Type 2 diabetes mellitus in adults
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Summary

The cornerstone of therapy for all patients with type 2 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 established cardiovascular and/or renal disease.

Blood pressure control, lipid management (statin therapy), 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. In the absence of unequivocal hyperglycemia, diabetes diagnosis is based on two confirmed values of: fasting plasma glucose >125 mg/dL; HbA1c of 6.5% or greater; or (less commonly) 75 g oral glucose tolerance test results greater than or equal to 200 mg/dL at 2 hours. Alternatively, diabetes can be diagnosed with a single random plasma glucose of ≥200 mg/dL plus symptoms of hyperglycemia or hyperglycemic crisis. 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]

Coronavirus disease 2019 (COVID-19) and diabetes:

- See our separate topic on the management of coexisting conditions in the context of COVID-19

- Further diabetes resources are available at:


Epidemiology

Diabetes prevalence is increasing worldwide, compounded by population growth and an aging population.[4] In 1980, the global age-standardized diabetes prevalence was 4.3%.[4] In 2019, the global age-standardized diabetes prevalence was estimated at 8.3%.[5] However, while the overall burden of diabetes is increasing, trends in the incidence rate of diabetes plateaued and now appear to be decreasing.[6] 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.[7] 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.[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] The prevalence of type 2 diabetes has risen steadily since 1950, driven by increasing prevalence in obesity and being overweight.[10] Improved survival of people with diabetes is also a factor as increasing numbers of people with diabetes are living longer.[6] [11]

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%).[12] 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.[13] Young-onset (<40 years) type 2 diabetes is associated with worse metabolic control and an increased risk of chronic complications and all-cause mortality.[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.

The epidemiology of complications of type 2 diabetes is changing.[14] Rates of macrovascular complications (e.g., myocardial infarction, lower extremity amputation) and hyperglycemic death have declined in high-income countries due to improvements in multiple-risk factor management and diabetes care.[11] [14] [15] Data on trends in microvascular complications (e.g., diabetic kidney disease, diabetic retinopathy, neuropathy) are scarce and trends are less conclusive.[14]

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.[10] 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

In type 2 diabetes, insufficient levels of insulin fail to meet the elevated demand caused by an increased insulin resistance.[16] Adaptive changes in beta-cell mass and beta-cell function typically allow the regulation of insulin demand during insulin resistance. If functional beta-cell compensation becomes insufficient, a cycle
Type 2 diabetes mellitus in adults

Theory

of incomplete glucose clearance and subsequent elevated blood glucose contributes to further deterioration of beta-cell mass and function. The increased beta-cell workload results in functional exhaustion, possible dedifferentiation, and, finally, beta-cell death.[16] Beta-cell function is estimated to be decreased by about 50% to 80% at the time of diagnosis of type 2 diabetes, and protection and recovery of beta-cell function should be a main treatment and prevention target.[16]

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 advanced glycosylation 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.[10] However, this theory is not universally accepted as more clinically useful than assessing individual cardiovascular risk factors.[17]

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 glucose 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 increased urination, thirst, and appetite; unexplained weight loss; blurred vision; fatigue; paresthesias; or urinary tract or candidal infections.

Hyperglycemic crisis (diabetic ketoacidosis or hyperosmolar hyperglycemic state) is the first presentation of diabetes in up to 20% of patients.[3]
**Approach**

For updates on the diagnosis and management of coexisting conditions during the coronavirus disease 2019 (COVID-19) pandemic, please see our topic "Management of coexisting conditions in the context of COVID-19".

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; African-American, Latino, Native American, Asian-American, or Pacific Islander 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: polyuria, polydipsia, polyphagia, or unintentional weight loss (usually when hyperglycemia is more severe, e.g., >300 mg/dL); fatigue; blurred vision; paresthesias; nocturia; skin infections (bacterial or candidal); urinary infections; or acanthosis nigricans.

*Acanthosis nigricans involving the axilla*

*From the collection of Melvin Chiu, MD; used with permission*
Because type 2 diabetes can often be present without diagnosis for many years, it is sometimes diagnosed at the time of presentation with microvascular complications of peripheral neuropathy, retinopathy, or nephropathy.

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) may be the initial presentation of type 2 diabetes, particularly if there is an underlying infection.[3] [46] [47] Patients are symptomatic of hyperglycemia (polyuria, polydipsia, weakness) and significant volume depletion (dry mucous membranes, poor skin turgor, tachycardia, hypotension, and, in severe cases, shock). This is a life-threatening emergency, which requires early diagnosis and management.[48] Compared with the acute presentation of DKA, people with HHS have an insidious onset (over days or weeks) of symptoms and are usually older than 60 years.[3] Certain medications, particularly antipsychotic agents, may precipitate HHS.[48] For further information, please see our topics "Diabetic ketoacidosis" and "Hyperosmolar hyperglycemic state".

**Diagnosis**

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

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

In the absence of unequivocal hyperglycemia, diagnosis requires confirmation with a second test, which may be the same test or a different test.[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. 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,[49] 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 patients (age <30 years), and has a more rapid onset and often more severe symptoms. Around one third of patients with newly diagnosed type 1 diabetes present with DKA.[50] However, DKA may also occur in type 2 diabetes, particularly if there is an underlying infection.[46] [47] 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. Although by definition HHS is characterized by negative ketone bodies, mild-to-moderate ketonemia may be present.[48]

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.[51] 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.[52] 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] [51] A
GST or non-fasting "random" blood C-peptide level >1 nanomol/L suggests type 2 diabetes.[51] C-peptide results must be interpreted in clinical context of disease duration, comorbidities, and family history.[52]

Although C-peptide can be helpful in evaluating the endogenous production of insulin, both type 1 and type 2 diabetes can be associated with insulinopenia, and endogenous insulin production can be detected in some individuals with type 1 diabetes for prolonged periods of time after diagnosis, especially in individuals diagnosed in adulthood. Testing for autoimmunity can therefore often be more helpful in identifying immune-mediated diabetes, the most prevalent form of type 1 diabetes. Autoantibodies to glutamic acid decarboxylase 65 (GAD65), islet cell antibodies (ICA), insulin antibodies, antibodies to tyrosine phosphatase-related islet antigen-2 (IA-2 and IA-2beta), and zinc-transporter-8 (ZnT8) antibodies can help to identify individuals with immune-mediated diabetes, although these antibodies fade with time after the onset of illness.[2] [53] [54]

**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 [ABI]) can be considered at diagnosis.[2] [44] Due to the potential for calcification of the arteries from atherosclerotic peripheral vascular disease (which falsely elevates the ABI), toe pressure testing is often done as an adjunct to ABI testing.[55] A normal ABI value is 1.0; a normal toe pressure value is over 0.7. Values below these levels are considered abnormal and are evidence of macrovascular arterial disease. 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] A comprehensive dilated eye exam is recommended at diagnosis of type 2 diabetes, as patients may have had years of undiagnosed diabetes and some manifestation of diabetic retinopathy is present in about 30% of patients.[2] [56] HbA1c, lipid levels, blood pressure, urine albumin excretion, renal function, and clinical assessment are monitored at periodic intervals.

**History and exam**

**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.

**polydipsia (common)**

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

**polyuria (common)**

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

**unintentional weight loss (common)**

- If marked hyperglycemia is present.
polyphagia (common)
- Usually in patients with fasting plasma glucose >300 mg/dL, HbA1c >11%.

hyperglycemic crisis (uncommon)
- Diabetic ketoacidosis and hyperosmolar hyperglycemic state may be the initial presentation of type 2 diabetes, particularly if there is an underlying infection.[3] [46] [47] Patients are symptomatic of hyperglycemia (polyuria, polydipsia, weakness) and significant volume depletion (dry mucous membranes, poor skin turgor, tachycardia, hypotension, and, in severe cases, shock). This is a life-threatening emergency and requires early diagnosis and management.[48]

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.

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

candidal infections (common)
- Most commonly vaginal, penile, or in skin folds.

skin infections (common)
- Cellulitis or abscesses.

urinary tract infections (common)
- Cystitis or pyelonephritis.

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

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.
Risk factors

Strong

older age

- Older patients are at increased risk, with the incidence of type 2 diabetes peaking between 70 and 79 years.[18] However, the incidence of type 2 diabetes in children and adolescents is increasing.[19]

The American Diabetes Association recommends, in the absence of other risk factors, that screening should begin at age 45 years.[2]
Type 2 diabetes mellitus in adults

Diagnosis

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.[20] Clinical trials have shown that weight loss is associated with delayed or decreased onset of diabetes in high-risk adults.[21][22][23][24][25][26] Screening should be considered if the BMI is greater than or equal to 25 kg/m² (greater than or equal to 23 kg/m² for Asian-Americans).[2]

gestational diabetes

- About 50% of women who have gestational diabetes mellitus will go on to develop overt diabetes mellitus within 10 years of delivery.[27] Women with gestational diabetes have a nearly 10-fold higher risk of developing type 2 diabetes than those with a normoglycemic pregnancy.[28] Screening for diabetes at least every 3 years is recommended in women with a history of gestational diabetes.[2]

prediabetes

- 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 and is a major risk factor for onset of type 2 diabetes.[2] Progression from prediabetes to overt type 2 diabetes occurs at the rate of about 2% to 4% per year.[1] Annual screening is recommended for people with prediabetes.[2]

first-degree relative with 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.[10]

African, Latino, or American-Indian ancestry

- Relative to white people, National Health and Nutrition Examination Survey (NHANES) and other data demonstrate higher risk of diabetes.[20][29]

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.[22][23][24][30]

polycystic ovary syndrome (PCOS)

- Elevated risk; testing for diabetes should be considered in overweight or obese women (BMI ≥25 kg/m² or ≥23 kg/m² in Asian Americans) with PCOS.[2]

hypertension

- Often associated with type 2 diabetes. Testing for diabetes should be considered in overweight or obese adults BMI (≥25 kg/m² or ≥23 kg/m² in Asian Americans) whose blood pressure is ≥140/90 mmHg or who are on therapy for hypertension.[2]

dyslipidemia

- Especially with low high-density lipoprotein (<35 mg/dL) and/or high triglycerides (>250 mg/dL). Testing should be considered in overweight or obese adults (BMI ≥25 kg/m² or ≥23 kg/m² in Asian Americans) whose HDL cholesterol level is <35 mg/dL and/or who have a triglyceride level >250 mg/dL.[2]
**cardiovascular disease**

- Testing should be considered in overweight or obese adults (BMI ≥25 kg/m² or ≥23 kg/m² in Asian Americans) who have a history of cardiovascular 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.[31]

**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.[32]

**Investigations**

**1st test to order**

<table>
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<tr>
<th>Test</th>
<th>Result</th>
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<tbody>
<tr>
<td>fasting plasma glucose</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>HbA1c</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 3-6 months.</td>
<td></td>
</tr>
<tr>
<td>2-hour post-load glucose after 75 g oral glucose</td>
<td>≥200 mg/dL</td>
</tr>
<tr>
<td>• More costly and inconvenient than fasting plasma glucose or HbA1c, and not commonly used for diagnosis of type 2 diabetes.[2]</td>
<td></td>
</tr>
<tr>
<td>random plasma glucose</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. Used for rapid assessment of glucose status if symptoms such as polyuria, polydipsia, or weight loss are present.[2]</td>
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## Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td><strong>urine ketones</strong></td>
<td><strong>positive in instances of ketoacidosis</strong></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. [50] [46] [47] Although by definition hyperosmolar hyperglycemic state is characterized by negative ketone bodies, mild-to-moderate ketonemia may be present.[48]</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.[51] 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] C-peptide results must be interpreted in clinical context of disease duration, comorbidities, and family history.[52] Although C-peptide can be helpful in evaluating the endogenous production of insulin, both type 1 and type 2 diabetes can be associated with insulinopenia, and endogenous insulin production can be detected in some individuals with type 1 diabetes for prolonged periods of time after diagnosis, especially in individuals diagnosed in adulthood.</td>
<td></td>
</tr>
<tr>
<td><strong>autoantibodies</strong></td>
<td>presence suggests immune-mediated diabetes</td>
</tr>
<tr>
<td>• Not done routinely for diagnosis of diabetes, but is an option for differentiating type 1 and type 2 diabetes. Autoantibodies to glutamic acid decarboxylase 65 (GAD65), islet cell antibodies (ICA), insulin antibodies, antibodies to tyrosine phosphatase-related islet antigen-2 (IA-2 and IA-2beta), and zinc-transporter-8 antibodies (ZnT8) can help to identify individuals with immune-mediated diabetes, although these antibodies fade with time after the onset of illness.[2] [53] [54]</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><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, especially low HDL and high triglycerides.</td>
<td></td>
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<tr>
<td><strong>ECG</strong></td>
<td>may indicate prior ischemia</td>
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<td></td>
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</tr>
<tr>
<td>Test</td>
<td>Result</td>
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<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>ankle-brachial index (ABI)</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>toe-brachial index (TBI)</td>
<td>≤0.7 is abnormal</td>
</tr>
<tr>
<td>• Due to the potential for calcification of the arteries from atherosclerotic peripheral vascular disease (which falsely elevates ABI), toe pressure testing is often done as an adjunct to ABI testing.[55]</td>
<td></td>
</tr>
<tr>
<td>dilated retinal examination</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, as patients may have had years of undiagnosed diabetes and some manifestation of diabetic retinopathy is present in about 30% of patients.[56]</td>
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## Differentials

<table>
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<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
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<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;30 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.[50]</td>
<td>• One or more autoantibodies (anti-glutamic acid decarboxylase 65 [GAD65] antibodies, islet cell antibodies [ICA], insulin autoantibodies, autoantibodies to the tyrosine phosphatase-related islet antigen-2 [IA-2 and IA-2beta], and zinc-transporter-8 [ZnT8] antibodies) are present in 85% of patients with type 1 at the time of diagnosis, but may disappear within a few years.[53] 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>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</td>
<td>• Positive for at least 1 of the 5 antibodies commonly found in type 1 diabetic patients (islet cell antibodies [ICA], autoantibodies to glutamic acid decarboxylase 65)</td>
</tr>
<tr>
<td>Condition</td>
<td>Differentiating signs / symptoms</td>
<td>Differentiating tests</td>
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<td>agents. Production of insulin gradually decreases (between 6 months and 5 years), such that treatment with insulin is required.[57]</td>
<td>(GAD65), autoantibodies to the tyrosine phosphatase-related islet antigen-2 [IA-2 and IA-2beta], insulin, and zinc-transporter-8 [ZnT8] antibodies).[54][58]</td>
</tr>
<tr>
<td></td>
<td>• LADA is considered a subset of autoimmune type 1 diabetes (immune-mediated diabetes); however, patients with LADA are frequently misclassified as having type 2 diabetes.</td>
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<tr>
<td>Monogenic diabetes</td>
<td>• Maturity-onset diabetes of the young (MODY) is the most common form of monogenic diabetes and affects 1% to 2% of people with diabetes.[59]</td>
<td>• Genetic testing in patients with high index of suspicion (genes encoding glucokinase and transcription factors are identified).[62]</td>
</tr>
<tr>
<td></td>
<td>• MODY is caused by mutation of a single gene (i.e., monogenic). At least 14 gene mutations of MODY are known.[60]</td>
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</tr>
<tr>
<td></td>
<td>• 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 at least one first-degree relative.[60]</td>
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</tr>
<tr>
<td></td>
<td>• Patients are often misclassified as type 1 or type 2 diabetes. Insulin treatment is often not needed.[61]</td>
<td></td>
</tr>
<tr>
<td>Ketosis-prone diabetes</td>
<td>• Presents with unprovoked ketosis or ketoacidosis.[63]</td>
<td>• Absent islet cell autoantibodies.</td>
</tr>
<tr>
<td></td>
<td>• Considered an &quot;idiopathic diabetes,&quot; 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).[64]</td>
<td>• C-peptide often low or undetectable during diabetic ketoacidosis; recovery may be used as reliable predictor of insulin discontinuation.[64]</td>
</tr>
<tr>
<td></td>
<td>• Patients are usually from a minority ethnic group, and</td>
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</table>
### Type 2 diabetes mellitus in adults

#### Diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>have a positive family history of diabetes.[64]</td>
<td>• Guidelines and expert consensus recommend screening for gestational diabetes in pregnant women at both high and usual risk.[2] [65] Women with risk factors for diabetes should be screened for type 2 diabetes (or prediabetes) at first prenatal visit.[2] At 24 to 28 weeks' gestation, all women not known to have diabetes (including high-risk women if the initial testing was normal) should undergo screening with glucose tolerance testing.[2] One-step or two-step screening strategies may be used.[2]</td>
</tr>
<tr>
<td>Diabetes, gestational</td>
<td>• Only occurs during pregnancy.</td>
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</tr>
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</table>

#### Criteria

**American Diabetes Association[2]**

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

- Fasting plasma glucose (FPG) ≥126 mg/dL (most commonly used)
- HbA1c ≥6.5%
- 2-hour post-load glucose ≥200 mg/dL on a 75 g oral glucose tolerance test
- Random plasma glucose ≥200 mg/dL with diabetes symptoms such as polyuria, polydipsia, fatigue, weight loss, or hyperglycemic crisis.

In the absence of unequivocal hyperglycemia, diagnosis requires 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.

#### 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.[66]

The American Diabetes Association has recommended routine screening of nonpregnant asymptomatic adults of any age with BMI ≥25 kg/m² (≥23 kg/m² for Asian-Americans) 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 a history of diabetes in a first-degree relative, overweight or obesity, sedentary lifestyle, high-risk ancestry, gestational diabetes, hypertension (>140/90 mmHg or on therapy for hypertension), dyslipidemia (low high-density lipoprotein-cholesterol and/or elevated triglycerides), cardiovascular disease, prediabetes (HbA1c ≥5.7%, impaired glucose tolerance or impaired fasting glucose), polycystic ovary syndrome, other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans or small-for-gestational-age birth weight) or HIV.[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]
Type 2 diabetes mellitus in adults

Management

Approach

For updates on the diagnosis and management of coexisting conditions during the coronavirus disease 2019 (COVID-19) pandemic, please see our topic "Management of coexisting conditions in the context of COVID-19".

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 dietician.[2] [70] 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.[71]

If antihyperglycemic pharmacotherapy is required, the 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.

About 80% of adults with type 2 diabetes have concurrent dyslipidemias or hypertension, 70% are overweight or obese, and around 15% are current smokers.[12] On average, adults with type 2 diabetes are up to 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.[72] [73] [74] However, data indicate that adults with type 2 diabetes who optimally manage glucose, blood pressure (BP), 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.[75] [76]

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, BP control, lipid control, antiplatelet and anticoagulant use for patients with known coronary heart disease, and ACE inhibitors or angiotensin-II receptor antagonists for nonpregnant adults with chronic kidney disease (CKD) or proteinuria.[2] [44] [77] In addition, use of antihyperglycemic agents such as sodium-glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) agonists, which reduce cardiovascular or overall mortality, cardiovascular events, or CKD progression, may be especially beneficial in those with type 2 diabetes and at risk of/with established cardiovascular disease (CVD) or CKD regardless of the level of glucose management.[2] [44] [78] [79] [80]

Diet

Nutrition therapy involves limiting caloric intake to achieve recommended weight, while offering a diversified and appealing menu of food choices.[81] Nutrition advice needs to be tailored to the needs of each individual patient, preferably by a nutritionist.[2] [33] The American Diabetes Association stresses that there is no ideal dietary macronutrient (carbohydrate, protein, and fat) distribution for people with diabetes, and that food plans should be individualized taking into account preferences and metabolic goals.[2] Low-carbohydrate diets appear to be beneficial for glycemic control in type 2 diabetes management.[82] Mediterranean diet and Dietary Approaches to Stop Hypertension (DASH) diets for people with hypertension have the best supporting evidence for use in patients with type 2 diabetes.[33] Saturated fat should be limited to <10% of calories.[33] Reducing sugary beverage consumption (including soda, energy drinks, and fruit juice) is of benefit to many patients.[33] 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.[33] [83] [84] 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 body mass index (BMI) of 27 kg/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.[83] At 2 years, more than a third of people with type 2 diabetes had sustained remission.[85]

**Exercise and sleep**

- To improve glycemic control, assist with weight maintenance, and reduce cardiovascular risk, moderate physical activity is recommended as tolerated. The American College of Cardiology/American Heart Association 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.[86] Well-fitting footwear is recommended for people with neuropathy or increased plantar pressure.[2]
- 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.[87]
- Older adults may benefit from flexibility training and balance training 2 to 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]

**Antihyperglycemic pharmacotherapy: initial considerations**

HbA1c goals should be individualized.[88] [89] For many patients, the goal HbA1c <7% is appropriate. However, HbA1c 7.0% to 7.5% may be more appropriate in older adults with few co-existing chronic illnesses and HbA1c <8.0% might be more appropriate in older adults with multiple co-existing chronic illnesses, more than 2 ADL impairments or mild-to-moderate cognitive impairment. For older adults with very complex or poor health, avoid reliance on HbA1c: glucose control decisions should be based on avoiding hypoglycemia and symptomatic hyperglycemia.[2] Individualized HbA1c goals improve quality of life compared with uniform tight control.[89]

Pharmacotherapy is recommended to reduce risk of both microvascular (nephropathy, retinopathy, neuropathy) and macrovascular (myocardial infarction, stroke, peripheral vascular disease) complications, and is guided by HbA1c goals or a unique indication (presence of atherosclerotic CVD, heart failure, CKD).[2] [78] [79] [80] [90] [91] Antihyperglycemic medications that reduce all-cause or cardiovascular mortality, or major cardiovascular events or renal complications in some patient subgroups are metformin, SGLT2 inhibitors, and GLP-1 agonists.[92] [93] [94] [95]

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.[96] [97] [98] [99] [100] However, SGLT2 inhibitors were not available and GLP-1 agonists were infrequently used in those studies.

Metformin is the recommended first-choice therapy at diagnosis in the absence of contraindications because of its safety profile and likely cardiovascular benefit.[90] [92] Metformin may be safely used in patients with reduced estimated glomerular filtration rates (eGFRs), but it is contraindicated if eGFR <30
Type 2 diabetes mellitus in adults

Management

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. 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 CVD, 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:

- SGLT2 inhibitor: canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin
- 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 CVD, heart failure, or CKD, metformin is used as initial treatment. Addition of a SGLT2 inhibitor or GLP-1 agonist is also recommended if not contraindicated, regardless of HbA1c and glycemic status, with choice of class dependent on patient-specific factors. Diagnosed atherosclerotic CVD favors either SGLT2 or GLP-1 therapy, while heart failure favors SGLT2 therapy and CKD favors SGLT2 therapy, with some benefit being demonstrated for GLP-1 therapy. 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.

- Metformin can promote weight loss and may reduce cardiovascular events and mortality.
- 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 BP. 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. Empagliflozin and canagliflozin have been shown to reduce cardiovascular risk in people with CVD and type 2 diabetes, and may have renal benefits. Empagliflozin and canagliflozin have been shown to significantly reduce cardiovascular or all-cause mortality in those with diabetes and established CVD. In one trial, treatment with dapagliflozin in patients with type 2 diabetes who had, or were...
Dapagliflozin also improves renal outcomes in patients with, and without, diabetes. One published trial on the CVD benefits of etregliflozin supports its use in patients with diabetes and heart failure. Adverse effects for different agents have included a higher rate of genital infections, diabetic ketoacidosis, acute kidney injury, fracture, and/or amputation. The Food and Drug Administration (FDA) and European Medicines Agency (EMA) warn of the potential increased risk of toe amputation with SGLT2 inhibitors and the need for appropriate monitoring. 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. 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. As a class of drugs, GLP-1 agonist treatment has beneficial effects on cardiovascular, mortality, and kidney outcomes in patients with type 2 diabetes. Liraglutide significantly reduced cardiovascular mortality and all-cause mortality in those with diabetes and CVD or high CVD risk in one randomized trial. Dulaglutide and semaglutide have both been shown to reduce major cardiovascular events, but not all-cause or cardiovascular mortality. Semaglutide is the only GLP-1 agonist to also be available in an oral form. Exenatide and lixisenatide have both been shown not to reduce major cardiovascular events. 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.

- 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. Along with metformin and human insulin, these are among the more affordable antihyperglycemic medications.

- Alpha-glucosidase inhibitors (acarbose, miglitol) can be added to metformin in people with large postprandial glucose excursions, but increased flatus and gastrointestinal 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. They may cause anemia and increase fracture rates in both women and men. In addition, rosiglitazone raises low-density lipoprotein (LDL)-cholesterol and mixed evidence suggests rosiglitazone may increase the risk of cardiovascular events. Rosiglitazone has been removed from the European market due to persistent safety concerns. However, in 2013, the FDA lifted previous restrictions applied to rosiglitazone in the US, based on newer data. 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.

- Bromocriptine and coleselvelam are oral agents approved by the FDA for glucose-lowering. They have limited impact on blood glucose in many patients. Bromocriptine may cause gastrointestinal 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 if there is evidence of ongoing catabolism (weight loss, hypertriglyceridemia and ketosis), symptoms of hyperglycemia (polyuria and polydipsia) or when HbA1c (>10.0%) or blood glucose (≥300 mg/dL) levels are very high and is an option when metformin monotherapy or multidrug regimens are inadequate.[2] Because of the progressive loss of beta-cell function that characterizes the natural history of type 2 diabetes, insulin therapy is often required over time to overcome the insulin deficiency that accompanies progressive beta-cell loss in longer-standing type 2 diabetes.

Insulin treatment should be considered at the time of diagnosis if glucose level is ≥300 mg/dL or if HbA1c is ≥10%. Metformin is typically used adjunctively, in the absence of nausea, vomiting, or volume depletion.

For individuals with severe hyperglycemia (HbA1c ≥11%; or fasting or postprandial glucose >350 mg/dL), or individuals with metabolic compromise related to hyperglycemia (polyuria, polydipsia, ongoing weight loss) but without ketonuria or dehydration, both basal (background) and bolus (mealtim/mealtime) insulin are typically recommended to reverse symptoms rapidly.[78] For individuals with less dramatic hyperglycemia, insulin can often be initiated with long-acting basal insulin at bedtime.[2] 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, observational studies suggest human insulins can be as effective as analog insulins for glucose control, serious hypoglycemia risk, and mortality and cardiovascular events.[137] Human insulins are significantly less expensive than analog insulins. For individuals with relaxed HbA1c goals, low rates of hypoglycemia, and prominent insulin resistance, as well as those with cost concerns, human insulin (NPH and regular) may be the appropriate choice of therapy.[2]

Premixed insulin is available in various ratios of rapid-acting/NPH and regular/NPH insulin combinations. When injected before (typically) breakfast and dinner meals, premixed insulin can sometimes be used effectively to cover both basal and prandial insulin needs in appropriate individuals (desire for no more than 2 injections per day, less insulin-sensitive and hypoglycemia-prone, and willing to eat consistent meals on a reasonably consistent schedule). For many, the greater flexibility and adaptability of a basal (background) and bolus (mealtime) regimen outweighs the potential convenience of premixed insulin.

Regimens should be individualized. Insulin delivery devices (insulin pens) that can be adjusted to administer set doses of insulin are widely available, and offer increased convenience and accuracy in insulin dosing. Less frequently, insulin pumps and patch pump systems are used in individuals with type 2 diabetes requiring multiple daily dose insulin. While allowing improved precision in insulin administration and dosing, insulin pump systems require significant engagement and involvement by the individuals using the systems to achieve clinical benefits beyond multiple daily dose injection-based therapy.

Metformin therapy is typically started or continued at the time of initiation of insulin in type 2 diabetes, unless contraindicated. While consideration should be given to discontinuing sulfonylurea therapy in individuals initiating insulin therapy because of additive hypoglycemia risk, other noninsulin therapies can often be continued if an individual is benefiting.[138] In particular, individuals on SGLT2 or GLP-1 therapy because of unique indications (atherosclerotic cardiovascular disease [ASCVD], heart failure, CKD) can be continued on those therapies when initiating insulin.
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 (fingerstick blood glucose testing) or continuous glucose monitoring. 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 (carbohydrate-based dosing, sometimes called “carb-counting”), rather than administered as a fixed mealtime dose. 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.

**Cardiovascular risk management**

**Blood pressure**

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

- The 2017 American College of Cardiology (ACC)/American Heart Association (AHA) guideline for management of high BP in adults recommends BP <130/80 mmHg for people with diabetes, and classifies BP using the following categories:[69]
  - 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 (ADA) 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 CVD or 10-year cardiovascular risk greater than 15%.[2] [139]
- Regardless of specific BP 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.[139] ACE inhibitors may reduce mortality and cardiovascular events more than angiotensin-II receptor antagonists.[77] Combination drug therapy (with ACE inhibitor/angiotensin-II receptor antagonist, calcium-channel blocker, thiazide diuretic) is often required to reach BP goals. Combined use of an ACE inhibitor and an angiotensin-II receptor antagonist is not recommended due to increased risk of adverse events.[140] 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.[139] 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.
- Consider initiation and titration of two antihypertensive medications along with lifestyle therapy if BP ≥160/100 mmHg.[2]
• Beta-blockers are not contraindicated in people with diabetes but are less-preferred antihypertensive agents\[139\] and may mask symptoms of hypoglycemia.

• If BP 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,[141] and/or refer to a hypertension specialist.

• BP 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 BP and at least one additional risk factor for heart disease.[142] However, people with diabetes were excluded from this trial.

• There is an increasing emphasis to incorporate the use of home BP monitoring into the diagnosis and management of hypertension in adults, including those with diabetes.[143]

Lipids

• The ACC/AHA guidelines recommend high-intensity statin therapy if tolerated in adults aged over 21 years if the patient has clinical ASCVD or LDL-cholesterol ≥190 mg/dL.[68] 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.[68] 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.[68] 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.[68] Statins are contraindicated in pregnancy.

• The ADA recommends that management of lipid abnormalities is driven by cardiovascular risk status rather than LDL cholesterol level.[2] Risk factors for CVD include LDL-cholesterol >100 mg/dL, high BP, smoking, and overweight and obesity. Lifestyle therapy is recommended for all people. For people with diabetes and overt CVD, 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 CVD, but with one or more 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 people 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] [144] [145] [146]

• In individuals with established CVD, or high cardiovascular risk on a statin with controlled LDL cholesterol but elevated triglycerides, the addition of icosapent ethyl has been shown to modestly reduce cardiovascular events.[2] [147]

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.[148] The ADA does not support e-cigarettes as an alternative to smoking or to facilitate smoking cessation.[2]
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Antithrombotic therapy

- Adults with CVD should receive aspirin for secondary prevention. Clopidogrel is an alternative for patients with aspirin allergy or intolerance. Dual antithrombotic therapy with low-dose aspirin and a P2Y12 inhibitor (e.g., clopidogrel, ticagrelor, prasugrel) is reasonable for up to 12 months after an acute coronary syndrome. Clopidogrel or ticagrelor can be used if no percutaneous intervention was performed, and clopidogrel or ticagrelor or prasugrel may be used if PCI was performed.[2] The main adverse effect is an increased risk of gastrointestinal bleeding.[2][149]

- 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 CVD, hypertension, dyslipidemias, smoking, CKD/albuminuria), unless they are at high risk of serious bleeding.[2]

- For patients aged over 70 years, the risk of bleeding increases and aspirin is generally not recommended for primary prevention in this population.[150]

- US Preventive Services Task Force (USPSTF) recommendations for primary prevention of heart attack or stroke in those ages 50 to 70 years are similar.[151]

Combination antithrombotic and anticoagulant therapy

- In people with low bleeding risk, the ADA recommends combination treatment with aspirin and lowdose rivaroxaban for secondary prevention.[2]

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.[152] [153] [154] [155] [156] as well as for possible prevention of type 2 diabetes.[157] 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.[158] [159] [160] 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, and more of a tendency to malabsorption of vitamins and minerals postoperatively. 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.[161]

Health insurers in the US generally restrict payment for bariatric surgery, but the eligibility criteria have been slowly expanding over time. Bariatric surgery is recommended to treat type 2 diabetes in adults with BMI ≥40 kg/m² (≥37.5 kg/m² for Asian-Americans) and adults with BMI 35.0 to 39.9 kg/m² (32.5 to 37.4 kg/m² for Asian-Americans) who do not achieve long-lasting weight loss and improvement in comorbidities, including hyperglycemia, despite lifestyle and optimal non-surgical medical management. It may be considered for those with BMI 30.0 to 34.9 kg/m² (27.5 to 32.4 kg/m² for Asian-Americans) who do not achieve long-lasting weight loss and improvement in co-morbidities, including hyperglycemia, despite lifestyle and optimal nonsurgical medical management.[2] Bariatric surgery is best done in a high-volume, specialized center.[2]
Type 2 diabetes mellitus in adults

Management

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] [162] American Diabetes Association 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 <6% 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.[20] Many factors have contributed to diabetes care improvement and better clinical outcomes for patients.[163] The principal model used to frame these strategies is the Chronic Care Model.[164] 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[165] [166]
- Advanced and integrated electronic medical record clinical decision support beyond simple reminder systems and alerts[167] [168]
- Simulated case-based learning interventions for clinicians.[169] [170] [171]

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.[172] [173] Diabetes management decisions should be timely, rely on evidence-based guidelines, and be made collaboratively with the patient.

Treatment algorithm 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 Management at initial diagnosis

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<td>Acute</td>
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<tr>
<td><strong>marked hyperglycemia nonpregnant:</strong> serum glucose ≥300 mg/dL or HbA1c ≥10% or symptomatic</td>
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<tr>
<td>1st basal-bolus insulin + cardiovascular risk reduction/lifestyle measures</td>
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<td>adjunct metformin</td>
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<td><strong>without marked hyperglycemia nonpregnant asymptomatic:</strong> serum glucose &lt;300 mg/dL or HbA1c &lt;10%</td>
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<td><strong>HbA1c above goal at diagnosis</strong></td>
<td>1st metformin + cardiovascular risk reduction/lifestyle measures</td>
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<tr>
<td><strong>HbA1c above goal on metformin</strong></td>
<td>1st sodium-glucose co-transporter 2 (SGLT2) inhibitor added to continued metformin + continued cardiovascular risk reduction/lifestyle measures</td>
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<td>1st glucagon-like peptide 1 (GLP-1) agonist added to continued metformin + continued cardiovascular risk reduction/lifestyle measures</td>
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<td>1st dipeptidyl peptidase-4 (DPP-4) inhibitor added to continued metformin + continued cardiovascular risk reduction/lifestyle measures</td>
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<td>1st sulfonylurea or meglitinide added to continued metformin + continued cardiovascular risk reduction/lifestyle measures</td>
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<td>1st basal insulin added to continued metformin + continued cardiovascular risk reduction/lifestyle measures</td>
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<td>2nd alpha-glucosidase inhibitor added to continued metformin + continued cardiovascular risk reduction/lifestyle measures</td>
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<td>2nd thiazolidinedione added to continued metformin + continued cardiovascular risk reduction/lifestyle measures</td>
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<tr>
<td><strong>HbA1c above goal on metformin + either basal insulin or second noninsulin agent</strong></td>
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</tr>
<tr>
<td></td>
<td>1st switch to basal-bolus insulin + continued cardiovascular risk reduction/lifestyle measures</td>
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</table>

**MANAGEMENT**

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<table>
<thead>
<tr>
<th>Acute</th>
<th>( summary )</th>
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<tr>
<td></td>
<td>adjunct continued metformin</td>
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<td></td>
<td>2nd bariatric surgery</td>
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<td>pregnant</td>
<td>1st diet + basal-bolus insulin</td>
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</tbody>
</table>
Treatment algorithm

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 management 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 dietician.[2] [70] 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.[71]

» 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] [33] [81] Reducing sugary beverage consumption (including 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.[86]

» 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.[33] [83] [84]

» Alcohol use (more than 2 drinks daily for men or 1 for women) increases risk of hypoglycemia, 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 depression prevention or control, and decreases risk of major cardiovascular events and onset or progression of microvascular complications.

### plus glycemic management
Initial

Treatment recommended for ALL patients in selected patient group

» All patients should receive stratified glycemic management upon diagnosis.

» HbA1c goals should be individualized,[88] and if HbA1c is above goal, pharmacotherapy recommended.

» Metformin (along with comprehensive lifestyle modifications) should be initiated in all patients at diagnosis unless contraindicated, and often continues to be used as monotherapy in individuals with modest hyperglycemia.[2]

» Choice of agents beyond metformin should be individualized, taking into account patient values and preferences, likelihood that an agent provides cardiorenal protection, adverse effect profiles, costs, and other factors.

» See sections below for more information on choice of medication and dose.

» Consult a specialist for guidance on treating pregnant women.

plus 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-
**Initial**

- **captopril**: 25 mg orally twice daily initially, increase gradually according to response, maximum 200 mg/day  
- **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--**

- **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 compared with those without diabetes, and they are more than 40 times more likely to die of macrovascular than microvascular complications of diabetes.[72] [73] [74] 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 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] [69] [139]
**Initial**

» 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 inhibitor, or an angiotensin-II receptor antagonist. Antihypertensive drugs for black people may be initiated with a thiazide diuretic or a calcium-channel blocker.\[139\] ACE inhibitors may reduce mortality and cardiovascular events more than angiotensin-II receptor antagonists.\[77\] Combining an ACE inhibitor with an angiotensin-II receptor antagonist is not recommended due to increased risk of adverse events.\[140\]

However, most people with chronic kidney disease (CKD) should receive an ACE inhibitor or an angiotensin-II receptor antagonist as part of their regimen.\[139\] 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,\[141\] and/or refer to a hypertension specialist.

» Beta-blockers are not contraindicated in people with diabetes but are less-preferred antihypertensive agents\[139\] and may mask symptoms of hypoglycemia.

» Although ACE inhibitors have been reported to increase risk for hypoglycemia in conjunction with insulin or insulin secretagogue (sulfonylurea or meglitinide), the clinical relevance of these findings is uncertain, and in clinical practice these combinations are routinely used safely and effectively.\[174\] Concerns of hypoglycemia should not limit the use of these combinations, given the significant clinical benefits of this class of antihypertensives for individuals with type 2 diabetes.

» 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
### Initial

<table>
<thead>
<tr>
<th>Primary options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>» atorvastatin</strong>: moderate intensity: 10-20 mg orally once daily; high intensity: 40-80 mg orally once daily</td>
</tr>
</tbody>
</table>

**OR**

| **» rosuvastatin**: moderate intensity: 5-10 mg orally once daily; high intensity: 20-40 mg orally once daily |

**OR**

| **» simvastatin**: moderate intensity: 20-40 mg orally once daily; increased risk of myopathy with 80 mg/day dose |

**OR**

| **» pravastatin**: moderate intensity: 40-80 mg orally once daily |

**OR**

| **» lovastatin**: moderate intensity: 40-80 mg orally (immediate-release) once daily |

**OR**

| **» fluvastatin**: moderate intensity: 40 mg orally (immediate-release) twice daily, or 80 mg orally (extended-release) once daily |

**OR**

| **» pitavastatin**: moderate intensity: 1-4 mg orally once daily |

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### Secondary options

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

- **or-**

| **» rosuvastatin**: moderate intensity: 5-10 mg orally once daily; high intensity: 20-40 mg orally once daily |

- **or-**

| **» simvastatin**: moderate intensity: 20-40 mg orally once daily; increased risk of myopathy with 80 mg/day dose |

- **or-**

| **» pravastatin**: moderate intensity: 40-80 mg orally once daily |
### Initial

- **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

#### 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

**OR**

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

Initial

- **or**
  - **rosuvastatin**: moderate intensity: 5-10 mg orally once daily; high intensity: 20-40 mg orally once daily
- **or**
  - **simvastatin**: moderate intensity: 20-40 mg orally once daily; increased risk of myopathy with 80 mg/day dose
- **or**
  - **pravastatin**: moderate intensity: 40-80 mg orally once daily
- **or**
  - **lovastatin**: moderate intensity: 40-80 mg orally (immediate-release) once daily
- **or**
  - **fluvastatin**: moderate intensity: 40 mg orally (immediate-release) twice daily, or 80 mg orally (extended-release) once daily
- **or**
  - **pitavastatin**: moderate intensity: 1-4 mg orally once daily
- **-AND-**
  - **icosapent ethyl**: 2 g orally twice daily

- **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.**[72] [73] [74] A primary goal of care is treatment of cardiovascular risk factors to individualized targets.[75]

- **High-intensity statin therapy is recommended as tolerated in diabetes patients with atherosclerotic cardiovascular disease, 10-year cardiovascular risk >20%, or low-density lipoprotein (LDL)-cholesterol ≥190 mg/dL. Otherwise, in those ages 40 to 75 years, moderate-intensity statin therapy should be considered.**[68] 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%. [68]

- **Combination therapy using statins and other lipid-lowering agents may be considered, especially in patients with very high CVD risk.**[175] [176] The risks of complications such as impaired liver or renal function, myositis, or rhabdomyolysis may increase when using statins in combination with other agents.[2]
Type 2 diabetes mellitus in adults

Management

**Initial**

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.[2] [144] [146]

» In individuals with established cardiovascular disease, or high cardiovascular risk on a statin with controlled LDL cholesterol but elevated triglycerides, the addition of icosapent ethyl has been shown to modestly reduce cardiovascular events.[2] [147]

» 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

-AND-

» clopidogrel: 75 mg orally once daily

-or-

» ticagrelor: 90mg orally twice daily

-or-

» prasugrel: body weight <60 kg: 5 mg orally once daily; body weight ≥60 kg: 10mg orally once daily

-OR-

» aspirin: 75-162 mg orally once daily

-and-

» rivaroxaban: 2.5 mg orally twice daily

» Adults with cardiovascular disease should receive aspirin for secondary prevention.
### Initial

| » 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. However, this should only be after a discussion and shared decision making regarding the benefits versus the comparable risks of complications of therapy from bleeding.[2] Aspirin use is not recommended for individuals at low cardiovascular risk. |
| — For patients aged over 70 years, the risk of bleeding increases and aspirin is generally not recommended for primary prevention in this population.[150] |
| » Clopidogrel is an alternative for patients with aspirin allergy or intolerance. |
| » Dual antiplatelet therapy with low-dose aspirin and a P2Y12 inhibitor (e.g., clopidogrel, ticagrelor, prasugrel) is often recommended for up to 1 year after an acute coronary syndrome. |
| » Clopidogrel or ticagrelor can be used if no percutaneous intervention was performed, and clopidogrel or ticagrelor or prasugrel may be used if PCI was performed.[2] The main adverse effect is an increased risk of gastrointestinal bleeding.[2] [149] |
| » In people with low bleeding risk, the ADA recommends combination treatment with aspirin and low-dose rivaroxaban for secondary prevention.[2] |
| » The Food and Drug Administration released a statement in 2014 citing inadequate evidence to support widespread use of aspirin for primary prevention of cardiovascular events.[177] |
| » Consult a specialist for guidance on treating pregnant women. |
### Acute

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

<table>
<thead>
<tr>
<th>1st</th>
<th>basal-bolus insulin + cardiovascular risk reduction/lifestyle measures</th>
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<tbody>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>» insulin NPH: injected subcutaneously twice daily</td>
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<td>-and-</td>
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<tr>
<td>» insulin regular: injected subcutaneously two to three times daily</td>
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<tr>
<td>OR</td>
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<tr>
<td>» insulin glargine: injected subcutaneously once daily</td>
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<td>-or-</td>
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<tr>
<td>» insulin detemir: injected subcutaneously twice daily</td>
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<td>-or-</td>
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<tr>
<td>» insulin degludec: injected subcutaneously once daily</td>
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<td>--AND--</td>
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<tr>
<td>» insulin lispro: injected subcutaneously premeals</td>
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<td>-or-</td>
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<tr>
<td>» insulin aspart: injected subcutaneously premeals</td>
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<tr>
<td>-or-</td>
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<tr>
<td>» insulin glulisine: injected subcutaneously premeals</td>
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<tr>
<td>OR</td>
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<tr>
<td>» insulin NPH/insulin regular: (50/50, 70/30) injected subcutaneously twice daily</td>
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<td>OR</td>
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<tr>
<td>» insulin aspart protamine/insulin aspart: (70/30) injected subcutaneously twice daily</td>
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<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» insulin lispro protamine/insulin lispro: (50/50, 75/25) injected subcutaneously twice daily</td>
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<tr>
<td>OR</td>
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</tr>
<tr>
<td>» insulin degludec/insulin aspart: (70/30) injected subcutaneously once or twice daily</td>
<td></td>
</tr>
</tbody>
</table>
Immediate insulin therapy should be considered for marked hyperglycemia.

For individuals with severe hyperglycemia (HbA1c 11% or greater; or fasting or postprandial glucose >350 mg/dL), or individuals with metabolic compromise related to hyperglycemia (polyuria, polydipsia, ongoing weight loss) but without ketonuria or dehydration, both basal (background) and bolus (mealtime/prandial) insulin are typically recommended to reverse symptoms rapidly. [78] Individuals with uncontrolled marked hyperglycemia will typically require initiation of basal and bolus insulin therapy at higher doses (0.2 units/kg/day of basal, and 0.2 units/kg/day of bolus mealtime/prandial insulin), with the mealtime/prandial insulin being divided between the three meals (e.g., if the dose is 24 units, then divide that by 3 to get 8 units per meal, with the option to redistribute these mealtime doses slightly if the size of the meal is known).

For individuals with more modest hypoglycemia, 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. Addition of mealtime/prandial insulin should be considered for individuals reaching a background insulin dose of 0.5 units/kg/day, individuals experiencing a greater than 50 mg/dL drop in glucose overnight, or individuals not reaching glycemic goals despite controlled fasting morning glucose values (uncontrolled postprandial glucose).[2]

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. Consult specialist as needed for guidance on dose.

Choice of insulin regimen should be individualized. For patients with type 2 diabetes, human insulins can be as effective as analog insulins in terms of glucose control, serious hypoglycemia risk, and mortality and cardiovascular events.[137] Human insulins are significantly less expensive than analog insulins.
Type 2 diabetes mellitus in adults

Management

Acute

For individuals with relaxed HbA1c goals, low rates of hypoglycemia, and prominent insulin resistance, as well as those with cost concerns, human insulin (NPH and regular) may be the appropriate choice of therapy.[2]

- Premixed insulin may start at a dose of 0.1 to 0.2 units/kg dosed twice a day before breakfast and evening meal, 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.[33] [70]

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

- Metformin therapy is typically started or continued at the time of initiation of insulin in type 2 diabetes, unless contraindicated. While consideration should be given to discontinuing sulfonylurea therapy in individuals initiating insulin therapy because of additive hypoglycemia risk, other noninsulin therapies can often be continued if an individual is benefiting.[138] In particular, individuals on SGLT2 or GLP-1 therapy because of unique indications (atherosclerotic cardiovascular disease, heart failure, chronic kidney disease) can be continued on those therapies when initiating insulin.

<table>
<thead>
<tr>
<th>adjunct</th>
<th>metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment recommended for SOME patients in selected patient group</td>
<td></td>
</tr>
</tbody>
</table>

Primary options

- **metformin**: 500 mg orally (immediate-release) twice daily initially, increase gradually according to response, maximum 2000 mg/day; 850 mg orally (immediate-release) once daily initially, increase gradually according to response, maximum 2000 mg/day; 500-1000 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 2000-2500 mg/day (depending on brand used)

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

- Metformin reduces hyperglycemia by decreasing hepatic gluconeogenesis and
Acute 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 consideration of a 50% dose reduction.[78]

» Metformin should be discontinued at the time of or before an iodinated contrast imaging procedure in patients with an eGFR between 30-60 mL/minute/1.73 m²; or in patients who will be administered intra-arterial iodinated contrast. Restart metformin if renal function is stable 48 hours after the imaging procedure.[178]

» Individuals treated with metformin are at increased risk for vitamin B12 deficiency, and periodic testing for vitamin B12 deficiency and B12 supplementation may be needed.[2]

» The extended-release formulation may improve tolerance in individuals experiencing gastrointestinal side effects with the immediate-release formulation.

<table>
<thead>
<tr>
<th>without marked hyperglycemia</th>
<th>nonpregnant asymptomatic: serum glucose &lt;300 mg/dL or HbA1c &lt;10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c above goal at diagnosis</td>
<td>1st metformin + cardiovascular risk reduction/ lifestyle measures</td>
</tr>
<tr>
<td>Primary options</td>
<td>» metformin: 500 mg orally (immediate-release) twice daily initially, increase gradually according to response, maximum 2000 mg/day; 850 mg orally (immediate-release) once daily initially, increase gradually according to response, maximum 2000 mg/day; 500-1000 mg orally (extended-</td>
</tr>
</tbody>
</table>
Acute release) once daily initially, increase gradually according to response, maximum 2000-2500 mg/day (depending on brand used).

» Pharmacotherapy is recommended to reduce risk of microvascular (nephropathy, retinopathy, neuropathy) and macrovascular (myocardial infarction, stroke, peripheral vascular disease) complications, and is guided by HbA1c goals or a unique indication (presence of atherosclerotic cardiovascular disease, heart failure, chronic kidney disease). [2] [78] [79] [80] [90] [91]

» The American Diabetes Association recommends that in the absence of contraindications 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. [90] [92]

» 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.

» Individuals treated with metformin are at increased risk for vitamin B12 deficiency, and 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. [78]
### Acute

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

- Metformin should be discontinued at the time of or before an iodinated contrast imaging procedure in patients with an eGFR between 30-60 mL/minute/1.73 m²; or in patients who will be administered intra-arterial iodinated contrast. Restart metformin if renal function is stable 48 hours after the imaging procedure.[178]

- The extended-release formulation of metformin may improve tolerance in individuals experiencing gastrointestinal side effects with the immediate-release formulation.

- Those unable to take metformin due to contraindication or intolerance can either use an alternative noninsulin agent or insulin therapy.

- General nutrition and healthy lifestyle knowledge (including an individualized nutrition and exercise plan) can improve glycemic control and quality of life.[33] [70]

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

#### Primary options

1. **HbA1c above goal on metformin**

   - **1st**

   - **Primary options**

     - **metformin**: 500 mg orally (immediate-release) twice daily initially, increase gradually according to response, maximum 2000 mg/day; 850 mg orally (immediate-release) once daily initially, increase gradually according to response, maximum 2000 mg/day; 500-1000 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 2000-2500 mg/day (depending on brand used)

       - AND-

     - **empagliflozin**: 10 mg orally once daily, increase according to response, maximum 25 mg/day

       - or-

     - **canagliflozin**: 100 mg orally once daily initially, increase according to response, maximum 300 mg/day

       - or-

     - **dapagliflozin**: 5 mg orally once daily initially, increase according to response, maximum 10 mg/day

       - or-
**Type 2 diabetes mellitus in adults**

**Management**

### Acute

- **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.[103] [104] [105] [94] [108] 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.[107] Canagliflozin also reduces cardiovascular mortality,[109] but may have more adverse effects than empagliflozin. In one trial, treatment with dapagliflozin did not result in a lower rate of major adverse cardiovascular events, but did result in a lower rate of hospitalization for heart failure.[110]

- Dapagliflozin also improves renal outcomes in patients with, and without, diabetes.[111] One published trial on the CVD benefits of ertugliflozin supports its use in patients with diabetes and heart failure.[112] [113] [114]

- 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 who are on a SGLT2 inhibitor should seek immediate medical attention for signs of ketoacidosis (difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness), and these agents should be stopped temporarily before scheduled surgery.[115] The FDA and the European Medicines Agency (EMA) warn of the potential increased risk of toe amputation with approved SGLT2 inhibitors and the need for appropriate monitoring.[119] [120] 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.[122] [123]

- General nutrition and healthy lifestyle knowledge (including an individualized nutrition
### Acute

and exercise plan) can improve glycemic control and quality of life.\[33\] [70]

» 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**

<table>
<thead>
<tr>
<th>Option</th>
<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>metformin</td>
<td>500 mg orally (immediate-release) twice daily initially, increase gradually according to response, maximum 2000 mg/day; 850 mg orally (immediate-release) once daily initially, increase gradually according to response, maximum 2000 mg/day; 500-1000 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 2000-2500 mg/day (depending on brand used)</td>
</tr>
<tr>
<td>liraglutide</td>
<td>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</td>
</tr>
<tr>
<td>dulaglutide</td>
<td>0.75 mg subcutaneously once weekly initially, may increase to 1.5 mg once weekly if response is inadequate</td>
</tr>
<tr>
<td>semaglutide</td>
<td>0.25 mg subcutaneously once weekly for 4 weeks initially, then increase to 0.5 mg once weekly for at least 4 weeks, then may increase to 1 mg once weekly if response is inadequate; 3 mg orally once daily for 30 days initially, then increase to 7 mg once daily for at least 30 days, then may increase to 14 mg once daily if response is inadequate</td>
</tr>
<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>
</tr>
<tr>
<td>lixisenatide</td>
<td>10 micrograms subcutaneously once daily for 14 days, then increase to 20 micrograms once daily thereafter</td>
</tr>
</tbody>
</table>

Important note: the subcutaneous formulation is given once weekly, while the oral formulation is given once daily

---AND---

- or -

*“*
As a class of drugs, GLP-1 agonist treatment has beneficial effects on cardiovascular, mortality, and kidney outcomes in patients with type 2 diabetes.[95] 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.[125] Dulaglutide and semaglutide have both been shown to reduce major cardiovascular events, but not all-cause or cardiovascular mortality.[126] [127] [129] Exenatide and lixisenatide have both been shown not to reduce major cardiovascular events.[130] 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 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 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.[131]

General nutrition and healthy lifestyle knowledge (including an individualized nutrition and exercise plan) can improve glycemic control and quality of life.[33] [70]

Cardiovascular risk reduction (blood pressure and lipid control, nonsmoking, and consideration of antiplatelet therapy) should continue.
Type 2 diabetes mellitus in adults

Management

Acute

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) twice daily initially, increase gradually according to response, maximum 2000 mg/day; 850 mg orally (immediate-release) once daily initially, increase gradually according to response, maximum 2000 mg/day; 500-1000 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 2000-2500 mg/day (depending on brand used)

--AND--

- **sitagliptin**: 100 mg orally once daily
  -or-
  - **linagliptin**: 5 mg orally once daily
  -or-
  - **alogliptin**: 25 mg orally once daily
  -or-
  - **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.

» 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.[179] In people with a recent acute coronary syndrome, alogliptin was not associated with increased risk of major adverse cardiovascular events over 40 months.[180]

» General nutrition and healthy lifestyle knowledge (including an individualized nutrition and exercise plan) can improve glycemic control and quality of life.[33][70]
Type 2 diabetes mellitus in adults

Management

Acute

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

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

Primary options

» metformin: 500 mg orally (immediate-release) twice daily initially, increase gradually according to response, maximum 2000 mg/day; 850 mg orally (immediate-release) once daily initially, increase gradually according to response, maximum 2000 mg/day; 500-1000 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 2000-2500 mg/day (depending on brand used)

--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) twice daily initially, increase gradually according to response, maximum 2000 mg/day; 850 mg orally (immediate-release) once daily initially, increase gradually according to response, maximum 2000 mg/day; 500-1000 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 2000-2500 mg/day (depending on brand used)

--AND--

» repaglinide: 0.5 to 1 mg orally up to four times daily initially, increase by 0.5 to 1 mg/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.
**Acute**

» 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, sulfas 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 sulfas 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.[33] [70]

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

<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) twice daily initially, increase gradually according to response, maximum 2000 mg/day; 850 mg orally (immediate-release) once daily initially, increase gradually according to response, maximum 2000 mg/day; 500-1000 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 2000-2500 mg/day (depending on brand used)</td>
</tr>
</tbody>
</table>
Type 2 diabetes mellitus in adults

Management

Acute

---AND---

- insulin NPH: injected subcutaneously, usually at bedtime
  - or -
  - insulin glargine: injected subcutaneously, usually at bedtime
  - or -
  - insulin detemir: injected subcutaneously, usually at bedtime
  - or -
  - 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.[33] [70]
Type 2 diabetes mellitus in adults

Management

Acute

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

» While consideration should be given to discontinuing sulfonylurea therapy in individuals initiating insulin therapy because of additive hypoglycemia risk, other noninsulin therapies can often be continued if an individual is benefiting.[138] In particular, individuals on SGLT2 or GLP-1 therapy because of unique indications (atherosclerotic cardiovascular disease, heart failure, chronic kidney disease) can be continued on those therapies when initiating insulin.

2nd alpha-glucosidase inhibitor added to continued metformin + continued cardiovascular risk reduction/lifestyle measures

Primary options

» metformin: 500 mg orally (immediate-release) twice daily initially, increase gradually according to response, maximum 2000 mg/day; 850 mg orally (immediate-release) once daily initially, increase gradually according to response, maximum 2000 mg/day; 500-1000 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 2000-2500 mg/day (depending on brand used)

--AND--

» 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.
Type 2 diabetes mellitus in adults

Management

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» 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.[33] [70]

» 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

» metformin: 500 mg orally (immediate-release) twice daily initially, increase gradually according to response, maximum 2000 mg/day; 850 mg orally (immediate-release) once daily initially, increase gradually according to response, maximum 2000 mg/day; 500-1000 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 2000-2500 mg/day (depending on brand used)

--AND--

» pioglitazone: 15 mg orally once daily initially, increase every 6-8 weeks, maximum 45 mg once daily

-or-

» rosiglitazone: 2-4 mg/day orally initially given as a single dose or in 2 divided doses, increase according to response, maximum 8 mg/day

» 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.[136]
### Acute

**HbA1c above goal on metformin + either basal insulin or second noninsulin agent**

1st **individualized augmented regimen + continued cardiovascular risk reduction/lifestyle measures**

- 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. In 2013, the Food and Drug Administration 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.

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

- 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 safety of other agents, and such data should be strongly considered when selecting treatments.

- 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, DPP-4 inhibitors, GLP-1 agonists, alpha-glucosidase inhibitors, thiazolidinediones, basal insulin, or SGLT2 inhibitors. 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.

- The American Diabetes Association recommends: basal insulin plus GLP-1 agonist, basal insulin plus rapid-acting insulin, or fixed-dose insulin as alternative combination injectable regimens.

- 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...
Type 2 diabetes mellitus in adults

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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.

» Liraglutide, empagliflozin, or canagliflozin can be considered for those with established cardiovascular disease as these agents have been shown to reduce cardiovascular mortality and all-cause mortality.[2] [107] [108] [109] [125] [128] Semaglutide has shown a reduction in major cardiovascular events, but not in all-cause or cardiovascular mortality.[127]

» The UK Medicines and Healthcare products Regulatory Agency 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.[131]

» General nutrition and healthy lifestyle knowledge (including an individualized nutrition and exercise plan) can improve glycemic control and quality of life.[33] [70]

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

1st switch to basal-bolus insulin + continued cardiovascular risk reduction/lifestyle measures

Primary options

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

OR

» insulin glargine: injected subcutaneously once daily
- or -
» insulin detemir: injected subcutaneously twice daily
- or -
» insulin degludec: injected subcutaneously once daily

--AND--

» insulin lispro: injected subcutaneously premeals
- or -
### Acute

<table>
<thead>
<tr>
<th>MANAGEMENT</th>
<th>Acute</th>
</tr>
</thead>
</table>

- **insulin aspart**: injected subcutaneously premeals  
  -or-  
  - **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 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** (insulin pens) that can be adjusted to administer set doses of insulin are widely available, and offer increased convenience and accuracy in insulin dosing.

- **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
Management

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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.[33] [70]

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

» Metformin therapy is typically started or continued at the time of initiation of insulin in type 2 diabetes, unless contraindicated. While consideration should be given to discontinuing sulfonylurea therapy in individuals initiating insulin therapy because of additive hypoglycemia risk, other noninsulin therapies can often be continued if an individual is benefiting.[138] In particular, individuals on SGLT2 or GLP-1 therapy because of unique indications (atherosclerotic cardiovascular disease, heart failure, chronic kidney disease) can be continued on those therapies when initiating insulin.

adjunct continued metformin

Treatment recommended for SOME patients in selected patient group

Primary options

» metformin: 500 mg orally (immediate-release) twice daily initially, increase gradually according to response, maximum 2000 mg/day; 850 mg orally (immediate-release) once daily initially, increase gradually according to response, maximum 2000 mg/day; 500-1000 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 2000-2500 mg/day (depending on brand used)

» Metformin can be continued with basal-bolus insulin.

» Metformin reduces hyperglycemia by decreasing hepatic gluconeogenesis and glycogenolysis. At maximal effective doses, 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
### Acute

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.[78]

» Metformin should be discontinued at the time of or before an iodinated contrast imaging procedure in patients with an eGFR between 30-60 mL/minute/1.73 m²; or in patients who will be administered intra-arterial iodinated contrast. Restart metformin if renal function is stable 48 hours after the imaging procedure.[178]

» The extended-release formulation of metformin may improve tolerance in individuals experiencing gastrointestinal side effects with the immediate-release formulation.

### 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 recommended to treat type 2 diabetes in adults with body mass index (BMI) ≥40 kg/m² (≥37.5 kg/m² for Asian-Americans) and adults with BMI 35.0 to 39.9 kg/m² (32.5 to 37.4 kg/m² for Asian-Americans) who do not achieve long-lasting weight loss and improvement in co-morbidities, including hyperglycemia despite lifestyle and optimal non-surgical medical management. It may be considered for those with BMI 30.0 to 34.9 kg/m² (27.5 to 32.4 kg/m² for Asian-Americans) who do not achieve long-lasting weight loss and improvement in co-morbidities, including hyperglycemia despite lifestyle and optimal nonsurgical medical management.[2]

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

### pregnant

#### 1st diet + basal-bolus insulin

**Primary options**

» insulin NPH: injected subcutaneously twice daily
Acute

--AND--

- insulin regular: injected subcutaneously two to three times daily
- insulin lispro: injected subcutaneously premeals
- insulin aspart: injected subcutaneously premeals

- 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] The American Diabetes Association 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 <6.0% (42-48 mmol/mol) is recommended; <6% may be optimal as pregnancy progresses if achievable without hypoglycemia.[2]

- 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 Food and Drug Administration-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. Premal 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.

- Diabetes patients who become pregnant require individualized dietary counseling and team care.
| Acute                  | Insulin dose varies; consult specialist for guidance on dose. |
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.

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.[33] [34] Several clinical trials have shown that weight loss is associated with delayed or decreased onset of diabetes in high-risk adults.[21] [22] [23] [24] [25] [26] 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.[22] 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] [30] [35] [36] [37] [38] Lifestyle change and/or metformin are preferred for most patients.[39] [40] [41] [42] More aggressive multi-agent pharmacologic approaches remain controversial.[43] Screening for prediabetes and cardiovascular risk reduction appropriate to the needs of the individual are also very important.[31] [44] [45]

Secondary prevention

Although the risk of macrovascular complications can be reduced by over 50% using effective multifactorial interventions,[217] 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.[218] More evidence indicates that sodium-glucose co-transporter 2 (SGLT2) and glucagon-like peptide-1 (GLP-1) therapy can play a significant role in reducing future risk in individuals with established atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease comorbidities, and use of one these agents should be strongly considered if not contraindicated in the secondary prevention of macrovascular complications.[78] [79]

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.

Patient discussions

- 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 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.[211] [216]

• 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]
**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. 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.

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. 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. Continuous glucose monitoring may be helpful in people with type 2 diabetes (particularly those on insulin therapy) to create a more complete picture of patients’ actual glucose status throughout the day and night. The data form an ambulatory glucose profile showing time in range and times of hypoglycemia, which can be used for personalized therapy decisions.

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 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation or equivalent
- 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 insensitive feet, foot deformities, or a history of foot ulcers should have their feet examined at every visit and are candidates for specialized footwear.

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.
Follow up

Type 2 diabetes mellitus in adults
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).[186] 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, and, to a lesser degree, glucagon-like peptide-1 [GLP-1] agonists).[103] [95]

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.

<table>
<thead>
<tr>
<th>impaired vision</th>
<th>long term</th>
<th>low</th>
</tr>
</thead>
</table>

In the US, approximately 25% of patients with type 2 diabetes have retinopathy at diagnosis, presumably as a consequence of unrecognized disease.[196] 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.[197] 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.[198] [199] The risk of all of these eye conditions is increased in diabetes.

<table>
<thead>
<tr>
<th>lower extremity amputation</th>
<th>long term</th>
<th>low</th>
</tr>
</thead>
</table>

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.[200] 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.[14]

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.

<table>
<thead>
<tr>
<th>cardiovascular disease</th>
<th>variable</th>
<th>high</th>
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</table>

Cardiovascular disease (CVD) and CVD-associated mortality is declining in patients with diabetes, particularly in high-income countries.[14] 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.[72] [73] To reduce cardiovascular risk, blood pressure, lipids, and tobacco use should be adequately managed. Use of statins, ACE inhibitors, metformin, aspirin, sodium-glucose co-transporter 2 (SGLT2) inhibitor or glucagon-like peptide-1 (GLP-1) agonist classes of drugs, and proprotein convertase subtilisin/kexin type 9 (PCSK9)
Complications | Timeframe | Likelihood
--- | --- | ---
inhibitors may reduce cardiovascular mortality or all-cause mortality in selected patients with type 2 diabetes.[2] [78] [79] 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 the SGLT2 or GLP-1 classes of drugs, or PCSK9 inhibitors. Many studies suggest that HbA1c ≥8% increases risk of major cardiovascular events.[96] [97] Increased fatigability 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>congestive heart failure</th>
<th>variable</th>
<th>high</th>
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</table>

Diabetes is a risk factor for congestive heart failure (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.[188] CHF occurs in up to 10% to 15% of patients with diabetes.[189] 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.

The sodium-glucose co-transporter 2 (SGLT2) class of drugs has been shown to significantly reduce the risk of hospitalization with congestive heart failure in individuals with a history of congestive heart failure, and should be considered as an adjunct to therapy in individuals with type 2 diabetes and a history of congestive heart failure.[110] [190]

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.

<table>
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<tr>
<th>stroke</th>
<th>variable</th>
<th>high</th>
</tr>
</thead>
</table>

Related to uncontrolled blood pressure, glucose, and lipids. Lifetime risk is higher in women than in men with diabetes.[191]

Prompt hospitalization and neurologic evaluation, with possible emergency use of tissue plasminogen activator or other therapeutic strategies, may minimize damage and maximize potential for recovery of function.

<table>
<thead>
<tr>
<th>infection</th>
<th>variable</th>
<th>medium</th>
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</thead>
</table>

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, *Haemophilus influenzae*, and influenza infections.

Aggressive infection-specific therapy and supportive therapy including adequate glucose control are key to successful treatment.

| periodontal disease | variable | medium |
Type 2 diabetes is associated with periodontal disease, but causality is not established. In one large epidemiologic survey, periodontal disease was an independent predictor of incident diabetes. Bidirectional risk has been postulated.

Control of periodontal disease and hyperglycemia are mutually beneficial. Routine preventive dental care is important for people with type 2 diabetes.

<table>
<thead>
<tr>
<th>Complications</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. 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.

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>depression</th>
<th>variable</th>
<th>medium</th>
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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. 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.

<table>
<thead>
<tr>
<th>obstructive sleep apnea</th>
<th>variable</th>
<th>medium</th>
</tr>
</thead>
</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 on glycemic control, as results have varied.

The American Diabetes Association recommends assessment of sleep pattern and duration should be considered as part of a comprehensive approach to lifestyle and glycemic control.

<table>
<thead>
<tr>
<th>diabetic ketoacidosis</th>
<th>variable</th>
<th>low</th>
</tr>
</thead>
</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.

Criteria of diabetic ketoacidosis is the same, regardless of type of diabetes and is potentially fatal if not properly treated.
Type 2 diabetes mellitus in adults

Complications | Timeframe | Likelihood
--- | --- | ---
Hydration, parenteral insulin therapy, intensive monitoring and careful management of electrolyte imbalances and acidosis are important for successful therapy.

**hyperosmolar hyperglycemic state**

Occurs most commonly in older people with type 2 diabetes with a precipitating infection or acute illness (e.g., myocardial infarction, cerebrovascular accident) and usually evolves insidiously over days to weeks.[3] Certain medications, particularly antipsychotic agents, may precipitate hyperosmolar hyperglycemic state.[48]

Characterized by severe hyperglycemia, hyperosmolality, and volume depletion, in the absence of severe ketoacidosis. Delayed recognition of hyperglycemic symptoms may lead to severe dehydration and progressive decline in mental status.[48]

Hydration, insulin therapy, and careful clinical and laboratory monitoring are the basis of successful therapy.

**autonomic or peripheral neuropathy**

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.[201] 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.[202]

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.[184] A HbA1c of 6% to 6.9% (42 mmol/mol to 52 mmol/mol) is associated with the lowest mortality.[184] 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.[14] 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.[13] 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.[72] [73]

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-Latino black people compared with non-Latino white people (9.3% vs. 3.2%, respectively).[185] 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.[186] 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
Type 2 diabetes mellitus in adults

ESRD.[187] 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>
<thead>
<tr>
<th>Guidelines</th>
<th>Published by</th>
<th>Last published</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standards of medical care in diabetes - 2021 (<a href="https://care.diabetesjournals.org/content/44/Supplement_1">https://care.diabetesjournals.org/content/44/Supplement_1</a>)</td>
<td>American Diabetes Association</td>
<td>2021</td>
</tr>
<tr>
<td>Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults (<a href="https://www.acc.org/guidelines">https://www.acc.org/guidelines</a>)</td>
<td>American College of Cardiology; American Heart Association</td>
<td>2017</td>
</tr>
</tbody>
</table>
# Treatment guidelines

## International

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Published by</th>
<th>Last published</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standards of medical care in diabetes - 2021</td>
<td>American Diabetes Association</td>
<td>2021</td>
</tr>
<tr>
<td>Treatment of diabetes in older adults</td>
<td>Endocrine Society</td>
<td>2019</td>
</tr>
<tr>
<td>Guideline on the management of blood cholesterol</td>
<td>American Heart Association; American College of Cardiology</td>
<td>2019</td>
</tr>
<tr>
<td>Diabetes Canada clinical practice guidelines</td>
<td>Diabetes Canada</td>
<td>2018</td>
</tr>
<tr>
<td>Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice update</td>
<td>American College of Physicians</td>
<td>2017</td>
</tr>
<tr>
<td>Guidelines on second- and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes mellitus</td>
<td>World Health Organization</td>
<td>2018</td>
</tr>
</tbody>
</table>
Online resources


## Evidence tables

What are the effects of self-management by regular blood glucose monitoring in people with type 2 diabetes?[212]

This table is a summary of the analysis reported in a guideline (underpinned by a systematic review) that focuses on the above important clinical question.

[View the full source guideline (https://www.nice.org.uk/guidance/ng28/evidence)]

Evidence C *  
Confidence in the evidence is very low or low where GRADE has been performed and there is a trade off between benefits and harms of the intervention.

**Population:** Adults with type 2 diabetes  
**Intervention:** Self-monitoring blood glucose  
**Comparison:** No self-monitoring blood glucose (including usual care and self-monitoring of urine glucose)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Effectiveness (BMJ rating)†</th>
<th>Confidence in evidence (GRADE)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin A1c (HbA1c) (follow up: 24-52 weeks)</td>
<td>Favors intervention</td>
<td>Low</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/L) (follow up: 26-52 weeks)</td>
<td>Favors intervention</td>
<td>Low</td>
</tr>
<tr>
<td>Postprandial blood glucose (mg/dL) at 26 weeks for adults with type 2 diabetes on diet, antidiabetic, and/or insulin medicines (follow up: 6 months)</td>
<td>Favors intervention</td>
<td>Low</td>
</tr>
<tr>
<td>Any hypoglycemia from 26-52 weeks (follow up: 6-12 months)</td>
<td>Favors comparison</td>
<td>Low</td>
</tr>
<tr>
<td>Severe hypoglycemia from 26-52 weeks (follow up: 6-12 months)</td>
<td>No statistically significant difference</td>
<td>Low</td>
</tr>
<tr>
<td>Adverse events at 6 months for adults with type 2 diabetes on oral antidiabetes medicines (follow up: 6 months)</td>
<td>No statistically significant difference</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

**Recommendations as stated in the source guideline**
The guideline development group states: do not routinely offer self-monitoring of blood glucose levels for adults with type 2 diabetes unless:

- the person is on insulin or
- there is evidence of hypoglycemic episodes or
- the person is on oral medication that may increase their risk of hypoglycemia while driving or operating machinery or
- the person is pregnant, or is planning to become pregnant.

**Note**
The guideline development group noted that self-monitoring of blood glucose provides the potential for tight glycemic control which reduces the risk of diabetes-related complications. However, the impact on hypoglycemic events is important in determining the safety and acceptability in patients.

* Evidence levels

The Evidence level is an internal rating applied by BMJ Best Practice. See the EBM Toolkit (https://bestpractice.bmj.com/info/evidence-tables/) for details.

Confidence in evidence

A - High or moderate to high
B - Moderate or low to moderate
C - Very low or low

† Effectiveness (BMJ rating)

Based on statistical significance, which demonstrates that the results are unlikely to be due to chance, but which does not necessarily translate to a clinical significance.

‡ Grade certainty ratings

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>High</td>
<td>The authors are very confident that the true effect is similar to the estimated effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>The authors are moderately confident that the true effect is likely to be close to the estimated effect.</td>
</tr>
<tr>
<td>Low</td>
<td>The authors have limited confidence in the effect estimate and the true effect may be substantially different.</td>
</tr>
<tr>
<td>Very Low</td>
<td>The authors have very little confidence in the effect estimate and the true effect is likely to be substantially different.</td>
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BMJ Best Practice EBM Toolkit: What is GRADE? (https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/)
Key articles


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References


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References


Images

Figure 1: Acanthosis nigricans involving the axilla

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Please note that recommended formulations and doses may differ between drug databases drug names and brands, drug formularies, or locations. A local drug formulary should always be consulted for full prescribing information.

Treatment recommendations in BMJ Best Practice are specific to patient groups. Care is advised when selecting the integrated drug formulary as some treatment recommendations are for adults only, and external links to a paediatric formulary do not necessarily advocate use in children (and vice-versa). Always check that you have selected the correct drug formulary for your patient.

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Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style
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