

Macrovascular disease: pathogenesis and risk assessment

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Abstract

Type 2 diabetes mellitus is characterized by obesity and insulin resistance. Macrovascular (cardiovascular) disease (CVD) encompasses myocardial infarction, stroke and peripheral arterial disease. It is caused by atherosclerosis, a complex pathological process that is accelerated in people with diabetes and therefore accounts for a higher proportion of total mortality. Risk is modified by established factors including hypertension and dyslipidaemia (which are linked to underlying insulin resistance), and microalbuminuria/renal impairment. Hyperglycaemia is a relatively weak risk factor for CVD once diabetes is established. Potential 'novel' predictors include elevated B-type natriuretic peptide, obstructive sleep apnoea, non-alcoholic fatty liver disease, hypoadiponectinaemia and testosterone deficiency, as well as chronic periodontitis and collagen vascular disorders. Early identification of cases and prompt management of risk factors is important in improving long-term outcome. Smoking cessation is a neglected area that requires urgent attention. Relative cardiovascular risk also remains high in type 1 diabetes, particularly in younger patients, and is also an important area for research.

Keywords Atherosclerosis; cardiovascular risk; cerebrovascular disease; coronary artery disease; diabetes; dyslipidaemia; endothelial dysfunction; glycaemic memory; hypertension; MRCP; peripheral arterial disease

Introduction

Diabetes mellitus is a complex, heterogeneous disorder characterized by an aggregation of established and 'novel' risk factors, which translates into a markedly increased risk of macrovascular and microvascular disease. The former is broadly defined by any of three 'large vessel' cardiovascular complications: coronary artery disease (CAD), cerebrovascular disease and peripheral arterial disease (PAD). These affect individuals with type 1 (T1DM) and type 2 (T2DM) diabetes mellitus; in this review, we highlight relevant pathophysiological processes in both conditions.

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Key points

- Diabetes mellitus is no longer automatically considered a 'cardiovascular disease equivalent'. However, lifetime risk of cardiovascular disease remains high, and specific (particularly 'traditional') risk factors increase cardiovascular risk earlier after diagnosis
- Potential 'novel' risk factors for atherosclerosis include severe hypoglycaemia, elevated B-type natriuretic peptide, cardiac troponin T, obstructive sleep apnoea, non-alcoholic fatty liver disease, hypoadiponectinaemia, collagen vascular disorders and testosterone deficiency
- Endothelial dysfunction and inflammation play key roles in the pathogenesis of atherosclerosis and are associated with underlying insulin resistance
- The cardiovascular burden of type 1 diabetes remains disproportionately high despite an apparently favourable lipid profile. Hyperglycaemia, dyslipidaemia, hypertension and renal impairment further increase this risk
- Widespread screening of asymptomatic diabetes patients for coronary artery disease may improve stratification but has not yet been shown to be effective in improving outcomes

Epidemiology

Established (but not recently diagnosed) T2DM confers a long-term cardiovascular risk. CAD remains the most common cause of death in diabetes, with a decrease in life expectancy of up to 4 years in T2DM,¹ and 11–13 years in T1DM.² Compared with normoglycaemic individuals, diabetic patients have higher rates of reinfarction and heart failure, as well as poorer outcomes after sustaining an acute coronary syndrome. Diabetes is also associated with a 2–4-fold increased risk of PAD, and particularly affects the distal lower extremity circulation, increasing the risk of ulceration and the requirement for amputation. Large vessel PAD carries a 6-fold higher risk of death from cardiovascular causes. Even after adjusting for hypertension and dyslipidaemia, diabetes remains an independent predictor of ischaemic neurological events. The spectrum of disease can range from large vessel to small vessel occlusive disease, and from symptomatic to clinically silent.

Endothelial dysfunction and atherosclerosis

Endothelial dysfunction is a key antecedent and modulator of atherosclerosis, and has been demonstrated in association with insulin resistance in pre-diabetes and T2DM, as well as in the first-degree relatives of T2DM patients. It results in disruption of the intricate physiological balance between vasoconstrictors (endothelin, angiotensin II) and vasodilators (nitric oxide, prostacyclin), growth-promoting and inhibitory factors, pro-

atherogenic and anti-atherogenic factors, and pro- and anticoagulant factors (Figure 1).

Established and ‘novel’ risk factors for atherosclerosis

Established risk factors

Age and gender: the Framingham study clearly documents the increasing prevalence of cardiovascular disease (CVD) with age, and that absolute risk is higher in men than women, although this sex-related difference is less pronounced among patients with diabetes. The transition from low (<10% risk estimate) to moderate (>10%) risk of CVD among patients with T2DM occurs at 35 years for men and 45 years for women, provided no other risk factor or evidence of CVD is present. Patients with early-

onset T2DM (mean age 35 years at diagnosis) were approximately twice as likely to develop a non-fatal CV event compared with individuals diagnosed at a later stage (mean age 55 years).

Family history: a family history of proven CVD in a first-degree relative before age 60 years approximately doubles the risk of a coronary event. The presence of two or more affected first-degree relatives further increases the risk of incident coronary heart disease (CHD). In a large Finnish cohort, men with a family history of stroke had an 86% higher risk of ischaemic stroke. Genetic studies are currently investigating the influence of the underlying genetic signatures of T1DM and T2DM on rates of CVD.

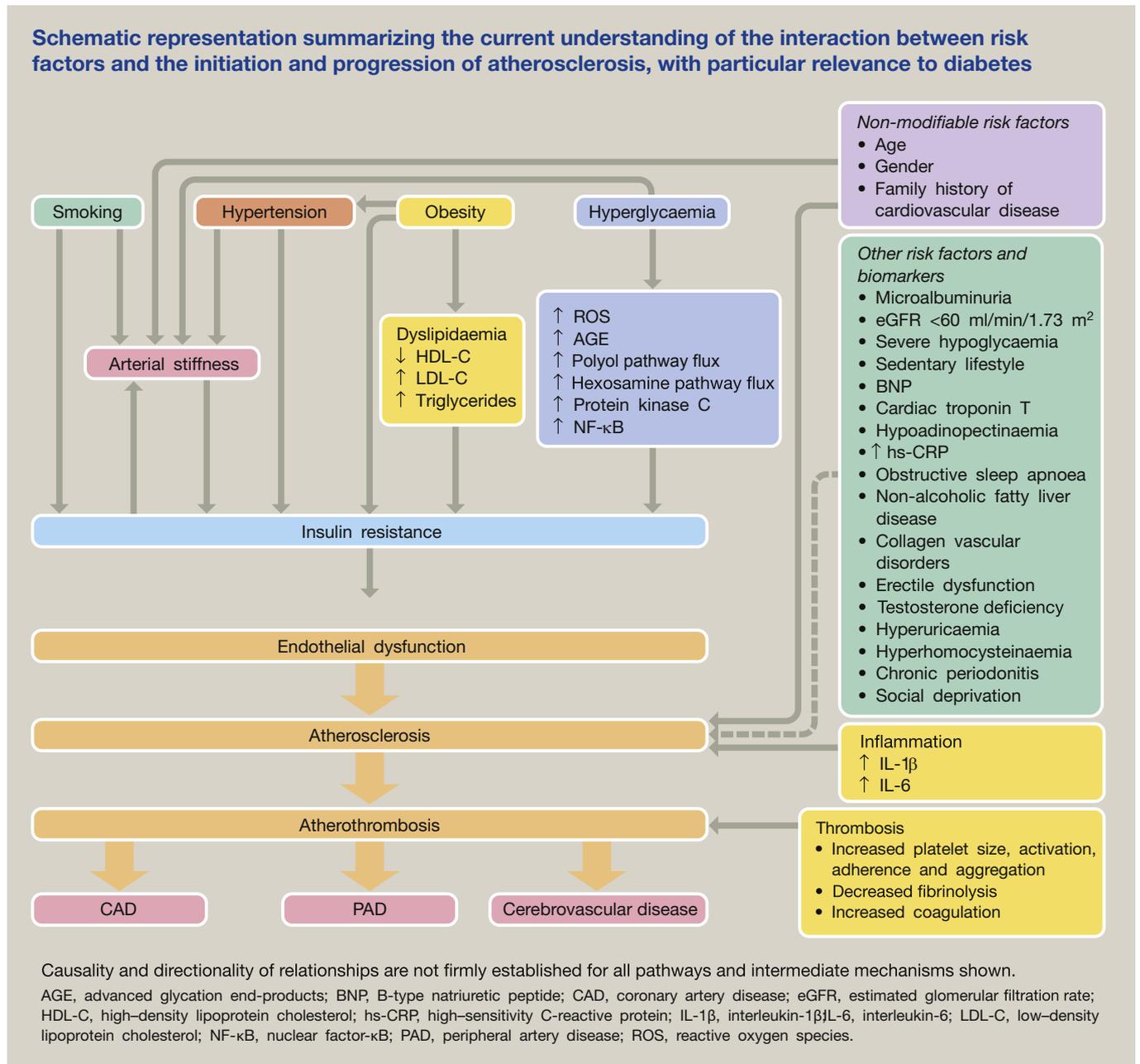


Figure 1

Hypertension: the prevalence of hypertension in those with T2DM increases from 40% in individuals aged 18–44 years to 72% by the age of 64, affecting >84% of patients thereafter. A recent systematic review and meta-analysis observed that a 10 mmHg lowering in systolic blood pressure translated into an 11% reduction in cardiovascular events and a 13% reduction in mortality.

Diabetic renal disease: the presence of sustained microalbuminuria reflects generalized endothelial dysfunction. It is associated with atherosclerosis and CVD, and hence a near-doubling of major cardiovascular events in both diabetic and non-diabetic patients; the increased risk starts even below the diagnostic cut-off point. Renal impairment with an estimated glomerular filtration (eGFR) of <60 ml/minute/1.73 m² is indicative of an even higher cardiovascular risk, whether the lowered eGFR results arise from diabetic nephropathy or other intermediate mechanisms of kidney injury (e.g. recurrent sepsis).

Dyslipidaemia: T2DM is characterized by an atherogenic lipid profile, typically comprising elevated concentrations of small, dense low-density lipoprotein (LDL)-cholesterol, and high concentrations of triglycerides (triacylglycerols), triglyceride-rich remnants, very low density lipoprotein (VLDL)-cholesterol and apolipoprotein B; these are usually seen in combination with low concentrations of apolipoprotein A-1 and low high-density lipoprotein (HDL)-cholesterol. These abnormalities are related to the presence of absolute or relative insulin deficiency. There is a strong relationship between total and LDL-cholesterol and vascular events, such that a 1 mmol/litre reduction in LDL-cholesterol with statin therapy is associated with a 21% reduction in the incidence of major vascular events, and a 9% reduction in all-cause mortality.

Glycaemic control and the glucose hypothesis: glucose control is crucial in reducing the risk of microvascular complications in people with diabetes. Epidemiological analysis of the UK Prospective Diabetes Study (UKPDS) Group indicates that long-term hyperglycaemia is also associated with a higher incidence of macrovascular complications in T2DM. Interestingly, this is also the case when glucose concentrations are high within the non-diabetic range. Hyperglycaemia induces mitochondrial generation of superoxide anions, which have a key role in activating the polyol pathway, the hexosamine pathway and protein kinase C, and in forming advanced glycosylation end products. These processes are mainly involved in the pathogenesis of microvascular disease; glucose is thought to play a less important role in macrovascular complications.

Although the UKPDS indicated specific cardiovascular benefits of glucose-lowering with metformin, positive effects of other older agents (sulfonylureas, insulin) were less well demonstrated, although they could be detected with long-term follow-up after the study had ended. The production of hypoglycaemia by these agents may be one reason for the failure to detect a clear macrovascular benefit (see below). Pioglitazone is associated with reduced cardiovascular risk (although it can cause weight gain, fluid retention and osteoporosis). The most striking breakthroughs in the field in the last 3 years have been the demonstration of remarkable decreases in rates of cardiovascular

events associated with use of: (1) the sodium glucose cotransporter (SGLT)-2 inhibitors empagliflozin (EMPA-REG trial), canagliflozin (CANVAS), dapagliflozin (DECLARE-TIMI); and (2) the glucagon-like peptide (GLP)-1 agonists liraglutide (LEADER), semaglutide (SUSTAIN-6), and albiglutide (HARMONY-outcomes). These trials have heralded a new era of ‘cardiovascular glucose-lowering’.

Severe hypoglycaemia: severe hypoglycaemia is associated with an approximate 6-fold increase in cardiovascular mortality in T1DM, and more than doubles the risk of all-cause death among patients with T2DM. In individuals with T1DM, this may be via an acute increase in proinflammatory and pro-atherosclerotic mediators such as plasminogen activator inhibitor (PAI)-1, vascular adhesion molecules, interleukin (IL)-6 and P-selectin.

Obesity: adiposity, particularly in visceral depots, is associated with insulin resistance, an atherogenic lipid profile, hypertension, inflammation and a prothrombotic state. Visceral adipocytes have a lower threshold for lipolysis than those in subcutaneous adipose tissue, favouring the release of free fatty acids. Caloric overload is associated with adipocyte hypertrophy, larger triglyceride stores, a higher lipolytic rate, increased production of leptin, decreased production of adiponectin (a high-molecular-weight polymeric protein widely thought to be insulin-sensitizing), macrophage infiltration and apoptosis, leading to systemic inflammation and insulin resistance.

Both obesity and significant fluctuations in body weight (cycles of weight gain and weight loss, particularly in individuals who were overweight or obese at baseline) have been associated with an increased risk of cardiovascular events. The recent DiRECT study has highlighted the powerful effects of radical weight loss using low-calorie liquid diets on inducing remission of T2DM. However, in the LOOK-AHEAD trial, a balanced lifestyle intervention including weight management and increased physical activity did not demonstrate improved cardiovascular outcomes in people with established T2DM despite long-term follow-up.

Smoking: unfortunately, in most populations sampled, around 20–30% of people with diabetes continue to smoke. Smoking is associated with systemic oxidative stress, hypercoagulability, impaired fibrinolysis and increased blood viscosity, which facilitate atherothrombosis. Smokers with T2DM also have increased hepatic lipase activity, favouring the generation of atherogenic small dense LDL-cholesterol. Compared with life-long non-smokers, the relative risk of CAD is 2.68 in diabetic women who smoke >15 cigarettes per day, 1.66 in women who smoke 1–14 cigarettes per day and 1.21 for past smokers, returning to baseline after 10 years of cessation. Smoking cessation in diabetes remains an under-researched area. However, available data suggest that, while cessation of smoking is associated with decreased risk of mortality and cardiovascular events, residual risk remains higher among individuals with diabetes.

Sedentary lifestyle: the INTERHEART study estimated that 12% of the population-attributable risk of CAD results from lack of physical exercise. Recent studies have shown that time spent sitting as opposed to standing is strongly associated with cardiovascular risk. Peak exercise capacity is a strong predictor of

mortality in men with and without CVD, independently of other cardiovascular risk factors.

Novel risk factors and biomarkers

Arterial stiffness: the proinflammatory state described accelerates ageing-associated disruption of the balance between the arterial wall scaffolding proteins, elastin and collagen, which determine vascular compliance. Vascular stiffening leads to widening of the arterial pulse pressure and increased pulsatile shear, exacerbating endothelial dysfunction and vascular disease.

B-type natriuretic peptide (BNP): BNP is secreted by ventricular cardiomyocytes mainly in response to pressure overload. Its concentration correlates with the Framingham cardiovascular risk score in T2DM patients, even within the normal range. Similarly, plasma N-terminal pro-BNP predicts cardiovascular events in T2DM patients with microalbuminuria, as well as cardiovascular mortality in T1DM patients with nephropathy.

Cardiac troponin T: in addition to its better known use in the diagnosis of myocardial infarction (MI), subclinical elevations of this myocardial biomarker are strongly predictive of CVD in the general population, as well as in women with T2DM.

Adiponectin: lower circulating concentrations of adiponectin are associated with insulin resistance, β -cell dysfunction, endothelial dysfunction, obesity, T2DM, hypertension, early CAD and multiple CAD lesions.

High-sensitivity C-reactive protein (hs-CRP): although hs-CRP is a strong predictor of cardiovascular events, Mendelian randomization studies strongly suggest that it acts as a marker rather than playing a causative role. Other upstream cytokines, including IL-6, may play a more direct role in the biological pathway between adiposity and atherosclerosis.

Obstructive sleep apnoea (OSA): both T1DM and T2DM are associated with an increased risk of OSA. Severe OSA (apnoea–hypopnoea index >30 events/hour) increases the risk of CVD, stroke and mortality in middle-aged populations. There is some evidence that treatment with oxygen therapy improves cardiovascular outcomes in T2DM, although conclusive evidence is lacking.

Aside from the risk of cirrhosis, **non-alcoholic fatty liver disease (NAFLD)** is associated with diastolic dysfunction, increased coronary artery calcium (CAC) scores and a 50% increase in rates of cardiovascular events.

Collagen vascular disorders: patients who have suffered from rheumatoid arthritis for >10 years have a 3-fold higher risk of CVD compared with individuals in whom the condition has been recently diagnosed. CVD risk is even higher in systemic lupus erythematosus, particularly in young women.

Erectile dysfunction: largely a manifestation of endothelial dysfunction, this is associated with a 2–3-fold increase in risk of cardiovascular events and CHD among patients with T2DM.

Testosterone deficiency: low testosterone concentrations are associated with increased concentrations of LDL-cholesterol,

increased production of proinflammatory cytokines, endothelial dysfunction and increased arterial wall thickness. Small-scale studies suggest that testosterone replacement in individuals with deficiency improves surrogate vascular markers, but further outcome studies are required to assess the effects of testosterone replacement on reducing cardiovascular events.

Hyperuricaemia and hyperhomocysteinaemia: these are both associated with cardiovascular risk. A large trial in the UK has randomized 5215 patients to allopurinol or placebo (ISRCTN32017426) to assess its effect on cardiovascular outcomes.

Infection: chronic periodontitis is associated with poor glucose control and increased cardiovascular risk, even after correcting for ‘traditional’ risk factors. The relationship appears to be bidirectional, that is, improving one will produce improvement in the other.

Social deprivation: for reasons that may extend beyond poorer control of multiple risk factors, those with T2DM living in affluent areas have a similar cardiovascular risk to those without T2DM living in a more deprived area. Further research on this topic is continuing.

Vitamin D deficiency: has been associated with more severe hypertension, hyperlipidaemia, and diabetes. Moreover, it has been implicated in arterial stiffening, left ventricular hypertrophy, incident CVD, CVD mortality and all-cause mortality. However, meta-analyses of vitamin D supplementation trials have failed to show clear benefits on cardiovascular protection.

Atherosclerosis in type 1 diabetes

Although absolute rates of mortality have declined in T1DM, there remains on average a dramatic loss of life expectancy. Contemporary population-based data indicate that the relative risk of CVD remains elevated by 3-fold in women and >2 -fold in men, compared with the general population.

Hyperglycaemia is the dominant risk factor for CVD in T1DM, second only to age (DCCT data on cardiovascular risk factors). A recent analysis from the DCCT indicates that early on, abnormalities in traditional risk factors (blood pressure, cholesterol, etc.) are largely driven by elevated glucose, starting to operate as independent risk factors with increasing duration of disease (particularly after >20 years since diagnosis). Renal impairment, when present, is a key risk factor, but rates of CVD remain high even in those with an eGFR in the normal range. Hypertension and, interestingly, a family history of T2DM are also important CVD risk factors in patients with childhood-onset T1DM. It should be noted that elevated concentrations of HDL-cholesterol, frequently observed in T1DM, are a consequence of hepatic (portal) insulinopenia – from the delivery of therapeutic insulin via the subcutaneous (peripheral) route – rather than reflecting a ‘low-risk’ lipid profile.

Assessing risk of macrovascular disease in diabetes

The clinical history should focus on past medical history of CVD and cigarette smoking (pack–years). Absent peripheral pulses on physical examination suggest established CVD. Clinically

important information is afforded by bedside measures of blood pressure, weight and waist circumference, and simple biochemical measurements, including total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride concentrations, glycated haemoglobin, eGFR and microalbuminuria. Concentrations of LDL-cholesterol (using the Friedewald equation) and non-HDL-cholesterol are usually derived from total and HDL-cholesterol concentrations, although LDL-cholesterol can be directly measured.

Coronary artery disease risk assessment

All people >40 years of age with diabetes should be considered at risk of CVD, although a number of current guidelines no longer consider diabetes as an automatic coronary risk equivalent. There is no universally accepted risk score that accurately detects those at highest risk. The efficacy of available interventions intended to reduce serum lipids or blood pressure is not dependent on the demonstration of a higher than average baseline risk. Most international bodies therefore do not recommend a policy of routine screening for CAD in asymptomatic individuals with diabetes, but advocate a more intensive lipid-lowering strategy in those thought to be clinically at highest risk (and not just for those who have had a previous event, i.e. secondary prevention).

A 12-lead electrocardiogram (ECG) is warranted when a past history of MI or resting ischaemia is suspected. ‘Silent’ myocardial ischaemia is recognized but infrequent. QTc prolongation and ST depression have been shown to predict all-cause mortality in T2DM patients. Resting ECG abnormalities and cardiac autonomic dysfunction are predictors of silent ischaemia in asymptomatic people with T1DM.

A number of screening approaches can be used in individuals with a normal resting ECG when clinical suspicion is high, as follows.

Exercise ECG testing: in this widely available and low-cost screening tool, an abnormal exercise response significantly increases the risk of all-cause mortality, death from CAD, and cardiovascular mortality, in some but not all studies. The negative predictive value (NPV) of a normal exercise ECG for subsequent cardiac events in diabetes is 97%. However, in a multicentre study, clinical assessment of ambulatory patients with suspected angina yielded virtually the same prognostic information provided by a resting or exercise ECG, highlighting the need for more effective risk stratification tools.

Coronary artery calcium (CAC) score testing: this is determined by electron-beam and multi-detector computed tomography. It is a non-invasive screening test best reserved for selected asymptomatic patients at intermediate risk of CVD, particularly as between one-third and one-half of asymptomatic diabetes patients have no or minimal CAC. Among patients with diabetes, CAC predicts cardiovascular endpoints and mortality.³ Higher CAC values are associated with higher sensitivity, although lower specificity. Routine use in risk stratification in diabetes has not been adopted by major guidelines because of concerns about cost-effectiveness and radiation exposure.

Pharmacological stress testing with myocardial perfusion scintigraphy (MPS): this can be used in patients with suspected CAD who are unable to exercise. Abnormal images are associated with a 7.4% annual risk of death or non-fatal MI, which is 12-fold higher than for patients with a normal test result.

Exercise testing combined with MPS – this is an alternative if the patient is able to exercise. Annual critical event (MI, cardiac death) rates increase from 2.2% to 3.4% in asymptomatic patients with diabetes. The NPV for MI and cardiac death was 98.8% after exercise MPS in a mixed population of patients with and without diabetes followed up for 36 months.

Exercise or pharmacological stress echocardiography – although data specific to diabetes remain limited, this approach can be useful for risk stratification in diabetes patients with known or suspected CAD. Among diabetes patients with exercise echocardiographic evidence of multivessel disease, 32.8% sustain a cardiac event within 5 years. Dobutamine stress echocardiography may afford a predictive power similar to MPS in diabetes patients over a 3-year observation period. One study reported an NPV for MI and cardiac death of 98.4% over 33 months after normal exercise echocardiography.

Myocardial perfusion imaging using positron emission tomography: this is still costly and not widely available; moreover, data supporting its usefulness in the clinical setting remain sparse. Available data suggest that it is particularly effective in investigating both focal and diffuse coronary stenosis and microvascular function. Moreover, it has the advantage of lower radiation exposure, superior spatial resolution and fewer attenuation artefacts.

Cardiac magnetic resonance imaging with pharmacological stress: where available, this technique can be used to identify patients at high risk of subsequent cardiac death or non-fatal MI. A meta-analysis of available data has reported a sensitivity of 89% and a specificity of 80%.

Multislice computed tomography (CT) angiography: this is promising for future clinical use in view of its good sensitivity (81%) and specificity (82%) and excellent negative NPV (98–100%) in T2DM. As with the CAC score, its use as a screening tool is hampered by radiographic contrast and (higher) radiation exposure, as well as cost factors.

Invasive coronary angiography: this remains the gold standard diagnostic tool for CAD, but it is not appropriate for screening asymptomatic individuals.

Cerebrovascular risk assessment

Ultrasound analysis of carotid artery intima–media thickness and plaque is the most widely used imaging surrogate marker of atherosclerosis in this vascular bed. It is, however, not recommended for CVD screening in asymptomatic patients. It has been shown to predict MI and stroke in a systematic review and a meta-analysis, but this was not replicated among diabetes

patients participating in the MESA study.⁴ Magnetic resonance angiography and CT angiography are more sensitive in detecting plaque ulceration, but are as yet not widely used in screening.

Peripheral arterial disease risk assessment

Ankle–brachial index (ABI) measurement (normal >0.9) is valuable for early detection of PAD. An ABI <0.5 is indicative of severely impaired peripheral circulation. Spuriously high values (ABI >1.4) can be seen in diabetes in association with stiff arterial walls. Despite its high specificity as a predictor of future CVD events, ABI is limited by low sensitivity, limiting its usefulness in the clinical setting. Nonetheless, an ABI <0.9 increases risk of all-cause mortality and CVD mortality in T2DM patients. Symptomatic individuals with a normal resting ABI should have their risk further stratified using an ABI treadmill test.

Applanation tonometry

Arterial stiffness can be quantified by measuring distensibility and compliance coefficients, pulse wave velocity and wave reflection, using applanation tonometry. As these techniques are simple and cost-effective, and can predict the development of cardiovascular events in patients with diabetes as well as in the general population, their more widespread use in the clinical arena has been advocated, although not yet widely adopted.

Risk engines

All individuals with T2DM and most >40 years of age with T1DM are assumed to have a sufficient CVD risk to benefit from currently known pharmacological and non-pharmacological preventive measures, such that risk assessment scoring systems are now less frequently used. Thus, the use of risk tables for people with diabetes has not been advocated in recent guidelines, including the 2016 European guidelines on CVD prevention.⁵ ♦

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online [here](#).

Question 1

A 54-year-old man presented for his annual review for diabetes. He had had type 2 diabetes for 5 years. He had no symptoms but was concerned about his future risk of myocardial infarction. He also had hypertension and dyslipidaemia, and a strong family history of ischaemic heart disease. He was taking perindopril 4 mg daily, atorvastatin 40 mg at night, metformin 500 mg 8-hourly and amlodipine 5 mg daily.

On clinical examination, his blood pressure was 120/75 mmHg, and body mass index 46 kg/m².

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Investigations

- HbA_{1c} 64 mmol/mol (20–42); 8% (4.0–6.0)
- Urea 11.2 mmol/litre (2.5–7.0)
- Creatinine 80 micromol/litre (60–110)
- Estimated glomerular filtration rate >60 ml/minute/1.73 m² (>60)
- Urine albumin:creatinine ratio 2.0 mg/mmol (<2.5)
- Total cholesterol 3.1 mmol/litre (<5.2)
- Low-density lipoprotein-cholesterol 1.5 mmol/litre (<3.36)
- 12-lead ECG showed normal sinus rhythm.

What is the most appropriate next step in his management?

- A. Change the atorvastatin to rosuvastatin
- B. Introduce liraglutide
- C. Start aspirin 75 mg daily
- D. Start insulin therapy
- E. Add gliclazide

Question 2

A 45-year-old woman presented for her annual review. She had type 2 diabetes. She was complaining of infrequent chest pains that were unrelated to meals, and breathlessness on minimal exertion. She also had hypertension and dyslipidaemia. She had a 20 pack-year history of smoking, and led a largely sedentary lifestyle.

Investigation

- 12-lead ECG was within normal limits

What is the most appropriate next step in her management?

- A. Consider a trial of omeprazole
- B. Measure the carotid artery intima-media thickness
- C. Coronary artery calcium score testing
- D. Exercise ECG testing
- E. Pharmacological stress testing with myocardial perfusion scintigraphy

Question 3

A 40-year-old man presented for annual review. He had morbid obesity, type 2 diabetes, hypertension and dyslipidaemia. He had

a 3-year history of heavy snoring, daytime somnolence and erectile dysfunction. He was taking metformin, amlodipine, gliclazide and atorvastatin.

On clinical examination, his blood pressure was 150/100 mmHg, and body mass index 34 kg/m².

Investigations

- HbA_{1c} 48 mmol/mol (20–42); 6.5% (4.0–6.0)
- Total cholesterol 3.1 mmol/litre (<5.2)
- Low-density lipoprotein-cholesterol 1.8 mmol/litre (<3.36)
- Urine albumin:creatinine ratio 40 mg/mmol (<2.5)
- Serum testosterone 6 nmol/litre (9–35)
- Luteinizing hormone 5.6 U/litre (1.0–9.0)
- Follicle-stimulating hormone 4.7 U/litre (1.0–10.0)
- Prolactin 245 mU/litre (45–375)
- Thyroid-stimulating hormone 2.5 mU/litre (0.4–5.0)
- Free T4 16 pmol/litre (10.0–22.0)
- 12-lead ECG was within normal limits

What would be most appropriate immediate step to reduce his cardiovascular risk?

- A. Trial of testosterone
- B. Referral for sleep studies
- C. Introduction of ramipril
- D. Measurement of N-terminal pro-B-type natriuretic peptide (NT-proBNP)
- E. Trial of oxygen therapy