Heart failure (HF) and diabetes mellitus are often labelled the ‘deadly duo’ as patients with existing HF and concomitant diabetes mellitus have a significantly adverse prognosis. While these conditions frequently coexist, each are independently correlated with a higher risk of death. Diabetes mellitus is also one of the major risk factors that directly contributes to the development of HF. As the absolute numbers of people diagnosed with diabetes mellitus have quadrupled over the last four decades to 425 million worldwide, the prevalence of HF is therefore likely to rise.

This article describes the rising incidence of heart failure in patients with diabetes and the factors that underpin this trend. It highlights the importance of identifying HF patients at risk of developing diabetes mellitus and the need to screen for diabetes mellitus in patients with HF. Furthermore, it summarises the current knowledge on disease pathophysiology and disease progression in HF in both type 1 (T1DM) and type 2 diabetes mellitus (T2DM).

Heart failure: a rising global epidemic?
Heart failure was recognised as an emerging global epidemic more than 20 years ago. Today, almost 1 million people in the UK are diagnosed with HF and it accounts for up to 2% of the whole health care expenditure. Incidence rates rise steeply with age and the median age at first diagnosis in the UK is 77 years. Importantly, the burden of disease is comparable to the incidence of the four most prevalent types of cancer (breast, prostate, lung and bowel) combined. There is, however, conflicting evidence regarding the incidence of HF. Studies suggest that the incidence of HF has been relatively stable or may have even decreased slightly over the last two decades, while others have described an increase in the incidence. This variation reflects the differences in disease definition, selection bias and lack of available data from general practices across the country.

A large study in the UK by Conrad et al. examined more than 4 million individuals over a study period of 12 years. They reported a decrease in HF incidence by almost 7% driven primarily by a decrease in the rates of myocardial infarction by more than 30%. In contrast, when they examined the prevalence of HF, they found a significant increase by 23%. This reduction in the incidence of HF can best be explained by improved primary prevention which has reduced the ischaemic risk. Conversely, changing demographics due to an ageing population have witnessed a substantial increase in the proportion of people aged over 65 years who are at risk of HF but who are also surviving for longer. Improved survival alongside enhanced physician awareness and superior clinical screening with better access to confirmatory investigations such as diagnostic imaging tools have further contributed to this rise in prevalence. Moreover, the introduction of the national care monitoring programme, which was initiated in the UK in 2004, as well as the roll-out of community heart failure nurses, have standardised the use of disease-modifying and prognostic therapies and thus have enhanced clinical outcomes.

Most observational studies describe a ‘changing epidemic’ with a reduction in HF with reduced ejection fraction (HFrEF) relative to HF with preserved ejection fraction (HFrEF), which is in keeping with the perceived increase of typical comorbidities such as T2DM, obesity, hypertension and hyperlipidaemia that fuel disease progression in HFrEF. This, again, likely reflects the utility of evidence-based prognostic medication and device therapies which, to date, have only been proven of value in HFrEF.

Overall, however, the reported prevalence of HF remains far below expected values. This suggests that we are only seeing the ‘tip of the iceberg’ and that many patients with HF, particularly within the elderly cohort, remain unrecognised and unaccounted for and are not receiving the specialist HF care that they require. Tapping into this hidden population therefore remains one of the most important current challenges in this area.

Toxic twosome: diabetes and heart failure
Similar to HF, diabetes mellitus presents a significant burden to many health care systems globally and it is the ninth major cause for reduced life expectancy. There are few data examining the association of T1DM as a risk factor for development of HF. Rosengren et al. compared registry data of established T1DM to matched controls in more than 30 000 patients (with a mean age of 35 years). They demonstrated that people with T1DM carried a 4-fold increased risk of developing HF than age-matched controls. They also demonstrated a 30% rise in the incidence of HF for each 1% increase in glycated haemoglobin A1c (HbA1c), denoting a direct link of glycaemic control with the progression of HF.

The registry based study OPTIMIZE-HF revealed a prevalence of diabetes as high as 42% in a general cohort of almost 43 000 HF patients with a reduced left ventricular ejection fraction (LVEF). Interestingly, HF patients with concomitant diabetes mellitus had modestly prolonged initial hospital stays and were re-hospitalised more frequently yet had a similar mortality rate when compared with their non-diabetes mellitus HF counterparts. The EVEREST trial demonstrated a prevalence of diabetes mellitus in 40% of HF patients. This study found that people with diabetes mellitus had a 17% increased risk of being hospitalised for HF but, in...
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Leader

contrast to the results from OPTIMIZE-HF, these patients had a higher cardiovascular mortality than matched non-diabetes mellitus controls.

The National Diabetes Audit Report 2a, which included over 170,000 patients with T1DM and almost 2 million patients with T2DM in England and Wales and examined complications from diabetes mellitus over a period of two consecutive years (2015–2016), confirmed that the prevalence of diabetes mellitus in the UK is rising and that an increasing number of patients with diabetes experience HF as the most frequent complication.\(^{19}\) Interestingly, the risk for cardiovascular complications was almost 2-fold greater in patients with T1DM compared to T2DM, yet both were significantly higher than in patients without diabetes. While patients with diabetes comprise only 5% of the general population, they account for almost one-third of all hospital admissions for cardiovascular complications and have longer in-hospital stays when compared with non-diabetic patients. This suggests the need for cross-specialty working between cardiovascular medicine and diabetology to optimally tackle disease prevention and minimise disease progression to reduce morbidity and mortality.

Irrespective of the underlying phenotype of HF (HFrEF or HfP EF), T2DM is associated with an adverse all-cause and cardiovascular mortality when compared with patients without T2DM.\(^{20}\) Patients with concomitant T2DM have also been shown to have a worse NYHA functional status and more burdensome HF-related signs and symptoms.\(^{21}\) Although there seems to be a predisposing genetic basis of disease, obesity is the single most important risk factor for the development of T2DM and its prevalence strongly correlates with the progression of obesity.\(^{22}\) Up to one-third of patients diagnosed with T2DM concomitantly exhibit HF.\(^{23}\) Vice versa, up to 40% of patients suffering from HF present with T2DM.\(^{24}\) Rao et al. found that a 50-year-old with T2DM will, on average, die six years earlier than an individual without diabetes, highlighting the adversity associated with diabetes. Almost half of this risk could not be attributed to macrovascular effects such as myocardial infarction or stroke.\(^{25}\) Thus, the long-standing concept of inadequate glycaemic control causing macrovascular complications which then leads to HF is rather outdated as most of the available evidence points to a higher mortality independent of an ischaemic or non-ischaemic HF-aitiology.\(^{26–28}\)

A significant proportion of patients with HFrEF and HfP EF have unrecognised diabetes mellitus,\(^{29}\) and pre-diabetes and T2DM are often missed in patients diagnosed with HF.\(^{5}\) Given that diabetes drugs have recently been shown to significantly reduce cardiovascular mortality and hospitalisation in HF (e.g. EMPA-REG OUTCOME utilising the SGLT2 inhibitor empagliflozin),\(^{30}\) it is prudent to screen patients with HF for undiagnosed glucose intolerance or diabetes since potential novel therapies offer the opportunity to improve clinical outcomes.

**Diagnosing and screening heart failure**

Heart failure is defined as a clinical syndrome in which patients have typical symptoms (e.g. breathlessness, ankle swelling and fatigue) and signs (e.g. elevated jugular venous pressure, fluid retention, pulmonary congestion and a displaced apex beat) which result from an abnormality of cardiac structure or function (either left ventricular systolic dysfunction [LVSD], also known as HFrEF) or diastolic dysfunction (termed HF with preserved ejection fraction [HfP EF]) which fails to deliver oxygen to meet the requirements of metabolising tissues.\(^{31,32}\)

Diagnosing HF is complex as there is marked pleiotropic aetiology and clinical heterogeneity. There is also no single diagnostic test that confirms the diagnosis and underlying aetiology. The diagnostic pathway therefore requires the observation of typical signs and symptoms, the presence of raised HF-related biomarkers such as brain natriuretic peptide (BNP) or n-terminal pro-brain natriuretic peptide (NT-proBNP) and the presence of abnormal imaging findings to derive the cause and assess the severity of myocardial dysfunction. Importantly, biomarkers are not specific for HF – there are many differential diagnoses that may cause their elevation. These include advanced age, non-heart failure related cardiac causes (acute coronary syndromes, myocarditis, hypertrophic [or other] cardiomyopathy, valvular heart disease, tachyarrhythmia), respiratory disease, renal or hepatic dysfunction, diabetes, liver cirrhosis, anaemia or metabolic abnormalities. (Table 1.) Therefore, while raised natriuretic peptides (NPs) are helpful diagnostically and relevant prognostically, a raised value should be regarded within the clinical context following a detailed evaluation to ensure their diagnostic accuracy in HF.

Natriuretic peptides are secreted into the circulation as a reaction to increased volume expansion and/or pressure and stiffness in the heart. Independent of the underlying aetiology, they are comparable in patients with HFrEF and HfP EF.\(^{35}\) Although the available evidence is conflicting, a recent meta-analysis reported no significant difference between the use of BNP and NT-proBNP in the accuracy of diagnosing HF in typical

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**Table 1. Different causes of elevated BNP/NT-proBNP concentrations due to cardiac and non-cardiac reasons.** (Modified from: Ponikowski P, et al. *Eur Heart J* 2016;37:2129–200)\(^{31}\)

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Non-cardiac</th>
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<tbody>
<tr>
<td>• Heart failure</td>
<td>• Advanced age</td>
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<tr>
<td>• Acute coronary syndromes</td>
<td>• Ischaemic stroke</td>
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<tr>
<td>• Pulmonary embolism</td>
<td>• Subarachnoid haemorrhage</td>
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<td>• Myocarditis</td>
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<td>• Left ventricular hypertrophy</td>
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<td>• Hypertrophic or restrictive cardiomyopathy</td>
<td>• Paraneoplastic syndromes</td>
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<td>• Valvular heart disease</td>
<td>• Chronic obstructive pulmonary disease</td>
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<td>• Severe infections</td>
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<tr>
<td>• Atrial and ventricular arrhythmia</td>
<td>• Anaemia</td>
</tr>
<tr>
<td>• Heart contusion</td>
<td>• Severe burns</td>
</tr>
<tr>
<td>• Cardioversion, ICD shock</td>
<td>• Severe metabolic disturbances</td>
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cohorts of HF patients (notably of whom 30–40% presented with T2DM). Interestingly, in an analysis of over 1000 patients with diabetes and concomitant HF, levels of NT-proBNP and troponin were generally higher in patients with diabetes. As expected, typical comorbidities (e.g. ischaemia, hypertension and kidney disease) were more prevalent in the diabetes cohort, as was a premature (earlier) diagnosis of HF. Diabetes or impaired glucose tolerance themselves have not, however, been reported to directly influence levels of NPs in patients with HF. Therefore, the diagnostic cut-off of NPs used remains identical across the spectrum of diabetes.

Type 2 diabetes is often associated with complex comorbidities, thus these confounding factors need to be taken into account when interpreting NP results in these patients. Studies have reported significantly lower levels of circulating NPs in obese patients. Obesity may also mask the typical signs and symptoms of HF and consequently lower the threshold for performing additional investigations to confirm the diagnosis. Kidney disease also has a higher prevalence in patients with diabetes, and renal dysfunction has been shown to affect plasma levels of NPs through the reduced renal clearance of NPs, reduced renal responsiveness and reduced counter-regulatory responses directed from the heart to the kidney. Renal dysfunction therefore limits the diagnostic accuracy of NPs in HF.

Beyond the classic NPs, multiple alternative HF-related, inflammation-related and renal function-related biomarkers (e.g. CT-proET-1, copeptin, MR-proADM, hs-CRP, procalcitonin, PAI-1, galectin-3, cystatin-C) have been explored in HF patients with and without diabetes, but there has been no significant demonstrable difference regarding their prognostic value. As yet, no cardiac biomarker other than the established NPs (BNP/NT-proBNP) and troponin has proven superiority – although research in this field is highly active and future targets, such as micro-RNAs, offer hope in improving the diagnostic accuracy.

Diagnosing HF and deriving its cause is key as it can, in some cases, guide disease-specific treatment and predict clinical outcomes. However, unravelling the underlying cause is often challenging, time consuming and cost exhaustive, hence many cardiomyopathies remain idiopathic. Widespread clinical experience in managing HF patients is thus imperative.

Phenotyping is, for historical reasons, primarily based on the echocardiographic assessment of LVEF. Arbitrary thresholds have been defined. An LVEF ≥50% with typical symptoms of HF defines HF with preserved ejection fraction (HFrEF). This is often attributed to diastolic dysfunction and due to complex comorbidities. HF with a reduced ejection fraction (HFrEF) is defined by an LVEF <40%, for which there are many causes. Patients with an LVEF between 40–49% are termed HF with mid-range ejection fraction (HFmrEF). Notably, the evidence base, pathophysiology and treatment options for HFrEF and HFmrEF are scarce.

Since NPs are highly sensitive but lack specificity, a result above the normal cut-off reference value requires additional investigation. Imaging techniques are therefore utilised to complement NPs and provide additional clarity in the phenotypic evaluation. Two-dimensional transthoracic echocardiography and tissue Doppler imaging is a readily available screening tool that can detect the presence of left ventricular hypertrophy or subclinical (precursor) stages of diabetic cardiomyopathy or indeed overt disease (HFrEF or HFrEF). However, suboptimal image quality, body habitus, limited spatial resolution and high inter- and intra-observer variability limit its use. New tools such as speckle-tracking echocardiography and strain-imaging (Figure 1), measuring the longitudinal or circumferential mechanical deformation of the myocardium, unravel cardiac abnormalities at a much earlier stage and appear to be less operator reliant. Whether or not such morphological changes represent early hallmarks of a preclinical phase of diabetic cardiomyopathy remains speculative as prognostic data are lacking.

Utilisation of advanced imaging modalities (such as cardiac magnetic resonance imaging [CMR]) offers an improved functional and morphological assessment including tissue characterisation and an assessment of cardiac tissue perfusion, oedema, energy metabolism and fibrosis. This enables a comprehensive diagnostic and phenotypic assessment as well as a superior prognostic evaluation and risk assessment than that offered by echocardiography alone. CMR can also detect ischaemia and by injecting gadolinium-based contrast agents, can determine viability and detail the pattern of fibrosis (whether subendocardial suggesting myocardial infarction or regional mid-wall or subepicardial reflecting an alternative cardiomyopathic process). This can help confirm the diagnosis and guide the underlying aetiology. Native and post-contrast T1 mapping techniques (Figure 2) can also be used to provide a pixel-wise illustration of the longitudinal relaxation time of protons in the heart to enable the assessment of diffuse cardiac fibrosis, a typical finding seen in the very early stages of diabetic hearts. Pharmacological CMR stress-perfusion imaging can also reveal underlying microvascular dysfunction, a phenomenon frequently observed in
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people with diabetes due to the distinct endothelial dysfunction. Cardiac magnetic resonance imaging thus facilitates symptom correlation with underlying disease-specific pathophysiology which can enhance our understanding of the aetiology of HF and the potential impact of concurrent diabetes.

Coronary artery disease is one of the leading causes of premature death in patients with diabetes. Whether it is feasible to utilise screening techniques in patients who are asymptomatic to identify those at risk of adverse disease-related outcomes and HF, remains unanswered. Establishing which test is superior also requires clarity. Exercise testing is a low-cost and widely available method. Limitations include patients with pre-existing ECG abnormalities (e.g. bundle branch block) and patients who are physically unable to exercise. The sensitivity and specificity of exercise testing is, however, considerably lower than echocardiography, nuclear or CMR stress testing. Furthermore, the prognostic value of a negative exercise stress test in asymptomatic patients with diabetes, remains elusive.

Ischaemia detected using dobutamine stress echocardiography (DSE) has been shown to be a strong and independent predictor of mortality in a large unselected cohort of almost 3000 individuals with diabetes and more than 11 000 non-diabetic people and thus offers higher prognostic value than exercise testing. Interestingly, however, those diabetes patients with a normal stress test had a 2-fold greater risk of adverse events than their non-diabetic counterparts, highlighting this technique’s limitation prognostically.

Radionuclide techniques (e.g. myocardial perfusion scanning [SPECT]) provide comparable detection rates of coronary lesions in both patients with and without diabetes. However, the risk of an adverse event in those with a negative scan is higher in patients with diabetes than in non-diabetes patients. Moreover, the ‘warranty period’ of a negative test result is significantly shorter in people with diabetes.

Prospective trials have also suggested that coronary artery calcium (CAC) (which has been histologically validated to correlate with total plaque burden) and obstructive coronary disease detected on computed tomography coronary angiography (CTCA), are independent predictors of future cardiovascular events. Given that people with diabetes harbour higher amounts of coronary calcium and coronary disease, CAC and CTCA are therefore potentially valuable tools in the disease assessment. However, while abnormalities detected on CAC or CTCA enable aggressive risk factor modification, their correlation with reducing event rates remains to be determined.

Current screening guidelines from the American College of Cardiology recommend the screening of asymptomatic diabetes patients at intermediate cardiovascular risk as a Class IIa recommendation. In contrast, the American Diabetes Association does not suggest the routine screening of asymptomatic diabetes individuals as they suggest that all subjects at higher risk should be receiving optimal medical therapy regardless and that randomised control data have not demonstrated a clinical benefit.

For patients with clinically established angina pectoris, CMR perfusion imaging seems to be advantageous at guiding an interventional strategy as it does not use ionising radiation and allows for the assessment of ischaemia without being biased by severe multi-vessel disease, a condition commonly seen in patients with diabetes. The randomised controlled CE-MARC trial, which enrolled 752 patients with suspected angina pectoris that were randomly assigned to either CMR or SPECT, demonstrated that CMR had a significantly higher diagnostic accuracy when compared to SPECT. The follow-up study (CE-MARC 2) also advised that this strategy reduced the number of unnecessary invasive coronary angiograms by 79% – although this did not translate into fewer adverse cardiac events after 12 months of follow-up.

The pathophysiology of heart failure in type 1 and type 2 diabetes

In diabetes mellitus, most of the underlying pathophysiological effects responsible for the development of cardiac dysfunction overlap but there is some discordance. For example, systolic function may be preserved and left ventricular hypertrophy less pronounced in T1DM compared to T2DM. Enhanced cardiomyocyte autophagy, the process of self-degradation of cellular structures, may be an underlying molecular mechanism although further research is needed to clarify the potential differences between diabetic cardiomyopathy in T1DM and T2DM.

Heart failure has emerged as the most frequent complication of T2DM with its incidence exceeding thromboembolic complications such as myocardial infarction or stroke. The most important causes of HF in patients with T2DM are myocardial ischaemia, arterial hypertension and a direct detrimental effect of the ‘diabetic cardiomyopathy’ on the myocardium. Notably, diabetes and HF also beget each other with pathophysiological factors being closely linked, potentiating their detrimental effects.

The diabetic and failing non-diabetic heart share a distinct metabolic pathology with insulin resistance
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and perturbations of cardiac energy metabolism (Figure 3). Importantly, these effects on the myocardium are at play during pre-clinical stages of disease, many years before a diabetic cardiomyopathy has overtly manifested itself.63

In T2DM, the early, asymptomatic stage of disease is typically characterised by increased diastolic stiffness and fibrosis within the myocardium. Cardiac steatosis increases cardiac stiffness and induces lipotoxicity which inhibits the efficient utilisation of fatty acids as a substrate for myocardial energy production and thus promotes a shift towards glucose utilisation. Systemic insulin resistance due to diabetes mellitus and concomitant HF prevents the cardiomyocytes from effectively using glucose as a fuel which further promotes perturbations in myocardial energy metabolism leaving the heart as an ‘engine out of fuel’.64 This propagates myocardial dysfunction.

Studies have shown that the ratio of the two main energy compounds in the heart, phosphocreatine (PCr) and adenosine-triphosphate (ATP), are sensitive markers for myocardial metabolism and its energetic state, and can be used to predict adverse clinical outcomes and disease progression.65 These parameters offer the future potential to non-invasively identify early energetic deficits that exist in pre-clinical stages of disease and in early diabetes mellitus.

Conclusions
The incidence and prevalence of diabetes are rising and a significant number of patients with diabetes display concomitant HF. The incidence of HF appears to be declining; however, its prevalence is increasing. Many HF patients present perturbed insulin metabolism or unrecognised diabetes mellitus and vice versa. Multiple studies have shown a markedly increased risk of adverse clinical outcomes in patients with concomitant HF and diabetes, regardless of the underlying HF phenotype. Recognition of both conditions is therefore critical in order to reduce morbidity and mortality. Molecular phenotyping offers a future potential target to identify pre-clinical phases of disease to modulate disease pathophysiology. Screening for HF in diabetes and vice versa is therefore critical for both the prevention of diabetic cardiomyopathy and to decrease the disease burden.

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Declaration of interests
There are no conflicts of interest declared.

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References are available in Practical Diabetes online at www.practicaldiabetes.com.
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