Heart disease and diabetes

A high-risk duo in need of extra vigilance

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Diabetes and heart disease are common conditions sharing many similar risk factors. Patients with both conditions are at high risk of adverse events. A multifaceted approach to management is essential to address the multiple risk factors that are often present in these patients. Early assessment and modification of lifestyle factors and treatment of hypertension, dyslipidaemia and hyperglycaemia to target are important.

Both cardiovascular disease (CVD) and diabetes are common conditions and these two ailments are intricately linked. Diabetes is a risk factor for CVD and the two conditions often coexist together. The most important cause of mortality in developed countries and a major cause of morbidity in patients with diabetes is CVD.

Diagnosing coronary artery disease (CAD) in people with diabetes is difficult as patients may have few, no or atypical symptoms, or their symptoms may be masked by multiple comorbidities that are often present. CAD in patients with diabetes is usually more diffuse and extensive, its treatment and the response to treatment may be different and it is associated with worse outcomes than in those who do not have diabetes. Furthermore, many patients with CAD have undiagnosed diabetes or are at risk of developing diabetes. The treatment targets for patients with both diabetes and CVD and their impact on outcomes are not well defined. Both the detection and management of CVD in people with diabetes therefore remains challenging.

Assessing cardiovascular risk in diabetes

A number of risk score models, including the *Guidelines for the Management of Absolute Cardiovascular Disease Risk* approved by the National Health and Medical Research Council,[1] have been developed for the assessment of absolute cardiovascular risk in primary care settings. However, routine assessment of the absolute cardiovascular risk in all patients with diabetes using risk score models developed for the general population is not recommended.[2] Patients with diabetes and one or more cardiovascular risk factors are already considered at high or very high risk for developing CVD.[3] Other vascular risk factors such as hypertension, smoking and hypercholesterolaemia have further additive effects. The presence of end organ damage in diabetes, such as microalbuminuria and retinopathy, are additional risk factors for the development of CVD.

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Key points

- **Diabetes and heart disease are common conditions, which often coexist and lead to increased risks of adverse events.**
- **Tight glycaemic control in people with diabetes reduces microvascular complications.**
- **The glycaemic target to reduce macrovascular complications in people with diabetes is less well established.**
- **Lifestyle measures are essential in people with heart disease and diabetes.**
- **A multifaceted approach targeting multiple risk factors is the key to management.**

Screening for coronary artery disease in diabetes

Routine screening for CAD in patients with diabetes is controversial. The American Diabetes Association does not recommend routine screening for CVD in asymptomatic patients with diabetes. However, silent myocardial ischaemia may be present in asymptomatic patients whose exercise tolerance may be limited by other noncardiovascular factors. Furthermore, the presence of autonomic neuropathy may alter patients' sensation of chest pain from myocardial ischaemia. Myocardial ischaemia, silent or not, is associated with an increased risk of fatal and nonfatal coronary events, and revascularisation may lead to a reduction of such risks. Therefore, routine assessment of cardiovascular risk in asymptomatic patients with diabetes using stress echocardiography or myocardial perfusion scans may be recommended in selected patients with diabetes and end organ damage and who are considered at very high risk of CAD (see the case study example in the Box).

Prevention of CVD in diabetes

Prevention of CVD is of paramount importance in people with diabetes, and lifestyle measures are essential. Patients who smoke should be given structured advice to stop smoking. Dietary recommendations include limiting saturated fats, trans fats and alcohol intake, monitoring carbohydrate consumption and increasing dietary fibre. Total daily fat intake should be less than 35% and saturated fat less than 10%, whereas monounsaturated fat intake should be more than 10% of total daily energy intake.[4,5] Moderate to vigorous exercise (using a combination of aerobic and resistance training) of 150 minutes or more per week is recommended. Calorie control is important in achieving optimal body weight in people with diabetes.

Glycaemic control

There have been controversies surrounding recommendations on glycaemic control in people with diabetes to reduce cardiovascular events. Although randomised trials have demonstrated that tight glycaemic control may reduce microvascular complications of diabetes, such as retinopathy and nephropathy, the evidence for this on reduction of macrovascular complications, such as myocardial infarction, is less compelling. The reduction of macrovascular complications with tight glycaemic control is modest and

Case example: Management of an older man with longstanding diabetes and hypertension

Case scenario

David is 65 years old and presents at your general practice today for the first time for a check up. He claims to be feeling well and has no active complaints. He has had type 2 diabetes for 15 years and he also has hypertension. He weighs 98 kg with a body mass index of 32 kg/m^2. He does not smoke but drinks a glass of red wine daily. He recently retired from his job as a bank teller and does not exercise regularly. He claims that osteoarthritis of his knees stops him from exercising. He is taking metformin 500 mg daily and amlodipine 5 mg daily. He has no documented coronary artery disease. His blood pressure is 145/95 mmHg and an ECG shows sinus rhythm with left ventricular hypertrophy (see ECG below). His renal function is normal but his urine tests indicate microalbuminuria. Fasting total cholesterol level is 6.5 mmol/L, LDL-cholesterol level is 4 mmol/L and HbA$_{1c}$ is 7.4%. Fundal examination is normal.

Management

David has longstanding diabetes with microalbuminuria. He is overweight and has a sedentary lifestyle. His blood pressure and LDL-cholesterol levels are not at target. He has left ventricular hypertrophy on ECG due to his longstanding hypertension. He is at a very high risk of having a cardiovascular event. His poor exercise tolerance may mask any symptoms of coronary artery disease. He should receive aggressive counselling for lifestyle changes, including diet, exercise and weight loss. A dietitian consultation is recommended. He should receive an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and a statin. His dose of metformin should be increased with additional antihyperglycaemic drugs if necessary. He should be referred for an echocardiography to assess his left ventricular function and presence of hypertrophy, and he should undergo stress echocardiography or myocardial perfusion scan to screen for coronary artery disease. Aspirin may be considered for primary prevention.

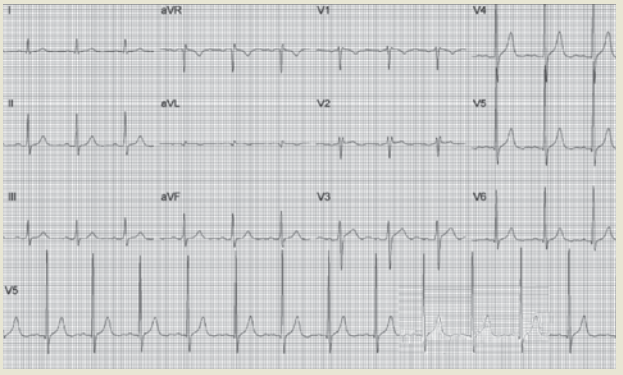

Figure. An ECG showing sinus rhythm with left ventricular hypertrophy.

may only be apparent after many years. In patients with diabetes, it is the tight control of vascular risk factors, such as hypertension and hypercholesterolaemia, together with glycaemic control that have the greatest impact on reduction of cardiovascular events.

Glycaemic targets

Tight glycaemic control with a target HbA$_{1c}$ of 6 to 7% has been consistently shown to reduce microvascular complications. However, in the Action to Control Cardiovascular Risks in Diabetes (ACCORD) trial, the intensive glucose control arm with a target HbA$_{1c}$ of 6.4% led to higher cardiovascular mortality compared with standard treatment with a target HbA$_{1c}$ of 7.5%.[6] Hypoglycaemia was more common in the intensive treatment arm although the increased mortality could not be attributed to hypoglycaemia alone. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial showed that intensive glycaemic control with a similar target HbA$_{1c}$ to the ACCORD study did not lead to a reduction in the macrovascular complications component of the primary endpoint although there was no excess mortality.[7] In studies with longer extended follow-up periods of more than 10 years, intensive glycaemic control led to a reduction in cardiovascular events.[8]

The interaction between glycaemic control and cardiovascular events is more complex than a simple direct relationship between a reduction in HbA$_{1c}$ and a reduction in cardiovascular events. Factors such as the baseline risk of the patients, the duration of diabetes, the presence of underlying CAD, the degree of glycaemic control before study entry and the duration of study follow up are all important in affecting the impact of tight glycaemic control on cardiovascular events. In general, an HbA$_{1c}$ of less than 7% is recommended to reduce microvascular complications. For reduction of macrovascular complications, it is also reasonable to aim for an HbA$_{1c}$ target of less than 7%. In general, a lower HbA$_{1c}$ target of 6 to 6.5% is reasonable, provided it can be achieved without hypoglycaemia, in patients with shorter duration of diabetes, younger patients, patients without coexisting CAD and those with historically good glycaemic control.

Blood pressure

Patients with diabetes often have coexisting hypertension. Such a combination leads to a fourfold increase in cardiovascular events.[9,10] Current evidence supports a blood pressure target of less than 140/85 mmHg. In selected patients with nephropathy and proteinuria, more intensive blood pressure lowering has been shown to slow deterioration in renal function and may be considered.[2] A meta-analysis of 13 randomised controlled trials of blood pressure lowering in patients with diabetes or prediabetes showed that a reduction of systolic blood pressure to 135 mmHg or less led to a 10% reduction in mortality and a 17% reduction in stroke but a 20% increase in serious adverse events.[11]

Some hypertension guidelines such as *Guidelines for the Management of Absolute Cardiovascular Disease Risk* recommend a treatment target blood pressure of less than 130/80 mmHg in patients with diabetes. However, the *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[12] recommends a target of less than 140/90 mmHg in people with diabetes, a goal similar to that in patients without diabetes.

Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are usually the recommended first-line drugs, especially in patients with albuminuria although their combination should be avoided. Calcium channel blockers may also be used. Thiazides and beta blockers are best avoided because of their possible metabolic consequences, as these agents have been associated with an increased risk of developing type 2 diabetes.

Dyslipidaemia

Dyslipidaemia is common in people with diabetes. Low HDL-cholesterol and high LDL-cholesterol levels have been independently associated with an increased risk of CVD. Although high triglyceride levels are also linked to an increased risk of CVD, this increased risk may be explained by the associated low HDL-cholesterol levels in such patients.

Clinical trials have demonstrated that primary prevention using statins in people with type 2 diabetes led to a significant reduction in cardiovascular events.[13-15] The beneficial effects were more marked in secondary prevention in which statins have been shown to result in a 9% reduction in mortality and a 21% reduction in major cardiovascular events per mmol/L reduction in LDL-cholesterol levels, with the benefits seen even in patients with low baseline LDL-cholesterol levels.[16] Recent trials (e.g. IMProved Reduction of Outcomes: VYTORIN Efficacy International Trial [IMPROVE-IT]) have reported that the addition of ezetimibe to statins in patients (27% of whom had diabetes) after an acute coronary syndrome resulted in a further reduction in LDL-cholesterol levels and cardiovascular events.[17] A target LDL-cholesterol level of less than 1.8 mmol/L or at least a 50% reduction in LDL-cholesterol level is recommended in high-risk patients with diabetes.

Antiplatelet agents

Aspirin is recommended for secondary prevention of cardiovascular events in all patients with diabetes and documented CVD. Clopidogrel may be used in patients intolerant to aspirin. The role of aspirin in primary prevention of CVD in patients with diabetes, however, is much less conclusive. Meta-analyses of trials of aspirin in primary prevention of CVD in patients with diabetes showed a nonsignificant reduction in coronary events or stroke but a significantly increased risk of bleeding of up to 55%.[18] Therefore, routine use of aspirin for primary prevention in people with diabetes cannot be recommended except for those at very high risk of cardiovascular events.

Managing heart disease in diabetes

Patients with known CAD and stable symptoms should receive treatment as recommended by the guidelines, including lifestyle measures, antiplatelet agents, ACEIs or ARBs, statins and beta blockers if there are no contraindications.[19,20] Beta blockers have shown significant benefits in patients with diabetes after myocardial infarction and also in those with left ventricular dysfunction, and should therefore be considered in these patients. However, use of beta blockers may worsen glycaemic control in patients with established diabetes or increase the risk of new-onset diabetes.[21] Nitrates should be used only for symptomatic treatment of angina. All patients with CAD should be screened for diabetes using measurement of fasting blood glucose levels or HbA_{1c} or an oral glucose tolerance test where appropriate.

Revascularisation for people with CAD and diabetes

Patients with stable CAD should be considered for revascularisation if they have limiting symptoms, a large area of myocardium at risk on exercise testing, or the presence of triple vessel, left main artery or proximal left anterior descending artery stenosis or impaired left ventricular function. It is in these latter groups of patients in which revascularisation has been shown to improve patient outcome compared with optimal medical management alone.

Patients with diabetes and CAD requiring revascularisation may be considered for either coronary artery bypass surgery or percutaneous coronary intervention. In patients with triple vessel disease or left main artery or proximal left anterior descending artery stenosis, bypass surgery leads to a better survival and lower risk of myocardial infarction and need for repeat procedures, and is the preferred treatment. The use of the left internal mammary artery to bypass stenoses of the left anterior descending artery has the most favourable impact on long-term outcome and therefore should be used in all cases if possible. Coronary stenting may be performed for patients with lesions in the left circumflex or right coronary arteries. The need for repeat procedures after coronary artery stenting is higher in patients with diabetes than in those without due to higher rates of restenosis. Drug eluting stents are preferred because bare metal stents are associated with high rates of restenosis. In general, patients with diabetes have more extensive and diffuse disease with poorer long-term outcomes compared with patients without diabetes.

Patients with diabetes and acute coronary syndrome should be managed in the same way as patients without diabetes. The benefits of early invasive strategies and aggressive revascularisation are more pronounced in patients with diabetes than in those without.

Heart failure in people with diabetes

The prevalence of heart failure is significantly higher in patients with diabetes than in those without. Although this increased prevalence may be due to traditional risk factors such as hypertension and CAD, there is evidence of the existence of the distinct clinical entity of diabetic cardiomyopathy. The severity of diabetic cardiomyopathy may vary from clinically unapparent left ventricular diastolic and systolic dysfunction (detectable only with cardiac imaging techniques), to symptomatic heart failure with advanced disease. The causes may be attributed to hyperglycaemia, microvascular disease, metabolic disturbances, myocardial fibrosis and steatosis, cardiac autonomic dysfunction and insulin resistance.

Patients with diabetes and heart failure should receive all guideline-recommended treatments, including ACEIs or ARBs, beta blockers and mineralocorticoid antagonists where appropriate. Loop diuretics can be used for relief of congestive symptoms. Indications for implantable cardiac defibrillators and cardiac resynchronisation device therapy are similar to that in patients without diabetes. Use of thiazolidinediones should be avoided due to their sodium and water retention effects. A recent trial suggested that dipeptidyl peptidase-4 inhibitors might increase the risk of hospitalisation for heart failure;[22] however, more studies are needed to further evaluate the cardiovascular safety of these drugs before specific recommendations can be made. There is no confirmed specific treatment for patients with diabetic cardiomyopathy apart from standard treatment of heart failure and treatment of the associated conditions such as hypertension. The impact of improving glycaemic control on left ventricular function and risk of heart failure is unclear.

Arrhythmia and sudden death in people with diabetes

There is an increased risk of developing atrial fibrillation in patients with diabetes although much of the increased risk may be due to coexisting conditions such as hypertension, CAD or heart failure. Diabetes increases the risk of thromboembolism in people with atrial fibrillation. Atrial fibrillation should be treated similarly in patients with diabetes to those without. Both warfarin and the novel oral anticoagulants are effective in stroke prevention in patients with diabetes and atrial fibrillation.

The risk of sudden cardiac death is increased in people with diabetes. The majority of such deaths are due to associated CAD or left ventricular dysfunction. Autonomic dysfunction may also contribute to the increased risk. Consideration for treatment for primary and secondary prevention of sudden cardiac death including the recommendations for implantable defibrillators should be along similar lines to those in patients without diabetes.

Table. Management targets of patients with diabetes or prediabetes and coronary artery disease

Parameters	Targets
Lifestyle measures – smoking – exercise – weight – diet	 • Stop smoking • 150 minutes per week or more of moderate to vigorous exercise • 30 minutes or more of moderate exercise on most days of the week • Weight stabilisation or weight loss • Waist measurement <94 cm (in men) and <80 cm (in women) • Body mass index 18.5 to 24.9 kg/m^2 • Total fat intake <35% • Saturated fat <10% • Monounsaturated fat >10% • Fibres >40 g/day
Lipid profile	• LDL-C level <1.8 mmol/L • HDL-C level >1.0 mmol/L • TG level <2.0 mmol/L • Non-HDL-C level <2.5 mmol/L • Use of statins preferred
Blood pressure	• <130/80 mmHg • <140/90 mmHg (from *2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults*[12]) • ACEI or ARB preferred
Antiplatelet drugs	• Aspirin 100 mg daily • Clopidogrel may be used
Glycaemic control	• HbA_{1c} <7% • HbA_{1c} 6 to 6.5% (on individual basis)
Post myocardial infarction	• Beta blockers • Mineralocorticoid antagonists if impaired left ventricular function

Abbreviations: ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blockers; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglycerides.

Conclusions

Patients with diabetes are at high risk of CVD and the management of any single risk factor alone would be insufficient. Patients with diabetes and established CAD are at very high risk of future cardiovascular events.

A multifaceted approach to management is essential to address the multiple risk factors that are often present in these patients (Table). Early assessment and modification of lifestyle factors, with guideline-recommended treatment of hypertension, dyslipidaemia and hyperglycaemia to target are important. Assessment and appropriate treatment of end organ damage and comorbidities (such as atrial fibrillation and heart failure) are recommended. Testing for myocardial ischaemia and assessment of left ventricular function and primary prevention of CVD with aspirin may be recommended in high-risk patients.

It is important to remember that diabetes is a life-long disease requiring life-long therapy. The beneficial effects of the above interventions may not be immediately apparent and patients must be counselled and encouraged throughout the course of their disease to keep them motivated. The treatment targets should be individualised according to each person's circumstances and a 'one size fits all' approach cannot be applied. **CT**

References

A list of references is included in the website version (www.medicinetoday.com.au) of this article.

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