Introduction
Cardiovascular disease is the most important cause of morbidity and mortality in patients with diabetes. The pathophysiology of heart failure in diabetes includes factors related to coronary heart disease, with myocardial ischaemia and myocardial scarring following myocardial infarction. Non-ischaemic mechanisms are also important, including structural, metabolic, and biochemical abnormalities. Treatment of heart failure in people with diabetes is in essence the same as for other patients, along with optimised diabetic control. ACE inhibitors and beta blockers should be commenced in all patients with a diagnosis of heart failure with reduced ejection fraction regardless of NYHA class. Aldosterone antagonists, cardiac resynchronisation therapy and heart transplantation all have a role in management of patients of NYHA class III and IV. In patients with heart failure with preserved ejection fraction, which is more common in people with diabetes, there is unfortunately no evidence of benefit for these therapies and a diuretic-based regimen is used to alleviate symptoms.

Epidemiology of heart failure in diabetes
Cardiac failure is a common complication of diabetes mellitus. In both sexes, the prevalence of heart failure is increased in people with diabetes compared to people without diabetes.3 In 1979 the Framingham Heart Study demonstrated a 2.4-fold increased risk and 5-fold increased risk of cardiac failure in men and women respectively aged 45–74 with diabetes compared to those without.4 More recent population-based studies have estimated an overall prevalence of 12% of heart failure in patients with diabetes,5 and the risk of heart failure increases markedly with age, with a prevalence of heart failure of 33 per 1000 in people with diabetes aged 45–54 which increased to a prevalence of 135 cases per 1000 in patients aged 65–74.6

Data from several studies demonstrate an even higher prevalence of diabetes mellitus in patients hospitalised with decompensated heart failure. Forty-two percent of 48 000 hospitalised patients in the OPTIMIZE-HF study had a diagnosis of diabetes.7 Similarly, 40% of hospitalised patients in the EVEREST study had a diagnosis of diabetes mellitus.8 Aside from having a higher incidence of heart failure, patients with diabetes who develop heart failure have worse outcomes than their non-diabetic counterparts, length of stay in hospital is longer, heart failure related hospital readmission rates are higher and overall cardiovascular mortality is higher.8,9

Pathophysiology of heart failure in diabetes
The pathophysiology of heart failure is complex and multifactorial. It is useful, however, to consider the aetiology of heart failure in diabetes...
as related to two interlinked mechanisms: ischaemic and non-ischaemic.

**Ischaemic mechanisms of heart failure in diabetes**

Atherosclerosis is a common aetiology for heart failure in the general population through a combination of the direct effects of coronary artery stenosis causing myocardial ischaemia, and a reduced cardiac output caused by scarring of the myocardium following myocardial infarction. Diabetes is a major risk factor for cardiovascular disease including ischaemic heart disease. Patients with diabetes have a higher burden of atherosclerosis than non-diabetic patients. It therefore follows that ischaemia is an important component when considering the causation of heart failure in diabetic patients. The underlying mechanisms for the development and progression of atherosclerosis in diabetes mellitus are multiple. The metabolic state of insulin resistance and hyperglycaemia is associated with the development of atheromatous coronary artery plaque formation with a multitude of evidence to support this association. The hyperglycaemic state is associated with endothelial dysfunction, oxidative stress and inflammation. These are key components in the development of atherosclerosis.

In the presence of this inflammatory state there is increased expression of endothelial surface adhesion molecules. This promotes migration of monocytes from the blood into the vessel intima. Here differentiation to tissue macrophages occurs and circulating lipids are ingested by these cells forming foam cells. At this stage, fatty streaks are present in the coronary vessel wall, with lipid in the intimal space. In diabetes there is commonly concomitant dyslipidaemia – present in around 60–70% of patients – creating an environment further conducive to atheroma development.

In this atheromatous state, there is cytokine and growth factor release which leads to the activation of quiescent vascular smooth muscle cells. These proliferate and migrate advancing the atheromatous plaque. In diabetes, calcification of these atheromatous plaques is more common. Calcification is associated with advanced plaques. In time, these advanced atheromatous plaques within the coronary arteries can become unstable and rupture leading to the acute consequences of coronary artery disease. This leads to ischaemia and myocardial necrosis, and impaired ventricular function. Areas of the heart with more subacute ischaemia can also have impaired myocardial function. The consequence of this is loss of myocardial contractility and the development of heart failure.

**Non-ischaemic mechanisms of heart failure in diabetes**

There are important non-ischaemic mediators of heart failure in people with diabetes. Knud Lundbaek described in the 1950s the phenomenon of ‘diabetic cardiomyopathy’ which led to further research and the description of myocardial dysfunction in patients with diabetes in the absence of coronary, valvular, hypertensive, congenital or alcoholic heart disease, and raised the prospect that diabetes per se was associated with myocardial dysfunction. Rubler et al. described pathological findings at post-mortem in these patients in the early 1970s, including microvascular changes and fibrosis with hypertrophy of cardiomyocytes. Similar findings were seen in myocardial biopsy specimens from patients with type 1 diabetes and myocardial dysfunction. The proposed mechanism for myocardial dysfunction was suggested to be related to myocardial microangiopathy and aberrant myocardial metabolism.

The underlying processes leading to non-ischaemic diabetic myocardial dysfunction are complex, and there is still ongoing uncertainty around the exact pathogenesis. Several mechanisms have been proposed, including metabolic disturbances of myocardial energy metabolism. In the insulin resistant hyperinsulinaemic state, there is increased circulation of free fatty acids. This is a source of energy for cardiomyocytes, and with increased uptake of these free fatty acids it is proposed that there is fatty acid associated lipotoxicity. In the insulin resistant state, there is a reduction in the availability of intramyocardial glucose due to a downregulation of myocardial glucose transporters such as GLUT-4 transporters resulting in decreased glucose oxidation. Fatty acids require a greater supply of oxygen substrate than is required for glucose metabolism. This leads to a state of relative ischaemia which is manifest by decreased myocardial contractility. There is increased lactate production which further contributes to myocardial dysfunction. Lipotoxicity can lead to myocardial apoptosis compounding a state of cardiac dysfunction.

It has been further proposed that dysfunction at the organelle level within the cardiomyocytes, more specifically mitochondrial dysfunction, is implicated in impaired cardiomyocyte energy formation. Calcium movement, a vital component to allow contraction of the actin and myosin filaments, is impaired in diabetic hearts. This has been proposed as a key component in non-ischaemic diabetic cardiomyopathy. Intramyocardial calcium movement is facilitated by a number of calcium transporters including the ryanodine receptor. This has been demonstrated to be dysfunctional in animal models of diabetes. Furthermore, the sarcoplasmic reticulum – at the organelle level – is involved in calcium sequestration and myocardial relaxation. In diabetes, it is proposed that there is impaired calcium movement through the SERCA-2A receptor. This leads to a state of impaired myocardial relaxation and changes to the conformation of the myosin heavy filaments within the contractile apparatus. This leads to a state of reduced contractility in addition to impaired myocardial relaxation.

From early descriptions of diabetic cardiomyopathy, structural alterations impairing function have been noted in the cardiomyocytes. It has been postulated that myocardial hypertrophy in this context is secondary to the growth factor effect mediated by a state of hyperinsulinaemia in type 2 diabetes mellitus.

Two further mechanisms have been implicated in non-ischaemic diabetic cardiac dysfunction. Firstly, there is evidence to suggest that neurohormonal changes are involved. It had previously been demonstrated...
that there is activation of the renin-angiotensin-aldosterone system in diabetes and in heart failure. Angiotensin II and aldosterone in this cascade have been associated with negative consequences at the cellular level within the heart. Hypertrophy, fibrosis and apoptosis have been associated to excess angiotensin II and aldosterone. Furthermore, chronic activation of this pathway can in time lead to hypertension with the added negative cardiac consequences that this brings.30

Cardiac autonomic neuropathy has also been associated with degeneration of cardiac sympathetic nerve fibres leading to impaired myocardial contractility. This may add to the state of myocardial dysfunction in diabetes patients.27,29

Evidently the pathophysiology of cardiac failure in diabetes is reflective of a complex interplay of ischaemic and non-ischaemic insults to the myocardium leading with time, as patients age, to a higher incidence of cardiac failure in diabetic patients. (Figure 1.)

**Diagnosis of heart failure**

**Clinical diagnosis of heart failure**
The diagnosis of heart failure is based on the presence of typical symptoms, signs and the identification of the underlying cardiac structural or functional abnormality. This diagnosis is therefore made firstly on a good clinical history demonstrating the typical symptoms of heart failure: breathlessness, ankle swelling and fatigue. Secondly, on clinical examination and identification of signs of cardiac failure: an elevated jugular venous pressure, peripheral oedema and basal lung field crepitation on auscultation. The third component is the use of diagnostic investigations including biochemical tests such as elevated brain natriuretic peptide levels and then confirmation with appropriate cardiac imaging such as echocardiography.31

The recent European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure now divide heart failure into three distinct diagnostic entities based on echocardiographic findings: heart failure with reduced ejection fraction, heart failure with mid-range ejection fraction and heart failure with preserved ejection fraction.31 Ejection fraction is a measurement of the volume of blood ejected from the ventricle with each heart beat expressed as a percentage of the end diastolic ventricular volume. Heart failure with reduced ejection fraction is defined as an ejection fraction <40%. Heart failure with mid-range ejection fraction is defined as ejection fractions between

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ASCVD = atherosclerotic cardiovascular disease; FFA = free fatty acids; AGE = advanced glycation endproducts; RAAS = renin-angiotensin-aldosterone system.

**Figure 1.** Pathophysiology of heart failure in diabetes
Mechanisms and treatment of heart failure in diabetes

40% and 49%. Heart failure with preserved ejection fraction is defined as having an ejection fraction $\geq 50\%$. Heart failure with a mid-range or preserved ejection fraction requires additional criteria. This includes raised biochemical markers such as B-type natriuretic peptide (BNP) and another additional echocardiographic marker such as left ventricular hypertrophy, left atrial enlargement or diastolic dysfunction (Table 1). Heart failure with preserved ejection fraction is more common in people with diabetes, which may reflect the non-ischaemic mechanisms described above.31

Commonly, heart failure is symptomatically classified using the New York Heart Failure Association (NYHA) criteria. This ranges from class I to class IV with increasing severity. Class I is used to describe patients with cardiac failure but no functional limitation on normal physical activity. Class II describes mild symptoms on ordinary daily activity such as mild dyspnoea. Class III patients are comfortable at rest but have marked symptoms limiting physical activity on minimal exertion such as walking 20m. Class IV NYHA describes patients who experience symptoms of heart failure such as dyspnoea at rest (Box 1).31

**Table 1. Definition of heart failure with preserved (HFrEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)**

<table>
<thead>
<tr>
<th>HFrEF Symptoms ± signs</th>
<th>HFmrEF Symptoms ± signs</th>
<th>HFrEF Symptoms ± signs</th>
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<tbody>
<tr>
<td>LVEF &lt;40%</td>
<td>LVEF 40–49%</td>
<td>LVEF ≥50%</td>
</tr>
<tr>
<td>1. Elevated levels of natriuretic peptide</td>
<td>1. Elevated levels of natriuretic peptide</td>
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<tr>
<td>2. At least one additional criterion:</td>
<td>2. At least one additional criterion:</td>
<td></td>
</tr>
<tr>
<td>• Relevant structural heart disease</td>
<td>• Relevant structural heart disease</td>
<td></td>
</tr>
<tr>
<td>• Diastolic dysfunction</td>
<td>• Diastolic dysfunction</td>
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</table>

LVEF = left ventricular ejection fraction.

**Box 1. New York Heart Association functional classification based on severity of symptoms and physical activity**

Class I No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations

Class II Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations

Class III Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations

Class IV Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased

**Treatment of heart failure in people with diabetes**

The aim of treatment for patients with heart failure is three-fold: firstly to provide symptomatic relief improving quality of life, secondly to reduce hospital admissions, and thirdly to prolong life and reduce mortality. There are a number of medical treatments for heart failure with a large evidence base (Table 2).31

**Medical therapies**

Angiotensin converting enzyme (ACE) inhibitors are a key facet for optimal management of patients with heart failure. Captopril, enalapril, lisinopril, ramipril and trandolapril have evidence for mortality benefit.31 In heart failure and in diabetes there is activation of the renin-angiotensin-aldosterone system with negative consequences as described previously, with direct effects on the myocardium and elevation of blood pressure. It is therefore important in patients with diabetes mellitus and heart failure that ACE inhibitors are initiated early. In patients with concomitant diabetic nephropathy ACE inhibitors can act also to reduce proteinuria and worsening renal disease.29 In 1991 in the SOLVD trial, enalapril reduced mortality by 16% on four-year follow up and decreased hospitalisations.33 The CONSENSUS trial similarly demonstrated benefit in heart failure from enalapril.34 In 1999 the ATLAS study demonstrated improved outcomes in patients treated with lisinopril including reduced mortality and hospitalisation – particularly those treated with higher therapeutic doses. In patients diagnosed with heart failure, early initiation and up-titration of ACE inhibitors, as tolerated, is important in improving survival.34 These studies contained large numbers of subjects with diabetes, and the benefits of ACE inhibitors were similar in people with diabetes.

Patients who are intolerant of ACE inhibitors due to side-effects such a cough should be switched to an angiotensin-II receptor blocker. They should not be used in addition to ACE inhibitors due to a lack of evidence of further benefit and risk of worsening renal function.31 The
Val-HeFT study in 2001 showed evidence for the use of valsartan in patients with heart failure. CHARM-Added in 2003 added further evidence for the use of candesartan in heart failure, while the VALIANT study in 2003 demonstrated that valsartan was as effective as captopril. More recently, combination therapy with neprilysin inhibitors such as sacubitril have been investigated in combination with angiotensin receptor blockers. This has been used as a combination of sacubitril and valsartan marketed as Erasto. The PARADIGM-HF study demonstrated reduced mortality in ambulatory patients who remain symptomatic despite optimal treatment with an ACE inhibitor, beta blocker and a mineralocorticoid receptor agonist (MRA) and had their ACE inhibitor replaced by an angiotensin receptor blocker/ neprilysin inhibitor combination drug. As many previous studies have identified, undiagnosed/diagnosed diabetes and impaired glucose tolerance were common in patients with heart failure in this study. The authors further investigated the effects of dysglycaemia on the effectiveness of this medication in patients with heart failure. It was demonstrated that, although there was no difference in the effectiveness of this drug, outcomes were generally worse for patients with diabetes mellitus – as has previously been demonstrated in several trials. 

Beta blockers should be initiated in all patients with a confirmed diagnosis of heart failure. Beta blockers act to counteract sympathetic nervous system activation, slowing the heart rate and allowing improved cardiac efficiency. Beta blockers should be commenced following adequate diuresis of the patient and care should be taken in the setting of acute decompensated cardiac failure as inhibiting the compensatory tachycardia may result in cardiogenic shock. Metoprolol, carvedilol and bisoprolol are used. Beta blockers should be commenced at low dose and up-titrated to the maximum tolerated dose. Like ACE inhibitors, there is a wealth of evidence from large randomised controlled trials, such as COPERNICUS, MERIT-HF and CIBIS-II, that beta-blocker therapy is associated with decreased morbidity and mortality in patients with heart failure. Again these studies contained large numbers of subjects with diabetes, and the overall benefit of beta blockers in patients with diabetes and heart failure was confirmed. Importantly, the cessation of both ACE inhibitor and beta blocker therapy in patients admitted unwell is associated with increased mortality. Therefore, care should be taken before considering the cessation of these medications in the acute setting. It should only be considered if there is profound hypotension or acute kidney injury. Both classes of medications should be restarted as soon as possible if temporary cessation is unavoidable. 

Aldosterone receptor antagonists such as spironolactone and eplerenone should be initiated in patients who remain symptomatic despite initiation of both ACE inhibitors and beta blockers that have been up-titrated to maximum tolerated doses. The RALES trial demonstrated morbidity and mortality benefit when spironolactone was added to such patients. Eplerenone was found to be similarly effective in reducing morbidity and mortality in such patients in the EMPHASIS-HF study. Furthermore, in the setting of heart failure following myocardial infarction, eplerenone was demonstrated to confer benefit in the EPHESUS study. Given the effect of inhibiting the action of aldosterone, monitoring for resultant hyperkalaemia

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<tr>
<th>Intervention</th>
<th>Major clinical trials and drug used</th>
<th>Diabetes recommendations</th>
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<tr>
<td>ACE inhibitors (ACE-i)</td>
<td>• CONSENSUS – enalapril • SOLVD-TREATMENT – enalapril • ATLAS – lisinopril</td>
<td>Recommended to reduce mortality and hospitalisation</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>• COPERNICUS – carvedilol • CIBIS-II – bisoprolol • MERIT-HF – metoprolol • SENIORS – nebivolol</td>
<td>Recommended to reduce mortality and hospitalisation</td>
</tr>
<tr>
<td>Mineralocorticoid receptor agonists (MRA)</td>
<td>• RALES – spironolactone • EMPHASIS-HF – eplerenone</td>
<td>Recommended for patients with persisting symptoms to reduce the risk of heart failure hospitalisation and premature death</td>
</tr>
<tr>
<td>Angiotensin receptor-neprilysin inhibitor (ARNI)</td>
<td>• PARADIGM-HF – sacubitril/valsartan</td>
<td>Recommended as a replacement for ACE-i in ambulatory patients who remain symptomatic despite optimal treatment with an ACE-i, beta-blocker and an MRA</td>
</tr>
<tr>
<td>Ichannel blocker</td>
<td>• SHIFT – ivabradine</td>
<td>Consider in patients with persisting symptoms and heart rate &gt;70bpm despite optimal tolerated dose of beta-blocker</td>
</tr>
<tr>
<td>Angiotensin receptor blockers (ARB)</td>
<td>• CHARM-Added – candesartan • CHARM-Alternative – candesartan • Val-HeFT – valsartan</td>
<td>May be used as an alternative to an ACE-i in patients who have clear intolerance due to side effects</td>
</tr>
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</table>

Table 2. Major clinical trials and treatment recommendations in patients with heart failure with reduced ejection fraction.
is important in these patients. Furthermore, monitoring of renal function should be undertaken after commencing an aldosterone receptor antagonist.

Ivabradine is a novel class of drug used in specific patients with heart failure. It acts on the sinus node inhibiting the ‘funny current’. This slows depolarisation and slows the heart rate in sinus rhythm, but not in arrhythmia. Efficacy of this drug demonstrates use-dependency meaning that benefit is most for higher heart rates. The use of this medication has been demonstrated to confer benefit in the setting of patients with persistent heart rate greater than 70 beats per minute despite maximal dose beta-blockade and use of other therapies. The SHIFT study demonstrated reduced cardiovascular mortality and hospitalisation in this subset of patients following commencing ivabradine.46

The DIG study was a single study examining the effect of digoxin in patients with heart failure with reduced ejection fraction. Patients in this study were in sinus rhythm. There may be a symptomatic improvement in such patients. This study failed to demonstrate a reduction in mortality but there was a significant reduction in heart failure hospitalisation. It is important to consider this evidence in the context that this study was before beta blockers were used in heart failure. Therefore, before consideration of digoxin is given, therapy should otherwise be optimised with ongoing symptoms.47 There is some evidence for the use of omega-3 polyunsaturated acids in heart failure. This is given as Omacor. The GISSI-HF-PUFA study demonstrated a just significant reduction in mortality, thought to be secondary to a reduced incidence of cardiac dysrhythmias.48

**Key points**

- Heart failure is an increasingly common cause of morbidity and mortality in people with diabetes and should be considered in any person with diabetes who has fatigue or breathlessness
- The diagnosis of heart failure is based on a combination of symptoms, signs, measurement of biomarkers, and cardiac imaging, most commonly echocardiography
- Treatment of heart failure in diabetes includes cardiological interventions (drugs, devices, surgery) and consideration of the most appropriate antidiabetes therapies

**Devices**

Aside from medical therapy, cardiac resynchronisation therapy (CRT) has a role in patients with chronic heart failure of NYHA class III or IV and evidence of conduction delay on ECG.

This is manifested as QRS duration greater than 130–150ms. In patients who remain symptomatic despite optimal therapy and ECG changes as described, CRT should be considered. Several randomised controlled trials such as MUSTIC, MIRACL-ICD, COMPANION and CARE-HF have demonstrated that CRT improves exercise tolerance, decreases hospital admission and reduces mortality. Cardiac resynchronisation therapy improves ventricular systolic contraction and diastolic relaxation improving cardiac efficiency.49–52

Implantable cardiac defibrillators have a role in a subset of patients with heart failure. These are reserved generally for patients who have had a dangerous arrhythmia associated with their cardiac failure such as ventricular tachycardia. They are, however, not routinely used outwith this setting.53

**Surgery**

Cardiac transplantation remains an option in appropriately selected patients without precluding comorbidities. It has been demonstrated in some studies that there is no significant difference in long-term survival in diabetic and non-diabetic patients who have received a cardiac transplant.54

**Conclusions**

Cardiac failure is a common and serious complication in patients with diabetes mellitus. It is a complex syndrome with multiple underlying aetiological pathways which have not all been fully elucidated. The care of patients with heart failure is challenging and should involve a changing regimen as the condition progresses.

**Declaration of interests**

There are no conflicts of interest declared.

**References**

References are available online at www.practicaldiabetes.com.
References