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Mechanisms of diabetic cardiomyopathy and potential therapeutic strategies: preclinical and clinical evidence

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Abstract

The pathogenesis and clinical features of diabetic cardiomyopathy have been well-studied in the past decade, but effective approaches to prevent and treat this disease are limited. Diabetic cardiomyopathy occurs as a result of the dysregulated glucose and lipid metabolism associated with diabetes mellitus, which leads to increased oxidative stress and the activation of multiple inflammatory pathways that mediate cellular and extracellular injury, pathological cardiac remodelling, and diastolic and systolic dysfunction. Preclinical studies in animal models of diabetes have identified multiple intracellular pathways involved in the pathogenesis of diabetic

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cardiomyopathy and potential cardioprotective strategies to prevent and treat the disease, including antifibrotic agents, anti-inflammatory agents and antioxidants. Some of these interventions have been tested in clinical trials and have shown favourable initial results. In this Review, we discuss the mechanisms underlying the development of diabetic cardiomyopathy and heart failure in type 1 and type 2 diabetes mellitus, and we summarize the evidence from preclinical and clinical studies that might provide guidance for the development of targeted strategies. We also highlight some of the novel pharmacological therapeutic strategies for the treatment and prevention of diabetic cardiomyopathy.

Although diabetic cardiomyopathy, characterized by abnormal cardiac structure and function in the absence of other cardiac risk factors, was described >40 years ago[1,2], the prevalence of this condition in patients with diabetes mellitus remains under-appreciated[3,4]. The incidence of heart failure (HF) in men and women with type 2 diabetes mellitus (T2DM) is at least 2.4-fold and 5.1-fold higher, respectively, than in sex-matched individuals without diabetes[2,5,6]. The prevalence of cardiac dysfunction in individuals with type 1 diabetes mellitus (T1DM) and T2DM has been reported to be as high as 14.5% and 35.0%, respectively[4,7]. The risks of diabetic cardiomyopathy and HF are correlated with the level of glycaemic control: patients with T1DM have a 30% increased risk and those with T2DM an 8% increased risk of HF for each 1% increase in glycated haemoglobin (HbA_{1c}) level[8].

Despite the exponential increase in the number of preclinical and clinical studies on diabetic cardiomyopathy in the past decade, the pathogenesis of this condition remains unclear. As a result, no consensus has been reached regarding the most effective preventive or therapeutic approaches to treat diabetic cardiomyopathy or diabetes-related HF. At present, the management of high blood glucose levels in patients with T2DM and cardiovascular disease is tailored to minimize the risk of cardiovascular complications, with metformin as first-line standard therapy, followed by sulfonylureas and insulin as the traditional second-line and third-line therapies, respectively[9]. Among the new antidiabetic agents, dipeptidyl peptidase 4 (DPP4) inhibitors did not lower the risk of cardiovascular disease and death in patients with T2DM compared with the risk in controls[10]. Moreover, treatment with the DPP4 inhibitor saxagliptin in patients with T2DM has been associated with an increased risk of HF-related hospitalization compared with placebo treatment[11]. However, the CARMELINA trial[12] showed that treatment with the DPP4 inhibitor linagliptin neither increased nor decreased the risk of HF-related hospitalization compared with placebo treatment. By contrast, treatment with sodium–glucose cotransporter 2 (SGLT2) inhibitors[13–15] and glucagon-like peptide 1 (GLP1) receptor antagonists[16–18] has been shown to reduce the risk of cardiovascular disease in patients with T2DM compared with placebo treatment. Furthermore, the DAPA-HF trial[19] reported in 2019 showed that treatment with the SGLT2 inhibitor dapagliflozin reduced the risk of worsening HF or cardiovascular death in patients with HF with reduced ejection fraction (HFrEF) with or without T2DM compared with placebo treatment. Given the cardioprotective benefits of dapagliflozin regardless of the presence of T2DM, the mechanism by which the drug reduces the risk of cardiac complications is most probably independent of the blood glucose-lowering properties of the drug. Together, these clinical trials highlight the need to further our understanding of the pathological mechanisms of diabetic cardiomyopathy and HF in patients with T2DM. In this

Review, we summarize data from preclinical and clinical studies that highlight potential mechanisms underlying the development of diabetic cardiomyopathy and discuss novel therapies that are currently under investigation. An in-depth understanding of the pathogenesis of diabetic cardiomyopathy might provide guidance for the development of strategies to prevent and treat cardiovascular disease in patients with diabetes.

Insulin resistance

Impaired signal transduction and biological actions in response to insulin stimulation.

β-oxidation

Catabolic process that takes place in the mitochondria to generate energy by breaking fatty acid molecules into acetyl coenzyme A, which enters the tricarboxylic acid cycle that generates reduced NAD and reduced flavin adenine dinucleotide, which are co-enzymes used in the electron transport chain.

Advanced glycation end products

(AGEs). Protein or lipid molecules that are modified by glycation when exposed to sugars; AGEs can induce cardiovascular injury through crosslinking of extracellular matrix molecules and by engaging the receptor for AGEs (RAGE) on cardiac cells.

Cardiomyopathy in T1DM and T2DM

Although the aetiologies of T1DM and T2DM differ (Box 1), systemic metabolic derangements such as hyperglycaemia and dyslipidaemia occur in both diseases[20,21]. In patients with T1DM or T2DM, the heart shows reduced insulin-mediated mitochondrial glucose oxidation, either owing to the absence of insulin (T1DM) or to insulin resistance (T2DM)[20,21]. Furthermore, the development of insulin resistance and T2DM leads to increased free fatty acid uptake by cardiomyocytes via the fatty acid translocase CD36. This excessive fatty acid intake in turn impairs mitochondrial fatty acid β-oxidation, resulting in greater mitochondrial dysfunction and accumulation of toxic lipid metabolites in the heart in patients with T2DM than in patients with T1DM[22–25].

The typical clinical features of diabetic cardiomyopathy associated with T2DM include reduced ventricular compliance with increased systemic and pulmonary venous pressures and congestion despite preserved systolic function[21]. Symptoms of systolic dysfunction, more typical in patients with T1DM, include classic HF symptoms of reduced exercise capacity, as well as the onset of arrhythmias owing to mitochondrial dysfunction[26], abnormal Ca^{2+} transport[27] and autonomic neuropathy[28,29].

Diabetic cardiomyopathy initially manifests as isolated diastolic dysfunction, but with time progresses to systolic dysfunction characterized by derangements in various metabolic and neurohumoral pathways[30–32]. In T2DM-associated diabetic cardiomyopathy, coronary

microvascular inflammation and paracrine effects on cardiomyocytes and endothelial cells mediate concentric left ventricular (LV) remodelling and hypertrophy that increase ventricular stiffness and promote diastolic dysfunction[33–35]. The symptoms of HF with preserved ejection fraction (HFpEF) in patients with T2DM are often early but subtle and can be detected with the use of sensitive, noninvasive measures of diastolic dysfunction (such as tissue Doppler imaging) starting in childhood[21,36,37]. By contrast, T1DM-associated diabetic cardiomyopathy is characterized by cardiomyocyte loss, LV remodelling and increased myocardial collagen deposition, which increase LV end-diastolic volume and impair systolic function[8,21,38]. Coronary vascular injury and dysfunction are common in both T1DM and T2DM. The symptoms of HFrEF occur later in the clinical progression of diabetic cardiomyopathy in T2DM[39,40] than in T1DM[36,38,41].

A similar progression in the development of HF in diabetes has also been shown in preclinical studies in animal models of T1DM and T2DM[20]. In a comparative assessment of the LV pressure–volume relationship in rat models of T1DM and T2DM, rats with T1DM had marked systolic dysfunction and delayed relaxation[31,42]. By contrast, rats with T2DM and hyperinsulinaemia showed more pronounced diastolic stiffness and preserved systolic function, a disease profile that is similar to that in patients with T2DM and concomitant HFpEF[31,42].

Pathophysiology of diabetic cardiomyopathy

The pathophysiology of diabetic cardiomyopathy is well established and has been the subject of many reviews[8,22,23,43,44]. In the setting of T1DM and T2DM, increased levels of glucose residues and metabolites upregulate the production of advanced glycation end products (AGEs), which can affect cardiomyocytes and endothelial cells[37] (FiG. 1). During the early stages of diabetes, a lack of insulin or insulin resistance induces a metabolic shift in cardiomyocytes, whereby fatty acid intake and β-oxidation are increased to maintain sufficient levels of ATP production. However, over time, β-oxidation cannot adequately metabolize all incoming fatty acids, resulting in intracellular lipid accumulation and lipotoxicity[45]. Increased intracellular fatty acid concentration and mitochondrial dysfunction lead to increased generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which together increase oxidative stress and endoplasmic reticulum (ER) stress and inhibit autophagy[46]. Together, these effects contribute to cardiomyocyte death, cardiac hypertrophy and inflammation and a progressive profibrotic response that induces extracellular matrix (ECM) remodelling and fibrosis[21]. Changes in the phosphorylation of titin, a protein anchored to the sarcomere Z-line that serves as a major determinant of myocardial passive tension and stiffness, can also contribute to the development of cardiomyocyte hypertrophy and myocardial stiffness by increasing cardiomyocyte passive tension[47]. Furthermore, disrupted Ca^{2+} cycling and increased fibrotic scarring in the diabetic heart can mediate contractile dysfunction and arrhythmia, contributing to HF and death[5,6,48,49]. The following sections discuss adverse changes in cardiac structure, such as cardiac hypertrophy and fibrosis, and cardiac functional changes such as diastolic dysfunction and impaired cardiomyocyte contractility on the basis of insights derived from preclinical and clinical studies.

Reactive oxygen species

(RoS). By-products of cellular respiration comprising unstable chemical species containing oxygen, including superoxide and hydroxyl radical; RoS have important roles in cell signalling and homeostasis but can induce cellular damage when dysregulated.

Reactive nitrogen species

(RNS). Reactive compounds derived from nitric oxide, including nitroxyl anion and nitrosonium cation, that are critical for the physiological regulation of living cells but can induce cellular damage when dysregulated.

Oxidative stress

An imbalance between the production of free radicals and the biological system's capacity to detoxify the reactive intermediates with antioxidants. oxidative stress is a common pathogenic mechanism in many diseases.

Endoplasmic reticulum (ER) stress

The endoplasmic reticulum (ER) is a major organelle in which proteins are synthesized, folded, modified and delivered to their final intracellular or extracellular destination. increased stress on this system results in the accumulation of unfolded proteins in the ER lumen.

Cardiac remodelling and dysfunction

Preclinical studies.—The systemic hyperglycaemia, hyperlipidaemia and inflammation associated with diabetes contribute to the development of cardiac hypertrophy and fibrosis, which increase myocardial stiffness and result in diastolic and systolic dysfunction (FiG. 2). Under physiological circumstances, cardiac fibroblasts synthesize small amounts of collagen to maintain ECM homeostasis, a process regulated by two key factors: matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs)[50,51]. However, under diabetic conditions, AGEs generated by the exposure of proteins and lipids to high glucose levels crosslink ECM proteins, impair ECM degradation by MMPs and increase cardiac stiffness, which together manifest as early diastolic dysfunction[33,52–54]. AGEs can also promote the differentiation of fibroblasts into myofibroblasts, which proliferate and induce ECM dyshomeostasis by secreting profibrotic cytokines and matrix proteins. Furthermore, the altered cardiac mechanics lead to the release of other stimuli including transforming growth factor-β (TGFβ), tumour necrosis factor (TNF), angiotensin II and various interleukins, which activate profibrotic responses in fibroblasts and myofibroblasts[55]. Activation of TGFβ and mothers against decapentaplegic homologue (SMAD) signalling in myofibroblasts increases the deposition of structural ECM proteins and matricellular macromolecules, which contribute to impaired cardiac contractility and

late systolic dysfunction (HFrEF profile)[33,50,51,56]. In addition to cardiac fibroblasts and myofibroblasts, endothelial and epicardial cells can also contribute to the development of cardiac fibrosis through endothelial-to-mesenchymal or epithelial-to-mesenchymal transition to myofibroblasts[57–59].

In diabetic settings, activated endothelial cells contribute to early myocardial stiffness and diastolic dysfunction by promoting the uncoupling of endothelial nitric oxide synthase (NOS) to generate superoxide, hydrogen peroxide and peroxynitrite, resulting in diminished nitric oxide (NO) levels[60]. As shown in FiG. 2, reduced NO signalling in endothelial cells and cardiomyocytes can increase cardiomyocyte hypertrophy and stiffness by decreasing soluble guanylate cyclase (sGC) activity and cyclic GMP (cGMP) content in the myocardium, which abolishes the protective effects of protein kinase G (PKG)[61–63].

Clinical studies.—The degree of cardiac fibrosis, as assessed by cardiac magnetic resonance imaging (MRI), correlates with increased mortality and the rate of HF-related hospitalization in patients with T2DM[64]. Diabetic cardiomyopathy in patients with T1DM or T2DM presents as LV hypertrophy, interstitial and perivascular fibrosis, and microvascular abnormalities[3,65,66]. Immunohistochemical studies in patients with T2DM revealed an accumulation of type I, III and VI collagens in the cardiac interstitium, but only the level of type III collagen was significantly higher in patients with T2DM than in individuals without diabetes[65–69].

Cardiac inflammation

Preclinical studies.—In the diabetic heart, cytokines, chemokines and exosomes secreted by inflammatory cells contribute to the development of cardiomyocyte hypertrophy and ECM remodelling (FiG. 3). A number of myocardial processes are activated by hyperglycaemia, hyperlipidaemia, elevated angiotensin II levels and other pro-inflammatory factors that are upregulated in the setting of diabetes. Together, these factors promote the accumulation and infiltration of pro-inflammatory macrophages and lymphocytes into the lesion site. These inflammatory cells secrete cytokines such as TNF, IL-6, IL-1β, interferon-γ and TGFβ that can induce or exacerbate cardiac injury, leading to further adverse remodelling[70–73]. Mice with streptozotocin (STZ)-induced T1DM have higher T cell infiltration into the myocardium that is associated with increased cardiac fibrosis and dysfunction than control mice[74]. Inhibition of T cell trafficking in diabetic mice prevented cardiac fibrosis and LV dysfunction[75,76]. Targeted deletion in T cells of the sphingosine-1-phosphate receptor 1 (S1PR1), which induces the transport of T cells from lymphoid organs into the lymphatic vessels, ameliorated cardiac fibrosis in mice with STZ-induced T1DM[77], suggesting that S1PR1-mediated T cell trafficking is essential for the development of cardiac fibrosis in these mice. Similarly, *Rag1*-knockout mice, which lack mature T cells, were protected against cardiac fibrosis induced by STZ administration[78].

Autophagy

A regulated cellular process that removes unnecessary or dysfunctional cellular components by lysosome-mediated or vacuole-mediated degradation and recycling.

Extracellular matrix

(ECM). A complex network of extracellular material such as proteins and polysaccharides that are secreted locally by cells and remain crosslinked with each other to provide structural, adhesive and biochemical signalling support.

TLR4 is expressed in inflammatory cells, cardiac fibroblasts and cardiomyocytes in both normal and failing hearts[79]. The role of TLR4-mediated inflammatory signalling in the development of diabetic cardiomyopathy has been described in animal models of T1DM and T2DM[80–83]. In mice with T1DM, hyperglycaemia-induced cardiomyocyte apoptosis and cardiac dysfunction were prevented by small interfering RNA-mediated silencing of *Tlr4* (REF.[80]) or by deleting *Tlr2* (REF.[84]), respectively. Furthermore, in hyperglycaemic, nonobese mice with T1DM, deletion of *Tlr4* did not affect plasma triglyceride levels but significantly reduced triglyceride accumulation and the activation of the proinflammatory factors myeloid differentiation factor 88 (MyD88), phosphorylated p38 mitogen-activated protein kinase (MAPK) and Jun N-terminal kinase (JNK) in the heart compared with its effects in wild-type mice with T1DM[81]. Reduction in these pro-inflammatory responses significantly attenuated cardiac remodelling and dysfunction in TLR4-deficient diabetic mice compared with the effects in wild-type diabetic mice[81]. Although the role of targeting TLR4 for the prevention of diabetic cardiomyopathy in animal models of T2DM has not been assessed, *Tlr4* deletion in mice protects against cardiac dysfunction associated with advanced age or with consumption of a high-fat diet[85,86].

High mobility group box 1 (HMGB1) is a nuclear chromatin protein that interacts with nucleosomes, transcription factors and histones to facilitate the transcription of many genes related to inflammatory processes[87–89]. Both in vitro and in vivo studies have revealed that plasma membrane receptor for AGEs (RAGE) is the primary mediator of HMGB1-induced pro-inflammatory responses[87–89]. Lipopolysaccharide (LPS) as the ubiquitous prototype TLR4 agonist needs to form a complex with CD14, which delivers LPS to TLR4 to activate inflammatory signalling, whereas HMGB1 binds to and facilitates the delivery of LPS to CD14. Therefore, HMGB1 is also involved in the activation of TLR4-mediated MyD88 signalling and the subsequent activation of numerous signalling cascades[90–93]. In mice subjected to ischaemia–reperfusion injury, HMGB1 expression in the heart was significantly elevated at both the transcript and protein levels in T1DM mice compared with the expression in control mice, and this was accompanied by an increase in the expression of proinflammatory cytokines[89,94]. Blockade of HMGB1 with the HMGB1 antagonist box A attenuated ischaemia–reperfusion injury-induced cardiac remodelling and tissue damage[89], suggesting that HMGB1 might be a potential therapeutic target for the prevention of diabetic cardiomyopathy.

Inflammatory factors including TNF and nuclear factor-κB (NF-κB) and protein kinases such as JNK and p38 MAPK can directly induce cardiomyocyte hypertrophy and promote cardiac fibrosis[95,96]. IL-1β, IL-6, IL-17 and TNF are involved in the development of a rapid and reversible contractile dysfunction that impairs cardiac contractility in mice[97–100]. These effects are mediated by the activation of inducible NOS to produce excess NO, which

interacts with superoxide to form peroxynitrite, a powerful oxidant that can interfere with cardiomyocyte excitation–contraction coupling[101,102]. Under diabetic conditions, NADPH oxidase (NOX) can generate excess superoxide[103]. IL-1β and IL-6 signalling can also directly impair Ca^{2+} handling in rat cardiomyocytes in vitro by inducing a reduction in the expression of sarcoplasmic/ER Ca^{2+} ATPase 2a[104–106]. Deletion of *Il6* (REF.[107]) or *Il17* (REF.[98]) in mice with STZ-induced T1DM attenuates the development of cardiac interstitial fibrosis and improves cardiac function. NF-κB activation has also been reported to have a role in diabetic cardiomyopathy[108]. In the setting of STZ-induced T1DM, transgenic mice expressing in the heart a mutated form of the NF-κB inhibitor IκBα that prevents the activation of canonical NF-κB signalling are protected from cardiac dysfunction and oxidative stress[108].

Activation of the NLRP3 inflammasome, a regulator of inflammation and cell death[109], has been associated with the cardiac inflammation, cell death and fibrosis triggered by a high-fat diet and STZ treatment in a rat model of T2DM[110]. These effects were attenuated by microRNA-mediated *Nlrp3* silencing[110] or with pharmacological suppression of NLRP3 inflammasome activation[111].

The 12-lipoxygenase (12-LOX) and 15-LOX enzymes are expressed in mammalian monocytes and macrophages, induced by the type 2 T helper cell cytokines IL-4 and IL-13 (REF.[112]). 12-LOX and 15-LOX oxygenate free polyenoic fatty acids, ester lipids and complex lipid–protein assemblies such as biomembranes and lipoproteins. The expression of 15-LOX in the heart is significantly upregulated in diabetic mice compared with the expression in nondiabetic mice[113]. Deletion of *Alox15* (which encodes 15-LOX) in diabetic mice resulted in reduced cardiac inflammation, oxidative stress and fibrosis and improved cardiac function compared with the effects in wild-type diabetic mice[113]. Furthermore, 15-LOX-mediated inflammation is a major contributor to the development of HF in mice[114], which adds to the body of evidence indicating that 15-LOX-mediated inflammation is critical in the development of diabetic cardiomyopathy.

Inflammasome

Multiprotein intracellular complex that can sense a variety of physiological and pathological stimuli and in response can activate the highly pro-inflammatory cytokines IL-1β and IL-18.

Together, these mechanistic studies highlight the essential role of diverse inflammatory responses in the development of diabetic cardiomyopathy (FiG. 3). These inflammatory pathways can both directly and indirectly contribute to the development of diabetic cardiomyopathy and HF by increasing cardiomyocyte apoptosis, promoting fibrotic growth and cardiomyocyte hypertrophy, and impairing cardiomyocyte contractility.

Clinical studies.—The Framingham Heart Study was the first study to demonstrate that patients without a history of acute myocardial infarction (MI) who have higher baseline levels of IL-6 and C-reactive protein (CRP) in serum and higher production of TNF by peripheral blood mononuclear cells have a significantly higher long-term risk of developing

HF than patients with lower levels of these inflammatory markers[115]. Higher circulating levels of inflammatory markers such as TNF and TGFβ correlate with higher LV mass and diastolic and systolic dysfunction in patients with hypertension, and this association is stronger in patients with hypertension and metabolic syndrome than in those without metabolic syndrome[116]. These findings have been corroborated by larger case studies[117,118], and systemic inflammation has subsequently been confirmed as an independent risk factor for HF[119].

Cardiac oxidative stress

Preclinical studies.—Oxidative stress is defined as an imbalance in the generation of free radicals and antioxidants. Excess generation of various ROS or RNS is considered to be a central mechanism for diabetes-associated inflammation and remodelling in the heart[120,121] and contributes to oxidative stress during both the early and late stages of diabetic cardiomyopathy[122–124] (FiG. 4). Defects in the antioxidant defence system further increase oxidative stress during the later stages of diabetic cardiomyopathy[122–124]. In the diabetic heart, a major source of excess ROS or RNS production is the activation of cellular and mitochondrial NOX, which leads to the generation of superoxide and hydrogen peroxide, as reviewed previously[120,121,125]. Within the cell, superoxide dismutases (SODs) constitute the first line of defence against ROS, given that these enzymes catalyse the dismutation of the superoxide radical into either oxygen or hydrogen peroxide[126].

SOD has an important role in preventing cardiac damage in the setting of diabetes. Injection of the SOD mimic mitochondria-targeted mito-TEMPO prevented the hyperglycaemia-induced increase in superoxide generation, reduced myocardial hypertrophy and improved myocardial function in STZ-induced T1DM mice and *db/db* T2DM mice compared with vehicle treatment[127] (TABLE 1). Moreover, transgenic overexpression of mitochondrial manganese SOD in the heart in OVE26 diabetic mice improved mitochondrial respiration and prevented the development of diabetes-induced changes in cardiac morphology and contractility[128]. Similarly, cardiac overexpression of catalase, an enzyme that catalyses the decomposition of hydrogen peroxide to water and oxygen, resulted in the preservation of normal cardiac morphology and the prevention of contractile defects in mouse models of T1DM and T2DM[129]. Furthermore, diabetic mice with transgenic overexpression of the potent antioxidant metallothionein in the heart had a morphologically normal heart, improved cardiac contractility and reduced cardiomyocyte cell death compared with wild-type diabetic mice[123,130,131].

The transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) is a crucial regulator of the antioxidant response with an important role in preventing diabetes-induced oxidative stress and cell death. *Nrf2*-knockout mouse cardiomyocytes were more susceptible to high-glucose-induced cell death in vitro than wild-type cells[132]. Furthermore, NRF2-deficient mice were more susceptible to diabetes-induced or angiotensin II-induced cardiomyopathy than wild-type mice, whereas cardiomyocyte-specific overexpression of *Nrf2* conferred resistance to angiotensin II-induced cardiomyopathy[133,134].

Clinical studies.—The role of zinc in the development of diabetic cardiovascular complications has been assessed in clinical studies. In an observational study involving 1,050 patients with T2DM, low serum zinc concentrations were significantly associated with higher risk of death from coronary heart disease[135]. Furthermore, low serum zinc concentrations were linked to impaired exercise capacity and a high risk of death in patients with decompensated HF[136], as well as to increased levels of markers of cardiac injury (such as serum creatine kinase and cardiac troponin T) and a higher prevalence of acute MI[137]. Deficient levels of zinc and selenium are often reported in patients with morbid obesity undergoing bariatric surgery[138,139], and zinc and selenium deficiencies are often linked to cardiac complications owing to the induction of oxidative stress[140–142].

Diabetes-induced metabolic disturbances

Preclinical studies.—The heart has the largest metabolic demand per gram of any organ in the body. ATP is produced at high rates to meet myocardial demands and is generated from the mitochondrial oxidation of various substrates, including fatty acids (60–70%), glucose (20%) and lactate (10%)[143]. The regulation of insulin-stimulated cardiac substrate utilization is complex and mediated by several cellular targets[143] (FiG. 5a). The uptake of glucose depends on the presence of glucose transporters (GLUTs) in the plasma membrane. Both GLUT1 and GLUT4 are expressed in the heart; GLUT1 is responsible for basal cardiac glucose uptake whereas GLUT4 is required for contraction or insulin-stimulated glucose uptake[144–146]. The phosphatidylinositol 3-kinase (PI3K)–RACα serine/threonine-protein kinase (AKT) signalling cascade regulates insulin-induced GLUT4 translocation[147].

In addition to stimulating glucose uptake, both insulin signalling[148] and cardiomyocyte contraction[149] can promote fatty acid uptake by cardiomyocytes via induction of CD36 translocation to the plasma and sarcolemma membranes[148,150]. The long-lasting presence of CD36 at the sarcolemma membrane results in an increased rate of long-chain fatty acid uptake and accumulation of triglycerides in cardiomyocytes, which contribute to lipotoxicity and diabetic cardiomyopathy[150,151]. Accordingly, CD36 inhibition prevented lipid accumulation and contractile dysfunction in cultured rat cardiomyocytes[152]. The transcription factor peroxisome proliferator-activated receptor-α (PPARα) is a major regulator of lipid metabolism and can increase the expression of genes encoding CD36, fatty acid-binding proteins and proteins involved in β-oxidation in the peroxisome and mitochondria[153]. Mice with cardiac-specific overexpression of *Ppara* showed cardiac lipid accumulation and dysfunction compared with control mice[154], which was prevented by systemic deletion of *Cd36* under both basal conditions and in response to high-fat diet feeding[155]. Insulin signalling-dependent glucose metabolism is defective in both T1DM and T2DM and can affect cardiac energy metabolism[156,157]. In the heart, defects in insulin signalling manifest as increased CD36 localization to the sarcolemma and reduced GLUT4 translocation to the plasma membrane[158,159] (FiG. 5b). Mice with cardiac-specific deletion of *Glut4* had normal cardiac function in the unstressed state but developed maladaptive hypertrophy and severe contractile dysfunction in response to LV pressure overload[160]. Therefore, GLUT4 is required for the maintenance of cardiac structure and function in response to pathological processes that increase energy demand, in part through secondary

changes in mitochondrial metabolism and cellular stress survival pathways such as PI3K–AKT[160].

The AKT kinase family comprises three highly homologous isoforms: AKT1, AKT2 and AKT3. Whereas AKT1 is an important signalling protein involved in cellular survival pathways (it can inhibit apoptosis and induce protein synthesis[161]), AKT2 is involved in insulin signalling[162,163]. *Akt1*$^{-/-}$ mice have normal glucose metabolism[161], whereas *Akt2*$^{-/-}$ mice develop insulin resistance and a T2DM-like syndrome[164,165]. Indeed, compared with hearts from nondiabetic mice, hearts from mice with STZ-induced T1DM had reduced levels of insulin-stimulated phosphorylation of total AKT and AKT2, but not AKT1, alongside a significant decrease in the AKT downstream target glycogen synthase kinase 3β (GSK3β)[156]. These changes were not observed in transgenic mice overexpressing metallothionein in the heart[156]. Similarly, short hairpin RNA (shRNA)-mediated knockout of *Akt2*, but not *Akt1*, in mouse cardiomyocytes in vitro completely abolished the protective effects of metallothionein overexpression against the inhibition of insulin signalling, glucose uptake and ATP production mediated by the oxidative compound *tert*-butyl hydroperoxide (tBHP)[156]. Together, these findings indicate that AKT2 has an important role in cardiac insulin signalling in diabetic cardiomyopathy.

AKT function in the context of insulin signalling is modulated by serine/threonine kinases and negative regulators such as phosphatase and tensin homologue (PTEN)[166], protein tyrosine phosphatase 1B (PTP1B)[167] and tribbles homologue 3 (TRB3)[168,169] (FiG. 5b). Upregulation of these negative regulators contributes to insulin resistance in the heart; conversely, downregulation of these negative regulators is cardioprotective. Mice lacking *Pten* specifically in adipose tissue[170], in the liver[171] or in muscle[172] had improved systemic glucose tolerance and insulin sensitivity compared with wild-type mice. Muscle-specific or cardiac-specific deletion of *Pten* in mice prevented the development of pathological cardiac hypertrophy induced by pressure overload[173] and protected the heart against ischaemia–reperfusion injury[174]. Furthermore, the finding that overexpression of mitochondrial aldehyde dehydrogenase prevented the diabetes-mediated increase in PTEN activation and diabetic cardiomyopathy development in mice with STZ-induced diabetes mellitus lends additional support to the importance of PTEN activation in the negative regulation of AKT-mediated glucose metabolism in the heart[175].

The role of PTP1B expression in systemic insulin resistance was first established more than two decades ago[176,177]. Global or muscle-specific deletion of *Ptp1b* in mice resulted in an increase in insulin sensitivity and improvement in glucose homeostasis[176,177]. Activation of PTP1B in response to cardiac pressure overload in the heart in both rats and humans was associated with cardiac insulin resistance, which preceded the development of HF[178]. Similarly, PTP1B deficiency in mice attenuated the development of myocardial dysfunction induced by consumption of a high-fat diet[179] or in the setting of HF[180].

TRB3 can directly bind to AKT and inhibit AKT phosphorylation[168,169]. The expression of TRB3 is upregulated in the heart in T1DM and T2DM rodent models[156,181], and in the skeletal muscle in patients with T2DM[169]. A rat model of T2DM induced by a high-fat diet and low-dose STZ had severe insulin resistance and features of diabetic cardiomyopathy,

including LV dysfunction, cardiac inflammation and myocardial fibrosis, in addition to increased expression of TRB3 compared with control rats[181]. Silencing of *Trb3* in diabetic rats ameliorated insulin resistance and metabolic disturbances, and attenuated myocardial hypertrophy, fibrosis and lipid accumulation[181]. TRB3 can also bind to AKT2 and accelerate its degradation via autophagy[182]. Accordingly, mice deficient in TRB3 are protected from insulin resistance induced by a high-fat diet[169], whereas transgenic mice with cardiac-specific *Trb3* overexpression showed abnormal cardiac insulin signal transduction and metabolism and reduced cardiac glucose oxidation rates compared with wild-type mice[183]. shRNA-mediated silencing of *Trb3* blocked the tBHP-induced inactivation of AKT2 and its downstream metabolic signals in mouse adult cardiomyocytes in vitro[156]. By contrast, overexpression of *Trb3* ex vivo and in vivo completely prevented insulin-stimulated AKT2 phosphorylation in mouse adult cardiomyocytes, and abolished the protective effects of metallothionein overexpression against tBHP-mediated inhibition of insulin-stimulated AKT2 phosphorylation and diabetic cardiomyopathy development[156]. These findings suggest that downregulation of cardiac TRB3 might be a potential therapeutic strategy to slow the progression of diabetes-induced cardiac dysfunction to clinically manifest HF.

Potential therapeutic strategies

Cardiac remodelling and dysfunction

Preclinical studies.—Numerous preclinical studies have investigated the efficacy of novel therapies targeting antifibrotic pathways to prevent adverse cardiac remodelling in animal models of diabetes (FiG. 2; TABLE 1). The antifibrotic agent cinnamoyl anthranilate reduced the collagen production stimulated by TGFβ signalling in cultured renal mesangial cells[184]. Administration of FT23 and FT011, which are derivatives of cinnamoyl anthranilate, attenuated cardiac structural and functional abnormalities in an animal model of diabetic cardiomyopathy[185,186]. A later study confirmed the efficacy of FT011 in improving cardiac function and ameliorating myocardial remodelling after induction of MI in rats compared with vehicle treatment[187].

Strategies to restore cGMP levels and protect against cardiac fibrosis and hypertrophy have also been investigated in preclinical models of diabetic cardiomyopathy by targeting intracellular receptors of cGMP such as cGMP-dependent PKG and cGMP-binding phosphodiesterase type 5 (PDE5)[188,189] (TABLE 1). Titin can be modulated via PKG-mediated phosphorylation. Low levels or complete absence of cGMP decreases cGMP-dependent PKG activity and, in turn, low PKG activity increases the resting tension of cardiomyocytes as a result of titin hypophosphorylation, which removes the brake on pro-hypertrophic stimuli to induce cardiomyocyte hypertrophy[188]. Therefore, preservation of cGMP levels might prevent the reduction in PKG activity and thereby prevent cardiomyocyte hypertrophy and stiffness. A potential cause of low cGMP availability in the heart is through cGMP binding to PDE5 (FiG. 2). Accordingly, PDE5 inhibitors, such as sildenafil, vardenafil and tadalafil (which are primarily used to treat erectile dysfunction in elderly individuals or in patients with diabetes), might have cardioprotective benefits. PDE5 is expressed in normal and failing hearts[190,191]. Zucker diabetic fatty (ZDF) rats treated with vardenafil had preserved diastolic function and attenuated myocardial hypertrophy and

fibrosis, through restoration of cGMP levels and PKG activation, and a reduction in nitro-oxidative stress compared with untreated rats[62]. Tadalafil treatment also protected diabetic mice from myocardial ischaemia–reperfusion injury[192]. Furthermore, diabetic mice treated with the SGLT2 inhibitor empagliflozin had reduced cardiac hypertrophy, fibrosis, oxidative stress and apoptosis compared with untreated mice, effects that were thought to be mediated by empagliflozin rescuing the diabetes-induced suppression of the sGC–cGMP–PKG pathway[193].

Relaxin is a critical antifibrotic hormone involved in the maintenance of tissue elasticity[194]. Relaxin has been shown to exert numerous beneficial cardiovascular effects, including suppression of arrhythmia and inflammation and protection against ischaemic injury[194,195]. In particular, relaxin can reduce cardiac fibrosis by preventing collagen production by cardiac fibroblasts, by downregulating fibroblast-to-myofibroblast transition and by stimulating MMP production[196–198]. Knockout of the relaxin gene in mice resulted in increased atrial hypertrophy and ventricular chamber stiffness, which could be reversed by administration of recombinant human relaxin[199]. Diabetes has a differential effect on the expression of relaxin subtypes in rats: *Rln1* mRNA expression had increased, whereas *Rln3* expression had decreased in the rat heart at 8 weeks after induction of diabetes[200]. In STZ-treated transgenic mRen2 rats, an animal model of diabetes with similar structural and functional abnormalities to those seen in patients with diabetes, treatment with human recombinant relaxin led to a significant reduction in interstitial and total collagen deposition in the left ventricle compared with placebo treatment, resulting in reduced myocardial stiffness and improved diastolic function[201]. This finding has been corroborated by subsequent studies in other rodent models of T1DM and T2DM[202,203] (TABLE 1). Adenovirus-mediated cardiac delivery and expression of relaxin diminished cardiac fibrosis in a transgenic mouse model of fibrotic cardiomyopathy induced by cardiac overexpression of the β_2-adrenergic receptor[204], further validating the role of relaxin in protecting against fibrosis. Together, these studies show that targeting antifibrotic pathways can attenuate adverse cardiac structural remodelling and improve diastolic function.

Clinical studies.—As mentioned above, strategies to restore cGMP levels might protect against cardiac fibrosis and subsequent diastolic dysfunction. In a randomized, controlled trial to examine the effect of chronic inhibition of PDE5A on cardiac structure and function in diabetes and HF, 59 men with T2DM and HFpEF were treated with sildenafil for 3 months and assessed using cardiac MRI[205]. Sildenafil treatment improved LV torsion, strain and contraction, and had favourable effects on chamber geometry and performance compared with placebo treatment (TABLE 2). Furthermore, sildenafil treatment reduced the levels in plasma of the pro-inflammatory factors C-X-C motif chemokine 10 and IL-8 in patients with diabetic cardiomyopathy compared with placebo treatment[206,207]. Upregulation of PDE9A levels in the heart has been found in rabbits with atherosclerosis, suggesting that PDE9A has a role in mediating cardiac hypertrophy and dysfunction[208]. Whereas PDE5A regulates NO-generated cGMP, PDE9A regulates natriuretic peptide-stimulated cGMP in cardiomyocytes[209]. PDE9A inhibition has been shown to reverse cardiac dysfunction independent of NOS activity, whereas PDE5A inhibition requires active NOS[209]. This finding is important given that NOS activity is often depressed in patients with

diabetes. Therefore, PDE9A inhibition might have a role in the prevention of diabetic cardiomyopathy.

Cardiac inflammation

Preclinical studies.—Numerous preclinical studies have assessed the efficacy of blunting inflammatory cell trafficking with the use of pharmacological inhibitors to prevent the development of diabetic cardiomyopathy (TABLE 1). Fingolimod (also known as FTY720) is an FDA-approved immunomodulatory drug used for the treatment of multiple sclerosis. Fingolimod is phosphorylated in the cells to form fingolimod phosphate, a functional antagonist of S1PR1. Fingolimod phosphate inhibits lymphocyte egress from lymphoid tissues by decreasing the levels of S1PR1 in the lymphocyte cell surface[210]. In diabetic rats, treatment with fingolimod ameliorated diabetes-induced cardiac microvascular barrier impairment and pathogenic angiogenesis[211] and improved coronary flow reserve[212] compared with no treatment. By contrast, in diabetic mice without mature lymphocytes, fingolimod treatment further exacerbated cardiac fibrosis and dysfunction[78].

Inhibitors of TLR4 signalling and pro-inflammatory cytokines have been assessed in preclinical studies for the prevention of diabetic complications (TABLE 1). Suppression of TLR4 signalling with matrine or triptolide improved cardiac function and reduced collagen deposition in rat models of diabetic cardiomyopathy[213,214]. Long-term blockade of TLR4 with the TLR4 inhibitor TAK-242 (also known as CLI-095) was associated with a slight improvement in diabetes-induced erectile dysfunction in rats compared with no treatment, mediated by the attenuation of oxidative stress and an increase in cGMP levels in penile tissue[215]. Rats with STZ-induced T1DM treated with an anti-TNF monoclonal antibody (C432A) had significantly lower levels of TNF and IL-1β in the heart, which were associated with improved LV function and reduced cardiac types I and III collagen levels in the heart, compared with untreated diabetic rats[216]. Similarly, treatment of mice with STZ-induced T1DM with a recombinant IL-1 receptor antagonist reduced ER stress-dependent cardiomyocyte apoptosis without affecting fasting blood glucose concentration compared with no treatment[217].

Numerous small-molecule inhibitors of the NLRP3 inflammasome have been developed in the past 5 years. The orally active, NLRP3 inhibitor 16673–34-0 prevented Western diet-induced systolic and diastolic dysfunction in obese mice[218]. Treatment with the potent and selective NLRP3 inflammasome inhibitor MCC950 reduced infarct size and preserved cardiac function in pigs subjected to MI compared with no treatment[219] (TABLE 1). MCC950 treatment also protected against cardiac damage induced by a high-sucrose plus high-fat diet[220] and against diabetic nephropathy[221] in mice.

The selective LOX inhibitor baicalein (5,6,7-trihydroxyflavone) is thought to have numerous anti-inflammatory, antioxidant and antitumour effects[222,223]. In angiotensin II-treated mice, baicalein administration prevented cardiac hypertrophy and fibrosis, in part through a reduction in macrophage and T cell accumulation in the heart and the attenuation of associated inflammatory responses[224], indicating a potential role for 15-LOX in the prevention of cardiac complications of diabetes.

Clinical studies.—Preclinical studies demonstrating the benefits of TLR4 antagonists in ameliorating diabetic complications have led to the investigation of this target in clinical trials. A trial involving treatment with the TLR4 inhibitor TAK-242 and the TLR4 antagonist eritoran, which in animal models were shown to block TLR4-mediated inflammation and cardiac hypertrophy[215,225], did not meet the clinical end points for the treatment of severe sepsis in two separate, randomized, placebo-controlled trials[226,227]. NI-0101, a monoclonal antibody that blocks TLR4 signalling independently of the TLR4 ligand type, reduced LPS-induced cytokine and CRP release both ex vivo and in vivo in a phase I, dose-escalation trial involving 73 healthy volunteers[228]. Clinical trials to test the efficacy of TLR4 ligand blockade in treating acute or chronic inflammatory diseases such as rheumatoid arthritis, including an ongoing trial that completed recruitment in 2018 (REF.[229]), might provide insights into the use of this strategy in preventing other inflammatory conditions such as diabetic cardiomyopathy.

The critical role of inflammatory cytokines in the development of cardiovascular disease in individuals with or without diabetes is well established. The CANTOS pilot study[230] demonstrated that the human monoclonal anti-IL-1β antibody canakinumab can reduce markers of inflammation (including CRP, IL-6 and fibrinogen levels in blood) without affecting glucose levels and the lipid profile in patients with T2DM. The expanded CANTOS trial[231,232] subsequently showed that targeting IL-1β with canakinumab significantly reduced recurrent cardiovascular events and HF-related hospitalization rates in patients with previous MI and increased high-sensitivity CRP levels compared with placebo treatment (TABLE 2). Although canakinumab treatment over a median period of 3.7 years did not reduce the risk of incident diabetes compared with placebo treatment, canakinumab had similar effects to placebo on the risk of major cardiovascular events in patients with or without diabetes[233]. Together, these data provide support for the use of anti-inflammatory therapy to treat cardiovascular disease. Additional data are needed to determine the efficacy of this strategy for the treatment or prevention of diabetic cardiomyopathy.

Given the expensive and time-consuming process of developing and validating novel therapeutic agents, the strategy of repurposing existing anti-inflammatory agents for the treatment of diabetic cardiomyopathy might have merit. Colchicine, an anti-inflammatory drug that has been approved for use in treating gout, has been used off-label to treat other inflammatory diseases such as acute and recurrent pericarditis[234]. The clinical benefits of colchicine therapy are predominantly derived from the inhibition of β-tubulin polymerization into microtubules (thus preventing the activation, degranulation and migration of neutrophils), but also might involve blockade of the NLRP3 inflammasome[235,236]. Colchicine therapy added to optimal medical therapy improved coronary plaque morphology compared with optimal medical therapy alone in patients with acute coronary syndrome[237]. Furthermore, colchicine therapy significantly reduced obesity-associated inflammatory markers (including plasma CRP levels, white blood cell counts and absolute neutrophil counts) compared with placebo treatment in patients with obesity and metabolic syndrome[238]. Therefore, currently available drugs with anti-inflammatory properties such as colchicine have the potential to be repurposed for use in preventing cardiovascular complications in patients with diabetes. Ongoing studies are investigating the

efficacy of colchicine in treating diabetic nephropathy[239] and coronary artery disease[240] in patients with T2DM.

Cardiac oxidative stress

Preclinical studies.—Naturally occurring activators of NRF2 have been shown to ameliorate diabetes-induced cardiac complications (TABLE 1). Sulforaphane is an organosulfur compound derived from cruciferous vegetables such as broccoli, brussels sprouts and cabbage that has been shown to upregulate the expression of numerous genes encoding antioxidant proteins by activating NRF2 signalling[241]. The cardioprotective benefits of sulforaphane in attenuating cardiac dysfunction, oxidative damage, inflammation, fibrosis and hypertrophy have been demonstrated in both T1DM and T2DM mouse models and in mice exposed to angiotensin II[133,134,242–244]. Administration of broccoli sprout extract, a natural sulforaphane-rich supplement, similarly upregulated NRF2 transcriptional activity in a mouse model of T2DM and significantly prevented diabetes-induced cardiac dysfunction, hypertrophy and fibrosis[243].

Administration of the antioxidant N-acetylcysteine (NAC) for 5 weeks to rat and mouse models of STZ-induced T1DM normalized the levels of oxidative stress and subsequently prevented the development of diabetic cardiomyopathy[245,246]. Interestingly, the earlier the NAC treatment protocol was initiated after induction of diabetes with STZ during the 12-week experiment, the greater the protection against diabetic cardiomyopathy[246], suggesting that early damage mediated by increased oxidative stress has a more important role in the development of diabetic cardiomyopathy. In diabetic rats, NAC treatment attenuated cardiac damage and dysfunction after myocardial ischaemia–reperfusion injury[247,248].

Consistent with the essential role of metallothionein in the prevention of diabetic cardiomyopathy in transgenic animal models[123,130,131], supplementation with zinc (a major metal that binds to metallothionein under physiological conditions) in mice and rats with STZ-induced diabetes increased cardiac expression of metallothionein and significantly attenuated cardiac fibrosis and dysfunction[249,250] (TABLE 1). Administration of zinc also prevented the development of diabetic cardiomyopathy in *db/db* mice[156,251] and ZDF rats[252] (TABLE 1). In addition, zinc supplementation in diabetic rats prevented diabetes-induced peripheral nerve damage and reduced oxidative stress by increasing metallothionein levels in the peripheral nerves[253].

Clinical studies.—Zinc supplementation has been shown to significantly improve clinical and echocardiography parameters in a patient presenting with dyspnoea and HF who had previously undergone bariatric surgery[254]. Whether the cardiac protection imparted by zinc supplementation in patients with or without diabetes is related to changes in the levels of metallothionein remains unclear, but evidence from Chinese and Italian populations with polymorphisms in the gene encoding metallothionein supports a relationship between alterations in metallothionein and diabetes-induced risk of cardiovascular complications[255,256]. Indeed, the oxidoreductive capacity of metal-thiolate clusters in metallothionein contributes to intracellular zinc homeostasis, given that metallothionein modulation in cells and tissues affects metal ion release, transport and distribution, and

regulates cellular redox status, enzyme function and cell signalling. Therefore, adequate endogenous expression levels of metallothionein might be critical for the successful use of zinc supplementation as an adjunct therapeutic or preventive approach in patients with diabetes[257–259].

Sulforaphane-rich, broccoli sprout extract has been shown to be both safe and effective in reducing cardiovascular inflammation in healthy individuals, in individuals who are overweight and in patients with hepatic abnormalities[260–262] (TABLE 2). Furthermore, long-term consumption of broccoli sprouts by patients who were overweight resulted in significantly reduced levels of inflammatory markers such as IL-6 and CRP[261]. Finally, a randomized, double-blind, placebo-controlled trial reported that broccoli sprout extract supplementation improved fasting glucose and HbA_{1c} levels in patients with obesity and dysregulated T2DM[263]. Whether the cardioprotective effects of broccoli sprout extract observed in preclinical models of diabetic cardiomyopathy could be translated to patients with diabetes remains to be seen.

Diabetes-induced metabolism disturbances

Preclinical studies.—To test the hypothesis that increased fatty acid oxidation in the diabetic heart leads to an increased risk of lipotoxicity and diabetic cardiomyopathy, hearts from rats with T2DM were infused ex vivo with the CD36 inhibitor sulfo-*N*-succinimidyl oleate (SSO) before inducing hypoxia, which resulted in a 29% reduction in the rate of fatty acid oxidation and a 48% reduction in triglyceride concentration compared with no treatment, restoring fatty acid metabolism to control levels following hypoxia–reoxygenation[264]. SSO-infusion into diabetic rat hearts ex vivo before hypoxia also prevented cardiac dysfunction[264]. This novel therapeutic approach not only reduced fatty acid oxidation but also lipotoxicity by targeting the primary step in the fatty acid metabolism pathway.

In addition to strategies targeting fatty acid oxidation to treat diabetic cardiomyopathy, insulin sensitizers that increase glucose oxidation and decrease lipid metabolism have also been assessed in preclinical models. GLP1 is derived from the tissue-specific, post-translational processing of the proglucagon peptide[265]. Like glucose-dependent insulinotropic peptide, GLP1 is an incretin that can reduce blood glucose levels in a glucose-dependent manner by increasing insulin secretion[265]. Incretin-based therapies, such as GLP1 receptor agonists and DPP4 inhibitors, are potent glucose-lowering drugs. The GLP1 analogue liraglutide protected against the development of diabetic cardiomyopathy in a rat model of STZ-induced T1DM by inhibiting the ER stress pathway[266]. Similarly, the GLP1 analogue exendin 4 and the DPP4 inhibitor saxagliptin prevented the development of diabetic cardiomyopathy via the amelioration of lipotoxicity in a mouse model of T2DM[267]. The DPP4 inhibitor sitagliptin reduced blood glucose levels, increased GLP1 levels and prevented T2DM-induced diabetic cardiomyopathy in mice by shifting the energy substrate utilization in the heart from fatty acids towards glucose[159,268].

Fibric acid derivatives, or fibrates, are a class of amphipathic carboxylic acids that are used to treat a range of metabolic disorders, particularly hypercholesterolaemia[269]. Fibrates activate PPARs, especially PPARα, to modulate carbohydrate and lipid metabolism. Two

preclinical studies have demonstrated the effect of chronic treatment with fenofibrate, the most commonly used drug in the fibrate class, on cardiac function in rat models of T2DM[270,271]. Fenofibrate treatment prevented diastolic dysfunction and fibrosis in the diabetic rats, probably through an improvement in systemic and cardiac lipid metabolism. Fenofibrate treatment was also associated with reductions in markers of cardiac hypertrophy and apoptosis in rats with STZ-induced T1DM[272]. Furthermore, fenofibrate treatment of mice with STZ-induced T1DM prevented diabetes-induced cardiac inflammation, oxidative stress, hypertrophy, dysfunction and autophagy, and increased cardiac expression of fibroblast growth factor 21 (FGF21) compared with no treatment[273]. These data suggest that in addition to directly stimulating fatty acid oxidation, fenofibrate treatment might also protect against the development of diabetic cardiomyopathy in both T1DM and T2DM by indirectly increasing FGF21 levels in the heart.

Clinical studies.—Evidence from preclinical studies in T1DM and T2DM animal models clearly establishes insulin resistance, abnormal glucose metabolism, excessive fatty acid oxidation and lipid accumulation in the heart as critical mechanisms involved in the development of diabetic cardiomyopathy. From a clinical standpoint, however, the treatment and management of patients with diabetes remain focused on the control of systemic hyperglycaemia with administration of insulin or insulin sensitizers, as well as other adjunct approaches targeting hypertension or hyperlipidaemia. Aggressive clinical management to prevent hyperglycaemia has resulted in a reduction in microvascular complications but only had a modest effect in reducing macrovascular complications[274]. Therefore, studies to determine whether glycaemic control might also have an effect on the development of diabetic cardiomyopathy are needed. Furthermore, whether the same treatment is appropriate for patients with diabetes at low risk or high risk of cardiovascular disease also needs to be determined.

The gold-standard treatment of T1DM is functional insulin therapy with a basal bolus insulin regimen[275]. Injectable and oral glucose-lowering drugs can be introduced as adjunct therapy. For example, pramlintide, a naturally occurring analogue of the β-cell peptide amylin, has been approved for use in adults with T1DM[275]. A small number of medications that are currently approved for the treatment of T2DM, including metformin, GLP1 receptor agonists and SGLT2 inhibitors, have been or are being evaluated as adjuncts to insulin therapy in patients with T1DM[275]. For instance, the addition of metformin to insulin therapy did not significantly improve glycaemic control in children[276] or adults with T1DM[277] but provided a modest reduction in total daily insulin dose and body mass index. Several phase III clinical trials have shown significant reductions in HbA_{1c} levels and total daily insulin dose without increases in the risk of hypoglycaemia following treatment for up to 52 weeks with insulin combined with SGLT2 inhibitors such as dapagliflozin, empagliflozin and sotagliflozin compared with the effects of treatment with insulin alone[278]. However, insulin therapy together with dapagliflozin or sotagliflozin was associated with a higher incidence of diabetic ketoacidosis than insulin therapy alone. In this context, appropriate patient selection for therapy and routine monitoring are essential to minimize the risks associated with this treatment regimen[275,278,279].

In terms of cardiac events in patients with T1DM, the DCCT/EDIC trial[280] that was designed to assess the effects of diabetes therapy on measures of cardiac function and structure revealed no differences between intensive and conventional treatment regimens in end-diastolic and end-systolic volume, LV mass, ejection fraction and aortic distensibility. This finding was further corroborated by the 30-year follow-up data that showed no significant effect of insulin therapy on cardiovascular disease outcomes in the T1DM patient population[281].

In patients with T2DM, the American Diabetes Association (ADA) recommends initial pharmacological therapy with metformin followed by the addition of insulin or other drugs such as SGLT2 inhibitors or GLP1 receptor agonists[275]. However, for the prevention of comorbid cardiovascular disease, the treatment pathway is less clear. Although good glycaemic control is associated with reduced risk of new-onset HF and other cardiovascular complications in patients with T2DM, data from both clinical trials and systematic reviews reveal that treatment with insulin alone or in combination with other oral glucose-lowering drugs is associated with worse outcomes in patients with T2DM and chronic HF[282–284]. Therefore, the use of insulin sensitizers, rather than insulin, might be warranted in this patient cohort.

The GLP1 receptor agonist liraglutide has been shown to provide protection against pathological cardiac remodelling and dysfunction when added to metformin therapy in patients with T2DM[285,286]. Furthermore, according to findings from a post hoc analysis of the LEADER trial[287,288], liraglutide reduced adverse cardiovascular outcomes both in patients with a history of MI or stroke and in those with established atherosclerotic cardiovascular disease without MI or stroke (TABLE 2). By contrast, the FIGHT trial[289] involving patients with HFrEF with or without T2DM, showed no changes in mortality or the rate of HF-related hospitalizations with liraglutide treatment compared with placebo treatment. These inconsistent findings further deepen the uncertainty regarding the utility of liraglutide in patients with T2DM and established HF. Encouragingly, however, results from a 2018 systematic review and meta-analysis that examined the overall cardiovascular benefit of lixisenatide, liraglutide, semaglutide and extended-release exenatide[16] and a register-based Scandinavian cohort study[17] both provide support for the cardiovascular effectiveness of GLP1 receptor agonists in patients with T2DM. Furthermore, a 2019 double-blind, clinical trial involving patients with T2DM showed that patients treated with liraglutide for 26 weeks had reduced early LV diastolic filling and LV filling pressure, which are pathogenic hallmarks of HFpEF, compared with placebo-treated patients[18]. On the basis of these favourable outcomes, the ADA and the European Association for the Study of Diabetes have recommended GLP1 receptor agonists as the first-line injectable agent for patients with T2DM and cardiovascular disease[290].

Conversely, data on the cardiovascular safety of DPP4 inhibitors have been more inconsistent. A meta-analysis of 236 trials that involved a total of 176,310 participants found that treatment with DPP4 inhibitors did not reduce all-cause mortality in patients with T2DM compared with placebo or no treatment[10]; moreover, DPP4 inhibitors might even increase the risk of HF-related hospitalization in these patients[291]. Of note, sitagliptin and alogliptin are distinct from other DPP4 inhibitors because they are primarily excreted in the

urine and suppress renal sodium–hydrogen exchanger 3 activity, and their use was not associated with an increased risk of HF-related hospitalization in patients with T2DM[292].

The aforementioned therapies primarily target insulin function to improve glycaemic control. However, whether these compounds can also function as insulin sensitizers in the heart to stimulate insulin-mediated glucose metabolism and reduce lipid metabolism and lipotoxicity requires further investigation.

In addition to improving glycaemic control, the reduction in excess fatty acid oxidation and lipotoxicity in the heart is another strategy to prevent diabetic cardiomyopathy. Statin therapy has been shown to reduce the incidence of coronary events and mortality in patients with T1DM or T2DM with or without a history of cardiovascular disease[293]. The 2013 American College of Cardiology/American Heart Association guidelines on blood cholesterol management to reduce the risk of atherosclerotic cardiovascular disease in adults introduced a recommendation of higher-intensity statin doses in patients with diabetes[294]. However, the long-term safety of statin use has become a concern, given the potential harmful effects on muscle and liver, as well as the increased risk of new-onset diabetes[295]. In 2016, the American College of Cardiology published the first expert consensus decision pathway for the use of non-statin therapies to manage the risk of atherosclerotic cardiovascular disease[296]. Given that the benefits of statin therapy far outweigh any real or perceived risks[295], and in light of their benefits in reducing the risk of cardiovascular disease and all-cause death among patients with T2DM[297,298], the use of statins to treat hypercholesterolaemia in patients with T2DM remains advisable.

The role of fenofibrate therapy in reducing the risk of cardiovascular disease in patients with T2DM has also been explored in numerous randomized, controlled trials (TABLE 2). In the FIELD[299,300] and ACCORD[301] trials, fenofibrate treatment did not reduce the rate of coronary events and fatal cardiovascular events, respectively, in patients with T2DM compared with placebo treatment. An extended follow-up of the ACCORD trial[302] confirmed the original neutral effect of fenofibrate therapy in the overall study cohort, but continued observation of the heterogeneity of response to therapy revealed that fenofibrate might reduce the risk of cardiovascular complications in patients with hypertriglyceridaemia and low LDL-cholesterol levels.

SGLT2 receptors are primarily located in the proximal convoluted tubule of the nephron and are responsible for >90% of tubular reabsorption of glucose in the nephron[303]. Therefore, several SGLT2 inhibitors, including canagliflozin, empagliflozin, dapagliflozin and ertugliflozin have been approved by the FDA for the treatment of T2DM. These inhibitors are not only beneficial in improving glycaemic control, but also have cardioprotective and renoprotective effects, as confirmed by several large trials[303]. In the DECLARE-TIMI 58 trial[13], a total of 17,160 patients with T2DM who had or were at risk of atherosclerotic cardiovascular disease were randomly assigned to receive dapagliflozin or placebo and followed up for a median of 4.2 years. Dapagliflozin treatment was associated with a lower rate of cardiovascular death or HF-related hospitalization than placebo treatment, but no differences in the occurrence of major adverse cardiovascular events were observed[13]. Dapagliflozin treatment is also associated with reduced HF-related hospitalization rates in

patients with or without HFrEF, and reduced cardiovascular mortality and all-cause mortality in patients with HFrEF[14] and in patients with T2DM and previous MI[15] compared with placebo treatment. Dapagliflozin has now been approved by the FDA for the reduction of the risk of HF-related hospitalization in patients with T2DM with established cardiovascular disease or multiple cardiovascular risk factors. Of note, the cardioprotective effects of dapagliflozin are independent of the hypoglycaemic effects of the drug given that dapagliflozin exerts the same protection in patients with or without diabetes[19].

Lastly, given the evidence that zinc supplementation can improve glycaemic control, insulin resistance, lipid profile and β-cell function, and can delay progression to diabetes in preclinical studies, the cardioprotective benefits of zinc supplementation have been explored in several clinical studies[304,305]. In a prospective study involving 58,646 healthy Japanese individuals, zinc intake was inversely associated with the risk of death from coronary heart disease in men but not in women[306]. Furthermore, a Finnish study showed that low serum zinc concentrations were significantly associated with a higher risk of death from coronary heart disease in patients with T2DM[135], which was further corroborated by data from a cross-sectional study that showed a negative correlation of serum B-type natriuretic peptide and Ca^{2+} levels with serum zinc levels in patients with T2DM[307]. In addition, zinc supplementation improved oxidative stress and vascular function in patients with T2DM and zinc deficiency, but not in patients with T2DM with normal zinc levels[308]. Although an earlier systematic review of prospective cohort studies including 14 studies on zinc status and cardiovascular risk found no association between zinc intake and cardiovascular events[309], a subsequent systematic review and meta-analysis of randomized, controlled trials from 36 publications concluded that several key glycaemic indicators, including fasting glucose levels, 2-h postprandial glucose levels, and HbA_{1c} and fasting insulin levels, were significantly reduced by zinc supplementation[310]. However, several animal and human studies have also shown an association between zinc intake and cardiac dysfunction, including a large longitudinal study involving middle-aged women that revealed a link between high dietary zinc intake and greater incidence of cardiovascular disease[311]. Therefore, additional mechanistic studies to investigate the effect of zinc on cardiac function are needed before a recommendation can be made as to whether dietary zinc supplementation can be used as an adjunct therapy for the management of diabetes and associated diabetic cardiomyopathy[312].

Future directions

To date, no consensus has been reached on the optimal management strategy to prevent or treat cardiovascular complications associated with diabetes. The current treatment regimens for patients with T1DM or T2DM aim to treat insulin resistance, lower inflammation and reduce oxidative stress, which all contribute to the pathogenesis of diabetic cardiomyopathy.

Although T1DM-associated and T2DM-associated diabetic cardiomyopathy have distinct aetiologies, these cardiomyopathies share common pathophysiological mechanisms. Metabolic disturbances, including hyperglycaemia, dyslipidaemia and associated glucotoxicity, lipotoxicity and oxidative stress are the predominant pathological mechanisms driving the development of diabetic cardiomyopathy in both T1DM and T2DM. Metabolic

disturbances might trigger a ‘metabolic memory’, which can initiate multiple epigenetic mechanisms involved in the development of diabetic cardiovascular complications[313], regardless of whether glucose levels are returned to normal in the later stages of the disease[314,315]. This observation suggests that a greater understanding of protective epigenetic mechanisms might lead to the development of novel therapeutics for diabetic cardiomyopathy that not only restore metabolic homeostasis in the early stage of diabetes but also erase the ‘epigenetic memory’ associated with metabolic disturbances responsible for triggering diabetic cardiomyopathy.

The current knowledge about diabetic cardiomyopathy is primarily derived from studies assessing the left ventricle. As a systemic disease, diabetes also affects right ventricular (RV) structure and function. For example, diabetes-induced LV diastolic dysfunction and contractile dysfunction can influence the RV via ventricular interdependence, similar to the effect of RV dysfunction on the LV[316]. Indeed, emerging evidence suggests that RV impairment is an important and clinically relevant component of the diabetic cardiomyopathy phenotype[317]. In contrast to LV remodelling, RV remodelling is characterized by early-onset eccentric hypertrophy, cardiac dilatation and systolic dysfunction owing to concomitant changes in both the RV and the pulmonary vasculature[317,318]. Unfortunately, very few studies have investigated the pathophysiology of RV dysfunction in diabetic cardiomyopathy. Additional studies are required to determine the time course and reversibility of RV pathology in diabetic cardiomyopathy and to determine whether therapies that improve LV performance are equally effective for RV performance.

Importantly, women with diabetes are at greater risk of developing diabetic cardiomyopathy[319,320], but the mechanisms underlying sex-specific differences in the pathophysiology of diabetic cardiomyopathy are unknown. However, a study involving ZDF rats has provided some clues. Female diabetic rats, but not male diabetic rats, have concentric cardiac hypertrophy in addition to diastolic and systolic dysfunction, which might be related to the female-specific loss of the cardioreparative type 2 angiotensin II receptor[321]. As we enter the era of precision medicine-based treatment approaches, sex-specific therapeutic strategies for diabetic cardiomyopathy will likely optimize therapy outcomes in all patients with diabetes.

Given the substantial time and cost required to advance new drugs from discovery to clinical use, drugs that are currently available might have the potential to be repurposed to treat diabetic cardiomyopathy. For example, the pathophysiological role of cGMP signalling in the development of diabetic cardiomyopathy with HFpEF has been validated in a preclinical study with ZDF rats to test the long-term preventive effects of the PDE5A inhibitor vardenafil (used to treat erectile dysfunction) on diabetes-associated HFpEF[62]. Vardenafil prevented the development of HFpEF in ZDF rats by restoring cGMP levels and preventing myocardial hypertrophy and fibrotic remodelling[62]. Promisingly, treatment with a PDE5 inhibitor was also associated with a reduction in the HF-related hospitalization rate in patients with HFpEF and combined pre-capillary and post-capillary pulmonary hypertension[322]. Whether patients with diabetes and HFpEF might benefit from treatment with PDE5A inhibitors will be of interest.

Finally, as mentioned previously, the cardiac benefits of the SGLT2 inhibitor empagliflozin have been shown in numerous preclinical studies, and these benefits were independent of the blood glucose-lowering effects of the drug[193,323,324]. Clinical studies have since shown that empagliflozin treatment is associated with reduced risk of cardiovascular disease, non-fatal MI and HF read-missions[325,326], which was further confirmed by the first interim analysis of the EMPRISE trial[327] that compared the efficacy of empagliflozin with sitagliptin on HF indices in 16,443 patients. Importantly, empagliflozin treatment reduced the risk of HF-related hospitalization among patients with T2DM with or without a history of cardiovascular disease[327]. Whether long-term treatment with empagliflozin can reduce other cardiovascular outcomes and mortality remains to be seen.

Conclusions

In summary, although diabetic cardiomyopathy has been recognized for >40 years through a broad range of investigations that have identified numerous pathogenic mechanisms and targets for prevention and treatment, effective strategies for diabetic cardiomyopathy prevention and treatment remain elusive. Although measures of myocardial performance can be used to assess subclinical systolic and diastolic LV dysfunction, the onset of myocardial injury clearly occurs early and before the onset of measurable cardiac dysfunction. Cardiac hypertrophy, fibrosis, increased stiffness and cardiomyocyte loss are all consequences of dysregulated glucose and lipid metabolism that impairs excitation–contraction coupling, triggers oxidative stress and AGE formation, disrupts normal regulation of cardiomyocyte hyperplasia and hypertrophy, and activates multiple inflammatory pathways in the setting of diabetes. Therefore, sensitive and specific markers for changes in intracellular signalling pathways involved in the pathogenesis of diabetic cardiomyopathy, as well as novel cardioprotective strategies targeting these pathways, will hopefully improve cardiovascular outcomes in patients with diabetes.

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Box 1 |

Type 1 and type 2 diabetes mellitus

Type 1 diabetes mellitus

Type 1 diabetes mellitus (T1DM) is an autoimmune-mediated disease that results from T cell-dependent destruction ofthe insulin-producing β-cells in the pancreas, ultimately leading to insulin deficiency[328]. One or more T1DM-related autoantibodies are present at diagnosis in nearly 95% of patients with T1DM[329], and high levels of these autoantibodies directly correlate with increased risk of developing T1DM[330]. T1DM can be diagnosed at any age, but is typically identified early in life, with a peak incidence at ages 13–15 years[331]. Although immune dysregulation that leads to T1DM seems to be influenced by yet-to-be-defined environmental factors, several genetic risk factors have been identified[332–335].

Type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM), once considered a simple, non-immune-mediated disease involving insulin resistance, is now seen as a highly complex, multisystem disorder. T2DM predominantly affects adults, but is increasingly being diagnosed during childhood owing to the rising rates of childhood obesity[336]. The risk factors for T2DM include advanced age, high body mass index and sedentary lifestyle[336]. Although not inherently an autoimmune disorder, immune activation, primarily via inflammatory mediators, has a large role in the pathogenesis of T2DM and the resulting cardiovascular comorbidities in advanced disease stages[336]. T2DM has a stronger genetic component than T1DM[337,338]. Genome-wide association studies have identified a large number of susceptibility loci, many with cross-trait effects in domains linked with obesity, glucose dysregulation and lipid metabolism. As expected, signal differences have been found in studies comparing various ethnic and racial populations, and differences have even been found between those diagnosed with T2DM in childhood and those diagnosed in adulthood[339].

Key points

- Diabetic cardiomyopathy is characterized by adverse structural remodelling (including cardiac hypertrophy and fibrosis), early-onset diastolic dysfunction and late-onset systolic dysfunction.
- At present, treatment regimens for diabetes-associated cardiovascular disease rely on conventional therapies that focus on optimizing glycaemic control, lowering lipid levels and reducing oxidative stress.
- Pathophysiological factors that contribute to diabetic cardiomyopathy include metabolic disturbances, insulin resistance, formation and crosslinking of advanced glycation end products, mitochondrial damage, oxidative stress, inflammation and cell death.
- Several new potential treatment strategies that target myocardial fibrosis, inflammation, oxidative stress and insulin resistance have shown promising results in preclinical studies but require validation in randomized clinical trials.

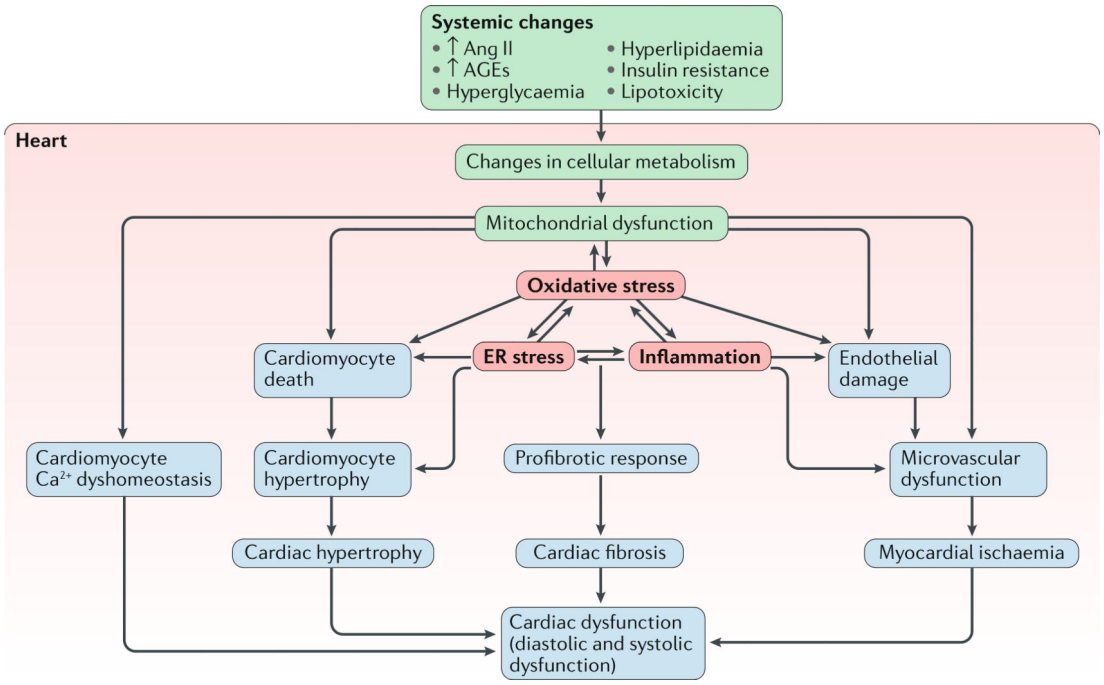

Fig. 1 |. Mechanisms of diabetic cardiomyopathy.

Insulin resistance in type 2 diabetes mellitus mediates systemic hyperglycaemia, hyperlipidaemia and lipotoxicity. Advanced glycation end products (AGEs) and angiotensin II (Ang II) overproduction induce metabolic changes in the heart that cause mitochondrial dysfunction in cardiomyocytes and endothelial cells. The diverse actions of Ang II are mediated by type 1 and type 2 Ang II receptors, which couple to various signalling molecules including NADPH oxidase to induce the generation of reactive oxygen species (ROS) or reactive nitrogen species. Dysfunctional mitochondria produce excess ROS, which increases oxidative stress. Abnormal cell metabolism and oxidative stress can trigger endoplasmic reticulum (ER) stress, cardiomyocyte death and hypertrophy, endothelial cell damage, microvascular dysfunction and profibrotic responses in fibroblasts and inflammatory cells. Oxidative stress, ER stress and inflammation can trigger reciprocal activation of these pathological processes. Furthermore, impaired mitochondrial Ca^{2+} signalling causes abnormalities in cardiomyocyte Ca^{2+} handling and contractility. Together, these changes mediate cardiac hypertrophy, fibrosis and ischaemia, resulting in diastolic and systolic dysfunction.

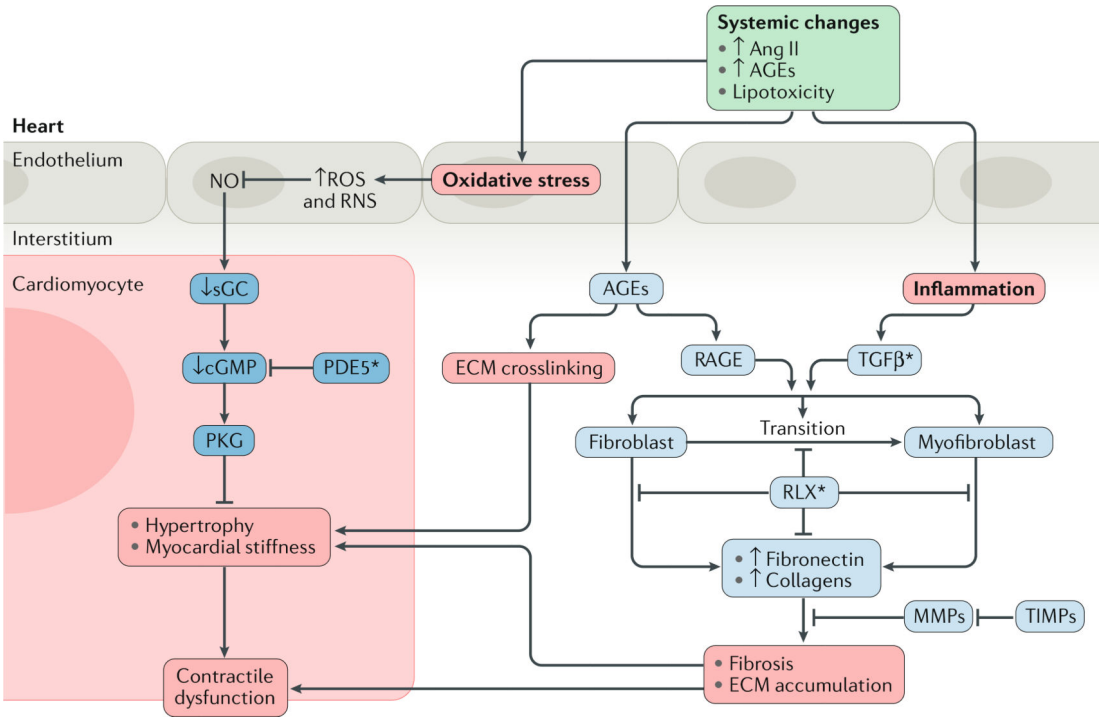

Fig. 2 |. Main signalling pathways that regulate cardiac remodelling in the diabetic heart.
The systemic glucotoxicity (as a result of increased production of advanced glycation end products (AGEs)), lipotoxicity and angiotensin II (Ang II) production associated with type 2 diabetes mellitus induce the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) by endothelial cells, resulting in decreased nitric oxide (NO) bioavailability. This reduced NO bioavailability diminishes soluble guanylate cyclase (sGC) activity and cyclic GMP (cGMP) levels, which leads to the loss of the protective effects of protein kinase G (PKG) against cardiomyocyte stiffness and hypertrophy. Together, these effects trigger coronary endothelial microvascular inflammation and infiltration of inflammatory cells such as macrophages and lymphocytes into the myocardial interstitial space. Transforming growth factor-β(TGFβ), which is secreted by activated inflammatory cells, and AGEs interact with their respective receptors to activate directly cardiac fibroblasts, myofibroblasts and fibroblast-to-myofibroblast transition. Together, these profibrotic responses trigger increased production of fibronectin and collagens, increased extracellular matrix (ECM) accumulation and upregulation of the activity of tissue inhibitors of metalloproteinases (TIMPs), which inhibit matrix metalloproteinases (MMPs) secreted by cardiac fibroblasts and myofibroblasts. The end result is the exacerbation of pathological cardiac remodelling (including cardiac stiffness and hypertrophy) and contractile dysfunction. Targets that have been tested preclinically or clinically are marked with an asterisk. PDE5, phosphodiesterase type 5; RAGE, receptor for AGEs; RLX, relaxin.

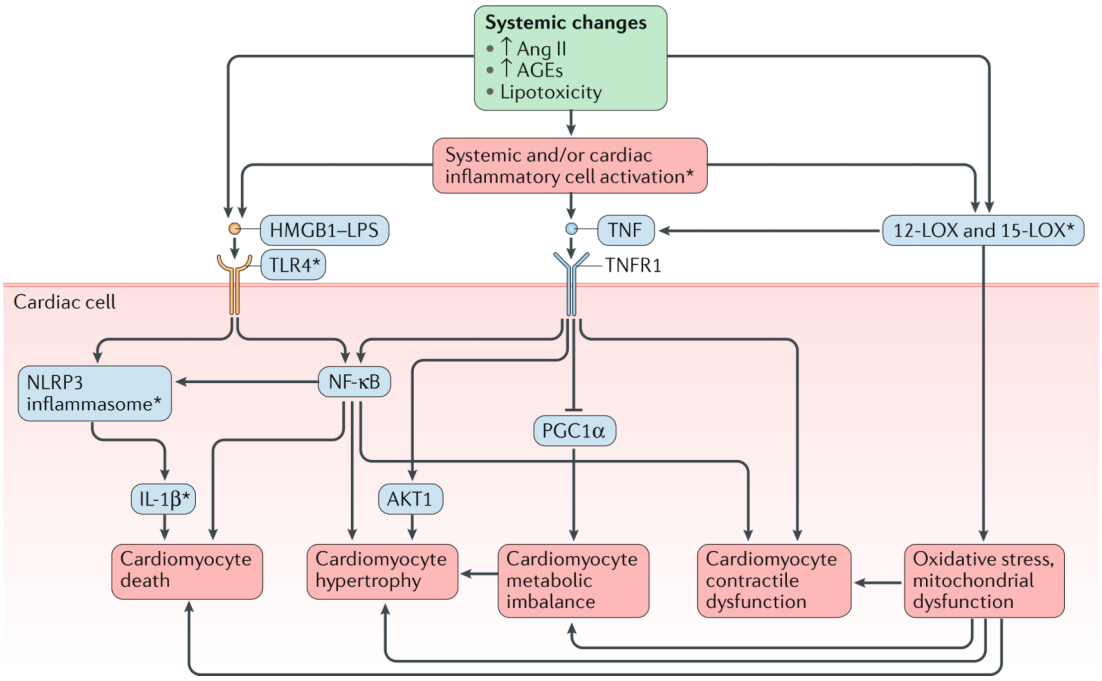

Fig. 3 |. Pro-inflammatory pathways that regulate the development of diabetic cardiomyopathy. The systemic glucotoxicity (through accumulation of advanced glycation end products (AGEs)), lipotoxicity and angiotensin II (Ang II) production associated with type 2 diabetes mellitus can activate high mobility group protein B1 (HMGB1) to bind to lipopolysaccharide (LPS) and activate Toll like receptor 4 (TLR4) on cardiac cells, which can promote cardiomyocyte hypertrophy and death. Systemic and cardiac inflammatory cells such as macrophages and lymphocytes can also be activated by type 2 diabetes mellitus-induced disturbances and secrete pro-inflammatory cytokines, such as tumour necrosis factor (TNF), which induce cardiomyocyte hypertrophy, metabolic imbalances and contractile dysfunction. In addition, type 2 diabetes-associated glucotoxicity and lipotoxicity can activate the 12-lipoxygenase (12-LOX) and 15-LOX enzymes, which promote oxidative stress and mitochondrial dysfunction, which can mediate cardiomyocyte death, hypertrophy, metabolic derangements and loss of contractility. Anti-inflammatory targets that have been tested in animal models or clinical studies are marked with an asterisk. AKT1, RACα serine/threonine-protein kinase; NF-κB, nuclear factor-κB; PGC1α, peroxisome proliferator-activated receptor-γ co-activator 1α; TNFR1, tumour necrosis factor receptor 1.

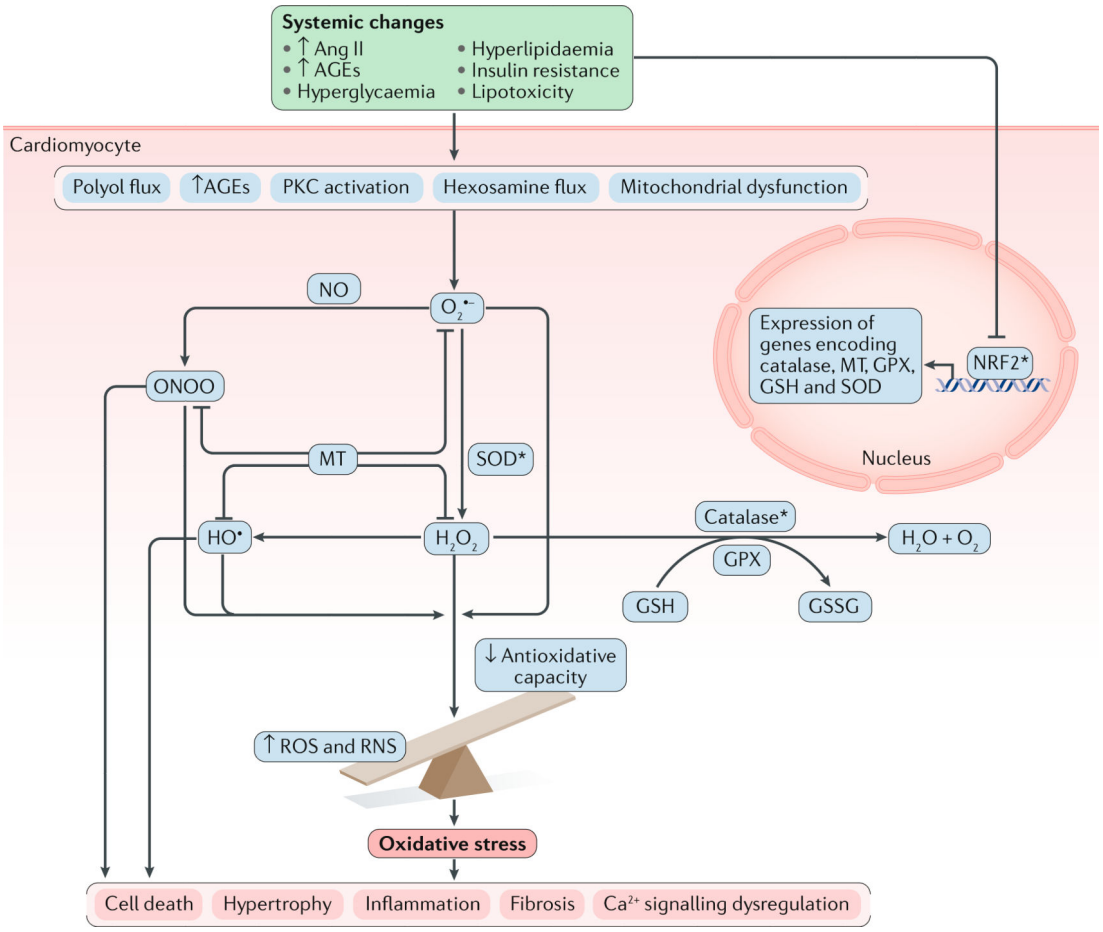

Fig. 4 |. Signalling pathways involved in promoting cardiac oxidative stress in type 2 diabetes mellitus.

The systemic hyperglycaemia, hyperlipidaemia, hyperinsulinaemia, lipotoxicity and increased levels of angiotensin II (Ang II) associated with type 2 diabetes mellitus together increase cardiac polyol flux, advanced glycation end product (AGE) formation, protein kinase C (PKC) activation, hexosamine flux, cardiac metabolic abnormalities and mitochondrial dysfunction. These pathways can all lead to the generation of reactive oxygen species (ROS) or reactive nitrogen species (RNS), particularly superoxide ($O_2^{\bullet-}$) that can be further converted to hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD) or converted to peroxynitrite (ONOO) by combining with nitric oxide (NO). H_2O_2 can be further converted to H_2O and O_2 mediated directly by catalase or indirectly by glutathione peroxidases (GPXs). Under diabetic conditions, levels of the antioxidant enzymes metallothionein (MT), SOD and catalase increase as an early-stage compensatory response to increased production of ROS or RNS, but decompensate over time. SOD can only convert O_2- to H_2O_2, whereas catalase can only convert H_2O_2 to H_2O. However, MT can indiscriminately scavenge almost all free radicals. Nuclear factor erythroid 2-related factor 2 (NRF2) is a stress-responsive transcription factor and a primary master regulator of the inducible cell defence system, which regulates the expression of >200 genes related to cytoprotective responses, encoding antioxidant proteins such as MTs, SODs, catalase, GPXs and reduced glutathione (GSH). NRF2 has a pivotal role in maintaining redox homeostasis

in the heart under diabetic conditions. Targets that have been tested in preclinical models or in clinical studies as antioxidative therapies are marked with an asterisk. GSSG, oxidized glutathione.

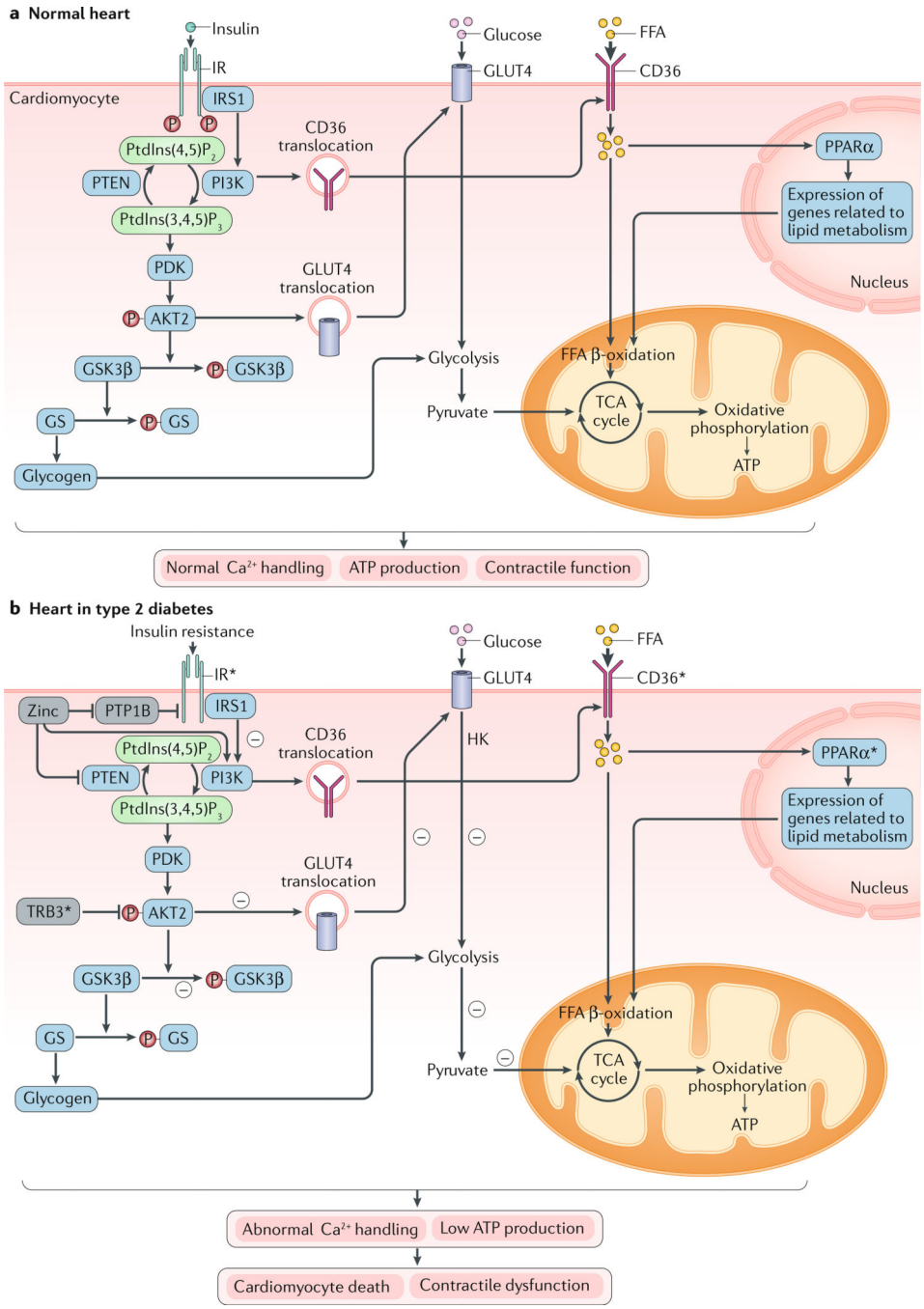

Fig. 5 |. Insulin signalling in the heart in normal conditions and in type 2 diabetes mellitus.

a | In normal conditions, insulin binds to the α-subunits of the insulin receptor (IR) in cardiomyocytes, which induces the phosphorylation of the IR β-subunits. This phosphorylation triggers the activation of the docking protein IR substrate 1 (IRS1), which subsequently activates phosphatidylinositol 3-kinase (PI3K) and RACβ serine/threonine-protein kinase 2 (AKT2), which has a critical role in glucose metabolism. PI3K and AKT2 activation promotes the translocation of glucose transporter 4 (GLUT4) and the free fatty acid (FFA) transporter CD36 from intracellular stores to the plasma membrane, thereby

leading to increased glucose and FFA uptake. FFAs can activate the transcription factor peroxisome proliferator-activated receptor-α (PPARα), which induces the expression of multiple genes related to lipid metabolism. Increased glucose and FFA uptake increases mitochondrial oxidative metabolism to generate ATP via the tricarboxylic acid (TCA) cycle and β-oxidation, which supports myocardial contractile function. Insulin-mediated activation of AKT2 leads to inhibitory phosphorylation of glycogen synthase kinase 3β (GSK3β), which increases glycogen synthesis by glycogen synthase (GS). **b|** In type 2 diabetes mellitus, insulin signalling in cardiomyocytes is impaired. Signalling through the insulin-dependent glucose intake pathway is diminished, leading to increased FFA intake via CD36 and to eventual lipid accumulation. However, the excessive amount of FFA exceeds the capacity of mitochondrial respiration to generate ATP, leading to cardiomyocyte death, impaired cardiac function and lipid accumulation and toxicity. Potential therapeutic targets for metabolic disturbances that have been tested in preclinical models or in clinical studies are marked with an asterisk. HK, hexokinase; P, phosphorylation; PDK, pyruvate dehydrogenase kinase; PtdIns(4,5)P_2, phosphatidylinositol (4,5)-bisphosphate; PtdIns(3,4,5)P_3, phosphatidylinositol (3,4,5)-trisphosphate; PTEN, phosphatase and tensin homologue; PTP1B, protein tyrosine phosphatase 1B; TRB3, tribbles homologue 3.

Table 1 |

Preclinical studies on diabetic cardiomyopathy

Target	Drug	Model	Main findings	Refs
Cardiac remodelling and dysfunction				
PDE5	Vardenafil	ZDF rat model of T2DM	↑cGMP levels and PKG activation; ↓ cardiomyocyte apoptosis; ↓ oxidative stress; ↓ myocardial hypertrophy and fibrosis; ↑ diastolic function (LV stiffness and LV relaxation time)	62
	Tadalafil	*db/db* mouse model of T2DM	↓ Oxidative stress; ↓ infarct size after IR injury	192
RLX receptor	H2-RLX	Hypertensive Ren2 rats injected with STZ	↓ Interstitial and LV collagen deposition and myocardial stiffness; ↓ TIMP1 expression and ↑ MMP13 expression; ↑ diastolic function	201
	H3-RLX	Rat model of STZ-induced T1DM	↓ Cardiac NLRP3 inflammasome activation and cardiomyocyte apoptosis; ↓ type I and III collagen accumulation and ↓ MMP2 and MMP9 expression; ↑ cardiac function	202
TGFβ	FT23	Hypertensive Ren2 rats injected with STZ	↓ Cardiac hypertrophy (↓ heart weight:body weight ratio); ↓ myocardial macrophage infiltration; ↓ type I collagen deposition and fibrosis; ↑ diastolic function	186
	FT011	Hypertensive Ren2 rats injected with STZ	↓ Myocardial macrophage infiltration and fibrosis; ↓ LV inner diameter at diastole; ↑ systolic function	185
Inflammation				
IL-1	IL-1 receptor antagonist	Rat model of STZ-induced T1DM	↓ Endoplasmic reticulum stress; ↓ cardiomyocyte apoptosis	217
NLRP3	MCC950	Mouse model of high-sucrose and high-fat diet-induced T2DM	↓ Systemic and cardiac inflammation; ↑ cardiac autophagy; ↓ cardiac oxidative stress and cardiomyocyte apoptosis	220
T cells	Fingolimod (FTY720)	Mouse model of STZ-induced T1DM	↓ Myocardial $CD3^+$T cell infiltration; ↓ myocardial S1PR1 and TGFβ1 expression; ↑ cardiac contractility	78
		Rat model of STZ-induced T1DM	↑ Cardiac microvascular barrier impairment and pathological angiogenesis; ↑ coronary flow reserve	211,212
TNF	Monoclonal antibody (C432A)	Rat model of STZ-induced T1DM	↓ Myocardial inflammatory cell infiltration and TNF expression; ↓ cardiac type I and III collagen content; ↑ cardiac contractility and relaxation	216
Oxidative stress				
Metallothionein	Zinc	Mouse model of STZ-induced T1DM, *db/db* mouse model of T2DM and ZDF rat model of T2DM	↑ Metallothionein expression; ↓ cardiac morphological impairment and fibrosis; ↑ systolic function	156,249,251,252
NRF2	BSE/SFN	Mouse model of STZ-induced T1DM, *db/db* mouse model of T2DM, and high-fat diet-fed and STZ-treated mouse model of T2DM	↑ NRF2 activity; ↓ cardiac oxidative stress, hypertrophy and fibrosis; ↑ systolic function	134,242–244
Oxidative stress	NAC	Mouse and rat models of STZ-induced T1DM	↓ Systemic and myocardial oxidative stress; ↓ myocardial hypertrophy and fibrosis; ↑ diastolic and systolic function; ↑ tolerance to IR-induced pathological and functional effects in STZ-treated rats	245–248

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Target	Drug	Model	Main findings	Refs
Superoxide	mito-TEMPO	Mouse model of STZ-induced T1DM and *db/db* mouse model of T2DM	↓ Cardiac mitochondrial ROS generation and oxidative stress; ↓ cardiomyocyte apoptosis and myocardial hypertrophy; ↑ diastolic function in *db/db* mice; ↑ diastolic and systolic function in STZ-treated mice	127
Metabolic disturbances				
CD36	SSO	High-fat diet-fed and STZ-treated rat model of T2DM	↓ Myocardial fatty acid oxidation rate and triglyceride concentration; ↑ fatty acid metabolism, glycolytic rate and pyruvate dehydrogenase activity; ↑ cardiac function after hypoxia and reoxygenation	264
DPP4	Saxagliptin	High-fat diet-fed and STZ-treated mouse model of T2DM	↓ Myocardial lipid accumulation and oxidative stress; ↓ myocardial apoptosis, hypertrophy and fibrosis; ↑ diastolic and systolic function	267
	Sitagliptin	GK rat model of T2DM and *db/db* mouse model of T2DM	↑ Myocardial GLUT4 and ↓ CD36 sarcolemmal translocation; ↑ diastolic function in GK rats; ↓ LV passive stiffness and ↑ global LV performance in *db/db* mice	159,268
GLP1R	Liraglutide	High-fat diet-fed and STZ-treated rat model of T2DM	↓ Cardiomyocyte apoptosis and myocardial endoplasmic reticulum stress; ↑ diastolic and systolic function independent of glycaemic control	266
	Exendin 4	High-fat diet-fed and STZ-treated rat model of T2DM	↓ Myocardial lipid accumulation and oxidative stress; ↓ myocardial apoptosis, hypertrophy and fibrosis; ↑ diastolic and systolic function	267
PPARα	Fenofibrate	OLETF rat model of T2DM	↑ Myocardial fatty acid metabolism; ↓ hyperglycaemia and hyperlipidaemia; ↑ diastolic function	270
		ZDF rat model of T2DM	↓ Plasma and LV triglyceride content; ↓ myocardial fibrosis	271
		Rat model of STZ-induced T1DM	↓ Myocardial free fatty acid and triglyceride levels; ↓ cardiac cell death and hypertrophy; ↓ LV papillary muscle tension (stiffness)	272

BSE, broccoli sprout extract; cGMP, cyclic GMP; DPP4, dipeptidyl peptidase 4; GK, Goto-Kakizaki; GLP1R, glucagon-like peptide 1 receptor; GLUT4, glucose transporter type 4; H2-RLX, human relaxin 2; H3-RLX, human relaxin 3; IR, ischaemia–reperfusion; LV, left ventricular; mito-TEMPO, mitochondria-targeted (2,2,6,6-tetramethylpiperidin-1-yl)oxyl or (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl; NAC, N-acetylcysteine; MMP, matrix metalloproteinase; NRF2, nuclear factor erythroid 2-related factor 2; OLETF, Otsuka Long-Evans Tokushima Fatty; PDE5, phosphodiesterase type 5; PKG, protein kinase G; PPARα, peroxisome proliferator-activated receptor-α; RLX, relaxin; ROS, reactive oxygen species; S1PR1, sphingosine-1-phosphate receptor 1; SFN, sulforaphane; SSO, sulfo-N-succinimidyl oleate; STZ, streptozotocin; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TGFβ, transforming growth factor-β; TIMP1, tissue inhibitor of metalloproteinase 1; TNF, tumour necrosis factor; ZDF, Zucker diabetic fatty.

Table 2 |

Clinical studies relevant to diabetic cardiomyopathy

Study (start year)	Target	Drug	Study design	Number of patients	Main findings	Refs
Cardiac remodelling and dysfunction						
CECSID (2008)	PDE5A	Sildenafil	Randomized, double-blind, placebo-controlled trial in patients with T2DM	59	Sildenafil improved the ratio of LV mass to end-diastolic volume and cardiac MRI-tagged torsion and strain; improved LV contraction, accompanied by consistent changes in chamber geometry and performance with an improvement in mass-to-volume ratio; reduced blood CCL2 and TGFβ levels; and did not affect endothelial cell function, cardiac afterload or metabolism	205
Inflammation						
CANTOS (2011)	IL-1β	Canakinumab	Randomized, double-blind, placebo-controlled, event-driven phase III trial in patients with MI and elevated hsCRP level ≥2 mg/l with or without T2DM	10,061	Canakinumab reduced hsCRP levels and the rate of recurrent cardiovascular events compared with placebo, independent of level of lipid-lowering; although canakinumab had similar effects on major cardiovascular events among those with or without T2DM, treatment over a median of 3.7 years did not reduce the rates of incident diabetes; canakinumab dose-dependently reduced the rate of hospitalization for HF and the composite of hospitalization for HF or HF-related mortality in patients with previous MI	231–233
Oxidative stress						
Axelsson et al. (2015)	NRF2	BSE	Randomized, double-blind, placebo-controlled phase II trial in patients with T2DM	97	BSE improved fasting glucose and HbA_{1c} levels in patients with obesity and T2DM; a clear association between serum SFN concentration and change in fasting blood glucose levels was observed in the BSE-treated patients; no severe adverse effects of BSE were observed	263
SPROUTvsFAT (2015)	NRF2	Broccoli sprouts	Single group assignment, open-label, interventional trial in patients who were overweight	40	Broccoli sprout consumption for 70 days reduced plasma IL-6 and CRP levels	261
Metabolic disturbances						
LEADER (2010)	GLP1R	Liraglutide	Multicentre, randomized, double-blind, placebo-controlled phase III trial in patients with T2DM	9,340	The time-to-event analysis showed a reduction in the rate of the first occurrence of death from cardiovascular causes, non-fatal MI or non-fatal stroke among patients with T2DM treated with liraglutide versus placebo; the post hoc analysis showed reduced cardiovascular outcomes both in patients with a history of MI or stroke and in those with established atherosclerotic CVD without MI or stroke	287,288
FIELD (1998)	PPARα	Fenofibrate	Randomized, placebo-controlled trial in patients with T2DM, with or without previous CVD	9,795	No differences in the effect of fenofibrate given in addition to statin therapy between patients with or without a history of CVD at baseline; patients already taking fenofibrate therapy who have a cardiovascular event might still benefit from continuing fenofibrate therapy	299,300
ACCORD (1999)	PPARα	Fenofibrate	Randomized, placebo-controlled trial in patients with T2DM	10,251	Compared with combined standard treatment, intensive blood-pressure control or intensive glycaemic control therapy alone improved major CVD outcomes, without additional benefit from combining the two treatments; intensive lipid-lowering or glycaemic control treatments did not have any overall benefit, but intensive glycaemic control treatment increased mortality	301

BSE, broccoli sprout extract; CCL2, C-C motif chemokine 2; CRP, C-reactive protein; CVD, cardiovascular disease; GLP1R, glucagon-like peptide 1 receptor; HbA_{1c}, glycated haemoglobin; HF, heart failure; hsCRP, high-sensitivity C-reactive protein; LV, left ventricular; MI, myocardial infarction; NRF2, nuclear factor erythroid 2-related factor 2; PDE5A, phosphodiesterase type 5A; PPARα, peroxisome proliferator-activated receptor-α; SFN, sulforaphane; T2DM, type 2 diabetes mellitus; TGFβ, transforming growth factor-β.