BMJ Best Practice

Diabetic cardiovascular disease

The right clinical information, right where it's needed

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Summary

- Cardiovascular disease (CVD) and stroke account for about two-thirds of deaths in people with diabetes.
- People with diabetes have a 2- to 4-fold increased risk of CVD and are up to 3 times more likely to die after MI than people without diabetes.
- Regular exercise training, individual dietary modification, and smoking cessation or non-initiation are important lifestyle changes for the primary prevention of CVD.
- Aggressive treatment of hypertension, use of statins, preventive anticoagulation, and coronary revascularisation (percutaneous transluminal coronary angioplasty or coronary artery bypass surgery during episodes of acute coronary syndrome) can lead to improved survival.

Definition

Diabetes mellitus is a group of metabolic diseases, characterised by hyperglycaemia, resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycaemia 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 ischaemic attack [TIA]), and peripheral arterial disease. This monograph will discuss CAD in greatest detail.

Epidemiology

Numerous studies have shown that the incidence of diabetes and its complications is rising in all age groups worldwide. Approximately 29.1 million people in the US (9.3% of adults) had diabetes in 2012, with 8.1 million of these people being undiagnosed.[2] Worldwide, 415 million adults had diabetes in 2015, and projections estimate that 642 million adults will have diabetes by 2040.[3] In 2012, it was estimated that $245 billion was spent on diabetes in the United States and average medical expenditures were 2.3 times higher in patients with diabetes.[2] In 2003-2006, death due to cardiovascular disease was 1.7 times higher among adults with diabetes as compared with adults who did not have diabetes.[2] The problem is no longer confined to Western countries. In 2011, China was reported to have the largest number of adults with diabetes (approximately 90 million), followed by India (approximately 61 million) and Bangladesh (approximately 8 million).[4]

Aetiology

The aetiology of CVD in diabetes is complex and multi-factorial. It results from the interplay of a constellation of metabolic risk factors, excessive oxidation, endothelial dysfunction, inflammation, and imbalance in prothrombotic and anti-fibrinolytic processes.[5] The unifying metabolic factor is hyperglycaemia, which results from both insulin deficiency and insulin resistance. Insulin resistance is associated with a variety of major metabolic risk factors including hyperinsulinaemia, dyslipidaemia, elevated BP, and obesity. Hyperglycaemia leads to excessive oxidation and accumulation of advanced glycation end-products, while peroxidation of lipids leads to foam cell formation within the arterial wall. 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. This cascade ultimately leads to arterial intimal thickening, increased plaque formation, and atherosclerosis.

Pathophysiology

The underlying mechanism for CVD in diabetes is accelerated atherosclerosis. 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 ischaemic attacks (TIAs) 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.[6] Under physiological conditions, the endothelial cell layer separates cells and circulating factors from the arterial intima and media

and serves as an anticoagulant and fibrinolytic surface.[6] 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.[6] 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.[6] [7] 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.

Primary prevention

A major component of primary prevention for CVD in people with diabetes is lifestyle modification. Most of the major CVD risk factors can be altered by aggressive lifestyle changes. Regular exercise training, individual dietary modification, and smoking cessation or non-initiation are important lifestyle interventions for the primary prevention of CVD in patients with diabetes.[1]

Overt type 2 diabetes can itself be prevented in people with impaired glucose tolerance. Lifestyle changes, including increased physical activity, can be effective, and multiple medications have also been shown to be effective (including use of metformin, or other drugs with greater potential for side effects such as thiazolidinediones[49] and alpha glucosidase inhibitors). Only orlistat is approved for this purpose in the US. However, it is not clear whether prevention of overt diabetes translates into eventual reduced cardiovascular risk, and rosiglitazone use has been withdrawn in Europe due to concerns about its associated increased cardiovascular risk. In people with impaired glucose tolerance and cardiovascular disease or risk factors, nateglinide for 5 years did not reduce the incidence of diabetes or composite cardiovascular outcomes.[50] Valsartan plus lifestyle modification produced a reduction in the incidence of diabetes but did not reduce the rate of cardiovascular events.[51]

Screening

Screening for diabetes

The American Diabetes Association recommends screening tests to detect type 2 diabetes and assess risk for future diabetes in asymptomatic adults who are overweight or obese (BMI ≥25 kg/m^2) and who have ≥1 of the following additional risk factors for diabetes: physical inactivity; first-degree relative with diabetes; high-risk ancestry (e.g., African American, Latino, Native American, Asian American, Pacific Islander); women diagnosed with gestational diabetes; hypertension (BP ≥140/90 mmHg or taking therapy for hypertension); HDL cholesterol level <0.90 mmol/L (<35 mg/dL) and/or a triglyceride level >2.82 mmol/L (>250 mg/dL); women with polycystic ovary syndrome; HbA1c ≥38 mmol/mol (≥5.7%); impaired glucose tolerance, or impaired fasting glucose on previous testing; other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans); or a history of CVD. In the absence of risk factors, testing is recommended starting at age 45 years.[1] If screening is normal, repeat testing at 3-year intervals is recommended.

The Agency for Healthcare Research and Quality/US Preventive Services Task Force recommends screening for type 2 diabetes in asymptomatic adults with sustained BP (treated or untreated) >135/80 mmHg. The guideline stated that current data were insufficient to assess the balance of benefits and harms of screening for type 2 diabetes in asymptomatic adults with blood pressure ≤135/80 mmHg.[85]

Screening for CVD in people with diabetes

The American Diabetes Association recommends that asymptomatic patients should be screened for cardiovascular risk factors that are associated with diabetes every 1 to 2 years. Based on the results of this screening, aggressive medical therapy to reduce cardiovascular risk is universally recommended.[1] It is important to note that the Framingham and UK Prospective Diabetes Study (UKPDS) risk equations may overestimate CVD risk in diverse samples that include ethnic minority groups, so these risk engines should be interpreted with caution in minority populations.[86] When HbA1C values are added to cardiovascular disease risk assessment models, there is little incremental benefit to predict risk.[87] The benefits of screening asymptomatic people with diabetes for CAD remain unclear. One meta-analysis suggested that systematic detection of silent ischaemia in high-risk asymptomatic people with diabetes may not add benefit to clinically important outcomes as compared with optimised medical management of cardiovascular risk factors alone.[88] Candidates for cardiac testing include those with typical or atypical cardiac symptoms, or an abnormal resting ECG. Cardiovascular risk factors should be assessed at least annually in people with diabetes: BP, lipid levels, smoking, family history of pre-mature coronary disease, and albuminuria. Usual therapies include antihypertensive therapy, statins, and (for those with established or high risk of CAD) aspirin.

Secondary prevention

Risk factors for CVD should be elicited and appropriate treatment given (e.g., for smoking, HTN, or dyslipidaemia). However, one study found that there was no significant reduction in cardiovascular events in overweight and obese patients with type 2 diabetes who underwent an intensive diet and exercise programme when compared with a control group.[123]

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 is mildly obese 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 CAD. In patients with diabetes, who often suffer from neuropathy and loss of sensation, ischaemia 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 CVD may include symptoms of claudication or stroke.

Step-by-step diagnostic approach

Coronary artery disease (CAD) is the most common manifestation of cardiovascular disease (CVD) in people with diabetes.

CAD (MI, angina, and heart failure)

Up to 30% of patients presenting with acute coronary syndromes have diabetes.[52] [53] In patients with diabetes, CAD accounts for 75% of all deaths.[54] Mortality from MI is about 1.5- to 2-fold greater in people with diabetes than in people without diabetes.[54] In the UK Prospective Diabetes Study, the odds ratio for acute MI case fatality was 1.17 per 1% increase in HbA1c.[55] Additionally, patients who are admitted with high risk non-ST elevation MI are known to have worse early outcomes, including mortality, compared with patients who present similarly but without diabetes.[56] Autopsy studies have shown that atherosclerotic burden is similar in people with and without diabetes.[57] However, angiographic data have shown that people with diabetes have more diffuse, extensive, multi-vessel (including left main), and distal disease than do people without diabetes.[58]

Cerebrovascular disease (stroke and transient ischaemic attack [TIA])

The risk of stroke is increased 1.5- to 4-fold in patients with diabetes.[2] [59] Diabetes doubles the risk of stroke recurrence. Stroke outcomes, including in-hospital and long-term mortality, are worse in people with diabetes.[59] Diabetes increases the risk of ischaemic stroke to a greater degree than haemorrhagic stroke. Lacunar infarcts are more common in patients with diabetes, and patients with diabetes are more likely to develop silent lacunar cerebral infarcts. However, TIAs are less common in people with diabetes than in those without diabetes.The risk of stroke increases with worsening glycaemic control. In the UK Prospective Diabetes Study, the odds ratio for stroke case fatality was 1.37 per 1% increase in HbA1c.[55]

Peripheral arterial disease

Cigarette smoking and diabetes are the 2 major risk factors for peripheral arterial disease (PAD).[60] Of symptomatic patients with PAD, 20% are known to have diabetes; however, most patients with PAD are asymptomatic. Diabetes is associated with increased risk of critical lower extremity ischaemia. People with diabetes who have lower extremity PAD are more likely to undergo a major amputation than are people without diabetes with lower extremity PAD.[61]

Aortic atherosclerosis

Abdominal aortic aneurysm (AAA) is considered to be present when the minimum anteroposterior diameter of the aorta reaches 3 cm.[60] The prevalence of AAA in the general population ranges from 7.6% for men and 1.3% for women.[62]

However, diabetes has been negatively associated with risk for AAA.[63] [64] [65] There is a suggestion that diabetes reduces risk for AAA expansion.[66]

Additional risk factors

Of the numerous CVD risk factors that have been identified, only a few are categorised as major risk factors by the American Heart Association, based on their direct causal relationship with CVD, high prevalence in the general population, and the significant CVD risk reduction associated with their modification.[67] In addition to diabetes, these include cigarette smoking, elevated BP, dyslipidaemia, hyperglycaemia, obesity, and insufficient physical activity. These major risk factors account for about 50% of the variability in high-risk populations and explain up to 90% of the excess population risk for CVD.[68] In addition to these major risk factors, male gender, albuminuria, and elevated C-reactive protein levels are strongly associated with increased risk of CVD among people with diabetes.[45] [46] [47] [48] The presence of diabetes negates the usual female pre-menopausal advantage in relation to CVD. Strong family history of CVD should also be considered a risk factor for CVD in diabetes. There is controversy as to whether the metabolic syndrome, as currently defined, captures any unique pathophysiology and whether it confers risk beyond its individual components.[69]

Symptoms

Symptoms specific to CVD should be elicited in the history.

CAD

- Chest discomfort (may be absent in 20% to 30% of patients with diabetes, often called 'silent ischaemia')[54]
- Dyspnoea on exertion; diaphoresis; nausea.

Cerebrovascular disease

- Numbness; tingling; headache; hemiparesis; aphasia.

PAD

- Intermittent claudication occurs in only 33% to 50% of patients with PAD[70]
- Rest pain in severe disease
- Numbness of the extremities, typically asymmetrical.

Physical findings

Hypertension

- In patients with diabetes, systolic BP >140 mmHg and/or diastolic BP >90 mmHg.[71]

Acute MI or CHF

- Rales; hypotension; peripheral oedema; tachycardia; S3 gallop; jugular venous distention (JVD).

Cerebrovascular accident

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

PAD

- Decreased or absent pulses; bruit over narrowed artery; hair loss; smooth, shiny skin; ulcers and necrosis.

Diagnostic testing

CAD

Non-invasive cardiac imaging can provide useful information in patients with suspected CAD and who are having symptoms. All patients should also have a baseline lipid profile. C-reactive protein is not a routine test but may be useful for risk stratification.[48] HbA1c is used to monitor glycaemic control. For patients with known disease, prior revascularisation, or those likely to have extensive coronary calcium, myocardial perfusion scanning remains the dominant approach.[72]

- Exercise testing: there is a paucity of data on the predictive power of exercise testing in patients with diabetes, but available data suggest that ischaemic findings on exercise ECG are predictive of prognosis.[5] In a study of 1282 patients (15% with diabetes), sensitivity (47% versus 52%) and specificity (81% versus 80%) for exercise treadmill testing were similar in people with and without diabetes.[73] Symptomatic patients who can exercise and have a resting ECG that is interpretable for ST-segment shifts, should undergo an exercise ECG as the first step.[74]
- Stress echo or nuclear scan: patients who are unable to exercise should undergo a pharmacological stress test with imaging.[74] Stress imaging studies are superior to exercise stress testing for diagnosis of CAD in women.[75]
- 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 ischaemia and should prompt further testing.[76] In patients with pre-test likelihood of CAD <50%, a CAC score of 0 provides very strong evidence against the presence of CAD, with a high degree of certainty.[72]
- CT coronary angiography (CTA): ≥16-slice CT scanners have 90% sensitivity and 90% specificity for >50% diameter stenosis, which is the minimal criterion for consideration of revascularisation.[72] CTA may be useful for patients with equivocal myocardial perfusion scanning; those with possible left main or triple-vessel CAD; patients with cardiomyopathy unrelated to CAD; and young patients undergoing valvular surgery.[72] Screening for asymptomatic obstructive CAD among type 1 and type 2 diabetic patients using CTA is not beneficial.[77]

Suspected cerebrovascular accident

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

PAD

- All patients with one or more of the following should have a baseline ankle-brachial index (ABI) measured to assess for PAD: exertional leg symptoms, non-healing wounds, age 65 years or older, or age 50 years or older with diabetes or smoking history.[60]
- 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.[60]

Risk factors

Strong

cigarette smoking

- Cigarette smoking is an independent risk factor for CVD. About 15% of adults with diabetes smoke.[8] [9]
- In addition, there is a strong link between smoking and progression of macro- and microvascular complications of diabetes.[10]
- Specifically, smoking is strongly associated with higher 24-hour BPs, poor glycaemic control, increased prevalence of microvascular complications, and diabetic nephropathy.[11] [12] [13]

hypertension (HTN)

- HTN is present in about 60% of adults with diabetes, and in this population it further increases the risk for CVD, diabetic retinopathy, and renal insufficiency.[8] [14] A 5 mmHg increase in systolic or diastolic BP increases the risk of CVD by 20% to 30%.[15]
- The UK Prospective Diabetes Study (UKPDS) found that each 10 mmHg drop in mean systolic BP led to an 11% decrease in MI risk, a 13% decrease in microvascular complications risk, and a 15% decrease in risk of death related to diabetes. However, the ACCORD trial demonstrated that intensive systolic blood pressure control to a goal of <120 mmHg, compared to a standard systolic blood pressure goal of <140 mmHg, did not change cardiovascular outcomes in diabetic patients.[16] The SPRINT trial excluded diabetic patients from enrolment.[17]

dyslipidaemia

- About 41% of adults with diabetes have dyslipidaemia. The most common variant is elevated triglycerides and decreased HDL cholesterol.[8] [18]
- Although hypercholesterolaemia and hypertriglyceridaemia are predictors of CVD in people with type 2 diabetes, low HDL cholesterol is even more powerful as a lipoprotein predictor of CVD in this population.[19]
- In the diabetic population, most studies of treatment of dyslipidaemia are based on secondary prevention of CVD. However, multiple clinical studies that included diabetic subgroups have suggested that lipid lowering is equally beneficial for primary prevention in patients with diabetes.1[B]Evidence

poor glycaemic control

- The risk for a CVD event increases by about 17% to 18% for every 1% increase in HbA1c.[20] [21] [22]
- There is growing evidence that intensive glycaemic control may decrease risk of CVD events in type 1 diabetes, as well as microvascular disease (retinopathy, nephropathy, or neuropathy) in type 2 diabetes.

- In type 1 diabetes the Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) study found a 50% reduction in CVD outcomes in people with type 1 diabetes who received intensive treatment (mean HbA1c 54 mmol/mol [7.2%]) compared with those that received conventional treatment (mean HbA1c 76 mmol/mol [9.1%]).[23]
- In type 2 diabetes glycaemic control has not been shown to reduce the risk of macrovascular complications, but rather only microvascular endpoints (e.g., retinal photocoagulation).
- Selected glucose-lowering agents (metformin, liraglutide, and empagliflozin) have reduced cardiovascular risk in some trials.[24] [25] [26] [27]
- Several large RCTs have found that very tight control (goal HbA1c 42 mmol/mol to 48 mmol/mol [6% to 6.5%]) was either not beneficial or detrimental to mortality in patients with type 2 diabetes and CVD, and increased the risk for hypoglycaemia.[28] [29] [30] [31] [32] [33] [34] A long-term follow-up study of intensive glycaemic control (median HbA1c 6.9% versus 8.4%) did show fewer major cardiovascular events per 1000 person-years, but no improvement in overall survival.[35] Furthermore, a follow-up of the ACCORD trial demonstrating intensive versus standard glycaemic control (<6.0% versus 7.0%-7.9%) showed that MI, coronary revascularisation, and unstable angina were less frequent in the intensive group than in the standard therapy group.[36] Controlling HbA1c to <53 mmol/mol (<7%) is recommended to prevent microvascular complications.[1]

physical inactivity

- About 66% of adults with diabetes are physically inactive (defined as absence of leisure-time physical activity or physical activity of <20 minutes' duration 3 or more times a week).[8]
- Increased physical activity decreases all-cause mortality and CVD-related mortality in men with type 2 diabetes.2[B]Evidence

albuminuria

- 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 endpoint (MI, stroke, or CVD death) among people with and without diabetes.[46] 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.[47]

elevated C-reactive protein

- Among 746 men with diabetes followed for an average of 5 years, those in the highest quartile had a 2.6-fold increased risk of CVD events compared with those in the lowest quartile.[48]

strong family history of CVD

- Further increases risk of developing CVD in patients with diabetes.

Weak

overweight and obesity

- The trend towards increasing prevalence of diabetes parallels increasing BMI.[37] [38] [39]
- A study of 7176 men aged 40 to 59 years with no prior history of CVD or diabetes followed for 20 years found that overweight and obesity are independent predictors of CVD and type 2 diabetes.[40]
- Excess weight gain related to intensive glycaemic control in type 1 diabetes has also been associated with risk factors for CVD development such as insulin resistance and dyslipidaemia.[41]

male gender

- A meta-analysis of 37 studies that included about 450,000 patients found that the relative risk of fatal coronary heart disease in patients with diabetes was 3.5 in men and 2.1 in women.[45] However, when pre-menopausal females develop diabetes they lose their cardiovascular risk advantage.

History & examination factors

Key diagnostic factors

presence of risk factors (common)

- Strong risk factors include poor glycaemic control, cigarette smoking, HTN, dyslipidaemia, physical inactivity, albuminuria, C-reactive protein, and family history of CVD.

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.
- Chest discomfort may be absent in 20% to 30% of patients with diabetes.[54]

dyspnoea on exertion (common)

- May be present with or without chest pain to indicate coronary disease or may be a symptom of CHF.

hypotension (common)

- Presentation for acute coronary syndrome or haemorrhagic stroke.

rales (common)

- Suggestive of LV dysfunction in the setting of acute coronary syndrome or CHF.
- Patients with rales, S3 gallop, or acute mitral regurgitation have a very high likelihood of severe underlying CAD.

S3 gallop (common)

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

BP >140/90 mmHg (common)

- BP goals in the setting of diabetes are systolic <140 mmHg, and diastolic <90 mmHg.[1] [71] 3[A]Evidence
- A lower target of <130/80 mmHg may be appropriate, if achievable, in certain patients, including younger patients, those with albuminuria, and those with one additional atherosclerotic cardiovascular disease risk factor.[1]

nausea (common)

- Commonly associated with chest pain in acute coronary syndrome.

diaphoresis (common)

- Commonly associated with chest pain in acute coronary syndrome.

tachycardia (common)

- Commonly associated with chest pain in acute coronary syndrome, aortic dissection, or haemorrhagic stroke.

indigestion (uncommon)

- An uncommon presentation for acute coronary syndrome.

Other diagnostic factors

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

- A presenting symptom in a significant proportion of patients with ischaemic stroke.

headache (common)

- Fifty percent of patients with haemorrhagic stroke present with headache.

intermittent claudication (common)

- The cardinal symptom of peripheral artery disease (PAD).
- Occurs in only 33% to 50% of patients with PAD.[70]

bruits (common)

- May be heard over narrowed vessels.

aphasia (uncommon)

- May occur in a small proportion of patients with ischaemic stroke.

hemisensory loss (uncommon)

- May indicate CVA.

cranial nerve palsies (uncommon)

- Seen in some patients with stroke.

seizures (uncommon)

- An uncommon presentation of haemorrhagic or ischaemic stroke.

vertigo (uncommon)

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

limb pain at rest (uncommon)

- Suggestive of critical limb ischaemia.

diminished/absent lower extremity pulses (uncommon)

- Suggestive of compromised lower extremity circulation and may be indicative of critical limb ischaemia.

ulcers or gangrene (uncommon)

- Suggestive of severe peripheral arterial disease and critical limb ischaemia.

peripheral oedema (uncommon)

- Often indicates heart failure or acute MI with left ventricular dysfunction.

smooth shiny skin with hair loss (uncommon)

- Can be seen in PAD.

pallor (uncommon)

- May occur in patients with acute coronary syndrome or haemorrhagic stroke.

Diagnostic tests

1st test to order

Test	Result
HbA1c • A value of ≥48 mmol/mol (≥6.5%) is also a diagnostic test for type 2 diabetes.[1]	**used to monitor long-term glycaemic control**
fasting lipid profile • Previous ACC/AHA guidelines used an LDL target of 70 mg/dL for people with diabetes. Guidelines published in 2013 recommend use of moderate to high doses of statins without specific numerical targets for LDL.[78]	**used to calculate individual ASCVD risk**

Other tests to consider

Test	Result
exercise stress test • In asymptomatic patients with diabetes, routine stress testing is not recommended but medical cardiovascular risk reduction efforts should be ongoing.[1] There is a paucity of data on the predictive power of exercise testing in patients with diabetes, but available data suggest that an ischaemic finding on exercise ECG is predictive of prognosis.[5] • In a study of 1282 patients (15% with diabetes), sensitivity (47% versus 52%) and specificity (81% versus 80%) for exercise treadmill testing were similar in people with and without diabetes.[73] • For patients in whom stress testing is indicated, who can exercise, and have resting ECG that is interpretable for ST-segment shifts, exercise ECG is a reasonable option.[74] • Patients who are unable to exercise should undergo a pharmacological stress test with imaging.[74] • Stress imaging studies are superior to exercise stress tests for diagnosis of CAD in women.[75]	**exercise or pharmacologically induced ST depression or arrhythmia**

Test	Result
treadmill or pharmacological stress echocardiogram • In asymptomatic patients with diabetes, there is no role for routine stress testing.[1] • Patients in whom stress testing is indicated and who are unable to exercise should get a pharmacological stress test with imaging.[74] • Stress imaging studies are superior to exercise stress tests for diagnosis of CAD in women.[75] • In one study dobutamine stress echo had a sensitivity of 89%, specificity of 87% for multi-vessel disease, and overall specificity of 52%.[79]	**reversible or irreversible wall motion abnormalities**
treadmill or pharmacological myocardial perfusion scanning • In asymptomatic patients with diabetes, routine stress testing is not recommended but medical cardiovascular risk reduction efforts should be ongoing.[1] Patients in whom stress testing is indicated and who are unable to exercise should get a pharmacological stress test with imaging.[74] • Stress imaging studies are superior to exercise stress tests for diagnosis of CAD in women.[75] • In one study, stress thallium scintigraphy had a sensitivity of 88% and overall specificity of 84%.[80] • Another study found that dipyridamole myocardial thallium scintigraphy had a sensitivity of 80% and overall specificity of 87%.[81]	**reversible or irreversible areas of decreased perfusion**
ankle-brachial index (ABI) • Indicated in all patients with one or more of the following: exertional leg symptoms; non-healing wounds; age 65 years or older; or age 50 years or older with diabetes or smoking history.[60]	**ABI 1.0-1.4 normal; 0.91-0.99 borderline; ≤0.9 abnormal**
CT angiography • CT angiography may be useful for patients with equivocal myocardial perfusion scanning, those with possible left main or triple-vessel CAD, patients with non-ischaemic cardiomyopathy, and young patients undergoing valvular surgery.[72] • Screening asymptomatic obstructive CAD among high-risk diabetic patients using CT angiography is not recommended.[77]	**defines coronary calcium burden, coronary anatomy, location and degree of stenosis**
coronary angiography • Coronary angiography after injection of radiopaque dye is indicated in the following situations:[82] high-risk criteria on non-invasive testing regardless of angina severity in patients with known or suspected CAD; contraindication to stress testing; evolving acute MI with intent to perform primary percutaneous transluminal coronary angioplasty (PTCA); and persistent or recurrent episodes of symptomatic ischaemia.	**defines coronary anatomy, location and degree of stenosis; directs medical or mechanical therapy**
non-contrast head CT • First test to obtain if symptoms suggest possible acute stroke.	**acute CVA**
MRI brain • Imaging modality used to further evaluate for possible acute stroke, especially white matter lesions, brainstem, and posterior fossa lesions.	**acute, subacute, or prior CVA**

Test	Result
duplex ultrasonography of carotid arteries • Patients with symptomatic stenosis ≥50% may be candidates for intervention as well as asymptomatic patients with a stenosis ≥70%.[83]	**degree of stenosis in carotid arteries**
C-reactive protein • Not a routine test but may be useful for risk stratification.[48] [84]	**may be elevated**

Differential diagnosis

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 and CK-MB levels should be normal.
ST-elevation MI (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 and CK-MB levels are elevated in STEMI.
Non-ST-elevation MI (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 and CK-MB 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.

Condition	Differentiating signs / symptoms	Differentiating tests
Congestive heart failure (CHF)	• Symptoms of cough, SOB, orthopnoea, paroxysmal nocturnal dyspnoea, or peripheral oedema. • Findings of jugular venous distension, pulmonary congestion, and S3 gallop.	• Diagnosis can be made clinically, but several studies may assist if diagnosis is not clear. • CXR may reveal cardiomegaly, pulmonary oedema, and cephalisation 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.
Diastolic heart failure	• 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 ischaemic attack (TIA)	• Sudden onset of neurological deficit. Most TIAs last between 5 and 15 minutes.	• Diagnosis is made by complete resolution of symptoms in <24 hours and no acute ischaemic findings on brain imaging. Acutely, non-contrast CT of the head is used to exclude intracerebral haemorrhage.
Ischaemic stroke	• Sudden onset of neurological deficit. Symptoms lasting ≥24 hours are classified as a stroke.	• CT or MRI will show ischaemic or haemorrhagic stroke. Acutely, non-contrast CT of the head is used to exclude intracerebral haemorrhage.
Haemorrhagic stroke	• Sudden onset of neurological deficit. Symptoms lasting ≥24 hours are classified as a stroke.	• Acutely, non-contrast CT of the head can show intracerebral haemorrhage.

Condition	Differentiating signs / symptoms	Differentiating tests
Peripheral artery disease (PAD)	• Pain, ache, cramp, or numbness in the muscles that develops with exercise and is relieved by rest. Pain in buttocks and thighs suggest aorto-iliac disease, while calf muscle pain suggests femoral or popliteal artery disease.	• All patients with one or more of the following should have a baseline ankle-brachial index (ABI) measured to assess for PAD: exertional leg symptoms; non-healing wounds; age ≥65 years; or age ≥50 years with diabetes or smoking history.[60] ABI results: 1.0-1.4 is normal; 0.91-0.99 is borderline; ≤0.9 is abnormal.

Diagnostic criteria

One of 4 criteria may be used to diagnose diabetes. Fasting is defined as no caloric intake for at least 8 hours.[1]

- Fasting plasma glucose >6.9 mmol/L (>125 mg/dL), confirmed on repeat testing OR
- Random plasma glucose >11 mmol/L (>199 mg/dL) with diabetes symptoms such as polyuria, polydipsia, fatigue, or weight loss OR
- 75 g oral glucose tolerance test, 2-hour post-load glucose >11 mmol/L (>199 mg/dL), confirmed on repeat testing OR
- HbA1c ≥48 mmol/mol (≥6.5%), confirmed on repeat testing.

Step-by-step treatment approach

Therapeutic lifestyle interventions such as medical nutrition therapy and aerobic exercise have been shown in large clinical trials to improve glycaemic, lipid, and BP control.[44] Intensive lifestyle interventions can produce sustained weight loss and improvements in fitness, glycaemic control, and CVD risk factors in individuals with type 2 diabetes.[89] [90] Data from multiple clinical trials have documented that treatment of dyslipidaemia, HTN, and hypercoagulability, as well as revascularisation during acute coronary syndromes, leads to event-free survival in people with diabetes and clinical CVD.

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.[91] The Mediterranean Diet,[92] DASH (Dietary Approaches to Stop Hypertension),[93] and vegan[94] diets have all been demonstrated to be effective for people with diabetes.[95] Monitoring carbohydrate intake is recommended. Protein and fat counting may also benefit some people (e.g., those using flexible insulin).[1] Dietary fat and cholesterol intake is as recommended for the general population.[1]

Physical activity

A sedentary lifestyle is a major risk factor for CVD. Approximately 66% of adults with diabetes are physically inactive. This is defined as <3 periods of physical activity of at least 20 minutes' duration each per week.[8]

Physical activity improves glycaemic control, decreases triglyceride-rich VLDL, decreases BP, and enhances weight loss in adults with diabetes.[42] In addition, increased physical activity decreases all-cause mortality and CVD-related mortality in men with type 2 diabetes.[42] Regular exercise training improves carbohydrate metabolism, decreases insulin resistance, enhances weight loss, reduces levels of triglycerides, and lowers BP.[43] 2[B]Evidence

At least 150 minutes per week of moderate-intensity aerobic physical activity at 50% to 70% of maximal heart rate is recommended. The physical activity should be spread over at least 3 days per week. In the absence of contraindications, resistance training is also recommended.[1] The American Diabetes Association (ADA) recommends interrupting sedentary activity every 30 minutes. Older adults may also benefit from flexibility and balance exercise.[1]

Glycaemic control: long term

Increasing severity of hyperglycaemia correlates with increasing cardiovascular risk.[28] However, 3 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 <42 mmol/mol to 48 mmol/mol [6% to 6.5%] over 3 to 5 years) did not reduce macrovascular events in adults with type 2 diabetes.[7] [28] [29] [30] [31] [32] [33] [34] In contrast, intensive glycaemic control appeared to have long-term beneficial effects on the risk of CVD in patients with type 1 diabetes.[23] A long-term follow-up study of intensive glycaemic control (median HbA1c 6.9% versus 8.4%) did show fewer major cardiovascular events per 1000 person-years, but no improvement in overall survival.[35] Furthermore, a follow-up of the ACCORD trial demonstrating intensive versus standard glycaemic control (<6.0% versus 7.0%-7.9%) showed that MI, coronary revascularisation, and unstable angina were less frequent in the intensive group than the standard therapy group.[36]

The reasons for the discrepancy are unclear. It appears that there may be a lag period before a benefit of glycaemic control on cardiovascular risk is realised.[25] Other possibilities that may have influenced results include the magnitude or rapidity of reductions in HbA1c in intensively treated patients; effect of specific antihyperglycaemic drugs or drug interactions; treatment-related hypoglycaemia; or age at which therapy is begun.[28]

Some individual glucose-lowering agents have reduced cardiovascular risk in trials. Of the FDA-approved agents, metformin, empagliflozin, and liraglutide have been shown to reduce all-cause mortality. The ADA has continued to recommend metformin as the initial antihyperglycaemic agent for most people with type 2 diabetes, and it has also added the suggestion to consider empagliflozin or liraglutide in patients with longstanding suboptimal glycaemic control plus established cardiovascular disease.[1] It is not yet clear whether cardiovascular effects of glucose-lowering drugs are class effects or apply only to individual agents.

The recommended HbA1c goal for most people with diabetes is <53 mmol/mol (7%) for preventing microvascular complications and should be individualised by the physician.[1] Less stringent goals may be appropriate for patients with history of severe hypoglycaemia, very young or older patients, and patients with comorbid conditions. Metformin is recommended as initial treatment in combination with medical nutrition therapy and exercise at the time of diagnosis of type 2 diabetes, if HbA1c is >53 mmol/mol (7%).[1]

Ongoing studies of antihyperglycaemic drugs continue to examine the cardiovascular effects of newer agents such as dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor (GLP-1) agonists, and sodium-glucose transporter-2 (SGLT-2) inhibitors.

- Studies of DPP-4 inhibitors showed that saxagliptin did not alter the rate of ischaemic events over about 2 years; although, hospital admissions for heart failure increased.[96]
- Another study compared DPP-4 inhibitors, sulfonylureas, and thiazolidinediones and found that DPP-4 inhibitors were associated with a lower risk of hospitalisation for heart failure compared with sulfonylureas.[97]
- In one large cohort study, a higher risk for heart failure was not observed in users of saxagliptin or sitagliptin compared with other selected antihyperglycaemic agents.[98]
- In a large observational study of people with diabetes, incretin-based drugs (DPP-4 inhibitors and GLP-1 analogues) were not associated with an increased risk of hospitalisation for heart failure, as compared with commonly used combinations of oral antihyperglycaemic drugs.[99]
- In people with a recent acute coronary syndrome, alogliptin was not associated with increased risk of major adverse cardiovascular events over 40 months.[100]

Controversies regarding glitazone agents for glycaemic control

Evidence from multiple RCTs and meta-analyses has raised concerns about the safety of rosiglitazone: in particular, possible increased risk of MI with its use.[101] [102] [103] [104] [105] [106] As a result, rosiglitazone has been withdrawn in Europe.

A meta-analysis found that pioglitazone is associated with a significantly lower risk of death, MI, or stroke among a diverse population of patients with diabetes.[107] However, 2 meta-analyses have confirmed that use of glitazones (rosiglitazone and pioglitazone) in patients with diabetes is associated with a 2-fold increased risk of CHF.[108] [109] Therefore, these studies suggest that rosiglitazone and pioglitazone are both associated with increased risk of fluid retention and CHF.[110] Thiazolidinedione use is not

recommended in patients with NYHA class III-IV heart failure and should be used with caution and frequent monitoring in patients with NYHA class I-II heart failure.[111]

Glycaemic control during acute CVD events or interventions

Trials of tight glycaemic control in critically ill patients have yielded mixed results.[112] [113]

In one study of patients with acute coronary syndrome who presented with hyperglycaemia, intensive glucose control was associated with harm and did not reduce infarct size.[114]

A large RCT raised questions about intensive blood glucose targets for inpatient glycaemic control and found a lower mortality for ICU patients with a blood glucose target of 10 mmol/L (180 mg/dL) than for those with a blood glucose target of 4.5 to 6.0 mmol/L (81 to 108 mg/dL).[115] A concern has been whether there is any additional benefit to lowering blood glucose levels below about 7.8 to 10 mmol/L (140 to 180 mg/dL) in the ICU setting.[116] The ADA recommends that in critically ill patients, insulin therapy should be started for persistent hyperglycaemia >10 mmol/L (>180 mg/dL). Once insulin therapy is started, a target glucose range of 7.8 to 10 mmol/L (140 to 180 mg/dL) was recommended for most critically ill patients. These patients require an intravenous insulin protocol that has demonstrated efficacy and safety for achieving targets without increasing risk for severe hypoglycaemia.[1]

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.[117] 4[A]Evidence

BP control

Both the Joint National Commission (JNC 8) and the ADA recommend a general BP goal of <140/90 mmHg in patients with diabetes and hypertension.[1] [71] 3[A]Evidence The ACCORD trial demonstrates no benefit to intensive systolic BP control (<120 mmHg) as compared with standard BP control (<140 mmHg).[16] The recently published SPRINT trial supporting intensive systolic BP control does not apply to a diabetic population as patients with diabetes were excluded from the trial.[17] All patients should receive lifestyle advice on topics such as weight management, sodium reduction, and physical activity. Combination therapy is often required to reach BP goals. JNC 8 guidelines recommend the use of ACE inhibitors, angiotensin-II receptor antagonists, calcium-channel blockers, or thiazide diuretics as initial antihypertensive therapy in non-black hypertensive patients with diabetes.[71] In black patients, it is recommended that a calcium-channel blocker or a thiazide diuretic be used as initial antihypertensive therapy. People with chronic kidney disease (CKD) should receive an ACE inhibitor or an angiotensin-II receptor antagonist as part of their regimen.[71] Combining ACE inhibitors and angiotensin-II receptor antagonists is not recommended because of an increased risk for acute kidney injury and hyperkalaemia.[120]

One meta-analysis found that ACE inhibitors reduced mortality and major cardiovascular 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 in patients with diabetes.[121] A meta-analysis showed that in patients with diabetes and kidney disease, no antihypertensive regimen improved survival. However, ACE inhibitors and angiotensin-II receptor antagonists (either alone or in combination) were effective in preventing end-stage renal disease.

Beta-blockers are not contraindicated in people with diabetes but are less preferred and may mask symptoms of hypoglycaemia.

ACE inhibitors have shown increased risk for hypoglycaemia in conjunction with insulin or insulin secretagogue (sulfonylurea or meglitinide).[122]

Based on the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) trial, the US Food and Drug Administration (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 hyperkalaemia. [FDA: new warning and contraindication for blood pressure medicines containing aliskiren (Tekturna)]

Dyslipidaemia and statin therapy

Lifestyle modification focused on reduced fat intake, weight loss, and increased physical activity has been shown to improve HDL and triglycerides in patients with diabetes.[89] However, the same study group found that there was no significant reduction in cardiovascular events in overweight and obese patients with type 2 diabetes who underwent this intensive programme when compared to a control group.[123]

American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend moderate- or high-dose statin use in adults aged >21 years who are candidates for statin therapy if the patient has clinical atherosclerotic cardiovascular disease (ASCVD) or LDL-cholesterol ≥4.9 mmol/L (≥190 mg/dL). In the absence of ASCVD or LDL-cholesterol ≥4.9 mmol/L (≥190 mg/dL), high-intensity statins are recommended for people with diabetes aged 40 to 75 years if the estimated 10-year ASCVD risk is ≥7.5%; otherwise, moderate-intensity statins should be used.[78] The guidelines recommend an individualised approach for people aged >75 years. A moderate-dose statin has been defined by the ACC/AHA as one that generally lowers LDL-cholesterol level by 30% to 50%, while a high-dose statin has been defined as one that lowers LDL-cholesterol level by ≥50%.

Choice of agents[1]

- Statins are the first-line agent for pharmacological treatment of dyslipidaemia and may have additional therapeutic effects independent of lipid-lowering action.
- Statins are contraindicated in pregnancy.
- Non-statin agents may be added to statins if additional therapy is needed to achieve goals, but the effect on clinical endpoints such as cardiovascular events has not been established.5[A]Evidence
- Fibrates are effective for lowering triglyceride levels. They are most often added to statin therapy. The combination may increase risk of elevated aminotransferases, myositis, or rhabdomyolysis.
- The role of ezetimibe as an adjunct to statin therapy has not been well demonstrated, but is undergoing investigation.[126]
- Supplementation with n-3 fatty acids has not been found to reduce the rate of cardiovascular events in diabetic patients at high risk for these events.[127]
- In the setting of true statin intolerance or suboptimal lipid management with statin therapy, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor can be considered.

Antiplatelet therapy

Aspirin is recommended for secondary prevention in those with a history of CVD.[1] Aspirin is recommended for primary prevention in people with type 1 and type 2 diabetes who are 50 years or older and have a 10-year risk of cardiovascular disease >10%.[1] Aspirin is not indicated for patients at low risk of cardiovascular events (<5% 10-year risk) and is contraindicated in people <21 years because of the risk of Reye's syndrome.[1] If patients have an aspirin allergy, then clopidogrel should be used. Following acute coronary syndrome, combination of aspirin and clopidogrel for up to a year is reasonable, and lifelong aspirin therapy is indicated in patients who have had an intracoronary stent placed.[128]

Smoking cessation

All patients with diabetes should be advised not to smoke or to quit smoking.[1] Smoking counselling and other forms of smoking cessation therapy should be incorporated into routine diabetes care.[1]

ST-elevation MI (STEMI)

For people with diabetes with STEMI, primary percutaneous coronary intervention (PCI) is superior to fibrinolytic therapy.[129] One randomised controlled trial (RCT) examining the effects of peri-procedural intensive glycaemic control during early PCI on the rate of re-stenosis in hyperglycaemic (glucose ≥140 mg/dL [7.8 mmol/L]) patients with a STEMI showed that, compared with conventional glycaemic control, intensive control led to a 50% reduction in re-stenosis at 6 months.[130] An analysis that included data from 11 clinical trials that compared percutaneous transluminal coronary angioplasty (PTCA) with fibrinolytic therapy in 2725 patients with STEMI included 367 patients with diabetes.[131] Among patients with diabetes, 30-day mortality or non-fatal reinfarction rate was 19.3% for those treated with fibrinolytics and 9.2% for those who underwent primary PTCA.

Non-ST-elevation MI (NSTEMI)

For patients with diabetes with NSTEMI, 2 large RCTs showed that a primary aggressive strategy using PTCA in the first 48 hours was associated with increased survival.6[A]Evidence

Glycoprotein IIb/IIIa receptor inhibitors in a meta-analysis of 6 large-scale trials with 23,072 patients (6458 with diabetes) with NSTEMI/unstable angina was associated with decreased mortality in patients with diabetes. Glycoprotein IIb/IIIa receptor inhibitors were also associated with decreased mortality in patients with diabetes undergoing PTCA for NSTEMI/unstable angina.7[A]Evidence

Revascularisation for left main or multi-vessel disease

The 2012 ACC/AHA/AATS/PCNA/SCAI/STS stable ischaemic heart disease guidelines state that use of CABG over PCI is reasonable in patients with diabetes and multi-vessel disease.[136] However, the 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the stable ischaemic heart disease guidelines adds that diabetic patients with complex multi-vessel CAD should undergo a Heart Team approach to revascularisation, inclusive of an interventional cardiologist and a cardiac surgeon.[137] It also states that CABG is generally recommended in preference to PCI to improve survival in diabetic patients with multi-vessel CAD for which mechanical revascularisation is likely to improve survival. This is particularly recommended if a LIMA-LAD (left internal mammary artery to left anterior descending artery) graft is used and the patient is a good surgical candidate.

The same guidelines recommend CABG for left main disease. The guidelines recognise that it is reasonable to consider PCI in high-risk surgical conditions or low-risk PCI patients for left main disease. One trial (EXCEL; about 30% participants with diabetes) found that PCI was noninferior to CABG for the

endpoint of MI, stroke, or mortality at 3 years.[138] Mortality after CABG is higher in people with diabetes. Nevertheless, among people with diabetes, survival after indicated CABG surgery is superior to survival after medical therapy or PCI.[134] [139] 8[A]Evidence

The pivotal trials are summarised as follows:

- In diabetic patients with left main coronary disease and/or 3-vessel CAD, the SYNTAX trial found that PCI resulted in higher rates of repeat revascularisation and major adverse cardiovascular or cerebrovascular events compared with patients who underwent CABG.[144] [145] However, there was no difference in rates of all-cause death, stroke, or MI.
- The FREEDOM trial evaluated diabetic patients with multi-vessel 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.[146]
- In the Bypass Angioplasty Revascularization Investigation (BARI) trial, when comparing CABG versus balloon-only PCI 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.[140] 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.[141]
- The Arterial Revascularization Trial (ART) compared CABG with PCI with bare metal stents in patients with multi-vessel disease.[147] Subgroup analysis of patients with diabetes showed 1-year event-free survival of 84.4% for CABG and 63.4% for PCI.[147] Multiple studies comparing CABG versus PCI with drug-eluting stents have shown that diabetes is an independent predictor of target lesion restenosis.[141] [143] 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 revascularisation. [148] [149] [150] [151] [152]

Revascularisation for single-vessel disease

In patients with proximal LAD disease, the 2012 ACC/AHA/AATS/PCNA/SCAI/STS stable ischaemic heart disease guidelines recommend CABG with a LIMA graft over PCI and do not differentiate between patients with or without diabetes with single-vessel proximal LAD lesions.[136] Yet, according to the recent European Society of Cardiology (ESC) guidelines, PCI is recommended in patients with single-vessel, non-proximal LAD disease.[153]

Treatment details overview

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see Disclaimer)

Presumptive		(summary)
Patient group	**Tx line**	**Treatment**

Presumptive (summary)

acute MI	1st	coronary intervention and medical management

Acute (summary)

Patient group	Tx line	Treatment
left main stenosis	1st	CABG and perioperative tight glycaemic control
multi-vessel CAD	1st	revascularisation and perioperative tight glycaemic control
single-vessel CAD	1st	revascularisation and perioperative tight glycaemic control

Ongoing (summary)

Patient group	Tx line	Treatment
diabetic CVD: stable and/or after intervention	1st	BP control
	plus	lipid control
	plus	glycaemic control
	plus	lifestyle and behavioural therapy
	adjunct	antiplatelet therapy

Treatment options

Presumptive

Patient group	Tx line	Treatment
acute MI	**1st**	**coronary intervention and medical management** » For patients with diabetes with ST-elevation MI (STEMI), primary percutaneous coronary intervention (PCI) is superior to fibrinolytic therapy. » For patients with diabetes with non-ST-elevation MI (NSTEMI), 2 large RCTs showed that a primary aggressive strategy using percutaneous transluminal coronary angioplasty (PTCA) in the first 48 hours was associated with increased survival.6[A]Evidence » Glycoprotein IIb/IIIa receptor inhibitors with NSTEMI/unstable angina was associated with decreased mortality in patients with diabetes.[154] 7[A]Evidence » All patients should receive aspirin, beta-blockers, nitrates, and ACE inhibitors as part of early management for STEMI and NSTEMI.[75] » Trials of tight glycaemic control in critically ill patients have yielded mixed results.[112] [113] In one study of acute coronary syndrome patients who presented with hyperglycaemia, intensive glucose control was associated with harm and did not reduce infarct size.[114] One large RCT raised questions about intensive blood glucose targets for inpatient glycaemic control and found a lower mortality for 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 (4.5-6.0 mmol/L).[115] A concern has been whether there is any additional benefit to lowering blood glucose levels below about 140 to 180 mg/dL (7.8-10 mmol/L) in the ICU setting.[116] One randomised controlled trial (RCT) examining the effects of peri-procedural intensive glycaemic control during early PCI on the rate of re-stenosis in hyperglycaemic (glucose ≥140 mg/dL [7.8 mmol/L]) patients with a STEMI showed that, compared with conventional glycaemic control, intensive control led to a 50% reduction in re-stenosis at 6 months.[130] » The American Diabetes Association recommends that in critically ill patients,

Presumptive

Patient group	Tx line	Treatment
		insulin therapy should be started for persistent hyperglycaemia >180 mg/dL (10 mmol/L). Once insulin therapy is started, a target glucose range of 140 to 180 mg/dL (7.8-10 mmol/L) was recommended for most critically ill patients. These patients require an intravenous insulin protocol that has demonstrated efficacy and safety for achieving targets without increasing risk for severe hypoglycaemia.[1]

Acute

Patient group	Tx line	Treatment
■ **left main stenosis**	**1st**	**CABG and perioperative tight glycaemic control** » Coronary artery bypass grafting (CABG) was superior to medical treatment for all patients with significant left main stenosis.[134] » However, it is reasonable to consider PCI in high-risk surgical situations and low-risk PCI patients for left main stenosis.[136] [137] [138] » 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.[117] 4[A]Evidence
■ **multi-vessel CAD**	**1st**	**revascularisation and perioperative tight glycaemic control** » The 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the stable ischaemic heart disease guidelines recommends that diabetic patients with complex multi-vessel CAD should undergo a Heart Team approach to revascularisation, inclusive of an interventional cardiologist and a cardiac surgeon.[137] Either PCI with drug-eluting stents or CABG may be suitable depending on factors such as anatomic location of lesions, lesion length, presence of chronic total occlusions, LV function, and comorbidity. CABG is generally recommended in preference to PCI to improve survival in diabetic patients with multi-vessel CAD for which mechanical revascularisation is likely to improve

Acute

Patient group	Tx line	Treatment
		survival. This is particularly recommended if a LIMA-LAD (left internal mammary artery to left anterior descending artery) graft is used and the patient is a good surgical candidate. » 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.[117] 4[A]Evidence
single-vessel CAD	**1st**	**revascularisation and perioperative tight glycaemic control** » In patients with proximal left anterior descending artery (LAD) disease, the 2012 ACC/AHA/AATS/PCNA/SCAI/STS stable ischaemic heart disease guidelines recommend CABG with a left internal mammary artery (LIMA) graft over PCI and do not differentiate between patients with or without diabetes with single-vessel proximal LAD lesions.[136] However, according to European Society of Cardiology (ESC) guidelines, PCI is recommended in patients with single-vessel with non-proximal LAD disease.[153]

Ongoing

Patient group	Tx line	Treatment
diabetic CVD: stable and/or after intervention	**1st**	**BP control** » Both the Joint National Commission (JNC 8) and the American Diabetes Association (ADA) recommend a general BP goal of <140/90 mmHg in patients with diabetes and hypertension.[1] [71] 3[A]Evidence In certain patient populations (younger, presence of albuminuria, or multiple atherosclerotic cardiovascular disease risk factors), a systolic BP goal of 130 mmHg and a diastolic BP goal of 80 mmHg can be considered.[1] All patients should receive lifestyle advice on topics such as weight management, sodium reduction, and physical activity. Combination therapy is often required to reach BP goals. JNC 8 and ADA guidelines recommend the use of ACE

Ongoing

Patient group	Tx line	Treatment

inhibitors, angiotensin-II receptor antagonists, calcium-channel blockers, or thiazide diuretics as initial antihypertensive therapy in non-black hypertensive patients with diabetes.[71] In black patients, it is recommended that a calcium-channel blocker or a thiazide diuretic be used as initial antihypertensive therapy. JNC 8 guidelines recommend initiation of an ACE inhibitor or angiotensin-II receptor antagonist as first-line therapy if chronic kidney disease is present.[71]

» One meta-analysis found that ACE inhibitors reduced mortality and major cardiovascular 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 in patients with diabetes.[121]A meta-analysis showed that in patients with diabetes and kidney disease, no antihypertensive regimen improved survival; however, ACE inhibitors and angiotensin-II receptor antagonists (either alone or in combination) were effective in preventing end-stage renal disease. It is noted that the combination of ACE inhibitors and angiotensin-II receptor antagonists should not be combined as this can increase the risk of acute kidney injury and hyperkalaemia.[120]

» Beta-blockers are not contraindicated in people with diabetes but are less preferred and may mask symptoms of hypoglycaemia.

» ACE inhibitors have shown increased risk for hypoglycaemia in conjunction with insulin or insulin secretagogue (sulfonylurea or meglitinide).[122]

Primary options

» lisinopril: 10 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day
-or-
» enalapril: 5 mg orally once daily initially, increase gradually according to response, maximum 40 mg/day as a single dose or in 2 divided doses
-or-
» captopril: 25 mg orally twice daily initially, increase gradually according to response, maximum 200 mg/day
-or-

TREATMENT

Ongoing

Patient group	Tx line	Treatment
		» candesartan: 4 mg orally once daily initially, increase gradually according to response, maximum 32 mg/day **-or-** » irbesartan: 75 mg orally once daily initially, increase gradually according to response, maximum 300 mg/day **-or-** » losartan: 50 mg orally once daily initially, increase gradually according to response, maximum 100 mg/day as a single dose or in 2 divided doses **-or-** » valsartan: 40-80 mg orally once daily initially, increase gradually according to response, maximum 320 mg/day
		--AND/OR--
		» hydrochlorothiazide: 12.5 to 25 mg/day orally once daily initially, increase gradually according to response, maximum 50 mg/day as a single dose or in 2 divided doses **-or-** » chlortalidone: 12.5 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 **-or-** » diltiazem: 120-180 mg orally (extended-release) once daily initially, increase gradually according to response, maximum 480 mg/day
	plus	**lipid control**
		» American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend moderate- or high-dose statin use in adults aged >21 years who are candidates for statin therapy if the patient has clinical atherosclerotic cardiovascular disease (ASCVD) or LDL-cholesterol ≥4.9 mmol/L (≥190 mg/dL). In the absence of ASCVD or LDL-cholesterol ≥4.9 mmol/L (≥190 mg/dL), high-intensity statins are recommended for people with diabetes aged 40 to 75 years if the estimated 10-year ASCVD risk

Ongoing

Patient group	Tx line	Treatment

is ≥7.5%; otherwise, moderate-intensity statins should be used.[78] The guidelines recommend an individualised approach for people aged >75 years. A moderate-dose statin has been defined by the ACC/AHA as one that generally lowers LDL-cholesterol level by 30% to 50%, while a high-dose statin has been defined as one that lowers LDL-cholesterol level by ≥50%.

» Combination therapy using statins and other lipid-lowering agents may also be considered, but studies of cardiovascular clinical outcomes and safety are lacking, and risks of complications such as aminotransferase elevation, myositis, or rhabdomyolysis may increase.5[A]Evidence

» Statin therapy has been shown to lead to reduction in definitive CVD outcomes including CHD, death, and non-fatal MI in people with diabetes and may have beneficial effects independent of lipid lowering.[1]

» Statins are contraindicated in pregnancy.

Primary options

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

OR

Primary options

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

OR

Primary options

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

OR

Primary options

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

OR

Primary options

Ongoing

Patient group	Tx line	Treatment
		» lovastatin: moderate intensity: 40 mg/day orally (immediate-release) given in 1-2 divided doses
		OR
		Primary options
		» fluvastatin: moderate intensity: 40 mg orally (immediate-release) twice daily, or 80 mg orally (extended-release) once daily
		OR
		Primary options
		» pitavastatin: moderate intensity: 2-4 mg orally once daily
	plus	**glycaemic control**
		» HbA1c goal for most patients is <53 mmol/mol (<7%) to prevent microvascular complication, but should be individualised.[1] Less stringent goals may be appropriate for patients with a history of severe hypoglycaemia, very young or older patients, and patients with comorbid conditions.[1] 9[A]Evidence
		» Metformin is recommended as initial treatment in combination with medical nutrition therapy and exercise at the time of diagnosis. Metformin has a long safety record, low cost, and may reduce cardiovascular risk.[24]
		» Liraglutide and empagliflozin may also reduce cardiovascular risk and may be considered for glucose lowering in people with longstanding suboptimal glucose control and established CVD.[1]
		» The glitazones as a class should be used with caution in patients who have CHF or are at risk of developing CHF.[110] Rosiglitazone has been withdrawn in Europe.
		Primary options
		» metformin: 500 mg orally (immediate-release) once daily initially, increase by 500 mg/day increments every week, maximum 1000 mg twice daily
	plus	**lifestyle and behavioural therapy**
		» Therapeutic lifestyle interventions such as medical nutrition therapy and aerobic exercise have been shown in large clinical trials to improve glycaemic, lipid, and BP control.[44]

Ongoing

Patient group	Tx line	Treatment
		» 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.[91] The Mediterranean Diet,[92] DASH (Dietary Approaches to Stop Hypertension),[93] and vegan[94] diets have all been demonstrated to be effective for people with diabetes.[95] » Physical activity: at least 150 minutes divided over 3 or more days per week of moderate-intensity aerobic physical activity at 50% to 70% of maximal heart rate.[1] In the absence of contraindications, resistance training is also recommended.[1] » All patients with diabetes should be advised to quit smoking or not start.
	adjunct	**antiplatelet therapy** » The American Diabetes Association recommends that aspirin therapy be considered for primary prevention in adults with type 1 or type 2 diabetes with a 10-year cardiovascular risk >10%.[1] This refers to men or women aged 50 years and over who have at least one additional major risk factor (family history of CVD; hypertension; smoking; dyslipidaemia; or albuminuria) and are not at risk for bleeding. Patients with a 10-year cardiovascular risk of <5% with diabetes should not have aspirin therapy initiated for primary prevention due to concerns that the bleeding risk outweighs the benefit.[1] Adults with CVD should receive aspirin for secondary prevention. Clopidogrel is an alternative for patients with aspirin allergy, although supporting data are limited.[155] Combination of aspirin and clopidogrel is recommended for up to 1 year after an acute coronary syndrome and lifelong aspirin therapy is indicated in patients who have had an intracoronary stent placed. The main adverse effect is an increased risk of gastrointestinal bleeding. Aspirin is not recommended for children because of a risk of Reye's syndrome. **Primary options** » aspirin: 75-162 mg orally once daily **OR** **Secondary options** » clopidogrel: 75 mg orally once daily

Emerging

Metabolic (bariatric) surgery

Metabolic surgery has improved glycaemic control and cardiovascular risk factors in obese people, but its role in reducing long-term diabetic complications and cardiovascular disease is yet to be determined.[1] The American Diabetes Association in 2017 expanded its recommendations for metabolic surgery to include appropriate Asian-American surgical candidates with BMI ≥37.5 kg/m^2 (in addition to others with BMI ≥40 kg/m^2) with any level of glycaemic control/any complexity of glucose-lowering regimen. Surgery should be done in a high-volume, experienced centre. Surgery was also recommended as an option for adults with: BMI 35.0-39.9 kg/m^2 (32.5-37.4 kg/m^2 for Asian-Americans) with hyperglycaemia inadequately controlled despite lifestyle and optimal medical management; or as a consideration for those with BMI 30.0-34.9 kg/m^2 (27.5-32.4 kg/m^2 for Asian-Americans) with hyperglycaemia inadequately controlled despite optimal use of oral or injectable medications (including insulin).

Recommendations

Monitoring

Patients with diabetes benefit from monitoring every 3 months if their diabetes is not well controlled and every 6 to 12 months otherwise.[1] BP, weight, and activity level should be monitored at each visit and healthy lifestyle modifications encouraged.

All patients with diabetes benefit from consideration at diagnosis of an ankle-brachial index (ABI) test to assess for peripheral arterial disease (PAD).[1] All patients with one or more of the following should have a baseline ankle-brachial index (ABI) measured to assess for PAD: exertional leg symptoms; non-healing wounds; age 65 years or older; or age 50 years or older with diabetes or smoking history.[60] ABI results: 1.0 to 1.4 is normal; 0.91 to 0.99 is borderline; ≤0.9 is abnormal.

In patients with known CVD, ACE inhibitors, statins, and aspirin are recommended. In patients with a prior MI, beta-blockers are continued for at least 2 years after the event. Thiazolidinediones should be avoided in patients with CHF or at risk for heart failure. Metformin may be used in patients with stable CHF if renal function is normal but should be avoided in unstable or hospitalised patients with CHF.

Patient instructions

Chest pain or dyspnoea associated with exertion and claudication should be evaluated by a physician immediately.

Medical nutrition therapy[1]

- Patients should be taught to monitor carbohydrate intake as a key strategy to achieve glycaemic control. Some people (e.g., those using flexible insulin) may also benefit from fat and protein counting.[1] 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.[91] The Mediterranean Diet,[92] DASH (Dietary Approaches to Stop Hypertension),[93] and vegan[94] diets have all been demonstrated to be effective for people with diabetes.[95] Monitoring carbohydrate intake is recommended. Dietary fat and cholesterol intake is as recommended for the general population.[1]

Physical activity[1]

- Patients should engage in at least 150 minutes per week of moderate-intensity aerobic physical activity at 50% to 70% of maximal heart rate. In the absence of contraindications, resistance training is also recommended.[1]
- This physical activity should be spread out over at least 3 days per week.
- Sedentary periods should be interrupted by activity every 30 minutes. Older adults may benefit from balance and flexibility training.[1]

Dyslipidaemia[1]

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

Smoking cessation[1]

- All patients with diabetes should be advised not to smoke or to stop smoking.

Resources:

[American Heart Association/American College of Cardiology: CV risk calculator]

FOLLOW UP

[National Institute of Diabetes and Digestive and Kidney Diseases: diabetes, heart disease, and stroke]

[US Department of Health and Human Services: dietary guidelines for Americans, 2015-2020; 8th edition]

Complications

Complications	Timeframe	Likelihood
CHF	**variable**	**medium**
Diabetes increases the risk for CHF 1.8-fold in men and 3.7-fold in women.[157] Mortality is 40% to 80% higher in people with diabetes with CHF than in people without diabetes with CHF.[157] The predominant aetiological factor for CHF in people with diabetes is ischaemic heart disease and subsequent left ventricular dysfunction. Other aetiological factors include concomitant comorbidities (obesity, dyslipidaemia, HTN, and renal impairment), cardiac dysfunction due to hyperglycaemia, and use of glitazones.		
dysrhythmia	**variable**	**medium**
Autonomic dysfunction occurs in 40% to 50% of patients with diabetes.[54] This may result in sympathovagal imbalance, which lowers the threshold for life-threatening arrhythmias.[54] Patients with arrhythmias should be monitored and referred for appropriate treatment.		
ischaemic toe/foot, gangrene, or amputation	**variable**	**medium**
All patients with one or more of the following should have a baseline ankle-brachial index (ABI) measured to assess for PAD: exertional leg symptoms; non-healing wounds; age 65 years or older; or age 50 years or older with diabetes or smoking history.[60] 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. Aetiological factors include vascular factors (cerebrovascular disease, cardiovascular risk factors, atherosclerosis, and peripheral arterial disease) and non-vascular factors (hyperglycaemia leading to excess formation of advanced glycated end-products, disturbed neuronal signalling leading to cerebral amyloidosis).[158]		

Prognosis

CAD is the leading cause of death in people with diabetes.[2] People with diabetes have a 1.5- to 2-fold increased risk of MI compared with people without diabetes. CAD in people with diabetes is more severe, starts at an earlier age, and is more costly. Survival after MI is worse in men and women with diabetes.

Diabetes is an independent predictor of cardiovascular morbidity and mortality in people with heart failure.[156] The relative risk of cardiovascular-related death or heart failure-related hospitalisation was greater in people with preserved ejection fraction (diastolic heart failure) than with low ejection fraction.

Multiple studies comparing CABG versus percutaneous intervention with drug-eluting stents have shown that diabetes is an independent predictor of target lesion re-stenosis.[122] [141] 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 revascularisation.[148] [149] [150] [151] [152]

Diagnostic guidelines

Europe

Management of diabetes: a national clinical guideline

Published by: Scottish Intercollegiate Guidelines Network **Last published:** 2010

North America

Standards of medical care in diabetes - 2017

Published by: American Diabetes Association **Last published:** 2017

Summary: Provides comprehensive diagnostic recommendations for diabetes.

2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes

Published by: American College of Cardiology; American Heart Association **Last published:** 2014

Summary: Provides comprehensive, evidence-based guidelines for the clinical management of non-ST elevation acute coronary syndromes, including diagnostic testing.

Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease

Published by: American Heart Association **Last published:** 2014

Summary: Guidelines on the use of non-invasive testing for the evaluation of ischaemic heart disease in women.

Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA guideline recommendations)

Published by: American College of Cardiology; American Heart Association **Last published:** 2013

Summary: Provides comprehensive, evidence-based guidelines for the clinical management of patients with peripheral artery disease, including screening and diagnostic testing.

Recommendations on screening for type 2 diabetes in adults

Published by: Canadian Task Force on Preventive Health Care **Last published:** 2012

Summary: Updated guidelines that for screening type 2 diabetes in adults.

Appropriateness criteria for stress echocardiography

Published by: American College of Echocardiography Foundation; American Society of Echocardiography; American College of Emergency Physicians; American Heart Association; American Society Society of Nuclear Cardiology; Society for Cardiovascular Angiography and Interventions; Society of Cardiovascular Computed Tomography; Society for Cardiovascular Magnetic Resonance **Last published:** 2008

North America

Primary prevention of cardiovascular diseases in people with diabetes mellitus

Published by: American Heart Association; American Diabetes Association **Last published:** 2007

Summary: Discusses approaches to primary prevention of CVD in people with diabetes, including diagnostic monitoring and tests.

Treatment guidelines

Europe

European guidelines on cardiovascular disease prevention in clinical practice

Published by: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice **Last published:** 2016

Summary: Provides a comprehensive review and a critical evaluation of diagnostic and therapeutic procedures, including assessment of the risk-benefit ratio for CVD.

Type 2 diabetes in adults: management

Published by: National Institute for Health and Care Excellence **Last published:** 2015

Cardiovascular disease: risk assessment and reduction, including lipid modification

Published by: National Institute for Health and Care Excellence **Last published:** 2014

Guidelines on diabetes, pre-diabetes, and cardiovascular diseases

Published by: European Association for the Study of Diabetes; European Society of Cardiology **Last published:** 2013

Summary: Comprehensive consensus guidelines and evidence-based recommendations endorsed by the joint partnership of 2 authoritative organisations, the EASD and ESC, into the management of diabetes and associated CVDs.

2013 ESC guidelines on the management of stable coronary artery disease

Published by: European Society of Cardiology **Last published:** 2013

Summary: Evidence-based guidelines on the management of stable coronary artery disease.

Myocardial infarction: cardiac rehabilitation and prevention of further MI

Published by: National Institute for Health and Care Excellence **Last published:** 2013

Summary: Evidence-based guidelines on secondary prevention for patients in primary and secondary care after an MI.

Europe

Management of diabetes: a national clinical guideline

Published by: Scottish Intercollegiate Guidelines Network **Last published:** 2010

Cardiovascular disease: identifying and supporting people most at risk of dying early

Published by: National Institute for Health and Care Excellence **Last published:** 2008

JBS2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice

Published by: British Cardiac Society; British Hypertension Society; Diabetes UK; Heart UK; Primary Care Cardiovascular Society; The Stroke Association **Last published:** 2005

North America

Standards of medical care in diabetes - 2017

Published by: American Diabetes Association **Last published:** 2017

Summary: Provides comprehensive management recommendations for diabetes.

Statin use for the primary prevention of cardiovascular disease in adults: preventive medication

Published by: US Preventive Services Task Force **Last published:** 2016

Summary: Recommendations from US Preventive Services Task Force.

Diabetes self-management education and support in type 2 diabetes: A joint position statement of the American Diabetes Association, the American Association of Diabetes Educators, and the Academy of Nutrition and Dietetics

Published by: American Association of Diabetes Educators **Last published:** 2015

Summary: Provides an algorithm and guidance to healthcare professionals on when to refer patients to diabetes educators and other support providers.

Toward optimized practice: prevention and management of cardiovascular disease risk in primary care

Published by: Toward Optimized Practice Program (Alberta, Canada) **Last published:** 2015

Summary: Detailed programme for the screening, risk assessment, management, and monitoring of adults at risk of CVD.

Diabetes care

Published by: British Columbia Ministry of Health Guidelines and Protocols Advisory Committee (Canada) **Last published:** 2015

North America

2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8)

Published by: National Heart, Lung, and Blood Institute **Last published:** 2014

Summary: Evidence-based recommendations regarding the management of high blood pressure. The guideline provides analysis of treatment thresholds, treatment goals, and strategies to achieve those goals.

2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes

Published by: American College of Cardiology; American Heart Association **Last published:** 2014

Summary: Provides comprehensive, evidence-based guidelines for the clinical management of non-ST elevation acute coronary syndromes.

Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease

Published by: American Heart Association **Last published:** 2014

Summary: Guidelines on the use of non-invasive testing for the evaluation of ischaemic heart disease in women.

Guidelines for the primary prevention of stroke

Published by: American Heart Association; American Stroke Association **Last published:** 2014

Summary: Evidence-based recommendations for the primary prevention of stroke.

2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults

Published by: American College of Cardiology; American Heart Association **Last published:** 2013

Summary: Comprehensive, evidence-based guidelines produced by an expert panel that contain clinical practice recommendations for the treatment of blood cholesterol levels to reduce risk for atherosclerotic cardiovascular disease.

Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA guideline recommendations)

Published by: American College of Cardiology; American Heart Association **Last published:** 2013

Summary: Provides comprehensive, evidence-based guidelines for the clinical management of patients with PAD.

North America

2013 clinical practice guidelines for the prevention and management of diabetes in Canada

Published by: Canadian Diabetes Association **Last published:** 2013

Summary: Complete guidelines that include the recognition and management of the micro- and macrovascular problems associated with diabetes.

AHA/ACC guidelines for secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update

Published by: American Heart Association **Last published:** 2011

VA/DoD clinical practice guideline for the management of diabetes mellitus

Published by: Department of Veteran Affairs, Department of Defense **Last published:** 2010

Summary: Provides comprehensive recommendations for the management of diabetes in adults.

American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control

Published by: American Association of Clinical Endocrinologists; American Diabetes Association **Last published:** 2009

Appropriateness criteria for stress echocardiography

Published by: American College of Echocardiography Foundation; American Society of Echocardiography; American College of Emergency Physicians; American Heart Association; American Society Society of Nuclear Cardiology; Society for Cardiovascular Angiography and Interventions; Society of Cardiovascular Computed Tomography; Society for Cardiovascular Magnetic Resonance **Last published:** 2008

Primary prevention of cardiovascular diseases in people with diabetes mellitus

Published by: American Heart Association; American Diabetes Association **Last published:** 2007

Summary: Discusses approaches to primary prevention of CVD in people with diabetes including lifestyle management, glucose management, lipid management, BP control, smoking cessation, and use of antiplatelet agents.

Oceania

Guidelines for the management of absolute cardiovascular disease (CVD) risk

Published by: National Vascular Disease Prevention Alliance; National Heart Foundation of Australia **Last published:** 2012

Oceania

Reducing risk in heart disease: an expert guide to clinical practice for secondary prevention of coronary heart disease

Published by: National Heart Foundation of Australia; Cardiac Society of Australia and New Zealand **Last published:** 2012

Physical activity in patients with cardiovascular disease: management algorithm and information for general practice

Published by: National Heart Foundation of Australia **Last published:** 2006

Summary: Comprehensive, evidence-based guidelines for general practitioners on the level and type of physical exercise they should recommend to patients with CVD. A useful algorithm is included.

Online resources

1. FDA: new warning and contraindication for blood pressure medicines containing aliskiren (Tekturna) *(external link)*

2. American Heart Association/American College of Cardiology: CV risk calculator *(external link)*

3. National Institute of Diabetes and Digestive and Kidney Diseases: diabetes, heart disease, and stroke *(external link)*

4. US Department of Health and Human Services: dietary guidelines for Americans, 2015-2020; 8th edition *(external link)*

Evidence scores

1. Reducing CVD risk: there is medium-quality evidence that supports the effectiveness of lowering LDL with atorvastatin in patients with diabetes.[19]
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

2. CVD and all-cause mortality: there is medium-quality evidence that increasing physical activity decreases CVD and all-cause mortality, as well as various intermediate measures such as lipids.[42] [43] [44]
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

3. Reducing cardiovascular risk: there is good-quality evidence that intensive blood-pressure lowering (targeting a systolic pressure <120 mmHg over 4.7 years, as compared with targeting <140 mmHg), did not lessen risk (composite outcome: non-fatal MI, non-fatal stroke, or death from cardiovascular cause) in people with type 2 diabetes. Intensive blood-pressure lowering did increase the risk of adverse events.[16]
Evidence level A: Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

4. Survival: there is good-quality evidence that supports the benefit of tight glucose control by insulin infusion in patients who have undergone CABG.[118] [119]
Evidence level A: Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

5. Reducing cardiovascular risk: there is good-quality evidence that long-term use of fibrates in patients with type 2 diabetes significantly reduced the risk of non-fatal myocardial infarction, but had no significant effect on mortality or on other adverse cardiovascular outcomes.[124] However, there is good-quality evidence from the ACCORD trial that adding a fibrate to a statin, compared with statin monotherapy (composite outcome: non-fatal MI, non-fatal stroke, or death from cardiovascular cause, over 4.7 years) did not reduce cardiovascular risk in people with type 2 diabetes.[125] More studies are needed to address the benefit of combination fibrate-statin therapy on CVD outcomes in type 2 diabetes.
Evidence level A: Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

6. Survival: there is good-quality evidence that supports benefit of percutaneous transluminal coronary angioplasty (PTCA) within 48 hours of non-ST elevation MI.[132] [133]

Evidence level A: Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

7. Survival: there is good-quality evidence that supports benefit of glycoprotein IIb/IIIa receptor inhibitors in non-ST elevation MI, with or without percutaneous transluminal coronary angioplasty (PTCA).[134] [135]
Evidence level A: Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

8. Survival: there is good-quality evidence that supports superiority of CABG over percutaneous coronary intervention in 3-vessel disease.[140] [141] Additionally, a subgroup analysis of a trial of CABG versus drug-eluting stents found that diabetic patients with left main and/or 3-vessel disease had overall 1-year major adverse cardiac and cerebrovascular event rate that were higher among those treated with drug-eluting stents as compared with CABG, mainly because of a need for repeat revascularisation. However, revascularisation method did not impact the death/stroke/myocardial infarction rate. Diabetes increased mortality risk after either procedure, as compared with absence of diabetes. Compared with CABG, mortality was higher after drug-eluting stents for diabetic patients with highly complex lesions.[142] [143]
Evidence level A: Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

9. Reducing CVD risk: there is good-quality evidence that increasing the severity of hyperglycaemia correlates with increasing cardiovascular risk.[28] However, 3 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 <42 mmol/mol to 48 mmol/mol [6% to 6.5%] over 3-5 years) did not reduce macrovascular events in adults with type 2 diabetes.[28] [29] [30] In contrast, intensive glycaemic control appeared to have long-term beneficial effects on the risk of CVD in patients with type 1 diabetes.[23]
Evidence level A: Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

Key articles

- American Diabetes Association. Standards of medical care in diabetes - 2017. Diabetes Care. 2017;40(suppl 1):S1-S129. Full text
- Rydén L, Grant PJ, Anker SD, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2013;34:3035-3087. Full text Abstract
- Cushman WC, Evans GW, Byington RP, et al; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362:1575-1585. Full text Abstract
- Gerstein HC, Miller ME, Genuth S et al; ACCORD Study Group. Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med. 2011;364:818-828. Full text Abstract
- Hayward RA, Reaven PD, Wiitala WL, et al; VADT Investigators. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015;37:2197-2206. Full text Abstract
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