The cornerstone of therapy for all patients with diabetes is a personalized self-management program, usually developed with the patient by a diabetes education nurse or nutritionist.

Lifestyle changes plus metformin are initial antihyperglycemic therapy for most patients. Glycemic goals and treatment choices are individualized.

Selected glucose-lowering drugs reduce all-cause and cardiovascular mortality. Addition of a sodium-glucose co-transporter 2 (SGLT2) inhibitor or glucagon-like peptide-1 (GLP-1) agonist is recommended in patients with longstanding suboptimal glycemic control plus established cardiovascular and/or renal disease.

Blood pressure control, lipid management, smoking cessation, and glycemic management reduce the risk of macrovascular complications such as heart attack and stroke. Glycemic control and blood pressure management reduce the risk of microvascular complications (neuropathy, nephropathy, retinopathy).
### Definition

Type 2 diabetes mellitus is a progressive disorder defined by deficits in insulin secretion and action that lead to abnormal glucose metabolism and related metabolic derangements.[1] Although the etiologies of type 1 and type 2 diabetes differ dramatically, both lead to hyperglycemic states, and both share common macrovascular (coronary heart, cerebrovascular, and peripheral vascular disease) and microvascular (retinopathy, nephropathy, and neuropathy) complications. Type 2 diabetes is most often diagnosed following routine screening. It is preceded by a state of prediabetes, which is defined by a single fasting plasma glucose of 100-125 mg/dL or a HbA1c of 5.7% to 6.4% in the absence of diabetes. Diabetes diagnosis is based on two confirmed values of: fasting plasma glucose >125 mg/dL; HbA1c of 6.5% or greater; or (less commonly) glucose tolerance test results, or a random plasma glucose of ≥200 mg/dL plus symptoms of hyperglycemia. A single blood sample is sufficient to establish a diabetes diagnosis if assays of both HbA1c and fasting plasma glucose meet criteria for diabetes diagnosis.[2]

### Epidemiology

Diabetes prevalence is increasing worldwide, compounded by population growth and an aging population.[3] In 1980, the global age-standardized diabetes prevalence was 4.3%.[3] In 2017, the global age-standardized diabetes prevalence was estimated at 8.6%.[4] However, while the overall burden of diabetes is increasing, trends in the incidence rate of diabetes plateaued and now appear to be decreasing. Data from the US National Health Interview Survey documented that the incidence of age-adjusted, diagnosed diabetes decreased 2007 to 2017, from 7.8 to 6.0 per 1000 adults.[5] Lifetime risk of diabetes is now 40% for both men and women in the overall US population, and is 50% in the US African-American population.[6] About 9.4% of the US population has diabetes.[7]

Incidence and prevalence of type 2 diabetes have risen steadily since 1950, driven by increasing prevalence in obesity and being overweight.[8] Type 2 diabetes accounts for over 90% of all diabetes cases, and has a prevalence of 8.5% in the US.[9] Clinical onset is usually preceded by many years of insulin resistance and hyperinsulinemia before elevated glucose levels are detectable.[1] Patients with type 2 diabetes have a very high risk of concurrent hypertension (80% to 90%), lipid disorders (70% to 80%), and overweight or obesity (60% to 70%).[10] When diabetes is diagnosed at age 40 years, men lose an average of 5.8 years of life, and women lose an average of 6.8 years of life, highlighting the importance of primary prevention of diabetes.[11] However, onset of diabetes at older ages has much less effect on life expectancy if acceptable glucose, blood pressure, and lipid control can be achieved and maintained.

### Etiology

Type 2 diabetes often presents on a background genetic predisposition and is characterized by insulin resistance and relative insulin deficiency. Insulin resistance is aggravated by aging, physical inactivity, and overweight (body mass index [BMI] 25-29.9 kg/m²) or obesity (BMI >30 kg/m²). Among obese patients, weight loss often reduces the degree of insulin resistance and may delay diabetes onset or ameliorate diabetes severity and thereby reduce risk of long-term complications. Insulin resistance affects primarily the liver, muscle, and adipocytes, and it is characterized by complex derangements in cellular receptors, intracellular glucose kinase function, and other intracellular metabolic processes.[8] The complexity and variety of these intracellular derangements suggest that what is now classified as type 2 diabetes may be in fact a larger group of conditions that await future definition.
Pathophysiology

The precise mechanism by which the diabetic metabolic state leads to microvascular and macrovascular complications is only partly understood but likely involves both uncontrolled blood pressure (BP) and uncontrolled glucose, increasing the risk of microvascular complications such as retinopathy and nephropathy. Mechanisms may involve defects in aldose reductase and other metabolic pathways, damage to tissues from accumulation of glycated end products, and other mechanisms. With respect to macrovascular complications, high BP and glucose raise risk, but so do lipid abnormalities and tobacco use. One unifying theory postulates the existence of a metabolic syndrome that includes diabetes mellitus, hypertension, dyslipidemias, and obesity, and predisposes to coronary heart disease, stroke, and peripheral artery disease.[8] However, this theory is not universally accepted as more clinically useful than assessing individual cardiovascular risk factors.[12]
Primary prevention

Lifestyle factors (obesity, physical inactivity, and stress) seem to be the main drivers of the current diabetes epidemic. With aggressive prevention of obesity in all age groups, type 2 diabetes is potentially preventable.[24] [25] Several clinical trials have shown that weight loss is associated with delayed or decreased onset of diabetes in high-risk adults.[15] [18] [19] [20] [26] [27] Progression to diabetes from prediabetic states can be reduced by 50% over 3 to 4 years through modest weight loss (7% of body weight) using diet and regular physical activity.[18] In addition, several pharmacologic agents, including metformin, alpha-glucosidase inhibitors, orlistat, glucagon-like peptide 1 (GLP-1) receptor agonists, and thiazolidinediones, have been shown to reduce progression from prediabetes to diabetes.[2] [21] [28] [29] [30] Lifestyle change and/or metformin are preferred for most patients.[31] [32] [33] [34] More aggressive multi-agent pharmacologic approaches remain controversial.[35] Screening for prediabetes and cardiovascular risk reduction appropriate to the needs of the individual are also very important.[22] [36] [37]

Screening

The US Preventive Services Task Force (USPSTF) now recommends screening for glucose status for adults ages 40 to 70 years who have body mass index (BMI) ≥25. Those with normal test results should be re-screened every 3 years. Those who have prediabetes should subsequently be screened annually for diabetes.[53]

The American Diabetes Association has recommended routine screening of nonpregnant asymptomatic adults of any age with BMI ≥25 kg/m² (≥23 kg/m² for people from South Asia) plus one or more risk factors for diabetes. Those without risk factors should be screened starting at age 45 years. Risk factors for diabetes include family history of diabetes, overweight or obesity, sedentary lifestyle, high-risk ancestry, gestational diabetes, hypertension, dyslipidemia (low HDL-cholesterol and/or elevated triglycerides), vascular disease, glucose intolerance, or polycystic ovary syndrome.[2]

Recommended screening tests include fasting plasma glucose (prediabetes if 100-125 mg/dL once, in the absence of diabetes) and/or HbA1c (prediabetes if 5.7% to 6.4% once, in the absence of diabetes; diabetes if ≥6.5% twice). Oral 75 g glucose tolerance test is less commonly used in nonpregnant adults.[2]

Secondary prevention

Although the risk of macrovascular complications can be reduced by over 50% using effective multifactorial interventions,[198] a US national survey found more than half of outpatients over age 50 years with diabetes and hypertension did not receive an antiplatelet agent, statin therapy, or ACE inhibitor/angiotensin-II receptor antagonist.[199]

Other preventive measures include:[2]

- Annual influenza immunizations
- Vaccination against pneumococcal disease
- Hepatitis B vaccination for unvaccinated diabetic adults ages 19 to 59 years; considered for unvaccinated diabetic adults ages 60 years and older
- Regular dental care
- Tailored diabetes education.
Case history

Case history #1

An overweight 55-year-old woman presents for preventive care. She notes that her mother died of diabetes, but reports no polyuria, polydipsia, or weight loss. BP is 144/92 mmHg, fasting blood sugar 148 mg/dL, HbA1c 8.1%, LDL-cholesterol 200 mg/dL, HDL-cholesterol 30 mg/dL, and triglycerides 252 mg/dL.

Other presentations

Patients with type 2 diabetes can also present with symptoms such as blurred vision; fatigue; erectile dysfunction; urinary tract or candidal infections; dry itchy skin; paresthesias; increased urination, thirst, and appetite; or unexplained weight loss.

Step-by-step diagnostic approach

Type 2 diabetes is most often diagnosed on routine screening. Strong risk factors, which also indicate the need for screening, include: older age; overweight/obesity; black, Hispanic, or Native American ancestry; family history of type 2 diabetes; history of gestational diabetes; presence of prediabetes; physical inactivity; polycystic ovary syndrome; hypertension; dyslipidemia; or known cardiovascular disease.[2] Symptomatic patients may present with: fatigue; polyuria, polydipsia, polyphagia, or weight loss (usually when hyperglycemia is more severe, e.g., >300 mg/dL); blurred vision; paresthesias; unintentional weight loss; nocturia; skin infections (bacterial or candidal); urinary infections; or acanthosis nigricans.

Diagnosis

One of four tests can be used to establish a firm diagnosis of diabetes:[2]

- Fasting plasma glucose (FPG) >125 mg/dL
- Random plasma glucose ≥200 mg/dL with diabetes symptoms such as polyuria, polydipsia, fatigue, or weight loss
- 2-hour post-load glucose ≥200 mg/dL on a 75 g oral glucose tolerance test
- HbA1c ≥6.5%.

All of these require confirmation with a second test, which may be the same test or a different test. This means a single blood sample is sufficient to establish a diabetes diagnosis if assays of both HbA1c and fasting plasma glucose meet criteria for diabetes diagnosis.[2] Some variability in HbA1c results is possible as a result of such factors as increased red blood cell turnover (e.g., sickle cell anemia), factors related to ancestry,[38] or laboratory variation.

Some individuals cannot be clearly classified as having type 1 or type 2 diabetes at the time of diagnosis.[2] However, at initial diagnosis of diabetes, it is important to determine if immediate treatment with insulin is required. Type 1 diabetes can occur at any age, but usually is diagnosed in younger (age <35), thinner patients, and has a more rapid onset and often more severe symptoms. Around one third of patients with newly diagnosed type 1 diabetes present with diabetic ketoacidosis (DKA).[39] However, DKA may also occur in type 2 diabetes, particularly if there is an underlying infection.[40] [41] Urine
ketones should be checked if patients are symptomatic of hyperglycemia (polyuria, polydipsia, weakness) and volume depletion (dry mucous membranes, poor skin turgor, tachycardia, hypotension, and, in severe cases, shock) at diagnosis or throughout course of disease.

C-peptide is produced in equal amounts to insulin and is the best measure of endogenous insulin secretion in patients with diabetes. There is no role for routine testing for C-peptide for diagnosis of diabetes, but measuring C-peptide may be useful in differentiating type 1 and type 2 diabetes.[42] The best evidenced C-peptide test is the glucagon stimulation test (GST), but non-fasting "random" blood C-peptide has been shown to correlate with fasting C-peptide and post-GST samples in subjects with well-defined type 1 or type 2 diabetes.[43] Development of absolute insulin deficiency is a key feature of type 1 diabetes, which results in low (<0.2 nanomol/L) or undetectable levels of plasma C-peptide.[2] [42] A GST or non-fasting "random" blood C-peptide level >1 nanomol/L suggests type 2 diabetes.[42] C-peptide results must be interpreted in clinical context of disease duration, comorbidities, and family history.[43]

**Evaluation of disease and risks of macrovascular/microvascular complications**

Blood pressure, smoking status, and fasting lipid levels should be assessed. Baseline urine albumin/creatinine ratio and serum creatinine with estimated glomerular filtration rate (eGFR) are also indicated, as signs of chronic kidney disease may be present at diagnosis.[2] Clinical assessment of cardiac, carotid, and peripheral circulation, with ECG and vascular investigation (e.g., an ankle-brachial index) can be considered at diagnosis.[2] [36] Examination of the feet, including assessment of ankle reflexes, pulses, vibratory sensation, and monofilament touch sensation, and a dilated retinal exam, should be part of the evaluation.[2] HbA1c, lipid levels, blood pressure, urine albumin excretion, renal function, and clinical assessment are monitored at periodic intervals.

**Risk factors**

**Strong**

older age

- Older patients are at increased risk. However, the incidence of type 2 diabetes in children and adolescents is increasing.[13]

overweight/obesity

- Appears to be the precipitating factor leading to clinical expression of diabetes. The mean body mass index (BMI) at the time of diagnosis of diabetes in several studies is around 31 kg/m², and there is a graded increase in risk of diabetes with increasing BMI.[14] Clinical trials have shown that weight loss is associated with delayed or decreased onset of diabetes in high-risk adults.[15]

gestational diabetes

- About 50% of women who have gestational diabetes mellitus will go on to develop overt diabetes mellitus within 10 years of delivery.[16]

prediabetes

- Major risk factor for onset of type 2 diabetes. Progression from prediabetes to overt type 2 diabetes occurs at the rate of about 2% to 4% per year.[1] [2]
family history of type 2 diabetes

- Although the specific genetic profile that confers risk has yet to be fully elucidated, epidemiological observations leave little doubt of a substantial genetic component.[8]

African, Hispanic, or American-Indian ancestry

- Relative to white people, National Health and Nutrition Examination Survey (NHANES) and other data demonstrate higher risk of diabetes.[14] [17]

physical inactivity

- While the impact on increased risk of diabetes is mediated in part through obesity/overweight, several interventions studies indicate that increased levels of physical activity delay or decrease onset of diabetes in high-risk adults.[18] [19] [20] [21]

polycystic ovary syndrome

- Elevated risk; should be periodically screened for diabetes.[2]

hypertension

- Often associated with type 2 diabetes. Periodic screening is recommended in people with essential hypertension due to increased prevalence of diabetes.[2]

dyslipidemia

- Especially with low high-density lipoprotein (HDL) and/or high triglycerides: periodic diabetes screening is recommended due to the high prevalence of diabetes in patients with dyslipidemia.[2]

cardiovascular disease

- Periodic diabetes screening is recommended due to the high prevalence of diabetes in patients with peripheral vascular and coronary artery disease.[2]
- American College of Cardiology/American Heart Association statements identify a number of additional risk factors for atherosclerotic cardiovascular disease, which include: C-reactive protein ≥2 mg/L; coronary artery calcium score ≥100 Agatston units or ≥75% for age, sex, and ethnicity; and ankle-brachial index <0.9.[22]

stress

- Stress provokes release of hormones that elevate glucose, and there is some evidence that life stress may predispose to onset of type 2 diabetes.[23]

History & examination factors

Key diagnostic factors

asymptomatic (common)

- It is very common for type 2 diabetes to be asymptomatic and detected on screening. Symptoms, when present, may indicate more overt hyperglycemia.

candidal infections (common)

- Most commonly vaginal, penile, or in skin folds.
Diagnosis

skin infections (common)
- Cellulitis or abscesses.

urinary tract infections (common)
- Cystitis or pyelonephritis.

Other diagnostic factors

fatigue (common)
- Increased fatigability may be an early warning sign of progressive cardiovascular disease; clinicians should have a low threshold for cardiac evaluation.

blurred vision (common)
- Due to elevated glucose.

polydipsia (uncommon)
- Usually in patients with fasting plasma glucose >300 mg/dL, HbA1c >11%.

polyphagia (uncommon)
- Usually in patients with fasting plasma glucose >300 mg/dL, HbA1c >11%.

polyuria (uncommon)
- Usually in patients with fasting plasma glucose >300 mg/dL, HbA1c >11%.

paresthesias (uncommon)
- May occur in the extremities as a result of neuropathy in those with prolonged undiagnosed diabetes.

nocturia (uncommon)
- Due to glucose-induced diuresis.

unintentional weight loss (uncommon)
- If marked hyperglycemia is present.

acanthosis nigricans (uncommon)
- A velvety, light brown-to-black marking, usually on the neck, under the arms, or in the groin. Can occur at any age. Most often associated with obesity.

[Fig-1]
## Diagnostic tests

### 1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c</strong></td>
<td>6.5% or greater</td>
</tr>
<tr>
<td>• Confirm with a repeat HbA1c or another diagnostic test.[2] HbA1c is also used to monitor glycemic control, usually every 3 months.</td>
<td></td>
</tr>
<tr>
<td><strong>fasting plasma glucose</strong></td>
<td>&gt;125 mg/dL</td>
</tr>
<tr>
<td>• Order after a minimum 8-hour fast. Confirm an elevated result with an HbA1c (which can be done on the same sample), a second fasting plasma glucose, or another diabetes diagnostic test.[2]</td>
<td></td>
</tr>
<tr>
<td><strong>random plasma glucose</strong></td>
<td>≥200 mg/dL</td>
</tr>
<tr>
<td>• Nonfasting test. Convenient, but less accurate than either fasting plasma glucose, HbA1c, or 75 g oral glucose tolerance test.[2] Used for rapid assessment of glucose status if symptoms such as polyuria, polydipsia, or weight loss are present.</td>
<td></td>
</tr>
<tr>
<td><strong>2-hour post-load glucose after 75 g oral glucose</strong></td>
<td>≥200 mg/dL</td>
</tr>
<tr>
<td>• More costly and inconvenient than fasting plasma glucose or HbA1c. Diabetes should be confirmed on a separate occasion with another diagnostic test.[2]</td>
<td></td>
</tr>
</tbody>
</table>
## Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>fasting lipid profile</strong></td>
<td>may show high LDL, low HDL, and/or high triglycerides</td>
</tr>
<tr>
<td>• Dyslipidemia is common in type 2 diabetes.</td>
<td></td>
</tr>
<tr>
<td><strong>urine ketones</strong></td>
<td>positive in instances of ketoacidosis</td>
</tr>
<tr>
<td>• Urine ketones should be checked if patients are symptomatic of hyperglycemia (polyuria, polydipsia, weakness) and volume depletion (dry mucous membranes, poor skin turgor, tachycardia, hypotension, and, in severe cases, shock) at diagnosis or throughout course of disease. Ketoacidosis is a common presentation of type 1 diabetes, but can also occur in type 2 diabetes.[39] [40] [41]</td>
<td></td>
</tr>
<tr>
<td><strong>random C-peptide</strong></td>
<td>&gt;1 nanomol/L</td>
</tr>
<tr>
<td>• Not done routinely for diagnosis of diabetes, but may be useful in differentiating type 1 and type 2 diabetes.[42] Absolute insulin deficiency is a key feature of type 1 diabetes, which results in low (&lt;0.2 nanomol/L) or undetectable levels of plasma C-peptide.[2] [42] C-peptide results must be interpreted in clinical context of disease duration, comorbidities, and family history.[43]</td>
<td></td>
</tr>
<tr>
<td><strong>urinary albumin excretion</strong></td>
<td>may be increased</td>
</tr>
<tr>
<td>• Indicates nephropathy and suggests possible other microvascular damage. Monitored yearly.</td>
<td></td>
</tr>
<tr>
<td>• May be assessed with albumin-to-creatinine ratio in a random urine sample.[2]</td>
<td></td>
</tr>
<tr>
<td><strong>serum creatinine and estimated GFR</strong></td>
<td>may show renal insufficiency</td>
</tr>
<tr>
<td>• GFR is calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) or Modification of Diet in Renal Disease (MDRD) formulas. The CKD-EPI formula is now recommended by the Kidney Disease Outcomes Quality Initiative (KDOQI) because it removes bias at higher GFR levels, allowing for reporting across a full range.</td>
<td></td>
</tr>
<tr>
<td>[VIDEO: Glomerular Filtration Rate Estimate by CKD-EPI Equation ]</td>
<td></td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td>may indicate prior ischemia</td>
</tr>
<tr>
<td>• Baseline assessment. A normal ECG does not rule out coronary artery disease. Patients with an abnormal resting ECG may require further cardiac investigation.[2]</td>
<td></td>
</tr>
<tr>
<td><strong>ankle-brachial index (ABI)</strong></td>
<td>≤0.9 is abnormal</td>
</tr>
<tr>
<td>• A noninvasive tool to detect peripheral arterial disease (PAD), which has a high prevalence in patients with diabetes. The American Diabetes Association recommends that ABI should be performed in patients with symptoms of PAD.[2] Can be used to screen for PAD.</td>
<td></td>
</tr>
<tr>
<td><strong>dilated retinal examination</strong></td>
<td>may show retinopathy</td>
</tr>
<tr>
<td>• Patients should be referred to an ophthalmologist at the time of diagnosis of type 2 diabetes.[2]</td>
<td></td>
</tr>
</tbody>
</table>
### Differential diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prediabetes</td>
<td>• Patients with prediabetes often have no specific differentiating signs or symptoms.</td>
<td>• Fasting plasma glucose level is 100-125 mg/dL in prediabetes.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 2-hour post-load glucose after 75 g of oral glucose is 140-199 mg/dL in prediabetes.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HbA1c of 5.7% to 6.4% indicates prediabetes and high risk of future diabetes.[2]</td>
</tr>
<tr>
<td>Diabetes mellitus, type 1</td>
<td>• Onset often at age &lt;35 years, but can occur in older individuals.</td>
<td>• Urine ketones are often present in type 1 diabetes, but may be positive in type 2 diabetes if there is severe volume depletion.</td>
</tr>
<tr>
<td></td>
<td>• Many patients are not obese.</td>
<td>• Low (&lt;0.6 nanogram/mL) or absent C-peptide level.</td>
</tr>
<tr>
<td></td>
<td>• More commonly presents with symptoms (polyuria, polydipsia, weight loss, generalized weakness, blurred vision) and ketosis, rather than being detected by screening.[39]</td>
<td>• One or more autoantibodies (antigliutamic acid decarboxylase [GAD] antibodies, islet cell antibodies [ICA], insulin autoantibodies, autoantibodies to the tyrosine phosphates IA-2 and IA-2beta) are present in 85% of patients with type 1 at the time of diagnosis, but may disappear within a few years.[44] Type 1 diabetes is defined by the presence of one or more of these autoimmune markers, but testing is usually not required for diagnosis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Glucose screening criteria cannot be used to differentiate type 1 and type 2 diabetes, as they are identical.</td>
</tr>
<tr>
<td>Latent autoimmune diabetes in adults (LADA)</td>
<td>• Typical age of onset of diabetes is over 30 years old. Patients are usually nonobese and respond initially to lifestyle modifications and oral agents. Production of insulin gradually decreases (between 6 months and 5</td>
<td>• Positive for at least 1 of the 4 antibodies commonly found in type 1 diabetic patients (ICAs and autoantibodies to GAD65, IA-2, and insulin).[46]</td>
</tr>
<tr>
<td>Condition</td>
<td>Differentiating signs / symptoms</td>
<td>Differentiating tests</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
|                                   | • Maturity-onset diabetes of the young (MODY) is the most common form of monogenic diabetes and affects 1% to 2% of people with diabetes.[47]  
• MODY is caused by mutation of a single gene (i.e., monogenic). As of 2011, at least 11 forms of MODY are known.[48]  
• It has autosomal dominant inheritance and should be suspected in cases of diabetes in nonobese, young patients (adolescence or young adult) with a family history of diabetes in two or more successive generations.[48]  
• Patients are often misclassified as type 1 or type 2 diabetes. Insulin treatment is often not needed. | • Genetic testing in patients with high index of suspicion (genes encoding glucokinase and transcription factors are identified).[49] |
| Monogenic diabetes                |                                                                                                  |                                                                                        |
| Ketosis-prone diabetes            | • Presents with unprovoked ketosis or ketoacidosis.[50]  
• Considered an "idiopathic diabetes," as patients have no evidence of autoimmunity. Often misclassified as type 1 diabetes, as individuals have episodic ketoacidosis and exhibit varying degrees of insulin deficiency between episodes. However, a type 2 diabetes phenotype is common (obesity, insulin resistance, metabolic syndrome).[51]  
• Patients are usually from a minority ethnic group, and have a positive family history of diabetes.[51]  
• On discontinuation of insulin therapy, the period of near-normoglycemic remission  
• Absent islet cell autoantibodies.  
• C-peptide often low or undetectable during diabetic ketoacidosis; recovery may be used as reliable predictor of insulin discontinuation.[51] |                                                                                         |
Type 2 diabetes mellitus in adults

**Diagnosis**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
</table>
|                         | may last for a few months to several years. However, almost half will be insulin dependent 10 years after diagnosis.  
[50] |          |
| Diabetes, gestational   | Only occurs during pregnancy.    | Gestational diabetes is generally detected by screening during pregnancy. Based on the current evidence, the US Preventive Services Task Force recommends screening for gestational diabetes in asymptomatic pregnant women after 24 weeks of gestation.  
[52] One-step or 2-step screening strategies may be used.  
[2] | When overt hyperglycemia occurs during pregnancy, it may be difficult to distinguish between undetected preexisting type 2 diabetes and gestational diabetes. |

**Diagnostic criteria**

**American Diabetes Association**  
[2]

One of four tests can be used to establish a firm diagnosis of diabetes:

- Fasting plasma glucose (FPG) >125 mg/dL (most commonly used)
- Random plasma glucose ≥200 mg/dL with diabetes symptoms such as polyuria, polydipsia, fatigue, or weight loss
- 2-hour post-load glucose ≥200 mg/dL on a 75 g oral glucose tolerance test
- HbA1c ≥6.5%.

All of these require confirmation with a second test, which may be the same test or a different test. One option is to test both HbA1c and FPG on a single blood sample.
Step-by-step treatment approach

The cornerstone of therapy for all patients with type 2 diabetes is a personalized management program that includes pharmacotherapy and ongoing self-management education by a diabetes education nurse or nutritionist.[57] [58] [59] Diabetes self-management education promotes diabetes self-care and supports beneficial lifestyle changes on an ongoing basis.[2] This requires general nutrition and health lifestyle knowledge and an individualized nutrition and exercise plan based on an initial assessment and treatment goals. Interventions that enhance self-management can significantly reduce diabetes distress.[60]

About 80% of adults with type 2 diabetes have concurrent dyslipidemias or hypertension, 70% are overweight or obese, and around 15% are current smokers.[10] On average, adults with type 2 diabetes are up to twice as likely to die of stroke or myocardial infarction (MI) compared with those without diabetes, and they are more than 40 times more likely to die of macrovascular than microvascular complications of diabetes.[61] [62] [63] However, data indicate that adults with type 2 diabetes who optimally manage glucose, blood pressure, lipids, smoking, and weight have a risk of major cardiovascular events that is not significantly above the risk of age and sex-matched non-diabetes peers.[64] [65]

Therefore, care of adults with type 2 diabetes must include management of all major cardiovascular risk factors to individualized targets. In addition to glucose control, this includes smoking cessation, blood pressure control, lipid control, antiplatelet use for patients with known coronary heart disease, and ACE inhibitors or angiotensin-II receptor antagonists for patients with chronic kidney disease or proteinuria.[2] [36] [66] In addition, use of antihyperglycemic agents that reduce cardiovascular or overall mortality or cardiovascular events may be especially beneficial in those who have type 2 diabetes and established cardiovascular disease.[2] [36] [67]

Diet

Nutrition therapy involves limiting caloric intake to achieve recommended weight, while offering a diversified and appealing menu of food choices.[68] Nutrition advice needs to be tailored to the needs of each individual patient, preferably by a nutritionist.[2] [24] The optimal mix of carbohydrate, fats, and protein depends upon renal status, achieved lipid levels, body mass index (BMI), and level of glycemic control, among other factors. Low-carbohydrate diets appear to be beneficial for glycemic control in type 2 diabetes management.[69] Saturated fat should be limited to <10% of calories.[24] Reducing sugary beverage consumption (including milk, soda, energy drinks, and fruit juice) is of benefit to many patients.[24] Weight loss management programs with a healthy eating and physical activity plan resulting in an energy deficit have the potential for type 2 diabetes remission.[24] [70] [71] The Diabetes Remission Clinical Trial (DiRECT) of supported weight loss management for people diagnosed with type 2 diabetes within the previous 6 years, and a BMI of 27kg/m² to 45 kg/m², found that almost half of participants achieved remission to a non-diabetic state and off antidiabetic drugs at 12 months.[70] At 2 years, more than a third of people with type 2 diabetes had sustained remission.[72]

Exercise and sleep

- To improve glycemic control, assist with weight maintenance, and reduce cardiovascular risk, moderate physical activity is recommended as tolerated. The ACC/AHA has recommended that, in general, adults should engage in 3 to 4 sessions of aerobic physical activity per week, with each session lasting on average 40 minutes, and involving moderate- to vigorous-intensity physical activity.[73] Walking frequently in proper footwear is a recommended activity.[2]
**Type 2 diabetes mellitus in adults**

**Treatment**

- In addition, gentle strength training that targets all major muscle groups may be beneficial if done for 20 minutes 2 to 3 times per week on nonconsecutive days. Patients with severe or symptomatic heart disease may require evaluation before increasing levels of physical activity.[2]
- People should be encouraged to limit the amount of time they spend being sedentary by avoiding extended amounts of time spent sitting.
- Older adults may benefit from flexibility training and balance training 2-3 times/week (e.g., with yoga or tai chi).
- An assessment of sleep duration and quality should be considered. Obesity, diabetes, hypertension, atrial fibrillation, and male sex are risk factors for sleep apnea, and inadequate sleep may affect glycemic control.[2]

**Cardiovascular risk management**

**Blood pressure**

Blood pressure guidelines differ regarding recommended targets for those with diabetes.

- The 2017 American College of Cardiology/American Heart Association guideline for management of high blood pressure (BP) in adults recommends BP <130/80 mmHg for people with diabetes, and classifies BP using the following categories:[56]
  - normal (<120/80 mmHg)
  - elevated (120-129/<80 mmHg)
  - stage 1 (130-139/80-89 mmHg)
  - stage 2 hypertension (≥140/90 mmHg).
- The American Diabetes Association Standards of Medical Care in Diabetes recommends goal BP <140/90 mmHg for people with diabetes, with consideration of a goal BP <130/80 mmHg for those with established hypertension and diabetes and who have established cardiovascular disease or 10-year cardiovascular risk greater than 15%. [2] [74]
- Regardless of specific blood pressure goal, initial treatment with an ACE inhibitor, an angiotensin-II receptor antagonist, a calcium-channel blocker, or a thiazide (or thiazide-like) diuretic is preferred. Black people may benefit most from a thiazide diuretic or a calcium-channel blocker.[74] ACE inhibitors may reduce mortality and cardiovascular events more than angiotensin-II receptor antagonists.[66] Combination drug therapy (with ACE inhibitor/angiotensin-II receptor antagonist, calcium-channel blocker, thiazide diuretic) is often required to reach blood pressure goals. Combined use of an ACE inhibitor and an angiotensin-II receptor antagonist is not recommended due to increased risk of adverse events.[75] However, most people with chronic kidney disease (CKD) should receive an ACE inhibitor or an angiotensin-II receptor antagonist as part of their antihypertensive regimen.[74]
  1[A Evidence CKD is defined as (a) age <70 years with glomerular filtration rate (GFR) <60 mL/minute/1.73 m², or (b) people of any age with albuminuria >30 mg albumin/g of creatinine at any level of GFR.
- Beta-blockers are not contraindicated in people with diabetes but are less-preferred antihypertensive agents[74] and may mask symptoms of hypoglycemia. ACE inhibitors may increase risk for hypoglycemia in conjunction with insulin or an insulin secretagogue (e.g., sulfonylurea or meglitinide).[77]
- If blood pressure remains uncontrolled on first-line therapies, discontinue or minimize interfering substances such as nonsteroidal anti-inflammatory drugs (NSAIDs), evaluate for secondary
Type 2 diabetes mellitus in adults

Treatment

causes of hypertension (including obstructive sleep apnea), and consider the addition of a mineralocorticoid receptor agonist,[78] and/or refer to a hypertension specialist.

• Blood pressure goals and guidelines are evolving as more studies are carried out. The Systolic Blood Pressure Intervention Trial (SPRINT) was terminated early, as it found that a lower systolic target of 120 mmHg reduced cardiovascular complications and deaths in people over age 50 years with high blood pressure and at least one additional risk factor for heart disease.[79] However, people with diabetes were excluded from this trial.

• There is an increasing emphasis to incorporate the use of home blood pressure monitoring into the diagnosis and management of hypertension in adults, including those with diabetes.[80]

Lipids

• The American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend high-intensity statin therapy if tolerated in adults ages over 21 years if the patient has clinical atherosclerotic cardiovascular disease (ASCVD) or low-density lipoprotein (LDL)-cholesterol ≥190 mg/dL.[55] In those ages 40 to 75 years with diabetes but no ASCVD, moderate-intensity statin therapy should be considered. In those with diabetes and 10-year ACC/AHA cardiovascular risk greater than 20%, consider adding ezetimibe to maximally-tolerated statin therapy to reduce LDL by 50% or more.[55] In diabetes patients over age 75 years, it is reasonable to consider and discuss with the patient advantages and disadvantages of initiation or continuation of statin therapy.[55] In those ages 20 to 39 years with diabetes, it may be reasonable to initiate statin therapy in the presence of albuminuria, estimated GFR <60 mL/minute/1.73 m², retinopathy, or neuropathy.[55] Statins are contraindicated in pregnancy.

• The American Diabetes Association (ADA) recommends that management of lipid abnormalities is driven by risk status rather than LDL cholesterol level.[2] Risk factors for cardiovascular disease include LDL-cholesterol >100 mg/dL, high blood pressure, smoking, and overweight and obesity. Lifestyle therapy is recommended for all people. For people with diabetes and overt cardiovascular disease, high-intensity statin therapy is added to lifestyle therapy, regardless of baseline lipid values. High-intensity statin therapy is also considered for those over age 40 years without overt cardiovascular disease, but with one or more cardiovascular disease (CVD) risk factors. For people with diabetes over age 40 years without additional CVD risk factors, moderate-intensity statin therapy is still considered. For some patients with diabetes and established coronary heart disease who have persistently elevated LDL despite maximally-tolerated statin therapy, addition of ezetimibe or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (e.g., alirocumab, evolocumab) may confer clinical benefit.[2] [81] [82] [83]

Smoking cessation

• Patients who smoke should be provided with smoking cessation resources, and be provided with smoking cessation assistance such as medications and counseling as appropriate. Varenicline combined with nicotine replacement therapy may be more effective than varenicline alone.[84] The ADA does not support e-cigarettes as an alternative to smoking or to facilitate smoking cessation.[2]

Antiplatelet therapy

• Adults with cardiovascular disease should receive aspirin for secondary prevention. Clopidogrel is an alternative for patients with aspirin allergy or intolerance. Dual antiplatelet therapy is reasonable for up to 12 months after an acute coronary syndrome. The main adverse effect is an increased risk of gastrointestinal bleeding.[2] [85]
• The ADA recommends that aspirin therapy be considered for primary prevention in adults with type 2 diabetes ages 50 to 70 years who are at increased cardiovascular risk (family history of premature cardiovascular disease, hypertension, dyslipidemias, smoking, chronic kidney disease/albuminuria), unless they are at high risk of serious bleeding.[2]
• US Preventive Services Task Force (USPSTF) recommendations for primary prevention of heart attack or stroke in those ages 50 to 70 years are similar.[86]

### Antihyperglycemic pharmacotherapy: initial considerations

HbA1c goals should be individualized.[87] [88] For many patients, the goal HbA1c <7% is appropriate. However, HbA1c 7.0% to 7.9% may be more appropriate in some patients, such as those with advanced age, limited life expectancy, known cardiovascular disease, high risk of severe hypoglycemia, or difficulty achieving lower HbA1c goals despite use of multiple antihyperglycemic medications and insulin.[2] Individualized HbA1c goals improve quality of life compared with uniform tight control.[88]

If HbA1c is above goal, pharmacotherapy is recommended to reduce risk of both microvascular (nephropathy, retinopathy, neuropathy) and macrovascular (myocardial infarction, stroke, peripheral vascular disease) complications.[89] [90] Data suggest that preventing major cardiovascular events and renal complications of diabetes may be affected not only by HbA1c levels but also by strategic selection of specific antihyperglycemic medications. Some specific antihyperglycemic medications significantly reduce all-cause or cardiovascular mortality, or major cardiovascular events or renal complications in some patient subgroups, and for such patients, these agents may be preferred.[67] Among the antihyperglycemic medications that reduce cardiovascular mortality in some patient subgroups are metformin,[91] empagliflozin, canagliflozin, and liraglutide.[67]

In older studies such as ACCORD, ADVANCE, and the Veterans Affairs Diabetes Trial (VADT), use of multiple drugs to achieve near-normal HbA1c was either not beneficial or increased mortality in type 2 diabetes patients with CVD or high CVD risk.[92] [93] [94] [95] [96] However, sodium-glucose co-transporter 2 (SGLT2) inhibitors were not available and glucagon-like peptide-1 (GLP-1) agonists were infrequently used in those studies.

Patients with type 2 diabetes using multiple daily insulin injections or an insulin pump should self-monitor blood glucose three or more times daily. For patients using less frequent insulin injections or noninsulin therapies, self-monitoring may be useful to guide therapy.[2]

Choice of agents should be individualized, taking into account patient values and preferences, the likelihood that an agent reduces all-cause or cardiovascular mortality, renal effects, adverse effects, costs, and other factors.

Metformin is the recommended first-choice therapy at diagnosis in the absence of contraindications because of its safety profile and likely cardiovascular benefit.[89] [91] Metformin may be safely used in patients with reduced estimated glomerular filtration rates (eGFRs), but it is contraindicated if eGFR <30 mL/minute/1.73 m².[2] [97] Metformin should not be initiated if the eGFR is <45 mL/minute/1.73 m², and, for patients taking metformin whose eGFR falls to within the 30-45 mL/minute/1.73 m² range, continued use can be considered with close monitoring of renal function and a dose reduction.[97] [98]

People who are unable to take metformin due to contraindications or intolerance can either use an alternative noninsulin agent or start insulin therapy. Basal-bolus insulin is used as initial treatment (without metformin) for those with type 2 diabetes and very high initial glucose levels (>300 mg/dL).
In patients with diabetes without diagnosed cardiovascular disease, if metformin is used as initial treatment and fails to achieve goals after 3 months, a second agent may be added based on individualized assessment of necessary clinical benefit, safety considerations, costs, and patient preference:[97]

- Sodium-glucose co-transporter 2 (SGLT2) inhibitor: canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin
- Glucagon-like peptide-1 (GLP-1) agonist: liraglutide, exenatide, lixisenatide, semaglutide, or dulaglutide
- Dipeptidyl peptidase-4 (DPP-4) inhibitor: sitagliptin, saxagliptin, linagliptin, or alogliptin
- Sulfonylurea: glimepiride or glipizide; meglitinides (e.g., repaglinide, nateglinide) are an alternative
- Alpha-glucosidase inhibitor: acarbose or miglitol
- Thiazolidinedione: pioglitazone or rosiglitazone
- Insulin.

In patients with diabetes and with diagnosed cardiovascular disease, if metformin is used as initial treatment and fails to achieve goals after 3 months, a second agent may be added. Addition of a SGLT2 inhibitor or GLP-1 agonist is recommended in patients with longstanding suboptimal glycemic control plus established cardiovascular and/or renal disease.[2] [97] [99]

- SGLT2 inhibitor: canagliflozin or empagliflozin may be preferred.
- GLP-1 agonist: liraglutide may be preferred.

There are many appropriate 3-agent combinations of glucose-lowering therapy that do not involve insulin. Choice of second and third antihyperglycemic medications may differ depending on cardiovascular comorbidities.[97] When 2- or 3-drug noninsulin regimens fail, basal insulin can be added. Bolus insulin can be subsequently added if needed to achieve or maintain adequate glucose control. To reduce the risk of hypoglycemia, a sulfonylurea is usually tapered if insulin is started.

**Clinical properties of specific oral antihyperglycemic agents**

Agents are often selected based on a discussion with the patient of the pros and cons of the agents. Agents that reduce all-cause or cardiovascular mortality may be preferred.[36]

- Metformin can promote weight loss and may reduce cardiovascular events and mortality.[89] [91]
- SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin) inhibit renal glucose reabsorption. The resulting increase in glycosuria improves glycemic control, promotes weight loss, and has a diuretic effect that reduces blood pressure.[100] There is evidence that use of SGLT2 inhibitors prevents major kidney outcomes (dialysis, transplantation, or death due to kidney disease) in people with type 2 diabetes.[101] Empagliflozin and canagliflozin have been shown to reduce cardiovascular risk in people with CVD and type 2 diabetes, and may have renal benefits.[67] [102] [103] [104] [105] Empagliflozin and canagliflozin have been shown to significantly reduce cardiovascular or all-cause mortality in those with diabetes and established cardiovascular disease.[106] [107] [108] In one trial, treatment with dapaglifozin in patients with type 2 diabetes who had, or were at risk for, atherosclerotic cardiovascular disease did not result in a lower rate of major adverse cardiovascular events, but did report a lower rate of hospitalization for heart failure.[109] Trials on the CVD benefits of ertugliflozin are ongoing.[110] [111] [112] Adverse effects for different agents have included a higher rate of genital infections, diabetic ketoacidosis, acute kidney injury, fracture, and/or amputation.[106] [113] [114] Notably, the Food and Drug Administration (FDA) has confirmed an increased risk of leg and foot amputations with
Type 2 diabetes mellitus in adults

Treatment

canagliflozin.[115] The European Medicines Agency (EMA) also warns of the potential increased risk of toe amputation with SGLT2 inhibitors.[116] The FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA) warn of cases of necrotizing fasciitis of the perineum (also known as Fournier gangrene) observed in post-marketing surveillance of SGLT2 inhibitors.[117][118] Thus, SGLT2 inhibitors should be avoided in patients with conditions that increase the risk for limb amputations, and in patients prone to urinary tract or genital infections.

• GLP-1 agonists (liraglutide, exenatide, lixisenatide, semaglutide, dulaglutide) are suitable for obese patients without gastroparesis who desire weight loss, are willing to take injections, and can tolerate the common adverse effect of initial nausea.[119] In one review, GLP-1 agonist use led to loss of 1.4 kg versus placebo, and loss of 4.8 kg versus insulin.[120] As a class of drugs, GLP-1 agonist treatment has beneficial effects on cardiovascular, mortality, and kidney outcomes in patients with type 2 diabetes.[121] Liraglutide significantly reduced cardiovascular mortality and all-cause mortality in those with diabetes and cardiovascular disease or high CVD risk in one randomized trial.[122] Dulaglutide and semaglutide have both been shown to reduce major cardiovascular events, but not all-cause or cardiovascular mortality.[123][124][125] Exenatide and lixisenatide have both been shown not to reduce major cardiovascular events.[126] The MHRA warns of cases of diabetic ketoacidosis in patients with type 2 diabetes on a combination of a GLP-1 receptor agonist and insulin who had doses of concomitant insulin rapidly reduced or discontinued.[127]

• DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin) are well tolerated, weight-neutral, but confer no mortality benefit.

• Sulfonylureas (glipizide, glimepiride, glyburide) are the subject of long clinical experience and may reduce microvascular complications, but confer no mortality benefit and may cause weight gain and hypoglycemia.[97] Along with metformin and human insulin, these are among the more affordable antihyperglycemic medications.[128]

• Alpha-glucosidase inhibitors (acarbose, miglitol) can be added to metformin in people with large postprandial glucose excursions, but increased flatus and gastrointestinal (GI) side effects are common. There is no strong evidence of a benefit on all-cause or cardiovascular mortality.

• Thiazolidinediones (pioglitazone, rosiglitazone) lower blood sugar effectively but more than double the risk of congestive heart failure, often causing weight gain and edema.[97] They may cause anemia and increase fracture rates in both women and men. In addition, rosiglitazone raises LDL-cholesterol and mixed evidence suggests rosiglitazone may increase the risk of cardiovascular events.[129] Rosiglitazone has been removed from the European market due to persistent safety concerns.[130] However, in 2013, the FDA lifted previous restrictions applied to rosiglitazone in the US, based on newer data.[131] As a result of an updated review, the FDA has concluded that use of pioglitazone may be linked to an increased risk of bladder cancer.[132]

• Bromocriptine and colesevelam are oral agents approved by the FDA for glucose-lowering. They have limited impact on blood glucose in many patients. Bromocriptine may cause GI side effects. Colesevelam, originally approved as a bile-acid sequestrant, requires multiple doses per day, and may bind other medications. Neither of these agents is widely used for glucose control at present.

**Insulin therapy**

Insulin therapy is required for severe hyperglycemia and is an option when metformin monotherapy or multidrug regimens are inadequate. Usually this is initiated with long-acting basal insulin at bedtime. Some patients’ blood sugars can be well controlled with a combination of noninsulin therapy and one injection of basal insulin. However, some patients will need to use both a long-acting basal insulin (e.g., detemir, glargine, or degludec) injection once daily and rapid-acting insulin (e.g., lispro, aspart, or glulisine) injected before each meal. Intermediate (NPH) and short-acting (regular) insulins are other
choices for basal-bolus regimens. For patients with type 2 diabetes, human insulins are as effective as analog insulins for glucose control, serious hypoglycemia risk, and mortality and cardiovascular events.[133] Human insulins are less expensive than analog insulins. Premixed insulin is available. Regimens should be individualized. Insulin delivery devices that can be programmed to administer set doses of insulin are now available and may be used by patients to help them achieve glycemic control. As insulin doses increase, any sulfonylurea should be tapered, but metformin may be continued.

Insulin treatment should be considered at the time of diagnosis if glucose level is ≥300 mg/dL or if HbA1c is ≥10%. For these patients with marked hyperglycemia, metformin can be used adjunctively, in the absence of nausea, vomiting, or volume depletion.

Exogenous insulin is a very effective way to lower serum glucose and lower HbA1c, but its use must be guided in most patients by regular self-monitored blood glucose testing. Hypoglycemia (glucose ≤70 mg/dL) is the most serious potential complication of insulin therapy. Another significant side effect is weight gain. Less common side effects may include hunger, nausea, diaphoresis, injection site irritation, or anaphylaxis.

**Correction doses of insulin**

When basal-bolus insulin is used by motivated and knowledgeable patients, the dose of rapid-acting insulin that is administered before each meal can be based on anticipated carbohydrate content of the upcoming meal and sometimes adjusted for anticipated physical activity. Correctional doses of rapid-acting insulin can also be applied based on premeal blood sugar readings (correctional algorithms). One acceptable method of determining a correction algorithm is to divide 1800 by the total daily dose of insulin to yield the expected blood sugar reduction per unit of insulin. For example, for a patient taking 60 units of insulin per day, the expected blood sugar lowering of 1 additional unit of insulin would be 1800/60=30 mg/dL.

**Bariatric surgery for treatment of diabetes in patients with obesity**

Randomized clinical trials have shown a benefit from bariatric surgery (also referred to as metabolic surgery) with regard to diabetes remission, glycemic control, need for glucose-lowering medications, quality of life, and reduction in cardiovascular risk factor markers over the short term (e.g., 1-3 years) in people with type 2 diabetes compared with medical therapy alone,[134] [135] [136] [137] [138] as well as for possible prevention of type 2 diabetes.[139] Cohort studies suggest that both Roux en Y bypass and sleeve gastrectomy procedures lead to diabetes remission that lasts a mean of about 5 years in more than half of patients, and significantly reduce mortality, stroke, myocardial infarction, and microvascular complications in those with type 2 diabetes.[140] [141] [142] Compared with sleeve gastrectomy, Roux en Y leads to somewhat greater weight loss and other benefits, but is a more technically challenging operation with higher reoperation and readmission rates. The benefits and risks of bariatric surgery also vary substantially across type 2 diabetes patient subgroups. In observational studies, average benefits appeared to be highest in those who are younger (age 40-50 years), those with more recent onset of type 2 diabetes, and those not on insulin therapy.[143]

Health insurers in the US generally restrict payment for bariatric surgery, but the eligibility criteria have been slowly expanding over time. Bariatric surgery may be considered for adults with BMI ≥40 kg/m² (≥37.5 kg/m² for Asian-Americans) with any level of glycemic control/any complexity of glucose-lowering regimen.[2] Surgery may also be considered for adults with BMI 35.0 to 39.9 kg/m² (32.5 to 37.4 kg/m² for Asian-Americans) with hyperglycemia inadequately controlled despite lifestyle and optimal medical
Type 2 diabetes mellitus in adults

management, and may be considered for those with BMI 30.0 to 34.9 kg/m² (27.5 to 32.4 kg/m² for Asian-Americans) with hyperglycemia inadequately controlled despite optimal use of oral or injectable medications (including insulin).[2] Bariatric surgery is best done in a high-volume, specialized center.[2]

Treatment of diabetes in pregnancy

Good glucose control with HbA1c as close to normal as is safely possible (ideally HbA1c <6.5% [48 mmol/mol]) before conception and during pregnancy optimizes maternal and fetal health outcomes.[2] [144] [2] Evidence ADA guidelines recommend the following blood glucose targets in pregnant women with preexisting type 2 diabetes (the same as for gestational diabetes): <95 mg/dL fasting, and either ≤140 mg/dL 1-hour postprandially or ≤120 mg/dL 2-hour postprandially, with HbA1c goal individualized between <6% and <6.5% or up to <7% as necessary to prevent hypoglycemia.[2]

In clinical practice, insulin is usually used when nutrition therapy fails to achieve these goals. NPH insulin may be combined with human short-acting or analog rapid-acting insulin. Long-acting analog insulins (glargine, detemir, or degludec) are not FDA-approved in pregnancy. ACE inhibitors, angiotensin-II receptor antagonists, and beta-blockers are not recommended in pregnancy and should be avoided. Statins are contraindicated in pregnancy. Retinal exam in those with diabetes prior to pregnancy should be performed prior to, during, and after pregnancy. Women with diabetes who anticipate pregnancy or who are pregnant benefit from care supervision by a specialized center whenever possible.

Care delivery models

Diabetes care in the US has, on average, dramatically improved in the past 20 years, with a 50% reduction in mortality rates, cardiovascular mortality rates, and cardiovascular event rates in adults with diabetes.[14] Many factors have contributed to diabetes care improvement and better clinical outcomes for patients.[147] The principal model used to frame these strategies is the Chronic Care Model.[148] The model includes 6 core elements: delivery system design, self-management support, decision support, clinical information systems, community resources and policies, and health systems.

Evidence is generally supportive of the following care improvement strategies.

- A multidisciplinary team approach to patient care, including the involvement of trained diabetes self-management educators, pharmacists, and case managers[149] [150]
- Advanced and integrated electronic medical record clinical decision support beyond simple reminder systems and alerts[151] [152]
- Simulated case-based learning interventions for clinicians.[153] [154] [155]

Other redesigns to the care delivery system such as alternative reimbursement methods, public policy changes to support healthier lifestyles, the patient-centered medical home, and mobile health (mHealth) technology may provide additional opportunities to improve care and are currently being evaluated.[156] [157] Diabetes management decisions should be timely, rely on evidence-based guidelines, and be made collaboratively with the patient.

Treatment details overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer.
### Initial treatment at initial diagnosis

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<th>1st</th>
<th>lifestyle changes</th>
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<tr>
<td>plus</td>
<td>glycemic management</td>
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<td>antiplatelet therapy</td>
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### Acute

#### marked hyperglycemia nonpregnant: serum glucose ≥300 mg/dL or HbA1c ≥10% or symptomatic

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<td>basal-bolus insulin + cardiovascular risk reduction/lifestyle measures</td>
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<td>metformin</td>
<td>alpha-glucosidase inhibitor added to continued metformin + continued cardiovascular risk reduction/lifestyle measures</td>
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#### marked hyperglycemia nonpregnant asymptomatic: serum glucose <300 mg/dL or HbA1c <10%

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<td>metformin + cardiovascular risk reduction/lifestyle measures</td>
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<td>HbA1c above goal at diagnosis</td>
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<td>HbA1c above goal on metformin</td>
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<td>switch to basal-bolus insulin + continued cardiovascular risk reduction/lifestyle measures</td>
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<td>pregnant</td>
<td>1st diet + basal-bolus insulin</td>
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Treatment options

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer.
### Initial treatment at initial diagnosis

**1st lifestyle changes**

- Although pharmacotherapy is usually indicated in patients with HbA1c >7%, lifestyle changes are key to diabetes management.

- The cornerstone of therapy for all patients with diabetes is a personalized self-management program, usually developed by a diabetes education nurse or nutritionist.[2] [57] [58] General nutrition and healthy lifestyle information and an individualized nutrition and exercise plan based on an initial assessment and treatment goals can significantly reduce diabetes distress.[60]

- Nutrition therapy involves limiting caloric intake to achieve recommended weight, while offering a diversified and appealing menu of food choices. Nutrition advice needs to be tailored to the needs of each individual patient.[2] [24] [68] The optimal mix of carbohydrate, fats, and protein depends upon renal status, achieved lipid levels, body mass index, and level of glycemic control, among other factors. Reducing sugary beverage consumption (including milk, soda, energy drinks, and fruit juice) is of benefit to many patients.

- Moderate physical activity is recommended as tolerated to improve glycemic control, assist with weight maintenance, and reduce cardiovascular risk. It is recommended that, in general, adults should engage in 3 to 4 sessions of aerobic physical activity per week, with each session lasting on average 40 minutes and involving moderate- to vigorous-intensity physical activity.[73]

- Weight loss management programs with a healthy eating and physical activity plan resulting in an energy deficit have the potential for type 2 diabetes remission.[24] [70] [71]

- Alcohol use (more than 2 drinks daily for men or 1 for women) increases risk of hypoglycaemia, as well as other untoward events.

- Smoking cessation is imperative. Patients who smoke should be provided with smoking cessation resources and assistance.

- Achieving recommended goals for weight management, nutrition, and physical activity benefits many aspects of health, including glucose, blood pressure, lipid control, and
### Initial

Depression prevention or control, and decreases risk of major cardiovascular events and onset or progression of microvascular complications.

### Glycemic management

Treatment recommended for ALL patients in selected patient group

- All patients should receive stratified glycemic management upon diagnosis.
  - HbA1c goals should be individualized,[87] and if HbA1c is above goal, pharmacotherapy recommended.
  - Choice of agents should be individualized, taking into account patient values and preferences, likelihood that an agent reduces all-cause or cardiovascular mortality, adverse effect profiles, costs, and other factors. For most patients, metformin will be initial therapy, but insulin may be required for marked hyperglycemia.
  - Consult a specialist for guidance on treating pregnant women.

### Blood pressure management

Treatment recommended for ALL patients in selected patient group

#### Primary options

- **Hydrochlorothiazide**: 12.5 to 25 mg/day orally once daily initially, increase gradually according to response, maximum 50 mg/day as a single dose or in 2 divided doses
  - or-
- **Chlorthalidone**: 12.5 mg orally once daily initially, increase gradually according to response, maximum 50 mg/day
  - or-
- **Indapamide**: 1.25 mg orally once daily initially, increase gradually according to response, maximum 5 mg/day
  - and/or-
- **Lisinopril**: 10 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day
  - or-
- **Enalapril**: 5 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day as a single dose or in 2 divided doses
  - or-
- **Captopril**: 25 mg orally twice daily initially, increase gradually according to response, maximum 200 mg/day
**Initial**

- **or** -
  - candesartan cilexetil: 4 mg orally once daily initially, increase gradually according to response, maximum 32 mg/day
- **or** -
  - irbesartan: 75 mg orally once daily initially, increase gradually according to response, maximum 300 mg/day
- **or** -
  - losartan: 50 mg orally once daily initially, increase gradually according to response, maximum 100 mg/day as a single dose or in 2 divided doses
- **or** -
  - valsartan: 40-80 mg orally once daily initially, increase gradually according to response, maximum 320 mg/day

--AND/OR--

- **or** -
  - amlodipine: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day
- **or** -
  - felodipine: 2.5 mg orally once daily initially, increase gradually according to response, maximum 10 mg/day
- **or** -
  - nifedipine: 30-60 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 90 mg/day
- **or** -
  - diltiazem: 120-180 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 480 mg/day

**Adults with type 2 diabetes are twice as likely to die of stroke or myocardial infarction (MI) compared with those without diabetes, and they are more than 40 times more likely to die of macrovascular than microvascular complications of diabetes.**[61] [62] [63] A primary goal of diabetes care is evidence-based management of cardiovascular risk factors to individualized goals.

- Blood pressure guidelines differ somewhat regarding recommended blood pressure targets for those with diabetes; however, American Diabetes Association (ADA) guidelines recommend a treatment goal of <140/90 mmHg or <130/80 mmHg for those with diabetes and cardiovascular disease or cardiovascular risk >15%. [2] [56] [74]

- Combination therapy is often required to reach blood pressure goals. Antihypertensive therapy may be initiated with a thiazide (or thiazide-like) diuretic, a calcium-channel blocker, an ACE
Type 2 diabetes mellitus in adults

Treatment

Initial

inhibitor, or an angiotensin-II receptor antagonist. Antihypertensive drugs for black people may be initiated with a thiazide diuretic or a calcium-channel blocker.[74] ACE inhibitors may reduce mortality and cardiovascular events more than angiotensin-II receptor antagonists.[66] Combining an ACE inhibitor with an angiotensin-II receptor antagonist is not recommended due to increased risk of adverse events.[75] However, most people with chronic kidney disease (CKD) should receive an ACE inhibitor or an angiotensin-II receptor antagonist as part of their regimen.[74].

Evidence CKD is defined as (a) age <70 years with glomerular filtration rate (GFR) <60 mL/minute/1.73 m², or (b) people of any age with albuminuria >30 mg albumin/g of creatinine at any level of GFR.

» If blood pressure remains uncontrolled on first-line therapies, discontinue or minimize interfering substances such as nonsteroidal anti-inflammatory drugs (NSAIDs), evaluate for secondary causes of hypertension (including obstructive sleep apnea), and consider the addition of a mineralocorticoid receptor agonist,[78] and/or refer to a hypertension specialist.

» Beta-blockers are not contraindicated in people with diabetes but are less-preferred antihypertensive agents[74] and may mask symptoms of hypoglycemia.

» ACE inhibitors may increase risk for hypoglycemia in conjunction with insulin or insulin secretagogue (sulfonylurea or meglitinide).[77]

» Consult a specialist for guidance on treating pregnant women. ACE inhibitors, angiotensin-II receptor antagonists, and beta-blockers are not recommended in pregnancy and should be avoided if possible.

plus lipid management

Treatment recommended for ALL patients in selected patient group

Primary options

» atorvastatin: moderate intensity: 10-20 mg orally once daily; high intensity: 40-80 mg orally once daily

OR
### Treatment

#### Initial

<table>
<thead>
<tr>
<th>Drug</th>
<th>Intensity</th>
<th>Dose and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>rosuvastatin</td>
<td>moderate intensity</td>
<td>5-10 mg orally once daily; high intensity: 20-40 mg orally once daily</td>
</tr>
<tr>
<td>simvastatin</td>
<td>moderate intensity</td>
<td>20-40 mg orally once daily; increased risk of myopathy with 80 mg/day dose</td>
</tr>
<tr>
<td>pravastatin</td>
<td>moderate intensity</td>
<td>40-80 mg orally once daily</td>
</tr>
<tr>
<td>lovastatin</td>
<td>moderate intensity</td>
<td>40-80 mg orally (immediate-release) once daily</td>
</tr>
<tr>
<td>fluvastatin</td>
<td>moderate intensity</td>
<td>40 mg orally (immediate-release) twice daily, or 80 mg orally (extended-release) once daily</td>
</tr>
<tr>
<td>pitavastatin</td>
<td>moderate intensity</td>
<td>1-4 mg orally once daily</td>
</tr>
</tbody>
</table>

#### Secondary options

<table>
<thead>
<tr>
<th>Drug</th>
<th>Intensity</th>
<th>Dose and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>atorvastatin</td>
<td>moderate intensity</td>
<td>10-20 mg orally once daily; high intensity: 40-80 mg orally once daily</td>
</tr>
<tr>
<td>rosuvastatin</td>
<td>moderate intensity</td>
<td>5-10 mg orally once daily; high intensity: 20-40 mg orally once daily</td>
</tr>
<tr>
<td>simvastatin</td>
<td>moderate intensity</td>
<td>20-40 mg orally once daily; increased risk of myopathy with 80 mg/day dose</td>
</tr>
<tr>
<td>pravastatin</td>
<td>moderate intensity</td>
<td>40-80 mg orally once daily</td>
</tr>
<tr>
<td>lovastatin</td>
<td>moderate intensity</td>
<td>40-80 mg orally (immediate-release) once daily</td>
</tr>
<tr>
<td>fluvastatin</td>
<td>moderate intensity</td>
<td>40 mg orally (immediate-release) twice daily, or 80 mg orally (extended-release) once daily</td>
</tr>
</tbody>
</table>
Type 2 diabetes mellitus in adults

Treatment

Initial

- **pitavastatin**: moderate intensity: 1-4 mg orally once daily
  --AND--
  - **ezetimibe**: 10 mg orally once daily

Tertiary options

- **atorvastatin**: moderate intensity: 10-20 mg orally once daily; high intensity: 40-80 mg orally once daily
  - **rosuvastatin**: moderate intensity: 5-10 mg orally once daily; high intensity: 20-40 mg orally once daily
  - **simvastatin**: moderate intensity: 20-40 mg orally once daily; increased risk of myopathy with 80 mg/day dose
  - **pravastatin**: moderate intensity: 40-80 mg orally once daily
  - **lovastatin**: moderate intensity: 40-80 mg orally (immediate-release) once daily
  - **fluvastatin**: moderate intensity: 40 mg orally (immediate-release) twice daily, or 80 mg orally (extended-release) once daily
  - **pitavastatin**: moderate intensity: 1-4 mg orally once daily
  --AND--
  - **ezetimibe**: 10 mg orally once daily
  --AND--
  - **evolocumab**: 140 mg subcutaneously every 2 weeks; or 420 mg subcutaneously once monthly
  - **alirocumab**: 75-150 mg subcutaneously every 2 weeks; or 300 mg subcutaneously once monthly

Adults with type 2 diabetes are twice as likely to die of stroke or myocardial infarction compared with those without diabetes, and they are more than 40 times more likely to die of macrovascular than microvascular complications of diabetes.[61] [62] [63] A primary goal of care is treatment of cardiovascular risk factors to individualized targets.[64]

- High-intensity statin therapy is recommended as tolerated in diabetes patients with atherosclerotic cardiovascular disease (ASCVD), 10-year cardiovascular risk >20%, or low-density lipoprotein (LDL)-cholesterol ≥190 mg/
### Treatment

| Initial | dL. Otherwise, in those ages 40 to 75 years, moderate-intensity statin therapy should be considered. The guidelines recommend an individualized approach for people aged >75 years. A moderate-intensity statin has been defined by the American College of Cardiology/American Heart Association as one that generally lowers LDL-cholesterol level by 30% to 50%, while a high-intensity statin has been defined as one that lowers LDL-cholesterol level by ≥50%. |

- Combination therapy using statins and other lipid-lowering agents may be considered, especially in patients with very high CVD risk. The risks of complications such as impaired liver or renal function, myositis, or rhabdomyolysis may increase when using statins in combination with other agents. Statin therapy may have some beneficial (e.g., anti-inflammatory) effects independent of lipid lowering.

- Ezetimibe or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (e.g., alirocumab, evolocumab) added to statin therapy may confer cardiovascular benefits to patients with diabetes and coronary heart disease who have LDL >70 mg/dL despite maximally-tolerated statin therapy.

- Consult a specialist for guidance on treating pregnant women. Statins are contraindicated in pregnancy. There is a lack of data on the use of ezetimibe and PCSK9 inhibitors in pregnancy.

#### adjunct antiplatelet therapy

Treatment recommended for SOME patients in selected patient group

**Primary options**

- **aspirin**: 75-162 mg orally once daily

**Secondary options**

- **clopidogrel**: 75 mg orally once daily

OR

- **aspirin**: 75-162 mg orally once daily
- **clopidogrel**: 75 mg orally once daily

Adults with cardiovascular disease should receive aspirin for secondary prevention.
Aspirin therapy may be considered for primary prevention in adults with type 2 diabetes ages 50 to 70 years who are at increased cardiovascular risk and do not have a contraindication to aspirin therapy.[2]

Clopidogrel is an alternative for patients with aspirin allergy or intolerance.

Dual antiplatelet therapy is often recommended for up to 1 year after an acute coronary syndrome. The main adverse effect is an increased risk of gastrointestinal bleeding.[2][85]

The FDA released a statement in 2014 citing inadequate evidence to support widespread use of aspirin for primary prevention of cardiovascular events.[160]

Consult a specialist for guidance on treating pregnant women.
<table>
<thead>
<tr>
<th>Acute</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>marked hyperglycemia nonpregnant: serum glucose ≥300 mg/dL or HbA1c ≥10% or symptomatic</td>
<td>1st</td>
<td>basal-bolus insulin + cardiovascular risk reduction/lifestyle measures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary options</td>
</tr>
<tr>
<td></td>
<td>» insulin NPH: injected subcutaneously twice daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-and-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>» insulin regular: injected subcutaneously two to three times daily</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>» insulin glargine: injected subcutaneously once daily</td>
<td>-or-</td>
<td></td>
</tr>
<tr>
<td>» insulin detemir: injected subcutaneously twice daily</td>
<td>-or-</td>
<td></td>
</tr>
<tr>
<td>» insulin degludec: injected subcutaneously once daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--AND--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>» insulin lispro: injected subcutaneously premeals</td>
<td>-or-</td>
<td></td>
</tr>
<tr>
<td>» insulin aspart: injected subcutaneously premeals</td>
<td>-or-</td>
<td></td>
</tr>
<tr>
<td>» insulin glulisine: injected subcutaneously premeals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>» insulin NPH/insulin regular: (50/50, 70/30) injected subcutaneously twice daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>» insulin aspart protamine/insulin aspart: (70/30) injected subcutaneously twice daily</td>
<td></td>
<td></td>
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<tr>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>» insulin lispro protamine/insulin lispro: (50/50, 75/25) injected subcutaneously twice daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>» insulin degludec/insulin aspart: (70/30) injected subcutaneously once or twice daily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Treatment

<table>
<thead>
<tr>
<th>Acute</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>with any main meal; administer a rapid- or short-acting insulin at other meals if needed</td>
<td></td>
</tr>
<tr>
<td>» Immediate insulin therapy should be considered for marked hyperglycemia.</td>
<td></td>
</tr>
<tr>
<td>» Multidose insulin therapy can be started with long-acting insulin at 0.1 to 0.2 units/kg/day in the morning or bedtime. Adjustments can be made by 2-4 units every 3 days until fasting blood sugar levels are within target range. If premeal sugars remain over target, rapid-acting insulin can be added at meals (approximately 4 units) and titrated by 2 units every 3 days until within the desired range. It is common to start rapid-acting insulin with the meal with the largest blood sugar excursion and add injections for other meals as needed. The need for prandial insulin becomes more likely as the total insulin doses exceed 0.5 units/kg.[97]</td>
<td></td>
</tr>
<tr>
<td>» Insulin dose varies, with some patients with very poor control needing more aggressive management; consult specialist as needed for guidance on dose.</td>
<td></td>
</tr>
<tr>
<td>» Choice of insulin regimen should be individualized. For patients with type 2 diabetes, human insulins are as effective as analog insulins for glucose control, serious hypoglycemia risk, and mortality and cardiovascular events.[133] Human insulins are much less expensive than analog insulins. Premixed insulin may start with a total of about 0.3 units/kg/day dose of insulin, with two-thirds dose in the morning and one third in the evening, and titrated up until goals are achieved or hypoglycemia prevents further titration. Insulin delivery devices that can be programmed to administer set doses of insulin are now available and may be used by patients to help them achieve glycemic control.</td>
<td></td>
</tr>
<tr>
<td>» General nutrition and healthy lifestyle knowledge (including an individualized nutrition and exercise plan) can improve glycemic control and quality of life.[24] [58]</td>
<td></td>
</tr>
<tr>
<td>» Cardiovascular risk reduction (blood pressure and lipid control, nonsmoking, and consideration of antiplatelet therapy) should be instituted.</td>
<td></td>
</tr>
</tbody>
</table>

**adjunct**

**metformin**

Treatment recommended for SOME patients in selected patient group

**Primary options**
### Acute

<table>
<thead>
<tr>
<th><strong>without marked hyperglycemia</strong></th>
<th><strong>nonpregnant asymptomatic: serum glucose &lt;300 mg/dL or HbA1c &lt;10%</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c above goal at diagnosis</td>
<td>1st metformin + cardiovascular risk reduction/lifestyle measures</td>
</tr>
<tr>
<td></td>
<td>Primary options</td>
</tr>
<tr>
<td></td>
<td>• metformin: 500 mg orally (immediate-release) once daily initially, increase by 500 mg/day increments every week, maximum 1000 mg twice daily</td>
</tr>
</tbody>
</table>

- Metformin may be given adjunctively, in the absence of nausea/vomiting or volume depletion.

- Metformin reduces hyperglycemia by decreasing hepatic gluconeogenesis and glycogenolysis. At maximal effective doses, metformin may reduce HbA1c by 1% to 2%. It confers a cardiovascular benefit, rarely is associated with weight gain, is inexpensive, and has a beneficial effect on low-density lipoprotein cholesterol.

- The most common side effects are diarrhea, gas, and nausea, which can be attenuated by initiating slowly 500 mg orally once a day with a meal, increasing as needed by 500 mg/day every 1 to 2 weeks until full dose of 1000 mg twice a day is reached.

- Metformin is contraindicated if estimated glomerular filtration rate (eGFR) is <30 mL/minute/1.73 m². It should not be initiated if the eGFR is <45 mL/minute/1.73 m², and for patients taking metformin whose eGFR falls to within the 30-45 mL/minute/1.73 m² range, continued use can be considered with close monitoring of renal function and a dose reduction.[97] [98]

- Metformin should be stopped before surgery or contrast dye studies with radiographic dye injection until adequate post-event renal function is documented.

- Periodic testing for vitamin B12 deficiency and B12 supplementation may be needed.[2]
If HbA1c is above individualized goal, pharmacotherapy is recommended to reduce risk of microvascular (nephropathy, retinopathy, neuropathy) and macrovascular (myocardial infarction, stroke, peripheral vascular disease) complications.[89] [90]

The American Diabetes Association (ADA) recommends that metformin be started concurrently with nonpharmacologic therapy when diabetes is diagnosed, because of the difficulty in achieving and maintaining lifestyle change.[2] People unable to take metformin should initiate individualized therapy with an alternative agent.

Metformin may reduce cardiovascular mortality in type 2 diabetes.[89] [91]

Metformin reduces hyperglycemia by decreasing hepatic gluconeogenesis and glycogenolysis. At maximal effective doses, metformin may reduce HbA1c by 1% to 2%. It rarely causes hypoglycemia when used as monotherapy, rarely is associated with weight gain, is inexpensive, and has a beneficial effect on low-density lipoprotein cholesterol.

The most common side effects are diarrhea, gas, and nausea, which can be attenuated by initiating slowly 500 mg orally once a day with a meal, increasing as needed by 500 mg/day every 1 to 2 weeks until full dose of 1000 mg orally twice per day is reached.

Periodic testing for vitamin B12 deficiency and B12 supplementation may be needed.[2]

Metformin is contraindicated if estimated glomerular filtration rate (eGFR) is <30 mL/minute/1.73 m². It should not be initiated if the eGFR is <45 mL/minute/1.73 m², and for patients taking metformin whose eGFR falls to within the 30-45 mL/minute/1.73 m² range, continued use can be considered with close monitoring of renal function and a dose reduction.[97] [98]

Metformin should be stopped before surgery or contrast dye studies with radiographic dye injection until adequate post-event renal function is documented.

Those unable to take metformin due to contraindication or intolerance can either use an alternative noninsulin agent or insulin therapy.
Type 2 diabetes mellitus in adults  
TREATMENT

### Acute

<table>
<thead>
<tr>
<th>HbA1c above goal on metformin</th>
<th>1st</th>
</tr>
</thead>
</table>

» General nutrition and healthy lifestyle knowledge (including an individualized nutrition and exercise plan) can improve glycemic control and quality of life.[24] [58]

» Cardiovascular risk reduction (blood pressure and lipid control, nonsmoking, and consideration of antiplatelet therapy) should be instituted.

sodium-glucose co-transporter 2 (SGLT2) inhibitor added to continued metformin + continued cardiovascular risk reduction/ lifestyle measures

#### Primary options

- **metformin**: 500 mg orally (immediate-release) once daily initially, increase by 500 mg/day increments every week, maximum 1000 mg twice daily

--AND--

- **empagliflozin**: 10 mg orally once daily, increase according to response, maximum 25 mg/day
  - **canagliflozin**: 100 mg orally once daily initially, increase according to response, maximum 300 mg/day
  - **dapagliflozin**: 5 mg orally once daily initially, increase according to response, maximum 10 mg/day
  - **ertugliflozin**: 5 mg orally once daily initially, increase according to response, maximum 15 mg/day

» Choice of agents should be individualized. The cardiovascular benefits and safety of some agents are much more strongly established than those of other agents, and such data should be strongly considered when selecting treatments.

» The SGLT2 inhibitors canagliflozin and empagliflozin have been shown to reduce cardiovascular risk in people with cardiovascular disease (CVD) and type 2 diabetes, and have renal benefits.[101] [102] [103] [104] [107] One study of patients with type 2 diabetes and established CVD treated with empagliflozin for a median of 2.6 years resulted in lower rates of cardiovascular mortality, all-cause mortality, and hospitalization for congestive heart failure, compared with placebo.[106] Canagliflozin also reduces cardiovascular mortality,[108] but may have more adverse effects than empagliflozin. In one trial, treatment with dapagliflozin did not result in a lower rate of major adverse effects.
### Acute

cardiovascular events, but did result in a lower rate of hospitalization for heart failure.[109] Trials on the CVD benefits of ertugliflozin are ongoing.[111] [112]

» The Food and Drug Administration (FDA) has issued a warning that the SGLT2 inhibitor class of drugs (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin) may lead to ketoacidosis. Patients should seek immediate medical attention for signs of ketoacidosis (difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness).[161] The FDA has confirmed an increased risk of leg and foot amputations with canagliflozin.[115] The European Medicines Agency (EMA) also warns of the potential increased risk of toe amputation with approved SGLT2 inhibitors.[116] The FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA) warn of cases of necrotizing fasciitis of the perineum (also known as Fournier gangrene) observed in post-marketing surveillance of SGLT2 inhibitors.[117] [118]

» General nutrition and healthy lifestyle knowledge (including an individualized nutrition and exercise plan) can improve glycemic control and quality of life.[24] [58]

» Cardiovascular risk reduction (blood pressure and lipid control, nonsmoking, and consideration of antiplatelet therapy) should continue.

**1st glucagon-like peptide 1 (GLP-1) agonist added to continued metformin + continued cardiovascular risk reduction/lifestyle measures**

### Primary options

- **metformin**: 500 mg orally (immediate-release) once daily initially, increase by 500 mg/day increments every week, maximum 1000 mg twice daily

--**AND**--

- **liraglutide**: 0.6 mg subcutaneously once daily initially, increase by 0.6 mg/day increments at weekly intervals according to response, maximum 1.8 mg/day

- **dulaglutide**: 0.75 mg subcutaneously once weekly initially, may increase to 1.5 mg once weekly if response is inadequate

- **semaglutide**: 0.25 mg subcutaneously once weekly for 4 weeks initially, then increase to 0.5 mg once weekly for at least 4 weeks,
## Type 2 diabetes mellitus in adults

### Treatment

#### Acute

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>exenatide</td>
<td>5 micrograms subcutaneously twice daily initially, increase to 10 micrograms twice daily in one month; 2 mg subcutaneously (extended-release) once weekly</td>
<td>-or-</td>
</tr>
<tr>
<td>lixisenatide</td>
<td>10 micrograms subcutaneously once daily for 14 days, then increase to 20 micrograms once daily thereafter</td>
<td>-or-</td>
</tr>
</tbody>
</table>

- As a class of drugs, GLP-1 agonist treatment has beneficial effects on cardiovascular, mortality, and kidney outcomes in patients with type 2 diabetes. Choice of agents should be individualized. The cardiovascular benefits and safety of some agents are much more strongly established than those of other agents, and such data should be strongly considered when selecting treatments.

- Liraglutide has been shown to reduce major cardiovascular events, cardiovascular mortality, and all-cause mortality in diabetes patients with coronary heart disease. Dulaglutide and semaglutide have both been shown to reduce major cardiovascular events, but not all-cause or cardiovascular mortality. Exenatide and lixisenatide have both been shown not to reduce major cardiovascular events. Semaglutide is the only GLP-1 agonist that is available in both oral and injectable formulations; the other GLP-1 agonists are only available in injectable formulations.

- GLP-1 agonists stimulate glucose-dependent release of insulin, suppress glucagon levels, and may slow gastric emptying and increase satiety. GLP-1 agonists may be associated with modest initial weight loss on the order of 2 to 7 kg in some patients. GLP-1 agents may lower HbA1c up to 0.9% and may lower postprandial glucose.

- Response to the drug is quite variable and some patients will lose ground on glycemic control due to reduction in doses of other glycemic medications when used as part of multidrug regimens. Patients should be cautioned about this as well as potential risk.
### Treatment

**Acute**

of hypoglycemia, and advised to check blood sugars frequently when initiating therapy. Patients should report any new problems with high or low readings.

- The UK Medicines and Healthcare products Regulatory Agency (MHRA) warns of cases of diabetic ketoacidosis in patients with type 2 diabetes on a combination of a GLP-1 receptor agonist and insulin who had doses of concomitant insulin rapidly reduced or discontinued.[127]

- General nutrition and healthy lifestyle knowledge (including an individualized nutrition and exercise plan) can improve glycemic control and quality of life.[24] [58]

- Cardiovascular risk reduction (blood pressure and lipid control, nonsmoking, and consideration of antiplatelet therapy) should continue.

1st **dipeptidyl peptidase-4 (DPP-4) inhibitor added to continued metformin + continued cardiovascular risk reduction/lifestyle measures**

**Primary options**

- **metformin**: 500 mg orally (immediate-release) once daily initially, increase by 500 mg/day increments every week, maximum 1000 mg twice daily

- **AND**

  - **sitagliptin**: 100 mg orally once daily
  - **linagliptin**: 5 mg orally once daily
  - **alogliptin**: 25 mg orally once daily
  - **saxagliptin**: 2.5 to 5 mg orally once daily

- Choice of agents should be individualized. The safety of some agents is more strongly established than the safety of other agents, and such data should be strongly considered when selecting treatments.

- DPP-4 inhibitors do not confer cardiovascular benefit, and do not lower glucose as much as metformin, sulfonylureas, or thiazolidinediones.

- Advantages include few identified side effects, less hypoglycemia than sulfonylureas, less risk of weight gain or congestive heart failure than thiazolidinediones, and easy dosing. DPP-4 inhibitors do not appear to confer major risk of hypoglycemia when studied as monotherapy.
Type 2 diabetes mellitus in adults

Treatment

Acute

» Studies of DPP-4 inhibitors showed that saxagliptin did not alter the rate of ischemic events over about 2 years, although hospital admissions for heart failure increased.[162] In people with a recent acute coronary syndrome, alogliptin was not associated with increased risk of major adverse cardiovascular events over 40 months.[163]

» General nutrition and healthy lifestyle knowledge (including an individualized nutrition and exercise plan) can improve glycemic control and quality of life.[24][58]

» Cardiovascular risk reduction (blood pressure and lipid control, nonsmoking, and consideration of antiplatelet therapy) should continue.

1st sulfonylurea or meglitinide added to continued metformin + continued cardiovascular risk reduction/lifestyle measures

Primary options

» metformin: 500 mg orally (immediate-release) once daily initially, increase by 500 mg/day increments every week, maximum 1000 mg twice daily

---AND---

» glimepiride: 1-2 mg orally once daily initially, increase by 1-2 mg/day increments every 1-2 weeks, maximum 4 mg twice daily

-or-

» glipizide: 2.5 to 5 mg orally (immediate-release) once daily initially, increase by 2.5 to 5 mg/day increments every 1-2 weeks, maximum 10 mg twice daily; 5 mg orally (extended-release) once daily initially, increase to 10 mg once daily in 1-2 weeks if necessary

Secondary options

» metformin: 500 mg orally (immediate-release) once daily initially, increase by 500 mg/day increments every week, maximum 1000 mg twice daily

---AND---

» repaglinide: 0.5 to 1 mg orally up to four times daily initially, increase by 0.5 to 1 mg/day/ day increments every week, maximum 4 mg four times daily

-or-

» nateglinide: 60-120 mg orally three times daily initially

» Choice of agents should be individualized.
## Type 2 diabetes mellitus in adults

### Treatment

#### Acute

<table>
<thead>
<tr>
<th>1st basal insulin added to continued metformin + continued cardiovascular risk reduction/lifestyle measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary options</strong></td>
</tr>
<tr>
<td>• metformin: 500 mg orally (immediate-release) once daily initially, increase by 500 mg/day increments every week, maximum 1000 mg twice daily</td>
</tr>
<tr>
<td>• insulin NPH: injected subcutaneously, usually at bedtime</td>
</tr>
</tbody>
</table>

#### Treatment

- **Sulfonylureas** (e.g., glimepiride, glipizide) enhance the release of insulin by pancreatic islet cells by altering potassium and sodium influx.

- Sulfonylureas may reduce HbA1c by 1% to 2%. Hypoglycemia is a major concern, especially in patients with irregular or unpredictable eating and exercise habits. Hypoglycemia risk is exacerbated by alcohol, salicylates, sulfa drugs, gemfibrozil, or coumadin. In general, longer-acting sulfonylureas such as glyburide are avoided because of concern about hypoglycemia.

- In older adult patients, treatment should start with very low doses. Glimepiride may be the preferred sulfonylurea in older individuals, due to its dual hepatic/renal clearance and potentially lower risk of hypoglycemia.

- Sulfonylureas can also be given as first-line oral agents when metformin is not tolerated or is contraindicated.

- Meglitinides (e.g., repaglinide, nateglinide) are an alternative to sulfonylureas, and can also be used as a first-choice secretagogue in people with sulfa allergies. Meglitinides have a modest effect on HbA1c, with an average reduction of only 0.5%, but may help with postprandial hyperglycemia. May cause hypoglycemia; if a meal is skipped, the dose of meglitinide should be held to avoid hypoglycemia.

- General nutrition and healthy lifestyle knowledge (including an individualized nutrition and exercise plan) can improve glycemic control and quality of life.[24][58]

- Cardiovascular risk reduction (blood pressure and lipid control, nonsmoking, and consideration of antiplatelet therapy) should continue.

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### Treatment

**Acute**

- **insulin glargine**: injected subcutaneously, usually at bedtime
- **insulin detemir**: injected subcutaneously, usually at bedtime
- **insulin degludec**: injected subcutaneously once daily

Choice of agents should be individualized. Basal insulin is generally added to metformin, usually at bedtime.

- Insulin is necessary treatment in at least 20% to 30% of those with type 2 diabetes in order to achieve recommended treatment goals, related to decreasing islet cell insulin secretion after long duration of type 2 diabetes.

Patients should perform periodic home glucose monitoring and be instructed to watch for signs of hypoglycemia (shaking, sweating, intensive hunger, irritability, weakness, confusion) and promptly treat with 15 to 20 g glucose orally. Recurrent severe hypoglycemia requires ongoing close monitoring and adjustment of eating and medications to prevent recurrence.

Treatment with basal insulin can be started with 0.1 units/kg/dose subcutaneously at bedtime and increase by 2 to 3 units every several days until morning fasting blood glucose averages 90 to 130 mg/dL (for those with a HbA1c goal of <7%). Consultation with a specialist should be considered for further guidance if the patient is having difficulty achieving blood glucose levels or experiencing symptoms of hyper- or hypoglycemia.

- In obese patients, who typically are insulin-resistant, 5% to 10% increases in insulin dose every 3 to 5 days are often needed until glucose control is achieved, while taking care to avoid hypoglycemia. As insulin dose increases, sulfonylureas should be tapered, but metformin may be continued. Home glucose readings should be used to guide therapy decisions.

- General nutrition and healthy lifestyle knowledge (including an individualized nutrition and exercise plan) can improve glycemic control and quality of life.[24] [58]

- Cardiovascular risk reduction (blood pressure and lipid control, nonsmoking, and consideration of antiplatelet therapy) should continue.

2nd **alpha-glucosidase inhibitor added to continued metformin + continued**
Type 2 diabetes mellitus in adults

**Treatment**

**Acute cardiovascular risk reduction/lifestyle measures**

**Primary options**

- **metformin**: 500 mg orally (immediate-release) once daily initially, increase by 500 mg/day increments every week, maximum 1000 mg twice daily

- **acarbose**: 25 mg orally once daily initially, increase to 25 mg twice daily in 1-2 weeks, then increase to 25 mg three times daily in 1-2 weeks, continue to increase according to response, maximum 50 mg three times daily

- **miglitol**: 25 mg orally once daily initially, increase to 25 mg twice daily in 1-2 weeks, then increase to 25 mg three times daily in 1-2 weeks, continue to increase according to response, maximum 50 mg three times daily

- Choice of agents should be individualized. Alpha-glucosidase inhibitors impede the enzyme needed to split disaccharides into monosaccharides prior to absorption from the gut.

- May be combined with most other classes of glucose-lowering medication. May be useful in older adult patients with marked postprandial glucose excursions.

- Rather modest impact on HbA1c, must be taken multiple times a day, and costly. Adverse effects can be minimized by low initial doses and by very slow titration of doses.

- Any episodes of hypoglycemia must be treated with glucose tablets, because this class of medication blocks gut absorption of carbohydrates such as sucrose or fructose.

- General nutrition and healthy lifestyle knowledge (including an individualized nutrition and exercise plan) can improve glycemic control and quality of life.[24] [58]

- Cardiovascular risk reduction (blood pressure and lipid control, nonsmoking, and consideration of antiplatelet therapy) should continue.

**2nd thiazolidinedione added to continued metformin + continued cardiovascular risk reduction/lifestyle measures**

**Primary options**
### Acute

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>» metformin</strong>: 500 mg orally (immediate-release) once daily initially, increase by 500 mg/day increments every week, maximum 1000 mg twice daily</td>
<td></td>
</tr>
<tr>
<td><strong>AND</strong></td>
<td></td>
</tr>
<tr>
<td><strong>» pioglitazone</strong>: 15 mg orally once daily initially, increase every 6-8 weeks, maximum 45 mg once daily</td>
<td></td>
</tr>
<tr>
<td><strong>-or-</strong></td>
<td></td>
</tr>
<tr>
<td><strong>» rosiglitazone</strong>: 2-4 mg/day orally initially given as a single dose or in 2 divided doses, increase according to response, maximum 8 mg/day</td>
<td></td>
</tr>
</tbody>
</table>

» Choice of agents should be individualized. The benefits and safety of some agents are much more strongly established than those of other agents, and such data should be strongly considered when selecting treatments.

» Neither pioglitazone nor rosiglitazone confers a mortality benefit. Thiazolidinediones may cause fluid retention and exacerbate heart failure. Pioglitazone may be linked to an increased risk of bladder cancer.[132]

» Thiazolidinediones enhance the action of endogenous or exogenous insulin by acting at PPAR-gamma receptors. The complete mechanism of action is not fully understood. May on average reduce HbA1c 1% to 1.5%; less than insulin, metformin, or sulfonylureas.

» Hypoglycemia is rare unless combined with sulfonylurea or insulin.

» Rosiglitazone has been removed from the European market due to persistent safety concerns.[130] In 2013, the FDA lifted previous restrictions applied to rosiglitazone in the US.

» General nutrition and healthy lifestyle knowledge (including an individualized nutrition and exercise plan) can improve glycemic control and quality of life.[24] [58]

» Cardiovascular risk reduction (blood pressure and lipid control, nonsmoking, and consideration of antiplatelet therapy) should continue.

<table>
<thead>
<tr>
<th>HbA1c above goal on metformin + either basal insulin or second noninsulin agent</th>
<th>1st</th>
</tr>
</thead>
<tbody>
<tr>
<td>individualized augmented regimen + continued cardiovascular risk reduction/ lifestyle measures</td>
<td></td>
</tr>
</tbody>
</table>

» Choice of agents should be tailored to account for patient values and preferences, advantages, and adverse effects. The safety of some agents is much more strongly established than the
Type 2 diabetes mellitus in adults

TREATMENT

Acute

<table>
<thead>
<tr>
<th>safety of other agents, and such data should be strongly considered when selecting treatments.</th>
</tr>
</thead>
<tbody>
<tr>
<td>» Metformin serves as the basis for most 3-drug combinations, in the absence of contraindications. Additional agents for 3-drug regimens are selected from the same choices as for 2-drug regimens: sulfonylureas/meglitinides, dipeptidyl-peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, alpha-glucosidase inhibitors, thiazolidinediones, basal insulin, or sodium-glucose co-transporter 2 (SGLT2) inhibitors.[97] However, evidence and guidelines do not support combining a DPP-4 inhibitor and a GLP-1 agonist in the same regimen, and they are not approved for this purpose.</td>
</tr>
<tr>
<td>» The American Diabetes Association has updated its combination injectables algorithm: basal insulin plus GLP-1 agonist, basal insulin plus rapid-acting insulin, or fixed-dose insulin regimens are all alternatives.[2]</td>
</tr>
<tr>
<td>» To reduce the risk of hypoglycemia, a sulfonylurea should be tapered if insulin is started. A reduction in dose of sulfonylurea or insulin or both may be needed when used with a GLP-1 agonist, in order to reduce the risk of hypoglycemia. A DPP-4 inhibitor (less commonly, a thiazolidinedione, considering risks versus benefit) might be considered as an add-on to a metformin/sulfonylurea combination in people at high risk for hypoglycemia.</td>
</tr>
<tr>
<td>» Liraglutide,[122] empagliflozin,[106] or canagliflozin[107] [108] can be considered for those with established cardiovascular disease as these agents have been shown to reduce cardiovascular mortality and all-cause mortality.[2] [125] Semaglutide has shown a reduction in major cardiovascular events, but not in all-cause or cardiovascular mortality.[124]</td>
</tr>
<tr>
<td>» The UK Medicines and Healthcare products Regulatory Agency (MHRA) warns of cases of diabetic ketoacidosis in patients with type 2 diabetes on a combination of a GLP-1 receptor agonist and insulin who had doses of concomitant insulin rapidly reduced or discontinued.[127]</td>
</tr>
<tr>
<td>» General nutrition and healthy lifestyle knowledge (including an individualized nutrition and exercise plan) can improve glycemic control and quality of life.[24] [58]</td>
</tr>
</tbody>
</table>
Type 2 diabetes mellitus in adults

**Treatment**

### Acute

<table>
<thead>
<tr>
<th>1st</th>
<th>switch to basal-bolus insulin + continued cardiovascular risk reduction/lifestyle measures</th>
</tr>
</thead>
</table>

**Primary options**

- **insulin NPH**: injected subcutaneously twice daily
- **insulin regular**: injected subcutaneously two to three times daily

**OR**

- **insulin glargine**: injected subcutaneously once daily
- **insulin detemir**: injected subcutaneously twice daily
- **insulin degludec**: injected subcutaneously once daily

**--AND--**

- **insulin lispro**: injected subcutaneously premeals
- **insulin aspart**: injected subcutaneously premeals
- **insulin glulisine**: injected subcutaneously premeals

**OR**

- **insulin NPH/insulin regular**: (50/50, 70/30) injected subcutaneously twice daily

**OR**

- **insulin aspart protamine/insulin aspart**: (70/30) injected subcutaneously twice daily

**OR**

- **insulin lispro protamine/insulin lispro**: (50/50, 75/25) injected subcutaneously twice daily

**OR**

- **insulin degludec/insulin aspart**: (70/30) injected subcutaneously once or twice daily
Acute

with any main meal; administer a rapid- or short-acting insulin at other meals if needed

» Basal-bolus insulin is often used when basal insulin or noninsulin multidrug regimens fail to control blood sugar. For patients already on basal insulin, consider starting 3 to 5 units of bolus (short- or rapid-acting) insulin at 1 or more meals. Titrate doses up 2 to 3 units at each meal every few days until desired levels of premeal (90-130 mg/dL) and bedtime (100-140 mg/dL) glucoses are achieved, unless hypoglycemia supervenes.

» Premeal insulin is tailored to anticipated meals as well as to premeal glucose testing.

» Insulin dose varies; consult specialist for guidance on dose.

» Insulin delivery devices that can be programmed to administer set doses of insulin are now available and may be used by patients to help them achieve glycemic control.

» Choice of insulin regimen should be individualized. Premixed insulin may start with a total of about 0.3 units/kg/day dose of insulin, with two-thirds dose in the morning and one third in the evening, and titrated up until goals are achieved or hypoglycemia prevents further titration.

» General nutrition and healthy lifestyle knowledge (including an individualized nutrition and exercise plan) can improve glycemic control and quality of life.[24] [58]

» Cardiovascular risk reduction (blood pressure and lipid control, nonsmoking, and consideration of antiplatelet therapy) should continue.

adjunct continued metformin

Treatment recommended for SOME patients in selected patient group

Primary options

» metformin: 500 mg orally (immediate-release) once daily initially, increase by 500 mg/day increments every week, maximum 1000 mg twice daily

» Metformin can be continued with basal-bolus insulin.

» Metformin reduces hyperglycemia by decreasing hepatic gluconeogenesis and glycogenolysis. At maximal effective doses,
## Type 2 diabetes mellitus in adults

### Treatment

#### Acute

- **Metformin** may reduce HbA1c by 1% to 2%. It rarely is associated with weight gain, is inexpensive, and has a beneficial effect on low-density lipoprotein cholesterol. The most common side effects are diarrhea, gas, and nausea, which can be attenuated by initiating slowly 500 mg orally once per day with a meal, increasing as needed by 500 mg/day every 1 to 2 weeks until full dose of 1000 mg twice per day is reached.

- Metformin is contraindicated if estimated glomerular filtration rate (eGFR) is <30 mL/minute/1.73 m². It should not be initiated if the eGFR is <45 mL/minute/1.73 m², and for patients taking metformin whose eGFR falls to within the 30-45 mL/minute/1.73 m² range, continued use can be considered with close monitoring of renal function and a dose reduction.[97][98]

- Metformin should be stopped before surgery or contrast dye studies with radiographic dye injection until adequate post-event renal function is documented.

#### 2nd bariatric surgery

- Bariatric (also known as metabolic) surgery is an option for type 2 diabetes management in some patients with obesity. Patients must be surgical candidates.

- Bariatric surgery is considered in adults with body mass index (BMI) ≥40 kg/m² (≥37.5 kg/m² for Asian-Americans) with any level of glycemic control and any complexity of glucose-lowering regimen.[2]

- Surgery may also be an option for adults with BMI 35.0 to 39.9 kg/m² (32.5 to 37.4 kg/m² for Asian-Americans) with hyperglycemia inadequately controlled despite lifestyle and optimal medical management, and may be considered for those with BMI 30.0 to 34.9 kg/m² (27.5 to 32.4 kg/m² for Asian-Americans) with hyperglycemia inadequately controlled despite optimal use of oral or injectable medications (including insulin).[2]

- Surgery should be done in a high-volume, experienced center.[2]

#### pregnant

<table>
<thead>
<tr>
<th>1st</th>
<th>diet + basal-bolus insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
</tbody>
</table>

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Type 2 diabetes mellitus in adults

Treatment

<table>
<thead>
<tr>
<th>Acute</th>
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</thead>
<tbody>
<tr>
<td>» insulin NPH: injected subcutaneously twice daily</td>
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<tr>
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<tr>
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<tr>
<td>-or-</td>
</tr>
<tr>
<td>» insulin lispro: injected subcutaneously premeals</td>
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<tr>
<td>-or-</td>
</tr>
<tr>
<td>» insulin aspart: injected subcutaneously premeals</td>
</tr>
</tbody>
</table>

» Good glucose control with HbA1c as close to normal as is safely possible (ideally HbA1c <6.5% [48 mmol/mol]) before conception and during pregnancy optimizes maternal and fetal health outcomes. Evidence

ADA guidelines recommend the following blood glucose targets in pregnant women with preexisting type 2 diabetes (same as for gestational diabetes): <95 mg/dL fasting and either ≤140 mg/dL 1-hour postprandially or ≤120 mg/dL 2-hour postprandially; HbA1c target of 6.0% to 6.5% (42-48 mmol/mol) is recommended; <6% may be optimal as pregnancy progresses if achievable without hypoglycemia.

» In clinical practice, insulin is usually used when nutrition therapy fails to achieve these goals. Intermediate-acting (NPH) insulin may be combined with human short-acting or analog rapid-acting insulin. Long-acting analog insulins (glargine or detemir) are not FDA-approved in pregnancy.

» Retinal exam in those with diabetes prior to pregnancy should be performed prior to and during pregnancy. Diabetes patients who become pregnant require care supervision by a specialized center whenever possible.

» Patients should monitor blood glucose from 4 to 7 times a day and have the pattern examined every few weeks early in pregnancy so that nutrition content and timing, exercise patterns, and the insulin doses can be modified to achieve optimal control. Premeal insulin is tailored to anticipated meals as well as to premeal glucose testing.

» Insulin requirements generally increase early in pregnancy, then decrease from about 8 to 16 weeks before rising throughout the rest of the pregnancy.
<table>
<thead>
<tr>
<th>Acute</th>
</tr>
</thead>
<tbody>
<tr>
<td>» Diabetes patients who become pregnant require individualized dietary counseling and team care.</td>
</tr>
<tr>
<td>» Insulin dose varies; consult specialist for guidance on dose.</td>
</tr>
</tbody>
</table>
Emerging

Insulin human inhalation powder

Rapid-acting inhaled insulin delivered through the lungs has again been approved by the Food and Drug Administration (FDA) for use in diabetes. A previous inhaled insulin product was removed from the market, with FDA-mandated screening of users of that earlier inhaled insulin product for lung cancer. Inhaled insulin is not preferred over injectable insulins with more established safety experience.
Recommendations

Monitoring

Optimal diabetes care requires a long-term relationship with the patient, appropriate use of consultants when needed, and regular monitoring and control of blood pressure, HbA1c, tobacco use, and statin/aspirin use. Most patients require diabetes assessments every 3 to 4 months, and some patients may benefit from more frequent (monthly) visits, especially when motivated to improve their care. Use of diabetes educators is recommended, although traditional information-based diabetes patient education mandated by some professional organizations is only moderately effective in randomized studies.[192][193] A multidisciplinary team with access to nurses, educators, dietitians, clinical pharmacists, psychologists, and other specialists as needed is recommended. Patient readiness to change is a strong predictor of improved care, and readiness to change may vary across the clinical domains of blood pressure, statin use, aspirin use, glucose, smoking, physical activity, and nutrition. Rapid assessment of readiness to change, and directing care to the domain with maximum potential to change, is advised.[194]

Self-management by regular blood glucose monitoring is not routinely recommended in patients with type 2 diabetes, because it does not significantly improve glycemic control, health-related quality of life, or hypoglycemia rates.[2][195][196] However, self-monitoring of blood glucose is recommended for those who (a) are on insulin; (b) have had prior hypoglycemic episodes; (c) drive or operate machinery and use oral medications that increase his or her risk of hypoglycemia; or (d) are pregnant, or planning to become pregnant.[196]

In addition to care required to achieve recommended levels of blood pressure, statin use, aspirin use, tobacco non-use, and glucose control, the following periodic monitoring for complications is advised:

- Dilated eye exam every 1 to 2 years
- Annual assessment of renal function including both a urinary albumin excretion test and a serum creatinine test with estimated glomerular filtration rate (eGFR) based on the CKD-EPI creatinine equation or equivalent

[VIDEO: Glomerular Filtration Rate Estimate by CKD-EPI Equation]
- Annually or more frequent foot exams including assessment of ankle reflexes, dorsalis pedis pulse, vibratory sensation, and 10-gram monofilament touch sensation. All patients with insensate feet, foot deformities, or a history of foot ulcers should have their feet examined at every visit and are candidates for specialized footwear.[2]

Due to disease progression, comorbidities, and nonadherence to lifestyle or medication, a substantial fraction of patients who achieve recommended goals for HbA1c, blood pressure, and lipid management relapse to uncontrolled states of one or more of these within 1 year. Relapse is usually asymptomatic; frequent monitoring of clinical parameters is desirable to anticipate or detect relapse early and adjust therapy.

Factors that may lead to loss of adequate glycemic control include medication nonadherence, depression, musculoskeletal injury or worsening arthritis, competing illnesses perceived by the patient as more serious than diabetes, social stress at home or at work, substance abuse, occult infections, use of medications (such as corticosteroids, certain depression medications [paroxetine], mood stabilizers, or atypical antipsychotics) that elevate weight or glucose, or other endocrinopathies such as Cushing disease.

Loss of control of blood pressure and lipids is also a common phenomenon. Close monitoring of patients with diabetes through frequent visits and lab work helps to maintain patients at treatment goals and proactively identify upward trends in blood pressure or HbA1c, and to reinforce the importance of statin adherence and nonsmoking.
**Patient instructions**

- Patients should be advised that frequent medication adjustments represent good care, and are not a sign of failure or a reason for self-blame or guilt.
- The use of self-monitoring of blood glucose data to promptly identify loss of glucose control and proactively adjust therapy is an essential self-management skill when using multidose insulin regimens, and requires patient education and easy access to health team members between scheduled office visits. Those on multidose insulin regimens often are advised to use continuous glucose monitoring (CGM) equipment, or to monitor blood sugars before meals and at bedtime.
- In other patients with diabetes, self-monitoring may be useful to assess the impact of changes in diet, medication regimen, and exercise, as well as to guide dietary and fluid intake and medication management during episodes of illness.[195][197]
- All women of childbearing age with diabetes should be counseled about the importance of strict glycemic control prior to conception.[2]
- Patients should receive counseling on how to prevent and promptly identify eye, foot, kidney, and cardiovascular complications.
- Patients should be advised that low blood sugar (glucose ≤70 mg/dL) is often accompanied by symptoms such as tachycardia, sweating, shakiness, intense hunger, or confusion, and must be dealt with promptly by ingesting 15-20 g of carbohydrate (equivalent to 3 to 4 glucose tablets of 5 grams per tablet). After self-treatment, blood sugar should be checked if possible. Instruct patients to promptly report nocturnal hypoglycemia or recurrent episodes of hypoglycemia so that therapy may be adjusted. Patients should have a carbohydrate snack prior to exercise if self-monitored blood glucose is <100 mg/dL and the patient is taking insulin or an insulin secretagogue (sulfonylurea or meglitinide). Patients using alpha-glucosidase inhibitors who experience hypoglycemia must use glucose tablets because absorption of conventional carbohydrates is slowed by the treatment.[2] Those at risk of clinically significant hypoglycemia (glucose <54 mg/dL) should have injectable glucagon available, and a close companion should be instructed on how to inject glucagon.[2]
## Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>diabetic kidney disease</td>
<td>long term</td>
<td>low</td>
</tr>
</tbody>
</table>

Chronic kidney disease occurs in about 40% of patients with type 2 diabetes over time. Prevalence of end-stage renal disease is about 1% in those with type 2 diabetes (cross-sectional data).[170] Chronic kidney disease is driven by uncontrolled blood pressure and glucose, and increases the risk of cardiovascular disease at least fourfold. An estimated glomerular filtration rate (eGFR) <60 mL/1.73m²/minute establishes a diagnosis of chronic kidney disease, and microalbuminuria or albuminuria establishes a diagnosis of nephropathy. Either of these findings should prompt increased efforts to aggressively manage systolic blood pressure, avoid nonsteroidal anti-inflammatory drugs (NSAIDs), and consider use of antihyperglycemic drugs with low risk of hypoglycemia and pronounced renal benefits (such as sodium-glucose co-transporter 2 [SGLT2] inhibitors or glucagon-like peptide-1 [GLP-1] agonists).[101] [121]

Also important are use of an ACE inhibitor or angiotensin-II receptor antagonist, and optimization of glucose control. When eGFR is lower than 30 mL/minute/1.73m², referral to a nephrologist for expectant management of end-stage renal disease is necessary.

Renal failure predisposes patients to anemia and hypoglycemia; in renal failure, insulin doses may need to be reduced.

| impaired vision              | long term | low        |

In the US, approximately 25% of patients with type 2 diabetes have retinopathy at diagnosis, presumably as a consequence of unrecognized disease.[180] In a global study, prevalence of diabetic retinopathy in newly diagnosed type 2 diabetes varied from 1.5% to 31%, with higher prevalence observed in developing countries.[181] Risk of vision loss is increased by poor blood pressure and glucose control, and by failure to regularly screen for retinopathy, macular degeneration, glaucoma, and cataracts.[182] [183] The risk of all of these eye conditions is increased in diabetes.

| lower extremity amputation   | long term | low        |

Incidence of lower extremity amputation (LEA) is between 2.5 and 4 per 1000 people with diabetes per year, with significant geographic variation in LEA rates within countries.[184] Incidence rates of major LEA, defined as loss of lower limb through or above the ankle, are declining in patients with diabetes; however, there is some evidence that minor LEA (loss of lower limb below the level of the ankle) incidence rates are increasing, with about half being toe or metatarsal amputations.[168]

Risk is aggravated by neuropathy and by peripheral vascular disease, and can be reduced by smoking cessation; aggressive management of glucose, blood pressure, and lipids; use of customized footwear in patients with known neuropathy or foot deformity; and prompt and aggressive management of lower extremity infections.

| cardiovascular disease       | variable  | high       |

Cardiovascular disease (CVD) and CVD-associated mortality is declining in patients with diabetes, particularly in high-income countries.[168] Adults with type 2 diabetes are twice as likely to die of stroke or myocardial infarction compared with those without diabetes, and they are more than 40 times more likely to die of macrovascular than to die of microvascular complications of diabetes.[61] [62] To reduce cardiovascular risk, blood pressure, lipids, and tobacco use should be adequately managed. Use of statins, ACE inhibitors, metformin, aspirin, empagliflozin, liraglutide, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors may reduce cardiovascular mortality or all-cause mortality in selected patients with type 2 diabetes. In the ACCORD and ADVANCE randomized trials, near-normal glucose...
control failed to decrease cardiovascular mortality or all-cause mortality in type 2 diabetes, and in one of those studies, increased all-cause mortality. However, ACCORD and ADVANCE trials did not use empagliflozin, liraglutide, or PCSK9 inhibitors. Many studies suggest that HbA1c ≥8% increases risk of major cardiovascular events.\[92\] \[93\] 3[A]Evidence

Increased fatigueability may be an early warning sign of progressive cardiovascular disease; clinicians should have a low threshold for cardiac evaluation of any symptoms that are potentially cardiac-related in patients with type 2 diabetes.

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>congestive heart failure (CHF)</td>
<td>variable</td>
<td>high</td>
</tr>
<tr>
<td>Diabetes is a risk factor for CHF, with poor glycemic control associated with greater risk for the development of CHF and worsening of clinical outcomes for patients with CHF and diabetes.[172] CHF occurs in up to 10% to 15% of patients with diabetes.[173] CHF in type 2 diabetes is often related to uncontrolled hypertension, or ischemic coronary disease, but may also occur as a microvascular complication of diabetes. Requires management with ACE inhibitor/angiotensin-II receptor antagonist, diuretics, and other medications. Must rule out underlying causes such as myocardial infarction, atrial fibrillation, thyroid disorders, anemia, or structural heart disease.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>stroke</td>
<td>variable</td>
<td>high</td>
</tr>
<tr>
<td>Related to uncontrolled blood pressure, glucose, and lipids. Lifetime risk is higher in women than in men with diabetes.[174] Prompt hospitalization and neurologic evaluation, with possible emergency use of tissue plasminogen activator (TPA) or other therapeutic strategies, may minimize damage and maximize potential for recovery of function.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>infection</td>
<td>variable</td>
<td>medium</td>
</tr>
<tr>
<td>Hyperglycemia compromises defense against bacterial infections by several mechanisms including impaired phagocytosis. Normalization of blood glucose reduces the risk of infections, especially cystitis, cellulitis, and pneumonia. Immunization reduces the risk of serious pneumococcal, <em>Haemophilus influenzae</em>, and influenza infections. Aggressive infection-specific therapy and supportive therapy including adequate glucose control are key to successful treatment.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>periodontal disease</td>
<td>variable</td>
<td>medium</td>
</tr>
<tr>
<td>Type 2 diabetes is associated with periodontal disease, but causality is not established.[175] In one large epidemiologic survey, periodontal disease was an independent predictor of incident diabetes.[175] Bidirectional risk has been postulated.[176] Control of periodontal disease and hyperglycemia are mutually beneficial. Routine preventive dental care is important for people with type 2 diabetes.[175]</td>
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</tbody>
</table>
## Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>treatment-related hypoglycemia</td>
<td>variable</td>
<td>medium</td>
</tr>
</tbody>
</table>

Related to treatment with insulin and/or insulin secretagogues (sulfonylureas or meglitinides), alone or in combination with other drugs. A glucose alert value is defined as ≤70 mg/dL, requiring treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy. Clinically significant hypoglycemia is defined as <54 mg/dL, indicating serious, clinically important hypoglycemia.[2] Low blood sugars are common in patients who are trying to achieve HbA1c <7%. Hypoglycemia is usually associated with warning signs, such as rapid heartbeat, perspiration, shakiness, anxiety, confusion, and hunger. Hypoglycemia unawareness (absence of symptoms during hypoglycemia) and severe hypoglycemia, defined as a blood sugar so low that assistance from another person or medical personnel is required to treat it, occurs in 1% to 3% of type 2 diabetes patients per year. Older people and those with comorbid heart disease, congestive heart failure, chronic kidney disease, or depression are at substantially increased risk for severe hypoglycemia.[177]

Patients should be counseled on recognition, prevention, and treatment of hypoglycemia and should carry with them glucose tablets or comparable 20 g fast-acting carbohydrate product. Patients using alpha-glucosidase inhibitors must use glucose tablets for hypoglycemia because absorption of conventional carbohydrates is slowed by the medication.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>depression</td>
<td>variable</td>
<td>medium</td>
</tr>
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</table>

When glycemic goals or adherence to treatment plan are difficult to achieve, the presence of depression should be considered. Screening with a validated tool such as the Patient Health Questionnaire (PHQ)-9 may help with identification and diagnosis. The cross-sectional prevalence of depression is 10% to 25% in people with diabetes.[187] Adults with type 2 diabetes diagnosed before age 40 years have excess hospitalizations across their lifespan, which includes a large burden of mental illness in young adulthood.[188]

<table>
<thead>
<tr>
<th>Complication</th>
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</thead>
<tbody>
<tr>
<td>obstructive sleep apnea</td>
<td>variable</td>
<td>medium</td>
</tr>
</tbody>
</table>

Obstructive sleep apnea is common among overweight and obese adults, and has been associated with insulin resistance and altered glucose metabolism. Further studies are needed to assess the effect of continuous positive airway pressure (CPAP) on glycemic control, as results have varied.[189] [190] [191]

The American Diabetes Association recommends assessment of sleep pattern and duration as part of a comprehensive approach to lifestyle and glycemic control.[2]

<table>
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<tbody>
<tr>
<td>diabetic ketoacidosis</td>
<td>variable</td>
<td>low</td>
</tr>
</tbody>
</table>

Commonly thought of in type 1 diabetes; however, can occur in type 2 diabetes and an unusual type of diabetes known as ketosis-prone diabetes. Infection and poor diabetic medication adherence are the most common reasons for developing diabetic ketoacidosis, but no precipitating factors may be apparent.[178]

Criteria of diabetic ketoacidosis is the same, regardless of type of diabetes and is potentially fatal if not properly treated.

Hydration, parenteral insulin therapy, intensive monitoring and careful management of electrolyte imbalances and acidosis are important for successful therapy.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Timeframe</th>
<th>Likelihood</th>
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</thead>
<tbody>
<tr>
<td>non-ketotic hyperosmolar state</td>
<td>variable</td>
<td>low</td>
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</table>

Occurs most commonly in older people with type 2 diabetes and usually evolves insidiously over days to weeks.[179] Characterized by severe hyperglycemia, hyperosmolality, and volume depletion, in the absence of severe ketoacidosis.
<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
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<td>Hydration, insulin therapy, and careful clinical</td>
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<tr>
<td>and laboratory monitoring are the basis of</td>
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<tr>
<td>successful therapy.</td>
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</table>

Diabetic peripheral neuropathy is the most common chronic complication of diabetes, characterized by the presence of peripheral nerve dysfunction, diagnosed after the exclusion of other causes.\[185\] Pain is the outstanding complaint in most patients, but many patients are completely asymptomatic.

Manifestations of autonomic neuropathy may include erectile dysfunction, diarrhea, gastroparesis, or orthostatic hypotension.

For type 2 diabetes the effects of glycemic control on peripheral or autonomic neuropathy are less clear than for type 1 diabetes, with early data suggesting that glucose control is beneficial if started earlier in the disease course, but later studies not confirming these findings.\[186\]

### Prognosis

Diabetes increases the likelihood of major cardiovascular events and death, but the increased risk is variable across patients depending on age at diabetes onset, duration of diabetes, glucose control, blood pressure control, lipid control, tobacco control, renal function, microvascular complication status, and other factors. The association of diabetes and increased mortality can be attenuated by cardiovascular risk factor control.\[167\] A HbA1c of 6% to 6.9% (42 mmol/mol to 52 mmol/mol) is associated with the lowest mortality.\[167\] Trends in data for complications in people with diabetes show a declining risk of cardiovascular disease (CVD) and CVD-associated mortality, particularly in high-income countries.\[168\]

When type 2 diabetes is diagnosed at age 40, men lose an average of 5.8 years of life, and women lose an average of 6.8 years of life.\[11\] The overall excess mortality in those with type 2 diabetes is around 15% higher, but ranges from ≥60% higher in younger adults with poor glucose control and impaired renal function, to better than those without diabetes for those who are age 65 and over with good glucose control and no renal impairment.\[61\] \[62\]

Cumulative prevalence of vision-threatening diabetic retinopathy in the US is about 4.4% among adults with type 2 diabetes, and appears to be higher for non-Hispanic black people compared with non-Hispanic white people (9.3% vs. 3.2%, respectively).\[169\] Prevalence of end-stage renal disease (ESRD) is about 1% in those with type 2 diabetes (cross-sectional data), but cumulative prevalence of nephropathy and/or chronic kidney disease is much higher.\[170\] Incidence rates of ESRD attributed to diabetes are declining; however, continued intervention to detect and manage diabetic kidney disease is required to limit the development of ESRD.\[171\] Effective treatment requires a motivated and informed patient who actively takes responsibility for the care of his or her diabetes, and a healthcare provider team willing to frequently adjust medications to support comprehensive disease management over a long period of time.
# Diagnostic guidelines

## International

<table>
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<tbody>
<tr>
<td><strong>Published by:</strong> American Diabetes Association</td>
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<tr>
<th>Primary prevention of ASCVD and T2DM in patients at metabolic risk [37]</th>
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<tr>
<td><strong>Published by:</strong> Endocrine Society</td>
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<th>Guideline on the primary prevention of cardiovascular disease [22]</th>
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<th>Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults [56]</th>
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<th>Abnormal blood glucose and type 2 diabetes mellitus: screening [53]</th>
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<tr>
<td><strong>Published by:</strong> US Preventive Services Task Force</td>
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# Treatment guidelines

## International

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<th>Last published</th>
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<td>Treatment of diabetes in older adults [54]</td>
<td>Endocrine Society</td>
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<td>Guideline on the management of blood cholesterol [55]</td>
<td>American Heart Association; American College of Cardiology</td>
<td>2019</td>
</tr>
<tr>
<td>Diabetes Canada clinical practice guidelines [164]</td>
<td>Diabetes Canada</td>
<td>2018</td>
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</table>
Evidence scores

1. Reducing cardiovascular risk: there is good-quality evidence that intensive BP lowering (targeting a systolic pressure <120 mmHg over 4.7 years, as compared with targeting <140 mmHg) does not lessen risk (composite outcome: nonfatal MI, nonfatal stroke, or death from cardiovascular cause) in people with type 2 diabetes. Intensive BP lowering increased the risk of adverse events.[76] Evidence level A: Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

2. Maternal and neonatal outcomes: there is medium-quality evidence suggesting that improved glycemic control before conception and in the first trimester improves outcomes.[2] [145] [146] Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

3. Mortality: there is good-quality evidence that therapy to target very tight glucose control (goal HbA1c 6% to 6.5% over 3 to 5 years) was either not beneficial or detrimental to mortality in patients with type 2 diabetes and cardiovascular disease or risk.[92] [93] [95] [96] Very tight control also increased the risk for hypoglycemia. Evidence level A: Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.
Key articles


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Type 2 diabetes mellitus in adults

References


## Type 2 diabetes mellitus in adults

<table>
<thead>
<tr>
<th>Reference</th>
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<th>Journal</th>
<th>Year</th>
<th>Full text</th>
<th>Abstract</th>
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98. US Food and Drug Administration. FDA drug safety communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. Apr 2016 [internet publication].  Full text


112. ClinicalTrials.gov. ERtugliflozin triAl in DIabetes With Preserved or Reduced ejeCtion FrAcTion mEchanistic Evaluation in Heart Failure (ERADICATE-HF). NCT03416270. May 2018 [internet publication]. Full text

113. US Food and Drug Administration (FDA). FDA drug safety communication: FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR). Jun 2016 [internet publication]. Full text


115. US Food and Drug Administration (FDA). FDA drug safety communication: FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR). May 2017 [internet publication]. Full text

116. European Medicines Agency (EMA). SGLT2 inhibitors: information on potential risk of toe amputation to be included in prescribing information. Feb 2017 [internet publication]. Full text

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118. Medicines and Healthcare products Regulatory Agency (UK). SGLT2 inhibitors: reports of Fournier’s gangrene (necrotising fasciitis of the genitalia or perineum). Feb 2019 [internet publication]. Full text


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Type 2 diabetes mellitus in adults


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<th>Reference</th>
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<td>161.</td>
<td>US Food and Drug Administration (FDA). FDA drug safety communication: FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections. Dec 2015 [internet publication]. Full text</td>
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</tbody>
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Image 1: Acanthosis nigricans involving the axilla

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Contact us
+1 855-458-0579 (toll free from USA)
ussupport@bmj.com

BMJ Americas Office
2 Hudson Place, Suite 300
Hoboken, New Jersey 07030
Contributors:

// Authors:

Patrick J. O’Connor, MD, MPH
Senior Clinical Investigator
HealthPartners Institute, Minneapolis, MN
DISCLOSURES: PJO receives research funding from the National Institutes of Health on multiple projects. PJO is an author of a number of references cited in this topic.

JoAnn M. Sperl-Hillen, MD
Senior Clinical Investigator
HealthPartners Institute, Minneapolis, MN
DISCLOSURES: JMS-H is an author of a number of references cited in this topic. She is an inventor on a US patent for Disease Treatment Simulation, a simulation-based technology developed without commercial support to educate health providers on chronic disease management in a virtual environment.

// Peer Reviewers:

David K. McCulloch, MD
Medical Director
Clinical Improvement Group Health Cooperative, Seattle, WA
DISCLOSURES: DKM declares that he has no competing interests.

Ashim K. Sinha, MBBS, MD, FRACP, FACE
Associate Professor
Director of Diabetes and Endocrinology, Cairns Base Hospital and Diabetes Centre, Queensland, Australia
DISCLOSURES: AKS declares that he has no competing interests.