it is not necessary to postpone exercise based simply on hyperglycemia, provided the patient feels well and urine and/or blood ketones are negative.

Hypoglycemia

In individuals taking insulin and/or insulin secretagogues, physical activity can cause hypoglycemia if medication dose or carbohydrate consumption is not altered. For individuals on these therapies, added carbohydrate should be ingested if pre-exercise glucose levels are <100 mg/dL (5.6 mmol/L). Hypoglycemia is less common in diabetic patients who are not treated with insulin or insulin secretagogues, and no preventive measures for hypoglycemia are usually advised in these cases.

Exercise in the Presence of Specific Long-Term Complications of Diabetes

Retinopathy

If proliferative diabetic retinopathy or severe nonproliferative diabetic retinopathy is present, then vigorous aerobic or resistance exercise may be contraindicated because of the risk of triggering vitreous hemorrhage or retinal detachment (106).

Peripheral Neuropathy

Decreased pain sensation and a higher pain threshold in the extremities result

in an increased risk of skin breakdown and infection and of Charcot joint destruction with some forms of exercise. However, studies have shown that moderate-intensity walking may not lead to an increased risk of foot ulcers or reulceration in those with peripheral neuropathy (107). In addition, 150 min/week of moderate exercise was reported to improve outcomes in patients with milder forms of neuropathy (106). 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 event through decreased cardiac responsiveness to exercise, postural hypotension, impaired thermoregulation, impaired night vision due to impaired papillary reaction, and higher susceptibility to hypoglycemia (108). Cardiovascular autonomic neuropathy is also an independent risk factor for cardiovascular death and silent myocardial ischemia (109). Therefore, individuals with diabetic autonomic neuropathy should undergo cardiac investigation before beginning physical activity more intense than that to which they are accustomed.

Albuminuria and Nephropathy

Physical activity can acutely increase urinary protein excretion. However, there is no evidence that vigorous exercise increases 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 (106).

SMOKING CESSATION

Recommendations

- Advise all patients not to smoke or use tobacco products. **A**
- Include smoking cessation counseling and other forms of treatment as a routine component of diabetes care. **B**

Results from epidemiological, case-control, and cohort studies provide convincing evidence to support the causal link between cigarette smoking and health risks. Much of the work documenting the effect of smoking on health does

not separately discuss results on subsets of individuals with diabetes, but it does suggest that the identified risks are at least equivalent to those found in the general population. Other studies of individuals with diabetes consistently demonstrate that smokers (and people exposed to secondhand smoke) have a heightened risk of CVD, premature death, and the microvascular complications of diabetes. Smoking may have a role in the development of type 2 diabetes (110). 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 (111).

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 quit lines, in reducing tobacco use. For the patient motivated to quit, the addition of pharmacological therapy to counseling is more effective than either treatment alone. Special considerations should include assessment of level of nicotine dependence, which is associated with difficulty in quitting and relapse (112). Although some patients may gain weight in the period shortly after smoking cessation, recent research has demonstrated that this weight gain does not diminish the substantial CVD risk benefit realized from smoking cessation (113).

There is no evidence that e-cigarettes are a healthier alternative to smoking or that e-cigarettes can facilitate smoking cessation. Rigorous study of their short- and long-term effects is needed in determining their safety and efficacy and their cardiopulmonary effects in comparison with smoking and standard approaches to smoking cessation (114).

PSYCHOSOCIAL ASSESSMENT AND CARE

Recommendations

- Include assessment of the patient's psychological and social situation as an ongoing part of the medical management of diabetes. **B**
- Psychosocial screening and follow-up may include, but are not limited

to, attitudes about the illness, expectations for medical management and outcomes, affect/mood, general and diabetes-related quality of life, resources (financial, social, and emotional), and psychiatric history. **E**

- Routinely screen for psychosocial problems such as depression, diabetes-related distress, anxiety, eating disorders, and cognitive impairment. **B**
- Older adults (aged ≥ 65 years) with diabetes should be considered a high-priority population for depression screening and treatment. **B**
- Patients with comorbid diabetes and depression should receive a stepwise collaborative care approach for the management of depression. **A**

Emotional well-being is an important part of diabetes care and self-management. Psychological and social problems can impair the individual's (115–117) or family's (118) ability to carry out diabetes care tasks and therefore compromise health status. There are opportunities for the clinician to routinely assess psychosocial status in a timely and efficient manner so that referral for appropriate services can be accomplished. A systematic review and meta-analysis showed that psychosocial interventions modestly but significantly improved A1C (standardized mean difference -0.29%) and mental health outcomes. However, there was a limited association between the effects on A1C and mental health, and no intervention characteristics predicted benefit on both outcomes (119).

Screening

Key opportunities for routine screening of psychosocial status occur at diagnosis, during regularly scheduled management visits, during hospitalizations, with new-onset complications, or when problems with glucose control, quality of life, or self-management are identified. 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. Depression affects about 20–25% of people

with diabetes (120) and increases the risk for myocardial infarction and postmyocardial infarction (121) and all-cause mortality (122). There appears to be a bidirectional relationship between depression and both diabetes (123) and metabolic syndrome (124).

Diabetes-related distress is distinct from clinical depression and is very common (125–127) among people with diabetes and their family members (118). Prevalence is reported as 18–45%, with an incidence of 38–48% over 18 months. High levels of distress are significantly linked to A1C, self-efficacy, dietary and exercise behaviors (13,126), and medication adherence (128). Other issues known to impact self-management and health outcomes include, but are not limited to, attitudes about the illness, expectations for medical management and outcomes, anxiety, general and diabetes-related quality of life, resources (financial, social, and emotional) (129), and psychiatric history (130). Screening tools are available for a number of these areas (23,131,132).

Referral to Mental Health Specialist

Indications for referral to a mental health specialist familiar with diabetes management may include gross disregard for the medical regimen (by self or others) (133), depression, overall stress related to work-life balance, possibility of self-harm, debilitating anxiety (alone or with depression), indications of an eating disorder (134), or cognitive functioning that significantly impairs judgment. It is preferable to incorporate psychological assessment and treatment into routine care rather than waiting for a specific problem or deterioration in metabolic or psychological status (23,125). In the Second Diabetes Attitudes, Wishes and Needs (DAWN2) study, significant diabetes-related distress was reported by 44.6% of the participants, but only 23.7% reported that their health care team asked them how diabetes impacted their life (125).

Although the clinician may not feel qualified to treat psychological problems (135), optimizing the patient-provider relationship as a foundation can increase the likelihood that the patient will accept referral for other services. Collaborative care interventions and use of a team approach have demonstrated efficacy in diabetes and

depression (136,137). Interventions to enhance self-management and address severe distress have demonstrated efficacy in diabetes-related distress (13).

IMMUNIZATION

Recommendations

- Provide routine vaccinations for children and adults with diabetes as for the general population. **C**
- Annually provide an influenza vaccine to all patients with diabetes ≥ 6 months of age. **C**
- Administer pneumococcal polysaccharide vaccine 23 (PPSV23) to all patients with diabetes ≥ 2 years of age. **C**
- Adults ≥ 65 years of age, if not previously vaccinated, should receive pneumococcal conjugate vaccine 13 (PCV13), followed by PPSV23 6–12 months after initial vaccination. **C**
- Adults ≥ 65 years of age, if previously vaccinated with PPSV23, should receive a follow-up ≥ 12 months with PCV13. **C**
- Administer hepatitis B vaccination to unvaccinated adults with diabetes who are aged 19–59 years. **C**
- Consider administering hepatitis B vaccination to unvaccinated adults with diabetes who are aged ≥ 60 years. **C**

As for the general population, all children and adults with diabetes should receive routine vaccinations (138,139). Influenza and pneumonia are common, preventable infectious diseases associated with high mortality and morbidity in vulnerable populations, such as the young and the elderly, and in people with chronic diseases. Although there are limited studies reporting the morbidity and mortality of influenza and pneumococcal pneumonia specifically in people with diabetes, observational studies of patients with a variety of chronic illnesses, including diabetes, show that these conditions are associated with an increase in hospitalizations for influenza and its complications. People with diabetes may be at an increased risk of 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% (140). In a case-control series,

influenza vaccine was shown to reduce diabetes-related hospital admission by as much as 79% during flu epidemics (141). There is sufficient evidence to support that people with diabetes have appropriate serologic and clinical responses to these vaccinations. The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices recommends influenza and pneumococcal vaccines for all individuals with diabetes (<http://www.cdc.gov/vaccines/recs>).

Pneumococcal Vaccines in Older Adults

The ADA endorses a recent CDC advisory panel that recommends that both PCV13 and PPSV23 should be administered routinely in series to all adults 65 years of age or older (142).

Pneumococcal Vaccine-Naïve People

Adults 65 years of age or older who have not previously received pneumococcal vaccine or whose previous vaccination history is unknown should receive a dose of PCV13 first, followed by PPSV23. A dose of PPSV23 should be given 6–12 months following a dose of PCV13. If PPSV23 cannot be given within this time period, a dose of PPSV23 should be given during the next visit. The two vaccines should not be coadministered, and the minimum interval between vaccine dosing should be 8 weeks.

Previous Vaccination With PPSV23

Adults 65 years of age or older who previously have received one or more doses of PPSV23 should also receive PCV13 if they have not yet received it. PCV13 should be given no sooner than 12 months after receipt of the most recent PPSV23 dose. For those for whom an additional dose of PPSV23 is indicated, this subsequent PPSV23 dose should be given 6–12 months after PCV13 and at least 5 years since the most recent dose of PPSV23.

References

- Haas L, Maryniuk M, Beck J, et al. National standards for diabetes self-management education and support. *Diabetes Care* 2013;37(Suppl. 1):S144–S153
- Marrero DG, Ard J, Delamater AM, et al. Twenty-first century behavioral medicine: a context for empowering clinicians and patients with diabetes: a consensus report. *Diabetes Care* 2013;36:463–470
- Norris SL, Lau J, Smith SJ, Schmid CH, Engelgau MM. Self-management education for adults with type 2 diabetes: a meta-analysis of

the effect on glycemic control. *Diabetes Care* 2002;25:1159–1171

- Martin D, Lange K, Sima A, et al.; SWEET group. Recommendations for age-appropriate education of children and adolescents with diabetes and their parents in the European Union. *Pediatr Diabetes* 2012;13(Suppl. 16):20–28
- Committee on Quality of Health Care in America. Institute of Medicine. *Crossing the Quality Chasm: A New Health System for the 21st Century* [Internet]. Washington, DC: National Academies Press, 2001. Available from <http://www.iom.edu/Reports/2001/Crossing-the-Quality-Chasm-A-New-Health-System-for-the-21st-Century.aspx>. Accessed 1 October 2014
- Barker JM, Goehrig SH, Barriga K, et al.; DAISY Study. Clinical characteristics of children diagnosed with type 1 diabetes through intensive screening and follow-up. *Diabetes Care* 2004;27:1399–1404
- Frosch DL, Uy V, Ochoa S, Mangione CM. Evaluation of a behavior support intervention for patients with poorly controlled diabetes. *Arch Intern Med* 2011;171:2011–2017
- Cooke D, Bond R, Lawton J, et al.; U.K. NIHR DAFNE Study Group. Structured type 1 diabetes education delivered within routine care: impact on glycemic control and diabetes-specific quality of life. *Diabetes Care* 2013;36:270–272
- Steinsbekk A, Rygg LØ, Lisulo M, Rise MB, Fretheim A. Group based diabetes self-management education compared to routine treatment for people with type 2 diabetes mellitus. A systematic review with meta-analysis. *BMC Health Serv Res* 2012;12:213
- Deakin TA, McShane CE, Cade JE, Williams R. Group based training for self-management strategies in people with type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2005;2:CD003417
- Cochran J, Conn VS. Meta-analysis of quality of life outcomes following diabetes self-management training. *Diabetes Educ* 2008;34:815–823
- Thorpe CT, Fahey LE, Johnson H, Deshpande M, Thorpe JM, Fisher EB. Facilitating healthy coping in patients with diabetes: a systematic review. *Diabetes Educ* 2013;39:33–52
- Fisher L, Hessler D, Glasgow RE, et al. REDEEM: a pragmatic trial to reduce diabetes distress. *Diabetes Care* 2013;36:2551–2558
- Robbins JM, Thatcher GE, Webb DA, Valdmanis VG. Nutritionist visits, diabetes classes, and hospitalization rates and charges: the Urban Diabetes Study. *Diabetes Care* 2008;31:655–660
- Duncan I, Ahmed T, Li QE, et al. Assessing the value of the diabetes educator. *Diabetes Educ* 2011;37:638–657
- Piatt GA, Anderson RM, Brooks MM, et al. 3-year follow-up of clinical and behavioral improvements following a multifaceted diabetes care intervention: results of a randomized controlled trial. *Diabetes Educ* 2010;36:301–309
- Tang TS, Funnell MM, Brown MB, Kurlander JE. Self-management support in “real-world” settings: an empowerment-based intervention. *Patient Educ Couns* 2010;79:178–184
- Renders CM, Valk GD, Griffin SJ, Wagner EH, Eijk Van JT, Assendelft WJ. Interventions to improve the management of diabetes in primary care, outpatient, and community settings: a systematic review. *Diabetes Care* 2001;24:1821–1833

- Glazier RH, Bajcar J, Kennie NR, Willson K. A systematic review of interventions to improve diabetes care in socially disadvantaged populations. *Diabetes Care* 2006;29:1675–1688
- Hawthorne K, Robles Y, Cannings-John R, Edwards AG. Culturally appropriate health education for type 2 diabetes mellitus in ethnic minority groups. *Cochrane Database Syst Rev* 2008;3:CD006424
- Sarkisian CA, Brown AF, Norris KC, Wintz RL, Mangione CM. A systematic review of diabetes self-care interventions for older, African American, or Latino adults. *Diabetes Educ* 2003;29:467–479
- Chodosh J, Morton SC, Mojica W, et al. Meta-analysis: chronic disease self-management programs for older adults. *Ann Intern Med* 2005;143:427–438
- Peyrot M, Rubin RR. Behavioral and psychosocial interventions in diabetes: a conceptual review. *Diabetes Care* 2007;30:2433–2440
- Naik AD, Palmer N, Petersen NJ, et al. Comparative effectiveness of goal setting in diabetes mellitus group clinics: randomized clinical trial. *Arch Intern Med* 2011;171:453–459
- Duke S-AS, Colagiuri S, Colagiuri R. Individual patient education for people with type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2009;1:CD005268
- Shah M, Kaselitz E, Heisler M. The role of community health workers in diabetes: update on current literature. *Curr Diab Rep* 2013;13:163–171
- Heisler M, Vijan S, Makki F, Piette JD. Diabetes control with reciprocal peer support versus nurse care management: a randomized trial. *Ann Intern Med* 2010;153:507–515
- Heisler M. Overview of peer support models to improve diabetes self-management and clinical outcomes. *Diabetes Spectrum* 2007;20:214–221
- Long JA, Jahnle EC, Richardson DM, Loewenstein G, Volpp KG. Peer mentoring and financial incentives to improve glucose control in African American veterans: a randomized trial. *Ann Intern Med* 2012;156:416–424
- Moskowitz D, Thom DH, Hessler D, Ghorob A, Bodenheimer T. Peer coaching to improve diabetes self-management: which patients benefit most? *J Gen Intern Med* 2013;28:938–942
- Foster G, Taylor SJ, Eldridge SE, Ramsay J, Griffiths CJ. Self-management education programmes by lay leaders for people with chronic conditions. *Cochrane Database Syst Rev* 2007 4: CD005108
- Siminerio L, Ruppert KM, Gabbay RA. Who can provide diabetes self-management support in primary care? Findings from a randomized controlled trial. *Diabetes Educ* 2013;39:705–713
- Duncan I, Birkmeyer C, Coughlin S, Li QE, Sherr D, Boren S. Assessing the value of diabetes education. *Diabetes Educ* 2009;35:752–760
- Johnson TM, Murray MR, Huang Y. Associations between self-management education and comprehensive diabetes clinical care. *Diabetes Spectrum* 2010;23:41–46
- Inzucchi SE, Bergenstal RM, Buse JB, et al.; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach.

- Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012;35:1364–1379
36. Evert AB, Boucher JL, Cypress M, et al. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care* 2014;37(Suppl. 1):S120–S143
37. DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: Dose Adjustment For Normal Eating (DAFNE) randomised controlled trial. *BMJ* 2002;325:746
38. Kulkarni K, Castle G, Gregory R, et al.; The Diabetes Care and Education Dietetic Practice Group. Nutrition practice guidelines for type 1 diabetes mellitus positively affect dietitian practices and patient outcomes. *J Am Diet Assoc* 1998;98:62–70; quiz 71–72
39. Rossi MCE, Nicolucci A, Di Bartolo P, et al. Diabetes Interactive Diary: a new telemedicine system enabling flexible diet and insulin therapy while improving quality of life: an open-label, international, multicenter, randomized study. *Diabetes Care* 2010;33:109–115
40. Laurenzi A, Bolla AM, Panigoni G, et al. Effects of carbohydrate counting on glucose control and quality of life over 24 weeks in adult patients with type 1 diabetes on continuous subcutaneous insulin infusion: a randomized, prospective clinical trial (GIOCAR). *Diabetes Care* 2011;34:823–827
41. Scavone G, Manto A, Pitocco D, et al. Effect of carbohydrate counting and medical nutritional therapy on glycaemic control in type 1 diabetic subjects: a pilot study. *Diabet Med* 2010;27:477–479
42. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854–865
43. Rickheim PL, Weaver TW, Flader JL, Kendall DM. Assessment of group versus individual diabetes education: a randomized study. *Diabetes Care* 2002;25:269–274
44. Ziemer DC, Berkowitz KJ, Panayioto RM, et al. A simple meal plan emphasizing healthy food choices is as effective as an exchange-based meal plan for urban African Americans with type 2 diabetes. *Diabetes Care* 2003;26:1719–1724
45. Wolf AM, Conaway MR, Crowther JQ, et al.; Improving Control with Activity and Nutrition (ICAN) Study. Translating lifestyle intervention to practice in obese patients with type 2 diabetes: Improving Control with Activity and Nutrition (ICAN) study. *Diabetes Care* 2004;27:1570–1576
46. Nield L, Moore H, Hooper L, et al. Dietary advice for treatment of type 2 diabetes mellitus in adults. *Cochrane Database Syst Rev* 2007;3:CD004097
47. Davis RM, Hitch AD, Salaam MM, Herman WH, Zimmer-Galler IE, Mayer-Davis EJ. Telehealth improves diabetes self-management in an underserved community: diabetes Telecare. *Diabetes Care* 2010;33:1712–1717
48. Coppel KJ, Kataoka M, Williams SM, Chisholm AW, Vorgers SM, Mann JI. Nutritional intervention in patients with type 2 diabetes who are hyperglycaemic despite optimised drug treatment—Lifestyle Over and Above Drugs in Diabetes (LOADD) study: randomised controlled trial. *BMJ* 2010;341:c3337
49. Franz MJ, Monk A, Barry B, et al. Effectiveness of medical nutrition therapy provided by dietitians in the management of non-insulin-dependent diabetes mellitus: a randomized, controlled clinical trial. *J Am Diet Assoc* 1995;95:1009–1017
50. Sämann A, Mühlhauser I, Bender R, Kloos Ch, Müller UA. Glycaemic control and severe hypoglycaemia following training in flexible, intensive insulin therapy to enable dietary freedom in people with type 1 diabetes: a prospective implementation study. *Diabetologia* 2005;48:1965–1970
51. McIntyre HD, Knight BA, Harvey DM, Noud MN, Hagger VL, Gilshenan KS. Dose Adjustment For Normal Eating (DAFNE) - an audit of outcomes in Australia. *Med J Aust* 2010;192:637–640
52. Pi-Sunyer X, Blackburn G, Brancati FL, et al.; Look AHEAD Research Group. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the Look AHEAD trial. *Diabetes Care* 2007;30:1374–1383
53. Estruch R, Ros E, Salas-Salvadó J, et al.; PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013;368:1279–1290
54. Metz JA, Stern JS, Kris-Etherton P, et al. A randomized trial of improved weight loss with a prepared meal plan in overweight and obese patients: impact on cardiovascular risk reduction. *Arch Intern Med* 2000;160:2150–2158
55. West DS, DiLillo V, Bursac Z, Gore SA, Greene PG. Motivational interviewing improves weight loss in women with type 2 diabetes. *Diabetes Care* 2007;30:1081–1087
56. Larsen RN, Mann NJ, Maclean E, Shaw JE. The effect of high-protein, low-carbohydrate diets in the treatment of type 2 diabetes: a 12 month randomised controlled trial. *Diabetologia* 2011;54:731–740
57. Brehm BJ, Lattin BL, Summer SS, et al. One-year comparison of a high-monounsaturated fat diet with a high-carbohydrate diet in type 2 diabetes. *Diabetes Care* 2009;32:215–220
58. Davis NJ, Tomuta N, Schechter C, et al. Comparative study of the effects of a 1-year dietary intervention of a low-carbohydrate diet versus a low-fat diet on weight and glycemic control in type 2 diabetes. *Diabetes Care* 2009;32:1147–1152
59. Guldbbrand H, Dizdar B, Bunjaku B, et al. In type 2 diabetes, randomisation to advice to follow a low-carbohydrate diet transiently improves glycaemic control compared with advice to follow a low-fat diet producing a similar weight loss. *Diabetologia* 2012;55:2118–2127
60. Krebs JD, Elley CR, Parry-Strong A, et al. The Diabetes Excess Weight Loss (DEWL) Trial: a randomised controlled trial of high-protein versus high-carbohydrate diets over 2 years in type 2 diabetes. *Diabetologia* 2012;55:905–914
61. Wing RR, Bolin P, Brancati FL, et al.; Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013;369:145–154
62. Esposito K, Maiorino MI, Ciotola M, et al. Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: a randomized trial. *Ann Intern Med* 2009;151:306–314
63. Li TY, Brennan AM, Wedick NM, Mantzoros C, Rifai N, Hu FB. Regular consumption of nuts is associated with a lower risk of cardiovascular disease in women with type 2 diabetes. *J Nutr* 2009;139:1333–1338
64. Wheeler ML, Dunbar SA, Jaacks LM, et al. Macronutrients, food groups, and eating patterns in the management of diabetes: a systematic review of the literature, 2010. *Diabetes Care* 2012;35:434–445
65. Elhayany A, Lustman A, Abel R, Attal-Singer J, Vinker S. A low carbohydrate Mediterranean diet improves cardiovascular risk factors and diabetes control among overweight patients with type 2 diabetes mellitus: a 1-year prospective randomized intervention study. *Diabetes Obes Metab* 2010;12:204–209
66. Azadbakht L, Fard NRP, Karimi M, et al. Effects of the Dietary Approaches to Stop Hypertension (DASH) eating plan on cardiovascular risks among type 2 diabetic patients: a randomized crossover clinical trial. *Diabetes Care* 2011;34:55–57
67. Turner-McGrievy GM, Barnard ND, Cohen J, Jenkins DJA, Gloede L, Green AA. Changes in nutrient intake and dietary quality among participants with type 2 diabetes following a low-fat vegan diet or a conventional diabetes diet for 22 weeks. *J Am Diet Assoc* 2008;108:1636–1645
68. Stern L, Iqbal N, Seshadri P, et al. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. *Ann Intern Med* 2004;140:778–785
69. Delahanty LM, Nathan DM, Lachin JM, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes. Association of diet with glycated hemoglobin during intensive treatment of type 1 diabetes in the Diabetes Control and Complications Trial. *Am J Clin Nutr* 2009;89:518–524
70. Thomas D, Elliott EJ. Low glycaemic index, or low glycaemic load, diets for diabetes mellitus. *Cochrane Database Syst Rev* 2009;1:CD006296
71. He M, van Dam RM, Rimm E, Hu FB, Qi L. Whole-grain, cereal fiber, bran, and germ intake and the risks of all-cause and cardiovascular disease-specific mortality among women with type 2 diabetes mellitus. *Circulation* 2010;121:2162–2168
72. Pan Y, Guo LL, Jin HM. Low-protein diet for diabetic nephropathy: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2008;88:660–666
73. Robertson L, Waugh N, Robertson A. Protein restriction for diabetic renal disease. *Cochrane Database Syst Rev* 2007;4:CD002181
74. Layman DK, Clifton P, Gannon MC, Krauss RM, Nuttall FQ. Protein in optimal health: heart disease and type 2 diabetes. *Am J Clin Nutr* 2008;87:1571S–1575S
75. Institute of Medicine. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids* [Internet]. 2002. Available from <http://www.iom.edu/Reports/2002/Dietary-Reference-Intakes-for-Energy-Carbohydrate-Fiber-Fat-Fatty-Acids>

- Cholesterol-Protein-and-Amino-Acids.aspx. Accessed 1 October 2014
76. Office of Disease Prevention and Health Promotion, U.S. Department of Health and Human Services. *Dietary Guidelines for Americans* [Internet], 2010. Available from <http://www.health.gov/dietaryguidelines>. Accessed 1 October 2014
77. Ros E. Dietary cis-monounsaturated fatty acids and metabolic control in type 2 diabetes. *Am J Clin Nutr* 2003;78(Suppl.):617S–625S
78. Shai I, Schwarzfuchs D, Henkin Y, et al.; Dietary Intervention Randomized Controlled Trial (DIRECT) Group. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med* 2008;359:229–241
79. Brunerova L, Smejkalova V, Potockova J, Andel M. A comparison of the influence of a high-fat diet enriched in monounsaturated fatty acids and conventional diet on weight loss and metabolic parameters in obese non-diabetic and type 2 diabetic patients. *Diabet Med* 2007;24:533–540
80. Harris WS, Mozaffarian D, Rimm E, et al. Omega-6 fatty acids and risk for cardiovascular disease: a science advisory from the American Heart Association Nutrition Subcommittee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Cardiovascular Nursing; and Council on Epidemiology and Prevention. *Circulation* 2009;119:902–907
81. Crochemore ICC, Souza AFP, de Souza ACF, Rosado EL. ω -3 polyunsaturated fatty acid supplementation does not influence body composition, insulin resistance, and lipemia in women with type 2 diabetes and obesity. *Nutr Clin Pract* 2012;27:553–560
82. Bot M, Pouwer F, Assies J, Jansen EHJM, Beekman ATF, de Jonge P. Supplementation with eicosapentaenoic omega-3 fatty acid does not influence serum brain-derived neurotrophic factor in diabetes mellitus patients with major depression: a randomized controlled pilot study. *Neuropsychobiology* 2011;63:219–223
83. Holman RR, Paul S, Farmer A, Tucker L, Stratton IM, Neil HA; Atorvastatin in Factorial with Omega-3 EE90 Risk Reduction in Diabetes Study Group. Atorvastatin in Factorial with Omega-3 EE90 Risk Reduction in Diabetes (AFORRD): a randomised controlled trial. *Diabetologia* 2009;52:50–59
84. Kromhout D, Geleijnse JM, de Goede J, et al. n-3 fatty acids, ventricular arrhythmia-related events, and fatal myocardial infarction in post-myocardial infarction patients with diabetes. *Diabetes Care* 2011;34:2515–2520
85. Bosch J, Gerstein HC, Dagenais GR, et al.; ORIGIN Trial Investigators. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med* 2012;367:309–318
86. Maillot M, Drewnowski A. A conflict between nutritionally adequate diets and meeting the 2010 dietary guidelines for sodium. *Am J Prev Med* 2012;42:174–179
87. Bray GA, Vollmer WM, Sacks FM, Obarzanek E, Svetkey LP, Appel LJ; DASH Collaborative Research Group. A further subgroup analysis of the effects of the DASH diet and three dietary sodium levels on blood pressure: results of the DASH-Sodium Trial. *Am J Cardiol* 2004;94:222–227
88. Thomas MC, Moran J, Forsblom C, et al.; FinnDiane Study Group. The association between dietary sodium intake, ESRD, and all-cause mortality in patients with type 1 diabetes. *Diabetes Care* 2011;34:861–866
89. Ekinci EI, Clarke S, Thomas MC, et al. Dietary salt intake and mortality in patients with type 2 diabetes. *Diabetes Care* 2011;34:703–709
90. Whelton PK, Appel LJ, Sacco RL, et al. Sodium, blood pressure, and cardiovascular disease: further evidence supporting the American Heart Association sodium reduction recommendations. *Circulation* 2012;126:2880–2889
91. Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393–403
92. Tuomilehto J, Lindström J, Eriksson JG, et al.; Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001;344:1343–1350
93. Pan X-R, Li G-W, Hu Y-H, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and Diabetes Study. *Diabetes Care* 1997;20:537–544
94. Boulé NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA* 2001;286:1218–1227
95. Colberg SR, Riddell MC. Physical activity: regulation of glucose metabolism, clinical management strategies, and weight control. In *Type 1 Diabetes Sourcebook*. Peters AL, Laffel LM, Eds. Alexandria, VA, American Diabetes Association, 2013
96. Boulé NG, Kenny GP, Haddad E, Wells GA, Sigal RJ. Meta-analysis of the effect of structured exercise training on cardiorespiratory fitness in type 2 diabetes mellitus. *Diabetologia* 2003;46:1071–1081
97. Rejeski WJ, Ip EH, Bertoni AG, et al.; Look AHEAD Research Group. Lifestyle change and mobility in obese adults with type 2 diabetes. *N Engl J Med* 2012;366:1209–1217
98. Colberg SR, Sigal RJ, Fernhall B, et al. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement executive summary. *Diabetes Care* 2010;33:2692–2696
99. Janssen I, Leblanc AG. Systematic review of the health benefits of physical activity and fitness in school-aged children and youth. *Int J Behav Nutr Phys Act* 2010;7:40
100. Office of Disease Prevention and Health Promotion; U.S. Department of Health and Human Services. 2008 Physical Activity Guidelines for Americans [Internet], 2008. Available from <http://www.health.gov/paguidelines/guidelines/default.aspx>. Accessed 1 October 2014
101. Katzmarzyk PT, Church TS, Craig CL, Bouchard C. Sitting time and mortality from all causes, cardiovascular disease, and cancer. *Med Sci Sports Exerc* 2009;41:998–1005
102. Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C. Physical activity/exercise and type 2 diabetes. *Diabetes Care* 2004;27:2518–2539
103. Church TS, Blair SN, Cocroham S, et al. Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial. *JAMA* 2010;304:2253–2262
104. Bax JJ, Young LH, Frye RL, Bonow RO, Steinberg HO, Barrett EJ. Screening for coronary artery disease in patients with diabetes. *Diabetes Care* 2007;30:2729–2736
105. Chu L, Hamilton J, Riddell MC. Clinical management of the physically active patient with type 1 diabetes. *Phys Sportsmed* 2011;39:64–77
106. Colberg SR. *Exercise and Diabetes: A Clinician's Guide to Prescribing Physical Activity*, 1st ed. Alexandria, VA, American Diabetes Association, 2013
107. Lemaster JW, Reiber GE, Smith DG, Heagerty PJ, Wallace C. Daily weight-bearing activity does not increase the risk of diabetic foot ulcers. *Med Sci Sports Exerc* 2003;35:1093–1099
108. Spallone V, Ziegler D, Freeman R, et al.; Toronto Consensus Panel on Diabetic Neuropathy. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. *Diabetes Metab Res Rev* 2011;27:639–653
109. Pop-Busui R, Evans GW, Gerstein HC, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes Care* 2010;33:1578–1584
110. Jankowich M, Choudhary G, Taveira TH, Wu W-C. Age-, race-, and gender-specific prevalence of diabetes among smokers. *Diabetes Res Clin Pract* 2011;93:e101–e105
111. Voulgari C, Katsilambros N, Tentolouris N. Smoking cessation predicts amelioration of microalbuminuria in newly diagnosed type 2 diabetes mellitus: a 1-year prospective study. *Metabolism* 2011;60:1456–1464
112. Ranney L, Melvin C, Lux L, McClain E, Lohr KN. Systematic review: smoking cessation intervention strategies for adults and adults in special populations. *Ann Intern Med* 2006;145:845–856
113. Clair C, Rigotti NA, Porneala B, et al. Association of smoking cessation and weight change with cardiovascular disease among adults with and without diabetes. *JAMA* 2013;309:1014–1021
114. Palazzolo DL. Electronic cigarettes and vaping: a new challenge in clinical medicine and public health. A literature review. *Front Public Health* 2013;1:56
115. Anderson RJ, Grigsby AB, Freedland KE, et al. Anxiety and poor glycemic control: a meta-analytic review of the literature. *Int J Psychiatry Med* 2002;32:235–247
116. Delahanty LM, Grant RW, Wittenberg E, et al. Association of diabetes-related emotional distress with diabetes treatment in primary care patients with type 2 diabetes. *Diabet Med* 2007;24:48–54
117. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care* 2001;24:1069–1078

118. Kovacs Burns K, Nicolucci A, Holt RIG, et al.; DAWN2 Study Group. Diabetes Attitudes, Wishes and Needs second study (DAWN2™): cross-national benchmarking indicators for family members living with people with diabetes. *Diabet Med* 2013;30:778–788
119. Harkness E, Macdonald W, Valderas J, Coventry P, Gask L, Bower P. Identifying psychosocial interventions that improve both physical and mental health in patients with diabetes: a systematic review and meta-analysis. *Diabetes Care* 2010;33:926–930
120. Bot M, Pouwer F, Zuidersma M, van Melle JP, de Jonge P. Association of coexisting diabetes and depression with mortality after myocardial infarction. *Diabetes Care* 2012;35:503–509
121. Scherrer JF, Garfield LD, Chrusciel T, et al. Increased risk of myocardial infarction in depressed patients with type 2 diabetes. *Diabetes Care* 2011;34:1729–1734
122. Sullivan MD, O'Connor P, Feeney P, et al. Depression predicts all-cause mortality: epidemiological evaluation from the ACCORD HRQL substudy. *Diabetes Care* 2012;35:1708–1715
123. Chen P-C, Chan Y-T, Chen H-F, Ko M-C, Li C-Y. Population-based cohort analyses of the bidirectional relationship between type 2 diabetes and depression. *Diabetes Care* 2013;36:376–382
124. Pan A, Keum N, Okereke OI, et al. Bidirectional association between depression and metabolic syndrome: a systematic review and meta-analysis of epidemiological studies. *Diabetes Care* 2012;35:1171–1180
125. Nicolucci A, Kovacs Burns K, Holt RIG, et al.; DAWN2 Study Group. Diabetes Attitudes, Wishes and Needs second study (DAWN2™): cross-national benchmarking of diabetes-related psychosocial outcomes for people with diabetes. *Diabet Med* 2013;30:767–777
126. Fisher L, Hessler DM, Polonsky WH, Mullan J. When is diabetes distress clinically meaningful? Establishing cut points for the Diabetes Distress Scale. *Diabetes Care* 2012;35:259–264
127. Fisher L, Glasgow RE, Strycker LA. The relationship between diabetes distress and clinical depression with glycemic control among patients with type 2 diabetes. *Diabetes Care* 2010;33:1034–1036
128. Aikens JE. Prospective associations between emotional distress and poor outcomes in type 2 diabetes. *Diabetes Care* 2012;35:2472–2478
129. Gary TL, Safford MM, Gerzoff RB, et al. Perception of neighborhood problems, health behaviors, and diabetes outcomes among adults with diabetes in managed care: the Translating Research Into Action for Diabetes (TRIAD) study. *Diabetes Care* 2008;31:273–278
130. Zhang X, Norris SL, Gregg EW, Cheng YJ, Beckles G, Kahn HS. Depressive symptoms and mortality among persons with and without diabetes. *Am J Epidemiol* 2005;161:652–660
131. Fisher L, Glasgow RE, Mullan JT, Skaff MM, Polonsky WH. Development of a brief diabetes distress screening instrument. *Ann Fam Med* 2008;6:246–252
132. McGuire BE, Morrison TG, Hermanns N, et al. Short-form measures of diabetes-related emotional distress: the Problem Areas in Diabetes Scale (PAID)-5 and PAID-1. *Diabetologia* 2010;53:66–69
133. Rubin RR, Peyrot M. Psychological issues and treatments for people with diabetes. *J Clin Psychol* 2001;57:457–478
134. Young-Hyman DL, Davis CL. Disordered eating behavior in individuals with diabetes: importance of context, evaluation, and classification. *Diabetes Care* 2010;33:683–689
135. Beverly EA, Hultgren BA, Brooks KM, Ritholz MD, Abrahamson MJ, Weinger K. Understanding physicians' challenges when treating type 2 diabetic patients' social and emotional difficulties: a qualitative study. *Diabetes Care* 2011;34:1086–1088
136. Ciechanowski P. Diapression: an integrated model for understanding the experience of individuals with co-occurring diabetes and depression. *Clinical Diabetes* 2011;29:43–49
137. Katon WJ, Lin EHB, Von Korff M, et al. Collaborative care for patients with depression and chronic illnesses. *N Engl J Med* 2010;363:2611–2620
138. Akinsanya-Beysolow I; Advisory Committee on Immunization Practices (ACIP); ACIP Child/Adolescent Immunization Work Group; Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices recommended immunization schedules for persons aged 0 through 18 years - United States, 2014. *MMWR Morb Mortal Wkly Rep* 2014;63:108–109
139. Bridges CB, Coyne-Beasley T; Advisory Committee on Immunization Practices (ACIP); ACIP Adult Immunization Work Group; Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older - United States, 2014. *MMWR Morb Mortal Wkly Rep* 2014;63:110–112
140. Smith SA, Poland GA. Use of influenza and pneumococcal vaccines in people with diabetes. *Diabetes Care* 2000;23:95–108
141. Colquhoun AJ, Nicholson KG, Botha JL, Raymond NT. Effectiveness of influenza vaccine in reducing hospital admissions in people with diabetes. *Epidemiol Infect* 1997;119:335–341
142. Tomczyk S, Bennett NM, Stoecker C, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2014;63:822–825

5. Prevention or Delay of Type 2 Diabetes

American Diabetes Association

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Recommendations

- Patients with impaired glucose tolerance (IGT) **A**, impaired fasting glucose (IFG) **E**, or an A1C 5.7–6.4% **E** should be referred to an intensive diet and physical activity behavioral counseling program targeting loss of 7% of body weight and increasing moderate-intensity physical activity (such as brisk walking) to at least 150 min/week.
- Follow-up counseling may be important for success. **B**
- Based on the cost-effectiveness of diabetes prevention, such programs should be covered by third-party payers. **B**
- Metformin therapy for prevention of type 2 diabetes may be considered in those with IGT **A**, IFG **E**, or an A1C 5.7–6.4% **E**, especially for those with BMI >35 kg/m², aged <60 years, and women with prior gestational diabetes mellitus (GDM). **A**
- At least annual monitoring for the development of diabetes in those with prediabetes is suggested. **E**
- Screening for and treatment of modifiable risk factors for cardiovascular disease is suggested. **B**
- Diabetes self-management education (DSME) and support (DSMS) programs are appropriate venues for people with prediabetes to receive education and support to develop and maintain behaviors that can prevent or delay the onset of diabetes. **C**

LIFESTYLE MODIFICATIONS

Randomized controlled trials have shown that individuals at high risk for developing type 2 diabetes (IFG, IGT, or both) can significantly decrease the rate of diabetes onset with particular interventions (1–5). These include intensive lifestyle modification programs that have been shown to be very effective (~58% reduction after 3 years). Follow-up of all three large studies of lifestyle intervention has shown sustained reduction in the rate of conversion to type 2 diabetes: 43% reduction at 20 years in the Da Qing study (6), 43% reduction at 7 years in the Finnish Diabetes Prevention Study (DPS) (7), and 34% reduction at 10 years in the U.S. Diabetes Prevention Program Outcomes Study (DPPOS) (8). A cost-effectiveness model suggested that lifestyle interventions in the Diabetes Prevention Program (DPP) are cost-effective (9). Actual cost data from the DPP and DPPOS confirm that the lifestyle interventions are highly cost-effective (10). Group delivery of the DPP intervention in community settings has the potential to be significantly less expensive while still achieving similar weight loss (11). The Centers for Disease Control and Prevention (CDC) helps coordinate the National Diabetes Prevention Program, a resource designed to bring evidence-based lifestyle change programs for preventing type 2 diabetes to communities (<http://www.cdc.gov/diabetes/prevention/index.htm>).

Given the clinical trial results and the known risks of progression of prediabetes to diabetes, people with an A1C 5.7–6.4%, IGT, or IFG should be counseled on lifestyle changes with goals similar to those of the DPP (7% weight loss and moderate-intensity physical activity of at least 150 min/week).

PHARMACOLOGICAL INTERVENTIONS

Pharmacological agents, such as metformin, α -glucosidase inhibitors, orlistat, and thiazolidinediones, have each been shown to decrease incident diabetes to various

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degrees. Metformin has the strongest evidence base and demonstrated long-term safety as pharmacological therapy for diabetes prevention (12). For other drugs, cost, side effects, and lack of a persistent effect require consideration.

Metformin was less effective than lifestyle modification in the DPP and DPPOS but may be cost-saving over a 10-year period (10). It was as effective as lifestyle modification in participants with BMI ≥ 35 kg/m² 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 (13). Metformin may be recommended for very high-risk individuals (e.g., with history of GDM, who are very obese, and/or those with more severe or progressive hyperglycemia).

People with prediabetes often have other cardiovascular risk factors, such as obesity, hypertension, and dyslipidemia, and are at an increased risk for cardiovascular disease events. While treatment goals are the same as for other patients without diabetes, increased vigilance is warranted to identify and treat these and other risk factors (e.g., smoking).

DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT

The standards for DSME and DSMS (see Section 4. Foundations of Care) can also apply to the education and support of 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 largely identical to those for people with diabetes. Given their training and experience, providers of DSME and DSMS are particularly well equipped to assist people with prediabetes in developing and maintaining behaviors that can prevent or delay the onset of diabetes (14–16).

References

1. Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393–403
2. Buchanan TA, Xiang AH, Peters RK, et al. Preservation of pancreatic β -cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk hispanic women. *Diabetes* 2002;51:2796–2803
3. Chiasson J-L, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trial Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002;359:2072–2077
4. Lin JS, O'Connor E, Evans CV, Senger CA, Rowland MG, Groom HC. Behavioral counseling to promote a healthy lifestyle in persons with cardiovascular risk factors: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2014;161:568–578
5. Paulweber B, Valensi P, Lindström J, et al. A European evidence-based guideline for the prevention of type 2 diabetes. *Horm Metab Res* 2010;42(Suppl. 1):S3–S36
6. Li G, Zhang P, Wang J, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet* 2008;371:1783–1789
7. Lindström J, Ilanne-Parikka P, Peltonen M, et al.; Finnish Diabetes Prevention Study Group. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet* 2006;368:1673–1679
8. Knowler WC, Fowler SE, Hamman RF, et al.; Diabetes Prevention Program Research Group. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009;374:1677–1686
9. Herman WH, Hoerger TJ, Brandle M, et al.; Diabetes Prevention Program Research Group. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. *Ann Intern Med* 2005;142:323–332
10. Diabetes Prevention Program Research Group. The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the DPP/DPPOS. *Diabetes Care* 2012;35:723–730
11. Ackermann RT, Finch EA, Brizendine E, Zhou H, Marrero DG. Translating the Diabetes Prevention Program into the community. The DEPLOY Pilot Study. *Am J Prev Med* 2008;35:357–363
12. Diabetes Prevention Program Research Group. Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study. *Diabetes Care* 2012;35:731–737
13. Ratner RE, Christophi CA, Metzger BE, et al.; Diabetes Prevention Program Research Group. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. *J Clin Endocrinol Metab* 2008;93:4774–4779
14. Parekh D, Sarathi V, Shivane VK, Bandgar TR, Menon PS, Shah NS. Pilot study to evaluate the effect of short-term improvement in vitamin D status on glucose tolerance in patients with type 2 diabetes mellitus. *Endocr Pract* 2010;16:600–608
15. Shah M, Kaselitz E, Heisler M. The role of community health workers in diabetes: update on current literature. *Curr Diab Rep* 2013;13:163–171
16. Heisler M. Overview of peer support models to improve diabetes self-management and clinical outcomes. *Diabetes Spectrum* 2007;20:214–221

6. Glycemic Targets

American Diabetes Association

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ASSESSMENT OF GLYCEMIC CONTROL

Two primary techniques are available for health providers and patients to assess the effectiveness of the management plan on glycemic control: patient self-monitoring of blood glucose (SMBG) or interstitial glucose and A1C. Continuous glucose monitoring (CGM) may be a useful adjunct to SMBG in selected patients.

Recommendations

- When prescribed as part of a broader educational context, SMBG results may help guide treatment decisions and/or self-management for patients using less frequent insulin injections **B** or noninsulin therapies. **E**
- When prescribing SMBG, ensure that patients receive ongoing instruction and regular evaluation of SMBG technique, SMBG results, and their ability to use SMBG data to adjust therapy. **E**
- Patients on multiple-dose insulin or insulin pump therapy should perform SMBG prior to meals and snacks, occasionally postprandially, at bedtime, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to critical tasks such as driving. **B**
- When used properly, CGM in conjunction with intensive insulin regimens is a useful tool to lower A1C in selected adults (aged ≥ 25 years) with type 1 diabetes. **A**
- Although the evidence for A1C lowering is less strong in children, teens, and younger adults, CGM may be helpful in these groups. Success correlates with adherence to ongoing use of the device. **B**
- CGM may be a supplemental tool to SMBG in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes. **C**
- Given variable adherence to CGM, assess individual readiness for continuing use of CGM prior to prescribing. **E**
- When prescribing CGM, robust diabetes education, training, and support are required for optimal CGM implementation and ongoing use. **E**

Self-monitoring of Blood Glucose

Major clinical trials of insulin-treated patients have included SMBG as part of the multifactorial interventions to demonstrate the benefit of intensive glycemic control on diabetes complications. SMBG is thus an integral component of effective therapy (1). SMBG allows patients to evaluate their individual response to therapy and assess whether glycemic targets are being achieved. Integrating SMBG 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). Evidence supports a correlation between greater SMBG frequency and lower A1C (2). The patient's specific needs and goals should dictate SMBG frequency and timing.

Optimization

SMBG accuracy is dependent on the instrument and user (3), 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, both by the patient and provider. Among patients who check their blood glucose at least once daily, many report taking no action when results are high or low (4). In a yearlong study of insulin-naïve patients with suboptimal initial glycemic control, a group trained in structured SMBG (a paper tool was used at least quarterly to collect and interpret 7-point SMBG profiles taken on 3 consecutive days) reduced their A1C by 0.3 percentage points more than the control group (5). Patients should

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be taught how to use SMBG data to adjust food intake, exercise, or pharmacological therapy to achieve specific goals. The ongoing need for and frequency of SMBG should be reevaluated at each routine visit. SMBG is especially important for insulin-treated patients to monitor for and prevent asymptomatic hypoglycemia and hyperglycemia.

For Patients on Intensive Insulin Regimens

Most patients on intensive insulin regimens (multiple-dose insulin or insulin pump therapy, including patients with type 1 diabetes) should consider SMBG prior to meals and snacks, occasionally postprandially, at bedtime, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to critical tasks such as driving. For many patients, this will require testing 6–10 (or more) 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 (6).

For Patients Using Basal Insulin or Oral Agents

The evidence is insufficient regarding when to prescribe SMBG and how often testing is needed for patients who do not use an intensive insulin regimen, such as those with type 2 diabetes using basal insulin or oral agents.

Several randomized trials have called into question the clinical utility and cost-effectiveness of routine SMBG in noninsulin-treated patients (7–9). A meta-analysis suggested that SMBG reduced A1C by 0.25% at 6 months (10), but the reduction subsides after 12 months (11). 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.

Continuous Glucose Monitoring

Real-time CGM measures interstitial glucose (which correlates well with plasma glucose) and includes sophisticated alarms for hypo- and hyperglycemic excursions, but the devices are still not approved by the U.S. Food and Drug Administration as a sole agent to monitor glucose. CGMs require calibration with

SMBG, with the latter still required for making acute treatment decisions.

A 26-week randomized trial of 322 type 1 diabetic patients showed that adults aged ≥ 25 years using intensive insulin therapy and CGM experienced a 0.5% reduction in A1C (from $\sim 7.6\%$ to 7.1%), compared with those using intensive insulin therapy with SMBG (12). Sensor use in those aged < 25 years (children, teens, and adults) did not result in significant A1C lowering, and there was no significant difference in hypoglycemia in any group. The greatest predictor of A1C lowering for all age-groups was frequency of sensor use, which was highest in those aged ≥ 25 years and lower in younger age-groups.

A recent registry study of 17,317 participants confirmed that more frequent CGM use is associated with lower A1C (13), while another study showed that children with $> 70\%$ sensor use missed fewer school days (14). Small randomized controlled trials in adults and children with baseline A1C 7.0–7.5% have confirmed favorable outcomes (A1C and hypoglycemia occurrence) in groups using CGM, suggesting that CGM may provide further benefit for individuals with type 1 diabetes who already have tight control (15,16).

A meta-analysis suggests that, compared with SMBG, CGM is associated with short-term A1C lowering of $\sim 0.26\%$ (17). The long-term effectiveness of CGM needs to be determined. This technology may be particularly useful in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes, although studies have not shown significant reductions in severe hypoglycemia (17,18). A CGM device equipped with an automatic low glucose suspend feature has been approved by the U.S. Food and Drug Administration. The Automation to Simulate Pancreatic Insulin Response (ASPIRE) trial of 247 patients showed that sensor-augmented insulin pump therapy with a low glucose suspend significantly reduced nocturnal hypoglycemia, without increasing A1C levels for those over 16 years of age (19). These devices may offer the opportunity to reduce severe hypoglycemia for those with a history of nocturnal hypoglycemia. Due to variable adherence, optimal CGM use requires an assessment of individual readiness for the technology as well as initial and ongoing education and support (13,20,21).

A1C Testing

Recommendations

- Perform the A1C test *at least* two times a year in patients who are meeting treatment goals (and who have stable glycemic control). **E**
- Perform the A1C test quarterly in patients whose therapy has changed or who are not meeting glycemic goals. **E**
- Use of point-of-care testing for A1C provides the opportunity for more timely treatment changes. **E**

A1C reflects average glycemia over several months (3) and has strong predictive value for diabetes complications (22,23). 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. Some patients with stable glycemia well within target may do well with testing only twice per year. Unstable or highly intensively managed patients (e.g., pregnant women with type 1 diabetes) may require testing more frequently than every 3 months (24).

A1C Limitations

The A1C test is subject to certain limitations. Conditions that affect red blood cell turnover (hemolysis, blood loss) and hemoglobin variants must be considered, particularly when the A1C result does not correlate with the patient's blood glucose levels (3). For patients in whom A1C/estimated average glucose (eAG) and measured blood glucose appear discrepant, clinicians should consider the possibilities of hemoglobinopathy or altered red blood cell turnover and the options of more frequent and/or different timing of SMBG or CGM use. Other measures of chronic glycemia such as fructosamine are available, but their linkage to average glucose and their prognostic significance are not as clear as for A1C.

The A1C does not provide a measure of glycemic variability or hypoglycemia. For patients prone to glycemic variability, especially type 1 diabetic patients or type 2 diabetic patients with severe insulin deficiency, glycemic control is best evaluated by the combination of results

from self-monitoring and the A1C. The A1C may also confirm the accuracy of the patient’s meter (or the patient’s reported SMBG results) and the adequacy of the SMBG testing schedule.

A1C and Mean Glucose

Table 6.1 shows the correlation between A1C levels and mean glucose levels based on two studies: the international A1C-Derived Average Glucose (ADAG) trial, which based the correlation with A1C on frequent SMBG and CGM in 507 adults (83% non-Hispanic whites) with type 1, type 2, and no diabetes (25), 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 (21). 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 eAG result when a clinician orders the A1C test. Clinicians should note that the mean plasma glucose numbers in the table are based on ~2,800 readings per A1C in the ADAG trial.

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 there was a trend toward a difference between the African/African American and non-Hispanic white cohorts. 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 (26). Whether there are significant differences in how A1C relates to average glucose in children or in different ethnicities is an area for further study (27,28). For the time being, the question has not led to different recommendations about testing A1C or to different interpretations of the clinical meaning of given levels of A1C in those populations.

A1C GOALS

For glycemic goals in children, please refer to Section 11. Children and Adolescents. For glycemic goals in pregnant women, please refer to Section 12. Management of Diabetes in Pregnancy.

Recommendations

- Lowering A1C to approximately 7% or less has been shown to reduce microvascular complications of diabetes, and, if implemented soon after the diagnosis of diabetes, it is associated with long-term reduction in macrovascular disease. Therefore, a reasonable A1C goal for many nonpregnant adults is <7%. **B**
- Providers might reasonably suggest more stringent A1C goals (such as <6.5%) for selected individual patients if this can be achieved without significant

hypoglycemia or other adverse effects of treatment. Appropriate patients might include those with short duration of diabetes, type 2 diabetes treated with lifestyle or metformin only, long life expectancy, or no significant cardiovascular disease (CVD). **C**

- Less stringent A1C goals (such as <8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. **B**

A1C and Microvascular Complications

Hyperglycemia defines diabetes, and glycemic control is fundamental to diabetes management. The Diabetes Control and Complications Trial (DCCT) (1), a prospective randomized controlled trial of intensive versus standard glycemic control in patients with relatively recently diagnosed type 1 diabetes showed definitively that improved glycemic control is associated with significantly decreased rates of microvascular (retinopathy and diabetic kidney disease) and neuropathic complications. Follow-up of the DCCT cohorts in the

Table 6.1—Mean glucose levels for specified A1C levels (21,25)

A1C (%)	Mean plasma glucose*		Mean fasting glucose mg/dL	Mean premeal glucose mg/dL	Mean postmeal glucose mg/dL	Mean bedtime glucose mg/dL
	mg/dL	mmol/L				
6	126	7.0				
<6.5			122	118	144	136
6.5–6.99			142	139	164	153
7	154	8.6				
7.0–7.49			152	152	176	177
7.5–7.99			167	155	189	175
8	183	10.2				
8–8.5			178	179	206	222
9	212	11.8				
10	240	13.4				
11	269	14.9				
12	298	16.5				

A calculator for converting A1C results into eAG, in either mg/dL or mmol/L, is available at <http://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, and no diabetes. The correlation between A1C and average glucose was 0.92 (25).

Epidemiology of Diabetes Interventions and Complications (EDIC) study (29,30) demonstrated persistence of these microvascular benefits in previously intensively treated subjects, even though their glycemic control approximated that of previous standard arm subjects during follow-up.

The Kumamoto Study (31) and UK Prospective Diabetes Study (UKPDS) (32,33) confirmed that intensive glycemic control was associated with significantly decreased rates of microvascular and neuropathic complications in type 2 diabetic patients. Long-term follow-up of the UKPDS cohorts showed enduring effects of early glycemic control on most microvascular complications (34).

Three landmark trials (Action to Control Cardiovascular Risk in Diabetes [ACCORD], Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation [ADVANCE], and Veterans Affairs Diabetes Trial [VADT]) showed that lower A1C levels were associated with reduced onset or progression of microvascular complications (35–37).

Epidemiological analyses of the DCCT (1) and UKPDS (38) 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% is associated with further reduction in the risk of microvascular complications, though the absolute risk reductions become much smaller. Given the substantially increased risk of hypoglycemia in type 1 diabetes trials and in recent type 2 diabetes trials, the risks of lower glycemic targets may, on a population level, outweigh the potential benefits on microvascular complications.

The concerning mortality findings in the ACCORD trial, discussed below (39), and the relatively intense efforts required to achieve near-euglycemia should also be considered when setting glycemic targets. However, based on physician judgment and patient preferences, select patients, especially those with little comorbidity and long life expectancy, may benefit from adopting

more intensive glycemic targets (e.g., A1C target <6.5%) as long as significant hypoglycemia does not become a barrier.

A1C and Cardiovascular Disease

Outcomes

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 study cohorts treated early in the course of type 1 and type 2 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 CVD death compared with those previously in the standard arm (40). The benefit of intensive glycemic control in this type 1 diabetic cohort has recently been shown to persist for several decades (41).

In type 2 diabetes, there is evidence that more intensive treatment of glycemia in newly diagnosed patients may reduce long-term CVD rates. During the UKPDS trial, 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 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) (34).

The ACCORD, ADVANCE, and VADT suggested no significant reduction in CVD outcomes with intensive glycemic control in participants followed for 3.5–5.6 years who had more advanced type 2 diabetes than UKPDS participants. All three trials were conducted in participants with more long-standing diabetes (mean duration 8–11 years) and either known CVD or multiple cardiovascular risk factors. The target A1C

among intensive control subjects was <6% in ACCORD, <6.5% in ADVANCE, and a 1.5% reduction in A1C compared with control subjects in VADT. Details of these studies are reviewed extensively in the ADA position statement “Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials: A Position Statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation and the American Heart Association” (42).

The glycemic control comparison in ACCORD was halted early due to an increased mortality rate in the intensive compared with the standard 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.

Key Points

1. Analysis of the ACCORD data did not identify a clear explanation for the excess mortality in the intensive arm (39).
2. A group-level meta-analysis of ACCORD, ADVANCE, and VADT suggested that glucose lowering had a modest (9%) but statistically significant reduction in major CVD outcomes, primarily nonfatal MI, with no significant effect on mortality.
3. Heterogeneity of the mortality effects across studies was noted.
4. A prespecified subgroup analysis suggested that major CVD outcome reduction occurred in patients without known CVD at baseline (hazard ratio 0.84 [95% CI 0.74–0.94]) (43).
5. Mortality findings in ACCORD (39) and subgroup analyses of the VADT (44) suggested that the potential risks of intensive glycemic control may outweigh its benefits in some patients.
6. Those with long duration of diabetes, known history of severe hypoglycemia, advanced atherosclerosis, or advanced age/frailty may benefit from less aggressive targets.
7. Severe hypoglycemia was significantly more likely in participants in all three trials randomized to the intensive glycemic control arm.

Table 6.2—Summary of glycemic recommendations for nonpregnant adults with diabetes

A1C	<7.0%*
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.

Providers should be vigilant in preventing severe hypoglycemia in patients with advanced disease and should not aggressively attempt to achieve near-normal A1C levels in patients in whom such targets cannot be safely and reasonably achieved. Severe or frequent hypoglycemia is an absolute indication for the modification of treatment regimens, including setting higher glycemic goals. Many factors, including patient preferences, should be taken into account when developing a patient’s individualized goals (Table 6.2).

A1C and Glycemic Targets

Numerous aspects must be considered when setting glycemic targets. The ADA proposes optimal targets, but each target must be individualized to the needs of each patient and their disease factors. When possible, such decisions should be made with the patient, reflecting his or her preferences, needs, and values. Figure 6.1 is not designed to be applied rigidly but used as a broad construct to guide clinical decision making (45), both in type 1 and type 2 diabetes.

Recommended glycemic targets for many nonpregnant adults are shown in Table 6.2. The recommendations include blood glucose levels that appear to correlate with achievement of an A1C of <7%. The issue of preprandial versus postprandial SMBG targets is complex (46). Elevated postchallenge (2-h oral glucose tolerance test) glucose values have been associated with increased cardiovascular risk independent of fasting plasma glucose in some epidemiological studies. In subjects with diabetes, surrogate measures of vascular pathology, such as endothelial dysfunction, are

negatively affected by postprandial hyperglycemia (47). 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%. However, outcome studies have clearly shown A1C to be the primary predictor of complications, and landmark glycemic control trials 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 (48). 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. Taking postprandial plasma glucose measurements 1–2 h after the start of a meal and using treatments aimed at reducing postprandial plasma glucose values to <180 mg/dL (10 mmol/L) may help lower A1C.

An analysis of data from 470 participants of the ADAG study (237 with type 1 diabetes and 147 with type 2 diabetes) found that actual average glucose levels associated with conventional A1C targets were higher than older DCCT and ADA targets (Table 6.1) (21,25). These findings support that premeal glucose targets may be relaxed without undermining overall glycemic control as measured by A1C. These data have prompted a revision in the ADA-recommended premeal target to 80–130 mg/dL (4.4–7.2 mmol/L).

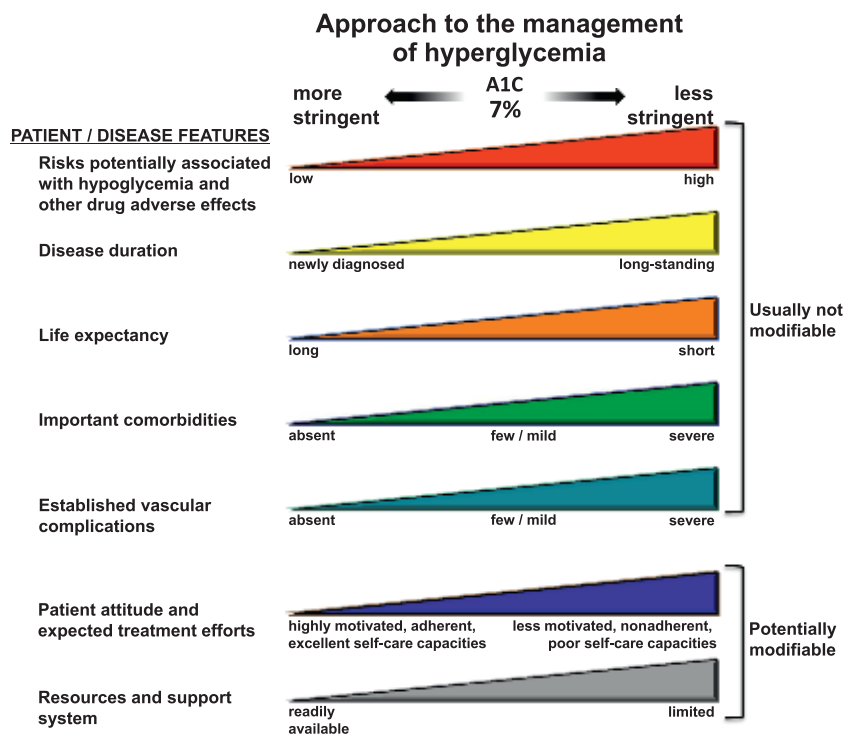


Figure 6.1—Depicted are patient and disease factors used to determine optimal A1C targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. Adapted with permission from Inzucchi et al. (45).

HYPOGLYCEMIA

Recommendations

- Individuals at risk for hypoglycemia should be asked about symptomatic and asymptomatic hypoglycemia at each encounter. **C**
- Glucose (15–20 g) is the preferred treatment for the conscious individual with hypoglycemia, 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. **E**
- Glucagon should be prescribed for all individuals at an increased risk of severe hypoglycemia, and caregivers or family members of these individuals should be instructed on its administration. Glucagon administration is not limited to health care professionals. **E**
- Hypoglycemia unawareness or one or more episodes of severe hypoglycemia should trigger reevaluation of the treatment regimen. **E**
- Insulin-treated patients with hypoglycemia unawareness or an episode of severe hypoglycemia should be advised to raise their glycemic targets to strictly avoid further hypoglycemia for at least several weeks in order to partially reverse hypoglycemia unawareness and reduce risk of future episodes. **A**
- Ongoing assessment of cognitive function is suggested with increased vigilance for hypoglycemia by the clinician, patient, and caregivers if low cognition and/or declining cognition is found. **B**

Hypoglycemia is the leading limiting factor in the glycemic management of type 1 and insulin-treated type 2 diabetes (49). Mild hypoglycemia may be inconvenient or frightening to patients with diabetes. Severe hypoglycemia can cause acute harm to the person with diabetes or others, especially if it causes falls, motor vehicle accidents, or other injury. A large cohort study suggested that among older adults with type 2 diabetes, a history of severe hypoglycemia was associated with greater risk of

dementia (50). Conversely, in a substudy of the ACCORD trial, cognitive impairment at baseline or decline in cognitive function during the trial was significantly associated with subsequent episodes of severe hypoglycemia (51). Evidence from the DCCT/EDIC, which involved younger adults and adolescents with type 1 diabetes, found no association between frequency of severe hypoglycemia and cognitive decline (52), as discussed in Section 11. Children and Adolescents.

Severe hypoglycemia was associated with mortality in participants in both the standard and intensive glycemia arms of the ACCORD trial, but the relationships between hypoglycemia, achieved A1C, and treatment intensity were not straightforward. An association of severe hypoglycemia with mortality was also found in the ADVANCE trial (53). An association between self-reported severe hypoglycemia and 5-year mortality has also been reported in clinical practice (54).

In 2013, the ADA and the Endocrine Society published the consensus report “Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and the Endocrine Society” (55) on the effect and treatment of hypoglycemia in patients with diabetes. Severe hypoglycemia was defined as an event requiring the assistance of another person. Young children with type 1 diabetes and the elderly were noted as particularly vulnerable due to their limited ability to recognize hypoglycemic symptoms and effectively communicate their needs. Individualized patient education, dietary intervention (e.g., bedtime snack to prevent overnight hypoglycemia), exercise management, medication adjustment, glucose monitoring, and routine clinical surveillance may improve patient outcomes.

Hypoglycemia Treatment

Hypoglycemia treatment requires ingestion of glucose- or carbohydrate-containing foods. 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. Ongoing insulin activity or insulin secretagogues may lead to

recurrent hypoglycemia unless further food is ingested after recovery.

Glucagon

Those in close contact with, or having custodial care of, people with hypoglycemia-prone diabetes (family members, roommates, school personnel, child care providers, correctional institution staff, or coworkers) should be instructed on the use of glucagon kits. An individual does not need to be a health care professional to safely administer glucagon. A glucagon kit requires a prescription. Care should be taken to ensure that glucagon kits 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 fasting for tests or procedures, during or 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 both are 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 awareness to some extent in many patients (56). Hence, patients with one or more episodes of severe hypoglycemia may benefit from at least short-term relaxation of glycemic targets.

INTERCURRENT ILLNESS

For further information on management of patients with hyperglycemia in the hospital, please refer to Section 13. Diabetes Care in the Hospital, Nursing

Home, and Skilled Nursing Facility. Stressful events (e.g., illness, trauma, surgery, etc.) frequently aggravate glycemic control and may precipitate diabetic ketoacidosis or nonketotic 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 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 temporarily require insulin. Adequate fluid and caloric intake must be assured. 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 diabetic ketoacidosis management or hyperglycemic nonketotic hyperosmolar state, please refer to the ADA statement “Hyperglycemic Crises in Adult Patients With Diabetes” (57).

References

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–986
2. Miller KM, Beck RW, Bergenstal RM, et al.; T1D Exchange Clinic Network. Evidence of a strong association between frequency of self-monitoring of blood glucose and hemoglobin A1c levels in T1D Exchange clinic registry participants. *Diabetes Care* 2013;36:2009–2014
3. Sacks DB, Arnold M, Bakris GL, et al.; National Academy of Clinical Biochemistry. Position statement executive summary: guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Diabetes Care* 2011;34:1419–1423
4. Wang J, Zgibor J, Matthews JT, Charron-Prochownik D, Sereika SM, Siminerio L. Self-monitoring of blood glucose is associated with problem-solving skills in hyperglycemia and hypoglycemia. *Diabetes Educ* 2012;38:207–218
5. Polonsky WH, Fisher L, Schikman CH, et al. Structured self-monitoring of blood glucose significantly reduces A1C levels in poorly controlled, noninsulin-treated type 2 diabetes: results from the Structured Testing Program study. *Diabetes Care* 2011;34:262–267
6. Ziegler R, Heidtmann B, Hilgard D, Hofer S, Rosenbauer J, Holl R; DPV-Wiss-Initiative. Frequency of SMBG correlates with HbA1c and acute complications in children and adolescents with type 1 diabetes. *Pediatr Diabetes* 2011;12:11–17
7. Farmer A, Wade A, Goyder E, et al. Impact of self monitoring of blood glucose in the management of patients with non-insulin treated diabetes: open parallel group randomised trial. *BMJ* 2007;335:132
8. O’Kane MJ, Bunting B, Copeland M, Coates VE; ESMON Study Group. Efficacy of self monitoring of blood glucose in patients with newly diagnosed type 2 diabetes (ESMON study): randomised controlled trial. *BMJ* 2008;336:1174–1177
9. Simon J, Gray A, Clarke P, Wade A, Neil A, Farmer A; Diabetes Glycaemic Education and Monitoring Trial Group. Cost effectiveness of self monitoring of blood glucose in patients with non-insulin treated type 2 diabetes: economic evaluation of data from the DIGEM trial. *BMJ* 2008;336:1177–1180
10. Willett LR. ACP Journal Club. Meta-analysis: self-monitoring in non-insulin-treated type 2 diabetes improved HbA1c by 0.25%. *Ann Intern Med* 2012;156:JC6–JC12
11. Malanda UL, Welschen LM, Riphagen II, Dekker JM, Nijpels G, Bot SD. Self-monitoring of blood glucose in patients with type 2 diabetes mellitus who are not using insulin. *Cochrane Database Syst Rev* 2012;1:CD005060
12. Tamborlane WV, Beck RW, Bode BW, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med* 2008;359:1464–1476
13. Wong JC, Foster NC, Maahs DM, et al.; T1D Exchange Clinic Network. Real-time continuous glucose monitoring among participants in the T1D Exchange clinic registry. *Diabetes Care* 2014;37:2702–2709
14. Hommel E, Olsen B, Battelino T, et al.; SWITCH Study Group. Impact of continuous glucose monitoring on quality of life, treatment satisfaction, and use of medical care resources: analyses from the SWITCH study. *Acta Diabetol* 2014;51:845–851
15. Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. *Diabetes Care* 2011;34:795–800
16. Beck RW, Hirsch IB, Laffel L, et al.; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. *Diabetes Care* 2009;32:1378–1383
17. Yeh H-C, Brown TT, Maruthur N, et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. *Ann Intern Med* 2012;157:336–347
18. Choudhary P, Ramasamy S, Green L, et al. Real-time continuous glucose monitoring significantly reduces severe hypoglycemia in hypoglycemia-unaware patients with type 1 diabetes. *Diabetes Care* 2013;36:4160–4162
19. Bergenstal RM, Klonoff DC, Garg SK, et al.; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. *N Engl J Med* 2013;369:224–232
20. McQueen RB, Ellis SL, Maahs DM, Anderson HD, Nair KV, Campbell JD. Frequency of continuous glucose monitoring use and change in hemoglobin A1c for adults with type 1 diabetes in a clinical practice setting. *Endocr Pract* 2014;20:1007–1015
21. Wei N, Zheng H, Nathan DM. Empirically establishing blood glucose targets to achieve HbA1c goals. *Diabetes Care* 2014;37:1048–1051
22. Albers JW, Herman WH, Pop-Busui R, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of prior intensive insulin treatment during the Diabetes Control and Complications Trial (DCCT) on peripheral neuropathy in type 1 diabetes during the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *Diabetes Care* 2010;33:1090–1096
23. Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321:405–412
24. Jovanović L, Savas H, Mehta M, Trujillo A, Pettitt DJ. Frequent monitoring of A1C during pregnancy as a treatment tool to guide therapy. *Diabetes Care* 2011;34:53–54
25. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ; A1c-Derived Average Glucose Study Group. Translating the A1c assay into estimated average glucose values. *Diabetes Care* 2008;31:1473–1478
26. Wilson DM, Kollman; Diabetes Research in Children Network (DirecNet) Study Group. Relationship of A1C to glucose concentrations in children with type 1 diabetes: assessments by high-frequency glucose determinations by sensors. *Diabetes Care* 2008;31:381–385
27. Buse JB, Kaufman FR, Linder B, Hirst K, El Ghormli L, Willi S; HEALTHY Study Group. Diabetes screening with hemoglobin A(1c) versus fasting plasma glucose in a multiethnic middle-school cohort. *Diabetes Care* 2013;36:429–435
28. Kamps JL, Hempe JM, Chalew SA. Racial disparity in A1C independent of mean blood glucose in children with type 1 diabetes. *Diabetes Care* 2010;33:1025–1027
29. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N Engl J Med* 2000;342:381–389
30. Martin CL, Albers J, Herman WH, et al.; DCCT/EDIC Research Group. Neuropathy among the Diabetes Control and Complications Trial cohort 8 years after trial completion. *Diabetes Care* 2006;29:340–344
31. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 1995;28:103–117
32. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854–865

33. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–853
34. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in veterans with type 2 diabetes. *N Engl J Med* 2008;359:1577–1589
35. Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;360:129–139
36. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560–2572
37. Ismail-Beigi F, Craven T, Banerji MA, et al.; ACCORD trial group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet* 2010;376:419–430
38. Adler AI, Stratton IM, Neil HAW, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ* 2000;321:412–419
39. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545–2559
40. Nathan DM, Cleary PA, Backlund J-YC, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353:2643–2653
41. Nathan DM, Zinman B, Cleary PA, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications and Pittsburgh Epidemiology of Diabetes Complications Experience (1983-2005). *Arch Intern Med* 2009;169:1307–1316
42. Skyler JS, Bergenstal R, Bonow RO, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA Diabetes Trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Diabetes Care* 2009;32:187–192
43. Turnbull FM, Abraira C, Anderson RJ, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* 2009;52:2288–2298
44. Duckworth WC, Abraira C, Moritz TE, et al.; Investigators of the VADT. The duration of diabetes affects the response to intensive glucose control in type 2 subjects: the VA Diabetes Trial. *J Diabetes Complications* 2011;25:355–361
45. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2015;38:140–149
46. American Diabetes Association. Postprandial blood glucose. *Diabetes Care* 2001;24:775–778
47. Ceriello A, Taboga C, Tonutti L, et al. Evidence for an independent and cumulative effect of postprandial hypertriglyceridemia and hyperglycemia on endothelial dysfunction and oxidative stress generation: effects of short- and long-term simvastatin treatment. *Circulation* 2002;106:1211–1218
48. Raz I, Wilson PWF, Strojek K, et al. Effects of prandial versus fasting glycemia on cardiovascular outcomes in type 2 diabetes: the HEART2D trial. *Diabetes Care* 2009;32:381–386
49. Cryer PE. Hypoglycaemia: the limiting factor in the glycaemic management of type I and type II diabetes. *Diabetologia* 2002;45:937–948
50. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA* 2009;301:1565–1572
51. Punthakee Z, Miller ME, Launer LJ, et al.; ACCORD Group of Investigators; ACCORD-MIND Investigators. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. *Diabetes Care* 2012;35:787–793
52. Jacobson AM, Musen G, Ryan CM, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group. Long-term effect of diabetes and its treatment on cognitive function. *N Engl J Med* 2007;356:1842–1852
53. Zoungas S, Patel A, Chalmers J, et al.; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med* 2010;363:1410–1418
54. McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA. Increased mortality of patients with diabetes reporting severe hypoglycemia. *Diabetes Care* 2012;35:1897–1901
55. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013;36:1384–1395
56. Cryer PE. Diverse causes of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med* 2004;350:2272–2279
57. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009;32:1335–1343

7. Approaches to Glycemic Treatment

American Diabetes Association

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PHARMACOLOGICAL THERAPY FOR TYPE 1 DIABETES

Recommendations

- Most people with type 1 diabetes should be treated with multiple-dose insulin (MDI) injections (three to four injections per day of basal and prandial insulin) or continuous subcutaneous insulin infusion (CSII). **A**
- Most people with type 1 diabetes should be educated in how to match prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity. **E**
- Most people with type 1 diabetes should use insulin analogs to reduce hypoglycemia risk. **A**

Insulin Therapy

There are excellent reviews to guide the initiation and management of insulin therapy to achieve desired glycemic goals (1,2,3). Although most studies of MDI versus pump therapy have been small and of short duration, a systematic review and meta-analysis concluded that there were no systematic differences in A1C or severe hypoglycemia rates in children and adults between the two forms of intensive insulin therapy (4). A large randomized trial in type 1 diabetic patients with nocturnal hypoglycemia reported that sensor-augmented insulin pump therapy with the threshold suspend feature reduced nocturnal hypoglycemia, without increasing glycated hemoglobin values (5). Overall, intensive management through pump therapy/continuous glucose monitoring and active patient/family participation should be strongly encouraged (6–8). For selected individuals who have mastered carbohydrate counting, education on the impact of protein and fat on glycemic excursions can be incorporated into diabetes management (9).

The Diabetes Control and Complications Trial (DCCT) clearly showed that intensive insulin therapy (three or more injections per day of insulin) or CSII (insulin pump therapy) was a key part of improved glycemia and better outcomes (10,11). The study was carried out with short- and intermediate-acting human insulins. Despite better microvascular outcomes, intensive insulin therapy was associated with a high rate of severe hypoglycemia (62 episodes per 100 patient-years of therapy). Since the DCCT, a number of rapid-acting and long-acting insulin analogs have been developed. These analogs are associated with less hypoglycemia in type 1 diabetes, while matching the A1C lowering of human insulins (1,12).

Recommended therapy for type 1 diabetes consists of the following:

1. Use MDI injections (three to four injections per day of basal and prandial insulin) or CSII therapy.
2. Match prandial insulin to carbohydrate intake, premeal blood glucose, and anticipated physical activity.
3. For most patients (especially those at an elevated risk of hypoglycemia), use insulin analogs.
4. For patients with frequent nocturnal hypoglycemia and/or hypoglycemia unawareness, a sensor-augmented low glucose threshold suspend pump may be considered.

Pramlintide

Pramlintide, an amylin analog, is an agent that delays gastric emptying, blunts pancreatic secretion of glucagon, and enhances satiety. It is a U.S. Food and Drug

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Administration (FDA)-approved therapy for use in type 1 diabetes. It has been shown to induce weight loss and lower insulin dose; however, it is only indicated in adults. Concurrent reduction of prandial insulin dosing is required to reduce the risk of severe hypoglycemia.

Investigational Agents

Metformin

Adding metformin to insulin therapy may reduce insulin requirements and improve metabolic control in overweight/obese patients with poorly controlled type 1 diabetes. In a meta-analysis, metformin in type 1 diabetes was found to reduce insulin requirements (6.6 U/day, $P < 0.001$) and led to small reductions in weight and total and LDL cholesterol but not to improved glycemic control (absolute A1C reduction 0.11%, $P = 0.42$) (13).

Incretin-Based Therapies

Therapies approved for the treatment of type 2 diabetes are currently being evaluated in type 1 diabetes. Glucagon-like peptide 1 (GLP-1) agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors are not currently FDA approved for those with type 1 diabetes, but are being studied in this population.

Sodium–Glucose Cotransporter 2 Inhibitors
Sodium–glucose cotransporter 2 (SGLT2) inhibitors provide insulin-independent glucose lowering by blocking glucose reabsorption in the proximal renal tubule by inhibiting SGLT2. These agents provide modest weight loss and blood pressure reduction. Although there are two FDA-approved agents for use in patients with type 2 diabetes, there are insufficient data to recommend clinical use in type 1 diabetes at this time (14).

PHARMACOLOGICAL THERAPY FOR TYPE 2 DIABETES

Recommendations

- Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacological agent for type 2 diabetes. **A**
- In patients with newly diagnosed type 2 diabetes and markedly symptomatic and/or elevated blood glucose levels or A1C, consider initiating insulin therapy (with or without additional agents). **E**
- If noninsulin monotherapy at maximum tolerated dose does not

achieve or maintain the A1C target over 3 months, add a second oral agent, a GLP-1 receptor agonist, or basal insulin. **A**

- A patient-centered approach should be used to guide choice of pharmacological agents. Considerations include efficacy, cost, potential side effects, weight, comorbidities, hypoglycemia risk, and patient preferences. **E**
- Due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes. **B**

An updated American Diabetes Association/European Association for the Study of Diabetes position statement (15) evaluated the data and developed recommendations, including advantages and disadvantages, for antihyperglycemic agents for type 2 diabetic patients. A patient-centered approach is stressed, including patient preferences, cost and potential side effects of each class, effects on body weight, and hypoglycemia risk. Lifestyle modifications that improve health (see Section 4. Foundations of Care) should be emphasized along with any pharmacological therapy.

Initial Therapy

Most patients should begin with lifestyle changes (lifestyle counseling, weight-loss education, exercise, etc.). When lifestyle efforts alone have not achieved or maintained glycemic goals, metformin monotherapy should be added at, or soon after, diagnosis, unless there are contraindications or intolerance. Metformin has a long-standing evidence base for efficacy and safety, is inexpensive, and may reduce risk of cardiovascular events (16). In patients with metformin intolerance or contraindications, consider an initial drug from other classes depicted in **Fig. 7.1** under “Dual therapy” and proceed accordingly.

Combination Therapy

Although there are numerous trials comparing dual therapy with metformin alone, few directly compare drugs as add-on therapy. A comparative effectiveness meta-analysis (17) suggests that overall each new class of noninsulin agents added to initial therapy lowers

A1C around 0.9–1.1%. A comprehensive listing, including the cost, is available in **Table 7.1**.

If the A1C target is not achieved after approximately 3 months, consider a combination of metformin and one of these six treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, or basal insulin (**Fig. 7.1**). Drug choice is based on patient preferences as well as various patient, disease, and drug characteristics, with the goal of reducing blood glucose levels while minimizing side effects, especially hypoglycemia. **Figure 7.1** emphasizes drugs commonly used in the U.S. and/or Europe.

Rapid-acting secretagogues (meglitinides) may be used instead of sulfonylureas in patients with irregular meal schedules or who develop late postprandial hypoglycemia on a sulfonylurea. Other drugs not shown in the figure (e.g., α -glucosidase inhibitors, colesevelam, bromocriptine, pramlintide) may be tried in specific situations, but are generally not favored due to modest efficacy, the frequency of administration, and/or side effects.

For all patients, consider initiating therapy with a dual combination when A1C is $\geq 9\%$ to more expeditiously achieve the target A1C level. Insulin has the advantage of being effective where other agents may not be and should be considered as part of any combination regimen when hyperglycemia is severe, especially if symptoms are present or any catabolic features (weight loss, ketosis) are in evidence. Consider initiating combination insulin injectable therapy when blood glucose is ≥ 300 – 350 mg/dL (16.7–19.4 mmol/L) and/or A1C is ≥ 10 – 12% . As the patient's glucose toxicity resolves, the regimen can, potentially, be subsequently simplified.

Insulin Therapy

Many patients with type 2 diabetes eventually require and benefit from insulin therapy. Providers may wish to consider regimen flexibility when devising a plan for the initiation and adjustment of insulin therapy in people with type 2 diabetes (**Fig. 7.2**). The progressive nature of type 2 diabetes and its therapies should be regularly and objectively explained to patients. Providers should avoid using insulin as a threat or describing it as a failure

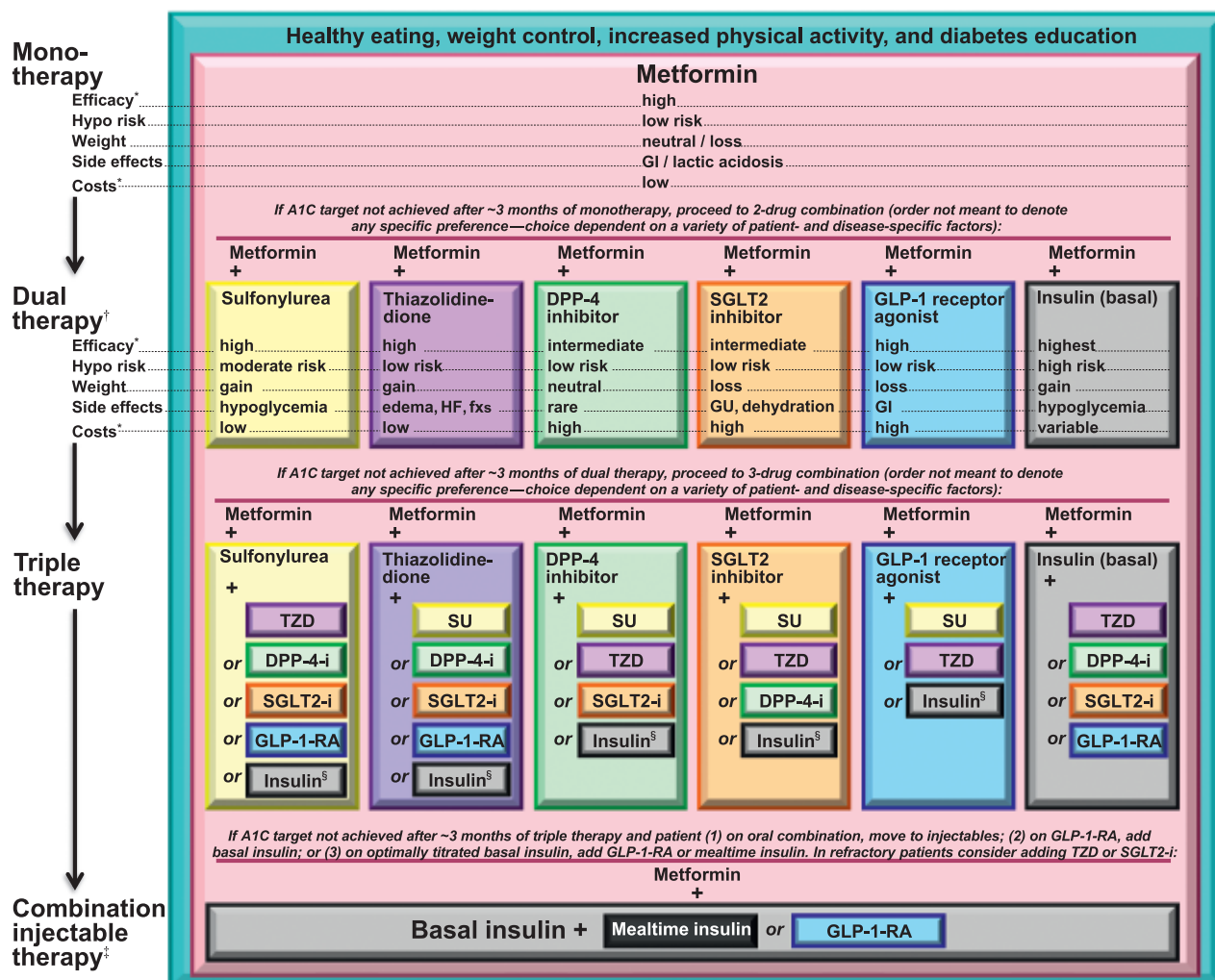


Figure 7.1—Antihyperglycemic therapy in type 2 diabetes: general recommendations (15). The order in the chart was determined by historical availability and the route of administration, with injectables to the right; it is not meant to denote any specific preference. Potential sequences of antihyperglycemic therapy for patients with type 2 diabetes are displayed, with the usual transition moving vertically from top to bottom (although horizontal movement within therapy stages is also possible, depending on the circumstances). DPP-4-i, DPP-4 inhibitor; fxs, fractures; GI, gastrointestinal; GLP-1-RA, GLP-1 receptor agonist; GU, genitourinary; HF, heart failure; Hypo, hypoglycemia; SGLT2-i, SGLT2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. *See ref. 15 for description of efficacy categorization. †Consider starting at this stage when A1C is $\geq 9\%$. ‡Consider starting at this stage when blood glucose is ≥ 300 – 350 mg/dL (16.7–19.4 mmol/L) and/or A1C is ≥ 10 – 12% , especially if symptomatic or catabolic features are present, in which case basal insulin + mealtime insulin is the preferred initial regimen. §Usually a basal insulin (NPH, glargine, detemir, degludec). Adapted with permission from Inzucchi et al. (15).

or punishment. Equipping patients with an algorithm for self-titration of insulin doses based on self-monitoring of blood glucose (SMBG) improves glycemic control in type 2 diabetic patients initiating insulin (18).

Basal insulin alone is the most convenient initial insulin regimen, beginning at 10 U or 0.1–0.2 U/kg, depending on the degree of hyperglycemia. Basal insulin is usually prescribed in conjunction with metformin and possibly one additional noninsulin agent. If basal insulin has been titrated to an acceptable fasting blood glucose level, but A1C remains above target, consider advancing to

combination injectable therapy (Fig. 7.2) to cover postprandial glucose excursions. Options include adding a GLP-1 receptor agonist or mealtime insulin, consisting of one to three injections of rapid-acting insulin analog (lispro, aspart, or glulisine) administered just before eating. A less studied alternative, transitioning from basal insulin to twice-daily premixed (or biphasic) insulin analog (70/30 aspart mix, 75/25 or 50/50 lispro mix), could also be considered. Regular human insulin and human NPH-Regular premixed formulations (70/30) are less costly alternatives to rapid-acting insulin analogs and

premixed insulin analogs, respectively, but their pharmacodynamic profiles make them suboptimal for the coverage of postprandial glucose excursions. A less commonly used and more costly alternative to “basal-bolus” therapy with multiple daily injections is CSII (insulin pump). In addition to the suggestions provided for determining the starting dose of mealtime insulin under a basal-bolus regimen, another method consists of adding up the total current insulin dose and then providing one-half of this amount as basal and one-half as mealtime insulin, the latter split evenly between three meals.

Table 7.1—Properties of available glucose-lowering agents in the U.S. and Europe that may guide individualized treatment choices in patients with type 2 diabetes (15)

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
Biguanides	<ul style="list-style-type: none"> Metformin 	Activates AMP-kinase (? other)	<ul style="list-style-type: none"> ↓ Hepatic glucose production 	<ul style="list-style-type: none"> Extensive experience No hypoglycemia ↓ CVD events (UKPDS) 	<ul style="list-style-type: none"> Gastrointestinal side effects (diarrhea, abdominal cramping) Lactic acidosis risk (rare) Vitamin B₁₂ deficiency Multiple contraindications: CKD, acidosis, hypoxia, dehydration, etc. 	Low
Sulfonylureas	<ul style="list-style-type: none"> 2nd Generation Glyburide/glibenclamide Glipizide Gliclazide† Glimepiride 	Closes K _{ATP} channels on β-cell plasma membranes	<ul style="list-style-type: none"> ↑ Insulin secretion 	<ul style="list-style-type: none"> Extensive experience ↓ Microvascular risk (UKPDS) 	<ul style="list-style-type: none"> Hypoglycemia ↑ Weight ? Blunts myocardial ischemic preconditioning Low durability 	Low
Meglitinides (glinides)	<ul style="list-style-type: none"> Repaglinide Nateglinide 	Closes K _{ATP} channels on β-cell plasma membranes	<ul style="list-style-type: none"> ↑ Insulin secretion 	<ul style="list-style-type: none"> ↓ Postprandial glucose excursions Dosing flexibility 	<ul style="list-style-type: none"> Hypoglycemia ↑ Weight ? Blunts myocardial ischemic preconditioning Frequent dosing schedule 	Moderate
TZDs	<ul style="list-style-type: none"> Pioglitazone‡ Rosiglitazone§ 	Activates the nuclear transcription factor PPAR-γ	<ul style="list-style-type: none"> ↑ Insulin sensitivity 	<ul style="list-style-type: none"> No hypoglycemia Durability ↑ HDL-C ↓ Triglycerides (pioglitazone) ? ↓ CVD events (PROactive, pioglitazone) 	<ul style="list-style-type: none"> ↑ Weight Edema/heart failure Bone fractures ↑ LDL-C (rosiglitazone) ? ↑ MI (meta-analyses, rosiglitazone) 	Low
α-Glucosidase inhibitors	<ul style="list-style-type: none"> Acarbose Miglitol 	Inhibits intestinal α-glucosidase	<ul style="list-style-type: none"> Slows intestinal carbohydrate digestion/absorption 	<ul style="list-style-type: none"> No hypoglycemia ↓ Postprandial glucose excursions ? ↓ CVD events (STOP-NIDDM) Nonsystemic 	<ul style="list-style-type: none"> Generally modest A1C efficacy Gastrointestinal side effects (flatulence, diarrhea) Frequent dosing schedule 	Moderate
DPP-4 inhibitors	<ul style="list-style-type: none"> Sitagliptin Vildagliptin† Saxagliptin Linagliptin Alogliptin 	Inhibits DPP-4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations	<ul style="list-style-type: none"> ↑ Insulin secretion (glucose-dependent) ↓ Glucagon secretion (glucose-dependent) 	<ul style="list-style-type: none"> No hypoglycemia Well tolerated 	<ul style="list-style-type: none"> Angioedema/urticaria and other immune-mediated dermatological effects ? Acute pancreatitis ? ↑ Heart failure hospitalizations 	High
Bile acid sequestrants	<ul style="list-style-type: none"> Colesevelam 	Binds bile acids in intestinal tract, increasing hepatic bile acid production	<ul style="list-style-type: none"> ? ↓ Hepatic glucose production ? ↑ Incretin levels 	<ul style="list-style-type: none"> No hypoglycemia ↓ LDL-C 	<ul style="list-style-type: none"> Generally modest A1C efficacy Constipation ↑ Triglycerides May ↓ absorption of other medications 	High

Continued on p. S45

Table 7.1—Continued

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)	Advantages	Disadvantages	Cost*
Dopamine-2 agonists	<ul style="list-style-type: none"> • Bromocriptine (quick release)[§] 	Activates dopaminergic receptors	<ul style="list-style-type: none"> • Modulates hypothalamic regulation of metabolism • ↑ Insulin sensitivity 	<ul style="list-style-type: none"> • No hypoglycemia • ? ↓ CVD events (Cycloset Safety Trial) 	<ul style="list-style-type: none"> • Generally modest A1C efficacy • Dizziness/syncope • Nausea • Fatigue • Rhinitis 	High
SGLT2 inhibitors	<ul style="list-style-type: none"> • Canagliflozin • Dapagliflozin[†] • Empagliflozin 	Inhibits SGLT2 in the proximal nephron	<ul style="list-style-type: none"> • Blocks glucose reabsorption by the kidney, increasing glucosuria 	<ul style="list-style-type: none"> • No hypoglycemia • ↓ Weight • ↓ Blood pressure • Effective at all stages of T2DM 	<ul style="list-style-type: none"> • Genitourinary infections • Polyuria • Volume depletion/hypotension/dizziness • ↑ LDL-C • ↑ Creatinine (transient) 	High
GLP-1 receptor agonists	<ul style="list-style-type: none"> • Exenatide • Exenatide extended release • Liraglutide • Albiglutide • Lixisenatide[†] • Dulaglutide 	Activates GLP-1 receptors	<ul style="list-style-type: none"> • ↑ Insulin secretion (glucose-dependent) • ↓ Glucagon secretion (glucose-dependent) • Slows gastric emptying • ↑ Satiety 	<ul style="list-style-type: none"> • No hypoglycemia • ↓ Weight • ↓ Postprandial glucose excursions • ↓ Some cardiovascular risk factors 	<ul style="list-style-type: none"> • Gastrointestinal side effects (nausea/vomiting/diarrhea) • ↑ Heart rate • ? Acute pancreatitis • C-cell hyperplasia/medullary thyroid tumors in animals • Injectable • Training requirements 	High
Amylin mimetics	<ul style="list-style-type: none"> • Pramlintide[§] 	Activates amylin receptors	<ul style="list-style-type: none"> • ↓ Glucagon secretion • Slows gastric emptying • ↑ Satiety 	<ul style="list-style-type: none"> • ↓ Postprandial glucose excursions • ↓ Weight 	<ul style="list-style-type: none"> • Generally modest A1C efficacy • Gastrointestinal side effects (nausea/vomiting) • Hypoglycemia unless insulin dose is simultaneously reduced • Injectable • Frequent dosing schedule • Training requirements 	High
Insulins	<ul style="list-style-type: none"> • Rapid-acting analogs <ul style="list-style-type: none"> - Lispro - Aspart - Glulisine • Short-acting <ul style="list-style-type: none"> - Human Regular • Intermediate-acting <ul style="list-style-type: none"> - Human NPH • Basal insulin analogs <ul style="list-style-type: none"> - Glargine - Detemir - Degludec[†] • Premixed (several types) 	Activates insulin receptors	<ul style="list-style-type: none"> • ↑ Glucose disposal • ↓ Hepatic glucose production • Other 	<ul style="list-style-type: none"> • Nearly universal response • Theoretically unlimited efficacy • ↓ Microvascular risk (UKPDS) 	<ul style="list-style-type: none"> • Hypoglycemia • Weight gain • ? Mitogenic effects • Injectable • Patient reluctance • Training requirements 	Variable#

CKD, chronic kidney disease; CVD, cardiovascular disease; GLP, glucose-dependent insulinotropic peptide; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; MI, myocardial infarction; PPAR-γ, peroxisome proliferator-activated receptor γ; PROactive, Prospective Pioglitazone Clinical Trial in Macrovascular Events (30); STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (31); TZD, thiazolidinedione; T2DM, type 2 diabetes mellitus; UKPDS, UK Prospective Diabetes Study (32,33). Cycloset trial of quick-release bromocriptine (34). *Cost is based on lowest-priced member of the class (see ref. 15). †Not licensed in the U.S. ‡Initial concerns regarding bladder cancer risk are decreasing after subsequent study. §Not licensed in Europe for type 2 diabetes. #Cost is highly dependent on type/brand (analogs > human insulins) and dosage. Adapted with permission from Inzucchi et al. (15).

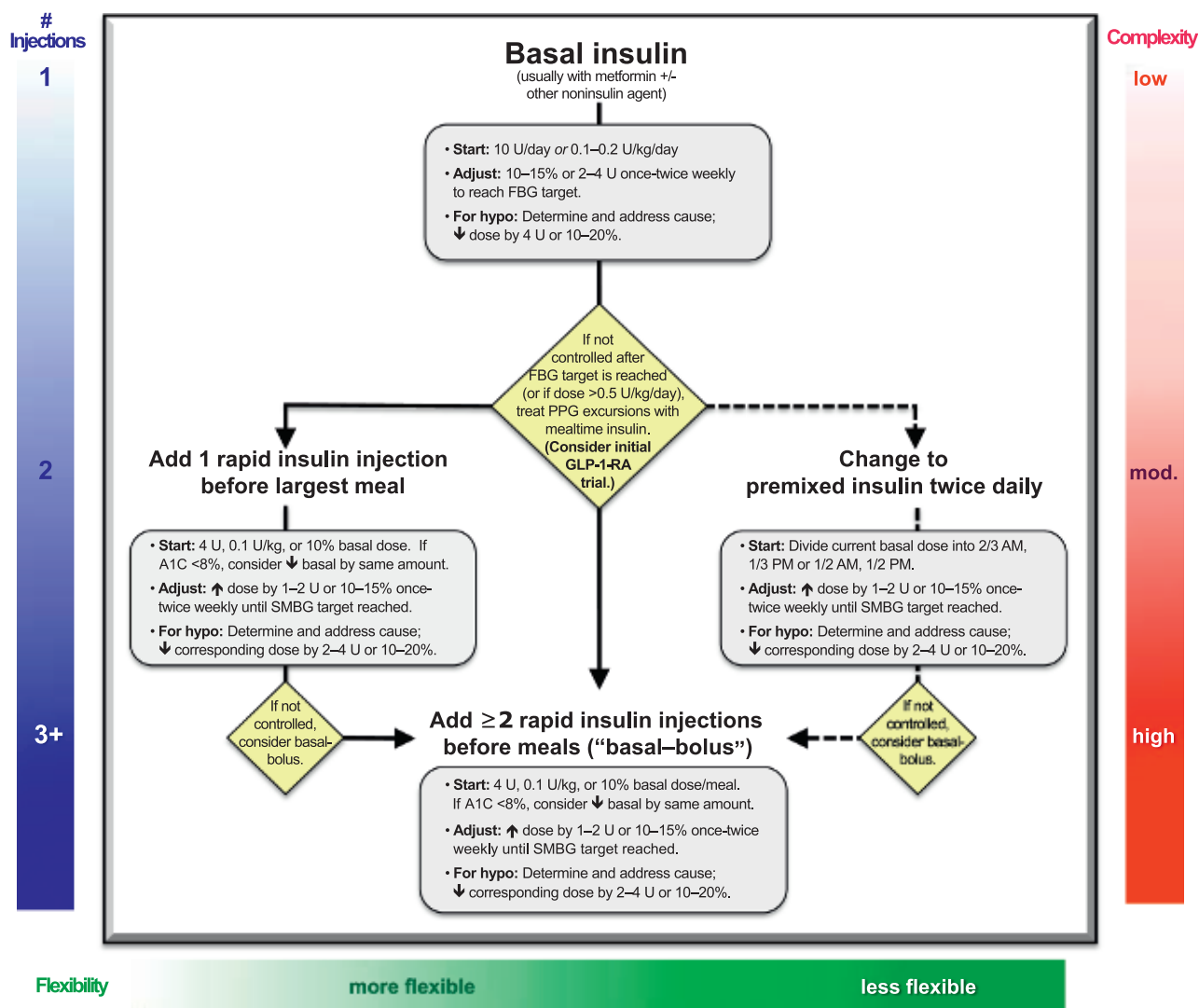


Figure 7.2—Approach to starting and adjusting insulin in type 2 diabetes (15). FBG, fasting blood glucose; GLP-1-RA, GLP-1 receptor agonist; hypo, hypoglycemia; mod., moderate; PPG, postprandial glucose; #, number. Adapted with permission from Inzucchi et al. (15).

Figure 7.2 focuses solely on sequential insulin strategies, describing the number of injections and the relative complexity and flexibility of each stage. Once an insulin regimen is initiated, dose titration is important, with adjustments made in both mealtime and basal insulins based on the prevailing blood glucose levels and an understanding of the pharmacodynamic profile of each formulation (pattern control).

Noninsulin agents may be continued, although sulfonylureas, DPP-4 inhibitors, and GLP-1 receptor agonists are typically stopped once more complex insulin regimens beyond basal are used. In patients with suboptimal blood glucose control, especially those requiring increasing insulin doses, adjunctive use of thiazolidinediones (usually pioglitazone) or SGLT2

inhibitors may be helpful in improving control and reducing the amount of insulin needed. Comprehensive education regarding SMBG, diet, exercise, and the avoidance of and response to hypoglycemia are critically important in any patient using insulin.

BARIATRIC SURGERY

Recommendations

- Bariatric surgery may be considered for adults with BMI >35 kg/m² and type 2 diabetes, especially if diabetes or associated comorbidities are difficult to control with lifestyle and pharmacological therapy. **B**
- Patients with type 2 diabetes who have undergone bariatric surgery

need lifelong lifestyle support and medical monitoring. **B**

- Although small trials have shown glycemic benefit of bariatric surgery in patients with type 2 diabetes and BMI 30–35 kg/m², there is currently insufficient evidence to generally recommend surgery in patients with BMI <35 kg/m². **E**

Bariatric and metabolic surgeries, either gastric banding or procedures that involve resecting, bypassing, or transposing sections of the stomach and small intestine, can be effective weight-loss treatments for severe obesity when performed as part of a comprehensive weight-management program with lifelong lifestyle support

and medical monitoring. National guidelines support consideration for bariatric surgery for people with type 2 diabetes with BMI >35 kg/m².

Advantages

Treatment with bariatric surgery has been shown to achieve near- or complete normalization of glycemia 2 years following surgery in 72% of patients (compared with 16% in a matched control group treated with lifestyle and pharmacological interventions) (19). A study evaluated the long-term (3-year) outcomes of surgical intervention (Roux-en-Y gastric bypass or sleeve gastrectomy) and intensive medical therapy (quarterly visits, pharmacological therapy, SMBG, diabetes education, lifestyle counseling, and encouragement to participate in Weight Watchers) compared with just intensive medical therapy on achieving a target A1C ≤6% among obese patients with uncontrolled type 2 diabetes (mean A1C 9.3%). This A1C target was achieved by 38% ($P < 0.001$) in the gastric bypass group, 24% ($P = 0.01$) in the sleeve gastrectomy group, and 5% in those receiving medical therapy (20). Diabetes remission rates tend to be higher with procedures that bypass portions of the small intestine and lower with procedures that only restrict the stomach.

Younger age, shorter duration of type 2 diabetes, lower A1C, higher serum insulin levels, and nonuse of insulin have all been associated with higher remission rates after bariatric surgery (21).

Although bariatric surgery has been shown to improve the metabolic profiles of morbidly obese patients with type 1 diabetes, the role of bariatric surgery in such patients will require larger and longer studies (22).

Disadvantages

Bariatric surgery is costly and has associated risks. Morbidity and mortality rates directly related to the surgery have decreased considerably in recent years, with 30-day mortality rates now 0.28%, similar to those for laparoscopic cholecystectomy (23). Outcomes vary depending on the procedure and the experience of the surgeon and center. Longer-term concerns include vitamin and mineral deficiencies, osteoporosis, and rare but often severe hypoglycemia from insulin hypersecretion. Cohort

studies attempting to match surgical and nonsurgical subjects suggest that the procedure may reduce longer-term mortality rates (19). In contrast, a propensity score-adjusted analysis of older, severely obese patients in Veterans Affairs Medical Centers found that bariatric surgery was not associated with decreased mortality compared with usual care (mean follow-up 6.7 years) (24). Retrospective analyses and modeling studies suggest that bariatric surgery may be cost-effective for patients with type 2 diabetes, but the results are largely dependent on assumptions about the long-term effectiveness and safety of the procedures (25–27). Understanding the long-term benefits and risks of bariatric surgery in individuals with type 2 diabetes, especially those who are not severely obese, will require well-designed clinical trials, with optimal medical therapy as the comparator (28). Unfortunately, such studies may not be feasible (29).

References

- DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. *JAMA* 2003;289:2254–2264
- American Diabetes Association. *Intensive Diabetes Management*. 4th ed. Wolfsdorf JJ, Ed. Alexandria, VA, American Diabetes Association, 2009
- Mooradian AD, Bernbaum M, Albert SG. Narrative review: a rational approach to starting insulin therapy. *Ann Intern Med* 2006;145:125–134
- Yeh H-C, Brown TT, Maruthur N, et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. *Ann Intern Med* 2012;157:336–347
- Bergenstal RM, Klonoff DC, Garg SK, et al.; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. *N Engl J Med* 2013;369:224–232
- Wood JR, Miller KM, Maahs DM, et al.; T1D Exchange Clinic Network. Most youth with type 1 diabetes in the T1D Exchange clinic registry do not meet American Diabetes Association or International Society for Pediatric and Adolescent Diabetes clinical guidelines. *Diabetes Care* 2013;36:2035–2037
- Kmietowicz Z. Insulin pumps improve control and reduce complications in children with type 1 diabetes. *BMJ* 2013;347:f5154
- Phillip M, Battelino T, Atlas E, et al. Nocturnal glucose control with an artificial pancreas at a diabetes camp. *N Engl J Med* 2013;368:824–833
- Wolpert HA, Atakov-Castillo A, Smith SA, Steil GM. Dietary fat acutely increases glucose concentrations and insulin requirements in patients with type 1 diabetes: implications for carbohydrate-based bolus dose calculation and intensive diabetes management. *Diabetes Care* 2013;36:810–816

- The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–986
- Nathan DM, Cleary PA, Backlund J-YC, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353:2643–2653
- Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A, Lin Z, Salzman A. Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. *Diabetes Care* 2005;28:950–955
- Vella S, Buetow L, Royle P, Livingstone S, Colhoun HM, Petrie JR. The use of metformin in type 1 diabetes: a systematic review of efficacy. *Diabetologia* 2010;53:809–820
- Chiang JL, Kirkman MS, Laffel LM, Peters AL; Type 1 Diabetes Sourcebook Authors. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. *Diabetes Care* 2014;37:2034–2054
- Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2015;38:140–149
- Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577–1589
- Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. *Ann Intern Med* 2011;154:602–613
- Blonde L, Merilainen M, Karwe V, Raskin P; TITRATE Study Group. Patient-directed titration for achieving glycaemic goals using a once-daily basal insulin analogue: an assessment of two different fasting plasma glucose targets - the TITRATE study. *Diabetes Obes Metab* 2009;11:623–631
- Sjöström L, Peltonen M, Jacobson P, et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. *JAMA* 2014;311:2297–2304
- Schauer PR, Bhatt DL, Kirwan JP, et al.; STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes—3-year outcomes. *N Engl J Med* 2014;370:2002–2013
- Still CD, Wood GC, Benotti P, et al. Preoperative prediction of type 2 diabetes remission after Roux-en-Y gastric bypass surgery: a retrospective cohort study. *Lancet Diabetes Endocrinol* 2014;2:38–45
- Brethauer SA, Aminian A, Rosenthal RJ, Kirwan JP, Kashyap SR, Schauer PR. Bariatric surgery improves the metabolic profile of morbidly obese patients with type 1 diabetes. *Diabetes Care* 2014;37:e51–e52
- Buchwald H, Estok R, Fahrenbach K, Banel D, Sledge I. Trends in mortality in bariatric surgery:

- a systematic review and meta-analysis. *Surgery* 2007;142:621–632
24. Maciejewski ML, Livingston EH, Smith VA, et al. Survival among high-risk patients after bariatric surgery. *JAMA* 2011;305:2419–2426
25. Hoerger TJ, Zhang P, Segel JE, Kahn HS, Barker LE, Couper S. Cost-effectiveness of bariatric surgery for severely obese adults with diabetes. *Diabetes Care* 2010;33:1933–1939
26. Makary MA, Clark JM, Shore AD, et al. Medication utilization and annual health care costs in patients with type 2 diabetes mellitus before and after bariatric surgery. *Arch Surg* 2010;145:726–731
27. Keating CL, Dixon JB, Moodie ML, Peeters A, Playfair J, O'Brien PE. Cost-efficacy of surgically induced weight loss for the management of type 2 diabetes: a randomized controlled trial. *Diabetes Care* 2009;32:580–584
28. Wolfe BM, Belle SH. Long-term risks and benefits of bariatric surgery: a research challenge. *JAMA* 2014;312:1792–1793
29. Courcoulas AP, Goodpaster BH, Egleton JK, et al. Surgical vs medical treatments for type 2 diabetes mellitus: a randomized clinical trial. *JAMA Surg* 2014;149:707–715
30. Dormandy JA, Charbonnel B, Eckland DJ, et al.; PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macrovascular Events): a randomised controlled trial. *Lancet* 2005;366:1279–1289
31. Chiasson JL, Gomis R, Hanefeld M, Josse RG, Karasik A, Laakso M; STOP-NIDDM Trial Research Group. The STOP-NIDDM Trial: an international study on the efficacy of an alpha-glucosidase inhibitor to prevent type 2 diabetes in a population with impaired glucose tolerance: rationale, design, and preliminary screening data. *Diabetes Care* 1998;21:1720–1725
32. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–853
33. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854–865
34. Gaziano JM, Cincotta AH, O'Connor CM, et al. Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. *Diabetes Care* 2010;33:1503–1508

8. Cardiovascular Disease and Risk Management

American Diabetes Association

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For prevention and management of diabetes complications in children and adolescents, please refer to Section 11. Children and Adolescents.

Cardiovascular disease (CVD) is the major cause of morbidity and mortality for individuals with diabetes and is the largest contributor to the direct and indirect costs of diabetes. The common conditions coexisting with type 2 diabetes (e.g., hypertension and dyslipidemia) are clear risk factors for CVD, and diabetes itself confers independent risk. Numerous studies have shown the efficacy of controlling individual cardiovascular risk factors in preventing or slowing CVD in people with diabetes. Large benefits are seen when multiple risk factors are addressed globally (1,2). 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 (3).

HYPERTENSION/BLOOD PRESSURE CONTROL

Recommendations

Screening and Diagnosis

- Blood pressure should be measured at every routine visit. Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day. **B**

Goals

- People with diabetes and hypertension should be treated to a systolic blood pressure (SBP) goal of <140 mmHg. **A**
- Lower systolic targets, such as <130 mmHg, may be appropriate for certain individuals, such as younger patients, if they can be achieved without undue treatment burden. **C**
- Individuals with diabetes should be treated to a diastolic blood pressure (DBP) <90 mmHg. **A**
- Lower diastolic targets, such as <80 mmHg, may be appropriate for certain individuals, such as younger patients, if they can be achieved without undue treatment burden. **B**

Treatment

- Patients with blood pressure >120/80 mmHg should be advised on lifestyle changes to reduce blood pressure. **B**
- Patients with confirmed office-based blood pressure higher than 140/90 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely subsequent titration of pharmacological therapy to achieve blood pressure goals. **A**
- Lifestyle therapy for elevated blood pressure consists of weight loss, if overweight or obese; a Dietary Approaches to Stop Hypertension (DASH)-style dietary pattern including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity. **B**
- Pharmacological therapy for patients with diabetes and hypertension should comprise a regimen that includes either an ACE inhibitor or an angiotensin receptor blocker (ARB). **B** If one class is not tolerated, the other should be substituted. **C**
- Multiple-drug therapy (including a thiazide diuretic and ACE inhibitor/ARB, at maximal doses) is generally required to achieve blood pressure targets. **B**

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- If ACE inhibitors, ARBs, or diuretics are used, serum creatinine/estimated glomerular filtration rate (eGFR) and serum potassium levels should be monitored. **E**
- In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 110–129/65–79 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth. ACE inhibitors and ARBs are contraindicated during pregnancy. **E**

Hypertension is a common diabetes comorbidity that affects the majority of patients, with the prevalence depending on type of diabetes, age, obesity, and ethnicity. Hypertension is a major risk factor for both CVD and microvascular complications. In type 1 diabetes, hypertension is often the result of underlying nephropathy, while in type 2 diabetes it usually coexists with other cardiometabolic risk factors.

Screening and Diagnosis

Blood pressure measurement should be done by a trained individual and 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.

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. Studies in individuals without diabetes found that home measurements may better correlate with CVD risk than office measurements (4,5). However, most of the evidence of benefits of hypertension treatment in people with diabetes is based on office measurements.

Treatment Goals

Epidemiological analyses show that blood pressure >115/75 mmHg is associated with increased cardiovascular event rates and mortality in individuals with diabetes and that SBP >120 mmHg predicts long-term end-stage renal disease. Randomized clinical trials have

demonstrated the benefit (reduction of CHD events, stroke, and diabetic kidney disease) of lowering blood pressure to <140 mmHg systolic and <90 mmHg diastolic in individuals with diabetes (6). There is limited prespecified clinical trial evidence for the benefits of lower SBP or DBP targets (7). A meta-analysis of randomized trials of adults with type 2 diabetes comparing intensive blood pressure targets (upper limit of 130 mmHg systolic and 80 mmHg diastolic) to standard targets (upper limit of 140–160 mmHg systolic and 85–100 mmHg diastolic) found no significant reduction in mortality or nonfatal myocardial infarction (MI). There was a statistically significant 35% relative risk (RR) reduction in stroke with intensive targets, but the absolute risk reduction was only 1%, and intensive targets were associated with an increased risk for adverse events such as hypotension and syncope (8).

Given the epidemiological relationship between lower blood pressure and better long-term clinical outcomes, two landmark trials, Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation–Blood Pressure (ADVANCE-BP), were conducted in the past decade to examine the benefit of tighter blood pressure control in patients with type 2 diabetes.

The ACCORD trial examined whether a lower SBP of <120 mmHg, in type 2 diabetic patients at high risk for CVD, provided greater cardiovascular protection than an SBP level of 130–140 mmHg (9). The study did not find a benefit in primary end point (nonfatal MI, nonfatal stroke, and cardiovascular death) comparing intensive blood pressure treatment (goal <120 mmHg, average blood pressure achieved = 119/64 mmHg on 3.4 medications) with standard treatment (average blood pressure achieved = 143/70 mmHg on 2.1 medications). In ACCORD, there was no benefit of aggressive blood pressure lowering, despite the extra cost and efforts.

In ADVANCE, the active blood pressure intervention arm (a single-pill, fixed-dose combination of perindopril and indapamide) showed a significant reduction in the risk of the primary composite end point (major macrovascular or microvascular event), as well as significant reductions in the risk of death from any cause and of death from

cardiovascular causes (10). The baseline blood pressure among the study subjects was 145/81 mmHg. Compared with the placebo group, the patients treated with a single-pill, fixed-dose combination of perindopril and indapamide experienced an average reduction of 5.6 mmHg in SBP and 2.2 mmHg in DBP. The final blood pressure in the treated group was 136/73 mmHg, not quite the intensive or tight control achieved in ACCORD. Recently published 6-year follow-up of the ADVANCE-BP study reported that the reductions in the risk of death from any cause and of death from cardiovascular causes in the intervention group were attenuated, but remained significant (11).

These results underscore the important clinical difference between patients who are able to easily achieve lower blood pressure levels (e.g., as seen in observational epidemiology studies) and patients who require intensive medical management to achieve these goals (e.g., the clinical trials).

Systolic Blood Pressure

The clear body of evidence that SBP >140 mmHg is harmful suggests that clinicians should promptly initiate and titrate therapy in an ongoing fashion to achieve and maintain SBP <140 mmHg in virtually all patients. Patients with long life expectancy may have renal benefits from long-term intensive blood pressure control. Additionally, individuals in whom stroke risk is a concern may, as part of shared decision making, have appropriately lower systolic targets such as <130 mmHg. This is especially true if lower blood pressure can be achieved with few drugs and without side effects of therapy.

Diastolic Blood Pressure

Similarly, the clearest evidence from randomized clinical trials supports DBP targets of <90 mmHg. Prior recommendations for lower DBP targets (<80 mmHg) were based primarily on a post hoc analysis of the Hypertension Optimal Treatment (HOT) trial (12). This level may still be appropriate for patients with long life expectancy and those with chronic kidney disease and elevated urine albumin excretion (12). The 2015 American Diabetes Association (ADA) Standards of Care have been revised to reflect the higher-quality evidence that exists to support a goal of DBP <90 mmHg, although lower targets may be appropriate

for certain individuals. This is in harmonization with a recent publication by the Eighth Joint National Committee that recommended, for individuals over 18 years of age with diabetes, a DBP threshold of <90 mmHg and SBP <140 mmHg (7).

Treatment Strategies

Lifestyle Modifications

Although there are no well-controlled studies of diet and exercise in the treatment of elevated blood pressure or hypertension in individuals with diabetes, the DASH study evaluated the impact of healthy dietary patterns in individuals without diabetes and has shown antihypertensive effects similar to those of pharmacological monotherapy.

Lifestyle therapy consists of restricting sodium intake (<2,300 mg/day); reducing excess body weight; increasing consumption of fruits, 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) (13); and increasing activity levels (14). For individuals with diabetes and hypertension, setting a sodium intake goal of <1,500 mg/day should be considered on an individual basis.

These lifestyle (nonpharmacological) strategies may also positively affect glycemia and lipid control and should be encouraged in those with even mildly elevated blood pressure. The effects of lifestyle therapy on cardiovascular events have not been established. Nonpharmacological therapy is reasonable in individuals with diabetes and mildly elevated blood pressure (SBP >120 mmHg or DBP >80 mmHg). If the blood pressure is confirmed to be \geq 140 mmHg systolic and/or \geq 90 mmHg diastolic, pharmacological therapy should be initiated along with nonpharmacological therapy (14). To enable long-term adherence, lifestyle therapy should be adapted to suit the needs of the patient and discussed as part of diabetes management.

Pharmacological Interventions

Lowering of blood pressure with regimens based on a variety of antihypertensive agents, including ACE inhibitors, ARBs, β -blockers, diuretics, and calcium channel blockers, has been shown to be effective in reducing cardiovascular events. Several studies have suggested

that ACE inhibitors may be superior to dihydropyridine calcium channel blockers in reducing cardiovascular events (15–17). However, several studies have also shown no specific advantage to ACE inhibitors as initial treatment of hypertension in the general hypertensive population, while showing an advantage of initial therapy with low-dose thiazide diuretics on cardiovascular outcomes (14,18,19).

In people with diabetes, inhibitors of the renin-angiotensin system (RAS) may have unique advantages for initial or early treatment of hypertension. In a trial of individuals at high risk for CVD, including a large subset with diabetes, an ACE inhibitor reduced CVD outcomes (20). In patients with congestive heart failure (CHF), including subgroups with diabetes, ARBs have been shown to reduce major CVD outcomes (21–24). In type 2 diabetic patients with significant diabetic kidney disease, ARBs were superior to calcium channel blockers for reducing heart failure (25). Although evidence for distinct advantages of RAS inhibitors on CVD outcomes in diabetes remains conflicting (10,19), the high CVD risks associated with diabetes, and the high prevalence of undiagnosed CVD, may still favor recommendations for their use as first-line hypertension therapy in people with diabetes (14).

The blood pressure arm of the ADVANCE trial demonstrated that routine administration of a fixed combination of the ACE inhibitor perindopril and the diuretic indapamide significantly reduced combined microvascular and macrovascular outcomes, as well as death from cardiovascular causes and total mortality. The improved outcomes could also have been due to lower achieved blood pressure in the perindopril-indapamide arm (10). Another trial showed a decrease in morbidity and mortality in those receiving benazepril and amlodipine versus benazepril and hydrochlorothiazide (HCTZ). The compelling benefits of RAS inhibitors in diabetic patients with albuminuria or renal insufficiency provide additional rationale for these agents (see Section 9. Microvascular Complications and Foot Care). If needed to achieve blood pressure targets, amlodipine, HCTZ, or chlorthalidone can be added. If eGFR is <30 mL/min/m², a loop diuretic, rather than HCTZ or chlorthalidone, should be prescribed. Titration of and/or addition of further blood

pressure medications should be made in timely fashion to overcome clinical inertia in achieving blood pressure targets.

Growing evidence suggests that there is an association between increase in sleep-time blood pressure and incidence of CVD events. A randomized controlled trial of 448 participants with type 2 diabetes and hypertension demonstrated reduced cardiovascular events and mortality with median follow-up of 5.4 years if at least one antihypertensive medication was given at bedtime (26). Consider administering one or more antihypertensive medications at bedtime (27).

An important caveat is that most patients with hypertension require multiple-drug therapy to reach treatment goals (13). Identifying and addressing barriers to medication adherence (such as cost and side effects) should routinely be done. If blood pressure remains uncontrolled despite confirmed adherence to optimal doses of at least three antihypertensive agents of different classifications, one of which should be a diuretic, clinicians should consider an evaluation for secondary forms of hypertension.

Pregnancy and Antihypertensive Medications

In a pregnancy complicated by diabetes and chronic hypertension, target blood pressure goals of SBP 110–129 mmHg and DBP 65–79 mmHg are reasonable, as they contribute to improved long-term maternal health. Lower blood pressure levels may be associated with impaired fetal growth. During pregnancy, treatment with ACE inhibitors and ARBs is contraindicated, since they may cause fetal damage. Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, diltiazem, clonidine, and prazosin. Chronic diuretic use during pregnancy has been associated with restricted maternal plasma volume, which may reduce uteroplacental perfusion (28).

DYSLIPIDEMIA/LIPID MANAGEMENT

Recommendations

Screening

- In adults, a screening lipid profile is reasonable at the time of first diagnosis, at the initial medical evaluation, and/or at age 40 years and periodically (e.g., every 1–2 years) thereafter. **E**

Treatment Recommendations and Goals

- Lifestyle modification focusing on the reduction of saturated fat, *trans* fat, and cholesterol intake; increase of omega-3 fatty acids, viscous fiber, and plant stanols/sterols; weight loss (if indicated); and increased physical activity should be recommended to improve the lipid profile in patients with diabetes. **A**
- 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** For patients with fasting triglyceride levels ≥ 500 mg/dL (5.7 mmol/L), evaluate for secondary causes and consider medical therapy to reduce risk of pancreatitis. **C**
- For patients of all ages with diabetes and overt CVD, high-intensity statin therapy should be added to lifestyle therapy. **A**
- For patients with diabetes aged < 40 years with additional CVD risk factors, consider using moderate- or high-intensity statin and lifestyle therapy. **C**
- For patients with diabetes aged 40–75 years without additional CVD risk factors, consider using moderate-intensity statin and lifestyle therapy. **A**
- For patients with diabetes aged 40–75 years with additional CVD risk factors, consider using high-intensity statin and lifestyle therapy. **B**
- For patients with diabetes aged > 75 years without additional CVD risk factors, consider using moderate-intensity statin therapy and lifestyle therapy. **B**
- For patients with diabetes aged > 75 years with additional CVD risk factors, consider using moderate- or high-intensity statin therapy and lifestyle therapy. **B**
- In clinical practice, providers may need to adjust intensity of statin therapy based on individual patient response to medication (e.g., side effects, tolerability, LDL cholesterol levels). **E**
- Cholesterol laboratory testing may be helpful in monitoring

adherence to therapy, but may not be needed once the patient is stable on therapy. **E**

- Combination therapy (statin/fibrate and statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone and is not generally recommended. **A**
- Statin therapy is contraindicated in pregnancy. **B**

Lifestyle Intervention

Lifestyle intervention, including MNT, increased physical activity, weight loss, and smoking cessation, may allow some patients to reduce CVD risk factors, such as by lowering LDL cholesterol. Nutrition intervention should be tailored according to each patient’s age, diabetes type, pharmacological treatment, lipid levels, and medical conditions. Recommendations should focus on reducing saturated fat, cholesterol, and *trans* unsaturated fat intake and increasing omega-3 fatty acids and viscous fiber (such as in oats, legumes, and citrus). Glycemic control can also beneficially modify plasma lipid levels, particularly in patients with very high triglycerides and poor glycemic control.

Statin Treatment

Initiating Statin Therapy Based on Risk

Patients with type 2 diabetes have an increased prevalence of lipid abnormalities, contributing to their high risk of CVD. Multiple clinical trials have demonstrated significant effects of pharmacological (primarily statin) therapy on CVD outcomes in individual subjects with CHD and for primary CVD prevention (29,30). Subgroup analyses of diabetic

patients in larger trials (31–35) and trials in patients with diabetes (36,37) showed significant primary and secondary prevention of CVD events +/- CHD deaths 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 reduction in LDL cholesterol (38). As in those without diabetes, absolute reductions in objective CVD outcomes (CHD death and nonfatal MI) are greatest in people with high baseline CVD risk (known CVD and/or very high LDL cholesterol levels), but the overall benefits of statin therapy in people with diabetes at moderate or high risk for CVD are convincing (39,40). Statins are the drugs of choice for LDL cholesterol lowering and cardioprotection.

Most trials of statins and CVD outcomes tested specific doses of statins against placebo or other statins, rather than aiming for specific LDL cholesterol goals (41). In light of this fact, the 2015 ADA Standards of Care have been revised to recommend when to initiate and intensify statin therapy (high versus moderate) based on risk profile (Table 8.1).

The American College of Cardiology/American Heart Association new Pooled Cohort Equation, the “Risk Calculator,” may be a useful tool to estimate 10-year atherosclerotic CVD (<http://my.americanheart.org>). Since diabetes itself confers increased risk for CVD, the Risk Calculator has limited use for assessing risk in individuals with diabetes. The following recommendations are

Table 8.1—Recommendations for statin treatment in people with diabetes

Age	Risk factors	Recommended statin dose*	Monitoring with lipid panel
<40 years	None	None	Annually or as needed to monitor for adherence
	CVD risk factor(s)**	Moderate or high	
	Overt CVD***	High	
40–75 years	None	Moderate	As needed to monitor adherence
	CVD risk factors	High	
	Overt CVD	High	
>75 years	None	Moderate	As needed to monitor adherence
	CVD risk factors	Moderate or high	
	Overt CVD	High	

*In addition to lifestyle therapy.

**CVD risk factors include LDL cholesterol ≥ 100 mg/dL (2.6 mmol/L), high blood pressure, smoking, and overweight and obesity.

***Overt CVD includes those with previous cardiovascular events or acute coronary syndromes.

supported by evidence from trials focusing specifically on patients with diabetes.

Age ≥ 40 Years

In all patients with diabetes aged ≥ 40 years, and if clinically indicated, moderate-intensity statin treatment should be considered, in addition to lifestyle therapy. Clinical trials in high-risk patients, such as those with acute coronary syndromes or previous cardiovascular events (42–44), have demonstrated that more aggressive therapy with high doses of statins led to a significant reduction in further events. Therefore, in patients with increased cardiovascular risk (e.g., LDL cholesterol ≥ 100 mg/dL [2.6 mmol/L], high blood pressure, smoking, and overweight/obesity) or with overt CVD, high-dose statins are recommended.

For adults with diabetes over 75 years of age, there are limited data regarding statin therapy. Statin therapy should be individualized based on risk profile. High-dose statins, if well tolerated, may still be appropriate and are recommended for older adults with overt CVD. However, the risk-benefit profile should be routinely evaluated in this population, with downward titration (e.g., high to moderate intensity) performed as needed. See Section 10. Older Adults for more details on clinical considerations for this unique population.

Age < 40 Years and/or Type 1 Diabetes

Very little clinical trial evidence exists for type 2 diabetic patients under the age of 40 years or for type 1 diabetic patients of any age. 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 to patients with type 2 diabetes (32). Even though the data are not definitive, similar statin treatment approaches should be considered for both type 1 and type 2 diabetic patients, particularly in the presence of cardiovascular risk factors. Please refer to “Type 1 Diabetes Mellitus and Cardiovascular Disease: A Scientific Statement From the American Heart Association and American Diabetes Association” (45) for additional discussion.

Treatment with a moderate dose of statin should be considered if the patient has increased cardiovascular risk (e.g., cardiovascular risk factors such as LDL cholesterol ≥ 100 mg/dL) and with a high dose of statin if the patient has overt CVD.

Ongoing Therapy and Monitoring With Lipid Panel

In adults with diabetes, a screening lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) is reasonable at the time of first diagnosis, at the initial medical evaluation, and/or at age 40 and periodically (e.g., every 1–2 years) thereafter. Once a patient is on a statin, testing for LDL cholesterol may be considered on an individual basis to, for example, monitor adherence and efficacy. In cases where patients are adherent, but LDL cholesterol level is not responding, 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 (46). Reduction of CVD events with statins correlates very closely with LDL cholesterol lowering (29). Clinicians should attempt to find a dose or alternative statin that is tolerable, if side effects occur. There is evidence for significant LDL cholesterol lowering from even extremely low, less than daily, statin doses (47).

When maximally tolerated doses of statins fail to significantly lower LDL cholesterol ($< 30\%$ reduction from the patient's baseline), there is no strong evidence that combination therapy should be used to achieve additional LDL cholesterol lowering. Although niacin, fenofibrate, ezetimibe, and bile acid sequestrants all offer additional LDL cholesterol lowering to statins alone, there is insufficient evidence that such combination therapy provides a significant increment in CVD risk reduction over statin therapy alone.

Treatment of Other Lipoprotein Fractions or Targets

Hypertriglyceridemia should be addressed with dietary and lifestyle changes. Severe hypertriglyceridemia ($> 1,000$ mg/dL) may warrant immediate pharmacological therapy (fibrates or fish oil) to reduce the risk of acute pancreatitis. If severe hypertriglyceridemia is absent, then therapy targeting HDL cholesterol or triglycerides lacks the strong evidence base of statin therapy. If HDL cholesterol is < 40 mg/dL and LDL cholesterol is between 100 and 129 mg/dL, a fibrate or niacin might be used, especially if a patient is intolerant to statins.

Low levels of HDL cholesterol, often associated with elevated triglyceride levels, are the most prevalent pattern of dyslipidemia in persons with type 2 diabetes.

However, the evidence base for drugs that target these lipid fractions is significantly less robust than that for statin therapy (48). In a large trial specific to diabetic patients, fenofibrate failed to reduce overall cardiovascular outcomes (49).

Combination Therapy

Statin and Fibrate

Combination therapy (statin and fibrate) may be efficacious for treatment for LDL cholesterol, HDL cholesterol, and triglycerides, but this combination is associated with an increased risk for abnormal transaminase levels, myositis, or rhabdomyolysis. The risk of rhabdomyolysis is more common with higher doses of statins and with renal insufficiency and seems to be lower when statins are combined with fenofibrate than gemfibrozil (50).

In the ACCORD study, in patients with type 2 diabetes who were at high risk for CVD, 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 according to sex, with a benefit of combination therapy for men and possible harm for women, and a possible benefit for patients with both triglyceride level ≥ 204 mg/dL (2.3 mmol/L) and HDL cholesterol level ≤ 34 mg/dL (0.9 mmol/L) (51).

Statin and Niacin

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 CVD, 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 matching placebo. The trial was halted early due to lack of efficacy on the primary CVD outcome (first event of the composite of death from CHD, nonfatal MI, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization) and a possible increase in ischemic stroke in those on combination therapy (52). Hence, combination therapy with niacin is not recommended given the lack of efficacy on major CVD outcomes, possible increase in risk of ischemic stroke, and side effects.

Diabetes With Statin Use

There is an increased risk of incident diabetes with statin use (53,54), which may be limited to those with diabetes risk factors. These patients may benefit from diabetes screening when on statin therapy. An analysis of one of the initial studies suggested that statins were linked to diabetes risk, the cardiovascular event rate reduction with statins far outweighed the risk of incident diabetes even for patients at highest risk for diabetes (55). The absolute risk increase was small (over 5 years of follow-up, 1.2% of participants on placebo developed diabetes and 1.5% on rosuvastatin) (56). 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 (54). The RR-benefit ratio favoring statins is further supported by meta-analysis of individual data of over 170,000 persons from 27 randomized trials. This demonstrated that individuals at low risk of vascular disease, including those undergoing primary prevention, received benefits from statins that included reductions in major vascular events and vascular death without increase in incidence of cancer or deaths from other causes (30).

ANTIPLATELET AGENTS

Recommendations

- Consider aspirin therapy (75–162 mg/day) as a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk (10-year risk >10%). This includes most men aged >50 years or women aged >60 years who have at least one additional major risk factor (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria). **C**
- Aspirin should not be recommended for CVD prevention for adults with diabetes at low CVD risk (10-year CVD risk <5%, such as in men aged <50 years and women aged <60 years with no major additional CVD risk factors), since the potential adverse effects from bleeding likely offset the potential benefits. **C**

- In patients in these age-groups with multiple other risk factors (e.g., 10-year risk 5–10%), clinical judgment is required. **E**
- Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of CVD. **A**
- For patients with CVD and documented aspirin allergy, clopidogrel (75 mg/day) should be used. **B**
- Dual antiplatelet therapy is reasonable for up to a year after an acute coronary syndrome. **B**

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). Its net benefit in primary prevention among patients with no previous cardiovascular events is more controversial, both for patients with and without a history of diabetes (57,58). Two randomized controlled trials of aspirin specifically in patients with diabetes failed to show a significant reduction in CVD end points, raising questions about the efficacy of aspirin for primary prevention in people with diabetes (59,60).

The Antithrombotic Trialists' (ATT) collaborators published an individual patient-level meta-analysis 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 vascular events by 12% (RR 0.88 [95% CI 0.82–0.94]). The largest reduction was for nonfatal MI with little effect on CHD death (RR 0.95 [95% CI 0.78–1.15]) or total stroke. There was some evidence of a difference in aspirin effect by sex: aspirin significantly reduced CVD events in men, but not in women. Conversely, aspirin had no effect on stroke in men but significantly reduced stroke in women. Sex differences in aspirin's effects have not been observed in studies of secondary prevention (57). In the six trials examined by the ATT collaborators, the effects of aspirin on major vascular events were similar for patients with or without diabetes: RR 0.88 (95% CI 0.67–1.15) and RR 0.87 (95% CI 0.79–0.96), respectively. The confidence interval was wider for those with diabetes because of smaller numbers.

Aspirin appears to have a modest effect on ischemic vascular events with the absolute decrease in events depending on the underlying CVD risk. The main adverse effects appear to be an increased risk of gastrointestinal bleeding. The excess risk may be as high as 1–5 per 1,000 per year in real-world settings. In adults with CVD risk greater than 1% per year, the number of CVD events prevented will be similar to or greater than the number of episodes of bleeding induced, although these complications do not have equal effects on long-term health (61).

Treatment Considerations

In 2010, a position statement of the ADA, the American Heart Association, and the American College of Cardiology Foundation recommended that low-dose (75–162 mg/day) aspirin for primary prevention is reasonable for adults with diabetes and no previous history of vascular disease who are at increased CVD risk (10-year risk of CVD events over 10%) and who are not at increased risk for bleeding. This generally includes most men over age 50 years and women over age 60 years who also have one or more of the following major risk factors: smoking, hypertension, dyslipidemia, family history of premature CVD, and albuminuria (62).

However, aspirin is no longer recommended for those at low CVD risk (women under age 60 years and men under age 50 years with no major CVD risk factors; 10-year CVD risk under 5%) as the low benefit is likely to be outweighed by the risks of significant 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; those with 10-year CVD risk of 5–10%) until further research is available. Aspirin use in patients under the age of 21 years is contraindicated due to the associated risk of Reye syndrome.

Average daily dosages used in most clinical trials involving patients with diabetes ranged from 50 to 650 mg but were mostly in the range of 100 to 325 mg/day. There is little evidence to support any specific dose, but using the lowest possible dose may help reduce side effects (63). 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, impact 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 A₂ and thus not sensitive to the effects of aspirin (64). Therefore, while “aspirin resistance” appears higher in patients with diabetes when measured by a variety of ex vivo and in vitro methods (platelet aggregometry, measurement of thromboxane B₂), these observations alone are insufficient to empirically recommend that higher doses of aspirin be used in this group at this time.

A P2Y₁₂ receptor antagonist in combination with aspirin should be used for at least 1 year in patients following an acute coronary syndrome. Evidence supports use of either ticagrelor or clopidogrel if no percutaneous coronary intervention (PCI) was performed and the use of clopidogrel, ticagrelor, or prasugrel if PCI was performed (65).

CORONARY HEART DISEASE

Recommendations

Screening

- In asymptomatic patients, routine screening for coronary artery disease (CAD) is not recommended because it does not improve outcomes as long as CVD risk factors are treated. **A**

Treatment

- In patients with known CVD, use aspirin and statin therapy (if not contraindicated) **A** and consider ACE inhibitor therapy **C** to reduce the risk of cardiovascular events.
- In patients with a prior MI, β-blockers should be continued for at least 2 years after the event. **B**
- In patients with symptomatic heart failure, thiazolidinedione treatment should not be used. **A**
- In patients with stable CHF, metformin may be used if renal function is normal but should be avoided in unstable or hospitalized patients with CHF. **B**

In all patients with diabetes, cardiovascular risk factors should be assessed at least annually. These risk factors include dyslipidemia, hypertension, smoking, a family history of premature coronary disease, and the presence of

albuminuria. Abnormal risk factors should be treated as described elsewhere in these guidelines.

Screening

Candidates for advanced or invasive cardiac testing include those with 1) typical or atypical cardiac symptoms and 2) an abnormal resting ECG. The screening of asymptomatic patients with high CVD risk is not recommended (39), in part because these high-risk patients should already be receiving intensive medical therapy, an approach that provides similar benefit as invasive revascularization (66,67). There is also some evidence that silent MI may reverse over time, adding to the controversy concerning aggressive screening strategies (68). A randomized observational trial demonstrated no clinical benefit to routine screening of asymptomatic patients with type 2 diabetes and normal ECGs (69). 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 CAD fails to identify which patients with type 2 diabetes will have silent ischemia on screening tests (70,71). Any benefit of newer noninvasive CAD screening methods, such as computed tomography and computed tomography angiography, to identify patient subgroups for different treatment strategies, remain unproven. Although asymptomatic diabetic patients with higher coronary disease burden have more future cardiac events (72–74), the role of these tests beyond risk stratification is not clear. 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 CVD risk factor control.

Lifestyle and Pharmacological 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 CVD risk factors. Patients at increased CVD risk should receive aspirin and a statin, and ACE inhibitor or ARB therapy if hypertensive, unless there are contraindications to a particular drug class. While clear benefit exists for ACE inhibitor and ARB therapy in patients with nephropathy or hypertension, the benefits in patients with CVD in the absence of these conditions are less clear, especially when LDL cholesterol is concomitantly controlled (75,76). In patients with a prior MI, β-blockers should be continued for at least 2 years after the event (77). A systematic review of 34,000 patients showed that metformin is as safe as other glucose-lowering treatments in patients with diabetes and CHF, even in those with reduced left ventricular ejection fraction or concomitant chronic kidney disease; however, metformin should be avoided in hospitalized patients (78).

References

1. Buse JB, Ginsberg HN, Bakris GL, et al.; American Heart Association; American Diabetes Association. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Diabetes Care* 2007;30:162–172
2. Gaede P, Lund-Andersen H, Parving H-H, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008;358:580–591
3. Ali MK, Bullard KM, Saaddine JB, Cowie CC, Imperatore G, Gregg EW. Achievement of goals in U.S. diabetes care, 1999–2010. *N Engl J Med* 2013;368:1613–1624
4. Bobrie G, Genès N, Vaur L, et al. Is “isolated home” hypertension as opposed to “isolated office” hypertension a sign of greater cardiovascular risk? *Arch Intern Med* 2001;161:2205–2211
5. Sega R, Facchetti R, Bombelli M, et al. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation* 2005;111:1777–1783
6. Arguedas JA, Leiva V, Wright JM. Blood pressure targets for hypertension in people with diabetes mellitus. *Cochrane Database Syst Rev* 2013;10:CD008277
7. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014;311:507–520

8. McBrien K, Rabi DM, Campbell N, et al. Intensive and standard blood pressure targets in patients with type 2 diabetes mellitus: systematic review and meta-analysis. *Arch Intern Med* 2012;172:1296–1303
9. ACCORD Study Group; Cushman WC, Evans GW, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575–1585
10. Patel A; ADVANCE Collaborative Group; MacMahon S, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007;370:829–840
11. Zoungas S, Chalmers J, Neal B, et al.; ADVANCE-ON Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med* 2014;371:1392–1406
12. Cruickshank JM. Hypertension Optimal Treatment (HOT) trial. *Lancet* 1998;352:573–574
13. Sacks FM, Svetkey LP, Vollmer WM, et al.; DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *N Engl J Med* 2001;344:3–10
14. Chobanian AV, Bakris GL, Black HR, et al.; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560–2572
15. Tatti P, Pahor M, Byington RP, et al. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care* 1998;21:597–603
16. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med* 1998;338:645–652
17. Schrier RW, Estacio RO, Mehler PS, Hiatt WR. Appropriate blood pressure control in hypertensive and normotensive type 2 diabetes mellitus: a summary of the ABCD trial. *Nat Clin Pract Nephrol* 2007;3:428–438
18. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981–2997
19. Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. *JAMA* 1997;277:739–745
20. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000;355:253–259
21. McMurray JJV, Ostergren J, Swedberg K, et al.; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003;362:767–771
22. Pfeffer MA, Swedberg K, Granger CB, et al.; CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003;362:759–766
23. Granger CB, McMurray JJV, Yusuf S, et al.; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003;362:772–776
24. Lindholm LH, Ibsen H, Dahlöf B, et al.; LIFE Study Group. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;359:1004–1010
25. Berl T, Hunsicker LG, Lewis JB, et al.; Irbesartan Diabetic Nephropathy Trial. Collaborative Study Group. Cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial of patients with type 2 diabetes and overt nephropathy. *Ann Intern Med* 2003;138:542–549
26. Hermida RC, Ayala DE, Mojó A, Fernández JR. Influence of time of day of blood pressure-lowering treatment on cardiovascular risk in hypertensive patients with type 2 diabetes. *Diabetes Care* 2011;34:1270–1276
27. Zhao P, Xu P, Wan C, Wang Z. Evening versus morning dosing regimen drug therapy for hypertension. *Cochrane Database Syst Rev* 2011;10:CD004184
28. Sibai BM. Treatment of hypertension in pregnant women. *N Engl J Med* 1996;335:257–265
29. Baigent C, Keech A, Kearney PM, et al.; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267–1278
30. Mihaylova B, Emberson J, Blackwell L, et al.; Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012;380:581–590
31. Pyörälä K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care* 1997;20:614–620
32. Collins R, Armitage J, Parish S, Sleight P, Peto R; Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003;361:2005–2016
33. Goldberg RB, Mellies MJ, Sacks FM, et al.; Care Investigators. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the Cholesterol and Recurrent Events (CARE) trial. *Circulation* 1998;98:2513–2519
34. Shepherd J, Barter P, Carmena R, et al. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. *Diabetes Care* 2006;29:1220–1226
35. Sever PS, Poulter NR, Dahlöf B, et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial—lipid-lowering arm (ASCOT-LLA). *Diabetes Care* 2005;28:1151–1157
36. Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN). *Diabetes Care* 2006;29:1478–1485
37. Colhoun HM, Betteridge DJ, Durrington PN, et al.; CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;364:685–696
38. Kearney PM, Blackwell L, Collins R, et al.; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* 2008;371:117–125
39. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2013;1:CD004816
40. Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. Risk of incident diabetes among patients treated with statins: population based study. *BMJ* 2013;346:f2610
41. Hayward RA, Hofer TP, Vijan S. Narrative review: lack of evidence for recommended low-density lipoprotein treatment targets: a solvable problem. *Ann Intern Med* 2006;145:520–530
42. Cannon CP, Braunwald E, McCabe CH, et al.; Pravastatin or Atorvastatin Evaluation and Infarction Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495–1504
43. de Lemos JA, Blazing MA, Wiviott SD, et al.; Investigators. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA* 2004;292:1307–1316
44. Nissen SE, Tuzcu EM, Schoenhagen P, et al.; REVERSAL Investigators. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA* 2004;291:1071–1080

45. de Ferranti SD, de Boer IH, Fonseca V, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. *Circulation* 2014;130:1110–1130
46. Chasman DI, Posada D, Subrahmanyam L, Cook NR, Stanton VP Jr, Ridker PM. Pharmacogenetic study of statin therapy and cholesterol reduction. *JAMA* 2004;291:2821–2827
47. Meek C, Wierzbicki AS, Jewkes C, et al. Daily and intermittent rosuvastatin 5 mg therapy in statin intolerant patients: an observational study. *Curr Med Res Opin* 2012;28:371–378
48. Singh IM, Shishehbor MH, Ansell BJ. High-density lipoprotein as a therapeutic target: a systematic review. *JAMA* 2007;298:786–798
49. Keech A, Simes RJ, Barter P, et al.; FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005;366:1849–1861
50. Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. *Am J Cardiol* 2005;95:120–122
51. Ginsberg HN, Elam MB, Lovato LC, et al.; ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1563–1574
52. Boden WE, Probstfield JL, Anderson T, et al.; AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011;365:2255–2267
53. Rajpathak SN, Kumbhani DJ, Crandall J, Barzilai N, Alderman M, Ridker PM. Statin therapy and risk of developing type 2 diabetes: a meta-analysis. *Diabetes Care* 2009;32:1924–1929
54. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010;375:735–742
55. Ridker PM, Danielson E, Fonseca FAH, et al.; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195–2207
56. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. *Lancet* 2012;380:565–571
57. Baigent C, Blackwell L, Collins R, et al.; Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;373:1849–1860
58. Perk J, De Backer G, Gohlke H, et al.; European Association for Cardiovascular Prevention & Rehabilitation (EACPR); ESC Committee for Practice Guidelines (CPG). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012;33:1635–1701
59. Ogawa H, Nakayama M, Morimoto T, et al.; Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial Investigators. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA* 2008;300:2134–2141
60. Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ* 2008;337:a1840
61. Pignone M, Earnshaw S, Tice JA, Pletcher MJ. Aspirin, statins, or both drugs for the primary prevention of coronary heart disease events in men: a cost-utility analysis. *Ann Intern Med* 2006;144:326–336
62. Pignone M, Alberts MJ, Colwell JA, et al.; American Diabetes Association; American Heart Association; American College of Cardiology Foundation. Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation. *Diabetes Care* 2010;33:1395–1402
63. Campbell CL, Smyth S, Montalescot G, Steinhilber SR. Aspirin dose for the prevention of cardiovascular disease: a systematic review. *JAMA* 2007;297:2018–2024
64. Davi G, Patrono C. Platelet activation and atherothrombosis. *N Engl J Med* 2007;357:2482–2494
65. Vandvik PO, Lincoff AM, Gore JM, et al.; American College of Chest Physicians. Primary and secondary prevention of cardiovascular disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(Suppl.):e637S–e668S
66. Boden WE, O'Rourke RA, Teo KK, et al.; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;356:1503–1516
67. BARI 2D Study Group; Frye RL, August P, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 2009;360:2503–2515
68. Wackers FJT, Chyun DA, Young LH, et al.; Detection of Ischemia in Asymptomatic Diabetics (DIAD) Investigators. Resolution of asymptomatic myocardial ischemia in patients with type 2 diabetes in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study. *Diabetes Care* 2007;30:2892–2898
69. Young LH, Wackers FJT, Chyun DA, et al.; DIAD Investigators. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. *JAMA* 2009;301:1547–1555
70. Wackers FJT, Young LH, Inzucchi SE, et al.; Detection of Ischemia in Asymptomatic Diabetics Investigators. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. *Diabetes Care* 2004;27:1954–1961
71. Scognamiglio R, Negut C, Ramondo A, Tiengo A, Avogaro A. Detection of coronary artery disease in asymptomatic patients with type 2 diabetes mellitus. *J Am Coll Cardiol* 2006;47:65–71
72. Hadamitzky M, Hein F, Meyer T, et al. Prognostic value of coronary computed tomographic angiography in diabetic patients without known coronary artery disease. *Diabetes Care* 2010;33:1358–1363
73. Elkeles RS, Godsland IF, Feher MD, et al.; PREDICT Study Group. Coronary calcium measurement improves prediction of cardiovascular events in asymptomatic patients with type 2 diabetes: the PREDICT study. *Eur Heart J* 2008;29:2244–2251
74. Choi E-K, Chun EJ, Choi S-I, et al. Assessment of subclinical coronary atherosclerosis in asymptomatic patients with type 2 diabetes mellitus with single photon emission computed tomography and coronary computed tomography angiography. *Am J Cardiol* 2009;104:890–896
75. Braunwald E, Domanski MJ, Fowler SE, et al.; PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med* 2004;351:2058–2068
76. Telmisartan Randomised Assessment Study in ACE Intolerant subjects with Cardiovascular Disease (TRANSCEND) Investigators; Yusuf S, Teo K, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet* 2008;372:1174–1183
77. Kezerashvili A, Marzo K, De Leon J. Beta blocker use after acute myocardial infarction in the patient with normal systolic function: when is it "ok" to discontinue? *Curr Cardiol Rev* 2012;8:77–84
78. Eurich DT, Weir DL, Majumdar SR, et al. Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: systematic review of observational studies involving 34,000 patients. *Circ Heart Fail* 2013;6:395–402

9. Microvascular Complications and Foot Care

American Diabetes Association

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NEPHROPATHY

Recommendations

- Optimize glucose control to reduce the risk or slow the progression of diabetic kidney disease. **A**
- Optimize blood pressure control to reduce the risk or slow the progression of diabetic kidney disease. **A**

Screening

- At least once a year, quantitatively assess urinary albumin (e.g., urine albumin-to-creatinine ratio [UACR]) and estimated glomerular filtration rate (eGFR) in patients with type 1 diabetes duration of ≥ 5 years and in all patients with type 2 diabetes. **B**

Treatment

- An ACE inhibitor or angiotensin receptor blocker (ARB) is not recommended for the primary prevention of diabetic kidney disease in patients with diabetes who have normal blood pressure and normal UACR (< 30 mg/g). **B**
- Either an ACE inhibitor or ARB is suggested for the treatment of the non-pregnant patient with modestly elevated urinary albumin excretion (30–299 mg/day) **C** and is recommended for those with urinary albumin excretion > 300 mg/day. **A**
- When ACE inhibitors, ARBs, or diuretics are used, monitor serum creatinine and potassium levels for the development of increased creatinine or changes in potassium. **E**
- Continued monitoring of UACR in patients with albuminuria is reasonable to assess progression of diabetic kidney disease. **E**
- When eGFR is < 60 mL/min/1.73 m², evaluate and manage potential complications of chronic kidney disease (CKD). **E**
- Consider referral to a physician experienced in the care of kidney disease when there is uncertainty about the etiology of kidney disease, difficult management issues, or advanced kidney disease. **B**

Nutrition

- For people with diabetic kidney disease, reducing the amount of dietary protein below the recommended daily allowance of 0.8 g/kg/day (based on ideal body weight) is not recommended because it does not alter glycemic measures, cardiovascular risk measures, or the course of GFR decline. **A**

The terms “microalbuminuria” (30–299 mg/24 h) and “macroalbuminuria” (> 300 mg/24 h) will no longer be used, since albuminuria occurs on a continuum. Albuminuria is defined as UACR ≥ 30 mg/g.

Diabetic kidney disease occurs in 20–40% of patients with diabetes and is the leading cause of end-stage renal disease (ESRD). Persistent increased albuminuria in the range of UACR 30–299 mg/g is an early indicator of diabetic kidney disease in type 1 diabetes and a marker for development of diabetic kidney disease in type 2 diabetes. It is a well-established marker of increased cardiovascular disease (CVD) risk (1–3). However, there is increasing evidence of spontaneous remission of UACR levels 30–299 mg/g in up to 40% of patients with type 1 diabetes. About 30–40% remain with UACR levels of 30–299 mg/g and do not

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progress to higher levels (≥ 300 mg/g) over 5–10 years of follow-up (4–7). Patients with persistent albuminuria are likely to develop ESRD (8,9).

Interventions

Glycemia

A number of interventions have been demonstrated to reduce the risk and slow the progression of diabetic kidney disease. Intensive diabetes management with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to delay the onset and progression of increased urinary albumin excretion and reduced eGFR in patients with type 1 (9) and type 2 diabetes (10–14).

Despite prior concerns and published case reports, current data indicate that the overall risk of metformin-associated lactic acidosis is low (14). GFR may be a more appropriate measure to assess continued metformin use than serum creatinine considering that the serum creatinine level can translate into widely varying eGFR levels depending on age, ethnicity, and muscle mass (15). A recent review (16) proposes that metformin use should be reevaluated at an eGFR < 45 mL/min/1.73 m² with a reduction in maximum dose to 1,000 mg/day and discontinued when eGFR < 30 mL/min/1.73 m² or in clinical situations in which there is an increased risk of lactic acidosis, such as sepsis, hypotension, and hypoxia, or in which there is a high risk of acute kidney injury resulting in a worsening of GFR, such as administration of radiocontrast dye in those with eGFR < 60 mL/min/1.73 m².

Blood Pressure

The UK Prospective Diabetes Study (UKPDS) provided strong evidence that blood pressure control can reduce the development of diabetic kidney disease (17). In addition, large prospective randomized studies in patients with type 1 diabetes have shown that ACE inhibitors have achieved lower systolic blood pressure levels (< 140 mmHg) and have provided a selective benefit over other antihypertensive drug classes in delaying the progression of increased urinary albumin excretion and can slow the decline in GFR in patients with higher levels of albuminuria (18,19). In patients with type 2 diabetes, hypertension,

and normoalbuminuria, renin-angiotensin system inhibition has been demonstrated to delay onset of elevated albuminuria (20,21). Of note, in the latter study, there was an unexpected higher rate of fatal cardiovascular events with olmesartan compared with placebo among patients with pre-existing CVD.

ACE inhibitors have been shown to reduce major CVD outcomes (i.e., myocardial infarction, stroke, death) in patients with diabetes (22), thus further supporting the use of these agents in patients with elevated albuminuria, a CVD risk factor. ARBs do not have the same beneficial effect on cardiovascular outcomes or prevent the onset of elevated albuminuria in normotensive patients with type 1 or type 2 diabetes (23). However, ARBs have been shown to reduce the progression of albuminuria, as well as ESRD, in patients with type 2 diabetes (24–26). In those with diabetic kidney disease, some evidence suggests that ARBs are associated with a smaller increase in serum potassium levels compared with ACE inhibitors (27).

Combination Therapy

Drug combinations that block the renin-angiotensin system (e.g., an ACE inhibitor plus an ARB, a mineralocorticoid antagonist, or a direct renin inhibitor) provide additional lowering of albuminuria (28). However, compared with single-agent use, such combinations have been found to provide no additional benefit on CVD or diabetic kidney disease and have higher adverse event rates (hyperkalemia or acute kidney injury) (29). *Therefore, the combined use of different inhibitors of the renin-angiotensin system should be avoided.*

Diuretics, calcium channel blockers, and β -blockers can be used as additional therapy to further lower blood pressure in patients already treated with maximum doses of ACE inhibitors or ARBs (30) or as alternate therapy in the rare individual unable to tolerate ACE inhibitors and ARBs.

Studies in patients with varying stages of diabetic kidney disease have shown that the limitation of dietary protein to avoid excess intake slows the progression of albuminuria, GFR decline, and occurrence of ESRD

(31–34), although more recent studies have provided conflicting results (35). Dietary protein limitation, if protein intake is high, is a consideration particularly in patients whose diabetic kidney disease is progressing despite optimal glucose and blood pressure control and use of an ACE inhibitor or ARB (34).

Assessment of Albuminuria Status and Renal Function

Screening for increased urinary albumin excretion can be performed by UACR in a random spot urine collection; 24-h or timed collections are more burdensome and add little to prediction or accuracy (36,37). 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 is less expensive but susceptible to false-negative and false-positive determinations as a result of variation in urine concentration due to hydration and other factors.

Abnormalities of albumin excretion and the linkage between UACR and 24-h albumin excretion are defined in **Table 9.1**. Because of variability in urinary albumin excretion, two of three specimens collected within a 3- to 6-month period should be abnormal before considering a patient to have developed albuminuria. Exercise within 24 h, infection, fever, congestive heart failure, marked hyperglycemia, and marked hypertension may elevate urinary albumin excretion over baseline values.

Abnormal urine albumin excretion and GFR level may be used to stage CKD. The National Kidney Foundation classification (**Table 9.2**) is primarily based on GFR levels and may be superseded by other systems in which staging

Table 9.1—Definitions of abnormalities in albumin excretion

Category	Spot collection (mg/g creatinine)
Normal	< 30
Increased urinary albumin excretion*	≥ 30

*Historically, ratios between 30 and 299 mg/g have been called “microalbuminuria” and those > 300 mg/g have been called “macroalbuminuria” (or clinical albuminuria).

includes other variables such as urinary albumin excretion (38). Studies have found decreased GFR without increased urine albumin excretion in a substantial percentage of adults with type 2 diabetes (39). Substantial evidence shows that in patients with type 1 diabetes and persistent UACR 30–299 mg/g, screening with albumin excretion rate alone would miss >20% of progressive disease (7). Serum creatinine with eGFR should therefore be assessed at least annually in all adults with diabetes, regardless of the degree of urine albumin excretion.

Serum creatinine should be used to estimate GFR and to stage the level of CKD, if present. eGFR is commonly coreported by laboratories or can be estimated using formulae such as the Modification of Diet in Renal Disease (MDRD) study equation (40) or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The latter is the current preferred GFR estimating equation. GFR calculators are available at <http://www.nkdep.nih.gov>.

The need for annual quantitative assessment of albumin excretion after diagnosis of albuminuria and institution of ACE inhibitor or ARB therapy and 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. Some suggest that reducing UACR to normal (<30 mg/g) or near normal may improve CKD and CVD prognosis, but this approach has not been formally evaluated in prospective trials, and evidence demonstrates spontaneous remission of albuminuria in up to 40% of type 1 diabetic patients.

Conversely, patients with increasing albumin levels, declining GFR, increasing blood pressure, retinopathy, macrovascular disease, elevated lipids and/or uric acid concentrations, or a family history of CKD are more likely to experience a progression of diabetic kidney disease (7).

Complications of kidney disease correlate with level of kidney function. When the eGFR is <60 mL/min/1.73 m², screening for complications of CKD is indicated (Table 9.3). Early vaccination against hepatitis B virus is

Table 9.2—Stages of CKD

Stage	Description	GFR (mL/min/1.73 m ²)
1	Kidney damage* with normal or increased GFR	≥90
2	Kidney damage* with mildly decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	Kidney failure	<15 or dialysis

*Kidney damage is defined as abnormalities on pathological, urine, blood, or imaging tests. Adapted from Levey et al. (37).

indicated in patients likely to progress to ESRD.

Referral to Nephrologist

Consider referral to a physician experienced in the care of kidney disease when there is uncertainty about the etiology of kidney disease (heavy proteinuria, active urine sediment, absence of retinopathy, rapid decline in GFR). Other triggers for referral may include difficult management issues (anemia, secondary hyperparathyroidism, metabolic bone disease, resistant hypertension, or electrolyte disturbance) or advanced kidney disease. The threshold for referral may vary depending on the frequency with which a provider encounters diabetic patients with significant kidney disease. Consultation with a nephrologist when stage 4 CKD develops has been found to reduce cost, improve quality of care, and delay dialysis (41). However, other specialists and providers should not delay educating their patients about the progressive nature of diabetic kidney disease, the kidney preservation benefits of proactive

treatment of blood pressure and blood glucose, and the potential need for renal transplant.

RETINOPATHY

Recommendations

- Optimize glycemic control to reduce the risk or slow the progression of retinopathy. **A**
- Optimize blood pressure control to reduce the risk or slow the progression of retinopathy. **A**

Screening

- 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**
- Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist shortly after the diagnosis of diabetes. **B**

Table 9.3—Management of CKD in diabetes (7)

GFR (mL/min/1.73 m ²)	Recommended management
All patients	Yearly measurement of creatinine, urinary albumin excretion, potassium
45–60	Referral to a nephrologist if possibility for nondiabetic kidney disease exists (duration of type 1 diabetes <10 years, persistent albuminuria, abnormal findings on renal ultrasound, resistant hypertension, rapid fall in GFR, or active urinary sediment on ultrasound) Consider the need for dose adjustment of medications Monitor eGFR every 6 months Monitor electrolytes, bicarbonate, hemoglobin, calcium, phosphorus, parathyroid hormone at least yearly Assure vitamin D sufficiency Consider bone density testing Referral for dietary counseling
30–44	Monitor eGFR every 3 months Monitor electrolytes, bicarbonate, calcium, phosphorus, parathyroid hormone, hemoglobin, albumin, weight every 3–6 months Consider the need for dose adjustment of medications
<30	Referral to a nephrologist

- If there is no evidence of retinopathy for one or more eye exams, then exams every 2 years may be considered. If diabetic retinopathy is present, subsequent examinations for patients with type 1 and type 2 diabetes should be repeated annually by an ophthalmologist or optometrist. If retinopathy is progressing or sight-threatening, then examinations will be required more frequently. **B**
- High-quality fundus photographs can detect most clinically significant diabetic retinopathy. Interpretation of the images should be performed by a trained eye care provider. While retinal photography may serve as a screening tool for retinopathy, it is not a substitute for a comprehensive eye exam, which should be performed at least initially and at intervals thereafter as recommended by an eye care professional. **E**
- Women with preexisting diabetes who are planning pregnancy or who have become pregnant should have a comprehensive eye examination and be counseled on the risk of development and/or progression of diabetic retinopathy. Eye examination should occur in the first trimester with close follow-up throughout pregnancy and for 1 year postpartum. **B**

Treatment

- Promptly refer patients with any level of macular edema, severe nonproliferative diabetic retinopathy (NPDR), or any proliferative diabetic retinopathy (PDR) to an ophthalmologist who is knowledgeable and experienced in the management and treatment of diabetic retinopathy. **A**
- Laser photocoagulation therapy is indicated to reduce the risk of vision loss in patients with high-risk PDR, clinically significant macular edema, and, in some cases, severe NPDR. **A**
- Antivascular endothelial growth factor (VEGF) therapy is indicated for diabetic macular edema. **A**
- 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 the duration of diabetes. Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20–74 years. 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 (42), nephropathy (43), and hypertension (44). 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 (11,45). Lowering blood pressure has been shown to decrease retinopathy progression, although tight targets (systolic <120 mmHg) do not impart additional benefit (45). Several case series and a controlled prospective study suggest that pregnancy in type 1 diabetic patients may aggravate retinopathy (46,47). Laser photocoagulation surgery can minimize this risk (47).

Screening

The preventive effects of therapy and the fact that patients with PDR or macular edema may be asymptomatic provide strong support for a screening program to detect diabetic retinopathy. 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 diabetes diagnosis (48). 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 shortly after diagnosis. Examinations should be performed by an ophthalmologist or optometrist who is knowledgeable and experienced in diagnosing diabetic retinopathy. Subsequent examinations for type 1 and type 2 diabetic patients are generally repeated annually. Exams every 2 years may be cost-effective after one or more normal eye exams, and

in a population with well-controlled type 2 diabetes, there was essentially no risk of development of significant retinopathy with a 3-year interval after a normal examination (49). Examinations will be required more frequently if retinopathy is progressing.

Retinal photography, with remote reading by experts, has great potential in areas where qualified eye care professionals are not readily available (50). It also may enhance efficiency and reduce costs when the expertise of ophthalmologists can be used for more complex examinations and for therapy (51). In-person exams are still necessary when the photos are unacceptable and for follow-up if abnormalities are detected. Photos are not a substitute for a comprehensive eye exam, which should be performed at least initially and at intervals thereafter as recommended by an eye care professional. Results of eye examinations should be documented and transmitted to the referring health care professional.

Treatment

One of the main motivations for screening for diabetic retinopathy is the long-established efficacy of laser photocoagulation surgery in preventing visual loss. 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 (52) showed 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 risk-benefit ratio in those with baseline disease (disc neovascularization or vitreous hemorrhage).

The ETDRS (53) established the benefit of focal laser photocoagulation surgery in eyes with macular edema, particularly those with clinically significant macular edema, with reduction of doubling of the visual angle (e.g., 20/50 to 20/100) from 20% in untreated eyes to 8% in treated eyes. The ETDRS also verified the benefits of panretinal photocoagulation for high-risk PDR and in older-onset patients with severe NPDR or less-than-high-risk PDR.

Laser photocoagulation surgery in both trials was beneficial in reducing

the risk of further visual loss, but generally not beneficial in reversing already diminished acuity. Recombinant monoclonal neutralizing antibody to VEGF improves vision and reduces the need for laser photocoagulation in patients with macular edema (54). Other emerging therapies for retinopathy include sustained intravitreal delivery of fluocinolone (55) and the possibility of prevention with fenofibrate (56,57).

NEUROPATHY

Recommendations

- All patients should be screened for diabetic peripheral neuropathy (DPN) starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter, using simple clinical tests, such as a 10-g monofilament. **B**
- Screening for signs and symptoms (e.g., orthostasis, resting tachycardia) of cardiovascular autonomic neuropathy (CAN) should be considered with more advanced disease. **E**
- Tight glycemic control is the only strategy convincingly shown to prevent or delay the development of DPN and CAN in patients with type 1 diabetes **A** and to slow the progression of neuropathy in some patients with type 2 diabetes. **B**
- Assess and treat patients to reduce pain related to DPN **B** and symptoms of autonomic neuropathy and to improve quality of life. **E**

The diabetic neuropathies are heterogeneous with diverse clinical manifestations. They may be focal or diffuse. The most prevalent neuropathies are DPN and autonomic neuropathy. Although DPN is a diagnosis of exclusion, complex investigations or referral for neurology consultation to exclude other conditions is rarely needed.

The early recognition and appropriate management of neuropathy in the patient with diabetes is important for a number of reasons:

1. Nondiabetic neuropathies may be present in patients with diabetes and may be treatable.
2. A number of treatment options exist for symptomatic diabetic neuropathy.
3. Up to 50% of DPN may be asymptomatic, and patients are at risk for insensate injury to their feet.

4. Autonomic neuropathy, particularly CAN, is an independent risk factor for cardiovascular mortality (58,59).

Specific treatment for the underlying nerve damage, other than improved glycemic control, is currently not available. Glycemic control was shown to effectively prevent DPN and CAN in type 1 diabetes (60,61) and may modestly slow progression in type 2 diabetes (13) but does not reverse neuronal loss. Therapeutic strategies (pharmacological and nonpharmacological) for the relief of specific symptoms related to painful DPN or autonomic neuropathy are recommended because they can potentially reduce pain (62) and improve quality of life.

Diagnosis

Diabetic Peripheral Neuropathy

Patients with diabetes should be screened annually for DPN symptoms using simple clinical tests. Symptoms vary according to the class of sensory fibers involved. The most common symptoms are induced by the involvement of small fibers and include pain, dysesthesias (unpleasant abnormal sensations of burning and tingling), and numbness. Clinical tests include assessment of pinprick sensation, vibration threshold using a 128-Hz tuning fork, light touch perception using a 10-g monofilament, and ankle reflexes. Assessment should follow the typical DPN pattern, starting distally (the dorsal aspect of the hallux) on both sides and move proximally until threshold is detected. Several clinical instruments that combine more than one test have >87% sensitivity in detecting DPN (63–65). 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 patients with severe or atypical neuropathy, causes other than diabetes should always be considered, such as neurotoxic medications, heavy metal poisoning, alcohol abuse, vitamin B₁₂ deficiency (66), renal disease, chronic inflammatory demyelinating neuropathy, inherited neuropathies, and vasculitis (67).

Diabetic Autonomic Neuropathy

The symptoms and signs of autonomic dysfunction should be elicited carefully during the history and physical

examination. Major clinical manifestations of diabetic autonomic neuropathy include resting tachycardia, exercise intolerance, orthostatic hypotension, gastroparesis, constipation, erectile dysfunction, sudomotor dysfunction, impaired neurovascular function, and, potentially, autonomic failure in response to hypoglycemia.

Cardiovascular Autonomic Neuropathy

CAN is the most studied and clinically important form of diabetic autonomic neuropathy because of its association with mortality independent of other cardiovascular risk factors (58,68). In early stages, CAN may be completely asymptomatic and detected by changes in heart rate variability with deep breathing and abnormal cardiovascular reflex tests (R-R interval response to deep breathing, standing, and Valsalva maneuver tests). Advanced disease may be indicated by resting tachycardia (>100 bpm) and orthostasis (a fall in systolic blood pressure >20 mmHg or diastolic blood pressure of at least 10 mmHg upon standing without an appropriate heart rate response). The standard cardiovascular reflex tests (deep breathing, standing, and Valsalva maneuver) are noninvasive, easy to perform, reliable, and reproducible, especially the deep breathing test, and have prognostic value (69). Although some societies have developed guidelines for screening for CAN, the benefits of sophisticated testing beyond risk stratification are not clear (69).

Gastrointestinal Neuropathies

Gastrointestinal neuropathies (e.g., esophageal enteropathy, gastroparesis, constipation, diarrhea, fecal incontinence) may involve any section of the gastrointestinal tract. Gastroparesis should be suspected in individuals with erratic glucose control or with upper gastrointestinal symptoms without another identified cause. Evaluation of solid-phase gastric emptying using double-isotope scintigraphy may be done if symptoms are suggestive, but test results often correlate poorly with symptoms. Constipation is the most common lower-gastrointestinal symptom but can alternate with episodes of diarrhea.

Genitourinary Tract Disturbances

Diabetic autonomic neuropathy is also associated with genitourinary tract disturbances. In men, diabetic autonomic

neuropathy may cause erectile dysfunction and/or retrograde ejaculation. Evaluation of bladder dysfunction should be performed for individuals with diabetes who have recurrent urinary tract infections, pyelonephritis, incontinence, or a palpable bladder.

Treatment

Glycemic Control

Tight glycemic control, implemented early in the course of diabetes, has been shown to effectively prevent or delay the development of DPN and CAN in patients with type 1 diabetes (70–73). While the evidence is not as strong for type 2 diabetes, some studies have demonstrated a modest slowing of progression (74,75) without reversal of neuronal loss. Several observational studies further suggest that neuropathic symptoms improve not only with optimization of glycemic control but also with the avoidance of extreme blood glucose fluctuations.

Diabetic Peripheral Neuropathy

DPN symptoms, and especially neuropathic pain, can be severe, have sudden onset, and are associated with lower quality of life, limited mobility, depression, and social dysfunction (76). There is limited clinical evidence regarding the most effective treatments for individual patients given the wide range of available medications (77,78). Several drugs have been approved specifically for relief of DPN pain in the U.S. (pregabalin, duloxetine, and tapentadol), but none affords complete relief, even when used in combination. Venlafaxine, amitriptyline, gabapentin, valproate, and other opioids (morphine sulfate, tramadol, oxycodone controlled release) may be effective and may be considered for treatment of painful DPN. Head-to-head treatment comparisons and studies 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 pharmacological 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 (62).

Autonomic Neuropathy

An intensive multifactorial cardiovascular risk intervention targeting glucose, blood pressure, lipids, smoking, and other lifestyle factors has been shown to reduce the progression and development of CAN among patients with type 2 diabetes (79). For those with significant CAN, referral to a cardiologist may be indicated.

Orthostatic Hypotension

Treatment of orthostatic hypotension is challenging. The therapeutic goal is to minimize postural symptoms rather than to restore normotension. Most patients require the use of both pharmacological and nonpharmacological measures (e.g., avoiding medications that aggravate hypotension, using compressive garments over the legs and abdomen). Midodrine is the only drug approved by the U.S. Food and Drug Administration for the treatment of orthostatic hypotension.

Gastroparesis Symptoms

Gastroparesis symptoms may improve with dietary changes and prokinetic agents such as erythromycin. Recently, the European Medicines Agency (www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/07/WC500146614.pdf) decided that risks of extrapyramidal symptoms with metoclopramide outweigh benefits. In Europe, metoclopramide use is now restricted to a maximum of 5 days and is no longer indicated for the long-term treatment of gastroparesis. Although the U.S. Food and Drug Administration's decision is pending, it is suggested that metoclopramide be reserved for only the most severe cases that are unresponsive to other therapies. Side effects should be closely monitored.

Erectile Dysfunction

Treatments for erectile dysfunction may include phosphodiesterase type 5 inhibitors, intracorporeal or intraurethral prostaglandins, vacuum devices, or penile prostheses. Interventions for other manifestations of autonomic neuropathy are described in the American Diabetes Association (ADA) statement on neuropathy (78). As with DPN treatments, these interventions do not change the underlying pathology and natural history of the disease process but may have a positive impact on the quality of life of the patient.

FOOT CARE

Recommendations

- For all patients with diabetes, perform an annual comprehensive foot examination to identify risk factors predictive of ulcers and amputations. The foot examination should include inspection and assessment of foot pulses. **B**
- Patients with insensate feet, foot deformities, and ulcers should have their feet examined at every visit. **E**
- Provide general foot self-care education to all patients with diabetes. **B**
- A multidisciplinary approach is recommended for individuals with foot ulcers and high-risk feet (e.g., dialysis patients and those with Charcot foot, prior ulcers, or amputation). **B**
- Refer patients who smoke or who have a loss of protective sensation (LOPS), structural abnormalities, or a history of prior lower-extremity complications to foot care specialists for ongoing preventive care and lifelong surveillance. **C**
- Initial screening for peripheral arterial disease (PAD) should include a history for claudication and an assessment of the pedal pulses. **C**
- Refer patients with significant claudication or a positive ankle-brachial index (ABI) for further vascular assessment and consider exercise, medications, and surgical options. **C**

Amputation and foot ulceration, which are consequences of diabetic neuropathy and/or PAD, are common and represent major causes of morbidity and disability in people with diabetes. Loss of 10-g monofilament perception and reduced vibration perception predict foot ulcers (78). Early recognition and management of risk factors can prevent or delay adverse outcomes.

The risk of ulcers or amputations is increased in people who have the following risk factors:

- Previous amputation
- Past foot ulcer history
- Peripheral neuropathy
- Foot deformities

- Peripheral vascular disease
- Visual impairment
- Diabetic nephropathy (especially patients on dialysis)
- Poor glycemic control
- Cigarette smoking

Clinicians are encouraged to review ADA screening recommendations for further details and practical descriptions of how to perform components of the comprehensive foot examination (80).

Examination

All adults with diabetes should undergo a comprehensive foot examination at least annually to identify high-risk conditions. Clinicians should ask about history of previous foot ulceration or amputation, neuropathic or peripheral vascular symptoms, impaired vision, tobacco use, and foot care practices. A general inspection of skin integrity and musculoskeletal deformities should be done in a well-lit room. Vascular assessment would include inspection and assessment of pedal pulses.

The neurological exam recommended is designed to identify LOPS rather than early neuropathy. The clinical examination to identify LOPS is simple and requires no expensive equipment. Five simple clinical tests (use of a 10-g monofilament, vibration testing using a 128-Hz tuning fork, tests of pinprick sensation, ankle reflex assessment, and testing vibration perception threshold with a biothesiometer), each with evidence from well-conducted prospective clinical cohort studies, are considered useful in the diagnosis of LOPS in the diabetic foot. Any of the five tests listed above could be used by clinicians to identify LOPS, although ideally two of these should be regularly performed during the screening exam—normally the 10-g monofilament and one other test. One or more abnormal tests would suggest LOPS, while at least two normal tests (and no abnormal test) would rule out LOPS. The last test listed, vibration assessment using a biothesiometer or similar instrument, is widely used in the U.S.; however, identification of the patient with LOPS can easily be carried out without this or other expensive equipment.

Screening

Initial screening for PAD should include a history for claudication and an assessment of the pedal pulses.

A diagnostic ABI should be considered in patients with PAD. Due to the high estimated prevalence of PAD in patients with diabetes and the fact that many patients with PAD are asymptomatic, an ADA consensus report on PAD (81) suggested that a screening ABI be performed in patients over 50 years of age and be considered in patients under 50 years of age who have other PAD risk factors (e.g., smoking, hypertension, hyperlipidemia, or duration of diabetes >10 years). Refer patients with significant symptoms or a positive ABI for further vascular assessment and consider exercise, medications, and surgical options (81).

Patient Education

Patients with diabetes and high-risk foot conditions should be educated about their risk factors and appropriate management. Patients at risk should understand the implications of LOPS; the importance of foot monitoring on a daily basis; the proper care of the foot, including nail and skin care; and the selection of appropriate footwear. Patients with LOPS should be educated on ways to substitute other sensory modalities (hand palpation, visual inspection) for surveillance of early foot problems. 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 in their care.

Treatment

People with neuropathy or evidence of increased plantar pressure (e.g., erythema, warmth, callus, or measured pressure) may be adequately managed with well-fitted walking shoes or athletic shoes that cushion the feet and redistribute pressure. Calluses can be debrided with a scalpel by a foot care specialist or other health professional with experience and training in foot care. People with bony deformities (e.g., hammertoes, prominent metatarsal heads, bunions) may need extra wide or deep shoes. People with extreme bony deformities (e.g., Charcot foot) who cannot be accommodated with

commercial therapeutic footwear may need custom-molded shoes.

Most diabetic foot infections are polymicrobial, with aerobic gram-positive cocci (GPC). Staphylococci 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 GPC in many acutely infected patients, 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 (82). 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. Guidelines for treatment of diabetic foot ulcers have recently been updated (82).

References

1. Krolewski AS, Niewczas MA, Skupien J, et al. Early progressive renal decline precedes the onset of microalbuminuria and its progression to macroalbuminuria. *Diabetes Care* 2014;37:226–234
2. Garg JP, Bakris GL. Microalbuminuria: marker of vascular dysfunction, risk factor for cardiovascular disease. *Vasc Med* 2002;7:35–43
3. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, et al. Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. *Circulation* 2004;110:32–35
4. de Boer IH, Rue TC, Cleary PA, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group. Long-term renal outcomes of patients with type 1 diabetes mellitus and microalbuminuria: an analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort. *Arch Intern Med* 2011;171:412–420
5. Molitch ME, Steffes M, Sun W, et al.; Epidemiology of Diabetes Interventions and Complications Study Group. Development and progression of renal insufficiency with and without albuminuria in adults with type 1 diabetes in the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications Study. *Diabetes Care* 2010;33:1536–1543
6. de Boer IH, Sun W, Cleary PA, et al.; DCCT/EDIC Research Group. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. *N Engl J Med* 2011;365:2366–2376
7. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. *Am J Kidney Dis* 2012;60:850–886
8. Gall M-A, Hougaard P, Borch-Johnsen K, Parving H-H. Risk factors for development of incipient and overt diabetic nephropathy in

- patients with non-insulin dependent diabetes mellitus: prospective, observational study. *BMJ* 1997;314:783–788
9. The Diabetes Control and Complications (DCCT) Research Group. Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. *Kidney Int* 1995;47:1703–1720
10. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854–865
11. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–853
12. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560–2572
13. Ismail-Beigi F, Craven T, Banerji MA, et al.; ACCORD Trial Group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet* 2010;376:419–430
14. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA consensus conference. *Diabetes Care* 2014;37:2864–2883
15. Skupien J, Warram JH, Smiles A, Galecki A, Stanton RC, Krolewski AS. Improved glycemic control and risk of ESRD in patients with type 1 diabetes and proteinuria. *J Am Soc Nephrol*. 5 June 2014 [Epub ahead of print]
16. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. *Diabetes Care* 2011;34:1431–1437
17. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998;317:703–713
18. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD; Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993;329:1456–1462
19. Laffel LM, McGill JB, Gans DJ; North American Microalbuminuria Study Group. The beneficial effect of angiotensin-converting enzyme inhibition with captopril on diabetic nephropathy in normotensive IDDM patients with microalbuminuria. *Am J Med* 1995;99:497–504
20. Remuzzi G, Macia M, Ruggenenti P. Prevention and treatment of diabetic renal disease in type 2 diabetes: the BENEDICT study. *J Am Soc Nephrol* 2006;17(Suppl. 2):S90–S97
21. Haller H, Ito S, Izzo JL Jr; et al.; ROADMAP Trial Investigators. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *N Engl J Med* 2011;364:907–917
22. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000;355:253–259
23. Bilous R, Chaturvedi N, Sjølie AK, et al. Effect of candesartan on microalbuminuria and albumin excretion rate in diabetes: three randomized trials. *Ann Intern Med* 2009;151:11–20
24. Lewis EJ, Hunsicker LG, Clarke WR, et al.; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345:851–860
25. Brenner BM, Cooper ME, de Zeeuw D, et al.; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;345:861–869
26. Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P; Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001;345:870–878
27. Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al.; INVEST Investigators. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA* 2003;290:2805–2816
28. Parving H-H, Persson F, Lewis JB, Lewis EJ, Hollenberg NK; AVOID Study Investigators. Aliskiren combined with losartan in type 2 diabetes and nephropathy. *N Engl J Med* 2008;358:2433–2446
29. Yusuf S, Teo KK, Pogue J, et al.; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;358:1547–1559
30. Berl T, Hunsicker LG, Lewis JB, et al.; Irbesartan Diabetic Nephropathy Trial. Collaborative Study Group. Cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial of patients with type 2 diabetes and overt nephropathy. *Ann Intern Med* 2003;138:542–549
31. Pijls LT, de Vries H, Donker AJ, van Eijk JT. The effect of protein restriction on albuminuria in patients with type 2 diabetes mellitus: a randomized trial. *Nephrol Dial Transplant* 1999;14:1445–1453
32. Pedrini MT, Levey AS, Lau J, Chalmers TC, Wang PH. The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a meta-analysis. *Ann Intern Med* 1996;124:627–632
33. Hansen HP, Tauber-Lassen E, Jensen BR, Parving H-H. Effect of dietary protein restriction on prognosis in patients with diabetic nephropathy. *Kidney Int* 2002;62:220–228
34. Kasiske BL, Lakatua JD, Ma JZ, Louis TA. A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. *Am J Kidney Dis* 1998;31:954–961
35. Wheeler ML, Dunbar SA, Jaacks LM, et al. Macronutrients, food groups, and eating patterns in the management of diabetes: a systematic review of the literature, 2010. *Diabetes Care* 2012;35:434–445
36. Eknoyan G, Hostetter T, Bakris GL, et al. Proteinuria and other markers of chronic kidney disease: a position statement of the National Kidney Foundation (NKF) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). *Am J Kidney Dis* 2003;42:617–622
37. Levey AS, Coresh J, Balk E, et al.; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003;139:137–147
38. Kramer H, Molitch ME. Screening for kidney disease in adults with diabetes. *Diabetes Care* 2005;28:1813–1816
39. Kramer HJ, Nguyen QD, Curhan G, Hsu C-Y. Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. *JAMA* 2003;289:3273–3277
40. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D; Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999;130:461–470
41. Smart NA, Dieberg G, Ladhani M, Titus T. Early referral to specialist nephrology services for preventing the progression to end-stage kidney disease. *Cochrane Database Syst Rev* 2014; 6:CD007333
42. Klein R. Hyperglycemia and microvascular and macrovascular disease in diabetes. *Diabetes Care* 1995;18:258–268
43. Estacio RO, McFarling E, Biggerstaff S, Jeffers BW, Johnson D, Schrier RW. Overt albuminuria predicts diabetic retinopathy in Hispanics with NIDDM. *Am J Kidney Dis* 1998;31:947–953
44. Leske MC, Wu S-Y, Hennis A, et al.; Barbados Eye Study Group. Hyperglycemia, blood pressure, and the 9-year incidence of diabetic retinopathy: the Barbados Eye Studies. *Ophthalmology* 2005;112:799–805
45. Chew EY, Ambrosius WT, Davis MD, et al.; ACCORD Study Group; ACCORD Eye Study Group. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med* 2010;363:233–244
46. Fong DS, Aiello LP, Ferris FL 3rd, Klein R. Diabetic retinopathy. *Diabetes Care* 2004;27:2540–2553
47. Diabetes Control and Complications Trial Research Group. Effect of pregnancy on microvascular complications in the diabetes control and complications trial. *Diabetes Care* 2000;23:1084–1091
48. Hooper P, Boucher MC, Cruess A, et al. Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of diabetic retinopathy. *Can J Ophthalmol* 2012;47(Suppl. 2):S1–S30
49. Agardh E, Tababat-Khani P. Adopting 3-year screening intervals for sight-threatening retinal vascular lesions in type 2 diabetic subjects without retinopathy. *Diabetes Care* 2011;34:1318–1319
50. Bragge P, Gruen RL, Chau M, Forbes A, Taylor HR. Screening for presence or absence of diabetic retinopathy: a meta-analysis. *Arch Ophthalmol* 2011;129:435–444
51. Ahmed J, Ward TP, Bursell S-E, Aiello LM, Cavallerano JD, Vigersky RA. The sensitivity and

- specificity of nonmydriatic digital stereoscopic retinal imaging in detecting diabetic retinopathy. *Diabetes Care* 2006;29:2205–2209
52. The Diabetic Retinopathy Study Research Group. Preliminary report on effects of photocoagulation therapy. *Am J Ophthalmol* 1976;81:383–396
53. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. *Arch Ophthalmol* 1985;103:1796–1806
54. Nguyen QD, Brown DM, Marcus DM, et al.; RISE and RIDE Research Group. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology* 2012;119:789–801
55. Pearson PA, Comstock TL, Ip M, et al. Fluocinolone acetonide intravitreal implant for diabetic macular edema: a 3-year multicenter, randomized, controlled clinical trial. *Ophthalmology* 2011;118:1580–1587
56. Chew EY, Ambrosius WT. Update of the ACCORD Eye Study. *N Engl J Med* 2011;364:188–189
57. Keech AC, Mitchell P, Summanen PA, et al.; FIELD study investigators. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet* 2007;370:1687–1697
58. Pop-Busui R, Evans GW, Gerstein HC, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes Care* 2010;33:1578–1584
59. Spallone V, Ziegler D, Freeman R, et al.; Toronto Consensus Panel on Diabetic Neuropathy. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. *Diabetes Metab Res Rev* 2011;27:639–653
60. Ang L, Jaiswal M, Martin C, Pop-Busui R. Glucose control and diabetic neuropathy: lessons from recent large clinical trials. *Curr Diab Rep* 2014;14:528
61. Martin CL, Albers JW, Pop-Busui R; DCCT/EDIC Research Group. Neuropathy and related findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. *Diabetes Care* 2014;37:31–38
62. Bril V, England J, Franklin GM, et al.; American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation [published correction appears in *Neurology* 2011;77:603]. *Neurology* 2011;76:1758–1765
63. Pop-Busui R, Lu J, Brooks MM, et al.; BARI 2D Study Group. Impact of glycemic control strategies on the progression of diabetic peripheral neuropathy in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) cohort. *Diabetes Care* 2013;36:3208–3215
64. Martin CL, Albers J, Herman WH, et al.; DCCT/EDIC Research Group. Neuropathy among the diabetes control and complications trial cohort 8 years after trial completion. *Diabetes Care* 2006;29:340–344
65. Herman WH, Pop-Busui R, Braffett BH, et al.; DCCT/EDIC Research Group. Use of the Michigan Neuropathy Screening Instrument as a measure of distal symmetrical peripheral neuropathy in type 1 diabetes: results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications. *Diabet Med* 2012;29:937–944
66. Wile DJ, Toth C. Association of metformin, elevated homocysteine, and methylmalonic acid levels and clinically worsened diabetic peripheral neuropathy. *Diabetes Care* 2010;33:156–161
67. Freeman R. Not all neuropathy in diabetes is of diabetic etiology: differential diagnosis of diabetic neuropathy. *Curr Diab Rep* 2009;9:423–431
68. Young LH, Wackers FJT, Chyun DA, et al.; DIAD Investigators. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. *JAMA* 2009;301:1547–1555
69. Spallone V, Bellavere F, Scionti L, et al.; Diabetic Neuropathy Study Group of the Italian Society of Diabetology. Recommendations for the use of cardiovascular tests in diagnosing diabetic autonomic neuropathy. *Nutr Metab Cardiovasc Dis* 2011;21:69–78
70. Diabetes Control and Complications Trial (DCCT) Research Group. Effect of intensive diabetes treatment on nerve conduction in the Diabetes Control and Complications Trial. *Ann Neurol* 1995;38:869–880
71. CDC Study Group. The effect of intensive diabetes therapy on measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT). *Diabetologia* 1998;41:416–423
72. Albers JW, Herman WH, Pop-Busui R, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of prior intensive insulin treatment during the Diabetes Control and Complications Trial (DCCT) on peripheral neuropathy in type 1 diabetes during the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *Diabetes Care* 2010;33:1090–1096
73. Pop-Busui R, Low PA, Waberski BH, et al.; DCCT/EDIC Research Group. Effects of prior intensive insulin therapy on cardiac autonomic nervous system function in type 1 diabetes mellitus: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study (DCCT/EDIC). *Circulation* 2009;119:2886–2893
74. Callaghan BC, Little AA, Feldman EL, Hughes RAC. Enhanced glucose control for preventing and treating diabetic neuropathy. *Cochrane Database Syst Rev* 2012;6:CD007543
75. Riddle MC, Ambrosius WT, Brillon DJ, et al.; Action to Control Cardiovascular Risk in Diabetes Investigators. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. *Diabetes Care* 2010;33:983–990
76. Sadosky A, Schaefer C, Mann R, et al. Burden of illness associated with painful diabetic peripheral neuropathy among adults seeking treatment in the US: results from a retrospective chart review and cross-sectional survey. *Diabetes Metab Syndr Obes* 2013;6:79–92
77. Snedecor SJ, Sudharshan L, Cappelleri JC, Sadosky A, Mehta S, Botteman M. Systematic review and meta-analysis of pharmacological therapies for painful diabetic peripheral neuropathy. *Pain Pract* 2014;14:167–184
78. Boulton AJM, Vinik AI, Arezzo JC, et al.; American Diabetes Association. Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care* 2005;28:956–962
79. Gaede P, Vedel P, Larsen N, Jensen GVH, Parving H-H, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003;348:383–393
80. Boulton AJM, Armstrong DG, Albert SF, et al.; American Diabetes Association; American Association of Clinical Endocrinologists. Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. *Diabetes Care* 2008;31:1679–1685
81. American Diabetes Association. Peripheral arterial disease in people with diabetes. *Diabetes Care* 2003;26:3333–3341
82. Lipsky BA, Berendt AR, Cornia PB, et al.; Infectious Diseases Society of America. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis* 2012;54:e132–e173

10. Older Adults

American Diabetes Association

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Recommendations

- Older adults who are functional and cognitively intact and have significant life expectancy should receive diabetes care with goals similar to those developed for younger adults. **E**
- Glycemic goals for some older adults might reasonably be relaxed, using individual criteria, but hyperglycemia leading to symptoms or risk of acute hyperglycemic complications should be avoided in all patients. **E**
- Other cardiovascular risk factors should be treated in older adults with consideration of the time frame of benefit and the individual patient. Treatment of hypertension is indicated in virtually all older adults, and lipid-lowering and aspirin therapy may benefit those with life expectancy at least equal to the time frame of primary or secondary prevention trials. **E**
- Screening for diabetes complications should be individualized in older adults, but particular attention should be paid to complications that would lead to functional impairment. **E**
- Older adults (≥ 65 years of age) with diabetes should be considered a high-priority population for depression screening and treatment. **B**

Diabetes is an important health condition for the aging population; at least 20% of patients over the age of 65 years have diabetes, and this number is expected to grow rapidly in the coming decades. Older individuals with diabetes have higher rates of premature death, functional disability, and coexisting illnesses, such as hypertension, coronary heart disease, and stroke, than those without diabetes. Older adults with diabetes are also at a greater risk than other older adults for several common geriatric syndromes, such as polypharmacy, cognitive impairment, urinary incontinence, injurious falls, and persistent pain. Screening for diabetes complications in older adults also should be individualized. Older adults are at an increased risk for depression and should therefore be screened and treated accordingly (1). Particular attention should be paid to complications that can develop over short periods of time and/or that would significantly impair functional status, such as visual and lower-extremity complications. Please refer to the American Diabetes Association consensus report “Diabetes in Older Adults” for details (2).

The care of older adults with diabetes is complicated by their clinical and functional heterogeneity. Some older individuals developed diabetes years earlier and may 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. Some older adults with diabetes are frail and have other underlying chronic conditions, substantial diabetes-related comorbidity, or limited physical or cognitive functioning. Other older individuals with diabetes have little comorbidity and are active. Life expectancies are highly variable for this population 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 (**Table 10.1**).

TREATMENT GOALS

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

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Table 10.1—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 (mg/dL)	Bedtime glucose (mg/dL)	Blood pressure (mmHg)	Lipids
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.5%	90–130	90–150	<140/90	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%	90–150	100–180	<140/90	Statin unless contraindicated or not tolerated
Very complex/poor health (long-term care or end-stage chronic illnesses** or moderate-to-severe cognitive impairment or 2+ ADL dependencies)	Limited remaining life expectancy makes benefit uncertain	<8.5%†	100–180	110–200	<150/90	Consider likelihood of benefit with statin (secondary prevention more so than primary)

This 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.

‡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. By "multiple," we mean at least three, but many patients may have five or more (6).

**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% equates to an estimated average glucose of ~200 mg/dL. Looser glycemic targets than this may expose patients to acute risks from glycosuria, dehydration, hyperglycemic hyperosmolar syndrome, and poor wound healing.

those for younger adults with diabetes. As with all diabetic patients, diabetes self-management education and ongoing diabetes self-management support are vital components of diabetes care for older adults and their caregivers.

For patients with advanced diabetes complications, life-limiting comorbid illness, or substantial cognitive or functional impairment, it is reasonable to set less intensive glycemic target goals. 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 at a minimum should avoid these consequences.

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 the elderly (3,4). There is less evidence for lipid-lowering and aspirin therapy, although the benefits of these interventions for primary and secondary prevention are likely to apply to older adults whose life expectancies equal or exceed the time frames seen in clinical trials.

HYPOGLYCEMIA

Older adults are at a higher risk of hypoglycemia for many reasons, including insulin deficiency and progressive renal insufficiency. In addition, older adults tend to have higher rates of unidentified cognitive deficits, causing difficulty in complex self-care activities (e.g., glucose monitoring, adjusting insulin doses, etc.). These deficits have been associated with increased risk of hypoglycemia and with severe hypoglycemia linked to increased dementia. Therefore, it is important to routinely screen older adults for cognitive dysfunction and discuss findings with the

caregivers. Hypoglycemic events should be diligently monitored, and glycemic targets may need to be adjusted to accommodate for the changing needs of the older adult (2).

PHARMACOLOGICAL THERAPY

Special care is required in prescribing and monitoring pharmacological therapy in older adults. Cost may be a significant factor, especially as older adults tend to be on many medications. Metformin may be contraindicated because of renal insufficiency or significant heart failure. Thiazolidinediones, if used at all, should be used very cautiously in those with, or at risk for, congestive heart failure and have been associated with fractures. Sulfonylureas, other insulin secretagogues, and insulin can cause hypoglycemia. Insulin use requires that patients or caregivers have good visual and motor skills and cognitive ability. GLP-1 agonists and dipeptidyl peptidase-4 inhibitors have few side effects, but their costs may be a barrier to some older patients. A clinical trial, Saxagliptin Assessment of Vascular

Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53), evaluated saxagliptin (a dipeptidyl peptidase-4 inhibitor) and its impact on cardiovascular outcomes (5). Patients treated with saxagliptin were more likely to be hospitalized for heart failure than were those given a placebo (3.5% vs. 2.8%, respectively, according to 2-year Kaplan-Meier estimates; hazard ratio 1.27 [95% CI 1.07–1.51]; $P = 0.007$).

References

1. Kimbro LB, Mangione CM, Steers WN, et al. Depression and all-cause mortality in persons with diabetes mellitus: are older adults at higher risk? Results from the Translating Research Into Action for Diabetes Study. *J Am Geriatr Soc* 2014; 62:1017–1022
2. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. *Diabetes Care* 2012;35:2650–2664
3. Beckett NS, Peters R, Fletcher AE, et al.; HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008;358:1887–1898
4. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014;311:507–520
5. Scirica BM, Bhatt DL, Braunwald E, et al.; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;369:1317–1326
6. Laiteerapong N, Iveniuk J, John PM, Laumann EO, Huang ES. Classification of older adults who have diabetes by comorbid conditions, United States, 2005-2006. *Prev Chronic Dis* 2012;9:E100

11. Children and Adolescents

American Diabetes Association

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TYPE 1 DIABETES

Three-quarters of all cases of type 1 diabetes are diagnosed in individuals <18 years of age. 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 sexual maturity and physical growth, ability to provide self-care, supervision in child care and school, and unique neurological vulnerability to hypoglycemia and possibly hyperglycemia as well as diabetic ketoacidosis. Attention to family dynamics, developmental stages, and physiological differences related to sexual maturity are all essential in developing and implementing an optimal diabetes regimen. Due to the paucity of clinical research in children, the recommendations for children and adolescents 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 statement “Care of Children and Adolescents With Type 1 Diabetes” (1) and have been updated in the recently published ADA position statement “Type 1 Diabetes Through the Life Span” (2).

A multidisciplinary team of specialists trained in pediatric diabetes management and sensitive to the challenges of children and adolescents with type 1 diabetes should provide care for this population. It is essential that diabetes self-management education (DSME) and support (DSMS), medical nutrition therapy (MNT), and psychosocial support be provided at diagnosis and regularly thereafter by individuals experienced with the educational, nutritional, behavioral, and emotional needs of the growing child and family. The balance between adult supervision and self-care should be defined at the first interaction and reevaluated at each clinic visit. This relationship will evolve as the child reaches physical, psychological, and emotional maturity.

Glycemic Control

Recommendation

- An A1C goal of <7.5% is recommended across all pediatric age-groups. **E**

Current standards for diabetes management reflect the need to lower glucose as safely as possible. This should be done with stepwise goals. Special consideration should be given to the unique risks of hypoglycemia in young children (aged <6 years), as they are often unable to recognize, articulate, and/or manage their hypoglycemic symptoms. This “hypoglycemia unawareness” should be considered when establishing individualized glycemic targets.

Although it was previously thought that young children were at risk for cognitive impairment after episodes of severe hypoglycemia, current data have not confirmed this (3–5). Furthermore, new therapeutic modalities, such as rapid- and long-acting insulin analogs, technological advances (e.g., continuous glucose monitors, low glucose suspend insulin pumps), and education, may mitigate the incidence of severe hypoglycemia (6). The Diabetes Control and Complications Trial (DCCT) 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 and insulin pumps in youth from infancy through adolescence has been associated with more children reaching the blood glucose targets set by the ADA (7–9) in those families in which both 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 compelling motivation for lowering glycemic targets (10).

In selecting glycemic goals, the long-term health benefits of achieving a lower A1C should be balanced against the risks of hypoglycemia and the developmental burdens

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of intensive regimens in children and youth. In addition, achieving lower A1C levels is more likely to be related to setting lower A1C targets (11). A1C goals are presented in **Table 11.1**.

Autoimmune Conditions

Recommendation

- Assess for the presence of additional autoimmune conditions at diagnosis and if symptoms develop. **E**

Because of the increased frequency of other autoimmune diseases in type 1 diabetes, screening for thyroid dysfunction, vitamin B₁₂ deficiency (due to autoimmune gastritis), and celiac disease should be considered based on signs and symptoms. Periodic screening in asymptomatic individuals has been recommended, but the effectiveness and optimal frequency are unclear.

Although less common than celiac disease and thyroid dysfunction, there are other autoimmune conditions that occur more commonly in type 1 diabetes, such as Addison’s disease (primary adrenal insufficiency), autoimmune hepatitis, dermatomyositis, myasthenia gravis, etc., which should be assessed and monitored as clinically indicated.

Celiac Disease

Recommendations

- Consider screening children with type 1 diabetes for celiac disease by measuring tissue transglutaminase or deamidated gliadin antibodies, with documentation of normal total serum IgA levels, soon after the diagnosis of diabetes. **E**
- Consider screening in children with a positive family history of celiac disease, growth failure, failure to gain weight, weight loss, diarrhea, flatulence, abdominal pain, or signs of malabsorption or in children with

frequent unexplained hypoglycemia or deterioration in glycemic control. **E**

- Children with biopsy-confirmed celiac disease should be placed on a gluten-free diet and have 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 (1–16% of individuals compared with 0.3–1% in the general population) (12,13).

Testing for celiac disease includes measuring serum levels of IgA antitissue transglutaminase antibodies or, with IgA deficiency, screening can include measuring IgG tissue transglutaminase antibodies or IgG deamidated gliadin peptide antibodies. A small-bowel biopsy in antibody-positive children is recommended to confirm the diagnosis (14). European guidelines on screening for celiac disease in children (not specific to children with type 1 diabetes) suggested that biopsy may not be necessary in symptomatic children with high-positive antibody titers as long as further testing such as genetic or HLA testing was supportive, but that asymptomatic at-risk children should have biopsies (15).

In symptomatic children with type 1 diabetes and confirmed celiac disease, gluten-free diets reduce symptoms and rates of hypoglycemia (16). The challenging dietary restrictions associated with having both type 1 diabetes and celiac disease place a significant burden on individuals. Therefore, we recommend a biopsy confirming the diagnosis of celiac disease before endorsing significant dietary changes, especially in asymptomatic children.

Thyroid Disease

Recommendations

- Consider testing children with type 1 diabetes for antithyroid

peroxidase and antithyroglobulin antibodies soon after diagnosis. **E**

- Measuring thyroid-stimulating hormone concentrations soon after diagnosis of type 1 diabetes is reasonable. If normal, consider rechecking every 1–2 years or sooner if the patient develops symptoms of thyroid dysfunction, thyromegaly, an abnormal growth rate, or unusual glycemic variation. **E**

Autoimmune thyroid disease is the most common autoimmune disorder associated with diabetes, occurring in 17–30% of patients with type 1 diabetes (17). About one-quarter of children with type 1 diabetes have thyroid autoantibodies at the time of diagnosis (18), and the presence of thyroid autoantibodies is predictive of thyroid dysfunction—most commonly hypothyroidism, although hyperthyroidism may occur (19). Subclinical hypothyroidism may be associated with increased risk of symptomatic hypoglycemia (20) and reduced linear growth. Hyperthyroidism alters glucose metabolism, potentially resulting in deterioration of metabolic control.

Management of Cardiovascular Risk Factors

Hypertension

Recommendations

Screening

- Blood pressure should be measured at each routine visit. Children found to have high-normal blood pressure (systolic blood pressure [SBP] or diastolic blood pressure [DBP] ≥90th percentile for age, sex, and height) or hypertension (SBP or DBP ≥95th percentile for age, sex, and height) should have blood pressure confirmed on three separate days. **B**

Table 11.1—Plasma blood glucose and A1C goals for type 1 diabetes across all pediatric age-groups

Plasma blood glucose goal range			
Before meals	Bedtime/overnight	A1C	Rationale
90–130 mg/dL (5.0–7.2 mmol/L)	90–150 mg/dL (5.0–8.3 mmol/L)	<7.5%	A lower goal (<7.0%) is reasonable if it can be achieved without excessive hypoglycemia

Key concepts in setting glycemic goals:

- Goals should be *individualized*, and lower goals may be reasonable based on benefit-risk assessment.
- Blood glucose goals 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 help assess glycemia in those on basal-bolus regimens.

Treatment

- Initial treatment of high-normal blood pressure (SBP or DBP consistently ≥ 90 th percentile for age, sex, and height) includes dietary intervention and exercise, aimed at weight control and increased physical activity, if appropriate. If target blood pressure is not reached with 3–6 months of lifestyle intervention, pharmacological treatment should be considered. **E**
- Pharmacological treatment of hypertension (SBP or DBP consistently ≥ 95 th percentile for age, sex, and height) should be considered as soon as hypertension is confirmed. **E**
- ACE inhibitors or angiotensin receptor blockers (ARBs) should be considered for the initial pharmacological treatment of hypertension, following appropriate reproductive counseling due to its potential teratogenic effects. **E**
- The goal of treatment is blood pressure consistently < 90 th percentile for age, sex, and height. **E**

Blood pressure measurements should be determined correctly, using the appropriate size cuff, and with the child seated and relaxed. Hypertension should be confirmed on at least three separate days. Evaluation should proceed as clinically indicated. Treatment is generally initiated with an ACE inhibitor, but an ARB can be used if the ACE inhibitor is not tolerated (e.g., due to cough). Normal blood pressure levels for age, sex, and height and appropriate methods for measurement are available online at www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf.

Dyslipidemia

Recommendations

Testing

- Obtain a fasting lipid profile on children ≥ 2 years of age soon after the diagnosis (after glucose control has been established). **E**
- If lipids are abnormal, annual monitoring is reasonable. If LDL cholesterol values are within the accepted risk levels (< 100 mg/dL [2.6 mmol/L]), a lipid profile repeated every 5 years is reasonable. **E**

Treatment

- Initial therapy may consist of optimization of glucose control and MNT using a Step 2 American Heart Association (AHA) diet aimed at a decrease in the amount of saturated fat in the diet. **B**
- After the age of 10 years, the addition of a statin in patients who, after MNT and lifestyle changes, 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 (CVD) risk factors is reasonable. **E**
- The goal of therapy is an LDL cholesterol value < 100 mg/dL (2.6 mmol/L). **E**

Children diagnosed with type 1 diabetes have a high risk of early subclinical (21,22) and clinical (23) CVD. Although intervention data are lacking, the AHA categorizes children with type 1 diabetes in the highest tier for cardiovascular risk and recommends both lifestyle and pharmacological treatment for those with elevated LDL cholesterol levels (24,25). Initial therapy should be with a Step 2 AHA diet, which restricts saturated fat to 7% of total calories and restricts 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 (26).

For children with significant family history of CVD, the National Heart, Lung, and Blood Institute recommends a fasting lipid panel beginning at 2 years of age (27). Abnormal results from a random lipid panel should be confirmed with a fasting lipid panel. Evidence has shown that improved glucose control correlates with a more favorable lipid profile. However, improved glycemic control alone will not reverse significant dyslipidemia (28).

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, improving endothelial function, and causing regression of carotid intimal thickening (29,30). Statins are not approved for use in patients under the age of 10 years, and statin treatment should generally not be used in children with type 1 diabetes prior to this age. For post-pubertal girls, issues of pregnancy

prevention are paramount, as statins are category X in pregnancy (see Section 12. Management of Diabetes in Pregnancy for more information).

Smoking

Recommendation

- Elicit smoking history at initial and follow-up diabetes visits and discourage smoking in nonsmoking youth and encourage smoking cessation in those who smoke. **B**

The adverse health effects of smoking are well recognized with respect to future cancer and CVD risk. In youth with diabetes, it remains important to avoid additional CVD risk factors; thus, discouraging cigarette smoking, including e-cigarettes, is important as part of routine diabetes care. In younger children, it is important to assess exposure to cigarette smoke in the home due to the adverse effects of secondhand smoke and to discourage youth from adopting smoking behaviors if exposed to them in childhood. In addition, smoking has been associated with onset of albuminuria; therefore, avoiding smoking is important to prevent both microvascular and macrovascular complications (31,32).

Microvascular Complications

Nephropathy

Recommendations

Screening

- At least an annual screening for albuminuria, with a random spot urine sample for albumin-to-creatinine ratio (UACR), should be considered once the child has had diabetes for 5 years. **B**
- Measure creatinine clearance/estimated glomerular filtration rate at initial evaluation and then based on age, diabetes duration, and treatment. **E**

Treatment

- Treatment with an ACE inhibitor, titrated to normalization of albumin excretion, should be considered when elevated UACR (> 30 mg/g) is documented with at least two of three urine samples. This should be obtained over a 6-month interval following efforts to improve glycemic control and normalize blood pressure for age. **B**

Recent research demonstrates the importance of tight glycemic and blood pressure control, especially as diabetes duration increases (33). A creatinine clearance using an estimated glomerular filtration rate can be obtained with the serum creatinine, height, age, and sex of the patient (34) and should be obtained at baseline and repeated as indicated based on clinical status, age, diabetes duration, and therapies. There are ongoing clinical trials assessing the efficacy of early treatment with ACE inhibitors for persistent albuminuria (35).

Retinopathy

Recommendations

- An initial dilated and comprehensive eye examination should be considered for the child at the start of puberty or at age ≥ 10 years, whichever is earlier, once the youth has had diabetes for 3–5 years. **B**
- After the initial examination, annual routine follow-up is generally recommended. Less frequent examinations, every 2 years, may be acceptable on the advice of an eye care professional. **E**

Although retinopathy (like albuminuria) most commonly occurs after the onset of puberty and after 5–10 years of diabetes duration (36), it has been reported in prepubertal children and with diabetes duration of only 1–2 years. Referrals should be made to eye care professionals with expertise in diabetic retinopathy, an understanding of retinopathy risk in the pediatric population, and experience in counseling the pediatric patient and family on the importance of early prevention/intervention.

Neuropathy

Recommendation

- Consider an annual comprehensive foot exam for the child at the start of puberty or at age ≥ 10 years, whichever is earlier, once the youth has had type 1 diabetes for 5 years. **E**

Neuropathy rarely occurs in prepubertal children or in youth with 1–2 years of duration of diabetes (36). A comprehensive foot exam, including inspection, palpation of dorsalis pedis and posterior

tibial pulses, assessment of the presence or absence of patellar and Achilles reflexes, and determination of proprioception, vibration, and monofilament sensation, should be performed annually along with assessment of symptoms of neuropathic pain. Foot inspection can be performed at each visit as education for youth regarding the importance of foot care.

Diabetes Self-management Education and Support

Recommendation

- Youth with type 1 diabetes and parents/caregivers (for patients aged < 18 years) should receive culturally sensitive and developmentally appropriate individualized DSME and DSMS according to national standards when their diabetes is diagnosed and routinely thereafter. **B**

No matter how sound the medical regimen, it can only be as good as the ability of the family and/or individual to implement it. Family involvement remains an important component of optimal diabetes management throughout childhood and adolescence. Health care providers who care for children and adolescents, therefore, 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. DSME and DSMS are activities that require ongoing reassessment, especially as the youth grows, develops, and acquires need for greater self-care skills. In addition, it may be necessary to assess the educational needs and skills of day care providers, school nurses, or school personnel who may participate in the care of the young child with diabetes (37).

School and Child Care

As a large portion of a child's day is spent in school, close communication with and cooperation of school or day care personnel is essential for optimal diabetes management, safety, and maximal academic opportunities. Please refer to the ADA position statements "Diabetes Care in the School and Day Care Setting" (38)

and "Care of Young Children With Diabetes in the Child Care Setting" (39) for additional details.

Transition From Pediatric to Adult Care

Recommendations

- As teens transition into emerging adulthood, health care providers and families must recognize their many vulnerabilities **B** and prepare the developing teen, beginning in early to mid-adolescence and at least 1 year prior to the transition. **E**
- Both pediatricians and adult health care providers should assist in providing support and links to resources for the teen and emerging adult. **B**

Care and close supervision of diabetes management are increasingly shifted from parents and other adults to the youth with diabetes throughout childhood and adolescence. However, the shift from pediatrics to adult health care providers often occurs very abruptly as the older teen enters the next developmental stage referred to as emerging adulthood (40), 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' home and must become fully responsible for their diabetes care. Their new responsibilities include the many aspects of managing self-care, making medical appointments, and financing health care, once they are no longer covered under their parents' health insurance (although ongoing coverage until age 26 years is possible with recent U.S. health care reform). In addition to lapses in health care, this is also a period of deterioration in glycemic control; increased occurrence of acute complications and psychosocial, emotional, and behavioral issues; and emergence of chronic complications (41–44).

Although scientific evidence continues to be limited, it is clear that comprehensive and coordinated planning, beginning early and with ongoing attention, facilitates a seamless transition from pediatric to adult health care (41,42). Transition planning should begin in early adolescence. Even after the transition to adult care is made, support and reinforcement are recommended.

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” (42).

The National Diabetes Education Program (NDEP) has materials available to facilitate the transition process (<http://ndep.nih.gov/transitions>), and the Endocrine Society in collaboration with ADA and other organizations has developed transition tools for clinicians and youth and families (http://www.endo-society.org/clinicalpractice/transition_of_care.cfm).

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.

The Centers for Disease Control and Prevention recently published projections for type 2 diabetes prevalence using the SEARCH database. Assuming a 2.3% annual increase, the prevalence of type 2 diabetes in those under 20 years of age will quadruple in 40 years (45,46). Given the current obesity epidemic, distinguishing between type 1 and type 2 diabetes in children can be difficult. For example, autoantibodies and ketosis may be present in patients with features of type 2 diabetes (including obesity and acanthosis nigricans). Nevertheless, accurate diagnosis is critical as treatment regimens, educational approaches, dietary counsel, and outcomes will differ markedly between the two diagnoses.

Significant comorbidities may already be present at the time of a type 2 diabetes diagnosis (47). It is recommended that blood pressure measurement, a fasting lipid panel, assessment for albumin excretion, and dilated eye examination be performed at diagnosis. Thereafter, screening guidelines and treatment recommendations for hypertension, dyslipidemia, albumin excretion, and retinopathy in youth with type 2 diabetes are similar to those for youth with type 1 diabetes. Additional problems that may need to be addressed include polycystic ovary disease and the various comorbidities associated with pediatric obesity, such as sleep apnea, hepatic steatosis, orthopedic complications, and psychosocial concerns. The

ADA consensus report “Type 2 Diabetes in Children and Adolescents” (48) provides guidance on the prevention, screening, and treatment of type 2 diabetes and its comorbidities in young people.

PSYCHOSOCIAL ISSUES

Recommendations

- At diagnosis and during routine follow-up care, assess psychosocial issues and family stresses that could impact adherence with diabetes management and provide appropriate referrals to trained mental health professionals, preferably experienced in childhood diabetes. **E**
- 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 nonadherence and deterioration in glycemic control. **B**

Diabetes management throughout childhood and adolescence places substantial burdens on the youth and family, necessitating ongoing assessment of psychosocial issues and distress during routine diabetes visits (49–51). Further, 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 prevent deterioration in glycemic control (52,53). In addition, 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 negotiate a plan for resolution or refer to an appropriate mental health specialist (54).

Screening for psychosocial distress and mental health problems is an important component of ongoing care. 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 as well as eating disorders, and symptoms of depression (55). Consider screening for depression and

disordered eating behaviors using available screening tools, and, with respect to disordered eating, it is important to recognize the unique and dangerous disordered eating behavior of insulin omission for weight control in type 1 diabetes (49,56). 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 nonadherence, suboptimal glycemic control, reduced quality of life, and higher rates of acute and chronic diabetes complications.

References

1. Silverstein J, Klingensmith G, Copeland K, et al. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. *Diabetes Care* 2005;28:186–212
2. Chiang JL, Kirkman MS, Laffel LMB, Peters AL; Type 1 Diabetes Sourcebook Authors. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. *Diabetes Care* 2014;37:2034–2054
3. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013;36:1384–1395
4. Wysocki T, Harris MA, Mauras N, et al. Absence of adverse effects of severe hypoglycemia on cognitive function in school-aged children with diabetes over 18 months. *Diabetes Care* 2003;26:1100–1105
5. Blasetti A, Chiuri RM, Tocco AM, et al. The effect of recurrent severe hypoglycemia on cognitive performance in children with type 1 diabetes: a meta-analysis. *J Child Neurol* 2011;26:1383–1391
6. Cooper MN, O’Connell SM, Davis EA, Jones TW. A population-based study of risk factors for severe hypoglycaemia in a contemporary cohort of childhood-onset type 1 diabetes. *Diabetologia* 2013;56:2164–2170
7. Zuidwijk CS, Cuerden M, Mahmud FH. Social determinants of health on glycemic control in pediatric type 1 diabetes. *J Pediatr* 2013;162:730–735
8. Nimri R, Weintrob N, Benzaquen H, Ofan R, Fayman G, Phillip M. Insulin pump therapy in youth with type 1 diabetes: a retrospective paired study. *Pediatrics* 2006;117:2126–2131
9. Doyle EA, Weinzimer SA, Steffen AT, Ahern JAH, Vincent M, Tamborlane WVA. A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine. *Diabetes Care* 2004;27:1554–1558
10. Barnea-Goraly N, Raman M, Mazaika P, et al.; Diabetes Research in Children Network (DirecNet). Alterations in white matter structure in young children with type 1 diabetes. *Diabetes Care* 2014;37:332–340

11. Maahs DM, Hermann JM, DuBose SN, et al.; DPV Initiative; T1D Exchange Clinic Network. Contrasting the clinical care and outcomes of 2,622 children with type 1 diabetes less than 6 years of age in the United States T1D Exchange and German/Austrian DPV registries. *Diabetologia* 2014;57:1578–1585
12. Holmes GKT. Screening for coeliac disease in type 1 diabetes. *Arch Dis Child* 2002;87:495–498
13. Rewers M, Liu E, Simmons J, Redondo MJ, Hoffenberg EJ. Celiac disease associated with type 1 diabetes mellitus. *Endocrinol Metab Clin North Am* 2004;33:197–214
14. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA; American College of Gastroenterology. ACG clinical guidelines: diagnosis and management of celiac disease. *Am J Gastroenterol* 2013;108:656–676
15. Husby S, Koletzko S, Korponay-Szabó IR, et al.; ESPGHAN Working Group on Coeliac Disease Diagnosis; ESPGHAN Gastroenterology Committee; European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr* 2012;54:136–160
16. Abid N, McGlone O, Cardwell C, McCallion W, Carson D. Clinical and metabolic effects of gluten free diet in children with type 1 diabetes and coeliac disease. *Pediatr Diabetes* 2011;12:322–325
17. Roldán MB, Alonso M, Barrio R. Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus. *Diabetes Nutr Metab* 1999;12:27–31
18. Triolo TM, Armstrong TK, McFann K, et al. Additional autoimmune disease found in 33% of patients at type 1 diabetes onset. *Diabetes Care* 2011;34:1211–1213
19. Kordonouri O, Deiss D, Danne T, Dorow A, Bassir C, Grüters-Kieslich A. Predictivity of thyroid autoantibodies for the development of thyroid disorders in children and adolescents with type 1 diabetes. *Diabet Med* 2002;19:518–521
20. Mohn A, Di Michele S, Di Luzio R, Tumini S, Chiarelli F. The effect of subclinical hypothyroidism on metabolic control in children and adolescents with type 1 diabetes mellitus. *Diabet Med* 2002;19:70–73
21. Hörtenhuber T, Rami-Mehar B, Satler M, et al. Endothelial progenitor cells are related to glycaemic control in children with type 1 diabetes over time. *Diabetes Care* 2013;36:1647–1653
22. Haller MJ, Samyn M, Nichols WW, et al. Radial artery tonometry demonstrates arterial stiffness in children with type 1 diabetes. *Diabetes Care* 2004;27:2911–2917
23. Orchard TJ, Forrest KY-Z, Kuller LH, Becker DJ; Pittsburgh Epidemiology of Diabetes Complications Study. Lipid and blood pressure treatment goals for type 1 diabetes: 10-year incidence data from the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes Care* 2001;24:1053–1059
24. Kavey R-EW, Allada V, Daniels SR, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation* 2006;114:2710–2738
25. McCrindle BW, Urbina EM, Dennison BA, et al. Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. *Circulation* 2007;115:1948–1967
26. Salo P, Viikari J, Hämäläinen M, et al. Serum cholesterol ester fatty acids in 7- and 13-month-old children in a prospective randomized trial of a low-saturated fat, low-cholesterol diet: the STRIP baby project. Special Turku coronary Risk factor Intervention Project for children. *Acta Paediatr* 1999;88:505–512
27. National Heart, Lung, and Blood Institute. Lipids and lipoproteins. In *Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report* [Internet]. Available from <http://www.nhlbi.nih.gov/health-pro/guidelines/current/cardiovascular-health-pediatric-guidelines/summary.htm#chap9>. Accessed 17 October 2014
28. Maahs DM, Dabelea D, D'Agostino RB, et al.; SEARCH for Diabetes in Youth Study. Glucose control predicts 2-year change in lipid profile in youth with type 1 diabetes. *J Pediatr* 2013;162:101–107.e1
29. McCrindle BW, Ose L, Marais AD. Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. *J Pediatr* 2003;143:74–80
30. Wiegman A, Hutten BA, de Groot E, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA* 2004;292:331–337
31. Scott LJ, Warram JH, Hanna LS, Laffel LM, Ryan L, Krolewski AS. A nonlinear effect of hyperglycemia and current cigarette smoking are major determinants of the onset of microalbuminuria in type 1 diabetes. *Diabetes* 2001;50:2842–2849
32. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics* 2011;128(Suppl. 5):S213–S256
33. Daniels M, DuBose SN, Maahs DM, et al.; T1D Exchange Clinic Network. Factors associated with microalbuminuria in 7,549 children and adolescents with type 1 diabetes in the T1D Exchange clinic registry. *Diabetes Care* 2013;36:2639–2645
34. Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. *Clin J Am Soc Nephrol* 2009;4:1832–1843
35. Marcovecchio ML, Woodside J, Jones T, et al.; AddIT Investigators. Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AddIT): urinary screening and baseline biochemical and cardiovascular assessments. *Diabetes Care* 2014;37:805–813
36. Cho YH, Craig ME, Hing S, et al. Microvascular complications assessment in adolescents with 2- to 5-yr duration of type 1 diabetes from 1990 to 2006. *Pediatr Diabetes* 2011;12:682–689
37. Driscoll KA, Volkening LK, Haro H, et al. Are children with type 1 diabetes safe at school? Examining parent perceptions. *Pediatr Diabetes*. 30 September 2014 [Epub ahead of print]
38. American Diabetes Association. Diabetes care in the school and day care setting. *Diabetes Care* 2014;37(Suppl. 1):S91–S96
39. Siminerio LM, Albanese-O'Neill A, Chiang JL, et al. Care of young children with diabetes in the child care setting: a position statement of the American Diabetes Association. *Diabetes Care* 2014;37:2834–2842
40. Arnett JJ. Emerging adulthood. A theory of development from the late teens through the twenties. *Am Psychol* 2000;55:469–480
41. Weissberg-Benchell J, Wolpert H, Anderson BJ. Transitioning from pediatric to adult care: a new approach to the post-adolescent young person with type 1 diabetes. *Diabetes Care* 2007;30:2441–2446
42. Peters A, Laffel L; American Diabetes Association Transitions Working Group. Diabetes care for emerging adults: recommendations for transition from pediatric to adult diabetes care systems: a position statement of the American Diabetes Association, with representation by the American College of Osteopathic Family Physicians, the American Academy of Pediatrics, the American Association of Clinical Endocrinologists, the American Osteopathic Association, the Centers for Disease Control and Prevention, Children with Diabetes, The Endocrine Society, the International Society for Pediatric and Adolescent Diabetes, Juvenile Diabetes Research Foundation International, the National Diabetes Education Program, and the Pediatric Endocrine Society (formerly Lawson Wilkins Pediatric Endocrine Society). *Diabetes Care* 2011;34:2477–2485
43. Bryden KS, Peveler RC, Stein A, Neil A, Mayou RA, Dunger DB. Clinical and psychological course of diabetes from adolescence to young adulthood: a longitudinal cohort study. *Diabetes Care* 2001;24:1536–1540
44. Laing SP, Jones ME, Swerdlow AJ, Burden AC, Gatling W. Psychosocial and socioeconomic risk factors for premature death in young people with type 1 diabetes. *Diabetes Care* 2005;28:1618–1623
45. Imperatore G, Boyle JP, Thompson TJ, et al.; SEARCH for Diabetes in Youth Study Group. Projections of type 1 and type 2 diabetes burden in the U.S. population aged <20 years through 2050: dynamic modeling of incidence, mortality, and population growth. *Diabetes Care* 2012;35:2515–2520
46. Pettitt DJ, Talton J, Dabelea D, et al.; SEARCH for Diabetes in Youth Study Group. Prevalence of diabetes in U.S. youth in 2009: the SEARCH for Diabetes in Youth study. *Diabetes Care* 2014;37:402–408
47. Eppens MC, Craig ME, Cusumano J, et al. Prevalence of diabetes complications in adolescents with type 2 compared with type 1 diabetes. *Diabetes Care* 2006;29:1300–1306

48. American Diabetes Association. Type 2 diabetes in children and adolescents. *Diabetes Care* 2000;23:381–389
49. Corathers SD, Kichler J, Jones N-HY, et al. Improving depression screening for adolescents with type 1 diabetes. *Pediatrics* 2013;132:e1395–e1402
50. Hood KK, Beavers DP, Yi-Frazier J, et al. Psychosocial burden and glycemic control during the first 6 years of diabetes: results from the SEARCH for Diabetes in Youth Study. *J Adolesc Health* 2014;55:498–504
51. Ducat L, Philipson LH, Anderson BJ. The mental health comorbidities of diabetes. *JAMA* 2014;312:691–692
52. Katz ML, Volkening LK, Butler DA, Anderson BJ, Laffel LM. Family-based psychoeducation and care ambassador intervention to improve glycemic control in youth with type 1 diabetes: a randomized trial. *Pediatr Diabetes* 2014;15:142–150
53. Laffel LMB, Vangsness L, Connell A, Goebel-Fabbri A, Butler D, Anderson BJ. Impact of ambulatory, family-focused teamwork intervention on glycemic control in youth with type 1 diabetes. *J Pediatr* 2003;142:409–416
54. Anderson BJ, Vangsness L, Connell A, Butler D, Goebel-Fabbri A, Laffel LMB. Family conflict, adherence, and glycaemic control in youth with short duration type 1 diabetes. *Diabet Med* 2002;19:635–642
55. Lawrence JM, Yi-Frazier JP, Black MH, et al. Demographic and clinical correlates of diabetes-related quality of life among youth with type 1 diabetes. *J Pediatr* 2012;161:201–207.e2
56. Markowitz JT, Butler DA, Volkening LK, Antisdel JE, Anderson BJ, Laffel LMB. Brief screening tool for disordered eating in diabetes: internal consistency and external validity in a contemporary sample of pediatric patients with type 1 diabetes. *Diabetes Care* 2010;33:495–500

12. Management of Diabetes in Pregnancy

American Diabetes Association

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For guidelines related to the diagnosis of gestational diabetes mellitus (GDM), please refer to Section 2. Classification and Diagnosis of Diabetes.

Recommendations

- Provide preconception counseling that addresses the importance of tight control in reducing the risk of congenital anomalies with an emphasis on achieving A1C <7%, if this can be achieved without hypoglycemia. **B**
- Potentially teratogenic medications (ACE inhibitors, statins, etc.) should be avoided in sexually active women of childbearing age who are not using reliable contraception. **B**
- GDM should be managed first with diet and exercise, and medications should be added if needed. **A**
- Women with pregestational diabetes should have a baseline ophthalmology exam in the first trimester and then be monitored every trimester as indicated by degree of retinopathy. **B**
- Due to alterations in red blood cell turnover that lower the normal A1C level in pregnancy, the A1C target in pregnancy is <6% if this can be achieved without significant hypoglycemia. **B**
- Medications widely used in pregnancy include insulin, metformin, and glyburide; most oral agents cross the placenta or lack long-term safety data. **B**

DIABETES IN PREGNANCY

The prevalence of diabetes in pregnancy has been increasing in the U.S. The majority is GDM with the remainder divided between pregestational type 1 diabetes and type 2 diabetes. Both pregestational type 1 diabetes and type 2 diabetes confer significantly greater risk than GDM, with differences according to type as outlined below.

PRECONCEPTION COUNSELING

All women of childbearing age with diabetes should be counseled about the importance of strict glycemic control prior to conception. Observational studies show an increased risk of diabetic embryopathy, especially anencephaly, microcephaly, and congenital heart disease, that increases directly with elevations in A1C. Spontaneous abortion is also increased in the setting of uncontrolled diabetes. While observational studies are confounded by the relationship between elevated periconceptional A1C and other poor self-care behaviors, the quantity and consistency of data are convincing, and the recommendation remains to aim for an A1C <7% prior to conception to minimize risk (1,2). There are opportunities to educate adolescents of reproductive age with diabetes about the risks of unplanned pregnancies and the opportunities for healthy maternal and fetal outcomes with pregnancy planning (3).

Targeted preconception counseling visits should include routine rubella, rapid plasma reagin, hepatitis B virus, and HIV testing as well as Pap smear, cervical cultures, blood typing, and prescription of prenatal vitamins (with at least 400 μ g of folic acid). Diabetes-specific management should include A1C, thyroid-stimulating hormone, creatinine, and urine albumin-to-creatinine ratio testing; review of the medication list for potentially teratogenic drugs (i.e., ACE inhibitors, statins); and referral for an ophthalmologic exam.

Specific risks of uncontrolled diabetes include fetal anomalies, preeclampsia, macrosomia, intrauterine fetal demise, neonatal hypoglycemia, and neonatal hyperbilirubinemia, among others. In addition, diabetes in pregnancy increases the risk of obesity and type 2 diabetes in offspring later in life (4,5).

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GLYCEMIC TARGETS IN PREGNANCY

The goals for glycemic control for GDM are based on recommendations from the Fifth International Workshop-Conference on Gestational Diabetes Mellitus (6) and have the following targets for maternal capillary glucose concentrations:

- Preprandial ≤ 95 mg/dL (5.3 mmol/L) and either
- One-hour postmeal ≤ 140 mg/dL (7.8 mmol/L) or
- Two-hour postmeal ≤ 120 mg/dL (6.7 mmol/L)

For women with preexisting type 1 diabetes or type 2 diabetes who become pregnant, the following are recommended as optimal glycemic goals if they can be achieved without excessive hypoglycemia (7):

- Premeal, bedtime, and overnight glucose 60–99 mg/dL (3.3–5.4 mmol/L)
- Peak postprandial glucose 100–129 mg/dL (5.4–7.1 mmol/L)
- A1C $< 6.0\%$

Metabolic physiology of pregnancy is characterized by fasting hypoglycemia due to insulin-independent glucose uptake by the placenta, postprandial hyperglycemia, and carbohydrate intolerance as a result of diabetogenic placental hormones. In addition, insulin resistance increases exponentially during the second trimester and levels off toward the end of the third trimester.

Reflecting this physiology, pre- and postprandial monitoring of blood glucose is recommended to achieve metabolic control. The American College of Obstetricians and Gynecologists (ACOG) recommends the following targets: fasting < 90 mg/dL, preprandial < 105 mg/dL, 1-h postprandial < 130 – 140 mg/dL, and 2-h postprandial < 120 mg/dL. If women cannot achieve these targets without significant hypoglycemia, the American Diabetes Association (ADA) suggests consideration of slightly higher targets: fasting < 105 mg/dL, 1-h postprandial < 155 mg/dL, and 2-h postprandial < 130 mg/dL. Until harmonization of these guidelines is achieved, the ADA recommends setting targets based on clinical experience, individualizing care, as needed.

Due to increases in red blood cell turnover associated with pregnancy, A1C levels fall during pregnancy. Additionally, as A1C represents an average, it may not fully capture physiologically relevant glycemic parameters in pregnancy. A1C should be used as a secondary measure, next to self-monitoring of blood glucose. The recommended A1C target in pregnancy is $< 6\%$ if this can be achieved without hypoglycemia. Given the alteration in red blood cell kinetics during pregnancy, A1C levels may need to be monitored more frequently than usual (e.g., monthly).

PREGNANCY AND ANTIHYPERTENSIVE DRUGS

In a pregnancy complicated by diabetes and chronic hypertension, target blood pressure goals of systolic blood pressure 110–129 mmHg and diastolic blood pressure 65–79 mmHg are reasonable, as they contribute to improved long-term maternal health. Lower blood pressure levels may be associated with impaired fetal growth. During pregnancy, treatment with ACE inhibitors and angiotensin receptor blockers is contraindicated because they may cause fetal damage. Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, diltiazem, clonidine, and prazosin. Chronic diuretic use during pregnancy has been associated with restricted maternal plasma volume, which may reduce uteroplacental perfusion (8).

MANAGEMENT OF GESTATIONAL DIABETES MELLITUS

As highlighted in Section 2. Classification and Diagnosis of Diabetes, GDM is characterized by increased risk of macrosomia and birth complications, without a risk threshold (9). Treatment starts with medical nutrition therapy, exercise, and glucose monitoring aiming for the targets described previously. A total of 70 to 85% of women diagnosed with GDM under older criteria can control GDM with lifestyle modification alone; it is anticipated that this number will increase using the lower International Association of the Diabetes and Pregnancy Study Groups (IADPSG) thresholds. Treatment has been demonstrated to improve perinatal outcomes in randomized studies and in a U.S. Preventive Services Task Force review (10). Historically, insulin has been

the recommended treatment for GDM in the U.S. Randomized controlled trials support the efficacy and short-term safety of glyburide (11) (pregnancy category B) and metformin (12,13) (pregnancy category B) for the treatment of GDM. However, both agents cross the placenta, and long-term safety data are not available (14). Insulin also may be used and should follow the guidelines below.

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

Insulin Use in Pregnancy

Insulin is the preferred agent for management of diabetes in pregnancy because of the lack of long-term safety data for noninsulin agents. The physiology of pregnancy requires frequent titration of insulin to match changing requirements. In the first trimester, there is often a decrease in total daily dose of insulin. In the second trimester, rapidly increasing insulin resistance requires weekly or biweekly increase in insulin dose to achieve glycemic targets. In general, a small proportion of the total daily dose should be given as basal insulin and a greater proportion as prandial insulin. Due to the complexity of insulin management in pregnancy, referral to a specialized center is recommended if this resource is available. All insulins are pregnancy category B except for glargine and glulisine, which are labeled C.

Concerns Related to Type 1 Diabetes in Pregnancy

Women with type 1 diabetes have an increased risk of hypoglycemia in the first trimester. Frequent hypoglycemia can be associated with intrauterine growth restriction. In addition, rapid implementation of tight glycemic control in the setting of retinopathy is associated with worsening of retinopathy (15). Insulin resistance drops rapidly with delivery of the placenta, and women become very insulin sensitive, requiring much less insulin than in the prepartum period.

Concerns Related to Type 2 Diabetes in Pregnancy

Pregestational 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. Glycemic control is often easier to achieve in type 2 diabetes than in type 1 diabetes, but hypertension and other comorbidities often render pregestational type 2 diabetes as high or higher risk than pregestational type 1 diabetes (16,17).

POSTPARTUM CARE

Lactation

All women should be supported in attempts to nurse their babies, given immediate nutritional and immunological benefits of breastfeeding for the baby; there may also be a longer-term metabolic benefit to both mother (18) and offspring (19), though data are mixed.

Gestational Diabetes Mellitus

Because GDM may represent preexisting undiagnosed type 2 diabetes, women with GDM should be screened for persistent diabetes or prediabetes at 6–12 weeks postpartum using nonpregnancy criteria and every 1–3 years thereafter depending on other risk factors. Women with a history of GDM have a greatly increased risk of conversion to type 2 diabetes over time and not solely within the 6–12 weeks' postpartum time frame (20). In the prospective Nurses' Health Study II (21), subsequent diabetes risk after a history of GDM was significantly lower in women who followed healthy eating patterns. 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 (22) and earlier progression to type 2 diabetes. Both metformin and intensive lifestyle intervention prevent or delay progression to diabetes in women with a history of GDM. Of women with a history of GDM and impaired glucose tolerance, only 5–6 individuals need to be treated with either intervention to prevent one case of diabetes over 3 years (23).

Type 1 Diabetes

Insulin sensitivity increases in the immediate postpartum period and then returns to normal over the following 1–2 weeks,

and many women will require significantly less insulin at this time than during the prepartum period. Breastfeeding may cause hypoglycemia, which may be ameliorated by consuming a snack (such as milk) prior to nursing. Diabetes self-management often suffers in the postpartum period.

Type 2 Diabetes

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.

Contraception

All women of childbearing age, including those who are postpartum, should have contraception options reviewed at regular intervals.

References

- Guerin A, Nisenbaum R, Ray JG. Use of maternal GHb concentration to estimate the risk of congenital anomalies in the offspring of women with prepregnancy diabetes. *Diabetes Care* 2007;30:1920–1925
- Jensen DM, Korsholm L, Ovesen P, et al. Peri-conceptual A1C and risk of serious adverse pregnancy outcome in 933 women with type 1 diabetes. *Diabetes Care* 2009;32:1046–1048
- Charron-Prochownik D, Sereika SM, Becker D, et al. Long-term effects of the booster-enhanced READY-Girls preconception counseling program on intentions and behaviors for family planning in teens with diabetes. *Diabetes Care* 2013;36:3870–3874
- Holmes VA, Young IS, Patterson CC, et al.; Diabetes and Pre-eclampsia Intervention Trial Study Group. Optimal glycemic control, pre-eclampsia, and gestational hypertension in women with type 1 diabetes in the diabetes and pre-eclampsia intervention trial. *Diabetes Care* 2011;34:1683–1688
- Dabelea D, Hanson RL, Lindsay RS, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. *Diabetes* 2000;49:2208–2211
- Metzger BE, Buchanan TA, Coustan DR, et al. Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care* 2007;30(Suppl. 2):S251–S260
- Kitzmillier JL, Block JM, Brown FM, et al. Managing preexisting diabetes for pregnancy: summary of evidence and consensus recommendations for care. *Diabetes Care* 2008;31:1060–1079
- Sibai BM. Treatment of hypertension in pregnant women. *N Engl J Med* 1996;335:257–265

- Metzger BE, Lowe LP, Dyer AR, et al.; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008;358:1991–2002
- Hartling L, Dryden DM, Guthrie A, Muise M, Vandermeer B, Donovan L. Benefits and harms of treating gestational diabetes mellitus: a systematic review and meta-analysis for the U.S. Preventive Services Task Force and the National Institutes of Health Office of Medical Applications of Research. *Ann Intern Med* 2013;159:123–129
- Langer O, Conway DL, Berkus MD, Xenakis EM-J, Gonzales O. A comparison of glyburide and insulin in women with gestational diabetes mellitus. *N Engl J Med* 2000;343:1134–1138
- Rowan JA, Hague WM, Gao W, Battin MR, Moore MP; MiG Trial Investigators. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med* 2008;358:2003–2015
- Gui J, Liu Q, Feng L. Metformin vs insulin in the management of gestational diabetes: a meta-analysis. *PLoS One* 2013;8:e64585
- Coustan DR. Pharmacological management of gestational diabetes: an overview. *Diabetes Care* 2007;30(Suppl. 2):S206–S208
- Chew EY, Mills JL, Metzger BE, et al.; National Institute of Child Health and Human Development Diabetes in Early Pregnancy Study. Metabolic control and progression of retinopathy: the Diabetes in Early Pregnancy Study. *Diabetes Care* 1995;18:631–637
- Clausen TD, Mathiesen E, Ekbom P, Hellmuth E, Mandrup-Poulsen T, Damm P. Poor pregnancy outcome in women with type 2 diabetes. *Diabetes Care* 2005;28:323–328
- Cundy T, Gamble G, Neale L, et al. Differing causes of pregnancy loss in type 1 and type 2 diabetes. *Diabetes Care* 2007;30:2603–2607
- Stuebe AM, Rich-Edwards JW, Willett WC, Manson JE, Michels KB. Duration of lactation and incidence of type 2 diabetes. *JAMA* 2005;294:2601–2610
- Pereira PF, Alfenas R de CG, Araújo RMA. Does breastfeeding influence the risk of developing diabetes mellitus in children? A review of current evidence. *J Pediatr (Rio J)* 2014;90:7–15
- Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes Care* 2002;25:1862–1868
- Tobias DK, Hu FB, Chavarro J, Rosner B, Mozaffarian D, Zhang C. Healthful dietary patterns and type 2 diabetes mellitus risk among women with a history of gestational diabetes mellitus. *Arch Intern Med* 2012;172:1566–1572
- Villamor E, Cnattingius S. Interpregnancy weight change and risk of adverse pregnancy outcomes: a population-based study. *Lancet* 2006;368:1164–1170
- Ratner RE, Christophi CA, Metzger BE, et al.; Diabetes Prevention Program Research Group. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. *J Clin Endocrinol Metab* 2008;93:4774–4779

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American Diabetes Association

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Recommendations

- Diabetes discharge planning should start at hospital admission, and clear diabetes management instructions should be provided at discharge. **E**
- The sole use of sliding scale insulin (SSI) in the inpatient hospital setting is strongly discouraged. **A**
- All patients with diabetes admitted to the hospital should have their diabetes type clearly identified in the medical record. **E**

Critically Ill Patients

- Insulin therapy should be initiated for treatment of persistent hyperglycemia starting at a threshold of no greater than 180 mg/dL (10 mmol/L). Once insulin therapy is started, a glucose range of 140–180 mg/dL (7.8–10 mmol/L) is recommended for the majority of critically ill patients. **A**
- More stringent goals, such as 110–140 mg/dL (6.1–7.8 mmol/L), may be appropriate for selected patients, as long as this can be achieved without significant hypoglycemia. **C**
- Critically ill patients require an intravenous insulin protocol that has demonstrated efficacy and safety in achieving the desired glucose range without increasing risk for severe hypoglycemia. **E**

Noncritically Ill Patients

- If treated with insulin, generally premeal blood glucose targets of <140 mg/dL (7.8 mmol/L) with random blood glucose <180 mg/dL (10.0 mmol/L) are reasonable, provided these targets can be safely achieved. More stringent targets may be appropriate in stable patients with previous tight glycemic control. Less stringent targets may be appropriate in those with severe comorbidities. **C**
- A basal plus correction insulin regimen is the preferred treatment for patients with poor oral intake or who are taking nothing by mouth (NPO). An insulin regimen with basal, nutritional, and correction components is the preferred treatment for patients with good nutritional intake. **A**
- 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**
- Consider obtaining an A1C in patients with diabetes admitted to the hospital if the result of testing in the previous 3 months is not available. **E**
- Consider obtaining an A1C in patients with risk factors for undiagnosed diabetes who exhibit hyperglycemia in the hospital. **E**
- Patients with hyperglycemia in the hospital who do not have a prior diagnosis of diabetes should have appropriate follow-up testing and care documented at discharge. **E**

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HYPERGLYCEMIA IN THE HOSPITAL

Hyperglycemia in the hospital can reflect previously known or previously undiagnosed diabetes or may be hospital related. The difficulty distinguishing between the second and third categories during the hospitalization may be overcome by measuring A1C, as long as conditions interfering with A1C equilibrium (such as hemolysis, blood transfusion, blood loss, or erythropoietin therapy) have not occurred. A1C values $\geq 6.5\%$ in undiagnosed patients suggest that diabetes preceded hospitalization (1). Hyperglycemia management in the hospital has often been considered secondary in importance to the condition that prompted admission. However, a body of literature now supports targeted glucose control in the hospital setting for improved clinical outcomes (2). Hyperglycemia in the hospital may result from stress or decompensation of type 1, type 2, or other forms of diabetes and/or may be iatrogenic due to withholding of antihyperglycemic medications or administration of hyperglycemia-provoking agents, such as glucocorticoids, vasopressors, and enteral or parenteral nutrition.

There is substantial observational evidence linking hyperglycemia in hospitalized patients (with or without diabetes) to poor outcomes. Cohort studies as well as a few early randomized controlled trials (RCTs) suggested that intensive treatment of hyperglycemia improved hospital outcomes (3,4). In general, these studies were heterogeneous in terms of patient population, blood glucose targets, insulin protocols, provision of nutritional support, and the proportion of patients receiving insulin, which limits the ability to make meaningful comparisons among them. Trials in critically ill patients have failed to show a significant improvement in mortality with intensive glycemic control or have even shown increased mortality risk (5). Moreover, RCTs have highlighted the risk of severe hypoglycemia resulting from such efforts (6–9).

The largest study to date, Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR), a multicenter, multinational RCT, compared the effect of intensive glycemic control (target 81–108 mg/dL [4.5–6.0 mmol/L];

mean blood glucose attained 115 mg/dL [6.4 mmol/L]) to standard glycemic control (target 144–180 mg/dL [8.0–10.0 mmol/L]; mean blood glucose attained 144 mg/dL [8.0 mmol/L]) on outcomes among 6,104 critically ill participants, almost all of whom required mechanical ventilation (6).

Ninety-day mortality was significantly higher in the intensive versus the conventional treatment group in both surgical and medical patients, as was mortality from cardiovascular causes. Severe hypoglycemia was also more common in the intensively treated group (6.8% vs. 0.5%; $P < 0.001$).

The study results lie in stark contrast to a 2001 single-center study that reported a 42% relative reduction in intensive care unit (ICU) mortality in critically ill surgical patients treated to a target blood glucose of 80–110 mg/dL (3). The NICE-SUGAR findings do not disprove the notion that glycemic control in the ICU is important. However, they do strongly suggest that it may not be necessary to target blood glucose values < 140 mg/dL (7.8 mmol/L) and that a highly stringent target of < 110 mg/dL (6.1 mmol/L) may actually be dangerous.

In a meta-analysis of 26 trials ($n = 13,567$), which included the NICE-SUGAR data, the pooled relative risk [RR] of death with intensive insulin therapy was 0.93 as compared with conventional therapy (95% CI 0.83–1.04) (9). Approximately half of these trials reported hypoglycemia, with a pooled RR of intensive therapy of 6.0 (95% CI 4.5–8.0). The specific ICU setting influenced the findings, with patients in surgical ICUs appearing to benefit from intensive insulin therapy (RR 0.63 [95% CI 0.44–0.91]), while those in other medical and mixed critical care settings did not. It was concluded that, overall, intensive insulin therapy increased the risk of hypoglycemia and provided no overall benefit on mortality in the critically ill, although a possible mortality benefit to patients admitted to the surgical ICU was suggested.

GLYCEMIC TARGETS IN HOSPITALIZED PATIENTS

Definition of Glucose Abnormalities in the Hospital Setting

Hyperglycemia in the hospital has been defined as any blood glucose > 140 mg/dL (7.8 mmol/L). Levels that are significantly

and persistently above this may require treatment in hospitalized patients. A1C values $\geq 6.5\%$ suggest, in undiagnosed patients, that diabetes preceded hospitalization (1). Hypoglycemia has been defined as any blood glucose < 70 mg/dL (3.9 mmol/L). This is the standard definition in outpatients and correlates with the initial threshold for the release of counterregulatory hormones. Severe hypoglycemia in hospitalized patients has been defined by many as < 40 mg/dL (2.2 mmol/L), although this is lower than the ~ 50 mg/dL (2.8 mmol/L) level at which cognitive impairment begins in normal individuals (10). Both hyperglycemia and hypoglycemia among inpatients are associated with adverse short- and long-term outcomes. Early recognition and treatment of mild to moderate hypoglycemia (40–69 mg/dL [2.2–3.8 mmol/L]) can prevent deterioration to a more severe episode with potential adverse sequelae (11).

Critically Ill Patients

Based on available evidence, for the majority of critically ill patients in the ICU setting, intravenous insulin infusion should be used to control hyperglycemia, with a starting threshold of no higher than 180 mg/dL (10.0 mmol/L). Once intravenous insulin is started, the glucose level should be maintained between 140–180 mg/dL (7.8–10.0 mmol/L). Greater benefit may be realized at the lower end of this range. Although strong evidence is lacking, lower glucose targets may be appropriate in select patients. One small study suggested that ICU patients treated to targets of 120–140 mg/dL (6.7–7.8 mmol/L) had less negative nitrogen balance than those treated to higher targets (12). However, targets < 110 mg/dL (6.1 mmol/L) are not recommended. Insulin infusion protocols with demonstrated safety and efficacy, resulting in low rates of hypoglycemia, are highly recommended (11).

Noncritically Ill Patients

With no prospective RCT data to inform specific glycemic targets in noncritically ill patients, recommendations are based on clinical experience and judgment (13). For the majority of noncritically ill patients treated with insulin, premeal glucose targets should generally be < 140 mg/dL (7.8 mmol/L) with

random blood glucose <180 mg/dL (10.0 mmol/L), as long as these targets can be safely achieved. To avoid hypoglycemia, consideration should be given to reassessing the insulin regimen if blood glucose levels fall below 100 mg/dL (5.6 mmol/L). Modifying the regimen is required when blood glucose values are <70 mg/dL (3.9 mmol/L), unless the event is easily explained by other factors (such as a missed meal). There is some evidence that systematic attention to hyperglycemia in the emergency room leads to better glycemic control in the hospital for those subsequently admitted (14).

Patients with a prior history of successful tight glycemic control in the outpatient setting who are clinically stable may be maintained with a glucose range below the aforementioned cut points. Conversely, higher glucose ranges may be acceptable in terminally ill patients or in patients with severe comorbidities, as well as in those in patient-care settings where frequent glucose monitoring or close nursing supervision is not feasible.

Clinical judgment combined with ongoing assessment of the patient's clinical status, including changes in the trajectory of glucose measures, the severity of illness, nutritional status, or concomitant medications that might affect glucose levels (e.g., glucocorticoids, octreotide), must be incorporated into the day-to-day decisions regarding insulin dosing (11).

ANTIHYPERGLYCEMIC AGENTS IN HOSPITALIZED PATIENTS

In most clinical situations in the hospital, insulin therapy is the preferred method of glycemic control (11). In the ICU, intravenous infusion is the preferred route of insulin administration. When the patient is transitioned off intravenous insulin to subcutaneous therapy, precautions should be taken to prevent hyperglycemia (15,16). Outside of critical care units, scheduled subcutaneous insulin that delivers basal, nutritional, and correction components (basal-bolus regimen) is recommended for patients with good nutritional intake. A basal plus correction insulin regimen is the preferred treatment for patients with poor oral intake or who are NPO. *SSI is strongly discouraged in hospitalized patients as the sole method of insulin treatment.*

For patients with type 1 diabetes, dosing insulin solely based on premeal glucose levels does not account for basal insulin requirements or caloric intake, increasing both hypoglycemia and hyperglycemia risks and potentially leading to diabetic ketoacidosis. It has been shown in an RCT that basal-bolus treatment improved glycemic control and reduced hospital complications compared with SSI in general surgery patients with type 2 diabetes (17). Typical dosing schemes are based on body weight, with some evidence that patients with renal insufficiency should be treated with lower doses (18). The reader is referred to publications and reviews that describe available insulin preparations and protocols and provide guidance in the use of insulin therapy in specific clinical settings, including parenteral nutrition (19), enteral tube feedings, and high-dose glucocorticoid therapy (11).

Recent studies have investigated the safety and efficacy of oral agents and injectable noninsulin therapies, such as GLP-1 analogs, in the hospital. A small study in general medicine and surgical wards showed that treatment with sitagliptin resulted in similar glycemic control as a basal-bolus regimen in patients with type 2 diabetes who had an A1C <7.5% and, in addition to a nutrition intervention, were treated with oral agents or low doses of insulin prior to hospitalization (20). Use of intravenous exenatide infusion resulted in improved glycemic control in patients admitted to a cardiac ICU (21). Further studies are needed to define the role of incretin mimetics in the inpatient management of hyperglycemia.

PREVENTING HYPOGLYCEMIA

Patients with or without diabetes may experience hypoglycemia in the hospital setting in association with altered nutritional state, heart failure, renal or liver disease, malignancy, infection, or sepsis. Additional triggering events leading to iatrogenic hypoglycemia include sudden reduction of corticosteroid dose, altered ability of the patient to report symptoms, reduced oral intake, emesis, new NPO status, inappropriate timing of short- or rapid-acting insulin in relation to meals, reduced infusion rate of intravenous dextrose, and unexpected interruption of enteral feedings or parenteral nutrition.

Despite the preventable nature of many inpatient episodes of hypoglycemia, institutions are more likely to have nursing protocols for hypoglycemia treatment than for its prevention. Tracking such episodes and analyzing their causes are important quality-improvement activities (22).

DIABETES CARE PROVIDERS IN THE HOSPITAL

Inpatient diabetes management may be effectively championed and/or provided by primary care physicians, endocrinologists, intensive care specialists, or hospitalists. Involvement of appropriately trained specialists or specialty teams may reduce length of stay, improve glycemic control, and improve outcomes (11). Standardized orders for scheduled and correction-dose insulin should be implemented, while sole reliance on an SSI regimen is strongly discouraged. As hospitals move to comply with "meaningful use" regulations for electronic health records, as mandated by the Health Information Technology for Economic and Clinical Health Act, efforts should be made to ensure that all components of structured insulin order sets are incorporated into electronic insulin order sets (23,24).

To achieve glycemic targets associated with improved hospital outcomes, hospitals will need a multidisciplinary approach to develop insulin management protocols that effectively and safely enable achievement of glycemic targets (25).

SELF-MANAGEMENT IN THE HOSPITAL

Diabetes self-management in the hospital may be appropriate for competent youth and adult patients who have a stable level of consciousness and reasonably stable daily insulin requirements, successfully conduct self-management of diabetes at home, have physical skills needed to successfully self-administer insulin and perform self-monitoring of blood glucose, have adequate oral intake, are proficient in carbohydrate counting, use multiple daily insulin injections or insulin pump therapy, and understand sick-day management. The patient and physician, in consultation with nursing staff, must agree that patient self-management is appropriate while hospitalized.

Patients who use continuous subcutaneous insulin infusion (CSII) pump therapy in the outpatient setting can be candidates for diabetes self-management in the hospital, provided that they have the mental and physical capacity to do so (11). Hospital policy and procedures delineating inpatient guidelines for CSII therapy are advisable, and availability of hospital personnel with expertise in CSII therapy is essential. It is important that nursing personnel document basal rates and bolus doses taken on a daily basis.

MEDICAL NUTRITION THERAPY IN THE HOSPITAL

The goals of medical nutrition therapy are to optimize glycemic control, provide adequate calories to meet metabolic demands, and create a discharge plan for follow-up care (2,26). The American Diabetes Association (ADA) does not endorse any single meal plan or specified percentages of macronutrients, and the term “ADA diet” should no longer be used. 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 (27). Because of the complexity of nutrition issues in the hospital, a registered dietitian, knowledgeable and skilled in medical nutrition therapy, should serve as an inpatient team member. The dietitian is responsible for integrating information about the patient’s clinical condition, meal planning, and lifestyle habits and for establishing treatment goals to determine a realistic plan for nutrition therapy (28).

BEDSIDE BLOOD GLUCOSE MONITORING

Bedside point-of-care (POC) blood glucose monitoring is used to guide insulin dosing. In the patient receiving nutrition, the timing of glucose monitoring should match carbohydrate exposure. In the patient not receiving nutrition, glucose monitoring is performed every 4–6 h (29,30). More frequent blood glucose testing ranging from every 30 min to every 2 h is required for patients on intravenous insulin infusions.

Safety standards should be established for blood glucose monitoring

that prohibit the sharing of finger-stick lancing devices, lancets, needles, and meters to reduce the risk of transmission of blood-borne diseases. Shared lancing devices carry essentially the same risk as sharing syringes and needles (31).

Accuracy of blood glucose measurements using POC meters has limitations that must be considered. Although the U.S. Food and Drug Administration currently allows a $\pm 20\%$ error for blood glucose meters, questions about the appropriateness of these criteria have been raised, especially for lower blood glucose readings (32). Glucose measures differ significantly between plasma and whole blood, terms that are often used interchangeably and can lead to misinterpretation. Most commercially available capillary blood glucose meters introduce a correction factor of ~ 1.12 to report a “plasma-adjusted” value (33).

Significant discrepancies between capillary, venous, and arterial plasma samples have been observed in patients with low or high hemoglobin concentrations, hypoperfusion, and interfering substances such as maltose (contained in immunoglobulins) (34). Analytical variability has been described with several meters (35). Increasingly, newer-generation POC blood glucose meters correct for variation in hematocrit and for interfering substances. Any glucose result that does not correlate with the patient’s status should be confirmed through conventional laboratory sampling of plasma glucose. The U.S. Food and Drug Administration has become increasingly concerned about POC blood glucose meter use in the hospital and is presently reviewing matters related to their use.

DISCHARGE PLANNING

Transition from the acute care setting is a high-risk time for all patients, not just those with diabetes or new hyperglycemia. Although there is extensive literature concerning safe transition within and from the hospital, little of it is specific to diabetes (36). Diabetes discharge planning is not a separate entity but is an important part of an overall discharge plan. As such, discharge planning begins at admission to the hospital and is updated as projected patient needs change.

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 assisted living or to home, the optimal program will need to consider the type and severity of diabetes, the effects of the patient’s illness on blood glucose levels, and the capacities and desires of the patient. Smooth transition to outpatient care should be ensured.

An outpatient follow-up visit with the primary care provider, endocrinologist, or diabetes educator within 1 month of discharge is advised for all patients having hyperglycemia in the hospital. 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 recommends that, at a minimum, discharge plans include the following:

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 physician as soon as possible after discharge.
- Appointment-keeping behavior is enhanced when the inpatient team schedules outpatient medical follow-up prior to discharge. Ideally, the inpatient care providers or case managers/discharge planners will schedule follow-up visit(s) with the appropriate professionals, including primary care provider, endocrinologist, and diabetes educator (37).

DIABETES SELF-MANAGEMENT EDUCATION

Teaching diabetes self-management to patients in hospitals is a challenging task. Patients are ill, under increased stress related to their hospitalization and diagnosis, and in an environment not conducive to learning. Ideally, people with diabetes should be taught at a time and place conducive to learning: as an outpatient in a recognized program of diabetes education. For the hospitalized patient, diabetes “survival skills” education is generally a feasible approach to provide sufficient information and training to enable safe care at home. Patients hospitalized because of a crisis related to diabetes management or poor care at home require education to prevent subsequent episodes of hospitalization. Assessing the need for a home health referral or referral to an outpatient diabetes education program should be part of discharge planning for all patients. Expanded diabetes education can be arranged in the community.

Diabetes self-management education should start upon admission or as soon as feasible, especially in those new to insulin therapy or in whom the diabetes regimen has been substantially altered during the hospitalization.

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 diagnosis of diabetes, self-monitoring of blood glucose, and explanation of home blood glucose goals
- Definition, recognition, treatment, and prevention of hyperglycemia and hypoglycemia
- Information on consistent eating patterns
- When and how to take blood glucose-lowering medications, including insulin administration (if going home on insulin)
- Sick-day management
- Proper use and disposal of needles and syringes

It is important that patients be provided with appropriate durable medical equipment, medication, supplies, and prescriptions at the time of

discharge in order to avoid a potentially dangerous hiatus in care. These supplies/prescriptions should include the following:

- Insulin (vials or pens), if needed
- Syringes or pen needles, if needed
- Oral medications, if needed
- Blood glucose meter and strips
- Lancets and lancing devices
- Urine ketone strips (type 1 diabetes)
- Glucagon emergency kit (insulin-treated patients)
- Medical alert application/charms

References

1. Saudek CD, Herman WH, Sacks DB, Bergenstal RM, Edelman D, Davidson MB. A new look at screening and diagnosing diabetes mellitus. *J Clin Endocrinol Metab* 2008;93:2447–2453
2. Clement S, Braithwaite SS, Magee MF, et al.; American Diabetes Association Diabetes in Hospitals Writing Committee. Management of diabetes and hyperglycemia in hospitals [published correction in *Diabetes Care* 2004;27:856]. *Diabetes Care* 2004;27:553–591
3. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001;345:1359–1367
4. Malmberg K, Norhammar A, Wedel H, Rydén L. Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. *Circulation* 1999;99:2626–2632
5. Finar S, Liu B, Chittock DR, et al.; NICE-SUGAR Study Investigators. Hypoglycemia and risk of death in critically ill patients. *N Engl J Med* 2012;367:1108–1118
6. Finfer S, Chittock DR, Su SY, et al.; NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009;360:1283–1297
7. Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. *Crit Care Med* 2007;35:2262–2267
8. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006;354:449–461
9. Griesdale DE, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ* 2009;180:821–827
10. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. *Diabetes Care* 2003;26:1902–1912
11. Moghissi ES, Korytkowski MT, DiNardo M, et al.; American Association of Clinical Endocrinologists; American Diabetes Association. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care* 2009;32:1119–1131
12. Hsu C-W, Sun S-F, Lin S-L, Huang H-H, Wong K-F. Moderate glucose control results in less negative nitrogen balances in medical intensive care unit patients: a randomized, controlled study. *Crit Care* 2012;16:R56
13. Umpierrez GE, Hellman R, Korytkowski MT, et al.; Endocrine Society. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2012;97:16–38
14. Bernard JB, Munoz C, Harper J, Muriello M, Rico E, Baldwin D. Treatment of inpatient hyperglycemia beginning in the emergency department: a randomized trial using insulins aspart and detemir compared with usual care. *J Hosp Med* 2011;6:279–284
15. Czosnowski QA, Swanson JM, Lobo BL, Broyles JE, Deaton PR, Finch CK. Evaluation of glycemic control following discontinuation of an intensive insulin protocol. *J Hosp Med* 2009;4:28–34
16. Shomali ME, Herr DL, Hill PC, Pehlivanova M, Sharretts JM, Magee MF. Conversion from intravenous insulin to subcutaneous insulin after cardiovascular surgery: Transition to Target Study. *Diabetes Technol Ther* 2011;13:121–126
17. Umpierrez GE, Smiley D, Jacobs S, et al. Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients with Type 2 Diabetes undergoing general surgery (RABBIT 2 Surgery). *Diabetes Care* 2011;34:256–261
18. Baldwin D, Zander J, Munoz C, et al. A randomized trial of two weight-based doses of insulin glargine and glulisine in hospitalized subjects with type 2 diabetes and renal insufficiency. *Diabetes Care* 2012;35:1970–1974
19. Pasquel FJ, Spiegelman R, McCauley M, et al. Hyperglycemia during total parenteral nutrition: an important marker of poor outcome and mortality in hospitalized patients. *Diabetes Care* 2010;33:739–741
20. Umpierrez GE, Gianchandani R, Smiley D, et al. Safety and efficacy of sitagliptin therapy for the inpatient management of general medicine and surgery patients with type 2 diabetes: a pilot, randomized, controlled study. *Diabetes Care* 2013;36:3430–3435
21. Abuannadi M, Kosiborod M, Riggs L, et al. Management of hyperglycemia with the administration of intravenous exenatide to patients in the cardiac intensive care unit. *Endocr Pract* 2013;19:81–90
22. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013;36:1384–1395
23. Schnipper JL, Liang CL, Ndumele CD, Pendergrass ML. Effects of a computerized order set on the inpatient management of hyperglycemia: a cluster-randomized controlled trial. *Endocr Pract* 2010;16:209–218
24. Wexler DJ, Shrader P, Burns SM, Cagliero E. Effectiveness of a computerized insulin order template in general medical inpatients with type 2 diabetes: a cluster randomized trial. *Diabetes Care* 2010;33:2181–2183
25. Furnary AP, Braithwaite SS. Effects of outcome on in-hospital transition from intravenous insulin infusion to subcutaneous therapy. *Am J Cardiol* 2006;98:557–564

26. Schafer RG, Bohannon B, Franz MJ, et al.; American Diabetes Association. Diabetes nutrition recommendations for health care institutions. *Diabetes Care* 2004;27(Suppl. 1):S55–S57
27. Curl M, Dinardo M, Noschese M, Korytkowski MT. Menu selection, glycaemic control and satisfaction with standard and patient-controlled consistent carbohydrate meal plans in hospitalised patients with diabetes. *Qual Saf Health Care* 2010;19:355–359
28. Evert AB, Boucher JL, Cypress M, et al. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care* 2014;37(Suppl. 1):S120–S143
29. Korytkowski MT, Salata RJ, Koerbel GL, et al. Insulin therapy and glycemic control in hospitalized patients with diabetes during enteral nutrition therapy: a randomized controlled clinical trial. *Diabetes Care* 2009;32:594–596
30. Umpierrez GE. Basal versus sliding-scale regular insulin in hospitalized patients with hyperglycemia during enteral nutrition therapy. *Diabetes Care* 2009;32:751–753
31. Klonoff DC, Perz JF. Assisted monitoring of blood glucose: special safety needs for a new paradigm in testing glucose. *J Diabetes Sci Tech* 2010;4:1027–1031
32. Vandvik PO, Lincoff AM, Gore JM, et al.; American College of Chest Physicians. Primary and secondary prevention of cardiovascular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(Suppl.):e637S–e668S
33. D’Orazio P, Burnett RW, Fogh-Andersen N, et al.; International Federation of Clinical Chemistry Scientific Division Working Group on Selective Electrodes and Point of Care Testing. Approved IFCC recommendation on reporting results for blood glucose (abbreviated). *Clin Chem* 2005;51:1573–1576
34. Dungan K, Chapman J, Braithwaite SS, Buse J. Glucose measurement: confounding issues in setting targets for inpatient management. *Diabetes Care* 2007;30:403–409
35. Boyd JC, Bruns DE. Quality specifications for glucose meters: assessment by simulation modeling of errors in insulin dose. *Clin Chem* 2001;47:209–214
36. Shepperd S, Lannin NA, Clemson LM, McCluskey A, Cameron ID, Barras SL. Discharge planning from hospital to home. *Cochrane Database Syst Rev* 2013;1:CD000313
37. Agency for Healthcare Research and Quality. AHRQ Patient Safety Network—adverse events after hospital discharge [Internet], 2014. Available from <http://psnet.ahrq.gov/primer.aspx?primerID=11>. Accessed 1 October 2014

14. Diabetes Advocacy

American Diabetes Association

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Managing the daily health demands of diabetes can be challenging. People living with diabetes should not have to face additional discrimination due to diabetes. By advocating for the rights of those with diabetes at all levels, the American Diabetes Association (ADA) can help ensure that they live a healthy and productive life. A strategic goal of the ADA is that by the end of 2015, more children and adults with diabetes will be living free from the burden of discrimination.

One tactic for achieving this goal is to implement the ADA's Standards of Medical Care through advocacy-oriented position statements. The ADA publishes evidence-based, peer-reviewed statements on topics such as diabetes and employment, diabetes and driving, and diabetes management in certain settings such as schools, child care programs, and correctional institutions. In addition to ADA's clinical position statements, these advocacy position statements are important tools in educating schools, employers, licensing agencies, policy makers, and others about the intersection of diabetes medicine and the law.

ADVOCACY POSITION STATEMENTS

Partial list, with most recent publications appearing first

Care of Young Children With Diabetes in the Child Care Setting (1)

First publication: 2014

Very young children (aged <6 years) with diabetes have legal protections and can be safely cared for by child care providers with appropriate training, access to resources, and a system of communication with parents and the child's diabetes provider. See the ADA position statement "Care of Young Children With Diabetes in the Child Care Setting" for further discussion: <http://care.diabetesjournals.org/content/37/10/2834>.

Diabetes and Driving (2)

First publication: 2012

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, which may lead to loss of employment or significant restrictions on a person's license. Presence of a medical condition that can lead to significantly impaired consciousness or cognition may lead to drivers being evaluated for fitness to drive. People with diabetes should be individually assessed by a health care professional knowledgeable in diabetes if license restrictions are being considered, and patients should be counseled about detecting and avoiding hypoglycemia while driving. See the ADA position statement "Diabetes and Driving" for further discussion: http://care.diabetesjournals.org/content/37/Supplement_1/S97.

Diabetes and Employment (3)

First publication: 1984 (revised 2009)

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. When questions arise about the medical fitness of a person with diabetes for a particular job, a health care professional with expertise in treating diabetes should perform an individualized assessment. See the ADA position statement "Diabetes and Employment" for further discussion: http://care.diabetesjournals.org/content/37/Supplement_1/S112.

Diabetes Care in the School and Day Care Setting (4)*

First publication: 1998 (revised 2008)

As a sizeable portion of a child's day is spent in school, close communication with and cooperation of school personnel are essential for optimal diabetes management, safety, and maximal academic opportunities. See the ADA position statement "Diabetes

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Care in the School and Day Care Setting” for further discussion: http://care.diabetesjournals.org/content/37/Supplement_1/S91.

*In October 2014, a separate statement on the care of young children with diabetes in the child care setting was published.

Diabetes Management in Correctional Institutions (5)

First publication: 1989 (revised 2008)

People with diabetes in correctional facilities should receive care that meets national standards. Because it is estimated

that nearly 80,000 inmates have diabetes, correctional institutions should have written policies and procedures for the management of diabetes and for training of medical and correctional staff in diabetes care practices. See the ADA position statement “Diabetes Management in Correctional Institutions” for further discussion: http://care.diabetesjournals.org/content/37/Supplement_1/S104.

References

1. Siminerio LM, Albanese-O’Neill A, Chiang JL, et al. Care of young children with diabetes in the

child care setting: a position statement of the American Diabetes Association. *Diabetes Care* 2014;37:2834–2842

2. American Diabetes Association. Diabetes and driving. *Diabetes Care* 2014;37(Suppl. 1):S97–S103

3. American Diabetes Association. Diabetes and employment. *Diabetes Care* 2014;37(Suppl. 1):S112–S117

4. American Diabetes Association. Diabetes care in the school and day care setting. *Diabetes Care* 2014;37(Suppl. 1):S91–S96

5. American Diabetes Association. Diabetes management in correctional institutions. *Diabetes Care* 2014;37(Suppl. 1):S104–S111

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