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CME: Diabetes

# Diabetes and the heart ☆

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ABSTRACT

Diabetes mellitus and cardiac problems frequently coexist, posing significant challenges for both generalists and specialists. This article discusses the common cardiac manifestations of diabetes including coronary artery disease, heart failure and arrythmia, outlining specific diagnostic strategies and management in people with diabetes. We also discuss specific cardiovascular risk stratification strategies in diabetes, as well as glucose-lowering therapies with potential cardiovascular benefits. Ultimately a holistic approach is needed for individuals with co-existent cardiac problems and diabetes, tailoring management strategies to specific patient needs.

## Epidemiology

People with diabetes have a 2- to 4-fold increased lifetime risk of cardiovascular disease (CVD) compared to the general population.[1] Globally, an estimated 45% of diabetes cases remain undiagnosed, as the condition is often asymptomatic for many years.[2] As a result, patients presenting with cardiac disease may have previously unrecognised diabetes. Fig. 1 outlines the main clinical manifestations of cardiac disease that occur in diabetes. Cardiovascular risk factors often cluster, with many people with diabetes exhibiting hypertension, hyperlipidaemia or obesity, underlining the need for comprehensive risk management.

## Cardiovascular risk stratification in diabetes

The European Society of Cardiology (ESC) recommends risk stratifying individuals with type 2 diabetes mellitus (T2DM) based on the presence of clinically established atherosclerosis or severe target organ dysfunction, along with calculation of SCORE2-Diabetes risk (see Fig. 2), which was developed using data from >200,000 individuals.[3] The National Institute for Health and Care Excellence (NICE), on the other hand, recommends using QRISK3 (see Fig. 2) to estimate CVD risk in people with diabetes without CVD; however, this scoring system has not been specifically designed for people with diabetes, but does include a more extensive risk assessment.[4]

## Coronary artery disease

Myocardial infarction (MI) remains a common cause of death in people with diabetes, and generally patients with diabetes have poorer outcomes in ischaemic heart disease (IHD) than people without diabetes.[5] Diabetes contributes to the pathophysiology of IHD through a variety of mechanisms outlined in Fig. 3.

It is well established that people with diabetes and MI are more likely to present with atypical symptoms (eg pain in the right side of the chest, neck, jaw, shoulders, upper part of back, epigastrium).[6] Pain in the epigastrium may resemble gastro-oesophageal reflux disease. Furthermore, symptoms can be mild or even absent in patients with diabetes. The effects of diabetes on the nervous system, in particular autonomic function, are a key driver of this phenomenon. This offers a challenge to clinicians, as patients with MI presenting with atypical or limited/no symptoms have demonstrated poorer outcomes, due to delays in presentation, diagnosis and treatment.[7] A high index of suspicion is therefore required in patients with diabetes to avoid missing cardiac events. Where suspected, a 12-lead ECG and high-sensitivity troponin at 0 h and 1–3 h from admission to the emergency department should be obtained, with rule in / rule out algorithms followed. Where meeting diagnostic criteria for MI, acute management is the same as for people without diabetes. Additional considerations need to be taken to manage hyperglycaemia >11 mmol/L. Guidelines recommend the use of dose-adjusted insulin infusions where needed, avoiding intensive glycaemic control to avoid hypoglycaemia.[8,9]

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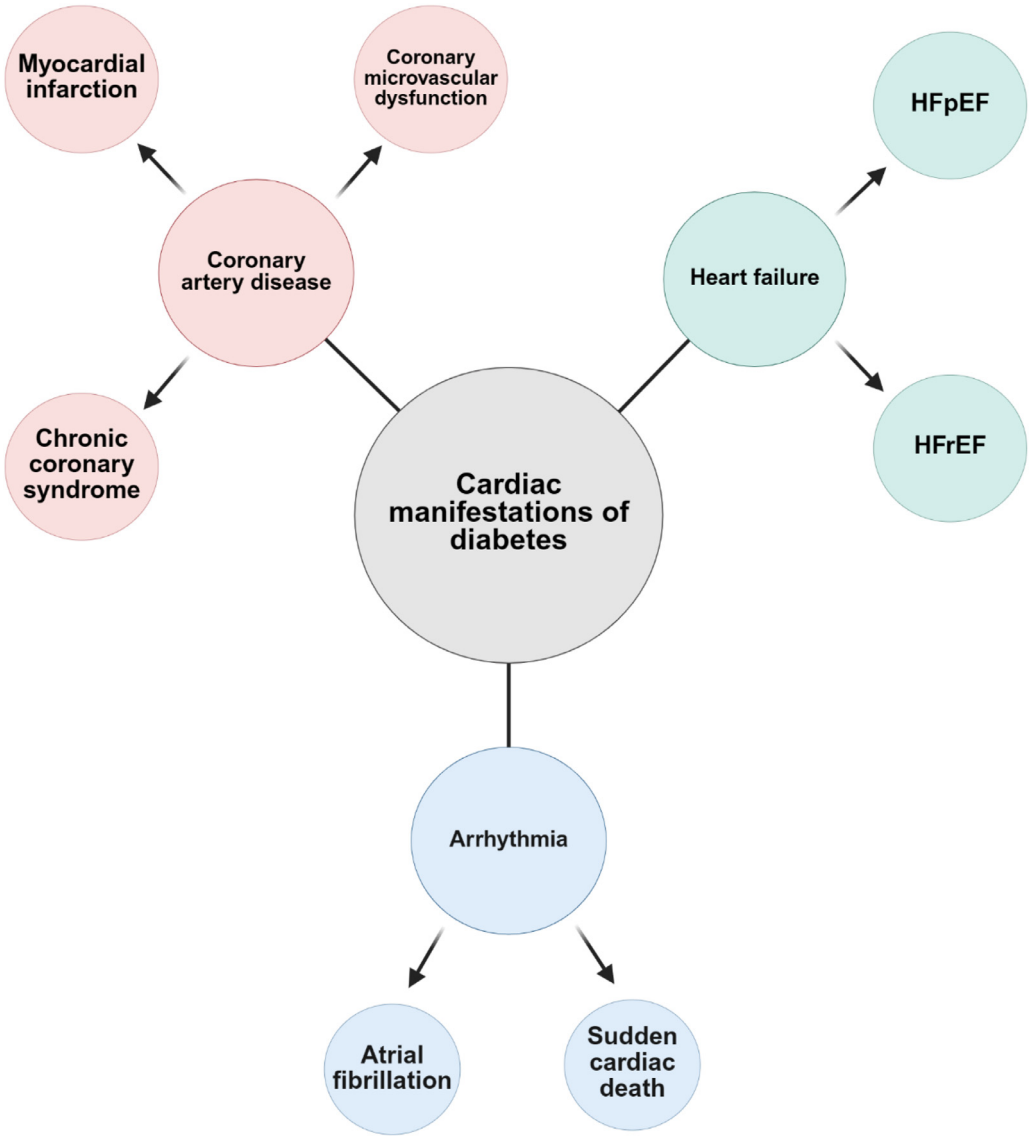


**Fig. 1.** The main clinical manifestations of cardiac disease in diabetes.
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### Coronary microvascular dysfunction

As well as epicardial disease, diabetes also increases the risk of coronary microvascular dysfunction (CMD). This forms part of the umbrella term ischaemia with no obstructive coronary artery disease (INOCA). CMD involves a combination of vascular inflammation, endothelial dysfunction, cardiomyocyte death and increased microvascular resistance. Importantly CMD appears to result in adverse outcomes rates similar to those of patients with epicardial disease**.** Clinical presentation is variable; patients can present with angina symptoms similar to obstructive chronic artery disease (CAD), but also with other symptoms such as shortness of breath, pain between the shoulder blades, nausea, fatigue and weakness, which can make recognition challenging. Initial work-up for these patients is the same as for suspected obstructive CAD, with a combination of non-invasive imaging, functional imaging and invasive angiography. The diagnosis of CMD is subsequently made using invasive physiological assessments during angiography, including fractional flow reserve, coronary flow reserve and the index of microvascular resistance. Vasoreactivity testing can also be carried out. Current management strategies are focused on traditional CVD risk factor modification and anti-anginal therapy. However, symptom management can be challenging, as there is no definitive evidence-based therapy for CMD, and existing studies are often small and heterogeneous.[10]

### Heart failure and diabetic cardiomyopathy

Heart failure is a common presentation of cardiac disease in diabetes, and people with diabetes are at increased risk of developing heart failure compared to those without. This can manifest across the spectrum, from heart failure with preserved ejection fraction (HFpEF) to heart failure with reduced ejection fraction (HFrEF). Risk of death is higher in people with diabetes and heart failure compared to those without heart failure, and vice versa in patients with heart failure with diabetes compared to people without diabetes.[11] The underlying aetiology of the heart failure can be related to a range of factors including ischaemic heart disease, hypertension and obesity. Cardiomyopathy occurring in diabetes in the absence of other clear aetiological factors has been suggested to exist as a specific clinical entity in the literature, namely diabetic cardiomyopathy. The main features are said to include cardiac stiffness, myocardial fibrosis and hypertrophy, with initial diastolic dysfunction progressing to systolic dysfunction and clinical heart failure (Fig. 4). However, as a condition it is yet to be formally defined as a distinct clinical entity,

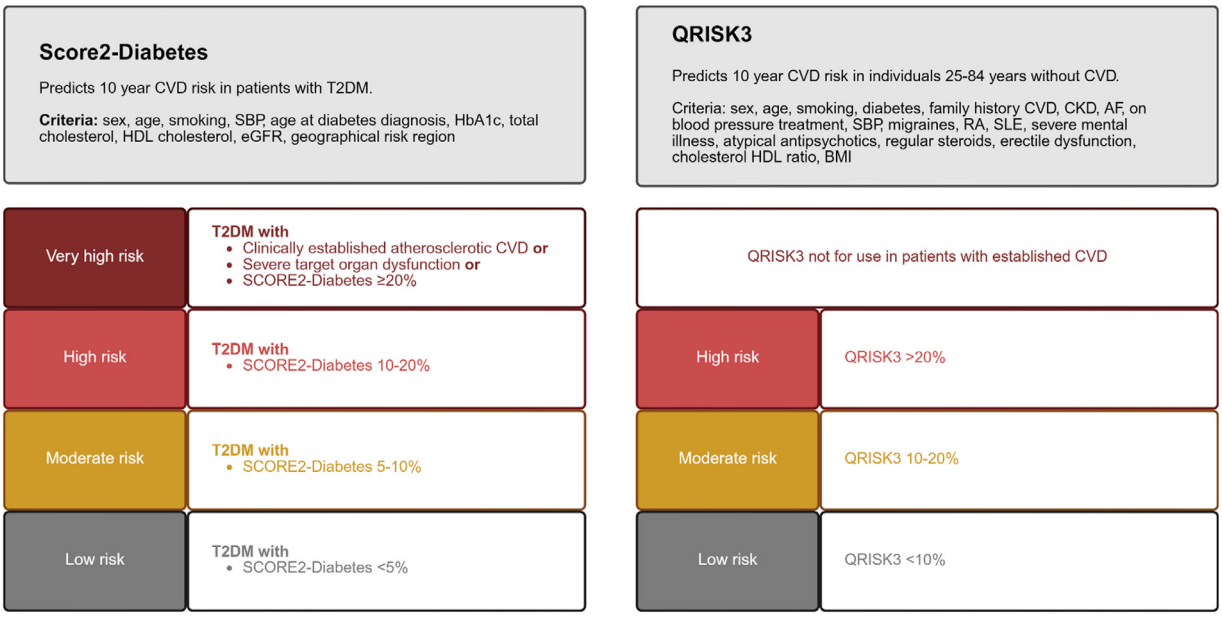


**Fig. 2.** SCORE2-Diabetes and QRISK3. CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus; SBP, systolic blood pressure; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; AF, atrial fibrillation; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; BMI, body mass index.
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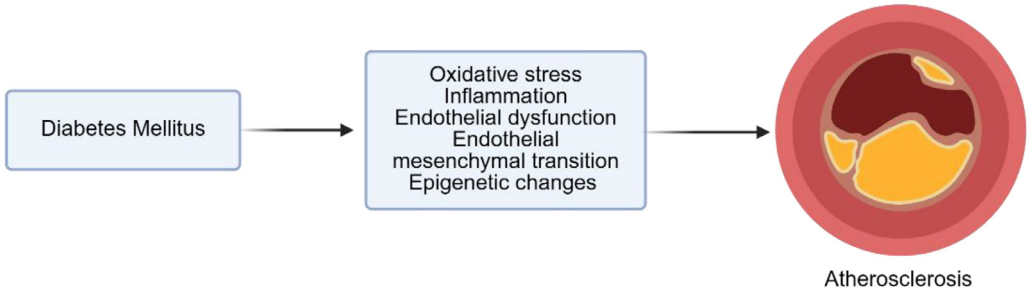


**Fig. 3.** Diabetes and atherosclerosis. A variety of pathophysiological mechanisms are involved in diabetes and the development of atherosclerosis. Common processes that diabetes contributes to include endothelial dysfunction and inflammation, with subsequent upregulation of vascular cell adhesion markers and migration of inflammatory cells into vessel walls. Furthermore, epigenetic changes in inflammatory cells leads to changes in immune cell function. Oxidative stress further contributes to inflammation and also contributes to endothelial mesenchymal transition, which is associated with plaque vulnerability.
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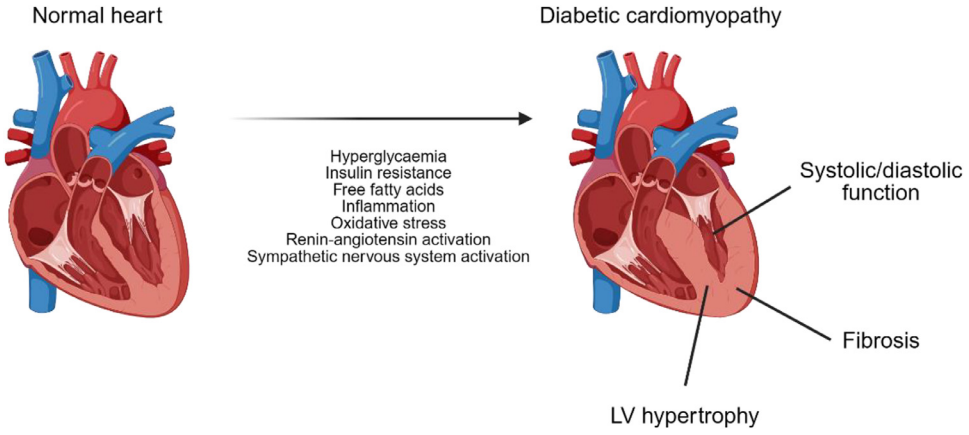


**Fig. 4.** Diabetic cardiomyopathy, proposed mechanisms and pathology.
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with a lack of specific histology, biomarkers or clinical manifestations to allow definitive diagnosis or targeted treatment.[12]

It is important to screen all patients with heart failure for diabetes. When screening for heart failure in patients with diabetes, regular assessment for symptoms or signs of heart failure and/or abnormalities on ECG is recommended, with measurement of BNP levels where heart failure is suspected.[3,13] The WATCH-DM score has been developed to predict heart failure risk in T2DM and can be used to stratify risk. This score includes BMI, age, hypertension, creatinine, HDL-C, fasting plasma glucose, QRS duration, MI and CABG history. A 1 unit increase in score corresponds to a 24% increase in 5-year risk of developing heart failure.[14] Management of heart failure in diabetes is as for people without diabetes. For HFrEF, this includes early initial quadruple therapy (angiotensin-converting enzyme inhibitors (ACE-I) / angiotensin receptor-neprilysin inhibitors (ARNI), beta-blockers, mineral corticoid receptor antagonists (MRA) and sodium-glucose co-transport inhibitors (SGLT2-I)), according to ESC guidance.[15] NICE guidelines broadly corroborate, but are more restrictive of the use of ARNI as a second-line therapy.[13] HFpEF recommendations include SGLT2 inhibitors and symptom management with diuretics.[15]

## Arrythmia and sudden cardiac death

Epidemiological studies suggest an association of diabetes with atrial fibrillation (AF), with a large meta-analysis of 1,686,097 patients, suggesting a 40% higher risk of AF in the presence of diabetes.[16] Patients with co-existent AF and diabetes have poorer cardiovascular outcomes. Detecting AF has important clinical consequences as the annual risk of stroke in AF is approximately 2% in diabetes, in the absence of other risk factors.[17] Asymptomatic patients with diabetes should be opportunistically screened by pulse palpation or ECG. Symptomatic patients should be investigated as for people without diabetes with 12-lead ECG and/or Holter monitoring.

Patients with diabetes have been seen to be at increased risk of sudden cardiac death (SCD) compared to the general population.[18] The most common cause of SCD in diabetes is IHD, but other important aetiological factors include cardiomyopathy and age. Diabetic assessments should include regular evaluation for structural heart disease, and further investigation if any evidence of symptoms of arrhythmia. The presence of frequent premature ventricular beats or episodes of ventricular tachycardia should also prompt assessments for structural heart disease and eligibility for implantable cardiac defibrillators.[3] In addition, a link between hypoglycaemia and SCD has also been suggested. In type 1 diabetes mellitus (T1DM), insulin-induced hypoglycaemia has been associated with nocturnal mortality, while in T2DM, trials have documented an increased incidence of arrhythmic death.[19] Furthermore, observational data from patients with T2DM have shown that hypoglycaemia episodes, particularly at night, were associated with higher risk of bradycardia, atrial ectopic beats and ventricular premature beats.[20]

## Specific glucose-lowering therapies with benefit in CVD

SGLT2-I were originally designated as a glucose-lowering therapy; however, they have also demonstrated significant benefit in improving cardiovascular outcomes in people with T2DM and those without. One meta-analysis of SGLT2-I randomised controlled trials (RCTs) reporting cardiovascular outcomes in people with T2DM demonstrated reduced composite time to first event of CV death, MI or stroke. This was most apparent in patients with established IHD. Largest benefits were seen in reducing hospitalisations for heart failure. More limited benefit has been seen in patients with T2DM without IHD.[21] Similarly, glucagon-like peptide 1 receptor agonists (GLP-1 RAs) improved cardiovascular outcomes in diabetes across several RCTs. A meta-analysis of seven of the eight RCT cardiovascular outcome trials showed significant reductions in adverse cardiovascular outcomes compared to placebo.[22] As a result, the ESC recommends both SGLT2-I and GLP-1RAs as preferred agents in patients with T2DM and established atherosclerotic CVD (ACVD) to modify cardiovascular risk. They also suggest consideration of these agents in patients with a high 10-year risk of CVD.[3] However, the long-term efficacy of these agents in modifying CVD risk in T2DM has not been fully established. NICE is more conservative in their recommendations, albeit they do recommend SGLT2-I as an add-on therapy in people with T2DM with established ACVD or high CVD risk. Stricter criteria are set out for GLP-1RAs by NICE.[4] There is also suggested benefit of metformin and pioglitazone in modifying CVD risk, although this is less clear-cut; furthermore, pioglitazone should be avoided in heart failure.[3]

## Type 1 diabetes and CVD risk

Risk stratification tools specifically for people with T1DM are less widely advocated than for T2DM. Age of onset and duration of diabetes are particularly important in defining risk. A number of specific T1DM risk tools do exist, including the Scottish/Swedish risk prediction model to estimate 10-year risk; however, this only receives a IIb recommendation in ESC guidance.[3] NICE does not recommend the use of a specific risk score, but instead advises a personalised risk factor-based approach for people with T1DM.[23] The mainstay of management in T1DM is insulin therapy, and intensive insulin therapy has been shown to be beneficial in reducing CVD risk.[24] Rigorous control of other CVD risk factors should also be implemented. Regarding SGLT2-I, these should also be avoided in T1DM due to risk of euglycaemic ketoacidosis. Furthermore, concerns over GLP-RA use in T1DM exist around rates of symptomatic hypoglycaemia and hyperglycaemia with ketosis.[3]

## Conclusion

Diabetes and cardiac disease frequently coexist, often alongside other risk factors and comorbidities. As such, effective management requires a personalised and holistic approach that integrates glucose-lowering therapies with cardiovascular risk-reducing strategies. This approach should also be tailored to patients' individual preferences, lifestyle and overall health status, ensuring that treatment is both evidence based and patient centred.

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## CRediT authorship contribution statement

**Andrew J. Sullivan:** Writing – original draft, Conceptualization. **Andrew Wragg:** Writing – original draft, Conceptualization. **Krishnaraj Rathod:** Writing – original draft, Conceptualization.

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