BMJ Best Practice

Diabetic cardiovascular disease

Straight to the point of care

Last updated: Mar 06, 2025

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Summary

Cardiovascular disease (CVD) is the leading cause of death in people with diabetes.

People with diabetes have up to a fourfold increased risk of stroke and are twice as likely to die after myocardial infarction than people without diabetes.

Regular physical activity, medical nutrition therapy, and smoking cessation or non-initiation are important lifestyle changes for the primary prevention of CVD.

Selected glucose-lowering drugs reduce all-cause and cardiovascular (CV) mortality. Addition of a sodium-glucose cotransporter-2 (SGLT2) inhibitor or a glucagon-like peptide-1 (GLP-1) receptor agonist is strongly recommended in patients with established atherosclerotic CV and/or chronic kidney disease. SGLT2 inhibitors are also indicated in patients with heart failure. Evidence also supports the use of a GLP-1 receptor agonist for primary prevention of stroke in patients at high CV risk.

Aggressive treatment of hypertension, use of lipid-lowering therapy, preventive anticoagulation, and coronary revascularization (percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery during episodes of acute coronary syndrome) can lead to improved survival.

Definition

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia, resulting from defects in insulin secretion, insulin action, or both.[1] The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.[1] Diabetes is an established major risk factor for the development of cardiovascular disease, including coronary artery disease (CAD), cerebrovascular disease (stroke or transient ischemic attack), and peripheral arterial disease.[2] This topic will discuss CAD in greatest detail.

Epidemiology

Diabetes prevalence is increasing worldwide, compounded by both population growth and aging.[3] In the US, 29.3 million adults (10.6% of the population) had diagnosed diabetes between 2017 and 2020, while a further 9.7 million (3.5% of the population) had undiagnosed diabetes.[4] Worldwide, 536.6 million adults had diabetes in 2021, and projections estimate that 783.2 million adults will have diabetes by 2045.[1] Total diabetes prevalence, especially among older adults, primarily reflects type 2 diabetes, which in 2021 accounted for 96% of diabetes cases.[5]

Diabetes confers a two- to fourfold excess lifetime risk of developing cardiovascular disease ([CVD]; coronary artery disease [CAD], stroke, heart failure, atrial fibrillation, and peripheral artery disease), independent of other risk factors.[6] CVD is the leading cause of hospital admission for people with diabetes, with CAD as the predominant subtype.[7] Data from the CALIBER UK cohort show the most common initial CVD complications for those with diabetes to be PAD (16.2%) and heart failure (14.1%), followed by stable angina (11.9%), nonfatal myocardial infarction (MI) (11.5%), and stroke (10.3%).[8]

Globally, it is estimated that 50% of deaths among patients with type 2 diabetes are due to CVD.[9] In 2014, death due to CVD was 1.7 times higher among adults with diabetes than in adults without diabetes.[10] While there was an overall decrease in cardiovascular (CV) mortality from 1998 to 2014, decreases were smaller for adults with type 2 diabetes compared with adults without diabetes.[11] One Danish population-based cohort study found that from 1996 to 2015, the 5-year risk of first-time ischemic stroke was approximately halved in patients with incident type 2 diabetes mellitus and no prior atherosclerotic CVD.[12] Increased use of medication to control CV risk factors has likely influenced the decrease in CV morbidity and mortality in patients with type 2 diabetes.[13]

Although the risk of CVD in patients with type 1 diabetes has also decreased over time, there remains considerable excess CV risk in this group compared with the general population.[14] [15] One Finnish study found the risk of CVD to be 64.3% in patients with type 1 diabetes of duration >50 years, compared with 7.4% in individuals without diabetes.[16]

CAD (MI, angina)

CAD is the most common manifestation of CVD in people with diabetes. In patients with established CAD, 70% to 75% have abnormal glucose regulation, with more than 30% having known diabetes, up to 20% having undiagnosed diabetes, and around 25% having impaired glucose tolerance or prediabetes.[17] [18] Mortality from MI is about 1.5- to 2-fold greater in people with diabetes than in people without diabetes.[19] In the UK Prospective Diabetes Study (UKPDS), the odds ratio for acute MI case fatality was 1.17 per 1% increase in hemoglobin A1c (HbA1c).[20] Additionally, patients with diabetes who are admitted with high-risk non-ST elevation MI are known to have worse early outcomes, including mortality, compared with patients without diabetes who present similarly.[21]

Heart failure

Although not as frequent as MI, hospitalization for heart failure is a common event in patients with type 2 diabetes.[22] People with type 2 diabetes are twice as likely to develop heart failure than those without type 2 diabetes and the prevalence of heart failure in people with type 2 diabetes in the US is estimated to be as high as 22%.[23] Greater levels of insulin resistance and dysglycemia are associated with increased risk of heart failure in patients with newly diagnosed type 2 diabetes.[23] [24] Type 2 diabetes duration has also been identified as an independent risk factor for heart failure, with each 5-year increase associated with a 17% increased risk.[23]

Women appear to be more at risk of heart failure than men, potentially due to a greater burden of cardiometabolic risk factors such as increased body mass index and systolic blood pressure at the time of diabetes diagnosis, therapeutic inertia that disproportionately affects women, and distinct hormone profiles.[23] Similarly, racial disparities have been reported in the type 2 diabetes-associated risk of heart failure, with black individuals at higher risk than those of other races; these differences largely seem to be driven by a higher burden of adverse social determinants of health, including lower income and lower access to health care.[23]

Cerebrovascular disease (stroke and transient ischemic attack)

The risk of stroke is increased 1.5- to 4-fold in patients with diabetes.[25] [26] Diabetes is associated with a significantly increased risk of stroke recurrence.[27] Stroke outcomes, including in-hospital and long-term mortality, are worse in people with diabetes.[26] Diabetes increases the risk of ischemic stroke to a greater degree than hemorrhagic stroke. Lacunar infarcts are more common in patients with diabetes, who are more likely to develop silent lacunar infarcts. However, transient ischemic attacks are less common in people with diabetes than in those without diabetes. The risk of stroke increases with worsening glycemic control. In the UKPDS, the odds ratio for stroke case fatality was 1.37 per 1% increase in HbA1c.[20]

Peripheral arterial disease (PAD)

Cigarette smoking and diabetes are the two major risk factors for PAD.[28] Risk factors associated with an increased risk for PAD in people with diabetes include increased age, hypertension, dyslipidemia, poor glycemic control, longer duration of diabetes, neuropathy, retinopathy, and a prior history of CVD.[29] Of symptomatic patients with PAD, 20% are known to have diabetes; however, most patients with PAD are asymptomatic. Up to two-thirds of people with asymptomatic PAD have been shown to have comorbid diabetes.[29] Diabetes is associated with increased risk of critical lower extremity ischemia and major amputation in patients with PAD.[30]

Etiology

The etiology of cardiovascular disease in diabetes is complex and multifactorial. It results from the interplay of a constellation of metabolic risk factors, excessive oxidation, endothelial dysfunction, inflammation, and imbalance in prothrombotic and antifibrinolytic processes.[31] The unifying metabolic factor is hyperglycemia, which results from both insulin deficiency and insulin resistance. Insulin resistance is associated with a variety of major metabolic risk factors including hyperinsulinemia, dyslipidemia, elevated blood pressure, and obesity.[32] [33] Hyperglycemia leads to excessive oxidation and accumulation of advanced glycation end-products, while peroxidation of lipids leads to foam cell formation within the arterial wall.[34] [35] Insulin resistance is an important precursor to endothelial dysfunction and associated with increased release of inflammatory proteins, including cytokines, C-reactive protein, and subsequent release of growth factors that stimulate smooth-muscle proliferation and platelet aggregation.[36] [37] This cascade ultimately leads to arterial intimal thickening, increased plaque formation, and atherosclerosis.[37]

Pathophysiology

The underlying mechanism for cardiovascular disease (CVD) in diabetes is accelerated atherosclerosis.[38] Autopsy studies have shown that type 2 diabetes is associated with a global coronary disease burden and a prevalence of high-grade atherosclerosis similar to that observed in nondiabetic patients with an antemortem diagnosis of coronary artery disease (CAD); among deceased patients with diabetes who had no diagnosis

of CAD, almost three quarters were found to have high-grade coronary atherosclerosis and more than half had multivessel disease.[39] Furthermore, angiographic data have shown that people with diabetes have more diffuse, extensive, multivessel (including left main), and distal disease than do people without diabetes.[40]

The clinical manifestations of atherosclerosis depend on the vascular bed involved. When atherosclerosis involves the coronary arteries it presents as angina pectoris and acute coronary syndromes. When it involves the cerebral or cerebellar arteries it presents as transient ischemic attacks and strokes. Involvement of the peripheral circulation presents as intermittent claudication or gangrene.

The process of atherosclerosis begins with damage to the endothelial cell layer.[38] Under physiologic conditions, the endothelial cell layer separates cells and circulating factors from the arterial intima and media and serves as an anticoagulant and fibrinolytic surface.[31] Circulating factors such as blood glucose, free fatty acids, and glycation end-products damage the endothelial layer, leading to adhesion and penetration of circulating monocytes and macrophages into the arterial intima. The endothelial cells and macrophages produce cytokines and growth factors that allow smooth-muscle migration and proliferation, leading to formation of the atherosclerotic plaque.[38] Continued exposure to circulating factors leads to cell death, and the combination of a large lipid core, necrotic tissue, macrophages, and a thin fibrous cap predisposes to plaque rupture.[31] Plaque rupture and thrombosis are responsible for the clinical events associated with CVD, including acute coronary syndromes and strokes. The development of atherosclerosis is usually a slow process, but in people with diabetes it is more rapid and aggressive and produces clinical disease at an earlier age.[38]

Aortic aneurysm is associated with atherosclerosis; however, current evidence suggests that patients with diabetes have a lower risk of developing abdominal aortic aneurysm compared with those without diabetes.[41] [42] The protective mechanism is yet to be determined; however, possibilities include reduced extracellular matrix volume, altered inflammatory pathways, and the effects of oral antihyperglycemic drug.[42] [43]

Due to the overlap in pathophysiology between diabetes, CVD, obesity, and chronic kidney disease, some groups argue that these conditions should be considered to be on a single spectrum known as cardiovascular-kidney-metabolic (CKM) syndrome. The American Heart Association, notably, has endorsed this terminology and proposed a four-stage model based on a patient's number of risk factors and the presence of overt CVD.[44] It has also developed a series of risk prediction equations, known as PREVENT, for estimating 10- and 30-year CVD risks based on the CKM concept.[45] It is hoped that this new approach will improve screening, prevention, and treatment of CKM risk factors, particularly in people with adverse social determinants of health.[44]

Disruption of the gut microbiome has been postulated to play an important role in the development of various obesity-related metabolic abnormalities, among them type 2 diabetes and CVD. The intestinal microbiota therefore appears to be a promising target for the nutritional or therapeutic management of these diseases.[46]

Case history

Case history #1

A 50-year-old man with type 2 diabetes presents with crushing substernal chest pain. He is taking metformin, glipizide, lisinopril, and atorvastatin. He has mild obesity and has a 20 pack-year history of smoking. Mild left-sided chest pain occurred 2 weeks ago while mowing the lawn. The pain lasted for only a few minutes and resolved with rest. Today more severe chest pain occurred while mowing the lawn, accompanied by shortness of breath and sweating.

Other presentations

In most patients, chest pain is the primary presenting symptom of coronary artery disease. In patients with diabetes, who often suffer from neuropathy and loss of sensation, ischemia may occur with no associated pain. Other patients may present with atypical symptoms, including shortness of breath, nausea, vomiting, epigastric pain, or arm numbness. Women also tend to have more atypical presentations compared with men. Presentations of other forms of cardiovascular disease may include symptoms of claudication or stroke.

Approach

Presence of risk factors

For prevention and management of both atherosclerotic cardiovascular disease (CVD) and heart failure, cardiovascular (CV) risk factors should be systematically assessed at least annually in all people with diabetes. These risk factors include duration of diabetes, obesity/overweight, hypertension, dyslipidemia, smoking, a family history of premature coronary disease, chronic kidney disease (CKD), and the presence of albuminuria.[2] [29]

Female sex and elevated C-reactive protein levels confer additional CVD risk.[77] [78] [81] [92]

The American College of Cardiology/American Heart Association atherosclerotic CVD risk calculator should be used to aid with overall CVD risk assessment and the 10-year risk for first CVD event. [AHA/ACC: ASCVD risk calculator] (http://static.heart.org/riskcalc/app/index.html#!/baseline-risk) A European equivalent, known as SCORE2-Diabetes, is recommended by the European Society of Cardiology for use in people ages 40 to 69 years with type 2 diabetes.[6]

Symptoms

Symptoms specific to CVD should be elicited in the history.

Coronary artery disease (CAD)

- Chest discomfort (may be absent in 20% to 30% of patients with diabetes, often called "silent ischemia")[19]
- Dyspnea on exertion; diaphoresis; nausea.

Cerebrovascular disease

- Numbness; tingling; headache; hemiparesis; aphasia.

Peripheral arterial disease (PAD)

- Most patients with PAD are asymptomatic. Intermittent claudication occurs in only 33% to 50% of patients.[139] Claudication presents as aching, burning, cramping, discomfort, or fatigue in the buttock, thigh, calf, or ankle on exertion. Symptoms occur consistently during walking, increase with progressive exercise intensity, and are quickly relieved by rest (usually within 10 minutes).[28]
- Rest pain in severe disease; often affects the forefoot and is worsened with limb elevation and relieved by dependency.[28]
- Other nonjoint-related exertional lower extremity symptoms (not typical of claudication) or symptoms of impaired walking function: may include leg muscle discomfort associated with walking that requires >10 minutes of rest to resolve, or leg weakness/numbness/fatigue during walking without pain.[28]
- Erectile dysfunction.[28]
- History of nonhealing or slow-healing lower extremity wound.[28]

Heart failure

- Dyspnea; persistent cough; ankle edema; fatigue.

Physical findings

Hypertension

- In patients with diabetes, blood pressure (BP) ≥130/80 mmHg confirmed using ≥2 measurements obtained on ≥2 occasions.[29]
- Patients with diabetic CVD may also be diagnosed with hypertension if BP ≥180/110 mmHg is recorded at a single visit.[29]

Acute myocardial infarction (MI) or congestive heart failure

- Rales; hypotension; peripheral edema; tachycardia; S3 gallop; jugular venous distention.

Cerebrovascular accident

- Aphasia; hemisensory loss; cranial nerve palsies; hemiparesis.

PAD

- Decreased or absent lower extremity pulses (femoral, popliteal, dorsalis pedis, or posterior tibial arteries); bruit over narrowed artery (e.g., epigastric, periumbilical, groin); hair loss; smooth, shiny skin; nonhealing lower extremity ulcers and necrosis; nail bed changes; calf muscle atrophy; elevation pallor/dependent rubor.[28]

Investigations

- All patients should have a baseline lipid profile and this should be repeated regularly.[29]
- C-reactive protein is not a routine test but may be useful for risk stratification.[81] [82] [83]
- Hemoglobin A1c (HbA1c) is used to monitor glycemic control.[29]

Suspected CAD and/or heart failure

In asymptomatic individuals, routine screening for CAD is not recommended as it does not improve outcomes as long as risk factors for atherosclerotic CVD are treated.[29] However, measurement of B-type natriuretic peptide (BNP) or N-terminal prohormone B-type natriuretic peptide (NT-proBNP) on at least a yearly basis should be considered to screen asymptomatic adults with diabetes for heart failure.[29] [140] This is because adults with diabetes are at increased risk for the development of asymptomatic cardiac structural or functional abnormalities (stage B heart failure) or symptomatic (stage C) heart failure.[29] If abnormal natriuretic peptide levels are detected, echocardiography is recommended. Identification, risk stratification, and early treatment of risk factors in people with diabetes and asymptomatic stages of heart failure reduce the risk for progression to symptomatic heart failure.[29]

All patients with symptoms or signs suggestive of CAD should have a resting 12-lead ECG. A chest x-ray (CXR) is not a routine test but may be useful to assess heart size and pulmonary congestion and evaluate for alternative causes of dyspnea. The sensitivity of CXR for making a diagnosis is poor. For example, 1 in 5 individuals with acute heart failure has no signs of congestion on a CXR.[140]

Diagnostic cardiac testing should be considered in those with: 1) typical or atypical cardiac symptoms; and 2) an abnormal resting ECG.

- Transthoracic doppler echocardiogram (echo): two-dimensional echo with Doppler assessment at rest is a key diagnostic test in the evaluation of chest pain or shortness of breath as well as establishing the initial diagnosis and cause of clinical heart failure.[140] Visualization of left and right ventricular function and regional wall motion abnormalities allows for the assessment of CAD risk and may help to guide clinical decision-making. Performance of echo at the bedside is ideal for patients with acute chest pain and can be done using point-of-care or handheld devices in institutions where such capabilities are available.[29]

- Exercise ECG: often used as an initial test. Can be used without or with imaging (e.g., stress echocardiography).[29] It is suitable for patients, who can exercise and who have a resting ECG that is interpretable for ST-segment shifts.[141] [142] Symptom-limited exercise ECG involves graded exercise until physical fatigue, limiting chest pain, marked ischemia, or a drop in blood pressure occurs. Candidates for exercise ECG are those: a) without disabling comorbidity (e.g., frailty, marked obesity [body mass index >40 kg/m²], PAD, chronic obstructive pulmonary disease, or orthopedic limitations) and capable of performing exercise safely; and b) without ST-T abnormalities on resting ECG (e.g., >0.5 mm ST depression, left ventricular hypertrophy, paced rhythm, left bundle branch block, Wolff-Parkinson-White pattern, or digoxin use).[142] There is a paucity of data on the predictive power of exercise testing in patients with diabetes, but available data suggest that ischemic findings on exercise ECG are predictive of prognosis.[143] In a study of 1282 patients (15% with diabetes), sensitivity (47% vs. 52%), and specificity (81% vs. 80%) for exercise treadmill testing were similar in people with and without diabetes.[144]
- Pharmacologic stress testing: patients who have resting ECG abnormalities that preclude exercise stress testing or those unable to exercise should undergo pharmacologic stress echo or nuclear imaging.[29] [141] [142] Stress echo can be used to define ischemia severity and for risk stratification purposes. Nuclear imaging (positron emission tomography [PET] or single-photon emission computed tomography [SPECT] myocardial perfusion imaging) enables detection of perfusion abnormalities, measurement of left ventricular function, and detection of high-risk findings, such as transient ischemic dilation.[142]
- Cardiac magnetic resonance imaging (MRI), or stress cardiac MRI (if available), may be useful in select patients with diabetes. Cardiac MRI can provide information about viability in patients with multivessel disease and severe left ventricular dysfunction.[145] These tests have the capability to accurately assess global and regional left and right ventricular function, detect and localize myocardial ischemia and infarction, and determine myocardial viability, without the need for radiation.[142] [145] They can also detect myocardial edema and microvascular obstruction, which can help differentiate acute versus chronic myocardial infarction, as well as other causes of acute chest pain, including myocarditis.[142] However, do not recommend performing stress cardiac MRI in patients with acute chest pain and high probability of CAD/acute coronary syndrome (ACS).[146] Stress cardiac MRI can increase risk and delay treatment in patients with acute chest pain and markers of high risk, such as ST segment elevation and/or positive cardiac biomarkers.[146]
- Computed tomography (CT) scan for coronary artery calcium (CAC): several studies have shown that using ≥16-slice CT scanners, CAC score >400 is associated with high likelihood of inducible myocardial ischemia and should prompt further testing.[147] In patients with pretest likelihood of CAD <50%, a CAC score of 0 provides very strong evidence against the presence of CAD, with a high degree of certainty.[148] Do not order a CAC test in patients with known atherosclerotic disease, including those with stents and bypass grafts, as it offers limited incremental prognostic value for these individuals.[149] [150]
- CT coronary angiography (CTA): ≥16-slice CT scanners have 90% sensitivity and 90% specificity for >50% diameter stenosis, which is the minimum criterion for consideration of revascularization.[148] CTA may be useful for patients with equivocal myocardial perfusion scanning; for ruling out left main or triple-vessel CAD; for patients with cardiomyopathy unrelated to CAD to rule out significant ischemic heart disease; and for young patients undergoing valvular surgery for preoperative planning.[148] Screening for asymptomatic obstructive CAD among patients with type 1 diabetes and patients with type 2 diabetes using CTA is not beneficial.[151] Do not use CTA in high-risk emergency patients presenting with acute chest pain.[150] [152]

- Invasive coronary angiography: usually reserved for patients with acute coronary syndrome, frequent angina, high-risk and/or high pretest probability of CAD that requires surgical or percutaneous intervention, and/or high-risk findings on stress testing.[142]

Suspected cerebrovascular accident

- CT or MRI of the head and duplex ultrasonography of carotids if indicated by symptoms.

Suspected PAD

- Joint American Heart Association and American College of Cardiology guidelines recommend that all patients with history or physical exam findings suggestive of PAD should have a resting ankle-brachial index (ABI), with or without ankle pulse volume recordings and/or Doppler waveforms.[28] Screening with resting ABI is also considered reasonable in patients with any of the following characteristics: age ≥65 years or older; age 50 to 64 years with risk factors for atherosclerosis (e.g., diabetes, smoking history, dyslipidemia, hypertension), CKD, or family history of PAD; age <50 years with diabetes and one additional risk factor for atherosclerosis; patients with known atherosclerotic disease in another vascular bed (e.g., coronary, carotid, subclavian, renal, mesenteric artery stenosis, or abdominal aortic aneurysm).[28] The American Diabetes Association recommends screening for PAD using ABI in asymptomatic people with any of the following characteristics: age ≥50 years; diabetes with duration ≥10 years; comorbid microvascular disease; clinical evidence of foot complications; or any end-organ damage from diabetes.[29]
- ABI of 1.0 to 1.4 is normal. ABI of ≤0.9 indicates the presence of PAD in the legs. ABI of 0.91 to 0.99 is borderline.[28]
- ABI may not be accurate in patients with noncompressible arteries, such as those with long-standing diabetes mellitus or CKD, particularly those on dialysis. Diagnosis of PAD should not be excluded based on normal or raised ankle brachial pressure index alone in people with diabetes or CKD.[28] See Peripheral arterial disease .

History and exam

Key diagnostic factors

chest pain (common)

- Most patients with acute coronary syndrome present with crushing left-sided substernal chest pain that may radiate to the left arm or jaw.[142]
- Chest discomfort may be absent in 20% to 30% of patients with diabetes.[19]

dyspnea on exertion (common)

- May be present with or without chest pain to indicate coronary disease or may be a symptom of congestive heart failure.[142]

hypotension (common)

- Presentation for acute coronary syndrome complicated by cardiogenic shock.[153]

rales (common)

- Could be suggestive of left ventricular dysfunction in the setting of acute coronary syndrome or congestive heart failure.
- Patients with rales, S3 gallop, or acute mitral regurgitation have a very high likelihood of severe underlying coronary artery disease (CAD).[142]

S3 gallop (common)

- Suggestive of left ventricular dysfunction in the setting of acute coronary syndrome or congestive heart failure.
- Patients with rales, S3 gallop, or acute mitral regurgitation have a very high likelihood of severe underlying CAD.[142]

hypertension (common)

- Blood pressure ≥130/80 mmHg is an established risk factor for atherosclerotic cardiovascular disease.[29]

nausea (common)

- Commonly associated with chest pain in acute coronary syndrome.[142]

diaphoresis (common)

- Commonly associated with chest pain in acute coronary syndrome.[142]

tachycardia (common)

- Commonly associated with chest pain in acute coronary syndrome, aortic dissection, or hemorrhagic stroke.[142]

indigestion (uncommon)

- An uncommon presentation for acute coronary syndrome. More common in women than men.[154]

Other diagnostic factors

unilateral weakness, numbness, and/or tingling (common)

- A presenting symptom in a significant proportion of patients with ischemic stroke.[155]

headache (common)

- One meta-analysis found that approximately 14% of patients with ischemic stroke have headache at the time of, or shortly following, their stroke diagnosis.[159]

intermittent claudication (common)

- The cardinal symptom of peripheral artery disease (PAD). An aching or burning in the muscles of the leg (calf, thigh, or buttock) that is reliably reproduced at a set distance of walking and is relieved within minutes on rest. It is never present at rest or exacerbated by position.[160]
- Occurs in only 33% to 50% of patients with PAD.[139]

bruits (common)

- May be heard over narrowed vessels.[163]

aphasia (uncommon)

- Occurs in 30% of patients with ischemic stroke.[156]

hemisensory loss (uncommon)

- May indicate cerebrovascular accident.[155]

cranial nerve palsies (uncommon)

- Seen in some patients with stroke.[157]

seizures (uncommon)

- An uncommon presentation of hemorrhagic or ischemic stroke.[158]

vertigo (uncommon)

- Rare, but may be seen in patients with strokes involving the posterior circulation.[155]

limb pain at rest (uncommon)

- Suggestive of critical limb ischemia.[160]

diminished/absent lower extremity pulses (uncommon)

- Suggestive of compromised lower extremity circulation and may be indicative of critical limb ischemia.[160]

ulcers or gangrene (uncommon)

- Suggestive of severe peripheral arterial disease and critical limb ischemia.[160]

peripheral edema (uncommon)

- Often indicates heart failure or acute myocardial infarction with left ventricular dysfunction.[161]

smooth shiny skin with hair loss (uncommon)

- Can be seen in peripheral artery disease.[162]

pallor (uncommon)

- May occur in patients with acute coronary syndrome, shock, or hemorrhagic stroke.

Risk factors

Strong

cigarette smoking

- Cigarette smoking (both active and passive) is an independent risk factor for both cardiovascular disease (CVD) and diabetes.[47] [48] [49] The risk of developing diabetes is 30% to 40% higher for active smokers than nonsmokers and there is a positive dose-response relationship between the number of cigarettes smoked and the risk of developing diabetes.[50]
- There is a well-established link between smoking cessation and reduction in CVD morbidity and mortality.[48]

hypertension

- Hypertension occurs in 50% to 80% of patients with type 2 diabetes and 30% of patients with type 1 diabetes.[51] In patients with diabetes, coexistent hypertension further increases the risk for CVD, diabetic retinopathy, and renal insufficiency.[52] [53] [54] A 5 mmHg reduction of systolic blood pressure (BP) has been shown to reduce the risk of major cardiovascular (CV) events by about 10%.[55]
- It is well accepted that BP control reduces CV risk in patients with diabetes; however, certain pivotal studies investigating the benefits of intensive (<120 mmHg) versus standard (<140 mmHg) BP control yielded discordant results.[56] [57] [58] [59] Guidelines recommend a BP treatment goal of <130/80 mmHg, providing this can be safely attained.[6] [29] [60] [61]

dyslipidemia

- People with diabetes can have various types of dyslipidemia. However, a major risk factor for CVD in patients with type 2 diabetes is a distinctive atherogenic triad of hypertriglyceridemia, reduced high-density lipoprotein cholesterol (HDL-C), and increased small dense low-density lipoprotein cholesterol (LDL-C).[62] [63]

poor glycemic control

- A 1% increase in hemoglobin A1c (HbA1c) increases the risk of myocardial infarction, stroke, or peripheral arterial disease by 18% in people with diabetes.[47] Increases in fasting blood glucose in mid-life are also associated with increased risk for CVD later in life.[64] In addition, evidence suggests that higher HbA1c variability (indicating higher fluctuations in glucose levels) is associated with increased CVD risk.[65] [66]
- Evidence for intensive glycemic control decreasing risk of CVD is stronger in type 1 than type 2 diabetes; however, controlling HbA1c to <7% (<53 mmol/mol) is recommended in most patients with type 2 diabetes to improve clinical outcomes.[29] [67] Achieving a target of <7% (<53 mmol/mol) has been shown to reduce CVD risk by 37% over 11 years.[47]

physical inactivity

- Sedentary behavior and insufficient physical activity are established risk factors for CVD in people with and without diabetes.[68] [69] Many individuals with type 2 diabetes do not meet the recommended exercise level per week.[29] [70]
- Increased physical activity decreases all-cause mortality and CVD-related mortality in type 2 diabetes.[47] [71] [72] One small-scale randomized controlled trial of patients with type 1 diabetes found that high-intensity interval training improved cardiac function and structure compared with standard of care.[73]

overweight and obesity

- There is a clear correlation between increasing prevalence of diabetes and increasing body mass index (BMI), with overweight (BMI >25 kg/m^2) and obesity (BMI >30 kg/m^2) significantly increasing the risk of CV events in patients with type 1 and type 2 diabetes.[54] [74] [75]
- It is estimated that obesity is associated with a twofold increased risk of CVD.[47] Obesity promotes CVD through its direct impact on cardiac functioning, and its indirect effects on hypertension, dyslipidemia, and inflammation.[47]

albuminuria

- Albumin levels ≥30 mg/g creatinine are associated with increased CVD risk in patients with diabetes.[76]
- In the Heart Outcomes and Prevention Evaluation (HOPE) trial, the presence of microalbuminuria was associated with a 1.97-fold increased relative risk of the primary aggregate end point (myocardial infarction [MI], stroke, or CVD death) among people with and without diabetes.[77] In the Losartan Intervention for Endpoint Reduction (LIFE) trial, every 10-fold increase in the albumin/creatinine ratio was associated with a 39% increased risk of CVD death, MI, or stroke among people with diabetes.[78] HOPE and LIFE findings are supported and strengthened by the results of a Danish cohort study of almost 70,000 patients with type 2 diabetes and no overt CVD.[79]

chronic kidney disease (CKD)

- CKD is a risk factor for cardiovascular disease, independent of diabetes and other traditional risk factors such as hypertension and dyslipidemia. Worsening kidney function (lower glomerular filtration rate, increased albuminuria) is associated with progressively increased risk of coronary disease.[80]

elevated C-reactive protein

- Among 746 men with diabetes followed for an average of 5 years, those in the highest quartile for C-reactive protein (CRP) had a 2.6-fold increased risk of CVD events compared with those in the lowest quartile.[81]
- Elevated CRP has also been associated with increased CV risk and dyslipidemia in Korean and sub-Saharan African populations.[82] [83]

family history of CVD

- Further increases risk of developing CVD in patients with diabetes.[2] [29] Premature CVD is defined as ages <55 years in males and ages <65 years in females.[76]

female sex

- Diabetes has a significantly greater impact on risk of adverse CV outcomes in women than in men.[84] [85] [86] [87] [88] [89]
- One study encompassing >850,000 individuals found that diabetes conferred a 44% greater excess risk for coronary heart disease in women compared with men.[87] Another study found that women with type 1 diabetes had an 86% greater excess risk of fatality from CVD than men with type 1 diabetes.[84] Excess risk of heart failure associated with both type 1 diabetes and type 2 diabetes is also significantly greater in women than in men.[88]
- There is a need for more research in this arena; however, potential mechanisms conferring excess risk include biologic/sex-specific factors, gender-related disparities, and traditional risk factors. Sex-specific factors include premature menopause, gestational diabetes, hypertensive diseases of pregnancy, breast cancer treatment, and systemic inflammatory or autoimmune disorders.[90] [91]
- Biologic factors such as early menopause (ages <45 years) and increased coronary artery calcification in women compared with men may also partly explain the difference in CVD risk.[84] [91] [92] Gender-related disparities such as intimate partner violence, psychosocial factors, and socioeconomic deprivation are also implicated.[90] [92]
- Transgender women, including those with diabetes, are also at higher risk for CVD, which observational data suggest may be due to estrogen use.[93]
- Evidence for the effect of menopausal hormone therapy (MHT) on CVD outcomes in women with type 2 diabetes is mostly lacking due to no or limited inclusion of participants with diabetes in clinical

studies. One study using pooled data from three landmark prospective CVD cohorts in the US found that MHT was associated with a small but statistically significant reduction in CVD risk among white, but not black, women with prediabetes or type 2 diabetes.[94]

- A 2023 scientific statement from the American Heart Association on the impact of race and ethnicity on CVD risk factors in women noted that CVD is the leading cause of death in women, with risk varying between different racial and ethnic groups.[95] It suggested that there is a need for an expanded approach to risk factors and primary prevention strategies for CVD in women of underrepresented races and ethnicities, who are particularly vulnerable to health disparities.[95]

gestational diabetes

- Gestational diabetes mellitus is associated with increased risks of overall and type-specific CV and cerebrovascular diseases. This is not solely attributed to conventional CV risk factors or subsequent type 2 diabetes.[96] [97]

mental illness

- Patients with severe mental illness have an increased risk of both type 2 diabetes and CVD, with a two- to fourfold higher rate of diabetes, hypertension, dyslipidemia, and metabolic syndrome compared with the general population.[98] Diabetes can be exacerbated by antipsychotic treatments which alter glucose metabolism and promote weight gain. Furthermore, these patients are more likely to smoke, be obese, have obstructive sleep apnoea, live a sedentary lifestyle, and eat unhealthily, leading to an increased risk of CVD.[98]
- The PRIMROSE (PRedIction and Management of cardiovascular Risk in peOple with SEvere mental illnesses) lipid model and the PRIMROSE body mass index model have been specifically developed and validated to predict the 10-year risk of incident CVD events in patients with severe mental illness.[99] The PRIMROSE model demonstrated that additional risk factors contributed to the development of CVD including social deprivation, severe mental illness subtype, prescriptions for antidepressants and antipsychotics, and reports of alcohol abuse.
- One study found that loneliness was associated with a higher risk of CVD among patients with diabetes.[100] Loneliness showed a weaker influence than kidney function, cholesterol, and BMI, but a stronger influence than depression, smoking, physical activity, and diet.

metabolic dysfunction-associated steatotic liver disease (previously nonalcoholic fatty liver disease)

- Metabolic dysfunction-associated steatotic liver disease (MASLD) is considered to be an independent risk factor for CVD.[101] [102] A nationwide longitudinal cohort study in Korea found that in patients with type 2 diabetes, MASLD was associated with a higher risk of CVD and all-cause death.[103]

Weak

atrial fibrillation

- Coexisting atrial fibrillation in patients with diabetes is associated with an increased risk of diabetes-related macrovascular complications, including a higher risk of all-cause mortality and CV mortality.[6] [104] [105]

Tests

1st test to order

Test	Result
HbA1c • A value of ≥6.5% (≥48 mmol/mol) is a diagnostic test for type 2 diabetes if confirmed with a repeat HbA1c or another type of test (fasting plasma glucose or plasma glucose 2 hours after 75 g oral glucose).[29] • HbA1c is also used to monitor long-term glycemic control.	**≥6.5% (≥48 mmol/mol)**
lipid profile • Consists of total cholesterol (TC), triglycerides, and LDL-, HDL-, and non-HDL-cholesterol. • TC, HDL-cholesterol (HDL-C), and LDL-cholesterol (LDL-C) levels are required for atherosclerotic CVD risk calculation. The level of LDL-C is a factor in determining intensity of LDL-lowering therapy such as statins, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, or other treatment.[113]	**may show elevated TC, LDL-C, and triglycerides, and low HDL-C**

Other tests to consider

Test	Result
B natriuretic peptide (BNP)/N-terminal prohormone B-natriuretic peptide (NT-proBNP) • Can be considered to screen asymptomatic adults with diabetes for heart failure.[29] If abnormal natriuretic peptide levels are detected, echocardiography is recommended. Identification, risk stratification, and early treatment of risk factors in people with diabetes and asymptomatic stages of heart failure reduce the risk for progression to symptomatic heart failure.[29]	**raised levels (BNP ≥35 nanograms/L [≥35 picograms/mL] or NT-proBNP ≥125 nanograms/L [≥125 picograms/mL]) are suggestive of heart failure and warrant further assessment with echocardiography**
transthoracic doppler echocardiogram • Transthoracic two-dimensional echocardiography with doppler assessment at rest is a key diagnostic test in evaluation of chest pain or shortness of breath as well as establishing the initial diagnosis and cause of clinical heart failure.[140] Visualization of left and right ventricular function and regional wall motion abnormalities allows for the assessment of CAD risk and may help to guide clinical decision-making. Performance of echocardiography at the bedside is ideal for patients with acute chest pain and can be done using point-of-care or handheld devices in institutions where such capabilities are available.[29]	**may be normal; focal wall motion abnormalities may indicate prior myocardial infarction and the extent of any impact on cardiac function**
exercise ECG • Exercise ECG testing, with or without echocardiography, may be used as an initial test for patients with cardiac symptoms plus abnormal resting ECG.[29] It is suitable for patients who can exercise and who have a resting ECG that is interpretable for ST-segment shifts.[141] [142] • Symptom-limited exercise ECG involves graded exercise until physical fatigue, limiting chest pain, marked ischemia, or a drop in blood pressure occurs. Candidates for exercise ECG are those: a) without disabling comorbidity (e.g., frailty, marked obesity [body mass index >40 kg/m²], peripheral artery disease, chronic obstructive pulmonary disease, or orthopedic limitations) and capable of performing exercise safely; and b) without ST-T abnormalities on resting ECG (e.g., >0.5 mm ST depression, left ventricular hypertrophy, paced rhythm, left bundle branch block, Wolff-Parkinson-White pattern, or digoxin use).[142] • There is a paucity of data on the predictive power of exercise testing in patients with diabetes, but available data suggest that an ischemic finding on exercise ECG is predictive of prognosis.[143] In a study of 1282 patients (15% with diabetes), sensitivity (47% vs. 52%), and specificity (81% vs. 80%) for exercise treadmill testing were similar in people with and without diabetes.[144]	**exercise-induced ST depression or arrhythmia**
exercise (stress) imaging test • Patients with cardiac symptoms plus abnormal resting ECG who are able to exercise should have an exercise stress test, with or without imaging.[29] If imaging is used, the modality (either echocardiography or nuclear scan [single-photon emission CT/PET) may depend on availability.[141] [142] Stress echocardiography can be used to define ischemia severity and for risk stratification purposes. Nuclear imaging enables detection of perfusion abnormalities, measures	**reversible or irreversible wall motion abnormalities**

Test	Result
of left ventricular function, and high-risk findings, such as transient ischemic dilation.[142]	
pharmacologic (stress) imaging test • Patients in whom stress testing is indicated, but who have resting ECG abnormalities that preclude exercise stress testing (e.g., left bundle branch block, ventricular pacing) or who are unable to exercise should undergo pharmacologic stress testing with echocardiographic or nuclear (single-photon emission CT or PET) imaging.[29] [141] [142] Stress echocardiography can be used to define ischemia severity and for risk stratification purposes. Nuclear imaging enables detection of perfusion abnormalities, measures of left ventricular function, and high-risk findings, such as transient ischemic dilation.[142]	**reversible or irreversible areas of decreased perfusion**
cardiac MRI or stress cardiac MRI • In select patients, such as patients with diabetes with multivessel disease and severe left ventricular dysfunction, cardiac MRI or stress cardiac MRI can be useful.[145] These tests have the capability to accurately assess global and regional left and right ventricular function, detect and localize myocardial ischemia and infarction, and determine myocardial viability, without the need for radiation.[142] [145] They can also detect myocardial edema and microvascular obstruction, which can help differentiate acute versus chronic myocardial infarction, as well as other causes of acute chest pain, including myocarditis.[142] • However, do not recommend performing stress cardiac MRI in patients with acute chest pain and high probability of CAD/ACS.[146] Stress cardiac MRI can increase risk and delay treatment in patients with acute chest pain and markers of high risk, such as ST segment elevation and/or positive cardiac biomarkers.[146]	**reversible or irreversible areas of decreased perfusion; also defines cardiac anatomy, chamber size/function, and valvular pathology**
ankle-brachial index (ABI) • Joint American Heart Association and American College of Cardiology guidelines recommend that all patients with history or physical examination findings suggestive of peripheral arterial disease (PAD) should have a resting ABI measured, with or without ankle pulse volume recordings and/or Doppler waveforms.[28] Screening with resting ABI is also considered reasonable in patients with any of the following characteristics: age ≥65 years or older; age 50 to 64 with risk factors for atherosclerosis (e.g., diabetes, smoking history, dyslipidemia, hypertension), chronic kidney disease, or family history of PAD; age <50 years with diabetes and one additional risk factor for atherosclerosis; patients with known atherosclerotic disease in another vascular bed (e.g., coronary, carotid, subclavian, renal, mesenteric artery stenosis, or abdominal aortic aneurysm).[28] The American Diabetes Association recommends screening for PAD using ABI in asymptomatic people with any of the following characteristics: age ≥50 years; diabetes with duration ≥10 years; comorbid microvascular disease; clinical evidence of foot complications; or any end-organ damage from diabetes.[29] • ABI may not be accurate in patients with noncompressible arteries, such as those with long-standing diabetes mellitus or chronic kidney disease (CKD), particularly those on dialysis. Diagnosis of PAD should not be excluded based on normal or raised ankle brachial	**ABI 1.0 to 1.4 normal; 0.91 to 0.99 borderline; ≤0.9 abnormal**

Test	Result
pressure index alone in people with diabetes or CKD.[28] See Peripheral arterial disease .	
CT coronary angiography • CT angiography may be useful for patients with equivocal myocardial perfusion scanning, for ruling out left main or triple-vessel coronary artery disease (CAD), patients with nonischemic cardiomyopathy, and young patients undergoing valvular surgery.[148] • Screening asymptomatic obstructive CAD among high-risk patients with diabetes using CT angiography is not recommended.[151] Do not use CT angiography in high-risk emergency patients presenting with acute chest pain.[150] [152]	**defines coronary anatomy, location and degree of stenosis**
CT coronary calcium scan • Studies using ≥16-slice CT scanners have shown that coronary artery calcium (CAC) score >400 is associated with high likelihood of inducible myocardial ischemia and should prompt further testing.[147] In patients with pretest likelihood of CAD <50%, a CAC score of 0 provides very strong evidence against the presence of CAD, with a high degree of certainty.[148] • Do not order a CAC scan in patients with known atherosclerotic disease, including those with stents and bypass grafts, as it offers limited incremental prognostic value for these individuals.[149][150]	**defines coronary calcium burden**
invasive coronary angiography • Coronary angiography after injection of radiopaque dye is usually reserved for patients with acute coronary syndrome, frequent angina, high-risk and/or high pretest probability of CAD that requires surgical or percutaneous intervention, and/or high-risk findings on stress testing.[142]	**defines coronary anatomy, location and degree of stenosis; directs medical or mechanical therapy**
noncontrast head CT • First test to obtain if symptoms suggest possible acute stroke.	**acute cerebrovascular accident**
brain MRI • Used to further evaluate for possible acute stroke, especially white matter lesions, brainstem, and posterior fossa lesions.	**acute, subacute, or prior cerebrovascular accident**
duplex ultrasonography of carotid arteries • Patients with symptomatic stenosis ≥50% may be candidates for intervention as well as asymptomatic patients with a stenosis ≥70%.[164]	**degree of stenosis in carotid arteries**
C-reactive protein • Not a routine test but may be useful for risk stratification.[81] [82] [83] [165]	**may be elevated**
chest x-ray • A chest x-ray is not a routine test but may be useful to assess heart size and pulmonary congestion and evaluate for alternative causes of dyspnea. • The sensitivity of chest x-ray for making a diagnosis is poor. For example, 1 in 5 individuals with acute heart failure has no signs of congestion on a chest x-ray.[140]	**can evaluate the lung parenchyma, pleural space, and cardiomegaly**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Unstable angina	• Unstable angina presents as new onset of severe angina, angina at rest or minimal activity, or recent increase in frequency or intensity of chronic angina.	• ECG typically shows ST depression and/or T-wave inversion for unstable angina, but can also be normal. Troponin levels should be normal.
ST-elevation myocardial infarction (STEMI)	• Acute MI may present as new onset of severe angina, angina at rest or minimal activity, or recent increase in frequency or intensity of chronic angina. • In a minority of people with diabetes, MI may present without symptoms.	• ECG changes for STEMI include ST-segment elevation, T-wave inversion, and Q-wave formation. Troponin levels are elevated in STEMI.
Non-ST-elevation myocardial infarction (NSTEMI)	• Acute MI may present as new onset of severe angina, angina at rest or minimal activity, or recent increase in frequency or intensity of chronic angina. • In a minority of people with diabetes, MI may present without symptoms.	• ECG typically shows ST depression and/or T-wave inversion for NSTEMI, but can also be normal. Troponin levels are elevated in NSTEMI.
Chronic stable angina	• Patients typically present with exertional chest pain relieved by rest.	• ECG is usually normal between episodes, but during angina episodes ST depression and/or T-wave inversion may be present. Cardiac enzymes are usually not elevated.
Congestive heart failure	• Symptoms of cough, shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, or peripheral edema. • Findings of jugular venous distention, pulmonary congestion, and S3 gallop.	• Diagnosis can be made clinically, but several studies may assist if diagnosis is not clear. • Chest x-ray may reveal cardiomegaly, pulmonary edema, and cephalization of pulmonary vasculature. • Serum brain natriuretic peptide is usually elevated. • Echo provides information about left ventricular function, differentiates systolic from diastolic dysfunction, and identifies underlying valvular or structural heart disease.

Condition	Differentiating signs / symptoms	Differentiating tests
Heart failure with preserved ejection fraction	• Clinical syndrome of heart failure, with symptoms of pulmonary and peripheral congestion.	• Normal left ventricular systolic function and increased diastolic filling pressures on echo.
Transient ischemic attack (TIA)	• Sudden onset of neurologic deficit. Most TIAs last between 5 and 15 minutes.	• Diagnosis is made by complete resolution of symptoms in <24 hours and no acute ischemic findings on brain imaging. Acutely, noncontrast CT of the head is used to exclude intracerebral hemorrhage.
Ischemic stroke	• Sudden onset of neurologic deficit. Symptoms lasting ≥24 hours are classified as a stroke.	• CT or MRI will show ischemic stroke. Acutely, noncontrast CT of the head is used to exclude intracerebral hemorrhage.
Hemorrhagic stroke	• Sudden onset of neurologic deficit. Symptoms lasting ≥24 hours are classified as a stroke.	• Acutely, noncontrast CT of the head can show intracerebral hemorrhage.
Peripheral artery disease (PAD)	• Intermittent claudication: pain, ache, cramp, burning, fatigue, weakness, or numbness in the leg muscles that develops predictably with exercise, increases with progressive exercise intensity, and is relieved by rest (usually within 10 minutes).[28] Pain in buttocks and thighs suggest aortoiliac disease, while calf muscle pain suggests femoral or popliteal artery disease. Patients with more severe disease may present with rest pain (often affecting the forefoot) or nonhealing/slow-healing leg ulcers. Erectile dysfunction is also a symptom in some patients.[28]	• Joint American Heart Association and American College of Cardiology guidelines recommend that all patients with history or physical exam findings suggestive of PAD should have a resting ankle-brachial index (ABI), with or without ankle pulse volume recordings and/or Doppler waveforms.[28] Screening with resting ABI is also considered reasonable in patients with the following characteristics: age ≥65 years or older; age 50 to 64 years with risk factors for atherosclerosis (e.g., diabetes, smoking history, dyslipidemia, hypertension), chronic kidney disease, or family history of PAD; age <50 years with diabetes and one additional risk factor for atherosclerosis; patients with known atherosclerotic disease in another vascular bed (e.g., coronary, carotid, subclavian, renal, mesenteric

Condition	Differentiating signs / symptoms	Differentiating tests
		artery stenosis, or abdominal aortic aneurysm).[28] The American Diabetes Association recommends screening for PAD using ABI in asymptomatic people with diabetes who have any of the following characteristics: age ≥50 years; diabetes with duration ≥10 years; comorbid microvascular disease; clinical evidence of foot complications; or any end-organ damage from diabetes.[29] ABI results: 1.0 to 1.4 is normal; 0.91 to 0.99 is borderline; ≤0.9 is abnormal.[28]

Screening

Screening for diabetes

The American Diabetes Association (ADA) recommends routine screening of nonpregnant asymptomatic adults of any age with body mass index (BMI) ≥25 kg/m² (≥23 kg/m² for Asian-Americans) in the presence of one or more risk factors for diabetes.[29] In the absence of risk factors, testing is recommended starting at age 35 years.[29]

Risk factors for diabetes include:[29]

- A history of diabetes in a first-degree relative
- Physical inactivity
- African-American, Latino, American-Indian, Asian-American, or Pacific Islander ancestry
- History of gestational diabetes
- Hypertension (≥130/80 mmHg or on therapy for hypertension)
- Dyslipidemia (high-density lipoprotein cholesterol <35 mg/dL [<0.90 mmol/L] and/or elevated triglycerides >250 mg/dL [>2.82 mmol/L])
- Cardiovascular disease (CVD)
- Prediabetes (hemoglobin A1c [HbA1c] ≥5.7% [≥39 mmol/mol], impaired glucose tolerance [IGT] or impaired fasting glucose [IFG])
- Polycystic ovary syndrome
- Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)

Screening should also be considered in people on certain medications, such as glucocorticoids, statins, thiazide diuretics, some HIV medications, and second-generation antipsychotic medications, as these agents are known to increase the risk of diabetes.[29]

If results are normal, the ADA recommends that testing should be repeated at least every 3 years, with consideration of more frequent testing depending on initial results and risk status. People with prediabetes (HbA1c ≥5.7% [≥39 mmol/mol], IGT, or IFG) should be tested yearly.[29]

The US Preventive Services Task Force recommends screening for prediabetes and type 2 diabetes in adults ages 35 to 70 years who have overweight (BMI ≥25 kg/m² or ≥23 kg/m² for Asian-Americans) or obesity

(BMI ≥30 kg/m²).[166] Screening should be considered at an earlier age in patients from a population with a disproportionately high prevalence of diabetes (American-Indian/Alaska Native, Black, Hawaiian/Pacific Islander, Hispanic/Latino).[166] Those with normal test results should be re-screened every 3 years.[166] Those who have prediabetes should be referred to effective preventive interventions.[166]

Fasting plasma glucose, plasma glucose 2 hours after 75 g oral glucose, and HbA1c are all appropriate screening tests.[29]

Screening for CVD in people with diabetes

Cardiovascular (CV) risk factors should be assessed at least annually in people with diabetes.[29] This includes an assessment of:[29]

- Diabetes duration
- Weight
- Blood pressure
- Lipids
- Smoking status
- Family history of premature coronary disease
- Presence of albuminuria (indicator of chronic kidney disease)

One large cohort study found that in those with type 2 diabetes without existing CVD, increased albuminuria levels were associated with higher risk of incident ischemic stroke, myocardial infarction, and all-cause mortality.[79]

Based on the results of this screening, aggressive medical therapy to reduce CV risk is universally recommended, which may include antihypertensive therapy, lipid-lowering therapy, and, for those with established or high risk of coronary artery disease (CAD), antiplatelet therapy.[29] The American College of Cardiology/American Heart Association atherosclerotic CVD risk calculator should be used to aid with overall CVD risk assessment and the 10-year risk for first CVD event. [AHA/ACC: ASCVD risk calculator] (http://static.heart.org/riskcalc/app/index.html#!/baseline-risk) A European equivalent, known as SCORE2-Diabetes, is recommended by the European Society of Cardiology for use in people ages 40 to 69 years with type 2 diabetes.[6] When HbA1c values are added to CVD risk assessment models, there is little incremental benefit for prediction of CV risk.[167]

While screening for CVD risk factors is important, the benefits of screening asymptomatic people with diabetes for CAD remain unclear, and as such it is not recommended by the ADA.[29] One meta-analysis suggested that systematic detection of silent ischemia in high-risk asymptomatic people with diabetes is unlikely to provide any major benefit to clinically important outcomes compared with optimized medical management of CV risk factors alone.[168] Another meta-analysis found that routine screening of asymptomatic patients with type 2 diabetes for CAD neither reduced mortality nor reduced a composite of nonfatal myocardial infarction and CV death.[169]

Investigations for CAD should be considered in the presence of any of the following:[29]

- Typical or atypical cardiac symptoms
- Abnormal resting ECG
- Signs and symptoms of associated vascular disease, including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease[29]

Although screening asymptomatic patients for CAD is not recommended, screening for heart failure with B natriuretic peptide (BNP)/N-terminal prohormone B-natriuretic peptide (NT-proBNP) levels can be considered.[29] If abnormal natriuretic peptide levels are detected, echocardiography is recommended. Identification, risk stratification, and early treatment of risk factors in people with diabetes and asymptomatic stages of heart failure have been shown to reduce the risk of progression to symptomatic heart failure.[29]

Approach

Patients with diabetes benefit from aggressive cardiovascular (CV) risk factor management.[170] One large prospective cohort study showed that patients with diabetes who met target ranges for hemoglobin A1c (HbA1c), low-density lipoproteins (LDLs), blood pressure (BP), albuminuria, and smoking had the same or only slightly increased long-term mortality compared with nondiabetic controls.[171] However, in a large US cohort study of patients with diabetes and known cardiovascular disease (CVD), only 6.9% received guideline-recommended medical therapies for CV risk reduction.[172]

Therapeutic lifestyle interventions such as medical nutrition therapy and aerobic exercise have been shown in large clinical trials to improve glycemic, lipid, and BP control, in addition to insulin sensitivity and markers of inflammation. They are also effective in achieving sustained weight loss and improvements in fitness.[47] [71] [173] [174] [175] [176] The US Preventive Services Task Force recommends behavioral counseling interventions to improve diet and increase physical activity for people with cardiometabolic risk factors to prevent longer term CV events.[177]

Recommendations for the management of CVD and risk in patients with diabetes include:[29] [178]

- Therapeutic lifestyle interventions (medical nutrition therapy/dietary advice, physical activity, and smoking cessation)
- Treatment for overweight or obesity
- Glycemic control
- BP control
- Dyslipidemia treatment
- Antiplatelet therapy

There is substantial evidence in support of the benefit of CV risk factor management in people with type 2 diabetes; however, robust evidence to support a comparable benefit in people with type 1 diabetes is lacking. Current treatment guidelines extrapolate clinical trial evidence obtained in people with type 2 diabetes to provide similar treatment recommendations for people with both type 1 and type 2 diabetes. There is evidence, however, to support the more aggressive treatment of CV risk factors in people with type 1 diabetes, who would likely benefit from early risk stratification and comprehensive risk factor management, including aggressive lipid-lowering therapy.[179]

Medical nutrition therapy

There is no ideal amount of macronutrients that people with diabetes should consume, and studies suggest that such recommendations should be decided on an individual basis.[173] [180] The Mediterranean Diet, Dietary Approaches to Stop Hypertension (DASH), vegetarian, and vegan diets have all demonstrated some efficacy in people with diabetes.[173] [181] [182] [183] [184] European guidelines recommend a Mediterranean or plant-based diet with high unsaturated fat content for lowering CV risk in people with diabetes.[6] One meta-analysis found that red meat consumption was associated with higher risk of CVD and diabetes, while another reported moderate certainty evidence that a shift from animal-based to plant-based foods is beneficially associated with cardiometabolic health and all-cause mortality.[185] [186]

Reducing overall carbohydrate intake has demonstrated some evidence for improving glycemia and one study found that among people with type 2 diabetes, greater adherence to low-carbohydrate diet patterns was associated with significantly lower all-cause mortality.[187] However, the optimal degree of carbohydrate restriction and long-term effects on CVD are still unclear.[29] Both World

Health Organization (WHO) and European guidelines emphasize that carbohydrate quality, rather than quantity, is key.[132] [188] The concept of carbohydrate quality refers to the nature and composition of carbohydrates in a food or in the diet, including the proportion of sugars, how quickly polysaccharides are metabolized and release glucose into the body (i.e., digestibility), and the amount of dietary fiber. It is recommended that carbohydrate intake should come primarily from high-fiber foods, such as whole grains, vegetables, whole fruits, and pulses.[132] [188] Diets high in naturally occurring fiber have been shown to be protective against cardiometabolic disease and premature mortality.[132] When choosing high-fiber foods, focus should be on minimally processed and largely intact whole grains, rather than products with finely milled whole grains that may also have added sugars, sodium, and saturated fats.[132] [188] Fiber-enriched foods and fiber supplements can be considered when sufficient intake cannot be obtained from diet alone.[132]

There is some evidence to suggest that reducing intake of high glycemic index foods, and generally reducing glycemic load, could be beneficial for preventing CVD; however, WHO guidelines do not make any recommendations on this, noting that there was a lack of consistent benefit from diets with lower glycemic index or glycemic load in observational studies, and little to no improvement in cardiometabolic risk factors in randomized controlled trials associated with lower glycemic index and glycemic load.[188] [189]

Replacing saturated fats and trans-fats with unsaturated fats and carbohydrates from foods containing naturally occurring dietary fiber (such as whole grains, vegetables, fruits, and pulses) reduces LDL-cholesterol (LDL-C) and also benefits CVD risk.[173] [190] [191] Saturated fat should comprise <10% of total energy intake and trans-fats <1%.[132] [191] Dietary fats should mainly come from plant-based foods high in mono- and poly-unsaturated fats, such as nuts, seeds, and nonhydrogenated nontropical vegetable oils (e.g., olive oil, rapeseed/canola oil, soybean oil, sunflower oil, linseed oil).[132]

People with diabetes who have overweight or obesity should be supported with evidence-based nutritional support to achieve and maintain weight loss.[132] European guidelines recommend that a variety of weight-loss diets can be used equally effectively, provided they can be followed and meet recommendations for protein, fat, micronutrient, and fiber intake. Neither extreme high-carbohydrate, nor very-low carbohydrate ketogenic diets are recommended, however.[132] One systematic umbrella review of published meta-analyses of studies comparing hypoenergetic diets for weight management in people with type 2 diabetes did not find evidence for any particular weight-loss diet over others (e.g., low-carbohydrate, high-protein, low-glycemic index, Mediterranean, high-monounsaturated fatty acid, or vegetarian diets).[192]

Intermittent fasting or time-restricted eating as strategies for weight and glucose management have gained popularity.[193] They have been shown to result in mild to moderate weight loss (3% to 8% loss from baseline), but no significant difference in weight loss when compared with continuous calorie restriction.[29] The ADA advises that due to its simplicity, intermittent fasting may lend itself as a useful strategy for people with diabetes who are looking for practical eating management tools.[29] People with diabetes who are on insulin and/or secretagogues should be medically monitored during the fasting period.[29]

Evidence indicates that low- and very-low-energy diets (<3500 kJ/day [<840 kcal/day]), using total diet replacement formula diet products (replacing all meals) or partial liquid meal replacement products (replacing 1-2 meals per day) for the weight-loss phase, are most effective for weight loss and reduction of other cardiometabolic risk factors when compared with the results from self-administered food-based weight-loss diets.[132] [194] Low-energy nutritionally complete formula diets with a total diet replacement

induction phase also appear to be the most effective dietary approach for achieving type 2 diabetes remission.[132] One population-based cohort study found that those who achieved remission from diabetes, even for a short time, had a much lower risk of CVD events, including myocardial infarction (MI) and stroke, as well macrovascular and microvascular complications.[195]

Physical activity

A sedentary lifestyle is a major risk factor for CVD.[68] [69] Many individuals with type 2 diabetes do not meet the recommended exercise level per week.[29] [70]

Physical activity improves glycemic control, lipids, BP, insulin sensitivity, and markers of inflammation in type 2 diabetes.[47] [71] [176] [196] Increased physical activity is associated with lower risk of CVD and reduced all-cause mortality in both type 1 and type 2 diabetes.[47] [72] [122] [197]

At least 150 minutes per week of moderate- to vigorous-intensity aerobic physical activity is recommended for adults with diabetes.[6] [29] The physical activity should be spread over at least 3 days per week, with no more than 2 consecutive days without exercise.[29] Younger and more physically fit individuals should aim for ≥75 minutes per week of vigorous-intensity exercise or interval training.[29] In the absence of contraindications, resistance training 2 to 3 times per week on nonconsecutive days is also recommended.[6] [29] The American Diabetes Association (ADA) recommends interrupting sedentary activity every 30 minutes with short bouts of physical activity.[29] Older adults may also benefit from flexibility and balance exercise 2 to 3 times per week.[29]

The ADA recommends assessment of the following prior to starting an exercise program: age; physical condition; BP; and presence or absence of autonomic neuropathy or peripheral neuropathy, balance impairment, history of foot ulcers or Charcot foot, or untreated proliferative retinopathy.[29] The European Society of Cardiology (ESC) recommends that any exercise interventions be tailored according to a patient's frailty and diabetes-associated comorbidities such as retinopathy.[6] The European Association of Preventive Cardiology recommends testing for silent myocardial ischemia prior to initiating an exercise program in patients with type 2 diabetes and CVD, whereas the ADA states that clinical judgment should be used in determining whether to screen asymptomatic individuals for coronary artery disease (CAD) prior to recommending an exercise program.[29] [198]

Smoking cessation

All patients with diabetes should be advised not to smoke or to quit smoking.[29] Smoking counseling and other forms of smoking cessation therapy should be incorporated into routine diabetes care.[29] Varenicline combined with nicotine replacement therapy may be more effective than varenicline alone.[199] The ADA does not support e-cigarettes as an alternative to smoking or to facilitate smoking cessation.[29]

Patients who quit smoking are prone to weight gain; therefore, it is important to have weight management strategies in place to maximize the CV benefits of smoking cessation.[47]

Weight management

In most patients with type 2 diabetes and overweight or obesity, ≥5% weight loss is recommended through diet, physical activity, and behavioral therapy.[2] [29] The benefits of weight loss are progressive, and so more intensive weight loss goals (i.e., 15%) may be useful to maximize benefit.[29]

Pharmacotherapy

Obesity pharmacotherapy should be considered as an adjunct to lifestyle interventions and behavioral counseling to improve CV risk factors in people with type 2 diabetes who have overweight or obesity.[6] [29] [178] For those with a BMI of ≥27 kg/m² (≥25 kg/m² for Asian-Americans) who are motivated to lose weight, an initial 3-month trial of medication should be undertaken. When weight loss is <5% after 3 months, the benefits of ongoing treatment need to be balanced in the context of the glycemic response, the availability of other potential treatment options, treatment tolerance, and overall treatment burden.[29]

The ADA advises that agents with both glucose-lowering and weight loss effects should be used first-line; this includes glucagon-like peptide-1 (GLP-1) receptor agonists and the dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonist tirzepatide.[29] Two phase 3 trials in adults with obesity demonstrated mean losses of 15% to 21% of body weight with the highest dose of tirzepatide, with adverse effects similar to those seen with GLP-1 receptor agonists.[200] [201] In the larger of the two trials, over 80% of participants in all tirzepatide treatment groups lost ≥5% of body weight, compared with 35% of those assigned to placebo.[200] With higher body weight reduction, there were greater reductions in HbA1c, triglycerides, waist circumference, and BP.[202] Tirzepatide is approved for chronic weight management in adults with obesity or those who are overweight with at least one weight-related condition (such as high BP, type 2 diabetes or high cholesterol), for use in addition to a reduced calorie diet and increased physical activity.

If these medications are not tolerated or contraindicated, other obesity treatment approaches should be considered, including phentermine, orlistat, phentermine/topiramate, or naltrexone/bupropion.[29]

The ESC recommends a GLP-1 receptor agonist or sodium-glucose cotransporter-2 (SGLT2) inhibitor as the agents of choice for glucose-lowering in patients with type 2 diabetes and overweight and obesity, in view of their proven CV benefits for these patients.[6] [203]

For those not reaching goals, the ADA recommends evaluation of weight management therapies and intensification of treatment with additional approaches (e.g., metabolic surgery, additional pharmacologic agents, and structured lifestyle management programs).[29]

As well as considering specific medications to treat obesity, healthcare professionals should carefully review the individual's other medications and, whenever possible, minimize or provide alternatives for medications that promote weight gain. Examples of medications associated with weight gain include antipsychotics (e.g., clozapine, olanzapine, risperidone), some antidepressants (e.g., tricyclic antidepressants, some selective serotonin-reuptake inhibitors, monoamine oxidase inhibitors), glucocorticoids, injectable progestins, some anticonvulsants (e.g., gabapentin, pregabalin), beta-blockers, and possibly sedating antihistamines and anticholinergics.[29]

Metabolic (bariatric) surgery

A large number of studies have demonstrated that metabolic surgery achieves superior glycemic management and reduction of CV risk in people with type 2 diabetes and obesity compared with nonsurgical intervention.[9] [204] It has also been shown to reduce microvascular complications, cancer risk, and all-cause mortality in people with obesity and type 2 diabetes.[29] [205] [206] [207] Of note, one meta-analysis reported a 50% reduction in macrovascular complications following metabolic surgery in patients with type 2 diabetes and extreme obesity (BMI ≥40 kg/m²).[205] Another meta-analysis found that metabolic surgery reduced the risk of any CV event by 44% and yielded a risk reduction of over 55% in overall mortality and 69% in CV mortality in patients with type 2 diabetes.[208]

Vertical sleeve gastrectomy (VSG) and Roux-en-Y gastric bypass (RYGB) are the most commonly performed procedures. Both result in an anatomically smaller stomach pouch; in VSG, approximately 80% of the stomach is removed, leaving behind a long, thin sleeve-shaped pouch, whereas RYGB creates a much smaller stomach pouch (roughly the size of a walnut), which is then attached to the distal small intestine, thereby bypassing the duodenum and jejunum.[29]

The ADA recommends metabolic surgery to treat type 2 diabetes in adults with BMI ≥30 kg/m² (≥27.5 kg/m² for Asian-Americans) who are otherwise good surgical candidates.[29] The ESC recommends that metabolic surgery be considered for all patients with type 2 diabetes and BMI ≥35 kg/m² who have not achieved sufficient weight loss through lifestyle interventions and medication.[6] Metabolic surgery is best done in a high-volume, specialized center to reduce the risk of perioperative and longer-term complications.[29] For more comprehensive information, see Obesity in adults .

Long-term glycemic control

Increasing severity of hyperglycemia correlates with increasing CV risk.[47] [209] One meta-analysis found that antihyperglycemic therapies reduce major adverse cardiac events in an HbA1c-dependent manner.[210] However, three large studies, Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease (ADVANCE), and Veterans Administration Diabetes Trial (VADT), found that very intensive glucose control (goal HbA1c <6.0% to 6.5% over 3-5 years) did not reduce macrovascular events in adults with type 2 diabetes.[6] [211] [212] [213] [214] In contrast, intensive glycemic control appeared to have long-term beneficial effects on the risk of CVD in patients with type 1 diabetes.[215]

One meta-analysis found that intensive versus standard glycemic control in patients with type 2 diabetes was associated with a reduced risk of nonfatal MI but no significant difference in the risk of major adverse CV events or other adverse CV outcomes.[216] A long-term follow-up study of intensive glycemic control (median HbA1c 6.9% vs. 8.4%) in type 2 diabetes did show fewer major CV events per 1000 person-years, but there was no improvement in overall survival.[217] Furthermore, a follow-up of the ACCORD trial, which studied intensive versus standard glycemic control (<6.0% vs. 7.0% to 7.9%), showed that MI, coronary revascularization, and unstable angina were less frequent in the intensive group than the standard therapy group.[218] The reasons for the discrepancy in study findings are unclear. It appears that there may be a lag period before a benefit of glycemic control on CV risk is realized.[219] Other possibilities that may have influenced results include the magnitude or rapidity of reductions in HbA1c in intensively treated patients; effect of specific antihyperglycemic drugs or drug interactions; treatment-related hypoglycemia; or age at which therapy is begun.[220]

The ADA recommends a general HbA1c goal of <7% (<53 mmol/mol) for nonpregnant adults with diabetes to optimize clinical outcomes, although this should be individualized by the physician following patient discussion.[29] If using a continuous glucose monitoring (CGM) device to assess glycemia, a parallel goal is time in range >70%, with time below range <4% and time below 54 mg/dL (<3 mmol/L) <1%.[29] Less stringent goals may be appropriate for: older adults; people with a history of severe hypoglycemia; and those with limited life expectancies, advanced microvascular or macrovascular complications, or comorbid conditions.[29] If using a CGM device, the ADA recommends a target of >50% time in range with <1% time below range for those with frailty or at high risk of hypoglycemia.[29]

A person-centered shared decision-making approach should guide the choice of pharmacologic agents for adults with type 2 diabetes, considering the effects on CV and renal comorbidities, effectiveness, hypoglycemia risk, impact on weight, cost and access, risk of adverse reactions and tolerability, and

individual preferences.[29] Medication plan and medication-taking behavior should be reevaluated at regular intervals (the ADA suggest 3 to 6 monthly) and treatment intensification, deintensification, or modification - as appropriate - for people not meeting individualized treatment goals should not be delayed.[29]

US and European guidelines continue to recommend metformin as the first-line treatment for glycemic control in patients with type 2 diabetes regardless of the presence or absence of established atherosclerotic CVD.[29] [221] [222] Evidence for the CV benefit of metformin is limited; however, it does not cause weight gain or hypoglycemia, and is widely available relative to other agents.[47] People who are unable to take metformin due to contraindications or intolerance can either use an alternative noninsulin agent or start insulin therapy. The ADA recommends a GLP-1 receptor agonist over insulin when possible.[29]

Early combination therapy can be considered in adults with type 2 diabetes at treatment initiation to shorten time to attainment of individualized treatment goals.[29] When selecting an additional therapy, clinicians should consider the evidence of benefits, harms, patient burden, and cost of medications in addition to performing an individualized assessment of each patient's preferences, glycemic control target, comorbid conditions, and risk for symptomatic hypoglycemia.[222] The American College of Physicians (ACP) now recommends that SGLT2 inhibitors or GLP-1 receptor agonists should be the add-on therapy of choice for patients with inadequate glycemic control.[222] It advises that sulfonylureas and long-acting insulins are inferior to these medications in reducing all-cause mortality and morbidity but may still have some limited value for glycemic control. Dipeptidyl peptidase-4 (DPP-4) inhibitors are not recommended as an add-on to metformin and lifestyle modifications in light of high-certainty evidence showing that this does not reduce morbidity or all-cause mortality.[222]

When considering glycemic control in patients who have overweight or obesity, the ADA recommends that healthcare professionals should prioritize glucose-lowering medications with a beneficial effect on weight.[29] One meta-analysis found that when glucose-lowering therapies were associated with weight loss, the risk of mortality was reduced by 22% for each 1% reduction in HbA1c.[223] In addition, concomitant reductions in HbA1c and body weight were associated with a significantly lower risk of mortality and vascular events.

- Agents associated with clinically meaningful weight loss include GLP-1 receptor agonists, tirzepatide, SGLT2 inhibitors, metformin, and amylin analogs.[29] One network meta-analysis of 531 trials with 279,118 participants confirmed that tirzepatide is the most effective drug for reducing body weight (mean reduction 8.57 kg), followed by GLP-1 receptor agonists, SGLT2 inhibitors, and metformin.[224] DPP-4 inhibitors, bromocriptine (a centrally acting dopamine agonist), alpha-glucosidase inhibitors, and bile acid sequestrants are considered weight neutral.[29]
- Insulin secretagogues (sulfonylureas and meglitinides), thiazolidinediones, and insulin are often associated with weight gain.[29]

See Type 2 diabetes mellitus in adults and Type 1 diabetes mellitus for further information.

Antihyperglycemic agents with cardiovascular and renal benefit

For patients with established atherosclerotic CVD, significant CVD risk factors, established heart failure (with either preserved or reduced ejection fraction), or established chronic kidney disease (CKD), addition of a GLP-1 receptor agonist or a SGLT2 inhibitor is strongly recommended (independent of HbA1c) to reduce the risk of adverse CV or kidney events.[29] [161] [225]

- The ADA and European Association for the Study of Diabetes (EASD) advise that for patients in whom atherosclerotic CVD predominates (e.g., previous MI, unstable angina, ischemic stroke, or indicators of high CV risk present) either a GLP-1 receptor agonist or an SGLT2 inhibitor can be used.[29] [221] While definitions of what constitutes high CV risk vary, most comprise ≥55 years of age with two or more additional risk factors such as obesity, hypertension, smoking, dyslipidemia, or albuminuria.[221] Guidelines published by the ACP and American Heart Association (AHA)/ American Stroke Association specify that GLP-1 receptor agonists should be prioritized in patients with an increased risk for stroke.[118] [222]
- For those patients in whom heart failure or CKD predominates, SGLT2 inhibitors should be favored.[29] [221] [222]
- Combination therapy with a GLP-1 receptor agonist and an SGLT2 inhibitor may be appropriate for some patients to provide additive reduction in risk of adverse CV and kidney outcomes (e.g., if HbA1c remains above target and the patient is taking either an SGLT2 inhibitor or a GLP-1 receptor agonist).[29]

SGLT2 inhibitors and GLP-1 receptor agonists have been shown to reduce CV events and mortality in outcome trials and in real-world studies, regardless of baseline HbA1c values and concurrent use of CV medications.[47] [226] [227] [228] [229] [230] [231] [232] [233] [234] One Cochrane meta-analysis concluded that SGLT2 inhibitors and GLP-1 receptor agonists reduce CVD and all-cause mortality with high certainty.[235] High-certainty evidence supported use of SGLT2 inhibitors to reduce risk of hospitalization for heart failure, with moderate-certainty evidence supporting use of GLP-1 receptor agonists to reduce fatal and nonfatal stroke.[235] Another meta-analysis found that in patients with type 2 diabetes, the hypotensive effects of SGLT2 inhibitors and GLP-1 receptor agonists were significantly associated with a reduction in mortality and cardiorenal events, suggesting that this BP-lowering effect could be seen as an additive indicator of the CV protective effects of these agents.[236]

SGLT inhibitors

- SGLT2 inhibitors reduce the risk for all-cause mortality, major adverse CV events, progression of CKD, and hospitalization due to congestive heart failure.[222] [237] [238] They have been shown to improve CV outcomes in patients with heart failure regardless of left ventricular ejection fraction, and irrespective of type 2 diabetes status.[224] [239] [240] [241] [242] [243] [244] [245] [246]
- The SGLT2 inhibitors with the strongest evidence for CVD risk reduction are dapagliflozin, canagliflozin, and empagliflozin.[120] [221] [247] [248] [249] [250] [251] [252] [253] Only empagliflozin and canagliflozin have shown reduction in major adverse cardiac events (MACE) in patients with type 2 diabetes.[254]
- CV outcome trials in patients with type 2 diabetes:
    - The EMPA-REG OUTCOME trial evaluated CV outcomes with empagliflozin in patients with established CVD. Empagliflozin was superior to placebo in reducing the risk of the primary composite outcome of 3-point MACE (nonfatal MI, nonfatal stroke, and CV mortality; MACE-3) and unexpectedly yielded a 35% relative risk reduction in hospitalization for heart failure. All-cause mortality was also significantly reduced by 32% compared with placebo.[252]
    - Similar findings were seen for canagliflozin in the CANVAS Program trial.[253] [255]
    - The DECLARE-TIMI 58 trial found that dapagliflozin did not significantly reduce MACE-3, but resulted in a 27% reduction in heart failure-related hospitalization compared with placebo.[120] However, it decreased CV outcomes in a subanalysis of the primary trial confined to participants with prior MI.[256]

- In the VERTIS-CV trial, ertugliflozin was not found to be superior to placebo in reducing MACE-3 or CV mortality; however, a significant reduction in heart failure hospitalizations was reported in the ertugliflozin arm.[257] [258]
- The CREDENCE trial primarily evaluated kidney-related outcomes with canagliflozin and found a significant 31% reduction in the secondary composite outcome of CV death and heart failure hospitalizations with canagliflozin compared to placebo.[248]
- One pooled meta-analysis of these trials revealed a significant reduction in MACE (most apparent in patients with established atherosclerotic CVD), all-cause mortality, CV deaths, and heart failure hospitalizations. The greatest magnitude of benefit was for reduction in risk for hospitalization for heart failure and kidney disease progression.[259]

- On the basis of these findings, SGLT2 inhibitors are recommended in the management of heart failure, regardless of diabetes status.[161] [260] [261] SGLT inhibitors, particularly empagliflozin, have been shown to significantly reverse cardiac remodeling in patients with heart failure.[262] [263] [264] [265] [266]
- One meta-analysis looked at the efficacy of SGLT2 inhibitors in older people with type 2 diabetes and heart failure and found they were associated with a significant reduction in all-cause mortality, cardiac death, and hospitalization for heart failure, confirming that their cardioprotective advantages extend to the frail/older population. However, they did not demonstrate a significant effect in reducing the risk of macrovascular events (acute coronary syndrome [ACS] or stroke).[267]
- The ESC recommends dapagliflozin or empagliflozin for all patients with type 2 diabetes and CKD to reduce risk of heart failure hospitalization or CV death, regardless of whether they have a preexisting heart failure diagnosis.[261]
- SGLT2 inhibitors also reduce the risk of serious hyperkalemia in people with type 2 diabetes at high CV risk without increasing the risk of hypokalemia, allowing the titration of guideline-directed medical therapy in patients with heart failure.[268]
- An initial decline in estimated glomerular filtration rate (eGFR) is commonly observed after initiating an SGLT2 inhibitor but this decline is not associated with subsequent risk of CV or kidney events.[269] Thus, SGLT2 inhibitors should not be interrupted or discontinued in response to an initial eGFR decline.
- SGLT2 inhibitors are generally well-tolerated; however, some serious adverse reactions have been documented, including a higher rate of diabetic ketoacidosis, acute kidney injury, fracture, and/or amputation. The European Medicines Agency (EMA) warns of the potential increased risk of toe amputation.[270] The Food and Drug Administration (FDA) states that the risk of amputation, while increased with canagliflozin, is lower than previously described, particularly when appropriately monitored.[271] One large network meta-analysis estimated that treatment with SGLT-2 inhibitors in 1000 patients for 5 years probably results in three additional amputations.[224] 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.[272] [273] 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.
- Sotagliflozin is the first dual SGLT inhibitor.[274] It inhibits both renal SGLT2 (promoting significant excretion of glucose in the urine, in the same way as other already available SGLT2 selective inhibitors) and intestinal SGLT1 (delaying glucose absorption and therefore reducing postprandial glucose).[274] It has been approved in people with heart failure (both with and without diabetes) and in patients with type 2 diabetes who have CKD or high risk of/established CVD, to reduce the risk of hospitalization for heart failure.[29] The approval was based on two randomized, double-

blind, placebo-controlled phase 3 CV outcome trials: SOLOIST-WHF (Effects of Sotagliflozin on Clinical Outcomes in Hemodynamically Stable Patients with Type 2 Diabetes Post Worsening Heart Failure) and SCORED (Effects of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes Mellitus, Cardiovascular Risk Factors and Moderately Impaired Renal Function).[275] [276] It is not currently approved for glycemic management of type 1 or type 2 diabetes.

- One concern with expanded use of SGLT inhibition is the infrequent but serious risk of diabetic ketoacidosis (DKA), including the atypical presentation of euglycemic ketoacidosis.[29] Of note, the studies that led to the approved indication of sotagliflozin for heart failure excluded individuals with type 1 diabetes or a history of DKA.[275] [276] In clinical trials of sotagliflozin in people with type 1 diabetes, results showed improvements in HbA1c and body weight; however, its use was associated with an eightfold increase in DKA compared with placebo.[29] [277] The risks and benefits of SGLT inhibitors in this population continue to be evaluated, with consensus statements providing guidance on patient selection and precautions.[29] [278]

GLP-1 receptor agonists

- Reduce the risk for all-cause mortality and major adverse CV events.[222] [279] The GLP-1 receptor agonists with the strongest evidence for atherosclerotic CVD risk reduction are injectable semaglutide, liraglutide, and dulaglutide.[221] [280] [281] [282] [283] [284]
- In addition to their beneficial effects on coronary artery disease, GLP-1 receptor agonists are the only drug class that has been shown to convincingly reduce non-fatal stroke.[222] [224] [285] [286] [287] [288]
- The addition of semaglutide to standard care has been shown to be associated with an important gain in life-years free of new/recurrent CVD events and a decrease in 10-year CVD risk.[289] It is the only GLP-1 receptor agonist that is available in both oral and injectable formulations. However, unlike for injectable semaglutide, conclusive evidence for the CV benefit of oral semaglutide has not yet been established in clinical studies.[281] For more information on oral semaglutide, see Emerging treatments .
- Unlike for SGLT2 inhibitors, the evidence for GLP-1 receptor agonists in reducing heart failure or improving CV outcomes in patients with heart failure has been inconsistent across trials.[290] One meta-analysis found that they may prevent new-onset heart failure and mortality in patients with type 2 diabetes; however, they did not reduce heart failure hospitalizations and mortality in those patients with preexisting heart failure.[291]
- Data from retrospective studies and meta-analyses have shown superiority of GLP-1 receptor agonists in comparison with other antidiabetic medications such as SGLT2 inhibitors and DPP-4 inhibitors in terms of peripheral arterial disease (PAD).[292] However, data from CV outcome trials regarding the impact of GLP-1 receptor agonists on PAD are scarce and further prospective studies are needed.
- The most common adverse effects of GLP-1 receptor agonists are gastrointestinal, particularly nausea, vomiting, and diarrhea; these are frequent but tend to reduce over time.[293]
- Patients should be counseled about potential for ileus.[29]
- An association with pancreatitis and pancreatic cancer has been reported in clinical trials, but causality has not been established; after a review of available data, the FDA and the EMA agreed that there was insufficient evidence to confirm an increased risk of pancreatic cancer with use of GLP-1-based therapies.[294] Nonetheless, GLP-1 receptor agonists should be used with caution in patients with a history of pancreatitis.[29] [293]

- GLP-1 receptor agonists have been associated with increased risk of gallbladder and biliary diseases including cholelithiasis and cholecystitis.[293]
- Hypoglycemia risk is increased with concomitant sulfonylureas and insulin use. Treatment deintensification of these agents or of diuretics, particularly in older and frail individuals, is recommended to avoid hypoglycemia and hypovolemia.[293]
- DKA has been reported in patients on a combination of a GLP-1 receptor agonists and insulin, when concomitant insulin was either rapidly reduced or discontinued; insulin reductions should therefore be undertaken in a cautious stepwise manner, with capillary blood glucose monitoring.[293]
- In rodent studies, GLP-1 receptor agonists were associated with medullary thyroid cancer, resulting in a black box warning for these agents in patients with a personal or family history of multiple endocrine neoplasia type 2 or medullary thyroid cancer; however, there is conflicting evidence as to whether this risk applies in humans.[293] [295] [296] [297] [298]
- The EMA is reviewing data on the risk of suicidal thoughts and thoughts of self-harm with GLP-1 receptor agonists, following reports of such occurrences in people using liraglutide and semaglutide.[299]
- There is some concern that GLP1-receptor agonists, through their rapid glucose-lowering effects, may increase the risk of transient worsening of preexisting diabetic retinopathy.[300] [301] [302] Further studies are required to elucidate this relationship.

One Swedish nationwide study found that the proportion of patients with type 2 diabetes who were eligible for treatment with an SGLT2 inhibitor or a GLP-1 receptor agonist was approximately 80% according to the 2019 ESC guidelines and around 50% according to the 2019 ADA/EASD consensus report. Uptake of these recommendations in routine clinical practice was limited, however, indicating that many eligible patients are missing out on the therapeutic benefits of these medications.[303]

Glycemic control during acute critical illness (CVD events or interventions)

Trials of tight glycemic control in critically ill patients have yielded mixed results.[304] [305]

In one study of patients with acute coronary syndrome who presented with hyperglycemia, intensive glucose control was associated with harm and did not reduce infarct size.[306]

One large RCT raised questions about intensive blood glucose targets for inpatient glycemic control and found a lower mortality for intensive care unit (ICU) patients with a blood glucose target of 180 mg/dL (10 mmol/L) than for those with a blood glucose target of 81 to 108 mg/dL (4.5 to 6.0 mmol/L).[307] A concern has been whether there is any additional benefit to lowering blood glucose levels below about 140 to 180 mg/dL (7.8 to 10 mmol/L) in the ICU setting.[308]

The ADA recommends that in critically ill patients, insulin therapy should be started for persistent hyperglycemia ≥180 mg/dL (≥10 mmol/L) (tested on two occasions).[29] Once insulin therapy is started, a target glucose range of 140 to 180 mg/dL (7.8 to 10 mmol/L) is recommended for most patients.[29] More stringent goals, such as 110 to 140 mg/dL (6.1 to 7.8 mmol/L), may be appropriate for selected patients (e.g., critically ill postsurgical patients or patients with cardiac surgery), as long as they can be achieved without significant hypoglycemia.[29] Critically ill patients require an intravenous insulin protocol that has demonstrated efficacy and safety for achieving targets without increasing risk for severe hypoglycemia.[29]

Intravenous infusion of insulin allows for more rapid titration (and more reliable absorption) in critically ill patients than does subcutaneous injection. In the perioperative period for coronary artery bypass grafting (CABG), good glucose control may reduce infectious complications, such as sternal wound infections and mediastinitis, cardiac mortality caused by pump failure, and the risk of supraventricular tachycardia.[309] [310] [311]

BP control

It is well accepted that BP control reduces CV risk in patients with diabetes; however, certain pivotal studies investigating the benefits of intensive versus standard BP control yielded discordant results:

- The UK Prospective Diabetes Study (UKPDS) found that tight BP control (<150 mmHg) led to a greater reduction in CV events than less tight BP control (<180 mmHg).[58]
- The Systolic Blood Pressure Intervention Trial (SPRINT) had similar findings, with intensive BP control (<120 mmHg) significantly reducing risk of CV events compared with standard control (<140 mmHg), although patients with diabetes were excluded from enrollment.[57]
- Conversely, the ACCORD-BP trial demonstrated that intensive BP control to a goal of <120 mmHg compared with a standard BP goal of <140 mmHg did not change CV outcomes in patients with diabetes.[56]
- The 2021 STEP trial found that, in older adults ages 60-80 years with hypertension, intensive BP control (target 110 to <130 mmHg) was associated with a 26% reduction in CV events compared with less intensive BP control (target 130 to <150 mmHg).[59]

The reason for the difference in findings between SPRINT and ACCORD-BP remains under debate. However, a post-hoc analysis of ACCORD-BP found that although dual intensive therapy for BP and glycemic control was detrimental, intensive BP control conferred modest CV benefits for patients on standard glycemic control.[312]

There is a lack of high-quality evidence regarding optimal treatment of hypertension in people with diabetes.[60] However, guidelines recommend a BP treatment goal of <130/80 mmHg, providing this can be safely attained.[6] [29][60] [61] The departure in the guidelines from the previous BP target of <140/90 mmHg was in response to studies like the meta-analysis of data from the ACCORD-BP and SPRINT trials, which showed a reduction in a composite of unstable angina, MI, acute heart failure, stroke, and CV death with intensive systolic BP targets of <120 mmHg compared with the traditional target of <140 mmHg.[313] Notably, the ADA recommends an individualized approach to BP targets, and recommends that patients and clinicians should engage in a shared decision-making process to determine individual BP targets, acknowledging that the benefits and risks of intensive BP targets are uncertain.[29]

People with diabetes plus hypertension should monitor their BP at home in addition to having it checked at regular intervals in the clinic setting, both to ensure accuracy of readings and to encourage adherence to treatment regimens.[29]

Guidelines also emphasize the importance of therapeutic lifestyle interventions in the management of hypertension; these include increased physical activity, weight management, a DASH-style eating pattern (including reduced sodium intake and increased potassium intake), moderation of alcohol intake, smoking cessation, and education to support long-term behavior change.[29] [61] These lifestyle interventions should be initiated alongside pharmacologic therapy when hypertension is diagnosed, and are also recommended for individuals with diabetes and mildly elevated blood pressure (systolic >120 mmHg or diastolic >80 mmHg).[29]

The ADA recommends starting one antihypertensive agent for patients with initial BP ≥130/80 mmHg and <150/90 mmHg, and starting two antihypertensive agents for those with initial BP ≥150/90 mmHg.[29] ACE inhibitors, angiotensin-II receptor antagonists, dihydropyridine calcium-channel blockers, or thiazide diuretics are all options for initial antihypertensive therapy.[29] [60] [61]

For patients with diabetes who have CAD or CKD and/or albuminuria (eGFR <60 mL/minute/1.73 m², urinary albumin-to-creatinine ratio ≥30 mg/g creatinine), initial antihypertensive therapy should be with an ACE inhibitor, or an angiotensin-II receptor antagonist if an ACE inhibitor is not tolerated (a dose reduction may be required in patients with renal impairment).[29] [60]

For those whose BP is >150/90 mmHg, a calcium-channel blocker or thiazide diuretic should be considered in addition at treatment initiation.[29] Combining ACE inhibitors and angiotensin-II receptor antagonists is not recommended because of an increased risk for acute kidney injury and hyperkalemia.[29] [314] ACE inhibitors have also shown increased risk for hypoglycemia in conjunction with insulin or insulin secretagogues (sulfonylurea or meglitinide).[315]

One meta-analysis found that ACE inhibitors reduced mortality and major CV events in patients with diabetes, while angiotensin-II receptor antagonists did not improve these outcomes. Neither ACE inhibitors or angiotensin-II receptor antagonists were found to reduce the risk of stroke.[316] Another meta-analysis showed that in patients with diabetes and kidney disease, no antihypertensive regimen improved survival. However, ACE inhibitors and angiotensin-II receptor antagonists were effective in preventing end-stage renal disease.[314] Some antihyperglycemic agents have demonstrated modest BP-lowering effects in clinical trials, including SGLT2 inhibitors and GLP-1 receptor agonists.[317] Further studies are warranted to investigate the effects of these agents on BP as the primary outcome measure.[317]

Based on the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) trial, the FDA recommends that combination of the renin inhibitor aliskiren with ACE inhibitors or angiotensin-II receptor antagonists is contraindicated in patients with diabetes due to the risk of renal impairment, hypotension, and hyperkalemia. [FDA: new warning and contraindication for blood pressure medicines containing aliskiren (Tekturna)] (https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-new-warning-and-contraindication-blood-pressure-medicines-containing)

Beta-blockers may be appropriate to improve outcomes as antihypertensive agents in patients with prior MI, active angina, atrial fibrillation with rapid ventricular response, or heart failure with reduced ejection fraction.[29] These patients are typically started on beta-blockers alone, with other antihypertensive therapies added as needed. If a beta-blocker is indicated, an agent should be selected that has concomitant vasodilatory effects to reduce potential for adverse metabolic impact.[114] Beta-blockers may mask symptoms of hypoglycemia and also have the potential to exacerbate hypoglycemic episodes, particularly when used concurrently with sulfonylureas.[29] [318] [319]

Multiple drug therapy is often required in order to achieve antihypertensive targets.[29] If BP remains uncontrolled on monotherapy, add an agent from a different first-line class.[29] If BP remains uncontrolled despite combination therapy with first-line agents (i.e., three classes of antihypertensive medication [including a diuretic] plus lifestyle modifications), discontinue or minimize interfering substances such as nonsteroidal anti-inflammatory drugs, evaluate for secondary causes of hypertension (including obstructive sleep apnea), and consider the addition of an aldosterone antagonist (e.g., spironolactone, eplerenone).[29] [114] Referral to a hypertension specialist may also be necessary.[29] [114]

Serum creatinine/eGFR and potassium should be checked within 7-14 days of initiation of treatment with an ACE inhibitor, angiotensin-II receptor antagonist, aldosterone antagonist, or diuretic, as well as following uptitration of dose and then at least annually.[29]

European and US guidelines also recommend considering use of an ACE inhibitor (or an angiotensin-II receptor antagonist) in patients with chronic coronary disease and diabetes mellitus to reduce risk of cardiovascular events, regardless of hypertension, and particularly in patients with heart failure or CKD.[6] [320] [321]

Dyslipidemia therapy

Lifestyle modification focusing on weight loss (if indicated); application of a Mediterranean or DASH eating pattern; reduction of saturated fat and trans fat; increase of dietary omega-3 fatty acids, viscous fiber, and plant stanol/sterol intake; and increased physical activity should be recommended to improve the lipid profile and reduce the risk of developing CVD in people with diabetes.[29]

LDL-C is the most extensively studied modifiable risk factor associated with atherosclerotic CVD. There is strong evidence that LDL-C is a causal factor in the pathophysiology of CVD, and CVD risk reduction is proportional to the absolute and relative LDL-C reduction achieved.[112] One meta-analysis which included data from over 18,000 people with diabetes from 14 randomized trials of statin therapy (mean follow-up 4.3 years) demonstrated a 9% proportional reduction in all-cause mortality and 13% reduction in vascular mortality for each 39 mg/dL (1 mmol/L) reduction in LDL-C.[124] The CV benefit did not depend on baseline LDL-C levels and was linearly related to the LDL-C reduction without a low threshold beyond which there was no benefit observed. Lowering of LDL-C has also been shown to have a significant positive impact on long-term outcomes for patients with diabetes and coronary heart disease undergoing percutaneous coronary intervention (PCI).[322]

For patients with diabetes and established CVD, both European and US guidelines recommend an LDL-C goal of <55 mg/dL (<1.42 mmol/L) and at least a 50% reduction from baseline.[6] [29] [113]

Statins

Statins are the first-line medication for LDL-C lowering and cardioprotection.[29] Moderate-intensity statin therapy has been defined by the American College of Cardiology (ACC)/AHA as therapy that generally lowers LDL-C level by 30% to 50%, while high-intensity statin therapy lowers it by ≥50%.[113] Guidelines recommend high-intensity statin therapy in adults of all ages with diabetes and atherosclerotic CVD, to target an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <55 mg/dL (<1.42 mmol/L).[29] [113] Low-dose statin therapy is generally not recommended in people with diabetes, but it is sometimes the only dose of statin that an individual can tolerate; for individuals who do not tolerate the intended intensity of statin, the maximum tolerated statin dose should be used.[29]

Ezetimibe

If target LDL-C is not achieved with a statin alone, addition of ezetimibe can be considered.[29] Ezetimibe works by reducing cholesterol absorption from the ileum.[6] One large RCT of 18,144 individuals compared the addition of ezetimibe to simvastatin therapy versus simvastatin alone in people ages ≥50 years who had experienced a recent acute coronary syndrome.[323] Overall, over an average treatment period of 6 years, addition of ezetimibe led to a 6.4% relative benefit and a 2% absolute reduction in major adverse atherosclerotic CV events, with the degree of benefit being directly proportional to the change in LDL-C. Subgroup analysis showed that the benefit of adding ezetimibe to statin therapy was

enhanced in patients with diabetes.[323] Another RCT showed that among patients with diabetes and atherosclerotic CVD, moderate-intensity statin with ezetimibe combined therapy was noninferior to high-intensity statin monotherapy with respect to the primary endpoint of CV death, major CV events, or nonfatal stroke.[324] Notably, the patients treated with moderate-intensity statin and ezetimibe had lower rates of drug discontinuation or dose reduction than patients receiving high-intensity statin. This study supports moderate-intensity statin with ezetimibe combination therapy as a suitable alternative to high-intensity statins if the latter cannot be tolerated, or further reduction in LDL-C is required among patients with diabetes and CVD.[324]

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

If target LDL-C is not achieved with a statin alone, addition of a PCSK9 inhibitor (e.g., alirocumab, evolocumab) can be considered as an alternative to ezetimibe (or in addition to ezetimibe if LDL-C is not at goal). PCSK9 inhibitors can also be used as monotherapy in patients who are statin-intolerant.[29] In placebo-controlled RCTs, alirocumab and evolocumab achieved a >50% reduction in LDL-C levels compared with placebo, with a 15% lower risk of ischemic CV events over a 2- to 3-year follow-up.[325] [326]

Bempedoic acid

Bempedoic acid, an adenosine triphosphate citrate lyase inhibitor, is a novel, oral LDL-C-lowering drug that works by inhibiting cholesterol synthesis.[6] It is approved in the US as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with established atherosclerotic CVD who require additional lowering of LDL-C. The ADA advises that it may be considered for patients who cannot use, or tolerate, other evidence-based LDL-C-lowering approaches, or for whom those other therapies are inadequately effective.[29] Bempedoic acid is also approved for this indication in Europe.[327] One meta-analysis found that bempedoic acid therapy lowered LDL-C levels by about 23% compared with placebo, while an RCT found that it was associated with a reduction in risk of major adverse CV events (death from CV causes, nonfatal MI, nonfatal stroke, or coronary revascularization) in statin-intolerant patients, providing some evidence for its use in this group.[328] [329]

Inclisiran

Inclisiran, a small interfering ribonucleic acid (siRNA) that inhibits hepatic synthesis of PCSK9, is now recommended by the ADA as an alternative lipid-lowering treatment for people who are intolerant of statins (off-label use).[29] In the ORION-10 and ORION-11 phase 3 trials, individuals with established CVD or at high risk of CVD were randomized to receive inclisiran or placebo.[330] Inclisiran allows less frequent administration compared with monoclonal antibodies and was administered on day 1, day 90, and every 6 months thereafter over a period of 540 days. Reductions in LDL-C levels of approximately 50% were obtained with inclisiran.[330] Adverse events were generally similar in the inclisiran and placebo groups, although injection-site adverse events were more frequent with inclisiran (2.6% vs. 0.9% in ORION-10 and 4.7% vs. 0.5% in ORION-11); such reactions were generally mild.[330] A CV outcome trial using inclisiran in people with established CVD is currently ongoing.[331]

Summary of ADA recommendations for lipid-lowering pharmacotherapy in patients with diabetes with established CVD:[29]

- High-intensity statin therapy for adults of all ages, to target an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <55 mg/dL (<1.42 mmol/L). For people who do not tolerate the intended statin intensity, the maximum tolerated statin dose should be used.

- Addition of ezetimibe or a PCSK9 inhibitor if this goal is not achieved on maximum tolerated statin therapy.
- For people intolerant of statin therapy, a PCSK9 inhibitor, bempedoic acid, or inclisiran should be considered as alternative cholesterol-lowering therapies.

For certain patients at intermediate or borderline risk, coronary artery calcium (CAC) measurement may be useful to support shared decision-making for statin therapy.[76] A CAC score ≥100 Agatston units or in the ≥75th age/sex/race percentile can reclassify CV risk as being increased.[76]

A lipid profile should be checked: at time of diagnosis of diabetes or prediabetes; at initiation of statins or other lipid-lowering therapy; 4-12 weeks after initiation or a change in dose; and annually thereafter.[29]

Role of other lipid-lowering pharmacotherapies

- Icosapent ethyl can be considered in patients with atherosclerotic CVD or other CV risk factors who are on a statin and have controlled LDL-C but elevated triglycerides (135 to 499 mg/dL [1.53 to 5.64 mmol/L]).[29] It has been shown to modestly reduce CV events.[114] [115] There have been some concerns about the use of mineral oil as the control treatment in pivotal clinical trials of icosapent ethyl; however, evaluation of whether this had an impact on trial outcomes remains inconclusive.[332] [333]
- Fibrates are effective for lowering very high triglyceride levels (i.e., >500 mg/dL [>5.65 mmol/L]) to reduce the risk of pancreatitis.[114] They are most often added to statin therapy, although the ADA notes that this approach is generally not recommended due to a lack of evidence of improvement in CVD outcomes.[29] Furthermore, caution is recommended as combination statin and fibrate therapy can increase the risk of myositis and rhabdomyolysis. To lower the risk, fenofibrate is recommended over gemfibrozil.[47]
- Supplementation with omega-3 fatty acids has not been found to reduce the rate of CV events in patients with diabetes at high risk for these events.[116]

Antiplatelet therapy

- Aspirin is recommended for secondary prevention in those with a history of atherosclerotic CVD.[29]
- Clopidogrel (a P2Y12 inhibitor) should be used in patients who have an aspirin allergy or intolerance.[29]
- In people with stable coronary and/or peripheral artery disease and low bleeding risk, the ADA and ESC recommend combination treatment with aspirin and low-dose rivaroxaban (a direct oral anticoagulant) for secondary prevention.[29] [334] Rivaroxaban has similar antiplatelet effects to aspirin, and may also improve endothelial function.[335]
- Dual antiplatelet therapy with aspirin and a P2Y12 receptor antagonist (clopidogrel, ticagrelor, or prasugrel) is indicated after ACS.[336] Evidence supports use of either ticagrelor or clopidogrel if no PCI was performed and clopidogrel, ticagrelor, or prasugrel if PCI was performed.[29] [337] Generally, prasugrel and ticagrelor have better efficacy in patients with diabetes and are preferred to clopidogrel for patients who undergo PCI.[334] [337]
- Short-term dual antiplatelet therapy is also recommended after high-risk transient ischemic attack (TIA) and minor stroke.[338]
- Dual antiplatelet therapy may have benefit beyond 1 year in reducing long-term risk of recurrent atherosclerotic events.[334] However, recommendations regarding length of treatment are rapidly evolving and should be determined by an interprofessional team approach that includes a cardiologist following ACS or a neurologist following TIA/stroke.[29] The benefits versus risk of

bleeding and thrombosis should be evaluated based on the coronary anatomy and extent of CAD, PCI complexity, bleeding risk, age, and patient's medical comorbidities such as anemia or renal failure.[339]

- To reduce risk of gastrointestinal bleeding, a proton-pump inhibitor is recommended for all patients on a combination of antiplatelet or anticoagulant therapy, and the ESC recommends that one should be considered for those on a single agent depending on their individual bleeding risk.[6]

ST-elevation myocardial infarction (STEMI)

For people with STEMI and ischemic symptoms for <12 hours, primary PCI is recommended to improve survival.[337] Primary PCI is superior to fibrinolytic therapy, and fibrinolytic therapy is therefore only recommended if PCI is not immediately available (i.e., within 120 minutes).[337] An analysis of data from 11 clinical trials compared PCI with fibrinolytic therapy in 2725 patients with STEMI, including 367 patients with diabetes.[340] Among the patients with diabetes, 30-day mortality or nonfatal reinfarction rate was 19.3% for those treated with fibrinolytics and 9.2% for those who underwent primary PCI. If onset of ischemic symptoms is ≥12 hours and the patient is in cardiogenic shock or experiencing hemodynamic instability, primary PCI is indicated, or CABG if PCI is not feasible.[337] PCI may also be reasonable in patients who are stable and presenting 12 to 24 hours after symptom onset, as well as in those whose STEMI is complicated by ongoing ischemia, acute severe heart failure, or life-threatening arrhythmia.[337]

For more comprehensive information on the acute management of this condition, see ST-elevation myocardial infarction .

Uncontrolled blood glucose levels in the perioperative or periprocedural period are associated with adverse outcomes for patients with diabetes. Benefits of good control include reductions in length of hospital stay and likelihood of readmission, as well as improved postoperative survival rates.[29] One RCT examining the effects of periprocedural intensive glycemic control during early PCI on the rate of restenosis in hyperglycemic (glucose ≥140 mg/dL [7.8 mmol/L]) patients with a STEMI showed that intensive control led to a 50% reduction in restenosis at 6 months compared with conventional glycemic control.[341]

Non-ST-elevation acute coronary syndrome

Non-ST-elevation acute coronary syndrome (NSTE-ACS) most commonly manifests as non-STEMI (NSTEMI) but may also present as unstable angina.[152]

Immediate invasive strategy (coronary angiography with intent of revascularization) is required in patients with NSTEMI and cardiogenic shock, refractory angina, or hemodynamic/electrical instability.[337] Early invasive strategy (usually within 24 hours) is recommended for patients at high risk for CV events: for example, those with a high Global Registry of Acute Coronary Events (GRACE) score. Patients with low- or intermediate-risk NSTEMI should undergo coronary angiography before discharge with the intent of revascularization. Invasive strategy is important in NSTEMI as it will help determine the suitability for revascularization and the appropriate mode (PCI vs. CABG).[337]

For more comprehensive information on the acute management of these conditions, see Non-ST-elevation myocardial infarction and Unstable angina .

Revascularization for left main or multivessel disease

Recommendations on the mode of revascularization in patients with diabetes differ slightly from those for the general population, particularly for patients with diabetes and multivessel disease.[342] Patients

with diabetes and complex multivessel CAD should undergo a heart team approach to revascularization, inclusive of an interventional cardiologist and a cardiac surgeon.[337]

CABG is generally recommended in preference to PCI to improve survival in patients with diabetes with multivessel CAD for which mechanical revascularization is likely to improve survival.[337] [343] [344] This is particularly recommended if a left internal mammary artery to left anterior descending artery (LIMA-LAD) graft is used and the patient is a good surgical candidate. In patients with diabetes and multivessel CAD who are poor surgical candidates, meet the criteria for revascularization, and have anatomy that is amenable to PCI, PCI can be beneficial to improve ischemic outcomes.[337] The survival benefit associated with CABG compared with PCI may be greater in patients with diabetes receiving insulin therapy than in those not receiving insulin therapy.[345]

The 2021 ACC/AHA/Society for Cardiovascular Angiography and Interventions (SCAI) guidelines recommend CABG for left main disease.[337] However, they recognize that PCI might be considered in patients with low- or intermediate-complexity CAD in the rest of the coronary anatomy.[337] One trial (EXCEL; about 30% participants with diabetes) found that PCI was noninferior to CABG for the end point of MI, stroke, or mortality at 3 years.[346] Mortality after CABG is higher in people with diabetes than in those without diabetes. Nevertheless, among people with diabetes, survival after indicated CABG surgery is superior to survival after medical therapy or PCI.[337] [347]

The pivotal trials are summarized as follows:

- In patients with diabetes with left main coronary disease and/or 3-vessel CAD, the SYNTAX trial found that PCI resulted in higher rates of repeat revascularization and major adverse CV or cerebrovascular events compared with patients who underwent CABG.[348] [349] However, there was no difference in rates of all-cause death, stroke, or MI. A long-term follow-up study of the SYNTAX cohort found the risk of mortality to be greater with PCI than with CABG at 5 years (19.6% vs. 13.3%), with the opposite observed between 5 and 10 years (20.8% vs. 24.4%).[345]
- The FREEDOM trial evaluated patients with diabetes with multivessel coronary disease (defined as stenosis of >70% in at least two epicardial vessels without left main disease) and found that CABG was superior to PCI in terms of reducing death and MI, but CABG patients had an increased rate of stroke.[350] In an extended follow-up study, the all-cause mortality rate was lower in the CABG group (18.7%) compared with the PCI group (23.7%).[344]
- In the Bypass Angioplasty Revascularization Investigation (BARI) trial, when comparing CABG versus balloon-only PCI (percutaneous transluminal coronary balloon angioplasty, PTCA) for 3-vessel disease, 7-year survival was 76.4% for patients with diabetes treated with CABG compared with 55.7% for those treated with PCI.[351] At 10 years, patients with diabetes who were assigned to the CABG group had higher survival than the PTCA-assigned group (PTCA 45.5% vs. CABG 57.8%).[352] This trial was performed prior to stents, aggressive statin therapy, and dual antiplatelet therapy.
- Subgroup analyses of the Emory Angioplasty versus Surgery Trial (EAST) and the Coronary Angioplasty versus Bypass Revascularization (CABRI) trials showed that CABG tended to be associated with better long-term survival over balloon-only PCI for 3-vessel disease.[353]
- The Arterial Revascularization Trial (ART) compared CABG with PCI with bare metal stents in patients with multivessel disease.[354] Subgroup analysis of patients with diabetes showed 1-year event-free survival of 84.4% for CABG and 63.4% for PCI.[354] Multiple studies comparing CABG versus PCI with drug-eluting stents have shown that diabetes is an independent predictor of target lesion restenosis.[353] [355] Drug-eluting stents appear to be superior to bare-metal stents

in people with diabetes, with regard to major adverse cardiac events such as death, MI, or need for repeat revascularization.[356] [357] [358] [359] [360]

- The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trials investigated the effects of an invasive approach (medical therapy plus revascularization) versus a conservative approach (medical therapy alone) in patients with chronic coronary disease.[361] Overall, no benefit was observed for invasive versus conservative management in patients with diabetes (43% of total cohort).[361]

Medical management with or without revascularization for single-vessel disease

In stable patients with single-vessel disease and no recent ACS or left ventricular dysfunction, the initial treatment is conservative and involves guideline-directed medical therapy for CAD. This may include antihypertensive agents, lipid-lowering agents, and antiplatelet therapy.[362] When optimized, medical therapy has demonstrated similar outcomes to revascularization.[363] [364] This approach needs patient-physician discussion to tailor therapy based on symptoms, response to therapy, available expertise, and patient's preferences.

The usefulness of coronary revascularization in improving survival is uncertain in patients with single-vessel disease involving the proximal left anterior descending artery with normal left ventricular function.[337] Revascularization may be considered after patient-physician discussion as well as heart team discussion in regards to utility and timing.[337] Coronary revascularization also has an important role in patients who are symptomatic with angina refractory to maximal medical therapy. If revascularization is indicated, and the anatomy is amenable to PCI, PCI is preferred over CABG for single-vessel CAD.[337] [343]

Considerations for patients with specific comorbidities

Heart failure (HF)

- HF is common in patients with diabetes, and in many patients, HF can be the initial presentation of CVD.[6] [140]
- Patients with diabetes and heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF) should receive HF therapy as per current HF guidelines.[29] [161] [260]
- Presence of HF in patients with type 2 diabetes influences choice of antihyperglycemic agent. SGLT2 inhibitors are recommended in all patients with HF and type 2 diabetes mellitus, as they reduce risk of HF-related hospitalization and mortality. Thiazolidinediones (e.g., pioglitazone) and saxagliptin (a DPP-4 inhibitor) have been associated with an increased risk of HF hospitalizations and are not recommended in patients with or at risk of HF. Metformin, insulin, and sitagliptin and linagliptin (DPP-4 inhibitors) are considered neutral in terms of their effect on HF outcomes.[6] In patients with obesity and HFpEF, semaglutide (a GLP-1 receptor agonist) has been shown to reduce HF-related symptoms, improve exercise function, and result in greater weight loss compared with placebo.[365] A GLP-1 receptor agonist may be preferred over other antihyperglycemic agents in those with HFpEF and obesity.
- Screening for HF in patients with diabetes is important for starting therapy early and optimizing prognosis. The ADA recommends annual screening of asymptomatic adults with diabetes for HF.[29]
- See Heart failure with reduced ejection fraction and Heart failure with preserved ejection fraction .

CKD

- CKD is a risk factor for CVD and worsening kidney function (lower glomerular filtration rate [GFR], increased albuminuria) is associated with progressively increased risk of coronary disease.[80] CVD (in addition to diabetes) is a risk factor for CKD progression and subsequent kidney failure with replacement therapy (dialysis or kidney transplant).[366] Patients with diabetes should be screened for CKD at least annually.[6] [29]
- Reducing the risk of both CV and kidney adverse events is key in these patients. Standard lifestyle and risk factor modifications (e.g., BP control, lipid control, glycemic control, weight control) are important. Additionally, specific pharmacologic interventions are recommended:[6] [29]
    - SGLT2 inhibitors, in addition to reducing hyperglycemia, have renal benefits through independent effects on renal tubular glucose reabsorption, weight, BP, intraglomerular pressures, albuminuria, and slowed GFR loss, and are recommended in patients with type 2 diabetes, established atherosclerotic CVD, and CKD to reduce the risk of both CV and kidney adverse events.
    - An ACE inhibitor or angiotensin-II receptor antagonist is recommended in patients with type 2 diabetes, established atherosclerotic CVD, and CKD, even if they are normotensive, to reduce the risk of cardiovascular events.[6] [29] [320]
    - Finerenone, a nonsteroidal mineralocorticoid receptor antagonist, has been shown in randomized trials to lower risks of CV events and CKD progression in patients with type 2 diabetes, CKD, and albuminuria.[367] [368] For people with type 2 diabetes and CKD with albuminuria treated with maximum tolerated doses of ACE inhibitors or angiotensin-II receptor antagonists, who are at an increased risk of cardiovascular events or CKD progression, the ADA and ESC recommend addition of finerenone.[6] [29]
    - If additional glycemic control is needed, a GLP-1 receptor agonist is recommended, as they improve renal outcomes independent of glucose lowering effect, and have benefits in CV risk reduction and weight control.
    - Low-dose aspirin is recommended in patients with diabetes, CKD, and atherosclerotic CVD.
    - In patients with diabetes, CKD, and stable moderate or severe CAD, either an intensive medical strategy or an initial invasive strategy may be considered.[6]
- Referral to a specialist should be considered.
- See Diabetic kidney disease .

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		(summary)
acute myocardial infarction or unstable angina		
	1st	**coronary intervention and medical management**

Acute (summary)

highly significant coronary artery disease: without acute myocardial infarction or unstable angina

■ left main stenosis	1st	coronary artery bypass graft and perioperative tight glycemic control
■ multivessel coronary artery disease	1st	revascularization and perioperative tight glycemic control
■ single-vessel coronary artery disease	1st	medical management
	adjunct	revascularization and perioperative tight glycemic control

Ongoing (summary)

diabetic cardiovascular disease: stable and/or after intervention

	1st	ACE inhibitor or angiotensin-II receptor antagonist
	adjunct	additional antihypertensive therapy
	plus	lipid control
	plus	metformin
	plus	glucagon-like peptide-1 receptor agonist or tirzepatide and/or sodium-glucose cotransporter inhibitor
	plus	lifestyle and behavioral therapy
	adjunct	weight management
	adjunct	antiplatelet therapy
■ with heart failure	adjunct	guideline-directed management and therapy
■ with chronic kidney disease	adjunct	management of cardiovascular risk and kidney failure risk

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

acute myocardial infarction or unstable angina

1st **coronary intervention and medical management**

» For people with ST-elevation myocardial infarction (STEMI) and ischemic symptoms for <12 hours, primary percutaneous coronary intervention (PCI) is recommended to improve survival.[337] Primary PCI is superior to fibrinolytic therapy and fibrinolytic therapy is therefore only recommended if PCI is not immediately available (i.e., within 120 minutes).[337] An analysis of data from 11 clinical trials compared PCI with fibrinolytic therapy in 2725 patients with STEMI, including 367 patients with diabetes.[340] Among patients with diabetes, 30-day mortality or nonfatal reinfarction rate was 19.3% for those treated with fibrinolytics and 9.2% for those who underwent primary PCI. If onset of ischemic symptoms is ≥12 hours and the patient is in cardiogenic shock or experiencing hemodynamic instability, primary PCI is indicated, or coronary artery bypass graft (CABG) if PCI is not feasible.[337] PCI may also be reasonable in patients who are stable and presenting 12-24 hours after symptom onset, as well as in those whose STEMI is complicated by ongoing ischemia, acute severe heart failure, or life-threatening arrhythmia.[337]

» Non-ST-elevation acute coronary syndrome (NSTE-ACS) most commonly manifests as non-ST-elevation MI (NSTEMI) but may also present as unstable angina.[152] Immediate invasive strategy (coronary angiography with intent of revascularization) is required in patients with NSTEMI and cardiogenic shock, refractory angina, or hemodynamic/electrical instability.[337] Early invasive strategy (usually within 24 hours) is recommended for patients at high risk for CV events: for example, those with a high Global Registry of Acute Coronary Events (GRACE) score. Patients with low- or intermediate-risk NSTEMI should undergo coronary angiography before discharge with the intent of revascularization. Invasive strategy is important in NSTEMI as it will help determine

Initial

the suitability for revascularization and the appropriate mode (PCI vs. CABG).[337]

» All patients should receive aspirin and consider beta-blockers, nitrates, ACE inhibitors, and P2Y12 inhibitors as part of early management for STEMI and NSTEMI.[362]

» For more comprehensive information on the acute management of these conditions, see ST-elevation myocardial infarction , Non-ST-elevation myocardial infarction , and Unstable angina .

» Uncontrolled blood glucose levels in the perioperative or periprocedural period are associated with adverse outcomes for patients with diabetes. Benefits of good control include reductions in length of hospital stay and likelihood of readmission, as well as improved postoperative survival rates.[29] However, trials of tight glycemic control in critically ill patients have yielded mixed results.[369] [370] In one study of acute coronary syndrome patients who presented with hyperglycemia, intensive glucose control was associated with harm and did not reduce infarct size.[306] One large randomized controlled trial raised questions about intensive blood glucose targets for inpatient glycemic control and found a lower mortality for intensive care unit (ICU) patients with a blood glucose target of 180 mg/dL (10 mmol/L) than for those with a blood glucose target of 81 to 108 mg/dL (4.5 to 6.0 mmol/L).[307] A concern has been whether there is any additional benefit to lowering blood glucose levels below about 140 to 180 mg/dL (7.8 to 10.0 mmol/L) in the ICU setting.[308] One randomized controlled trial examining the effects of periprocedural intensive glycemic control during early PCI on the rate of restenosis in hyperglycemic (glucose ≥140 mg/dL [≥7.8 mmol/L]) patients with a STEMI showed that intensive control led to a 50% reduction in restenosis at 6 months compared with conventional glycemic control.[341]

» The American Diabetes Association (ADA) recommends that in critically ill patients, insulin therapy should be started for persistent hyperglycemia ≥180 mg/dL (≥10 mmol/L) (tested on two occasions).[29] Once insulin therapy is started, a target glucose range of 140 to 180 mg/dL (7.8 to 10.0 mmol/L) is recommended for most critically ill patients.[29] More stringent goals, such as 110 to 140 mg/dL (6.1 to 7.8 mmol/L), may be appropriate for selected patients (e.g., critically ill postsurgical patients or patients with cardiac surgery),

Initial

as long as they can be achieved without significant hypoglycemia.[29] Critically ill patients require an intravenous insulin protocol that has demonstrated efficacy and safety for achieving targets without increasing risk for severe hypoglycemia.[29]

Acute

highly significant coronary artery disease: without acute myocardial infarction or unstable angina

left main stenosis — **1st** — **coronary artery bypass graft and perioperative tight glycemic control**

» The 2021 American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions coronary artery revascularization guidelines recommend coronary artery bypass graft (CABG) for left main disease.[337] However, they recognize that it is reasonable to consider PCI in patients with low- or intermediate-complexity disease in the rest of the coronary anatomy.[337]

» Intravenous infusion of insulin allows for more rapid titration (and more reliable absorption) in critically ill patients than does subcutaneous injection. In the perioperative period for CABG, good glucose control may reduce infectious complications, such as sternal wound infections and mediastinitis, cardiac mortality caused by pump failure, and the risk of supraventricular tachycardia.[309] [310] [311]

multivessel coronary artery disease — **1st** — **revascularization and perioperative tight glycemic control**

» Patients with diabetes and complex multivessel coronary artery disease (CAD) should undergo a heart team approach to revascularization, inclusive of an interventional cardiologist and a cardiac surgeon.[337]

» Either PCI with drug-eluting stents or coronary artery bypass graft (CABG) may be suitable depending on factors such as anatomic location of lesions, lesion length, presence of chronic total occlusions, left ventricular function, and comorbidity. CABG is generally recommended in preference to PCI to improve survival in patients with diabetes with multivessel CAD for which mechanical revascularization is likely to improve survival.[337] [343] [344] This is particularly recommended if a left internal mammary artery to left anterior descending artery (LIMA-LAD) graft is used and the patient is a good surgical candidate.[337]

» Intravenous infusion of insulin allows for more rapid titration (and more reliable absorption) in critically ill patients than does subcutaneous injection. In the perioperative period for CABG, good glucose control may reduce infectious

Acute

complications, such as sternal wound infections and mediastinitis, cardiac mortality caused by pump failure, and the risk of supraventricular tachycardia.[309] [310] [311]

single-vessel coronary artery disease

1st **medical management**

» In stable patients with single-vessel disease and no recent acute coronary syndrome or left ventricular dysfunction, the initial treatment is conservative and involves guideline-directed medical therapy for CAD. This may include antihypertensive agents, lipid-lowering agents, and antiplatelet therapy.[362] When optimized, medical therapy has demonstrated similar outcomes to revascularization.[363] [364] This approach needs patient-physician discussion to tailor therapy based on symptoms, response to therapy, available expertise, and patient's preferences.

adjunct **revascularization and perioperative tight glycemic control**

Treatment recommended for SOME patients in selected patient group

» The usefulness of coronary revascularization in improving survival is uncertain in patients with single-vessel disease involving the proximal left anterior descending artery with normal left ventricular function.[337]

» Revascularization may be considered after patient-physician discussion as well as heart team discussion in regards to utility and timing.[337]

» Coronary revascularization also has an important role in patients who are symptomatic with angina refractory to maximal medical therapy.[337]

» If revascularization is indicated, and the anatomy is amenable to PCI, PCI is preferred over coronary artery bypass graft (CABG) for single-vessel CAD.[337] [343]

» Intravenous infusion of insulin allows for more rapid titration (and more reliable absorption) in critically ill patients than does subcutaneous injection. In the perioperative period for CABG, good glucose control may reduce infectious complications, such as sternal wound infections and mediastinitis, cardiac mortality caused by pump failure, and the risk of supraventricular tachycardia.[310] [311]

Ongoing

diabetic cardiovascular disease: stable and/or after intervention

1st **ACE inhibitor or angiotensin-II receptor antagonist**

Primary options

» lisinopril: 5 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day

OR

» enalapril: 2.5 mg orally twice daily initially, increase gradually according to response, maximum 40 mg/day

OR

» captopril: 6.25 mg orally three times daily initially, increase gradually according to response, maximum 150 mg/day

Secondary options

» 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: 25-50 mg orally once daily initially, increase gradually according to response, maximum 150 mg/day

OR

» valsartan: 40 mg orally twice daily initially, increase gradually according to response, maximum 320 mg/day

» European and US guidelines recommend use of an ACE inhibitor (or an angiotensin-II receptor antagonist if an ACE inhibitor is not tolerated) in patients with diabetic CVD to reduce risk of cardiovascular events, regardless of hypertension, and particularly in patients with heart failure or chronic kidney disease (CKD).[6] [320] [321]

Ongoing

» ACE inhibitors and angiotensin-II receptor antagonists should not be used in combination due to increased risk for acute kidney injury and hyperkalemia.[29][314] A dose reduction may be required in patients with renal impairment. ACE inhibitors have also shown increased risk for hypoglycemia in conjunction with insulin or insulin secretagogue (sulfonylurea or meglitinide).[315]

» Serum creatinine/estimated glomerular filtration rate (eGFR) and potassium should be checked within 7-14 days of initiation of treatment with an ACE inhibitor or angiotensin-II receptor antagonist, as well as following uptitration of dose and then at least annually.[29]

adjunct **additional antihypertensive therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» hydrochlorothiazide: 12.5 to 25 mg orally once daily initially, increase gradually according to response, maximum 50 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

--AND/OR--

» metoprolol tartrate: 50 mg orally (immediate-release) twice daily initially, increase gradually according to response, maximum 450 mg/day

-or-

» bisoprolol: 2.5 to 5 mg orally once daily initially, increase gradually according to response, maximum 20 mg/day

-or-

» carvedilol: 6.25 mg orally (immediate-release) twice daily initially, increase gradually according to response, maximum 50 mg/day

--AND/OR--

» spironolactone: 25-100 mg/day orally given in 1-2 divided doses

-or-

Ongoing

» eplerenone: 50 mg orally once or twice daily

» The American Diabetes Association (ADA) recommends an individualized approach to blood pressure (BP) management, with consideration of antihypertensive drug therapy for all nonpregnant patients with diabetes whose BP is persistently elevated above ≥130/80 mmHg. Guidelines recommend a target goal of <130/80 mmHg for nonpregnant people with diabetes, providing this can be safely attained.[6] [29][60] [61]

» The ADA recommends starting one antihypertensive agent for patients with initial BP ≥130/80 and <150/90 mmHg, and starting two antihypertensive agents for those with initial BP ≥150/90 mmHg.[29]

» Patients with diabetic CVD, even if normotensive, should be treated with an ACE inhibitor, or an angiotensin-II receptor antagonist if an ACE inhibitor is not tolerated.[29] [60] However, additional antihypertensive agents may be required.

» For those whose BP is ≥150/90 mmHg, a calcium-channel blocker (e.g., amlodipine, felodipine, nifedipine) or a thiazide diuretic (e.g., hydrochlorothiazide) should be considered in addition at treatment initiation.[29]

» Beta-blockers (e.g., metoprolol, bisoprolol, carvedilol) may be appropriate to improve outcomes as antihypertensive agents in patients with prior myocardial infarction (MI), active angina, atrial fibrillation with rapid ventricular response, or heart failure with reduced ejection fraction.[29] These patients are typically started on beta-blockers alone, with other antihypertensive therapies added as needed. If a beta-blocker is indicated, an agent should be selected that has concomitant vasodilatory effects to reduce potential for adverse metabolic impact.[114] Beta-blockers may mask symptoms of hypoglycemia and also have the potential to exacerbate hypoglycemic episodes, particularly when used concurrently with sulfonylureas.[29] [318] [319]

» Multiple drug therapy is often required in order to achieve antihypertensive targets.[29] If BP remains uncontrolled on monotherapy, add an agent from a different first-line class.[29] If BP remains uncontrolled despite combination therapy with first-line agents (i.e., three classes of antihypertensive medication including a

Ongoing

diuretic, plus lifestyle modifications), 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 an aldosterone antagonist (e.g., spironolactone, eplerenone).[29][114] Referral to a hypertension specialist may also be necessary.[29][114] The number of antihypertensive therapies required will vary between patients and is dependent on their clinical situation and tolerance.

» People with diabetes and hypertension should monitor their BP at home in addition to having it checked regularly in the clinic setting.[29]

» Serum creatinine/eGFR and potassium should be checked within 7-14 days of initiation of treatment with an aldosterone antagonist or diuretic, as well as following uptitration of dose and then at least annually.[29]

plus **lipid control**

Treatment recommended for ALL patients in selected patient group

Primary options

» atorvastatin: high intensity: 40-80 mg orally once daily

OR

» rosuvastatin: high intensity: 20-40 mg orally once daily

OR

» atorvastatin: high intensity: 40-80 mg orally once daily
-or-
» rosuvastatin: high intensity: 20-40 mg orally once daily
--AND--
» ezetimibe: 10 mg orally once daily

OR

» atorvastatin: high intensity: 40-80 mg orally once daily
-or-
» rosuvastatin: high intensity: 20-40 mg orally once daily
--AND--

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» evolocumab: 140 mg subcutaneously every 2 weeks; or 420 mg subcutaneously once monthly
-or-
» alirocumab: 75-150 mg subcutaneously every 2 weeks; or 300 mg subcutaneously once monthly

OR

» atorvastatin: high intensity: 40-80 mg orally once daily
-or-
» rosuvastatin: high intensity: 20-40 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
-or-
» alirocumab: 75-150 mg subcutaneously every 2 weeks; or 300 mg subcutaneously once monthly

Secondary options

» bempedoic acid: 180 mg orally once daily

OR

» inclisiran: 284 mg subcutaneously every 3 months for 2 doses, followed by 284 mg every 6 months

OR

» evolocumab: 140 mg subcutaneously every 2 weeks; or 420 mg subcutaneously once monthly

OR

» alirocumab: 75-150 mg subcutaneously every 2 weeks; or 300 mg subcutaneously once monthly

Tertiary options

» atorvastatin: high intensity: 40-80 mg orally once daily
-or-
» rosuvastatin: high intensity: 20-40 mg orally once daily

Ongoing

--AND--

» icosapent ethyl: 2 g orally twice daily

» For patients with diabetes and established CVD, guidelines recommend a low-density lipoprotein cholesterol (LDL-C) goal of <55 mg/dL (<1.42 mmol/L) and at least a 50% reduction from baseline.[6] [29] [113]

» Statins are the first-line agent for pharmacologic treatment of dyslipidemia and may have additional therapeutic effects independent of lipid-lowering action.[29] Moderate-intensity statin therapy lowers LDL-C level by 30% to 50%, while high-intensity statin therapy lowers it by ≥50%.[113] Low-dose statin therapy is generally not recommended in people with diabetes, but it is sometimes the only dose of statin that an individual can tolerate.[29]

» Guidelines recommend high-intensity statin therapy in adults of all ages with diabetes and atherosclerotic CVD.[29] [113] For people who do not tolerate the intended statin intensity, the maximum tolerated statin dose should be used.

» Addition of ezetimibe and/or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (e.g., evolocumab, alirocumab) is recommended if the LDL-C reduction goal is not achieved on maximum tolerated statin therapy.[29]

» For people intolerant of statin therapy, a PCSK9 inhibitor, bempedoic acid, or inclisiran should be considered as alternative cholesterol-lowering therapies.[29]

» A lipid profile should be checked: at initiation of statins or other lipid-lowering therapy; 4-12 weeks after initiation or a change in dose; and annually thereafter.[29]

» Icosapent ethyl can be considered in patients with CVD who are on a statin and have controlled LDL-C but elevated triglycerides (135 to 499 mg/dL [1.53 to 5.64 mmol/L).[29] It has been shown to modestly reduce CV events.[114] [115]

» If triglyceride levels exceed 500 mg/dL (5.65 mmol/L), fibrate therapy may be beneficial to reduce the risk of pancreatitis.[114] Fibrates are most often added to statin therapy, although the ADA notes that this approach is generally not recommended due to a lack of evidence of improvement in CVD outcomes.[29] Furthermore, caution is recommended as

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combination statin and fibrate therapy can increase the risk of myositis and rhabdomyolysis. To lower the risk, fenofibrate is recommended over gemfibrozil.[47]

plus **metformin**

Treatment recommended for ALL patients in selected patient group

Primary options

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

» Hemoglobin A1c (HbA1c) goal for most nonpregnant adult patients is <7% (<53 mmol/mol) to optimize clinical outcomes, but should be individualized.[29] Less stringent goals may be appropriate for very young children; older adults; people with a history of severe hypoglycemia; and those with limited life expectancies, advanced microvascular or macrovascular complications, or comorbid conditions.[29]

» US and European guidelines continue to recommend metformin, in combination with medical nutrition therapy and exercise, as the first-line treatment for glycemic control in patients with type 2 diabetes, regardless of the presence or absence of established atherosclerotic CVD.[29][221] [222] Evidence for the CV benefit of metformin is limited; however, it does not cause weight gain or hypoglycemia, and is widely available relative to other agents.[47]

plus **glucagon-like peptide-1 receptor agonist or tirzepatide and/or sodium-glucose cotransporter inhibitor**

Treatment recommended for ALL patients in selected patient group

Primary options

» empagliflozin: 10 mg orally once daily initially, 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-

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» sotagliflozin: 200 mg orally once daily initially, increase according to response, maximum 400 mg/day

--AND/OR--

» liraglutide: 0.6 mg subcutaneously once daily for 1 week, then increase to 1.2 mg once daily, adjust dose according to response, maximum 1.8 mg/day

-or-

» semaglutide: 0.25 mg subcutaneously once weekly for 4 weeks, then increase to 0.5 mg once weekly for 4 weeks, adjust dose according to response, maximum 1 mg/week

-or-

» dulaglutide: 0.75 mg subcutaneously once weekly, then increase to 1.5 mg once weekly, adjust dose according to response, maximum 4.5 mg/week

» For patients with established atherosclerotic CVD, significant CVD risk factors, established heart failure (with either preserved or reduced ejection fraction), or established CKD, addition of a glucagon-like peptide-1 (GLP-1) receptor agonist or a sodium-glucose cotransporter 2 (SGLT2) inhibitor is strongly recommended to reduce the risk of adverse CV or kidney events.[29][161] [225]

» The American Diabetes Association and European Association for the Study of Diabetes advise that for patients in whom atherosclerotic CVD predominates (e.g., previous MI, unstable angina, ischemic stroke, or indicators of high CV risk present), either a GLP-1 receptor agonist or an SGLT2 inhibitor can be used.[29] [221] While definitions of what constitutes high CV risk vary, most comprise ≥55 years of age with two or more additional risk factors such as obesity, hypertension, smoking, dyslipidemia, or albuminuria.[221] Guidelines published by the American College of Physicians and American Heart Association/American Stroke Association specify that GLP-1 receptor agonists should be prioritized in patients with an increased risk for stroke.[118] [222]

» For those patients in whom heart failure or CKD predominates, SGLT2 inhibitors should be favored.[29][221] [222]

» If HbA1c remains above target and the patient is taking either an SGLT2 inhibitor or a GLP-1 receptor agonist, then combined therapy with an SGLT2 inhibitor plus a GLP-1 receptor agonist may be considered, since this may provide

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additive reduction in the risk of adverse CV and kidney events.[29]

» Liraglutide, injectable semaglutide, and dulaglutide are the GLP-1 receptor agonists with the strongest evidence of CV risk reduction in patients with diabetes.[221][280] [281] [282] [283][284] In addition to their beneficial effects on CAD, GLP-1 receptor agonists are the only drug class that has been shown to convincingly reduce nonfatal stroke.[222] [224] [285][286] [287] [288] Unlike for SGLT2 inhibitors, the evidence for GLP-1 receptor agonists in reducing heart failure or improving CV outcomes in patients with heart failure has been inconsistent across trials.[290] Data from retrospective studies and meta-analyses have shown superiority of GLP-1 receptor agonists in comparison with other antidiabetic medications such as SGLT2 inhibitors and DPP-4 inhibitors in terms of peripheral arterial disease (PAD).[292] However, data from CV outcome trials regarding the impact of GLP-1 receptor agonists on PAD are scarce and further prospective studies are needed.

» Semaglutide is the only GLP-1 receptor agonist that is available in both oral and injectable formulations. However, conclusive evidence for the CV benefit of oral semaglutide has not yet been established in clinical studies.[281] For more information on oral semaglutide, see Emerging treatments .

» The most common adverse effects of GLP-1 receptor agonists are gastrointestinal, particularly nausea, vomiting, and diarrhea; these are frequent but tend to reduce over time.[293] Patients should be counseled about potential for ileus.[29] An association with pancreatitis and pancreatic cancer has been reported in clinical trials, but causality has not been established; nonetheless, GLP-1 receptor agonists should be used with caution in patients with a history of pancreatitis.[29] [293] After a review of available data, the FDA and European Medicines Agency (EMA) agreed that there was insufficient evidence to confirm an increased risk of pancreatic cancer with use of GLP-1-based therapies.[294] GLP-1 receptor agonists have also been associated with increased risk of gallbladder and biliary diseases including cholelithiasis and cholecystitis.[293]

» Hypoglycemia risk is increased when GLP-1 receptor agonists are used with sulfonylureas and insulin. Treatment deintensification of these agents or of diuretics, particularly in

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older and frail individuals, is recommended to avoid hypoglycemia and hypovolemia.[293] Diabetic ketoacidosis (DKA) has been reported in patients on a combination of a GLP-1 receptor agonists and insulin, when concomitant insulin was either rapidly reduced or discontinued; insulin reductions should therefore be undertaken in a cautious stepwise manner, with capillary blood glucose monitoring.[293]

» In rodent studies, GLP-1 receptor agonists were associated with medullary thyroid cancer, resulting in a black box warning for these agents in patients with a personal or family history of multiple endocrine neoplasia type 2 or medullary thyroid cancer; however, there is conflicting evidence as to whether this risk applies in humans.[293] [295] [296] [297] [298]

» The EMA is reviewing data on the risk of suicidal thoughts and thoughts of self-harm with GLP-1 receptor agonists, following reports of such occurrences in people using liraglutide and semaglutide.[299]

» There is also some concern that GLP1-receptor agonists, through their rapid glucose-lowering effects, may increase the risk of transient worsening of preexisting diabetic retinopathy.[300] [301] [302] Further studies are required to elucidate this relationship.

» Empagliflozin, dapagliflozin, and canagliflozin are the SGLT2 inhibitors with the strongest evidence of CV risk reduction in patients with diabetes.[120] [221][247] [248] [249] [250] [251] [252] [253] Ertugliflozin has shown benefit in reducing heart failure hospitalization, but not major adverse cardiac events, in patients with type 2 diabetes.[257] [258] The European Society of Cardiology (ESC) recommends dapagliflozin or empagliflozin for all patients with type 2 diabetes and CKD to reduce risk of heart failure hospitalization or CV death, regardless of whether they have a pre-existing heart failure diagnosis.[261]

» SGLT2 inhibitors also reduce the risk of serious hyperkalemia in people with type 2 diabetes at high CV risk without increasing the risk of hypokalemia, allowing the titration of guideline-directed medical therapy in patients with heart failure.[268]

» An initial decline in eGFR is commonly observed frequent after initiating an SGLT2 inhibitor but this decline is not associated with subsequent risk of CV or kidney events.[269]

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Thus, SGLT2 inhibitors should not be interrupted or discontinued in response to an initial eGFR decline.

» SGLT2 inhibitors are generally well-tolerated; however, some serious adverse reactions have been documented. Adverse effects include a higher rate of diabetic ketoacidosis, acute kidney injury, fracture, and/or amputation. The EMA also warns of the potential increased risk of toe amputation.[270] The FDA states the risk of amputation, while increased with canagliflozin, is lower than previously described, particularly when appropriately monitored.[271] 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.[272] [273] 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.

» Sotagliflozin is the first dual SGLT inhibitor.[274] It inhibits both renal SGLT2 (promoting significant excretion of glucose in the urine, in the same way as other already available SGLT2 selective inhibitors) and intestinal SGLT1 (delaying glucose absorption and therefore reducing postprandial glucose).[274] It has been approved in people with heart failure (both with and without diabetes) and in patients with type 2 diabetes who have CKD or high risk of/established CVD, to reduce the risk of hospitalization for heart failure.[29] It is not currently approved for glycemic management of type 1 or type 2 diabetes. One concern with expanded use of SGLT inhibition is the infrequent but serious risk of diabetic ketoacidosis (DKA), including the atypical presentation of euglycemic ketoacidosis.[29]

» Of note, the studies that led to the approved indication of sotagliflozin for heart failure excluded individuals with type 1 diabetes or a history of DKA.[275] [276] In clinical trials of sotagliflozin in people with type 1 diabetes, results showed improvements in HbA1c and body weight; however, its use was associated with an eightfold increase in DKA compared with placebo.[29] [277] The risks and benefits of SGLT inhibitors in people with type 1 diabetes continue to be evaluated, with consensus statements providing guidance on patient selection and precautions.[29] [278]

plus **lifestyle and behavioral therapy**

Ongoing

Treatment recommended for ALL patients in selected patient group

» Therapeutic lifestyle interventions such as medical nutrition therapy and increased physical activity have been shown in large clinical trials to improve glycemic, lipid, and blood pressure control, and to improve insulin sensitivity and markers of inflammation. They are also effective in achieving sustained weight loss and improvements in fitness.[47] [71] [173] [174] [175][176]

» There is no ideal amount of macronutrients that people with diabetes should consume, and studies suggest that such recommendations should be decided on an individual basis.[173] [180] The Mediterranean Diet, Dietary Approaches to Stop Hypertension (DASH), vegetarian, and vegan diets have all been demonstrated to be effective for people with diabetes.[173] [181] [182] [183] [184] European guidelines recommend a Mediterranean or plant-based diet with high unsaturated fat content for lowering CV risk in people with diabetes.[6] One meta-analysis found that red meat consumption was associated with higher risk of CVD and diabetes, while another reported moderate certainty evidence that a shift from animal-based to plant-based foods is beneficially associated with cardiometabolic health and all-cause mortality.[185] [186]

» Reducing overall carbohydrate intake has demonstrated some evidence for improving glycemia and one study found that among people with type 2 diabetes, greater adherence to low-carbohydrate diet patterns was associated with significantly lower all-cause mortality.[187] However, the optimal degree of carbohydrate restriction, and long-term effects on CVD, are still unclear.[29]

» Both World Health Organization (WHO) and European guidelines emphasize that carbohydrate quality, rather than quantity, is key.[132] [188] The concept of carbohydrate quality refers to the nature and composition of carbohydrates in a food or in the diet, including the proportion of sugars, how quickly polysaccharides are metabolized and release glucose into the body (i.e., digestibility), and the amount of dietary fiber. It is recommended that carbohydrate intake should come primarily from high-fiber foods, such as whole grains, vegetables, whole fruits, and pulses.[188] [132] Diets high in naturally occurring fiber have been shown to be protective against cardiometabolic

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disease and premature mortality. When choosing high-fiber foods, focus should be on minimally processed and largely intact whole grains, rather than products with finely milled whole grains that may also have added sugars, sodium, and saturated fats.[132] [188] Fiber-enriched foods and fiber supplements can be considered when sufficient intake cannot be obtained from diet alone.[132]

» There is some evidence to suggest that reducing intake of high glycemic index foods, and generally reducing glycemic load, could be beneficial for preventing CVD; however, WHO guidelines do not make any recommendations on this, noting that there was a lack of consistent benefit from diets with lower glycemic index or glycemic load in observational studies, and little to no improvement in cardiometabolic risk factors in randomized controlled trials associated with lower glycemic index and glycemic load.[188] [189]

» Replacing saturated fats and trans-fats with unsaturated fats and carbohydrates from foods containing naturally occurring dietary fiber (such as whole grains, vegetables, fruits, and pulses) reduces low-density lipoprotein cholesterol and also benefits CVD risk.[173] [190] [191] Saturated fat should comprise <10% of total energy intake and trans-fats <1%.[132] [191] Dietary fats should mainly come from plant-based foods high in mono- and poly-unsaturated fats, such as nuts, seeds, and nonhydrogenated nontropical vegetable oils (e.g., olive oil, rapeseed/canola oil, soybean oil, sunflower oil, linseed oil).[132]

» People with diabetes who have overweight or obesity should be supported with evidence-based nutritional support to achieve and maintain weight loss.[132] European guidelines recommend that a variety of weight-loss diets can be used equally effectively for weight management with type 2 diabetes, provided they can be followed and meet recommendations for protein, fat, micronutrient, and fiber intake. Neither extreme high-carbohydrate, nor very-low carbohydrate ketogenic diets are recommended, however.[132] One systematic umbrella review of published meta-analyses of studies comparing hypoenergetic diets for weight management in people with type 2 diabetes did not find evidence for any particular weight-loss diet over others (e.g., low-carbohydrate, high-protein, low-glycemic index, Mediterranean, high-

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monounsaturated fatty acid or vegetarian diets).[192]

» Intermittent fasting or time-restricted eating as strategies for weight and glucose management have gained popularity.[193] They have been shown to result in mild to moderate weight loss (3% to 8% loss from baseline) with no significant difference in weight loss when compared with continuous calorie restriction.[29] The ADA advises that due to its simplicity, intermittent fasting may lend itself as a useful strategy for people with diabetes who are looking for practical eating management tools.[29] People with diabetes who are on insulin and/or secretagogues should be medically monitored during the fasting period.[29]

» Evidence indicates that low- and very-low-energy diets (<3500 kJ/day [<840 kcal/day]), using total diet replacement formula diet products (replacing all meals) or partial liquid meal replacement products (replacing 1-2 meals per day) for the weight-loss phase, are most effective for weight loss and reduction of other cardiometabolic risk factors when compared with the results from self-administered food-based weight-loss diets.[132] [194] Low-energy nutritionally complete formula diets with a total diet replacement induction phase also appear to be the most effective dietary approach for achieving type 2 diabetes remission.[132] One population-based cohort study found that those who achieved remission from diabetes, even for a short time, had a much lower risk of CVD events, including MI and stroke, as well macrovascular and microvascular complications.[195]

» Physical activity: at least 150 minutes divided over ≥3 days per week of moderate- to vigorous-intensity aerobic physical activity with no more than 2 consecutive days without exercise.[6] [29] Younger and more physically fit individuals should aim for ≥75 minutes per week of vigorous-intensity exercise or interval training.[29] In the absence of contraindications, resistance training 2-3 times per week on nonconsecutive days is also recommended.[6] [29] The ADA recommends interrupting sedentary activity every 30 minutes with short bouts of physical activity.[29] Older adults may benefit from flexibility and balance exercise 2-3 times per week.[29]

» All patients with diabetes should be advised to quit smoking or not start.[29] Smoking counseling and other forms of smoking cessation

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therapy should be incorporated into routine diabetes care.[29] Varenicline combined with nicotine replacement therapy may be more effective than varenicline alone.[199] The ADA does not support e-cigarettes as an alternative to smoking or to facilitate smoking cessation.[29] Patients who quit smoking are prone to weight gain; therefore, it is important to have weight management strategies in place to maximize the CV benefits of smoking cessation.[47]

adjunct **weight management**

Treatment recommended for SOME patients in selected patient group

» Obesity pharmacotherapy should be considered as an adjunct to lifestyle interventions and behavioral counseling to improve cardiovascular (CV) risk factors in people with type 2 diabetes who have overweight or obesity.[6] [29] [178] For those with a body mass index (BMI) of ≥27 kg/m² (≥25 kg/m² for Asian-Americans) who are motivated to lose weight, an initial 3-month trial of medication should be undertaken. When weight loss is <5% after 3 months of use, the benefits of ongoing treatment need to be balanced in the context of the glycemic response, the availability of other potential treatment options, treatment tolerance, and overall treatment burden.[29]

» The American Diabetes Association (ADA) advises that agents with both glucose-lowering and weight loss effects should be used first-line; this includes glucagon-like peptide 1 (GLP-1) receptor agonists (e.g., semaglutide, liraglutide) and tirzepatide (a dual glucose-dependent insulinotropic polypeptide [GIP] and GLP-1 receptor agonist). Two phase 3 trials have demonstrated the potential for use of tirzepatide for obesity, with adverse effects similar to those seen with GLP-1 receptor agonists.[200] [201] If these medications are not tolerated or contraindicated, other obesity treatment options should be considered. Alternative pharmacologic options include phentermine, orlistat, phentermine/topiramate, or naltrexone/bupropion.[29]

» The European Society of Cardiology (ESC) recommends GLP-1 receptor agonists or sodium-glucose cotransporter-2 (SGLT2) inhibitors as the glucose-lowering agents of choice for weight loss in type 2 diabetes, in view of their proven CV benefits for these patients.[6] [203]

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» For those not reaching goals, the ADA recommends evaluating weight management therapies and intensifying treatment with additional approaches (e.g., metabolic surgery, additional pharmacologic agents, and structured lifestyle management programs).[29]

» As well as considering specific medications to treat obesity, healthcare professionals should carefully review the individual's concomitant medications and, whenever possible, minimize or provide alternatives for medications that promote weight gain. Examples of medications associated with weight gain include antipsychotics (e.g., clozapine, olanzapine, risperidone), some antidepressants (e.g., tricyclic antidepressants, some selective serotonin-reuptake inhibitors, monoamine oxidase inhibitors), glucocorticoids, injectable progestins, some anticonvulsants (e.g., gabapentin, pregabalin), beta-blockers, and possibly sedating antihistamines and anticholinergics.[29]

» A large number of studies have demonstrated that metabolic surgery achieves superior glycemic management and reduction of CV risk in people with type 2 diabetes and obesity compared with nonsurgical intervention.[9] [204] It has also been shown to reduce microvascular complications, cancer risk, and all-cause mortality in people with obesity and type 2 diabetes.[29][205] [206] [207] Of note, one meta-analysis reported a 50% reduction in macrovascular complications following bariatric surgery in patients with type 2 diabetes and extreme obesity (BMI ≥40 kg/m²).[205] Another meta-analysis found that metabolic surgery reduced the risk of any CV event by 44% and yielded a risk reduction of over 55% in overall mortality and 69% in CV mortality in patients with type 2 diabetes.[208]

» Vertical sleeve gastrectomy (VSG) and Roux-en-Y gastric bypass (RYGB) are the most commonly performed procedures. Both result in an anatomically smaller stomach pouch; in VSG, approximately 80% of the stomach is removed, leaving behind a long, thin sleeve-shaped pouch, whereas RYGB creates a much smaller stomach pouch (roughly the size of a walnut), which is then attached to the distal small intestine, thereby bypassing the duodenum and jejunum.[29]

» The ADA recommends metabolic surgery to treat type 2 diabetes in adults with BMI ≥30 kg/m² (≥27.5 kg/m² for Asian-Americans) who

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are otherwise good surgical candidates.[29] The ESC recommends that bariatric surgery be considered for all patients with type 2 diabetes and BMI ≥35 kg/m² who have not achieved sufficient weight loss through lifestyle interventions and medication.[6] Metabolic surgery is best done in a high-volume, specialized center to reduce the risk of perioperative and longer-term complications.[29]

» For more comprehensive information, see Obesity in adults .

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-
» rivaroxaban: 2.5 mg orally twice daily

OR

» aspirin: 325 mg orally as a loading dose, followed by 75-162 mg once daily
--AND--
» ticagrelor: 180 mg orally as a loading dose, followed by 90 mg twice daily for 12 months, then 60 mg twice daily if treatment is required beyond 12 months
-or-
» prasugrel: 60 mg orally as a loading dose, followed by 10 mg once daily
-or-
» clopidogrel: 300 mg orally as a loading dose, followed by 75 mg once daily

» Aspirin is recommended for secondary prevention in those with a history of atherosclerotic CVD. Clopidogrel (a P2Y12 inhibitor) is an alternative for patients with aspirin allergy or intolerance.[29]

» In people with stable coronary and/or peripheral artery disease and low bleeding risk, the ADA and ESC recommend combination treatment with aspirin and low-dose rivaroxaban

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(a direct oral anticoagulant) for secondary prevention.[29][334] Rivaroxaban has similar antiplatelet effects to aspirin, and may also improve endothelial function.[335]

» Following acute coronary syndrome (ACS), dual antiplatelet therapy with a combination of aspirin and a P2Y12 inhibitor (clopidogrel, ticagrelor, or prasugrel) is indicated.[336] Evidence supports use of either ticagrelor or clopidogrel if no PCI was performed and clopidogrel, ticagrelor, or prasugrel if PCI was performed.[29] [337] Generally, prasugrel and ticagrelor have better efficacy in patients with diabetes and are preferred to clopidogrel for patients who undergo PCI.[334] [337]

» Short-term dual antiplatelet therapy is also recommended after high-risk transient ischemic attack (TIA) and minor stroke.[338]

» Dual antiplatelet therapy may have benefit beyond 1 year in reducing long-term risk of recurrent atherosclerotic events.[334] However, recommendations regarding length of treatment are rapidly evolving and should be determined by an interprofessional team approach that includes a cardiologist following ACS or a neurologist following TIA/stroke.[29] The benefits versus risk of bleeding and thrombosis should be evaluated based on the coronary anatomy and extent of CAD, PCI complexity, bleeding risk, age, and patient's medical comorbidities such as anemia or renal failure.[339]

» To reduce risk of gastrointestinal bleeding, proton-pump inhibitors are recommended for all patients on a combination of antiplatelet or anticoagulant therapy, and should be considered for those on a single agent depending on their individual bleeding risk, according to the ESC.[6]

with heart failure — **adjunct** — **guideline-directed management and therapy**

Treatment recommended for SOME patients in selected patient group

» Patients with diabetes and heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF) should receive heart failure (HF) therapy as per current HF guidelines.[29] [161] [260]

» Presence of HF in patients with type 2 diabetes influences choice of antihyperglycemic agent. Sodium-glucose cotransporter-2 (SGLT2) inhibitors are recommended in all patients with HF and type 2 diabetes mellitus, as they

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reduce risk of HF-related hospitalization and mortality. Thiazolidinediones (e.g., pioglitazone) and saxagliptin (a dipeptidyl peptidase-4 [DPP-4] inhibitor) have been associated with an increased risk of HF hospitalizations and are not recommended in patients with or at risk of HF. Metformin, insulin, and sitagliptin and linagliptin (DPP-4 inhibitors) are considered neutral in terms of their effect on HF outcomes.[6] In patients with obesity and HFpEF, semaglutide (a GLP-1 receptor agonist) has been shown to reduce HF-related symptoms, improve exercise function, and result in greater weight loss compared with placebo.[365] A GLP-1 receptor agonist may be preferred over other antihyperglycemic agents in those with HFpEF and obesity.

» Screening for HF in patients with diabetes is important for starting therapy early and optimizing prognosis. The ADA recommends annual screening of asymptomatic adults with diabetes for HF.[29]

» See Heart failure with reduced ejection fraction and Heart failure with preserved ejection fraction .

with chronic kidney disease — **adjunct** — **management of cardiovascular risk and kidney failure risk**

Treatment recommended for SOME patients in selected patient group

» Reducing the risk of both cardiovascular (CV) and kidney adverse events is key in these patients. Standard lifestyle and risk factor modifications (e.g., BP control, lipid control, glycemic control, weight control) are important. Additionally, specific pharmacologic interventions are recommended.

» Sodium-glucose cotransporter-2 (SGLT2) inhibitors, in addition to reducing hyperglycemia, have renal benefits through independent effects on renal tubular glucose reabsorption, weight, BP, intraglomerular pressures, albuminuria, and slowed glomerular filtration rate (GFR) loss, and are recommended in patients with type 2 diabetes, established atherosclerotic CVD, and chronic kidney disease (CKD) to reduce the risk of both CV and kidney adverse events.[6] [29]

» An ACE inhibitor or angiotensin-II receptor antagonist is recommended in patients with type 2 diabetes, established atherosclerotic CVD, and CKD, even if they are normotensive, to reduce the risk of cardiovascular events.[6] [29][320]

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» Finerenone, a nonsteroidal mineralocorticoid receptor antagonist, has been shown in randomized trials to lower risks of CV events and CKD progression in patients with type 2 diabetes, CKD, and albuminuria.[367] [368] In one trial, 45.3% of participants also had a history of CVD.[368] For people with type 2 diabetes and CKD with albuminuria treated with maximum tolerated doses of ACE inhibitors or angiotensin-II receptor antagonists, who are at an increased risk of cardiovascular events or CKD progression, the ADA and ESC recommend addition of finerenone.[6] [29]

» If additional glycemic control is needed, a glucagon-like peptide-1 (GLP-1) receptor agonist is recommended, as they improve renal outcomes independent of glucose lowering effect, and have benefits in CV risk reduction and weight control.[6] [29]

» Low-dose aspirin is recommended in patients with diabetes, CKD, and atherosclerotic CVD to protect against cardiovascular events.[6]

» In patients with diabetes, CKD, and stable moderate or severe CAD, either an intensive medical strategy or an initial invasive strategy may be considered.[6]

» Referral to a specialist should be considered.

» See Diabetic kidney disease .

Emerging

Efpeglenatide

Efpeglenatide is an investigational exendin-based GLP-1 receptor agonist in phase 3 clinical trials for type 2 diabetes.[371] It is administered as a subcutaneous injection. Results from the AMPLITUDE-O study showed that efpeglenatide reduced the risk of CV events versus placebo in patients with type 2 diabetes and either a history of CV disease or current kidney disease plus ≥1 other CV risk factor.[372] Data suggest that this benefit may be dose-dependent.[373] The most common adverse events with efpeglenatide treatment were gastrointestinal.[372] An exploratory analysis of AMPLITUDE-O found that the beneficial effect of efpeglenatide on CV outcomes was independent of baseline SGLT2 inhibitor use.[374] Moreover, a post-hoc analysis of earlier phase 2 data showed that efpeglenatide may be able to prevent patients with prediabetes from developing type 2 diabetes.[375] Efpeglenatide has yet to be submitted for regulatory approval.

Oral semaglutide

Both the oral and subcutaneous formulations of the GLP-1 receptor agonist semaglutide are approved for the treatment of type 2 diabetes. While the CV benefit of subcutaneous semaglutide has been well established in randomized controlled trials (RCTs), oral semaglutide failed to significantly improve major adverse CV events compared with placebo, and therefore only demonstrated noninferiority.[281] Further evidence is required to recommend the oral formulation of semaglutide for CV risk reduction in patients with type 2 diabetes at high risk for or with established atherosclerotic cardiovascular disease (CVD). A long-term CV outcomes trial comparing oral semaglutide to placebo in people with type 2 diabetes and a history of heart disease is ongoing (SOUL; NCT03914326).

Retatrutide

Retatrutide is an investigational novel single peptide with agonist activity at the glucose-dependent insulinotropic polypeptide (GIP), GLP-1, and glucagon (GCGR) receptors. It is administered as a subcutaneous injection. Retatrutide demonstrated clinically meaningful glucose- and weight-lowering efficacy in people with type 2 diabetes in a 12-week phase 1 study.[376] One phase 2 RCT aimed to assess the safety and efficacy of retatrutide versus dulaglutide and placebo in individuals with type 2 diabetes.[377] The primary outcome of this study was mean change in hemoglobin A1c (HbA1c) at 24 weeks, while a key secondary outcome included mean change in body weight at 36 weeks. Retatrutide resulted in significant reductions in glycemic control and body weight compared to dulaglutide and placebo. Furthermore, there were improvements in lipid profile and blood pressure. The majority of adverse effects were gastrointestinal and mild-to-moderate in nature with no reported deaths.[377] A phase 3 study is currently underway.[378]

Orforglipron

Orforglipron is an investigational oral nonpeptide GLP-1 receptor agonist that is in development for type 2 diabetes and obesity. One phase 2 study evaluated orforglipron at varying doses for the treatment of type 2 diabetes compared to placebo and dulaglutide.[379] Orforglipron achieved meaningful reductions in HbA1c and body weight at 26 weeks with an adverse events profile consistent with other GLP-1 receptor agonists. Mean reduction in HbA1c (from a mean baseline of 8.1%) with orforglipron at 26 weeks was up to 2.1%, compared to 0.4% with placebo and 1.1% with dulaglutide. Orforglipron also demonstrated weight reductions up to 10.1 kg in adults with type 2 diabetes (from a mean baseline of 100.3 kg) compared to 2.2 kg with placebo and 3.9 kg for dulaglutide. With orforglipron, 65% to 96% of participants achieved an HbA1c of less than 7.0% at 26 weeks versus 64% in the dulaglutide group and 24% in the placebo group. Similar to other GLP-1 receptor agonists, orforglipron produced improvements in the blood pressure and levels of circulating lipids.[379] Phase 3 trials are in progress.[380] [381] [382] [383] [384]

Cagrilintide/semaglutide

A subcutaneous combination drug formulation containing semaglutide (a GLP-1 receptor agonist) and cagrilintide (an investigational long-acting amylin analog). In one network meta-analysis, cagrilintide/semaglutide was found to be the most effective GLP-1 receptor agonist for lowering body weight in adults

with type 2 diabetes (mean loss 14.03 kg).[385] The efficacy and safety of cagrilintide/semaglutide was assessed in a 32-week, multicenter, double-blind, phase 2 trial.[386] Adults with type 2 diabetes and a body mass index (BMI) ≥27 kg/m² on metformin, with or without an SGLT2 inhibitor, were randomly assigned to cagrilintide/semaglutide , semaglutide alone, or cagrilintide alone. The primary endpoint was change from baseline in HbA1c; secondary endpoints were bodyweight, fasting plasma glucose, continuous glucose monitoring (CGM) parameters, and safety. Treatment with cagrilintide/semaglutide resulted in clinically relevant improvements in glycemic control (including CGM parameters). The mean change in HbA1c with cagrilintide/semaglutide was greater versus cagrilintide alone, but not versus semaglutide alone. Treatment with cagrilintide/semaglutide resulted in significantly greater weight loss versus semaglutide alone and cagrilintide alone and was well tolerated. Adverse events were reported by 68% of participants in the cagrilintide/semaglutide group, 71% in the semaglutide alone group, and 80% in the cagrilintide alone group. Mild or moderate gastrointestinal adverse events were most common; no fatal adverse events were reported.[386] Longer and larger phase 3 studies are needed.

Colchicine

Colchicine is an anti-inflammatory drug that has been in use for many decades for indications such as gout. More recently, it has been approved for risk reduction in atherosclerotic CVD. In one randomized, double-blinded, placebo-controlled trial of patients with type 2 diabetes and recent MI (COLCOT; Colchicine Cardiovascular Outcomes Trial), colchicine led to a large reduction in CV events compared with placebo.[387] The COLCOT-T2D study is currently recruiting 10,000 patients in Canada with type 2 diabetes and no history of CVD; it will evaluate whether low-dose colchicine in addition to standard treatment is effective in reducing the risk of CV events in this population, with the aim of establishing whether colchicine could have a role in primary prevention of CVD in patients with type 2 diabetes.[388]

Mazdutide

An investigational synthetic peptide analog of mammalian oxyntomodulin which acts as a dual GLP-1 and glucagon receptor (GCGR) agonist. It is administered as a subcutaneous injection. Mazdutide has shown promise for the treatment of type 2 diabetes and obesity in phase 1 trials.[389] [390] In a phase 2 trial in Chinese patients with diabetes, treatment with mazdutide for 20 weeks showed significant improvement in glycemic control and weight loss compared with placebo. The drug appears to be safe with a similar adverse effect profile to GLP-1 receptor agonists (with gastrointestinal adverse effects most frequently reported).[391] Phase 3 trials are in progress.

Bexagliflozin

Bexagliflozin, an oral SGLT2 inhibitor, is approved in the US as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. It is not available in Europe. Phase 3 clinical trials have studied bexagliflozin as monotherapy and in combination with metformin in adults with type 2 diabetes; it has also been studied in phase 3 trials in adults with type 2 diabetes and moderate renal impairment, and in adults with type 2 diabetes and established or increased risk of CVD.[392] [393] [394] [395] [396] [397] [398] [399] Treatment with bexagliflozin reduced HbA1c compared to placebo and efficacy was noninferior to glimepiride and sitagliptin, with reduction in HbA1c being shown across subgroups of age, sex, race, and geographic region. It also showed clinically meaningful improvement in weight, eGFR, and systolic blood pressure. A head-to-head double-blind RCT demonstrated that bexagliflozin was noninferior to dapagliflozin as an adjunct to metformin in Chinese patients with type 2 diabetes mellitus, where the primary endpoint was reduction in HbA1c.[400] Secondary efficacy endpoint analyses showed results in both groups consistent with previous clinical trials, including a reduction in body weight and systolic blood pressure.

Primary prevention

Primary prevention of cardiovascular disease (CVD) in people with diabetes

Lifestyle modifications

- A major component of primary prevention for CVD in people with diabetes is lifestyle modification.[106] Most of the major CVD risk factors can be altered by aggressive lifestyle changes.[29] Lifestyle

modification focusing on weight loss (if indicated); application of a Mediterranean or Dietary Approaches to Stop Hypertension (DASH) eating pattern; reduction of saturated fat and trans fat; increase of dietary omega-3 fatty acids, viscous fiber, and plant stanol/sterol intake; smoking cessation or noninitiation; and increased physical activity should be recommended to improve the lipid profile and reduce the risk of developing CVD in people with diabetes.[29]
- Evidence suggests that patients with type 2 diabetes who achieve remission of their diabetes at any point in time have a substantially lower incidence of CVD compared with those who do not achieve remission. The greater the duration of remission, the greater the reduction in CVD risk.[107]
- Alcohol consumption should be limited, with one study suggesting that alcohol abstinence may prevent new-onset atrial fibrillation in patients with type 2 diabetes.[47] [108]

Aspirin

- The routine use of aspirin for primary prevention of diabetic CVD is not generally recommended. However, in patients with diabetes ages ≥50 years who have at least one additional risk factor (e.g., hypertension, hyperlipidemia, family history of premature coronary artery disease, current or past smoker, or chronic kidney disease [CKD]/albuminuria) with no indicators of high bleeding risk (e.g., older age, anemia, renal disease, or prior significant bleeding episodes), the American Diabetes Association (ADA) advises that aspirin therapy may be considered as a primary prevention strategy following discussion of the benefits versus increased risk of bleeding.[29]
- Coronary calcium score can be used to assess CVD risk and therefore help determine an indication for aspirin therapy.[29] [76] [109]
- For patients ages >70 years the risk of bleeding increases, and ADA guidelines state that aspirin is generally not recommended for primary prevention in this population.[29] [110]
- The US Preventive Services Task Force recommends against the use of aspirin for the primary prevention of CVD in adults ages 60 years or older.[111]

Blood pressure (BP) control

- It is well accepted that BP control reduces cardiovascular (CV) risk. There is a lack of high-quality evidence regarding optimal treatment of hypertension in people with diabetes.[60] However, guidelines recommend a BP treatment goal of <130/80 mmHg for all patients with diabetes, providing this can be safely attained.[29] [60] [61]
- For more information on BP control, see Management approach .

Lipid management

- Low-density lipoprotein cholesterol (LDL-C) is the most extensively studied modifiable risk factor associated with atherosclerotic CVD. There is strong evidence that LDL-C is a causal factor in the pathophysiology of CVD, and CVD risk reduction is proportional to the absolute and relative LDL-C reduction achieved.[112]
- Statins are the first-line medication for LDL-C lowering and cardioprotection.[29] Moderate-intensity statin therapy is defined as therapy that generally lowers LDL-C level by 30% to 50%, while high-intensity statin therapy lowers it by ≥50%.[113] Low-dose statin therapy is generally not recommended in people with diabetes, but it is sometimes the only dose of statin that an individual can tolerate; for individuals who do not tolerate the intended intensity of statin, the maximum tolerated statin dose should be used.[29]
- A lipid profile should be checked: at time of diagnosis of diabetes; at initiation of statins or other lipid-lowering therapy; 4-12 weeks after initiation or a change in dose; and annually thereafter.[29]
- For certain patients at intermediate or borderline risk, coronary artery calcium (CAC) measurement may be useful to support shared decision-making for statin therapy.[76] A CAC score ≥100 Agatston units or in the ≥75th age/sex/race percentile can reclassify CV as being increased.[76]
- For primary prevention of CVD in adults with diabetes without established CVD, ADA guidelines recommend:[29]
    - Consideration of statin therapy in patients ages 20 to 39 years with additional atherosclerotic CVD risk factors (being mindful that statins are contraindicated in pregnancy).
    - Moderate-intensity statin therapy in people ages 40 to 75 years.

- High-intensity statin therapy in people ages 40 to 75 years at higher CV risk, including those with one or more CVD risk factors, to reduce LDL-C by ≥50% of baseline and to target an LDL-C goal of <70 mg/dL (<1.81 mmol/L).
- Consider addition of ezetimibe or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor to maximum tolerated statin therapy in people ages 40 to 75 years at higher CV risk, especially those with multiple CVD risk factors and LDL-C ≥70 mg/dL (≥1.81 mmol/L). [PCSK9 inhibitors and ezetimibe for the reduction of cardiovascular events] (https://www.bmj.com/content/377/bmj-2021-069066/infographic)
- For adults ages >75 years already established on statin therapy, it is reasonable to continue statin treatment. It may be reasonable to initiate moderate-intensity statin therapy in this age group following discussion of the potential benefits and risks.
- In people intolerant of statin therapy, treatment with bempedoic acid is recommended as an alternative cholesterol-lowering therapy.

- European guidelines recommended a more aggressive target for LDL-C of <55 mg/dL (<1.42 mmol/L) in very high-risk patients (again, aiming for at least a 50% reduction in LDL-C).[6] This includes patients with diabetes with severe target end-organ damage or a 10-year CVD risk of 20% or more using the SCORE2-Diabetes risk calculator.[6]
- Role of other lipid-lowering pharmacotherapies

- Icosapent ethyl can be considered in patients with additional CV risk factors who are on a statin and have controlled LDL-C but elevated triglycerides (135 to 499 mg/dL [1.53 to 5.64 mmol/L]).[29] It has been shown to modestly reduce CV events.[114] [115]
- Fibrates are effective for lowering very high triglyceride levels (i.e., >500 mg/dL [>5.65 mmol/L]) to reduce the risk of pancreatitis.[114] They are most often added to statin therapy, although the ADA notes that this approach is generally not recommended due to a lack of evidence of improvement in atherosclerotic CVD outcomes.[29] Furthermore, caution is recommended as combination statin and fibrate therapy can increase the risk of myositis and rhabdomyolysis. To lower the risk, fenofibrate is recommended over gemfibrozil.[47]
- Supplementation with omega-3 fatty acids has not been found to reduce the rate of CV events in patients with diabetes at high risk for these events.[116]

- For more information about these lipid-lowering treatments, see Management approach .

Sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists

- Beyond their role in the treatment of established CVD, SGLT2 inhibitors and GLP-1 receptor agonists may also have a role in primary prevention.
- One retrospective study of patients with type 2 diabetes and no existing CVD found treatment with these agents to be beneficial in preventing major adverse cardiac and cerebrovascular events and heart failure.[117]
- Based on evidence from randomized controlled trials (RCTs), the American Heart Association and American Stroke Association advise that for patients with diabetes who have high CV risk and HbA1c ≥7% (53 mmol/mol), treatment with a GLP-1 receptor agonist is effective for reducing the risk of stroke.[118] They note that RCT evidence to support a similar role for SGLT2 inhibitors in primary prevention is lacking, however.[118]
- Canagliflozin was shown to reduce a composite of CV death, nonfatal myocardial infarction (MI), or nonfatal stroke in patients with type 2 diabetes and elevated CV risk; however, it did not reduce overall mortality, and led to an increase in lower extremity amputation in certain patient subgroups.[119]
- Dapagliflozin has failed to show reduction in CV outcomes in patients with diabetes without overt CVD.[120] [121]
- One meta-analysis found that SGLT2 inhibitors significantly reduced atherosclerotic major adverse cardiac events in patients with type 2 diabetes and coexisting CKD without established CVD; however, this benefit was not observed in patients without CKD.[122]
- Further large-scale randomized clinical trials investigating SGLT2 inhibitors for the primary prevention of diabetic CVD are warranted.[117]

Primary prevention of CVD in people with prediabetes

- People with prediabetes are at increased risk of major adverse CV events, and often have other CV risk factors, including hypertension and dyslipidemia; it is therefore important to screen for and address CV risk factors in this population as well as in those with established type 2 diabetes.[29] [123]
- Of note, statin therapy may increase the risk of developing type 2 diabetes in those already at high risk.[124] For these patients, the ADA recommends regular monitoring of glucose status alongside the reinforcement of diabetes prevention approaches.[29]
- In people with a history of stroke, and insulin resistance and prediabetes, the ADA recommends that clinicians consider offering pioglitazone (a thiazolidinedione medication) to lower the risk of future stroke and myocardial infarction, noting that the benefit of lower CV risk with pioglitazone must be balanced against the associated increased risks of weight gain, edema, and fracture.[29] Pioglitazone has also been linked to an increased risk of bladder cancer, although this association is controversial, with studies yielding conflicting results; nonetheless, it should be avoided in patients with active bladder cancer and used with caution in those with a history of the disease.[125] [126] [127] [128] [129]

Primary prevention of type 2 diabetes

Primordial prevention

- Prevention of cardiometabolic disease begins at the primordial stage and involves targeting potential behaviors that put the population, especially youth, at risk for insulin resistance and adiposity. Such population-level interventions include community-based education around healthy eating patterns, improving nutrition during pregnancy to optimize fetal development, and regulating the marketing and taxation of sugar-sweetened beverages.[130] [131]

Lifestyle changes

- Progression from prediabetes to overt type 2 diabetes can itself be prevented with lifestyle changes, including increased physical activity, healthy diet, and weight loss/prevention of weight gain. People with overweight or obesity are at increased risk of type 2 diabetes, and should aim for at least 5% weight loss by adopting an intensive lifestyle intervention involving an energy-restricted diet and increased physical activity.[132]
- Other dietary patterns and food-based approaches that do not primarily target weight loss have also been associated with reduced type 2 diabetes risk. These include Mediterranean, Nordic, and vegetarian dietary patterns, or diets high in vegetables, fruit, wholegrains and fiber, or low in glycemic index and load.[132]
- Diets rich in magnesium (e.g., wholegrains, nuts, and green leafy vegetables) have also been shown to reduce risk of type 2 diabetes and stroke in a dose-dependent manner.[133] One large US cohort study found that total ultra-processed food consumption was associated with higher risk of developing type 2 diabetes.[134]

Pharmacologic preventive treatment

- People at high risk of type 2 diabetes may also benefit from pharmacotherapeutic preventive treatment. However, no pharmacologic agent has been approved for prevention of type 2 diabetes, and it is not clear whether prevention of overt diabetes translates into eventual reduced CV risk. The risk versus benefit of each medication in support of person-centered goals must be weighed, in addition to cost and burden of administration.[29]
- Metformin, alpha-glucosidase inhibitors, GLP-1 receptor agonists, thiazolidinediones, and insulin have been shown to lower the incidence of diabetes in specific populations.[29]
- Dapagliflozin (an SGLT2 inhibitor) reduced the incidence of new-onset type 2 diabetes in patients with CKD or heart failure compared with placebo, although no improvement in glycemic control was observed.[135]
- In people with impaired glucose tolerance and CVD or risk factors, nateglinide (a meglitinide medication) for 5 years did not reduce the incidence of diabetes or composite CV outcomes.[136]

Treatment of hypertension

- One study investigating the effect of BP lowering on the risk of new-onset type 2 diabetes found that reducing systolic BP by 5 mmHg decreased the risk of type 2 diabetes by 11%.[137] Antihypertensive treatment with ACE inhibitors and angiotensin-II receptor agonists led to more favorable outcomes than treatment with beta-blockers, thiazide diuretics, or calcium-channel blockers.[137]

- Another study found that valsartan plus lifestyle modification produced a reduction in the incidence of diabetes but did not reduce the rate of CV events.[138]

Secondary prevention

Risk factors for atherosclerotic cardiovascular disease (CVD) should be elicited and appropriate treatment given. See Management approach .

A large international trial showed that 29% of patients studied could attain all 5 common secondary prevention parameters (smoking cessation, lipid reduction, blood pressure control, aspirin use, and ACE or angiotensin-II receptor antagonist use) with intensive risk factor modification, while 71% of patients studied could achieve 4 out of the 5 parameters.[419] However, in a large US cohort study of patients with diabetes and known CVD, only 6.9% received guideline-recommended medical therapies for cardiovascular risk (CV) reduction.[172] Although diet and exercise are commonly recommended, one study found no significant reduction in CV events in patients with type 2 diabetes and overweight or obesity who underwent an intensive diet and exercise program when compared with a control group.[420]

Sodium-glucose cotransporter-2 (SGLT2) and glucagon-like peptide-1 (GLP-1) receptor agonist therapy can play a significant role in reducing future risk in individuals with established atherosclerotic CVD, heart failure, or chronic kidney disease, and use of one these agents should be strongly considered, if not contraindicated, for the secondary prevention of macrovascular complications.[221][421] The American Heart Association and American Stroke Association advise that in patients with diabetes who have established CVD and hemoglobin A1c ≥7%, treatment with a GLP-1 receptor agonist is effective for reducing the risk of stroke.[118] Despite the overwhelming evidence of CVD benefit from large CV outcome trials, the number of patients receiving these drugs remains low. Several reasons have been proposed for this: clinical inertia, a lack of knowledge in healthcare practitioners about the results of CV outcome trials, uncertainty in prescribing these agents, and concerns about potential side effects.[422] An analysis of patients in the Swedish National Diabetes Register estimated that giving semaglutide to people with a very high CVD risk who have already had a CV event may prevent around 803 CV events each year.[423]

Patient discussions

Medical nutrition therapy

- There is no ideal amount of macronutrients that people with diabetes should consume, and studies suggest that such recommendations should be decided on an individual basis.[173] [180] The Mediterranean Diet, Dietary Approaches to Stop Hypertension (DASH), vegetarian, and vegan diets have all demonstrated some efficacy in people with diabetes.[173] [181] [182] [183] [184] Disclosing and communicating CV risk levels to at-risk patients has been shown to increase self-reported dietary modification.[418]
- Reducing overall carbohydrate intake for individuals with diabetes has demonstrated evidence for improving glycemia.[29] However, the optimal degree of carbohydrate restriction, and long-term effects on cardiovascular disease (CVD), are still unclear.[29] Both World Health Organization (WHO) and European guidelines emphasize that carbohydrate quality, rather than quantity, is key, with the primary marker of quality being the amount of dietary fiber consumed.[188]
- Replacing saturated fats with unsaturated fats and carbohydrates from foods containing naturally occurring dietary fiber (such as whole grains, vegetables, fruits and pulses) reduces low-density lipoprotein (LDL)-cholesterol and also benefits CVD risk.[173] [190] [191] Saturated fat should comprise <10% of total energy intake and trans-fats <1%.[132] [191] Dietary fats should mainly come from plant-based foods high in mono- and poly-unsaturated fats, such as nuts, seeds, and nonhydrogenated nontropical vegetable oils (e.g., olive oil, rapeseed/canola oil, soybean oil, sunflower oil, linseed oil).[132]
- Evidence indicates that low- and very low- (<3500 kJ/day [<840 kcal/day]) energy diets, using total diet replacement formula diet products (replacing all meals) or partial liquid meal replacement products (replacing 1 to 2 meals per day) for the weight-loss phase, are most effective for weight loss and reduction of other cardiometabolic risk factors when compared with the results from self-administered food-based weight-loss diets.[132] [194] Low-energy nutritionally complete formula diets with a total diet replacement induction phase also appear to be the most effective dietary

approach for achieving type 2 diabetes remission.[132] One population-based cohort study found that those who achieved remission from diabetes, even for a short time, had a much lower risk of CVD events, including myocardial infarction and stroke, as well macrovascular and microvascular complications.[195]

Physical activity

- The American Diabetes Association (ADA) recommends assessment of the following prior to starting an exercise program; age; physical condition; blood pressure; and presence or absence of autonomic neuropathy or peripheral neuropathy, balance impairment, history of foot ulcers or Charcot foot, or untreated proliferative retinopathy.[29]
- Adults with diabetes should engage in at least 150 minutes per week of moderate- to vigorous-intensity aerobic physical activity.[6] [29] The physical activity should be spread over at least 3 days per week, with no more than 2 consecutive days without exercise.[29]
- Younger and more physically fit individuals should aim for ≥75 minutes per week of vigorous-intensity exercise or interval training.[29]
- In the absence of contraindications, 20 minutes of resistance training 2 to 3 times per week on nonconsecutive days is also recommended.[6] [29]
- Sedentary periods should be interrupted by activity every 30 minutes.[29]
- Older adults may benefit from balance and flexibility training 2 to 3 times per week.[29]
- Regular motivational feedback is important to maintain patient adherence to the exercise program.[198]

Dyslipidemia

- Lifestyle modification focused on reduced saturated fat intake, weight loss, and increased physical activity has been shown to improve lipid control in patients with diabetes.[29]

Smoking cessation

- All patients with diabetes should be advised not to smoke or to quit smoking.[29] Smoking counseling and other forms of smoking cessation therapy should be incorporated into routine diabetes care.[29] Varenicline combined with nicotine replacement therapy may be more effective than varenicline alone.[199] The ADA does not support e-cigarettes as an alternative to smoking or to facilitate smoking cessation.[29]
- Patients who quit smoking are often prone to weight gain; it is therefore important to have weight management strategies in place to maximize the CV benefits of smoking cessation.[47]

Hypertension

- People with diabetes and hypertension should monitor their blood pressure at home in addition to having it checked regularly in the clinic setting, both to ensure accuracy of readings and to encourage adherence to treatment regimens.[29]

Heterogeneity between different racial and ethnic groups requires culturally sensitive, peer-led community and healthcare professional education.[95] Key considerations in providing culturally sensitive care are the patient's preferred language and religion, dietary restrictions, sex identity, cultural norms and practices, health literacy, and cultural differences in communication style.[95]

Resources:

[AHA/ACC: ASCVD risk calculator] (http://static.heart.org/riskcalc/app/index.html#!/baseline-risk)

[NIDDK: diabetes, heart disease, and stroke] (https://www.niddk.nih.gov/health-information/diabetes/overview/preventing-problems/heart-disease-stroke?dkrd=hispt0020)

[HHS: dietary guidelines for Americans, 2020-2025] (https://www.dietaryguidelines.gov/resources/2020-2025-dietary-guidelines-online-materials)

Monitoring

Monitoring

Patients with diabetes benefit from monitoring at least every 3 months if their diabetes is not well controlled and every 6 to 12 months otherwise.[29] Blood pressure, weight, and activity level should be monitored at each visit and healthy lifestyle modifications encouraged.[29]

Joint American Heart Association and American College of Cardiology guidelines recommend that all patients with signs or symptoms suggestive of peripheral arterial disease (PAD) (e.g., calf claudication; decreased or absent pedal pulses; nonhealing wounds) should have an ankle-brachial index (ABI) measured, with or without ankle pulse volume recordings and/or Doppler waveforms.[28] Screening with resting ABI is also considered reasonable in patients with any of the following characteristics: age ≥65 years or older; age 50-64 years with risk factors for atherosclerosis (e.g., diabetes, smoking history, dyslipidemia, hypertension), chronic kidney disease, or family history of PAD; age <50 years with diabetes and one additional risk factor for atherosclerosis; patients with known atherosclerotic disease in another vascular bed (e.g., coronary, carotid, subclavian, renal, mesenteric artery stenosis, or abdominal aortic aneurysm).[28] The American Diabetes Association recommends screening for PAD using ABI in asymptomatic patients with diabetes who have any of the following characteristics: age ≥50 years; diabetes with duration ≥10 years; comorbid microvascular disease; clinical evidence of foot complications; or any end-organ damage from diabetes.[29] See Diabetes-related foot disease .

In patients on lipid-lowering therapy, a lipid profile should be checked: at initiation of statins or other lipid-lowering therapy, 4-12 weeks after initiation or a change in dose, and annually thereafter.[29]

Serum creatinine/estimated glomerular filtration rate and potassium should be checked within 7-14 days of initiation of treatment with an ACE inhibitor, angiotensin-II receptor antagonist, aldosterone antagonist, or diuretic, as well as following uptitration of dose and then at least annually.[29]

Screening for heart failure in patients with diabetes is important for starting therapy early and optimizing prognosis. The American Diabetes Association recommends annual screening of asymptomatic adults with diabetes for heart failure.[29] Opportunistic screening for atrial fibrillation is recommended by the European Society of Cardiology in all patients with diabetes ages under 65 years; systematic screening should be considered for those ages 75 years and over or at high stroke risk.[6]

FOLLOW UP

Complications

Complications	Timeframe	Likelihood
atrial fibrillation (AF) and other dysrhythmias	**variable**	**medium**
Autonomic dysfunction occurs in 40% to 50% of patients with diabetes.[19] This may result in sympathovagal imbalance, which lowers the threshold for life-threatening arrhythmias.[19] Patients who have diabetes and AF have a substantially increased risk of all-cause mortality, cardiovascular (CV) mortality, stroke, kidney disease, and heart failure.[6] Patients with arrhythmias should be monitored and referred for appropriate treatment. Opportunistic screening for AF, by pulse taking or ECG, is recommended in European guidelines for all patients with diabetes ages under 65 years; systematic screening should be considered for those ages 75 years and over or at high stroke risk.[6] When indicated by risk stratification (e.g., CHA_2DS_2-VASc score), long-term oral anticoagulant therapy is used in patients with AF for reduction of ischemic stroke and other ischemic events. A bleeding risk score should also be used to identify and address potential bleeding risk factors, for example, concomitant use of antiplatelet agents.[6]		
ischemic toe/foot, gangrene, or amputation	**variable**	**medium**
Joint American Heart Association and American College of Cardiology guidelines recommend that all patients with history or physical exam findings suggestive of peripheral arterial disease (PAD) should have a resting ankle-brachial index (ABI), with or without ankle pulse volume recordings and/or Doppler waveforms.[28] Screening with resting ABI is also considered reasonable in patients with any of the following characteristics: age ≥65 years or older; age 50 to 64 years with risk factors for atherosclerosis (e.g., diabetes, smoking history, dyslipidemia, hypertension), chronic kidney disease (CKD), or family history of PAD; age <50 years with diabetes and one additional risk factor for atherosclerosis; patients with known atherosclerotic disease in another vascular bed (e.g., coronary, carotid, subclavian, renal, mesenteric artery stenosis, or abdominal aortic aneurysm).[28] The American Diabetes Association recommends screening for PAD using ABI in asymptomatic people with any of the following characteristics: age ≥50 years; diabetes with duration ≥10 years; comorbid microvascular disease; clinical evidence of foot complications; or any end-organ damage from diabetes.[29] ABI results: 1.0 to 1.4 is normal; 0.91 to 0.99 is borderline; ≤0.9 is abnormal.		
vascular dementia	**variable**	**medium**
Diabetes is associated with an increased risk of dementia. Etiologic factors include vascular factors (cerebrovascular disease, cardiovascular risk factors, atherosclerosis, and peripheral arterial disease) and nonvascular factors (hyperglycemia leading to excess formation of advanced glycated end-products, disturbed neuronal signaling leading to cerebral amyloidosis).[415]		
depression	**variable**	**medium**
The prevalence of depressive disorders is twice as high in patients with diabetes compared with those without diabetes. Depression is also common in patients with coronary disease, particularly after acute infarction. It is associated with worse health behaviors and possibly worse cardiovascular outcomes.[416] Evidence on the cardiac effects of depression treatment is limited, but it is reasonable to screen patients and treat as indicated.[320] [321] [417]		

Prognosis

Cardiovascular disease (CVD) is the leading cause of death in people with diabetes.[10] People with diabetes have a 1.5- to 2-fold increased risk of myocardial infarction (MI) compared with people without diabetes. Coronary artery disease in people with diabetes is more severe, starts at an earlier age, and is more costly. In addition, patients with type 1 diabetes are at higher risk of death after MI than patients without diabetes.[408]

Diabetes is an independent predictor of cardiovascular (CV) morbidity and mortality in people with heart failure.[409] [410] The relative risk of CV-related death or heart failure-related hospitalization is greater in people with preserved ejection fraction (diastolic heart failure) than with low ejection fraction.

Multiple studies comparing coronary artery bypass graft versus percutaneous intervention with drug-eluting stents have shown that diabetes is an independent predictor of target lesion restenosis.[315] [353] Drug-eluting stents appear to be superior to bare-metal stents in people with diabetes, with regard to major adverse cardiac events such as death, MI, or need for repeat revascularization.[356] [357] [358] [359] [360]

While the benefits of optimizing CVD risk factors are clear in patients with diabetes, in practice many patients are not achieving recommended targets.[411] [412] [413] Data from the US Diabetes Collaborative Registry of 74,393 adults with diabetes demonstrate a prevalence of 74% with HbA1c <7%, 40% with blood pressure <130/80 mmHg, and 49% with low density lipoprotein-cholesterol <100 mg/dL (<70 mg/dL if with atherosclerotic CVD), but only 15% at target for all 3 factors.[414] Newer evidence-based therapies for diabetes proven to reduce CVD risk, including sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists, remain highly underused.[4]

Diagnostic guidelines

International

Standards of care in diabetes (https://diabetesjournals.org) [29]

Published by: American Diabetes Association **Last published:** 2024

2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS guideline for the management of lower extremity peripheral artery disease (https://www.acc.org/guidelines) [28]

Published by: American College of Cardiology; American Heart Association **Last published:** 2024

Management of heart failure (https://professional.heart.org/en/guidelines-statements) [161]

Published by: American Heart Association; American College of Cardiology; Heart Failure Society of America **Last published:** 2022

Primary prevention of cardiovascular disease (https://www.acc.org/guidelines) [76]

Published by: American College of Cardiology; American Heart Association **Last published:** 2019

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol (https://www.acc.org/guidelines) [113]

Published by: American College of Cardiology; American Heart Association **Last published:** 2019

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults (https://www.acc.org/guidelines) [60]

Published by: American College of Cardiology; American Heart Association **Last published:** 2018

ESC guidelines for the management of acute coronary syndromes (https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Acute-Coronary-Syndromes-ACS-Guidelines) [152]

Published by: European Society of Cardiology **Last published:** 2023

Treatment guidelines

International

2024 guideline for the primary prevention of stroke (https://professional.heart.org/en/guidelines-statements) [118]

Published by: American Heart Association/American Stroke Association **Last published:** 2024

Standards of care in diabetes (https://diabetesjournals.org) [29]

Published by: American Diabetes Association **Last published:** 2024

Newer pharmacological treatments in adults with type 2 diabetes (https://www.acponline.org/clinical-information/clinical-guidelines-recommendations) [222]

Published by: American College of Physicians **Last published:** 2024

2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS guideline for the management of lower extremity peripheral artery disease (https://www.acc.org/guidelines) [28]

Published by: American College of Cardiology; American Heart Association **Last published:** 2024

Comprehensive type 2 diabetes management algorithm - 2023 update (https://pro.aace.com/clinical-guidance) [178]

Published by: American Association of Clinical Endocrinology **Last published:** 2023

Guideline for the management of patients with chronic coronary disease (https://www.acc.org/guidelines) [320]

Published by: American Heart Association; American College of Cardiology; American College of Clinical Pharmacy; American Society for Preventive Cardiology; National Lipid Association; Preventive Cardiovascular Nurses Association **Last published:** 2023

Clinical practice guidelines for the prevention and management of diabetes in Canada (https://guidelines.diabetes.ca/cpg) [401]

Published by: Diabetes Canada **Last published:** 2023

American Association of Clinical Endocrinology clinical practice guidelines for developing a diabetes mellitus comprehensive care plan (https://pro.aace.com/clinical-guidance/diabetes) [61]

Published by: American Association of Clinical Endocrinology **Last published:** 2022

Comprehensive management of cardiovascular risk factors for adults with type 2 diabetes (https://professional.heart.org/en/guidelines-statements) [47]

Published by: American Heart Association **Last published:** 2022

International

Management of heart failure (https://professional.heart.org/en/guidelines-statements) [161]

Published by: American Heart Association; American College of Cardiology; Heart Failure Society of America **Last published:** 2022

Statin use for the primary prevention of cardiovascular disease in adults: preventive medication (https://www.uspreventiveservicestaskforce.org/uspstf/index.php/topic_search_results?topic_status=P) [402]

Published by: US Preventive Services Task Force **Last published:** 2022

Aspirin use to prevent cardiovascular disease: preventive medication (https://www.uspreventiveservicestaskforce.org/uspstf/index.php/topic_search_results?topic_status=P) [111]

Published by: US Preventive Services Task Force **Last published:** 2022

Coronary artery revascularization (https://www.acc.org/guidelines) [337]

Published by: American College of Cardiology; American Heart Association; Society for Cardiovascular Angiography and Interventions **Last published:** 2021

Clinical management of stable coronary artery disease in patients with type 2 diabetes mellitus (https://professional.heart.org/en/guidelines-statements) [114]

Published by: American Heart Association **Last published:** 2020

Diabetes self-management education and support in adults with type 2 diabetes: a consensus report (https://www.adces.org/practice/practice-documents) [403]

Published by: American Diabetes Association; American Association of Diabetes Educators; Academy of Nutrition and Dietetics; American Academy of Family Physicians; American Academy of PAs; American Association of Nurse Practitioners; American Pharmacists Association **Last published:** 2020

Lipid management in patients with endocrine disorders (https://www.endocrine.org/clinical-practice-guidelines/cardiovascular-endocrinology) [404]

Published by: Endocrine Society **Last published:** 2020

Primary prevention of ASCVD and T2DM in patients at metabolic risk (https://www.endocrine.org/clinical-practice-guidelines/cardiovascular-endocrinology) [106]

Published by: Endocrine Society **Last published:** 2019

Primary prevention of cardiovascular disease (https://www.acc.org/guidelines) [76]

Published by: American College of Cardiology; American Heart Association **Last published:** 2019

International

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol (https://www.acc.org/guidelines) [113]

Published by: American College of Cardiology; American Heart Association **Last published:** 2019

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults (https://www.acc.org/guidelines) [60]

Published by: American College of Cardiology; American Heart Association **Last published:** 2018

American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease (https://pro.aace.com/clinical-guidance/cardiometabolic-and-lipids) [405]

Published by: American Association of Clinical Endocrinologists; American College of Endocrinology **Last published:** 2017

Evaluation and treatment of hypertriglyceridemia (https://www.endocrine.org/clinical-practice-guidelines/cardiovascular-endocrinology) [406]

Published by: Endocrine Society **Last published:** 2012

Guidelines on obesity (https://www.worldgastroenterology.org/guidelines) [407]

Published by: World Gastroenterology Organisation and International Federation for the Surgery of Obesity and Metabolic Disorders **Last published:** 2023

ESC guidelines for the management of acute coronary syndromes (https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines) [152]

Published by: European Society of Cardiology **Last published:** 2023

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes (https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/CVD-and-Diabetes-Guidelines) [6]

Published by: European Society of Cardiology **Last published:** 2023

Evidence-based European recommendations for the dietary management of diabetes (https://www.easd.org/guidelines/statements-and-guidelines.html) [132]

Published by: The Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD) **Last published:** 2023

International

ESC/EACTS guidelines on myocardial revascularization (https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines) [342]

Published by: European Society of Cardiology; European Association for Cardio-Thoracic Surgery **Last published:** 2018

Online resources

1. PCSK9 inhibitors and ezetimibe for the reduction of cardiovascular events (https://www.bmj.com/content/377/bmj-2021-069066/infographic) *(external link)*

2. AHA/ACC: ASCVD risk calculator (http://static.heart.org/riskcalc/app/index.html#!/baseline-risk) *(external link)*

3. FDA: new warning and contraindication for blood pressure medicines containing aliskiren (Tekturna) (https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-new-warning-and-contraindication-blood-pressure-medicines-containing) *(external link)*

4. NIDDK: diabetes, heart disease, and stroke (https://www.niddk.nih.gov/health-information/diabetes/overview/preventing-problems/heart-disease-stroke?dkrd=hispt0020) *(external link)*

5. HHS: dietary guidelines for Americans, 2020-2025 (https://www.dietaryguidelines.gov/resources/2020-2025-dietary-guidelines-online-materials) *(external link)*

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

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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DISCLOSURES: MA is a speaker for Kiniksa Pharmaceuticals in relation to pericarditis/rilonacept.

// Acknowledgements:

Dr Mohamed Al-Kazaz would like to gratefully acknowledge Dr Alexander Meyer, Dr Laura Davidson, Dr Charles Davidson, and Dr Leonard E. Egede, the previous contributors to this topic, and would like to gratefully acknowledge the review by Dr Shreenidhi Venuraju, MB BS, MRCP, Wellington Hospital South, UK.
DISCLOSURES: AM, LD, CD, and LE declare that they have no competing interests. LEE is an author of a number of references cited in this topic. SV not disclosed.

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