Overview of general medical care in nonpregnant adults with diabetes mellitus

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INTRODUCTION

The estimated overall prevalence of diabetes among adults in the United States varies with race/ethnicity and ranges from 6.8 to 15.3 percent [1]. The large majority of patients have type 2 diabetes. More health care resources are estimated to be spent on diabetes than any other condition [2]. Numerous factors, in addition to diabetes-associated complications, contribute to the impact of diabetes on quality of life and health care costs. Diabetes is associated with a high prevalence of depression [3] and adversely impacts employment, absenteeism, and work productivity [4,5].

This review will provide an overview of general medical management for nonpregnant adult patients with diabetes, with a particular emphasis on nonglycemic management (table 1). The approach is consistent with guidelines from the American Diabetes Association (ADA) for health maintenance in patients with diabetes, which are updated yearly [6,7]. Detailed discussions relating to screening, diagnosis, and initial evaluation of diabetes mellitus as well as management of hyperglycemia are discussed separately.

- (See "Screening for type 2 diabetes mellitus".)
- (See "Clinical presentation, diagnosis, and initial evaluation of diabetes mellitus in adults".)
- (See "Initial management of hyperglycemia in adults with type 2 diabetes mellitus".)
- (See "Management of persistent hyperglycemia in type 2 diabetes mellitus".)
- (See "Gestational diabetes mellitus: Glycemic control and maternal prognosis".)
- (See "Pregestational (preexisting) diabetes mellitus: Antenatal glycemic control".)

EVALUATION

Diabetes-related complications — Patients with diabetes require ongoing evaluation for diabetes-related complications.

- We perform a history and physical examination two to four times yearly to obtain information on nutrition, physical activity, management of diabetes and cardiovascular risk factors, and diabetes-related complications (table 1).

- We check blood pressure and visually inspect the feet at every visit, and in addition, we perform a more thorough foot examination and refer patients for a dilated eye examination, usually annually. The frequency of eye examinations may vary based on the presence and severity of eye findings and other factors.

- We measure glycated hemoglobin (A1C) every three months if A1C is not in the goal range and therapy requires adjustment. We measure A1C every six months in patients with stable glycemic control who are meeting A1C goals. We measure fasting lipids and urine albumin-to-creatinine ratio annually.

Morbidity from diabetes is a consequence of both macrovascular disease (atherosclerosis) and microvascular disease (retinopathy, nephropathy, and neuropathy). In type 2 diabetes, disease onset is often insidious, and diagnosis is therefore delayed. As a result, diabetes complications may be present at the time of diagnosis [8], and their frequency increases over time (figure 1). The development of complications can be delayed with management of hyperglycemia, hypertension, and dyslipidemia. Similarly, once present, the progression of these complications can be slowed with the same management strategies. In addition to management of hypertension, administration of an angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) and, if indicated, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, may specifically reduce progression of nephropathy. Laser therapy or intraocular injection of vascular endothelial growth factor (VEGF)-inhibiting agents can ameliorate advanced retinopathy and ameliorate vision loss. (See "Management of low density lipoprotein cholesterol (LDL-C) in the secondary prevention of cardiovascular disease" and "Diabetic retinopathy: Prevention and treatment" and "Moderately increased albuminuria (microalbuminuria) in type 1 diabetes mellitus" and "Moderately increased albuminuria (microalbuminuria) in type 2 diabetes mellitus" and "Treatment of diabetic kidney disease".)

These interventions appear to reduce the incidence of several diabetes-related complications, including myocardial infarction (MI), stroke, lower-extremity amputation, and end-stage kidney disease. In the United States, the greatest absolute declines have been reported for acute MI and stroke (between 1990 and 2010, 95.6 and 58.9 fewer cases per 10,000 persons per year for MI and stroke, respectively) [9]. Other countries have similarly reported reductions in the rate of cardiovascular complications and lower-extremity amputation [10-12]. (See 'Reducing the risk of macrovascular disease' below.)

Routine eye examination — Patients with diabetes are at increased risk for vision loss, related both to refractive errors (correctable visual impairment), cataracts and glaucoma (which are more prevalent in persons with diabetes [13,14]), and to retinopathy.

- **Visual impairment** – A study using data from the National Health and Nutrition Examination Survey (NHANES) in the United States found that 20 percent of Americans with diabetes aged 40 years and older without retinopathy (or with only mild and moderate nonproliferative diabetic retinopathy [NPDR]) had visual-related functional impairment [15]. For those with severe NPDR or proliferative diabetic retinopathy, the prevalence was 48 percent. These data indicate the need for visual acuity assessment in addition to dilated eye examinations for retinopathy to identify individuals with reduced acuity, address treatable causes, and improve quality of life.

- **Diabetic retinopathy** – Recommendations for the type and frequency of routine eye examinations vary based upon the type of diabetes mellitus, the presence of specific eye findings, and the level of risk factors, such as A1C levels (table 2) [7,16]. Serial examinations are indicated because of the increased incidence of retinopathy over time in patients with diabetes and the ability to intervene and reduce risk for vision loss with timely interventions (figure 2). Screening for diabetic retinopathy is reviewed in detail separately. (See "Diabetic retinopathy: Screening".)

  General measures to reduce risk and progression of retinopathy include good glycemic and blood pressure control. Prevention and treatment of retinopathy is reviewed separately. (See "Diabetic retinopathy: Prevention and treatment".)

Routine foot examination — The feet should be visually inspected at each routine visit to identify problems with nail care, poorly fitting footwear resulting in barotrauma, fungal infections, and callus formation that may result in more severe foot problems. A comprehensive foot examination should be performed annually on patients with diabetes to identify risk factors predictive of ulcers and amputation [7,17]. It can be accomplished in the primary care setting and should include inspection, assessment of pedal pulses, and testing for loss of protective sensation (table 3). Systematic screening examinations for neuropathic and vascular involvement of the lower extremities and careful inspection of feet may substantially reduce morbidity from foot problems. (See "Evaluation of the diabetic foot".)

Foot problems due to vascular and neurologic disease are a common and important source of morbidity. Patients who may have neuropathy (based on abnormal results from a microfilament or other test) or who have calluses or other foot deformities should be referred to clinicians with expertise in diabetic foot care (podiatrist, nurse, diabetes foot clinic, or other, depending on available local resources).

Screening for increased urinary albumin excretion — Measurement of the urine albumin-to-creatinine ratio in an untimed urinary sample is the preferred screening strategy in all patients with diabetes to detect elevation. It should be repeated yearly. Increased urinary protein excretion is the earliest clinical finding of diabetic nephropathy.

Screening for increased urinary albumin excretion can be deferred for five years after the onset of disease in patients with type 1 diabetes because it is uncommon before this time. Screening should begin at diagnosis in patients with type 2 diabetes because many have had diabetes for several years before diagnosis [7]. Abnormal results should be repeated at least two or three times for confirmation over a three- to six-month period because of the large number of false positives that can occur [18]. Fever, exercise, heart failure, and acute poor glycemic control are among the factors that can cause transient elevation in urinary albumin-to-creatinine ratio [18].

The urine albumin-to-creatinine ratio test (mg/g) gives a quantitative result that correlates with the 24-hour urine values (mg/day) over a wide range of protein excretion. The normal rate of albumin excretion is less than 30 mg/day (20 mcg/min) (calculator 1).

- Persistent urine albumin-to-creatinine ratio values between 30 and 300 mg/gram creatinine suggest that albumin excretion is between 30 and 300 mg/day. This is considered moderately increased albuminuria (historically called microalbuminuria) and is usually indicative of diabetic nephropathy (unless there is some other coexistent renal disease).

- Persistent urine albumin-to-creatinine ratio values above 300 mg/gram creatinine (or 300 mg/day if a 24-hour urine is collected) are considered to represent severely increased albuminuria (the new terminology for what was formerly called macroalbuminuria) and is also called overt proteinuria, clinical renal disease, or dipstick positive proteinuria.

The availability of effective therapy for diabetic nephropathy with ACE inhibitors, ARBs, and SGLT2 inhibitors is the rationale for yearly screening of all patients with either type 1 or type 2 diabetes for increased albumin excretion. Once a patient with diabetes is taking medication for increased urinary albumin excretion, the value of continued yearly monitoring of the urine albumin-to-creatinine ratio is uncertain [19]. The treatment of increased urinary albumin excretion and diabetic nephropathy is reviewed in detail elsewhere. (See "Moderately increased

albuminuria (microalbuminuria) in type 2 diabetes mellitus", section on 'Effect of interventions on albuminuria' and "Moderately increased albuminuria (microalbuminuria) in type 1 diabetes mellitus", section on 'Treatment' and "Treatment of diabetic kidney disease".)

Screening for coronary heart disease — We perform an annual assessment of risk criteria (blood pressure, fasting lipid profile, smoking history) to identify patients who might benefit from more intensive cardiovascular risk factor management. (See 'Blood pressure control' below and 'Dyslipidemia' below.)

We do not routinely perform exercise stress testing in asymptomatic patients with diabetes, including patients with type 2 diabetes who are at higher risk for atherosclerotic cardiovascular disease (ASCVD) than people without diabetes [20]. For sedentary adults (age >50 years) with diabetes who are beginning an exercise program, we typically obtain a resting electrocardiogram (ECG) and counsel initiation of a gentle exercise program with gradual progression as tolerated. The increased risk for asymptomatic coronary artery disease in those with diabetes and other risk factors suggests that the decision to perform stress testing prior to beginning an exercise program should be individualized, with consideration given to those at very high risk, such as patients with diabetes who also have peripheral or carotid artery disease. Despite the relatively high frequency of silent ischemia in patients with diabetes, identifying asymptomatic disease or providing early intervention beyond guideline-recommended ASCVD risk factor management has not been shown to improve outcomes in this population [20]. (See "Screening for coronary heart disease in patients with diabetes mellitus".)

The evaluation and treatment of patients with diabetes and known ASCVD is reviewed in detail elsewhere. (See "Acute myocardial infarction: Patients with diabetes mellitus" and "Coronary artery revascularization in stable patients with diabetes mellitus".)

Comorbid conditions — In addition to the coincident hypertension, obesity, dyslipidemia, and ASCVD, adults with type 2 diabetes are at risk for other comorbidities. These disorders, which may be present at diagnosis or may develop over time, include hearing impairment, sleep apnea, fatty liver disease, periodontal disease, cognitive impairment, depression, eating disorders, anxiety, and fractures [6]. For patients with signs or symptoms of these conditions, additional assessment is warranted. Annual examination by a dentist is recommended for all patients with diabetes, even those without teeth [21]. (See "Etiology of hearing loss in adults" and "Clinical presentation and diagnosis of obstructive sleep apnea in adults" and "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults" and "Overview of gingivitis and periodontitis in adults" and "Risk factors for cognitive decline and dementia" and "Screening for depression in adults" and "Bone disease in diabetes mellitus".)

Some studies suggest an increased risk of certain cancers (liver, pancreas, endometrium, colon/rectum, breast, bladder) in patients with type 2 diabetes, possibly related to the coincident obesity [22-28]. Adults with type 2 diabetes also have an increased risk of cancer mortality. In a systematic review of individual patient data from 97 prospective studies (820,900 patients), adults with diabetes compared with those without had an increased risk of death from cancer (hazard ratio [HR] 1.25, 95% CI 1.19-1.31) [29]. The increased risk of death was associated specifically with cancers of the liver, pancreas, ovary, colorectum, lung, bladder, and breast. In addition, the relative risk was substantially reduced when adjusting for A1C levels in multivariate analyses, consistent with a mediating effect of hyperglycemia on cancer risk. (See "Colorectal cancer: Epidemiology, risk factors, and protective factors" and "Epidemiology and risk factors for hepatocellular carcinoma" and "Epidemiology and risk factors of urothelial (transitional cell) carcinoma of the bladder" and "Epidemiology and nonfamilial risk factors for exocrine pancreatic cancer" and "Epidemiology, pathology, and pathogenesis of renal cell carcinoma", section on 'Diabetes mellitus'.)

Patients with diabetes should undergo recommended age- and gender-specific cancer screening [6]. (See "Overview of preventive care in adults", section on 'Cancer screening'.)

GLYCEMIC CONTROL

Blood glucose monitoring and target A1C — All patients with diabetes mellitus who use insulin and some patients who take other glucose-lowering medications that can cause hypoglycemia should self-monitor their glucose concentrations to help maintain safe, target-driven glucose control. Self-monitoring is generally unnecessary in patients who are treated with diet alone or who take oral or injectable agents that do not cause hypoglycemia. (See "Glucose monitoring in the management of nonpregnant adults with diabetes mellitus".)

A1C goals in patients with diabetes should be tailored to the individual, balancing the demonstrated benefits with regard to prevention and delay of microvascular complications (intensive glycemic management) with the risk of hypoglycemia.

- A reasonable goal of therapy is an A1C value of ≤7.0 percent (53 mmol/mol) (calculator 2) for most patients (using a Diabetes Control and Complications Trial [DCCT]/United Kingdom Prospective Diabetes Study [UKPDS]-aligned assay in which the upper limit of normal is 6.0 percent) [30]. (See "Glycemic control and vascular complications in type 2 diabetes mellitus", section on 'Choosing a glycemic target'.)

  In order to achieve this A1C goal, a fasting glucose of 80 to 130 mg/dL (4.4 to 7.2 mmol/L) and a postprandial glucose (90 to 120 minutes after a meal) less than 180 mg/dL (10 mmol/L) are generally given as targets, but higher achieved levels may suffice (table 4) [31].

- The A1C goal should be set somewhat higher (eg, <8 percent [<64 mmol/mol]) for older patients and those with comorbidities, a history of severe hypoglycemia or other significant adverse medication effects or polypharmacy, or a limited life expectancy and little likelihood of benefit from intensive therapy. (See "Treatment of type 2 diabetes mellitus in the older patient", section on 'Controlling hyperglycemia'.)

- More stringent control (A1C <6 percent [<42 mmol/mol]) is indicated during pregnancy, and individuals with type 1 diabetes may aim for A1C <6.5 percent (47.5 mmol/mol) if this can be achieved safely. (See "Pregestational (preexisting) diabetes mellitus: Antenatal glycemic control", section on 'Target A1C level' and "Glycemic control and vascular complications in type 1 diabetes mellitus", section on 'Glycemic targets'.)

- Obtain an A1C at least twice yearly in patients who are meeting treatment goals and who have stable glycemic control and quarterly in patients whose therapy has changed or requires adjustment, or who are not meeting glycemic goals.

- If interpretation of the A1C result is problematic (ie, owing to hemoglobinopathies or in the setting of altered red cell turnover [eg, hemolytic anemia], resulting in discrepancies between A1C and true mean glycemia [detected by more intensive or targeted self-monitoring of blood glucose or use of continuous glucose monitoring]), glucose testing should be used to assess degree of control. (See "Measurements of glycemic control in diabetes mellitus", section on 'Unexpected or discordant values'.)

Lifestyle intervention — There are three major components to nonpharmacologic therapy of blood glucose and overall health in type 2 diabetes (see "Initial management of hyperglycemia in adults with type 2 diabetes mellitus", section on 'Intensive lifestyle modification'):

- Dietary modification
- Exercise
- Weight reduction

In addition to improving glycemic control, lifestyle change and modest weight loss also reduce the development of obstructive sleep apnea, improve mobility and quality of life, and reduce the need for glucose-lowering and blood pressure medications [32-34]. Diet and exercise are important components of therapy in patients with type 1 diabetes. (See "Nutritional considerations in type 1 diabetes mellitus" and "Nutritional considerations in type 2 diabetes mellitus" and "Effects of exercise in adults with diabetes mellitus", section on 'A program for physical activity'.)

Bariatric surgical treatment of obese patients with diabetes results in a large degree of sustained weight loss and, in parallel, large improvements in blood glucose control, including remissions of type 2 diabetes (see "Management of persistent hyperglycemia in type 2 diabetes mellitus", section on 'Surgical treatment of obesity'). Pharmacotherapy for weight loss may also be used for patients with type 2 diabetes. (See "Obesity in adults: Drug therapy".)

Pharmacologic therapy for hyperglycemia

Type 2 diabetes – Initiating metformin early in the course of type 2 diabetes, assuming that no contraindications are present, remains the consensus recommendation. (See "Initial management of hyperglycemia in adults with type 2 diabetes mellitus".)

The therapeutic options for patients who fail initial therapy with lifestyle intervention and metformin are to add a second oral or injectable agent, including insulin (figure 3). (See "Management of persistent hyperglycemia in type 2 diabetes mellitus" and "Insulin therapy in type 2 diabetes mellitus".)

Regardless of the initial response to therapy, the natural history of most patients with type 2 diabetes is for blood glucose concentrations and A1C to rise over time (figure 4) [35,36]. The UKPDS suggested that worsening beta cell dysfunction with decreased insulin release was primarily responsible for disease progression [36]. More severe insulin resistance or decreased compliance with the dietary regimen also may contribute to progression.

- **Type 1 diabetes** – Treatment of type 1 diabetes includes the coordination of meals/diet and activity with physiologic insulin replacement, which involves the frequent monitoring of blood glucose levels. (See "Management of blood glucose in adults with type 1 diabetes mellitus", section on 'Insulin regimens'.)

REDUCING THE RISK OF MACROVASCULAR DISEASE

Prevention of cardiovascular morbidity is a major priority for patients with diabetes, especially type 2. Men and women with diabetes are at increased risk for developing and dying from atherosclerotic cardiovascular disease (ASCVD); compared with those without diabetes, men and women with diabetes have decreased life expectancy (six to eight years less) [29,37-39]. At the time of diagnosis of type 2 diabetes, many patients already have one or more risk factors for macrovascular disease (obesity, hypertension, dyslipidemia, smoking) and many have evidence of overt atherosclerosis (past myocardial infarction [MI], ischemic changes on electrocardiogram [ECG], or peripheral vascular disease).

Multifactorial risk factor reduction — Management of ASCVD risk factors, including hypertension, hypercholesterolemia, and smoking, has been shown to reduce cardiovascular mortality. Smoking cessation is essential for patients who smoke. In addition, use of aspirin (75 to 162

mg/day), and use of certain glucose-lowering medications in patients with or at high risk for ASCVD can reduce recurrent ASCVD events and mortality. (See "Initial management of hyperglycemia in adults with type 2 diabetes mellitus", section on 'Established cardiovascular or kidney disease' and "Management of persistent hyperglycemia in type 2 diabetes mellitus", section on 'Monotherapy failure'.)

The benefits of multifactorial risk factor reduction are illustrated by the following:

- In a Swedish cohort study (median follow-up 5.7 years), among nonsmoking patients with type 2 diabetes who had A1C, low-density lipoprotein (LDL) cholesterol, urinary albumin, and blood pressure within target ranges, there was little or no excess risk of death, MI, or stroke compared with the general population [40].

- In the Steno-2 trial, 160 patients with microalbuminuria were randomly assigned to either conventional therapy or an intensive therapy regimen, which included lifestyle modification, glycemic control (target A1C <6.5 percent), blood pressure control (target <140/85 mmHg for most of the study and <130/80 mmHg for the last two years), and lipid-lowering therapy, angiotensin-converting enzyme (ACE) inhibitor regardless of blood pressure, and aspirin [41]. After a mean of 7.8 years, patients on intensive therapy had a significant reduction in the primary aggregate endpoint of cardiovascular death, nonfatal MI, coronary artery bypass grafting, percutaneous coronary intervention, stroke, amputation, or peripheral vascular surgery (18 versus 38 percent, hazard ratio [HR] 0.47, 95% CI 0.22-0.74). Significant reductions were also seen in progression of nephropathy, retinopathy, and autonomic neuropathy.

  After the intervention study ended, 130 remaining patients participated in an observational follow-up study (5.5 years), during which time all participants were encouraged to follow intensive multifactorial treatment regimens, and A1C values, blood pressure, body mass index (BMI), and cholesterol levels in the two groups became similar [42]. During the entire follow-up period (13.3 years), there were fewer deaths (30 versus 50 percent) in the intensive therapy group (HR for death 0.54, 95% CI 0.32-0.89). Intensive therapy was also associated with a lower risk of cardiovascular deaths (HR 0.43, 95% CI 0.19-0.94), which was a predefined secondary endpoint. Progression of diabetic retinopathy, nephropathy, and autonomic neuropathy occurred less frequently in the intensive group. These results suggest a sustained benefit of multifactorial risk reduction.

In spite of evidence that aggressive risk factor reduction lowers the risk of both micro- and macrovascular complications in patients with diabetes, a minority of adults with diabetes achieve all of the recommended goals for A1C, blood pressure control, and management of dyslipidemia [41,43,44]. It is notable that only one patient in the observational Steno study described above reached all five treatment goals at the end of follow-up. Thus, renewed efforts to implement multifactorial risk factor reduction strategies early in the course of type 2 diabetes are necessary. (See 'Adequacy of care' below.)

Smoking cessation — A survey in the United States (2001 to 2010) found that the adjusted prevalence of cigarette smoking was lower and quit attempts higher among adults with versus without diabetes [45]. A meta-analysis of many of the cardiovascular risk reduction trials showed that cessation of smoking had a much greater benefit on survival than most other interventions [46]. These findings suggest that discontinuation of smoking is one of the most important aspects of therapy in patients with diabetes who smoke. (See "Overview of smoking cessation management in adults".)

Aspirin

Candidates — For the secondary prevention of ASCVD in patients with diabetes, we recommend aspirin (75 to 162 mg daily). For the primary prevention of ASCVD in patients with diabetes at increased cardiovascular risk (10-year risk >10 percent), we suggest aspirin (75 to 162 mg daily), although the evidence supporting this approach is weak and needs to be balanced with the increased risk of gastrointestinal bleeding. We do not routinely use aspirin for the prevention of ASCVD in adults with diabetes at low risk (10-year ASCVD risk <10 percent). (See 'Guidelines' below.)

The decision to use aspirin for the prevention of cardiovascular events in patients with diabetes should be made using shared decision-making on an individual basis, taking into account potential benefits and risks (see 'Bleeding' below). It is likely that there is some level of risk of ASCVD events that would result in a positive benefit-to-risk ratio. Large trials investigating the role of aspirin for the primary prevention of cardiovascular events in patients with diabetes have been completed or are underway [47-50].

Prevention of cardiovascular events

- **Secondary prevention** – The merits of daily aspirin therapy in patients with existing ASCVD are widely accepted. A meta-analysis from the Antithrombotic Trialists' Collaboration of randomized trials of antiplatelet therapy for the secondary prevention of ASCVD in high-risk patients showed that aspirin produced statistically significant and clinically important reductions in the risk of subsequent MI, stroke, and vascular death among a wide range of high-risk patients (acute MI or ischemic stroke, unstable angina, prior MI or stroke, peripheral artery disease, and other high-risk groups) [51]. (See "Aspirin for the secondary prevention of atherosclerotic cardiovascular disease".)

  In the subset of patients with diabetes, there was a nonsignificant, 7 percent decrease in serious cardiovascular events [51].

The use of dual antiplatelet therapy and the use of combination therapy with aspirin plus anticoagulant therapy are reviewed in detail separately. (See "Overview of the prevention of cardiovascular disease events in those with established disease (secondary prevention) or at very high risk", section on 'Adjunctive therapies'.)

- **Primary prevention** – The benefits of daily aspirin for the primary prevention of ASCVD in patients with diabetes and ASCVD risk factors (but without known ASCVD) is uncertain [52]. In a meta-analysis of 10 trials evaluating aspirin for the primary prevention of ASCVD in patients with diabetes, aspirin modestly but significantly reduced the risk of major cardiovascular events compared with placebo or no treatment (relative risk [RR] 0.90, 95% CI 0.81-0.99) [53]. Aspirin did not significantly reduce the risk of any of the individual endpoints (MI, coronary heart disease, stroke, ASCVD, or all-cause mortality). There were differences in effect according to underlying ASCVD risk, gender, and compliance.

  In a subsequent trial, 15,480 patients with diabetes (94 percent with type 2 diabetes) but no evidence of ASCVD were randomly assigned to aspirin (100 mg daily) or placebo [50]. (Participants were also randomly assigned to receive 1 gram n-3 fatty acid or placebo once daily.) The majority of patients were taking statins and antihypertensive medication. After a mean follow-up of 7.4 years, serious vascular events (a composite of MI, stroke [excluding intracranial hemorrhage], transient ischemic attack, or death from any vascular cause [except intracranial hemorrhage]) occurred in a smaller proportion of patients in the aspirin group (8.5 versus 9.6 percent, rate ratio 0.88, 95% CI 0.79-0.97). Aspirin did not significantly reduce the risk of any of the individual endpoints. The benefits of aspirin in reducing serious vascular events were offset by an approximate 1 percent absolute increased risk of bleeding, largely gastrointestinal and extracranial. (See 'Bleeding' below.)

  In exploratory analyses, the effects of aspirin on serious vascular events and on safety events did not clearly vary according to baseline patient characteristics, including group assignment to n-3 fatty acids and baseline ASCVD risk.

Bleeding — The main adverse effect of aspirin is bleeding. In the trial described above, major bleeding events (the first occurrence of a composite of intracranial hemorrhage, sight-threatening bleeding in the eye, gastrointestinal bleeding, or bleeding that resulted in hospitalization, transfusion, or fatality) occurred in a higher proportion of patients in the aspirin group (4.1 versus 3.2 percent, rate ratio 1.29, 95% CI 1.09-1.52) [50]. Aspirin did not significantly increase the risk of any of the individual endpoints. In a Japanese trial, however, there was an increase in nonfatal intracranial hemorrhage (23 versus 10 events) and subarachnoid hemorrhage (8 versus 4 events) in patients taking aspirin [54]. Extracranial hemorrhage requiring transfusion or hospitalization was also more common in the aspirin group (62 versus 34 events, HR 1.85, 95% CI 1.22-2.81).

Aspirin does not appear to increase retinal hemorrhagic complications in patients with diabetic retinopathy, even if advanced. In the Early Treatment Diabetic Retinopathy Study, patients with mild to severe nonproliferative or early proliferative diabetic retinopathy had one eye treated with scatter retinal photocoagulation. The 3711 participants were also randomly assigned to receive either aspirin (650 mg/day) or placebo. During the study, periodic fundus photography of the eyes not receiving photocoagulation detected vitreous or pre-retinal hemorrhages in 32 versus 30 percent of patients treated with aspirin or placebo, respectively [55]. Approximately 40 percent of these hemorrhages produced a loss of visual acuity to less than 20/40. However, the severity and rate of resolution of these hemorrhages were not different between the aspirin- and placebo-treated groups. Similarly, in the large trial described above (15,480 patients with diabetes), the risk of sight-threatening bleeding did not differ between the aspirin and placebo groups (0.7 and 0.8 percent, respectively, rate ratio 0.89, 95% CI 0.62-1.27) [50]. These studies, as well as a meta-analysis of other randomized clinical trials, concluded that there were no ocular contraindications to the use of aspirin (650 mg/day) in persons with diabetes who require this medicine for treatment of ASCVD or for other medical indications [55,56].

Guidelines — Based upon these data, the American Diabetes Association (ADA) recommends the following approach [20]:

- Aspirin (75 to 162 mg/day) is recommended for secondary prevention in diabetic patients with a history of MI, vascular bypass, stroke or transient ischemic attack, peripheral vascular disease, claudication, or angina.
  - Dual antiplatelet therapy (low-dose aspirin plus a P2Y12 inhibitor) is reasonable for a year after an acute coronary syndrome. Longer-term treatment should be considered for patients with prior coronary intervention, high ischemic risk, and low bleeding risk to prevent major adverse cardiovascular events.
  - Combination therapy with aspirin plus low-dose rivaroxaban should be considered for patients with stable coronary and/or peripheral artery disease and low bleeding risk to prevent major adverse limb and cardiovascular events.
- Aspirin (75 to 162 mg/day) should be considered for primary prevention in any patient with diabetes at increased cardiovascular risk (10-year risk >10 percent) after a discussion of the benefits (reduction in major adverse cardiovascular events) versus increased risk of bleeding (primarily gastrointestinal). Increased cardiovascular risk may include most men or women >50 years who have at least one additional cardiovascular risk factor (eg, cigarette smoking, hypertension, obesity, albuminuria, dyslipidemia, or a family history of coronary heart disease). The ADA recognizes that the evidence to support this recommendation is weak.

- Aspirin is not recommended for ASCVD prevention for adults with diabetes at low risk (10-year risk <5 percent), such as men or women with diabetes aged <50 years with no major additional risk factors. In this population, the potential adverse effects from bleeding likely offset the potential benefits.
- For adults <50 years with diabetes who have multiple other cardiovascular risk factors (10-year risk between 5 and 10 percent), clinical judgement and shared decision-making is required.
- Clopidogrel (75 mg/day) is recommended for patients with ASCVD and documented aspirin allergy. (See "Overview of the prevention of cardiovascular disease events in those with established disease (secondary prevention) or at very high risk", section on 'Antiplatelet therapy'.)
- Dual antiplatelet therapy is reasonable for up to one year after an acute coronary syndrome.

Blood pressure control — Hypertension is a common problem in type 1 and especially in type 2 diabetes. Early and effective treatment of high blood pressure is important, both to prevent cardiovascular disease (CVD) and to minimize the rate of progression of diabetic nephropathy and retinopathy.

The ADA recommends measuring blood pressure at every routine diabetes visit, with individualization of treatment goals. For most patients with hypertension, the ADA recommends treating to systolic and diastolic blood pressures of <140 and <90 mmHg, respectively [20]. Lower treatment targets, ie, 130/80 mmHg, may be appropriate for individuals at high risk of CVD, if they can be achieved without undue treatment burden.

The 2017 American College of Cardiology/American Heart Association (ACC/AHA) hypertension guidelines recommend a goal blood pressure in patients with diabetes mellitus of <130/80 mmHg [57,58]. The data supporting these goals and the choice of antihypertensive drugs are discussed in detail separately. (See "Goal blood pressure in adults with hypertension", section on 'Patients with diabetes mellitus' and "Treatment of hypertension in patients with diabetes mellitus", section on 'Choice of antihypertensive drug therapy' and "Treatment of diabetic kidney disease".)

Dyslipidemia — Lipid abnormalities are common in patients with diabetes mellitus and undoubtedly contribute to the increase in risk of ASCVD. The ADA recommends screening for lipid disorders at the time of diabetes diagnosis, at an initial medical evaluation, and every five years thereafter if under age 40 and more often if indicated, as is usually the case in patients age 40 and older [20].

We and others recommend lifestyle intervention (diet, weight loss, increased physical activity) to improve the lipid profile in all patients with diabetes [20,59]. The initiation of statins is based upon cardiovascular risk rather than an LDL cholesterol level. In patients **with** clinical ASCVD, statin therapy should be added to lifestyle intervention regardless of baseline lipid levels. For patients **without** clinical ASCVD, we use a risk estimator, such as the ACC/AHA risk estimator (calculator 3), to guide shared decision-making for statin use and dose. We typically administer statins to patients over age 40 years. For patients under age 40 years, statin therapy can be considered in addition to lifestyle intervention in those with multiple ASCVD risk factors.

The intensity of statin therapy can be adjusted based upon ASCVD risk, side effects, tolerability, and LDL cholesterol levels. For patients with clinical ASCVD, high-intensity statin therapy is typically added to lifestyle therapy.

The optimal therapy of dyslipidemia is discussed in detail separately. (See "Management of elevated low density lipoprotein-cholesterol (LDL-C) in primary prevention of cardiovascular disease", section on 'Use of statins' and "Management of low density lipoprotein cholesterol (LDL-C) in the secondary prevention of cardiovascular disease" and "Hypertriglyceridemia", section on 'Management'.)

Diabetes medications — Metformin does not have adverse cardiovascular effects, and it appears to decrease cardiovascular events in certain populations. In trials primarily focusing on secondary prevention of CVD in patients with type 2 diabetes, there was a reduction in CVD outcomes with some sodium-glucose co-transporter 2 (SGLT2) inhibitors and some glucagon-like peptide 1 (GLP-1) receptor agonists. Cardiovascular effects of the diabetes medications are reviewed in detail separately. (See "Metformin in the treatment of adults with type 2 diabetes mellitus", section on 'Cardiovascular effects' and "Sodium-glucose co-transporter 2 inhibitors for the treatment of hyperglycemia in type 2 diabetes mellitus", section on 'Cardiovascular effects' and "Glucagon-like peptide 1 receptor agonists for the treatment of type 2 diabetes mellitus", section on 'Cardiovascular effects'.)

OTHER ASPECTS OF HEALTH MAINTENANCE

Routine health maintenance — The potential exists for the clinician to overlook health maintenance not specifically targeted at diabetes, given the intensity and complexity of care required for prevention and treatment of complications of diabetes itself [60]. (See "Overview of preventive care in adults".)

Vaccination — Patients with diabetes mellitus should receive (table 1):

- Influenza vaccination yearly, with adults 65 years of age and older administered the high-dose vaccine. In observational studies, influenza vaccine has been shown to be similarly effective in adults <65 years of age with diabetes as in older patients with or without diabetes [61,62].
- Pneumococcal vaccination, per US Center for Disease Control and Prevention (CDC) protocol, with one pneumococcal conjugate vaccine (PCV13) in adults ≥65 years and pneumococcal polysaccharide vaccine (PPSV23) once before and once after age 65.
- Hepatitis B vaccination for unvaccinated adults younger than 60 years of age without evidence of prior infection. For older adult patients with diabetes, vaccination can be administered at the discretion of the treating clinician based upon the risk of acquiring hepatitis B virus, including the need for blood glucose monitoring, and the likelihood of an adequate immune response to vaccination. The effectiveness of the hepatitis B vaccine decreases with age [63]. This recommendation is based on outbreaks of hepatitis B in patients who were undergoing blood glucose monitoring in nursing homes or assisted-living facilities, a subsequent analysis of the risk of acquiring hepatitis B virus among all diabetics in the United States, and a cost-effectiveness analysis [64]. (See "Hepatitis B virus immunization in adults", section on 'Indications'.)
- Tetanus and diphtheria vaccinations, updated as per CDC guidelines. (See "Tetanus-diphtheria toxoid vaccination in adults".)
- Herpes zoster, recombinant vaccine, based on CDC guidelines. (See "Vaccination for the prevention of shingles (herpes zoster)".)

Women of childbearing age — Women in the reproductive years should receive counseling at regular intervals regarding contraception and pregnancy planning, including the need for tight glycemic control prior to pregnancy and the risk of pregnancy to the woman and fetus.

- For women with diabetes who are contemplating pregnancy, prepregnancy counseling is important (table 5). Healthy pregnancy requires virtually normal blood glucose levels. Prior to pregnancy, glycemic control should be optimized and both angiotensin-converting enzyme (ACE) inhibitor and statin medications should be discontinued. (See "Pregestational (preexisting) diabetes: Preconception counseling, evaluation, and management", section on 'Glycemic control'.)
- For women who do not wish to become pregnant, the most reliable method of contraception should be used, when not contraindicated by other health concerns, because of the risk of hyperglycemia to the developing fetus. American Diabetes Association (ADA) guidelines state that the selection of a contraceptive method for an individual patient should use the same guidelines that apply to women without diabetes [65]. Types of hormonal and nonhormonal contraception and important factors in choosing a contraceptive method are reviewed separately. (See "Pregestational (preexisting) diabetes: Preconception counseling, evaluation, and management", section on 'Contraception and timing of pregnancy' and "Contraception: Counseling and selection" and "Combined estrogen-progestin contraception: Side effects and health concerns".)

ADEQUACY OF CARE

Despite extensive data suggesting large benefits with preventive and treatment strategies and despite increasing media attention, many patients with diabetes are not receiving recommended levels of health care, including older patients [66-68]; patients with limited proficiency in English, financial hardships, or complex comorbidities; and those from countries with fewer resources to manage diabetes [69-71]. Even when recommended clinical data are obtained, rates of medication adjustment to address abnormal results are low [72-74].

There are several reasons for the large discrepancy between what should be done and what is being done, including clinical inertia and lack of an organized system for care [75-78]. Several approaches have been tried in order to improve the care of patients with diabetes. These include the following:

- "Diabetes mini-clinics" [79,80]
- Better organization and delivery of patient education [81,82]
- Structured behavioral intervention [83,84]
- Management by nurse specialists under the supervision of a diabetologist [85-87]
- Multidisciplinary disease management programs [88-90]
- Group medical visits [91,92]
- Telecare intervention via web-based systems or mobile devices [93-95]

The growing use of electronic health records with embedded guidelines and reminders at the point of care about appropriate interventions may make it easier to deliver more appropriate diabetes care in a number of settings. Processes of care (performance of retinal examination, foot examination, A1C measurements, lipid testing, nephropathy screening, flu vaccination, aspirin therapy) may be more readily improved by disease management interventions than intermediate outcomes (blood pressure control, lipid control, or A1C level) [90].

INDICATIONS FOR REFERRAL

Intensive insulin therapy is recommended for the majority of patients with type 1 diabetes, and therefore, patients with type 1 diabetes should be referred to an endocrinologist for management of diabetes.

The majority of patients with type 2 diabetes (greater than 90 percent) receive their routine care from primary care providers. A major unresolved controversy is the place of the generalist and the specialist in the treatment of patients with type 2 diabetes. Studies comparing care by specialists and generalists have generated conflicting findings [96-100]. For most patients with type 2 diabetes, care can be delivered by primary care providers and their health care teams in coordination with other specialists where appropriate. Patients in need of insulin therapy should be managed by or in consultation with an endocrinologist, if at all possible.

The decision to refer to an endocrinologist with expertise in diabetes management usually hinges on the complexity of the patient, the ability of the primary care team to achieve established goals of care in an individual, the need to manage diverse complications, and other factors such as the capacity of the primary care practitioner to teach self-management skills such as monitoring and insulin injections. Conversely, some specialty diabetes treatment practices have recognized the large overlap in the care that they provide with primary care and have taken on the responsibility of providing primary care for their patients. The ideal balance between primary and subspecialty care for the ever-increasing population of patients with type 2 diabetes will vary based on the resources and expertise available in different communities.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Diabetes mellitus in adults" and "Society guideline links: Assessment of cardiovascular risk".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: The ABCs of diabetes (The Basics)" and "Patient education: Type 1 diabetes (The Basics)" and "Patient education: Type 2 diabetes (The Basics)" and "Patient education: Treatment for type 2 diabetes (The Basics)" and "Patient education: Diabetic retinopathy (The Basics)" and "Patient education: Coping with high drug prices (The Basics)")

- Beyond the Basics topics (see "Patient education: Type 1 diabetes: Overview (Beyond the Basics)" and "Patient education: Type 2 diabetes: Overview (Beyond the Basics)" and "Patient education: Type 2 diabetes: Treatment (Beyond the Basics)" and "Patient education: Coping with high drug prices (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Morbidity from diabetes involves both macrovascular (atherosclerosis) and microvascular (retinopathy, nephropathy, and neuropathy) disease. Interventions can limit end-organ damage, and therefore, patients with diabetes require initial and ongoing evaluation for diabetes-related complications. We perform a history and physical examination two to four times yearly to obtain information on nutrition, physical activity, reduction of cardiovascular risk factors, current management, and diabetes-related complications (table 1). (See 'Diabetes-related complications' above.)

- Glycemic control can minimize risks for retinopathy, nephropathy, and neuropathy in both type 1 and type 2 diabetes and has been shown to decrease the risk for cardiovascular disease (CVD) for type 1 diabetes. (See 'Glycemic control' above and "Glycemic control and vascular complications in type 2 diabetes mellitus" and "Glycemic control and vascular complications in type 1 diabetes mellitus".)

- Glycated hemoglobin (A1C) goals in patients with diabetes should be tailored to the individual, balancing the improvement in microvascular complications with the risk of hypoglycemia. A reasonable goal of therapy is an A1C value of ≤7.0 percent for most patients (using an assay in which the upper limit of normal is 6.0 percent). Glycemic targets are generally set somewhat higher (eg, <8 percent) for older adult patients and those with comorbidities or a limited life expectancy and little likelihood of benefit from intensive therapy. More stringent control (A1C <6 percent) may be indicated for individual patients with type 1 diabetes and during pregnancy. (See 'Blood glucose monitoring and target A1C' above and "Glycemic control and vascular complications in type 2 diabetes mellitus", section on 'Choosing a glycemic target' and

"Pregestational (preexisting) diabetes mellitus: Antenatal glycemic control", section on 'Target blood glucose values: SMBG' and "Glycemic control and vascular complications in type 1 diabetes mellitus", section on 'Glycemic targets'.)

- Prevention of cardiovascular morbidity is a major priority for patients with diabetes, especially type 2. Smoking cessation is essential for patients who smoke. Cardiovascular morbidity can also be significantly reduced with aggressive management of hypertension, cholesterol, use of aspirin (75 to 162 mg/day), and use of certain glucose-lowering medications in patients with or at high risk for cardiovascular disease (CVD). (See 'Reducing the risk of macrovascular disease' above and "Treatment of hypertension in patients with diabetes mellitus", section on 'Approach to lowering blood pressure' and "Management of persistent hyperglycemia in type 2 diabetes mellitus", section on 'Monotherapy failure'.)

- Many patients with diabetes are not receiving recommended levels of health care, and development of systems of care involving disease management principles may be important in delivering improved care. (See 'Adequacy of care' above.)

- Intensive insulin therapy is recommended for the majority of patients with type 1 diabetes, and therefore, patients with type 1 diabetes should be referred to an endocrinologist for management of diabetes. For most patients with type 2 diabetes, care can be delivered by primary care providers and their health care teams in coordination with other specialists where appropriate. Patients in need of multiple daily injections of insulin therapy should be managed by or in consultation with an endocrinologist, if at all possible. The decision to refer to an endocrinologist with expertise in diabetes management usually hinges on the complexity of the patient, the ability of the primary care team to achieve established goals of care in an individual, the need to manage diverse complications, and other factors such as the capacity of the primary care practitioner to teach self-management skills such as monitoring and insulin injections. (See 'Indications for referral' above.)

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Topic 1750 Version 84.0

GRAPHICS

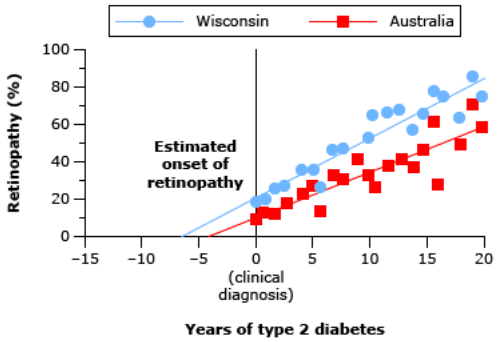
Monitoring in patients with diabetes mellitus

Intervention	Frequency	Notes
History and physical examination		
Height, weight, and BMI	Every visit	
Smoking cessation counseling	Every visit	For smokers only.
Blood pressure	Every visit	Goal systolic pressure 125 to 130 mmHg.*
Dilated eye examination	Annually ¶	Begin at onset of type 2 diabetes, 3 to 5 years after onset of type 1 diabetes. Examine yearly (or more frequently) if retinopathy present, every 2 to 3 years if there is no evidence of retinopathy.
Comprehensive foot examination	Annually	Every visit if peripheral vascular disease or neuropathy.
Dental examination	Annually	Periodontal disease is more severe but not necessarily more prevalent in patients with diabetes.
Laboratory studies		
Lipid profile	Initially, as indicated	In people without dyslipidemia and not on cholesterol-lowering therapy, testing may be infrequent.
A1C	Every 3 to 6 months	Goal ≤7% (may be lower or higher in selected patients).
Urinary albumin-to-creatinine ratio	Annually	Begin 3 to 5 years after onset of type 1 diabetes and at diagnosis in patients with type 2 diabetes; protein excretion should also be monitored if persistent albuminuria is present.
Serum creatinine	Initially, as indicated	Typically annually; more often in the presence of chronic kidney disease.
Vaccinations		
Pneumococcus		
▪ PPSV23	1 dose, ages 19 to 64 years	Once the patient is ≥65 years (and ≥1 year after PCV13 and >5 years after previous dose of PPSV23), give a second dose of PPSV23. Revaccinate every 10 years.
▪ PCV13	1 dose at age ≥65 years	Once the patient is ≥65 years (and ≥1 year after PPSV23), give PCV13.
Influenza	Annually	
Hepatitis B	3-dose series	Administer to unvaccinated adults who are ages 19 to 59 years. For older patients, administer based upon risk of acquiring hepatitis B, including the need for assisted blood glucose monitoring and the likelihood of an adequate immune response to vaccination.
Provide other routine vaccinations for adults with diabetes according to age-related recommendations.		
Education, self-management review	Annually	More often at onset of diabetes and when there is a change in regimen.

BMI: body mass index; A1C: glycated hemoglobin.
* When manual auscultatory method is used to measure blood pressure.
¶ Less frequent screening (every 2 to 3 years) may be appropriate for some patients (eg, patients with little or no retinopathy and near-normal A1C levels).

Graphic 63002 Version 19.0

Onset of retinopathy precedes diagnosis of type 2 diabetes



Prevalence of retinopathy in relation to years after onset of diabetes among patients in southern Wisconsin (blue circles) and rural western Australia (red squares). At diagnosis (year 0), clinical retinopathy was already present in 10 to 20% of patients. The lines extrapolate back to an estimated onset of retinopathy 4 to 7 years before the clinical diagnosis was made.

Data from: Harris MI, Klein R, Welborn TA, Knuiman MW. Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. Diabetes Care 1992; 15:815.

Graphic 58736 Version 6.0

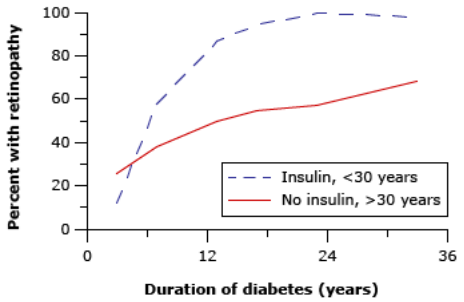
Ophthalmologic examination schedule

Patient group	Recommended first examination	Minimum routine follow-up
Type 1 diabetes	Within 5 years after diagnosis of diabetes once patient is age 10 years or older.	Yearly, if retinopathy present* Every 2 years if there is no evidence of retinopathy
Type 2 diabetes	At time of diagnosis of diabetes.	Yearly, if retinopathy present* Every 2 years if there is no evidence of retinopathy
Pregnancy in preexisting diabetes	Prior to conception and during first trimester. Counsel on the risk of development and/or progression of retinopathy.	Close follow-up throughout pregnancy and for 1 year postpartum

* Abnormal findings necessitate more frequent follow-up.

Graphic 61833 Version 7.0

Incidence of diabetic retinopathy increases over time



Percent of patients with diabetic retinopathy according to duration of disease in patients under the age of 30 years who were treated with insulin (primarily type 1 diabetes) and patients over the age of 30 years who were not treated with insulin (primarily type 2 diabetes). Retinopathy increased over time in both groups, affecting virtually all patients with type 1 diabetes by 20 years. The increased incidence in type 2 diabetes at 3 years is a probable reflection of the difficulty in determining the time of onset of that disease.

Adapted from: Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Arch Ophthalmol 1984; 102:527.

Graphic 70042 Version 7.0

Key components of the diabetic foot exam

Inspection
Dermatologic
Skin status – color, thickness, dryness, cracking
Sweating
Infection – check between toes for fungal infection
Ulceration
Calluses/blistering – hemorrhage into callus?
Musculoskeletal
Deformity (eg, claw toes, prominent metatarsal heads, Charcot joint)
Muscle wasting (guttering between metatarsals)
Neurologic assessment
10 g monofilament + 1 of the following 4
Vibration using 128 Hz tuning fork
Pinprick sensation
Ankle reflexes
VPT
Vascular assessment
Foot pulses
ABI, if indicated

VPT: vibration-perception threshold; ABI: ankle brachial index.

Graphic 59069 Version 4.0

Average glucose levels before and after meals for specified A1C levels

	A1C percentage (mmol/mol)				
	5.5-6.49 (37-47)	**6.5-6.99 (48-52)**	**7.0-7.49 (52-58)**	**7.5-7.99 (58-64)**	**8.0-8.5 (64-69)**
	Estimated average glucose as mg/dL (95% CI)				
	111-139	**140-153**	**154-168**	**169-182**	**183-197**
Pre-breakfast	122 (117-127)	142 (135-150)	152 (143-162)	167 (157-177)	178 (164-192)
Pre-lunch	113 (108-117)*	127 (121-133)*	147 (139-155)	140 (132-149)*	167 (151-182)
Pre-supper	119 (115-123)	145 (138-152)	155 (148-162)	163 (153-173)	186 (168-205)
Post-breakfast	150 (144-157)¶	177 (170-184)¶	192 (181-203)¶	206 (193-219)¶	219 (204-234)Δ
Post-lunch	140 (135-145)	158 (151-164)	172 (164-180)	181 (170-191)	194 (178-209)
Post-supper	142 (136-146)	159 (152-166)	169 (162-177)	182 (171-193)	211 (195-227)

A1C: glycated hemoglobin.

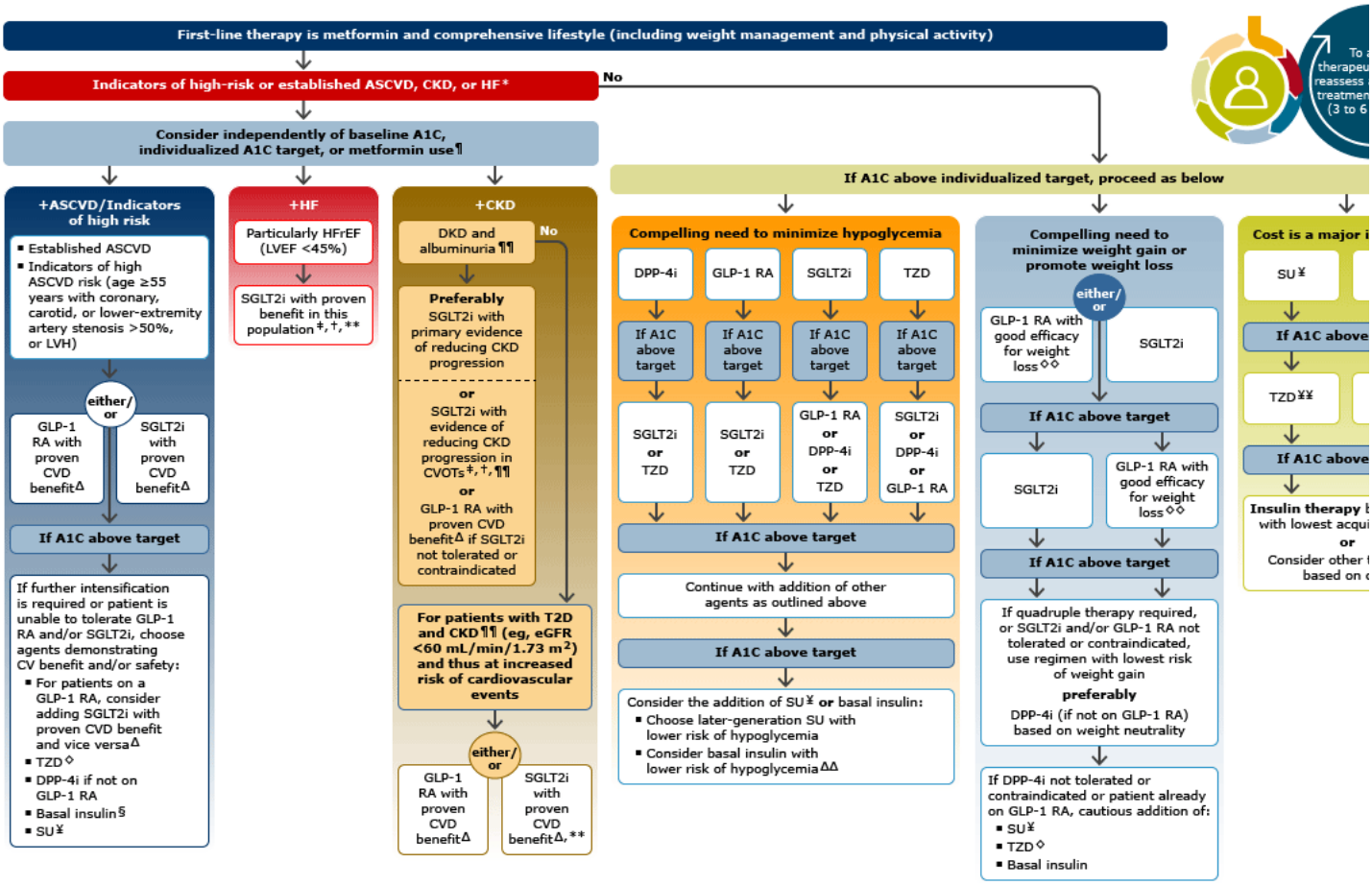
* p<0.05 comparing mean pre-lunch glucose with pre-breakfast and pre-supper.

¶ p<0.05 comparing mean post-breakfast glucose with post-lunch and post-supper.

Δ p<0.05 comparing mean post-breakfast glucose with post-lunch.

Graphic 121967 Version 2.0

Glucose-lowering medication in type 2 diabetes: Overall approach



ASCVD: atherosclerotic cardiovascular disease; CKD: chronic kidney disease; HF: heart failure; A1C: glycated hemoglobin; LVH: left ventricular hypertrophy; GLP-1 RA: glucagon-like peptide 1 receptor agonist; CVD: car disease; SGLT2i: sodium-glucose co-transporter 2 inhibitor; CV: cardiovascular; TZD: thiazolidinedione; DPP-4i: dipeptidyl peptidase-4 inhibitor; SU: sulfonylurea; HFrEF: heart failure reduced ejection fraction; LVEF: left ejection fraction; DKD: diabetic kidney disease; CVOTs: cardiovascular outcomes trials; T2D: type 2 diabetes mellitus; eGFR: estimated glomerular filtration rate.

* Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

¶ Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

Δ Proven CVD benefit means it has label indication of reducing CVD events.

◊ Low dose may be better tolerated though less well studied for CVD effects.

§ Degludec or U-100 glargine have demonstrated CVD safety.

¥ Choose later-generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i.

‡ Be aware that SGLT2i labeling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use.

† Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin outcome data.

** Proven benefit means it has label indication of reducing HF in this population.

¶¶ Refer to Section 11: Microvascular Complications and Foot Care[1].

ΔΔ Degludec/glargine U-300 < glargine U-100 / detemir < NPH insulin.

◊◊ Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide.

§§ If no specific comorbidities (ie, no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities).

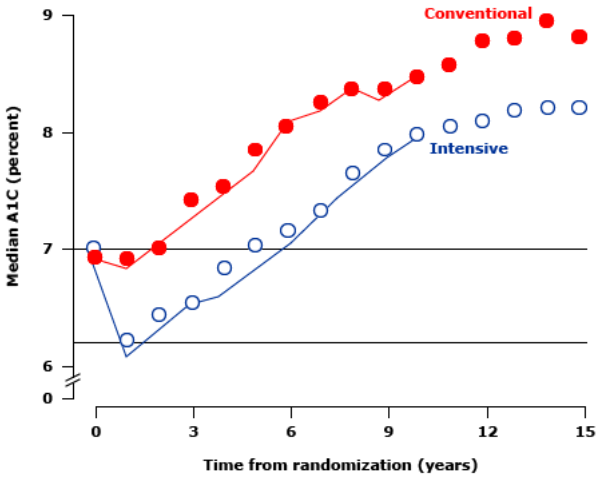
¥¥ Consider country- and region-specific cost of drugs. In some countries, TZDs are relatively more expensive and DPP-4i are relatively cheaper.

References:

1. American Diabetes Association. 11. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes - 2021. Diabetes Care 2021; 44:S151.

Graphic 111617 Version 5.0

Glycemic control in type 2 diabetes



Glycemic control, estimated from the median hemoglobin A1C value, in patients with type 2 diabetes mellitus in the United Kingdom Prospective Diabetes Study (UKPDS) who were randomly assigned to receive intensive therapy with a sulfonylurea or insulin or to conventional treatment with diet; drugs were added if there were hyperglycemic symptoms or if the fasting blood glucose concentration was greater than 270 mg/dL (15 mmol/L). The A1C values were lower in the intensive therapy group but rose in both groups over time. The circles represent data for all patients, while the lines represent data for patients followed for 10 years.

A1C: HbA1c, glycated hemoglobin.

Data from: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 352:837.

Graphic 81706 Version 4.0

Preconception evaluation and management of women with type 1 or type 2 diabetes

History and physical examination
Hypertension
Goal systolic blood pressure 110 to 129 mmHg and diastolic blood pressure 65 to 79 mmHg in women with preexisting hypertension.
Stop antihypertensive drugs, if possible, or switch to agents with fewest risks to fetus.
Retinopathy
Ophthalmology consult.
Treat active proliferative retinopathy before pregnancy.
Cardiac
Screen for coronary heart disease as per guidelines for nonpregnant women with diabetes.
Renal
Measure serum creatinine concentration and total protein-to-creatinine ratio.
Women with an elevated serum creatinine concentration are at risk for deterioration of renal status.
Thyroid
Obtain serum TSH and free T4.
Diabetes
Achieve good glucose control before conception.
If A1C is above 7%, intensive insulin therapy is warranted.
Three to four injections/day of short- and long-acting insulin subcutaneously are usually required to achieve good glycemic control. Either subcutaneous insulin injections or an insulin infusion pump is acceptable.
Self-monitoring of blood glucose is performed before and after each meal and at bedtime.
Repeat A1C one month after initiation of this program.
Retest every month until target A1C value is achieved. Once in the target range, the patient can try to conceive.
A pregnancy test is done one week after a missed period to confirm pregnancy.
Psychosocial
Assess "readiness" of patient for pregnancy.
Other
Advise patient to stop smoking and stop use of illicit drugs.
Review medications. Discontinue those that are associated with potential fetal risks or change to medications with fewer fetal effects, if possible.

TSH: thyroid-stimulating hormone; T4: thyroxine; A1C: glycated hemoglobin.

Graphic 79625 Version 5.0

Contributor Disclosures

Deborah J Wexler, MD, MSc Consultant/Advisory Boards: Novo Nordisk – Data Monitoring Committee [Cardiovascular and renal outcome trials]. **David M Nathan, MD** Nothing to disclose **Jean E Mulder, MD** Nothing to disclose

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