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REVIEW IN TRANSLATIONAL CARDIOVASCULAR MEDICINE

The role of hyperglycaemia in the development of diabetic cardiomyopathy

Le rôle de l'hyperglycémie dans le développement de la cardiomyopathie diabétique

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KEYWORDS

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Summary Diabetes mellitus is a metabolic disorder with a chronic hyperglycaemic state. Cardiovascular diseases are the primary cause of mortality in patients with diabetes. Increasing evidence supports the existence of diabetic cardiomyopathy, a cardiac dysfunction with impaired cardiac contraction and relaxation, independent of coronary and/or valvular complications. Diabetic cardiomyopathy can lead to heart failure. Several preclinical and clinical studies have aimed to decipher the underlying mechanisms of diabetic cardiomyopathy. Among all the co-factors, hyperglycaemia seems to play an important role in this pathology.

Abbreviations: AGE, advanced glycosylated end-product; ATP, adenosine triphosphate; CaMKII, calmodulin kinase II; CI, confidence interval; DM, diabetes mellitus; DPP4, dipeptidyl-peptidase-4; GLP-1, glucagon-like peptide-1; GRK2, β -adrenergic receptor kinase; HbA1c, glycated haemoglobin; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; MACE3, three-point major adverse cardiovascular events; O-GlcNAc, O-linked-N-acetylglucosamine; O-GlcNAcylation, O-linked-N-acetylglucosaminylation; ROS, reactive oxygen species; SERCA, sarco/endoplasmic reticulum Ca^{2+} adenosine triphosphatase; SGLT2, sodium/glucose co-transporter 2.

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Hyperglycaemia has been shown to alter cardiac metabolism and function through several deleterious mechanisms, such as oxidative stress, inflammation, accumulation of advanced glycated end-products and upregulation of the hexosamine biosynthesis pathway. These mechanisms are responsible for the activation of hypertrophic pathways, epigenetic modifications, mitochondrial dysfunction, cell apoptosis, fibrosis and calcium mishandling, leading to cardiac stiffness, as well as contractile and relaxation dysfunction. This review aims to describe the hyperglycaemic-induced alterations that participate in diabetic cardiomyopathy, and their correlation with the severity of the disease and patient mortality, and to provide an overview of cardiac outcomes of glucose-lowering therapy.

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MOTS CLÉS

Diabète ;
Glucose ;
Cardiomyopathie

Résumé Le diabète est une maladie métabolique avec une hyperglycémie chronique. Chez les patients diabétiques, les maladies cardiovasculaires représentent la principale cause de mortalité. De nombreux travaux soutiennent l'existence d'une cardiomyopathie diabétique, qui se définit par une dysfonction cardiaque, incluant une altération de la contraction et de la relaxation, qui est indépendante des complications coronaires et/ou valvulaires. La cardiomyopathie diabétique peut conduire à l'insuffisance cardiaque. De nombreuses études précliniques et cliniques ont tenté de décrypter les mécanismes sous-jacents de la cardiomyopathie diabétique. Parmi les éléments impliqués, l'hyperglycémie semble jouer un rôle important dans cette pathologie. En effet, l'hyperglycémie altère le métabolisme et la fonction cardiaque en activant plusieurs mécanismes délétères, tels que le stress oxydatif, l'inflammation, l'accumulation de produits de glycation et l'activation de la voie de biosynthèse des hexosamines. Ces mécanismes sont responsables de l'activation des voies hypertrophiques, des modifications épigénétiques, du dysfonctionnement mitochondrial, de l'apoptose cellulaire, de la fibrose et de l'altération de la signalisation calcique conduisant à une chute de la contraction et de la relaxation cardiaque. Cette revue vise à décrire les altérations induites par l'hyperglycémie, qui participent au développement de la cardiomyopathie diabétique, ainsi que la corrélation avec la gravité de la maladie et la mortalité des patients. Dans cette revue, nous abordons également l'effet bénéfique des traitements hypoglycémisants sur la fonction cardiovasculaire.

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Background

Diabetes mellitus (DM) is ranked as the seventh leading cause of death and is responsible for a considerable health burden worldwide [1], with cardiovascular complications being the main cause of death. The Framingham study has shown that heart failure (HF) is the major contributor to morbidity, with a risk that is doubled in patients with DM compared with in those without DM [2]. In 1972, in patients with DM, Rubler et al. [3] reported HF with left ventricular hypertrophy, but no coronary artery disease or other aetiologies, introducing for the first time the concept of diabetic cardiomyopathy, which was also described subsequently by Regan et al. [4]. The Strong Heart Study [5,6] and others [7–9] have shown that patients with DM are at 1.5-fold higher risk of HF, after adjustment for multiple co-factors, including age, sex, obesity, fat distribution, atrial fibrillation, cholesterol concentration and glycated haemoglobin (HbA1c). Since then, diabetic cardiomyopathy has been defined as a contractile and relaxation dysfunction that leads to HF, independent of coronary and/or valvular complications,

hypertension, congenital cardiomyopathy or other known HF aetiologies, the underlying mechanism of which remains unclear.

Clinical studies have highlighted a correlation between glycaemia and HF prevalence in DM [10–12]. Irbarren et al. [12] showed that a 1% increase in HbA1c was associated with an 8% rise in HF hospitalization in DM, after excluding the factors cited earlier (Fig. 1). As DM is a multifactorial disease, the respective contribution of hyperglycaemia, insulin resistance and obesity to cardiac dysfunction is not clear. Interestingly, Montaigne et al. [13] found that ex vivo contractile dysfunction was associated with mitochondrial dysfunction, and was related to HbA1c level, regardless of insulin resistance or obesity, supporting the idea that hyperglycaemia is a key component of diabetic cardiac dysfunction. Similarly, preclinical studies have recently shown that hyperglycaemia alters Ca²⁺ signalling, advanced glycated end-products (AGEs) and upregulation of the hexosamine biosynthesis pathway, leading to cell apoptosis, structural modifications and contractile dysfunction.

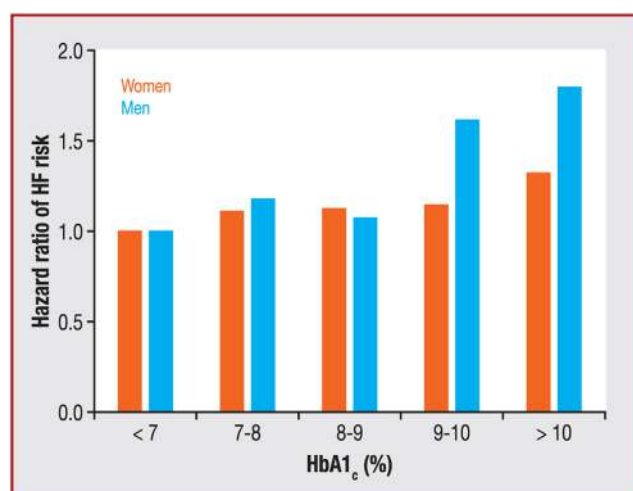


Figure 1. Relationship between glycated haemoglobin (HbA1c) level and risk of heart failure (HF) hospitalization in patients with diabetes mellitus, after adjustment for race/ethnicity, education level, cigarette smoking, alcohol consumption, hypertension, obesity, angiotensin-converting enzyme inhibitors, beta-blockers, diabetes type, diabetes duration and interim myocardial infarction. Adapted from Irbarren et al. [12].

More recently, O-linked-N-acetylglucosaminylation (O-GlcNAcylation), a post-translational modification of proteins, has emerged as a key player in DM and HF [14]. O-GlcNAcylation modifies protein activity by the addition of a N-acetylglucosamine to serine and threonine residues. Like phosphorylation, O-GlcNAcylation is a dynamic and rapid modification. However, in contrast to phosphorylation, O-GlcNAcylation is regulated by two different enzymes (versus hundreds for phosphorylation): O-linked-N-acetylglucosamine (O-GlcNAc) transferase (OGT) and O-GlcNAcase (OGA), which respectively add or remove the N-acetylglucosamine. Contrary to the N- and O-glycosylation process (which is restricted to the endoplasmic reticulum, the Golgi apparatus or secreted extracellular proteins), O-GlcNAcylation affects nuclear, cytosolic and mitochondrial proteins. In the heart, increased O-GlcNAc levels have been shown to reduce rodent myocardial infarct size [15] and ischaemia/reperfusion injury damage [16]. However, in HF, O-GlcNAcylation is increased, showing that equilibrium in O-GlcNAc homeostasis is key for normal cardiomyocyte function [17]. In patients with DM and in animal models [18], O-GlcNAcylation is upregulated and participates in diabetic cardiomyopathy. Once O-GlcNAcylation is inhibited, cardiac function is improved in DM [19,20]. Additionally, in DM, proteins undergo modification through AGE formation, involving the non-enzymatic addition of a sugar moiety (fructose or glucose) to a protein, leading to cell damage, such as oxidative stress, inflammation, alteration of Ca^{2+} signalling and cardiac stiffness [21].

This review is a translational overview of hyperglycaemia-mediated dysregulation of cardiomyocyte function and the impact on the cardiac function, with an overview of the effect of glucose-lowering drug therapy on cardiac outcomes.

Clinical evidence for the role of hyperglycaemia in the development of diabetic cardiomyopathy

Recently, two forms of HF have been described in DM: HF with reduced ejection fraction (HFrEF; defined as an ejection fraction <40%); and HF with preserved ejection fraction (HFpEF; defined as an ejection fraction >50%). Among patients with HFpEF, the prevalence of DM is 45%; however, little is known about the characteristics and outcomes of this population.

Epidemiological studies support a strong association between DM and HF, with a 2.4-fold increase in men with DM versus a 5-fold increase in women with DM [22], with higher hospitalization for HF (hazard ratio [HR] 1.45, 95% confidence interval [CI] 1.34–1.57) [23]. This relationship between DM and HF is bidirectional, with patients with HF having a 4-fold higher prevalence of type 2 DM than those without, rising to 40% in hospitalized patients with HF [24], and worsened HF prognosis, with a 1-year mortality rate of 30% (~1.5-fold higher in DM versus non-DM) [25]. In the CHARM trial (Candesartan in HF: Assessment of Reduction in Mortality and Morbidity), a median follow-up of 37.7 months showed, in DM, an HR of 2.0 (95% CI 1.70–2.36) in HFpEF and an HR of 1.60 (95% CI 1.44–1.77) in HFrEF [26], with an increased risk of mortality or hospitalization for HF – an observation also made in the I-PRESERVE trial [27]. The mortality risk rises to 10-fold higher with age (>65 years) [28]. Finally, in the EVEREST trial, including patients with HFrEF, patients with DM had higher rates of postdischarge cardiovascular mortality and HF hospitalization than those without DM (HR 1.17, 95% CI 1.04–1.31) [29]. DM unfavourably affects left ventricular remodelling in patients with left ventricular pressure or volume overload [30–32], and increases the risk of arrhythmia, notably atrial fibrillation, by up to 40% [33,34]. Although a population-based control study reported a correlation between HbA1c level and HF [35], the relationship between HbA1c level and atrial fibrillation prevalence is unclear.

High glucose: epidemiologic data on HbA1c levels and mortality

Controversies concerning the link between glycaemic control, HbA1c (<7.0%) and cardiovascular outcome have arisen from observational studies and randomized trials [36,37]. In the UKPDS study, despite an early loss of glycaemic differences, a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause were observed during 10 years of post-trial follow-up [36]. However, the Diabetes Control and Complications trial (DCCT), including patients with type 1 DM, reported that intensive glucose treatment had a beneficial effect on cardiovascular events [38]. Finally, in a recent observational study, HbA1c $\geq 7\%$ was a strong predictor for all outcomes (death, acute myocardial infarction, stroke and hospitalization for HF), especially atherothrombotic events [23]. Conversely, follow-up in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [39], the Action in Diabetes and Vascular disease (ADVANCE) trial [40] and the Veterans Affairs Diabetes trial (VADT) [41] showed no

evidence of cardiovascular benefit from intensive compared with standard glycaemic control.

Evolution of diabetic cardiomyopathy

Consensus definition

Nowadays, diabetic cardiomyopathy is recognized in international guidelines [42,43] as a specific and direct aetiology of HF in the absence of coronary artery disease, long-standing hypertension, valvular complications or any other aetiology of HF. Diabetic cardiomyopathy relies on a diagnosis of exclusion based on the presence of symptomatic cardiomyopathy and a long history of DM, with many exclusion criteria. However, because of frequent associated comorbidities, diagnosing diabetic cardiomyopathy is challenging.

Early phenotype of diabetic cardiomyopathy

American Heart Association guidelines [44] classically classify preclinical stages of HF as stage A in patients with HF risk factors, and stage B in asymptomatic patients with structural and/or functional abnormalities, whereas stages C and D refer to symptomatic HF. In asymptomatic patients with DM, an early phenotype of diabetic cardiomyopathy (stage B HF) is observed in one quarter to one third of patients. This phenotype may include left ventricular concentric remodelling or hypertrophy [6,45], left ventricular diastolic dysfunction [46,47] and mildly decreased global longitudinal strain [48–50]. Alteration of global longitudinal strain is a sensitive marker of systolic dysfunction in patients with normal ejection fraction (HFpEF) and can be the first alteration seen in the early form of diabetic cardiomyopathy [46]. Alteration of global longitudinal strain is associated with left ventricular remodelling [51] and a poorer prognosis, as assessed by all-cause mortality after a 10-year follow-up [52]. HFpEF is very common and is reported in around 40–50% of patients [46,53,54]. Diastolic dysfunction is also associated with a poorer prognosis, with an increased risk of overt HF [55]. Interestingly, when testing the exercise capacity in patients declared asymptomatic, an increased number of components of the early phenotype of stage B HF (left ventricular concentric remodelling/hypertrophy, diastolic dysfunction and altered strain) is associated with decreased exercise capacity, as assessed by peak oxygen uptake (VO_2), compared with healthy subjects [56].

Obesity and hypertension are frequent comorbidities of type 2 DM, in addition to age and sex, which may also influence cardiac phenotype. The specific contribution of all these potential causative factors is unclear, as is their synergistic contribution to cardiac dysfunction in patients with type 2 DM. Cluster analysis is an exploratory technique (without prespecified hypothesis) that provides tools to identify unknown subgroups, to classify individuals with similar characteristics into the same group (or cluster), and individuals with distinct characteristics into different clusters. Using cluster analysis in a large set of asymptomatic patients with DM, three clusters were recently identified in this population: a first cluster with preserved systolic and diastolic function (mainly men), associated with a favourable prognosis; a second cluster with obesity, hypertension and diastolic dysfunction (mostly women); and a

third cluster with left ventricular hypertrophy and systolic dysfunction as assessed by strain (mainly men). The latter two clusters had similar prognoses, which were less favourable than that of the first cluster, with an increased risk of cardiovascular mortality and hospitalization [57]. Despite these data, current evidence is not strong enough to support systematic screening for stage B HF phenotype in asymptomatic patients with DM [58].

Diabetic cardiomyopathy in type 1 DM

As type 1 DM is a rare disease, finding evidence of a specific diabetic cardiomyopathy in these patients is much more challenging than in those with type 2 DM. In the early phase, the Thousand & 1 Study included 1093 patients with type 1 DM without known heart disease, with a mean age of 49.6 ± 15 years (men, 53%; mean duration of DM, 25.5 years) [59]. Among these patients, 15.5% ($n = 169$) had abnormal systolic or diastolic function, including 1.7% with left ventricular ejection fraction $< 45\%$ and 14.4% with diastolic dysfunction ($E/e \geq 12$ or $E/e = 8-12$ and left atrial volume $> 34 \text{ mL/m}^2$). The authors reported decreased global longitudinal strain only in patients with macroalbuminuria [60]. Using positron emission tomography imaging, increased myocardial fatty acid metabolism has been reported in patients with type 1 DM [61]. In addition, impaired myocardial energetics, as assessed by magnetic resonance spectroscopy, has been shown in young subjects with uncomplicated type 1 DM, irrespective of the duration of DM [62].

In a large case-control study based on the Swedish National Diabetes Registry, and including patients with type 1 DM, DM was associated with a HR of 4.69 (95% CI 3.64–6.04), after adjustment for time-updated age, sex, time-updated DM duration and baseline comorbidities [63]. Poor glycaemic control and impaired renal function substantially increased the risk of HF.

Therefore, clinical evidence also supports the existence of a specific diabetic cardiomyopathy in patients with type 1 DM. In these patients, because of the autoimmune process, dilated phenotype with HFpEF seems to be more common than the restrictive phenotype with HFpEF [64].

Preclinical evidence for the role of hyperglycaemia in the development of diabetic cardiomyopathy

Over the years, preclinical studies have shown that glucose toxicity participates in defective cardiac metabolism and cardiomyocyte dysfunction via oxidative stress, accumulation of AGEs and the O-GlcNAcylation pathway, leading to hypertrophy, epigenetic modifications, mitochondrial dysfunction, cell apoptosis, fibrosis and Ca^{2+} mishandling. Altogether, these alterations induce cardiac stiffness and impaired cardiac contraction and relaxation, as described below (Fig. 2).

Glucose and structural modification

Structural modification of the left ventricle, leading to cardiac stiffness and impaired cardiac function, is a common feature of diabetic cardiomyopathy [58,65]. Lombarda

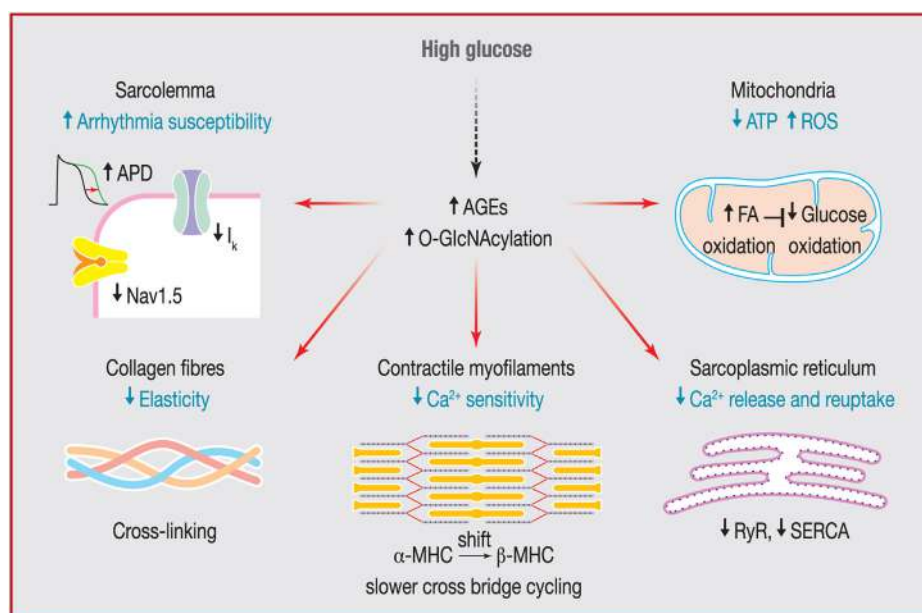


Figure 2. High glucose-mediated cellular dysfunction involved in diabetic cardiomyopathy development. High glucose induces both advanced glycated end-product (AGE) formation and upregulation of protein O-linked-N-acetylglucosaminylation (O-GlcNAcylation), which mediate several molecular alterations: (1) an increase in arrhythmia susceptibility related to action potential duration (APD) prolongation caused by a decrease in potassium outward current (I_k) and voltage-gated sodium channel (Nav1.5) function by O-GlcNAcylation; (2) reduced cardiac elasticity caused by AGE-mediated collagen cross-linking molecules; (3) a decrease in contractile myofilament Ca^{2+} sensitivity as a result of the shift from α -myosin heavy chain to the foetal isoform β -myosin heavy chain, as well as myosin light chain and actin O-GlcNAcylation, slowing cross-bridge cycling; (4) a decrease in Ca^{2+} release and reuptake at the sarcoplasmic reticulum, related to AGE-mediated alteration of the ryanodine receptor (RyR) and sarco/endoplasmic reticulum Ca^{2+} adenosine triphosphatase (SERCA), underlying cardiac contraction and relaxation; (5) a decrease in adenosine triphosphate (ATP) and an increase in reactive oxygen species (ROS) production in the mitochondria, as a result of fatty acid (FA) oxidation enhancement, which inhibits glucose oxidation.

et al. [66] have shown that in patients with type 1 DM, myocardial deformation is correlated with HbA1c level. Hyperglycaemia-mediated AGE formation induces loss of collagen elasticity, with subsequent reduction of myocardial compliance. In addition, AGEs increase the production of reactive oxygen species (ROS), which are known to promote myocardial fibrosis [67]. Nevertheless, the underlying fibrotic mechanisms remain unclear in diabetic cardiomyopathy. The fibrogenic agent transforming growth factor beta (TGF- β) may be involved in diabetic cardiac fibrosis (for more details see review [68]). Besides fibrosis, high glucose induces cardiac hypertrophy via, for example, the activation of the peroxisome proliferator-activated receptor gamma (PPAR γ), as described in adult rat cardiomyocytes treated for 48 hours with a high glucose concentration (25 mM) [69]. The increase in fibronectin production described in rats with streptozotocin-induced type 1 DM also participates in cardiac hypertrophy and fibrosis, as seen in the diabetic heart [70].

The glucose memory

Large-scale clinical trials [36,71,72] have pointed out the importance of early tight glucose control in limiting micro- and macrovascular damage in DM, induced by persistent glucose-mediated cell damage (even after glucose normalization), which correlates with the severity of hyperglycaemic history. This concept, known as

“metabolic memory”, was first evoked by Engerman et al. [73] in 1987, who showed that early control of glucose level, using insulin, in dogs with type 1 DM, prevented retinal damage induced by hyperglycaemia, a phenomenon well described in retinal and renal cells [74]. In cardiomyocytes, a few papers have described some long-lasting high-glucose cellular effects related to “metabolic memory”. For instance, in rats with streptozotocin-induced type 1 DM, an increase in cardiac fibronectin messenger ribonucleic acid levels persisted 2 weeks after glucose normalization by insulin [75]. Moreover, in the cardiomyocyte line H9c2, the “metabolic memory”, induced by 25 mM glucose (24 hours), increased interleukin-6 expression, despite glucose normalization, through interleukin-6 promotor methylation [76]. This mechanism seems to be related to high glucose-mediated epigenetic alterations (long-lasting modification of chromatin structure and gene transcription without modification of gene sequence) involved in “metabolic memory” development [77,78]. In aortic endothelial cells and mesangial renal cells [79,80], high glucose mediates mitochondrial superoxide production to activate several glucotoxic pathways (e.g. the polyol pathway, protein kinase C and AGEs). All of these mechanisms, found in diabetic cardiomyopathy [65], might be activated, and pave the way to a better understanding of the long-lasting high-glucose deleterious effects observed in cardiomyocytes.

Glucose and metabolic alterations

Normally, the heart uses either fatty acid (60–80%) or glucose oxidation to produce adenosine triphosphate (ATP), depending on substrate availability. However, the diabetic heart lacks this substrate flexibility, which deeply impacts cardiac metabolic activity. Indeed, fatty acid oxidation increases and glucose oxidation is inhibited. Then, the increase in fatty acid oxidation promotes acetyl coenzyme A and citrate production. Through the Krebs cycle, these substrates generate nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH₂), which enter the mitochondrial respiratory chain to produce ATP, associated with oxygen consumption. Because these molecules are very rich in electrons, the increase in their production and, thus, mitochondrial membrane flux and hyperpolarization, inhibits the respiratory chain complex, leading to ROS generation, with less ATP production [81,82]. The O-GlcNAcylation pathway also alters mitochondrial respiratory complex I, III and IV in neonatal rat cardiomyocytes in the presence of high glucose. Indeed, 30 mM glucose (48 hours) results in lower ATP production and mitochondrial respiration efficiency [83]. Besides altering the mitochondrial respiratory chain, the excess of acetyl coenzyme A and citrate inhibits glycolysis in cardiomyocytes, and switches the glucose to the pentose pathway, promoting ROS formation, AGE production and O-GlcNAcylation upregulation. For example, in neonatal rat cardiomyocytes, hyperglycaemia mediates O-GlcNAcylation of mitochondrial transcriptional factor A [84], which is involved in mitochondrial deoxyribonucleic acid (DNA) transcription and replication. These alterations result in reduced mitochondrial activity, with greater ROS and less ATP production, and participate in cell death. Indeed, in mice with streptozotocin-induced type 1 DM and H9c2 cardiomyocytes with high glucose (48 hours), the increase in ROS production is associated with cytochrome c release and activation of the caspase 3 apoptotic pathway, leading to cell death [85,86]. Na⁺/K⁺ ATPase activation protects H9c2 myocardial cells against high glucose-induced cell apoptosis by decreasing the level of ROS and alleviating cytosolic Ca²⁺ overload [86]. A higher ROS level is also associated with high sensitivity to Ca²⁺-induced mitochondrial permeability transition pore and activation of the caspase 9-mediated apoptotic pathway, as seen in atrial myoblasts from patients with type 2 DM [81,87]. 30 mM glucose (72 hours) also induces nuclear expression of FOXO1, a key transcription factor in insulin signal transduction, in H9c2 rat cardiomyocytes. Then, FOXO1 promotes β -adrenergic receptor kinase (GRK2) expression, which increases caspase 3-mediated cell apoptosis by promoting ROS production [88]. ROS can also promote apoptosis by inhibiting the insulin-like growth factor 1/phosphatidylinositol-3-kinase/Akt (IGF-1/PI3K/Akt) survival pathway in H9c2 cardiomyocytes treated with 33 mM glucose (36 hours) [89]. All of these mechanisms promote ROS production, decreasing mitochondrial ATP production and promoting cell death.

Glucose and excitation-contraction coupling

Studies in animal models of type 1 and type 2 DM have clearly shown that diastolic and systolic dysfunction are

associated with defective Ca²⁺ handling [90]. In cardiomyocytes, Ca²⁺ plays a key role in the initiation of contraction through excitation-contraction coupling. Indeed, during cardiomyocyte depolarization, Ca²⁺ enters into the cell through the L-type voltage-dependent Ca²⁺ channel, activating a massive release of Ca²⁺ from the ryanodine receptor of the sarcoplasmic reticulum, which binds to the myofilaments and generates contraction. Then, Ca²⁺ returns to diastolic levels through sarcoplasmic reticulum reuptake and cellular extrusion. In animal models of DM, the [Ca²⁺]_i transient is reduced as a result of a decrease in expression and/or activity of L-type voltage-dependent Ca²⁺ channel Ca²⁺ entry (although this is still a matter of debate), as well as reduced expression of ryanodine receptors [90–94]. The aforementioned upregulation of AGEs has been shown to directly alter ryanodine receptor activity, participating in abnormal diastolic sarcoplasmic reticulum Ca²⁺ release and decreasing sarcoplasmic reticulum Ca²⁺ content, which is necessary for the next contraction [95,96]. In addition, in diabetic models, [Ca²⁺]_i transient decay time is prolonged, as a result of impaired sarcoplasmic reticulum Ca²⁺ reuptake by the sarco/endoplasmic reticulum Ca²⁺ ATPase (SERCA), impairing relaxation [90,91]. SERCA dysfunction has been attributed to modification of phospholamban (an inhibitor of SERCA activity) by O-GlcNAcylation. This O-GlcNAcylation of phospholamban decreases its phosphorylation, thus promoting its inhibition of SERCA activity [97]. Moreover, high glucose leads to transcription factor O-GlcNAcylation, notably the specificity protein 1 (Sp1), which also downregulates SERCA expression [19,98]. SERCA is also an AGE target, which reduces its activity and depresses cardiac relaxation [96]. Taken together, these mechanisms alter SERCA-dependent Ca²⁺ reuptake, leading to cardiomyocyte contractile dysfunction by emptying sarcoplasmic reticulum Ca²⁺ load [90,91,94,99]. In addition, in rats with type 1 diabetes, myofilament sensitivity to Ca²⁺ decreases, which results from a shift from α -myosin heavy chain to the foetal isoform β -myosin heavy chain messenger ribonucleic acid [100,101] and slower cross-bridge cycling [102], slowing relaxation. Myosin heavy chain, myosin light chain and actin are also O-GlcNAcyated, as observed in cardiac muscle fibres in rats with streptozotocin-induced type 1 DM [103], decreasing myofibril sensitivity to Ca²⁺ [104] and contractile dysfunction. Finally, it is worth noting that high glucose-mediated alteration of excitation-contraction coupling increases the propensity for arrhythmia in animal models. Indeed, Erickson et al. [105] have shown that hyperglycaemia induces sarcoplasmic reticulum abnormal diastolic Ca²⁺ release via calmodulin kinase II (CaMKII) O-GlcNAcylation, and exacerbates arrhythmia in diabetic rats under β -adrenergic stimulation. Moreover, studies in rat ventricular cardiomyocytes showed that 25.5 mM glucose (24 hours) prolonged the action potential duration [106] by decreasing the outward potassium current amplitude in a diabetic rat model [107,108], which is arrhythmogenic. Furthermore, in rats with type 1 DM, O-GlcNAcylation of the cardiac voltage-gated sodium channel Nav1.5 decreases its expression and slows its inactivation, participating in action potential prolongation and ventricular arrhythmia susceptibility under β -adrenergic stimulation [109].

Treatment

The Food and Drug Administration and the European Medicines Agency have required evidence of cardiovascular safety for glucose-lowering agents since 2008, using three-point major adverse cardiovascular events (MACE3), a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke, as a primary endpoint. Therefore, data regarding the cardiovascular effects of glucose-lowering therapies are increasingly available. Since 2008, none of the new cardiovascular safety trials (known as "cardiovascular outcome trials") of antidiabetic drugs have shown an increase in ischaemic cardiovascular risk, but in some cases have shown cardiac protection. Therefore, the Food and Drug Administration is recommending that broader safety trials are conducted, including a large spectrum of patients with diverse risk factors, thus evaluating a wide range of safety concerns, instead of focusing only on cardiovascular safety [110]. Metformin is one of the first-line treatments for patients with type 2 DM. Although there is an absence of randomized clinical trials assessing the potential beneficial effect of metformin in patients with HF, a meta-analysis of nine cohort studies, involving 34,000 patients, suggested that metformin was associated with a reduced risk of all-cause mortality and hospitalization compared with controls (mostly sulphonylurea therapy) (pooled adjusted risk estimate 0.93, 95% CI 0.89–0.98; $I^2 = 0\%$; $P = 0.01$) [111]. As for metformin, no randomized clinical trials have been undertaken to assess the cardiovascular outcomes of sulphonylurea treatment. The results from observational studies and meta-analyses are controversial, with either an increase in or no effect on cardiovascular risk [112,113]. The increased risk of HF with thiazolidinedione has been established, caused in part by fluid retention and oedema side effects [114]. The effects of dipeptidyl-peptidase-4 (DPP4) inhibitors are controversial. Although the EXAMINE [115] and TECOS [116] trials did not reveal an increase in HF hospitalization in patients with DM receiving alogliptin and sitagliptin, respectively, the SAVOR-TIMI 53 trial [117] showed an increase in HF hospitalization of patients with type 2 DM treated with saxagliptin compared with placebo. As for linagliptin, the CARMELINA trial evaluated its effect on cardiovascular outcomes as a non-inferior risk of a composite cardiovascular outcome over a median 2.2-year follow-up [118].

Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists, injectable or daily oral intestinal-derived incretin peptides, stimulate postprandial insulin secretion and inhibit glucagon release. The results of GLP-1 analogue cardiovascular outcome trials are shown in Table 1. The LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Result) randomized trial demonstrated a decreased rate of the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke in the liraglutide group compared with placebo in patients with type 2 DM with an established cardiovascular disease [119]. The SUSTAIN-6 [120] and PIONEER-6 [121] trials demonstrated non-inferiority in terms of cardiovascular outcomes for semaglutide, with >80% of the

Table 1 Results of glucagon-like peptide-1 analogue cardiovascular outcome trials.

Study	MACE3		Cardiovascular mortality		Non-fatal MI		Non-fatal stroke	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
LEADER [119]	0.87 (0.78–0.97)	0.01	0.78 (0.66–0.93)	0.07	0.88 (0.75–1.03)	NS	0.89 (0.72–1.11)	NS
SUSTAIN-6 [120]	0.74 (0.58–0.95)	<0.001 ^a	0.98 (0.65–1.48)	NS	0.75 (0.51–1.08)	NS	0.61 (0.38–0.99)	0.04
REWIND [122]	0.88 (0.79–0.99)	0.026	0.91 (0.78–1.06)	NS	0.96 (0.79–1.16)	NS	0.76 (0.61–0.95)	0.017
PIONEER 6 [121]	0.79 (0.57–1.11)	<0.001 ^a	0.49 (0.27–0.92)	NT	1.18 (0.73–1.90)	NT	0.74 (0.35–1.57)	NT

CI: confidence interval; HR: hazard ratio; MACE3: three-point major adverse cardiovascular events; MI: myocardial infarction; NS: not significant; NT: not tested.

^a For non-inferiority.

population with cardiovascular disease. Although the LEADER and SUSTAIN-6 trials reported no changes in the rate of hospitalization for HF, only a small proportion of the included patients had HF at baseline. The REWIND TRIAL [122], evaluating a weekly injection of dulaglutide versus placebo, demonstrated a favourable effect on MACE3 (HR 0.88, 95% CI 0.79–0.99; $P=0.026$). In this trial, two-thirds of the patients were considered to be in primary prevention.

The FIGHT [123] and LIVE [124] smallest randomized trials specifically explored the effects of liraglutide in patients with HFrEF. In the FIGHT trial, including patients with and without type 2 DM, no reduction in HF hospitalization or cardiovascular death was observed. In the LIVE trial, no significant differences were observed between the groups for the primary endpoint (increase in left ventricular ejection fraction). However, liraglutide-treated patients had a higher number of serious cardiac events, probably as a result of an increased heart rate. Therefore, the effects of GLP-1 receptor agonists might differ between patients with type 2 DM and those with symptomatic HFrEF.

Sodium/glucose co-transporter 2 inhibitors

Sodium/glucose cotransporter-2 (SGLT2) inhibitors inhibit glucose reabsorption in the proximal renal tubules, independent of insulin, and reduce Na^+ reabsorption, leading to increased natriuresis [125]. SGLT2 inhibitor use reduces the rate of HF hospitalizations, as seen in cardiovascular outcome trials (Table 2) and, in the case of empagliflozin, markedly reduce cardiovascular death. The EMPAREG OUTCOME (Empagliflozin Cardiovascular Outcomes and Mortality in Type 2 Diabetes) trial [126] included patients with type 2 DM with established cardiovascular disease who presented a reduction in MACE3 after a median follow-up of 3.1 years in the empagliflozin group versus placebo (10.5% versus 12.1%; HR 0.86, 95% CI 0.74–0.99; $P=0.04$ for superiority). In addition, the trial demonstrated lower rates of cardiovascular mortality and hospitalization for HF (9.4% vs 14.5%; HR 0.65; 95% CI 0.50–0.85) in the empagliflozin group, a finding that was consistent across all major subgroups, including those with and without HF.

The CANVAS (Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes) programme included 10,142 patients with either established cardiovascular disease (65%) or a high risk of cardiovascular events (35%), and randomly assigned to canagliflozin (100 mg or 300 mg) or placebo [127]. The rate of the primary outcome, MACE3, was lower in the canagliflozin group than in the placebo group (26.9 vs 31.5 per 1000 patient-years). Although the reduction in cardiovascular and all-cause death with canagliflozin versus placebo did not reach significance, patients under canagliflozin showed a significant 33% reduction in the risk ratio for HF hospitalization. However, adverse effects occurred more often under canagliflozin than placebo—most notably, lower extremity amputations [127].

DECLARE-TIMI 58 [128], the cardiovascular outcome trial of dapagliflozin, included 17,160 patients (40.6% with and 59.3% without established cardiovascular disease) randomized to placebo or dapagliflozin over 4.2 years, with co-primary endpoints of MACE3 and a composite of cardiovascular death or hospitalization for HF. The trial did not show superiority for dapagliflozin in terms of MACE3

Table 2 Results of sodium/glucose co-transporter 2 inhibitor cardiovascular outcome trials.

Study	MACE3	Cardiovascular mortality		Hospitalization for HF		Cardiovascular mortality and hospitalization for HF		All-cause mortality		
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	
EMPAREG-OUTCOME [126]	0.86 (0.74–0.99)	<0.001	0.62 (0.49–0.77)	<0.001	0.65 (0.50–0.85)	0.002	0.66 (0.55–0.79)	<0.001	0.68 (0.57–0.82)	<0.001
CANVAS [127]	0.86 (0.75–0.97)	0.02	0.87 (0.72–1.06)	NT	0.67 (0.52–0.87)	NT	0.78 (0.67–0.91)	NT	0.87 (0.74–1.01)	0.24
DECLARE-TIMI 58 [128]	0.93 (0.84–1.03)	0.17	0.98 (0.82–1.17)	NT	0.73 (0.61–0.88)	NT	0.83 (0.73–0.95)	0.005	0.93 (0.82–1.04)	NT
CI: confidence interval; HF: heart failure; HR: hazard ratio; MACE3: three-point major adverse cardiovascular events; NT: not tested.										

CI: confidence interval; HF: heart failure; HR: hazard ratio; MACE3: three-point major adverse cardiovascular events; NT: not tested.

compared with control but did show superiority for the composite of cardiovascular death or hospitalization for HF (Table 2). The real-life study CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors) confirmed reduced HF hospitalization with SGLT2 inhibitors compared with other glucose-lowering medications [129].

Although the effect of SGLT2 inhibitors on HF hospitalization is impressive (the EMPAREG outcome), the CANVAS and DECLARE-TIMI 58 trials enrolled very few patients with established HF. The potential protective role of SGLT2 inhibitors against hospitalization for HF and/or cardiovascular death in patients with HF has been recently evaluated in the EMPEROR-REDUCED [130] and DAPA-HF [131] clinical trials, each of which enrolled > 3000 patients with HF with or without type 2 DM, with a reduced ejection fraction ($\leq 40\%$), New York Heart Association functional class II–IV and an elevated concentration of N-terminal pro-B type natriuretic peptide (NT-proBNP), a biomarker of cardiac injury. Patients were randomly assigned to dapagliflozin (DAPA-HF trial) or empagliflozin (EMPEROR-REDUCED) or matching placebo. Both trials showed superiority of SGLT2 inhibitors in preventing cardiovascular death and/or hospitalization for HF, regardless of DM, in patients under contemporary guideline-based HF therapies. The protective effects of SGLT2 inhibitors have revolutionized the standard of care for patients with reduced ejection fraction, as observed in the European Society of Cardiology 2019 guidelines, where SGLT2 inhibitors are recommended as first-line treatment, to lower the risk of hospitalization for HF in patients with type 2 DM [132]. Furthermore, the American Heart Association/American College of Cardiology 2019 guidelines support the use of SGLT2 inhibitors in patients with DM hospitalized for HF [133]. Without doubt, in the upcoming guidelines, SGLT2 inhibitors will soon be considered the standard of care for patients with HFrEF, despite their diabetic status, in light of the EMPEROR-REDUCED and DAPA-HF trial results.

The mechanism underlying the beneficial effects of SGLT2 inhibitors in HF is still under investigation, but seems to be beyond glucose lowering or diuresis *per se* (Fig. 3). A possible mechanism could be a direct myocardial effect through cardiac energy metabolism (higher ketone body oxidation). Increasing ketone levels participate in attenuation of the inflammation profile in HF under SGLT2 inhibitors, although the underlying mechanism is not fully understood. Furthermore, SGLT2 inhibitors inhibit the cardiac Na^+/H^+ exchanger, lowering myocardial Na^+ and Ca^{2+} levels increased in HF. SGLT2 inhibitors also reduce CaMKII activity, and prevent the sarcoplasmic reticulum Ca^{2+} mishandling observed in HF. Besides their direct action on the cardiomyocyte, the beneficial effect of SGLT2 inhibitors is also related to their renal action, through higher natriuresis, lowering renal intraglomerular pressure, with a subsequent reductions in sympathetic system activation and blood pressure, which indirectly improve cardiac function. Other theories have also been proposed, such as a reduction in ROS, increasing autophagy and provascular cell progenitors, and should be further investigated [134].

Although SGLT2 inhibitors emerge as a strong therapeutic class in both DM and HF, it should be noted that they present some adverse events, such as mycotic genital infections, which are outweighed by their cardiac benefits. As already

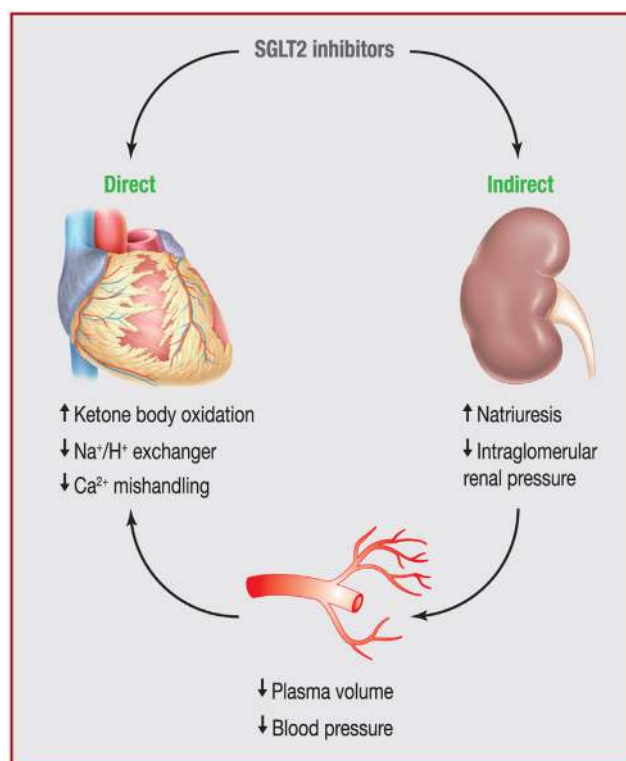


Figure 3. Schematic representation of the potential beneficial effects of sodium/glucose co-transporter 2 (SGLT2) inhibitors on cardiac function, both direct and indirect. SGLT2 inhibitors seem to have a direct effect on the heart, by increasing ketone body oxidation and decreasing Na^+/H^+ exchanger activity and Ca^{2+} mishandling via calmodulin kinase II; they also have indirect effects, related to an increase in renal natriuresis and a decrease in intraglomerular pressure, leading to lower plasma volume and blood pressure, reducing cardiac workload.

discussed, the increase in ketones bodies might explain, in part, the cardioprotective effect of SGLT2 inhibitors, with a risk, however, of diabetic ketoacidosis, which is still rare, but is twice as frequent compared with other antidiabetic drugs. The increased risk of fractures and lower limb amputations with this class remains controversial [135].

Conclusions

Several clinical studies have demonstrated a higher risk of HF during DM, caused, in part, by coronary artery disease and valvulopathy, and also specific cardiac dysfunction. Hyperglycaemia, among several factors, contributes to the development of diabetic cardiomyopathy. Although the beneficial effect of HbA1c tight control on cardiovascular event reduction is still controversial, it is well established that an increase in HbA1c level increases the risk of HF; this is correlated to glucose toxicity, leading to metabolic alterations, with a decrease in energy substrate production and an increase in oxidative stress production. The upregulation of the hexosamine pathway and the production of AGEs, mediated by high glucose, induce structure alteration and participate in Ca^{2+} mishandling, affecting cardiac compliance, contraction and relaxation. As cardiac safety is

a major challenge in drug development, several studies have deciphered the cardiovascular effects of glucose-lowering agents. Although thiazolidinediones are known to promote HF, studies are still controversial regarding DPP4 inhibitors. GLP-1 agonists have demonstrated a non-inferiority effect compared with placebo, whereas the new therapeutic class of SGLT2 inhibitors seems to be promising in terms of cardiovascular outcomes.

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Disclosure of interest

The authors declare that they have no competing interest.

References

- [1] Cho NH, Shaw JE, Karuranga S, et al. IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract* 2018;138:271–81.
- [2] Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA* 1979;241:2035–8.
- [3] Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am J Cardiol* 1972;30:595–602.
- [4] Regan TJ, Lyons MM, Ahmed SS, et al. Evidence for cardiomyopathy in familial diabetes mellitus. *J Clin Invest* 1977;60:884–99.
- [5] de Simone G, Devereux RB, Chinali M, et al. Diabetes and incident heart failure in hypertensive and normotensive participants of the Strong Heart Study. *J Hypertens* 2010;28:353–60.
- [6] Devereux RB, Roman MJ, Parancas M, et al. Impact of diabetes on cardiac structure and function: the Strong Heart Study. *Circulation* 2000;101:2271–6.
- [7] Garcia MJ, McNamara PM, Gordon T, Kannel WB. Morbidity and mortality in diabetics in the Framingham population. Sixteen year follow-up study. *Diabetes* 1974;23:105–11.
- [8] Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol* 1974;34:29–34.
- [9] Thrainsdottir IS, Aspelund T, Thorgeirsson G, et al. The association between glucose abnormalities and heart failure in the population-based Reykjavik study. *Diabetes Care* 2005;28:612–6.
- [10] Elder DH, Singh JS, Levin D, et al. Mean HbA1c and mortality in diabetic individuals with heart failure: a population cohort study. *Eur J Heart Fail* 2016;18:94–102.
- [11] Erqou S, Lee CT, Suffoletto M, et al. Association between glycated haemoglobin and the risk of congestive heart failure in diabetes mellitus: systematic review and meta-analysis. *Eur J Heart Fail* 2013;15:185–93.
- [12] Iribarren C, Karter AJ, Go AS, et al. Glycemic control and heart failure among adult patients with diabetes. *Circulation* 2001;103:2668–73.
- [13] Montaigne D, Marechal X, Coisne A, et al. Myocardial contractile dysfunction is associated with impaired mitochondrial function and dynamics in type 2 diabetic but not in obese patients. *Circulation* 2014;130:554–64.
- [14] Hart GW, Housley MP, Slawson C. Cycling of O-linked beta-N-acetylglucosamine on nucleocytoplasmic proteins. *Nature* 2007;446:1017–22.
- [15] Jones SP, Zachara NE, Ngoh GA, et al. Cardioprotection by N-acetylglucosamine linkage to cellular proteins. *Circulation* 2008;117:1172–82.
- [16] Liu J, Marchase RB, Chatham JC. Increased O-GlcNAc levels during reperfusion lead to improved functional recovery and reduced calpain proteolysis. *Am J Physiol Heart Circ Physiol* 2007;293:H1391–9.
- [17] Mailleux F, Gelinas R, Beauloye C, Horman S, Bertrand L. O-GlcNAcylation, enemy or ally during cardiac hypertrophy development? *Biochim Biophys Acta* 2016;1862:2232–43.
- [18] Qin CX, Sleaby R, Davidoff AJ, et al. Insights into the role of maladaptive hexosamine biosynthesis and O-GlcNAcylation in development of diabetic cardiac complications. *Pharmacol Res* 2017;116:45–56.
- [19] Fricovsky ES, Suarez J, Ihm SH, et al. Excess protein O-GlcNAcylation and the progression of diabetic cardiomyopathy. *Am J Physiol Regul Integr Comp Physiol* 2012;303:R689–99.
- [20] Hu Y, Belke D, Suarez J, et al. Adenovirus-mediated overexpression of O-GlcNAcase improves contractile function in the diabetic heart. *Circ Res* 2005;96:1006–13.
- [21] Bodiga VL, Eda SR, Bodiga S. Advanced glycation end products: role in pathology of diabetic cardiomyopathy. *Heart Fail Rev* 2014;19:49–63.
- [22] Leroy J, Richter W, Mika D, et al. Phosphodiesterase 4B in the cardiac L-type Ca(2+)(+) channel complex regulates Ca(2+)(+) current and protects against ventricular arrhythmias in mice. *J Clin Invest* 2011;121:2651–61.
- [23] Rawshani A, Rawshani A, Franzen S, et al. Risk Factors. Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2018;379:633–44.
- [24] Mentz RJ, Kelly JP, von Lueder TG, et al. Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction. *J Am Coll Cardiol* 2014;64:2281–93.
- [25] Gustafsson I, Brendorp B, Seibaek M, et al. Influence of diabetes and diabetes-gender interaction on the risk of death in patients hospitalized with congestive heart failure. *J Am Coll Cardiol* 2004;43:771–7.
- [26] MacDonald MR, Petrie MC, Varyani F, et al. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur Heart J* 2008;29:1377–85.
- [27] Kristensen SL, Mogensen UM, Jhund PS, et al. Clinical and echocardiographic characteristics and cardiovascular outcomes according to diabetes status in patients with heart failure and preserved ejection fraction: a report from the I-Preserve Trial (Irbesartan in Heart Failure With Preserved Ejection Fraction). *Circulation* 2017;135:724–35.
- [28] Bertoni AG, Hundley WG, Massing MW, Bonds DE, Burke GL, Goff Jr DC. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. *Diabetes Care* 2004;27:699–703.
- [29] Sarma S, Mentz RJ, Kwasny MJ, et al. Association between diabetes mellitus and post-discharge outcomes in patients hospitalized with heart failure: findings from the EVEREST trial. *Eur J Heart Fail* 2013;15:194–202.
- [30] Ernande L, Beaudoin J, Piro V, Meziani S, Scherrer-Crosbie M. Adverse impact of diabetes mellitus on left ventricular remodeling in patients with chronic primary mitral regurgitation. *Arch Cardiovasc Dis* 2018;111:487–96.

- [31] Raher MJ, Thibault H, Poh KK, et al. In vivo characterization of murine myocardial perfusion with myocardial contrast echocardiography: validation and application in nitric oxide synthase 3 deficient mice. *Circulation* 2007;116:1250–7.
- [32] Raher MJ, Thibault HB, Buys ES, et al. A short duration of high-fat diet induces insulin resistance and predisposes to adverse left ventricular remodeling after pressure overload. *Am J Physiol Heart Circ Physiol* 2008;295:H2495–502.
- [33] Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA* 1994;271:840–4.
- [34] Huxley RR, Filion KB, Konety S, Alonso A. Meta-analysis of cohort and case-control studies of type 2 diabetes mellitus and risk of atrial fibrillation. *Am J Cardiol* 2011;108:56–62.
- [35] Qi W, Zhang N, Korantzopoulos P, et al. Serum glycated hemoglobin level as a predictor of atrial fibrillation: A systematic review with meta-analysis and meta-regression. *PLoS One* 2017;12:e0170955.
- [36] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577–89.
- [37] Marx SO, Marks AR. Dysfunctional ryanodine receptors in the heart: new insights into complex cardiovascular diseases. *J Mol Cell Cardiol* 2013;58:225–31.
- [38] Armstrong AC, Ambale-Venkatesh B, Turkbey E, et al. Association of cardiovascular risk factors and myocardial fibrosis with early cardiac dysfunction in Type 1 Diabetes: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study. *Diabetes Care* 2017;40:405–11.
- [39] ACCORD Study Group. Nine-year effects of 3.7 years of intensive glycemic control on cardiovascular outcomes. *Diabetes Care* 2016;39:701–8.
- [40] Zoungas S, Chalmers J, Neal B, et al. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med* 2014;371:1392–406.
- [41] Davis SN, Duckworth W, Emanuele N, et al. Effects of severe hypoglycemia on cardiovascular outcomes and death in the veterans affairs diabetes trial. *Diabetes Care* 2019;42:157–63.
- [42] Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37:2129–200.
- [43] Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* 2017;70:776–803.
- [44] Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;62:e147–239.
- [45] Galderisi M, Anderson KM, Wilson PW, Levy D. Echocardiographic evidence for the existence of a distinct diabetic cardiomyopathy (the Framingham Heart Study). *Am J Cardiol* 1991;68:85–9.
- [46] Ernande L, Bergerot C, Rietzschel ER, et al. Diastolic dysfunction in patients with type 2 diabetes mellitus: is it really the first marker of diabetic cardiomyopathy? *J Am Soc Echocardiogr* 2011;24, 1268-75 e1.
- [47] Poirier P, Bogaty P, Garneau C, Marois L, Dumesnil JG. Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes: importance of maneuvers in echocardiographic screening for preclinical diabetic cardiomyopathy. *Diabetes Care* 2001;24:5–10.
- [48] Ernande L, Rietzschel ER, Bergerot C, et al. Impaired myocardial radial function in asymptomatic patients with type 2 diabetes mellitus: a speckle-tracking imaging study. *J Am Soc Echocardiogr* 2010;23:1266–72.
- [49] Ernande L, Thibault H, Bergerot C, et al. Systolic myocardial dysfunction in patients with type 2 diabetes mellitus: identification at MR imaging with cine displacement encoding with stimulated echoes. *Radiology* 2012;265:402–9.
- [50] Fang ZY, Najos-Valencia O, Leano R, Marwick TH. Patients with early diabetic heart disease demonstrate a normal myocardial response to dobutamine. *J Am Coll Cardiol* 2003;42:446–53.
- [51] Ernande L, Bergerot C, Girerd N, et al. Longitudinal myocardial strain alteration is associated with left ventricular remodeling in asymptomatic patients with type 2 diabetes mellitus. *J Am Soc Echocardiogr* 2014;27:479–88.
- [52] Holland DJ, Marwick TH, Haluska BA, et al. Subclinical LV dysfunction and 10-year outcomes in type 2 diabetes mellitus. *Heart* 2015;101:1061–6.
- [53] Boyer JK, Thanigaraj S, Schechtman KB, Perez JE. Prevalence of ventricular diastolic dysfunction in asymptomatic, normotensive patients with diabetes mellitus. *Am J Cardiol* 2004;93:870–5.
- [54] Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2016;17:1321–60.
- [55] From AM, Scott CG, Chen HH. The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction a population-based study. *J Am Coll Cardiol* 2010;55:300–5.
- [56] Koskela W, Jellis CL, Marwick TH. Exercise limitation associated with asymptomatic left ventricular impairment: analogy with stage B heart failure. *J Am Coll Cardiol* 2015;65: 257–66.
- [57] Ernande L, Audureau E, Jellis CL, et al. Clinical Implications of Echocardiographic Phenotypes of Patients With Diabetes Mellitus. *J Am Coll Cardiol* 2017;70:1704–16.
- [58] Marwick TH, Ritchie R, Shaw JE, Kaye D. Implications of underlying mechanisms for the recognition and management of diabetic cardiomyopathy. *J Am Coll Cardiol* 2018;71:339–51.
- [59] Jensen MT, Sogaard P, Andersen HU, et al. Prevalence of systolic and diastolic dysfunction in patients with type 1 diabetes without known heart disease: the Thousand & 1 Study. *Diabetologia* 2014;57:672–80.
- [60] Jensen MT, Sogaard P, Andersen HU, et al. Global longitudinal strain is not impaired in type 1 diabetes patients without albuminuria: the Thousand & 1 study. *JACC Cardiovasc Imaging* 2015;8:400–10.
- [61] Herrero P, Peterson LR, McGill JB, et al. Increased myocardial fatty acid metabolism in patients with type 1 diabetes mellitus. *J Am Coll Cardiol* 2006;47:598–604.
- [62] Shiva GN, Phan TT, Abozguia K, et al. Relationship between coronary microvascular dysfunction and cardiac energetics impairment in type 1 diabetes mellitus. *Circulation* 2010;121:1209–15.
- [63] Rosengren A, Vestberg D, Svensson AM, et al. Long-term excess risk of heart failure in people with type 1 diabetes: a prospective case-control study. *Lancet Diabetes Endocrinol* 2015;3:876–85.

- [64] Seferovic PM, Paulus WJ. Clinical diabetic cardiomyopathy: a two-faced disease with restrictive and dilated phenotypes. *Eur Heart J* 2015;36, 1718–27, 27a–27c.
- [65] Bugger H, Abel ED. Molecular mechanisms of diabetic cardiomyopathy. *Diabetologia* 2014;57:660–71.
- [66] Labombarda F, Leport M, Morello R, et al. Longitudinal left ventricular strain impairment in type 1 diabetes children and adolescents: a 2D speckle strain imaging study. *Diabetes Metab* 2014;40:292–8.
- [67] Aronson D. Cross-linking of glycated collagen in the pathogenesis of arterial and myocardial stiffening of aging and diabetes. *J Hypertens* 2003;21:3–12.
- [68] Yue Y, Meng K, Pu Y, Zhang X. Transforming growth factor beta (TGF-beta) mediates cardiac fibrosis and induces diabetic cardiomyopathy. *Diabetes Res Clin Pract* 2017;133:124–30.
- [69] Aloud BM, Raj P, O'Hara K, et al. Conjugated linoleic acid prevents high glucose-induced hypertrophy and contractile dysfunction in adult rat cardiomyocytes. *Nutr Res* 2016;36:134–42.
- [70] Chiu J, Farhangkhoei H, Xu BY, Chen S, George B, Chakrabarti S. PARP mediates structural alterations in diabetic cardiomyopathy. *J Mol Cell Cardiol* 2008;45:385–93.
- [71] Diabetes Control and Complications Trial Research Group Nathan DM, Genuth S, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–86.
- [72] Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353:2643–53.
- [73] Engerman RL, Kern TS. Progression of incipient diabetic retinopathy during good glycemic control. *Diabetes* 1987;36:808–12.
- [74] Berezin A. Metabolic memory phenomenon in diabetes mellitus: achieving and perspectives. *Diabetes Metab Syndr* 2016;10:S176–83.
- [75] Roy S, Sala R, Cagliero E, Lorenzi M. Overexpression of fibronectin induced by diabetes or high glucose: phenomenon with a memory. *Proc Natl Acad Sci U S A* 1990;87:404–8.
- [76] Yu XY, Geng YJ, Liang JL, et al. High levels of glucose induce "metabolic memory" in cardiomyocyte via epigenetic histone H3 lysine 9 methylation. *Mol Biol Rep* 2012;39:8891–8.
- [77] Cooper ME, El-Osta A. Epigenetics: mechanisms and implications for diabetic complications. *Circ Res* 2010;107:1403–13.
- [78] Villeneuve LM, Natarajan R. The role of epigenetics in the pathology of diabetic complications. *Am J Physiol Renal Physiol* 2010;299. F14–25.
- [79] Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes* 2005;54:1615–25.
- [80] Nishikawa T, Edelstein D, Du XL, et al. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. *Nature* 2000;404:787–90.
- [81] Bugger H, Abel ED. Molecular mechanisms for myocardial mitochondrial dysfunction in the metabolic syndrome. *Clin Sci (Lond)* 2008;114:195–210.
- [82] Teshima Y, Takahashi N, Nishio S, et al. Production of reactive oxygen species in the diabetic heart. Roles of mitochondria and NADPH oxidase. *Circ J* 2014;78:300–6.
- [83] Hu Y, Suarez J, Fricovsky E, et al. Increased enzymatic O-GlcNAcylation of mitochondrial proteins impairs mitochondrial function in cardiac myocytes exposed to high glucose. *J Biol Chem* 2009;284:547–55.
- [84] Suarez J, Hu Y, Makino A, Fricovsky E, Wang H, Dillmann WH. Alterations in mitochondrial function and cytosolic calcium induced by hyperglycemia are restored by mitochondrial transcription factor A in cardiomyocytes. *Am J Physiol Cell Physiol* 2008;295:C1561–8.
- [85] Cai L, Li W, Wang G, Guo L, Jiang Y, Kang YJ. Hyperglycemia-induced apoptosis in mouse myocardium: mitochondrial cytochrome C-mediated caspase-3 activation pathway. *Diabetes* 2002;51:1938–48.
- [86] Yan X, Xun M, Li J, Wu L, Dou X, Zheng J. Activation of Na⁺/K⁺ATPase attenuates high glucose-induced H9c2 cell apoptosis via suppressing ROS accumulation and MAPKs activities by DRm217. *Acta Biochim Biophys Sin (Shanghai)* 2016;48:883–93.
- [87] Anderson EJ, Rodriguez E, Anderson CA, Thayne K, Chitwood WR, Kypson AP. Increased propensity for cell death in diabetic human heart is mediated by mitochondrial-dependent pathways. *Am J Physiol Heart Circ Physiol* 2011;300:H118–24.
- [88] Yang M, Lin Y, Wang Y, Wang Y. High-glucose induces cardiac myocytes apoptosis through Foxo1/GRK2 signaling pathway. *Biochem Biophys Res Commun* 2019;513:154–8.
- [89] Huang YT, Liu CH, Yang YC, et al. ROS- and HIF1alpha-dependent IGFBP3 upregulation blocks IGF1 survival signaling and thereby mediates high-glucose-induced cardiomyocyte apoptosis. *J Cell Physiol* 2019;234:13557–70.
- [90] Pereira L, Matthes J, Schuster I, et al. Mechanisms of [Ca²⁺]i transient decrease in cardiomyopathy of db/db type 2 diabetic mice. *Diabetes* 2006;55:608–15.
- [91] Choi KM, Zhong Y, Hoit BD, et al. Defective intracellular Ca²⁺ signaling contributes to cardiomyopathy in Type 1 diabetic rats. *Am J Physiol Heart Circ Physiol* 2002;283:H1398–408.
- [92] Lee SL, Ostadalo I, Kolar F, Dhalla NS. Alterations in Ca²⁺ channels during the development of diabetic cardiomyopathy. *Mol Cell Biochem* 1992;109:173–9.
- [93] Lu Z, Jiang YP, Xu XH, Ballou LM, Cohen IS, Lin RZ. Decreased L-type Ca²⁺ current in cardiac myocytes of type 1 diabetic Akita mice due to reduced phosphatidylinositol 3-kinase signaling. *Diabetes* 2007;56:2780–9.
- [94] Yaras N, Ugur M, Ozdemir S, et al. Effects of diabetes on ryanodine receptor Ca release channel (RyR2) and Ca²⁺ homeostasis in rat heart. *Diabetes* 2005;54:3082–8.
- [95] Shao CH, Tian C, Ouyang S, et al. Carbonylation induces heterogeneity in cardiac ryanodine receptor function in diabetes mellitus. *Mol Pharmacol* 2012;82:383–99.
- [96] Tian C, Alomar F, Moore CJ, et al. Reactive carbonyl species and their roles in sarcoplasmic reticulum Ca²⁺ cycling defect in the diabetic heart. *Heart Fail Rev* 2014;19:101–12.
- [97] Yokoe S, Asahi M, Takeda T, et al. Inhibition of phospholamban phosphorylation by O-GlcNAcylation: implications for diabetic cardiomyopathy. *Glycobiology* 2010;20:1217–26.
- [98] Clark RJ, McDonough PM, Swanson E, et al. Diabetes and the accompanying hyperglycemia impairs cardiomyocyte calcium cycling through increased nuclear O-GlcNAcylation. *J Biol Chem* 2003;278:44230–7.
- [99] Pereira L, Ruiz-Hurtado G, Rueda A, Mercadier JJ, Benitah JP, Gomez AM. Calcium signaling in diabetic cardiomyocytes. *Cell Calcium* 2014;56:372–80.
- [100] Depre C, Young ME, Ying J, et al. Streptozotocin-induced changes in cardiac gene expression in the absence of severe contractile dysfunction. *J Mol Cell Cardiol* 2000;32:985–96.
- [101] Hofmann PA, Menon V, Gannaway KF. Effects of diabetes on isometric tension as a function of [Ca²⁺] and pH in rat skinned cardiac myocytes. *Am J Physiol* 1995;269:H1656–63.
- [102] Ishikawa T, Kajiwara H, Kurihara S. Alterations in contractile properties and Ca²⁺ handling in streptozotocin-induced diabetic rat myocardium. *Am J Physiol* 1999;277:H2185–94.
- [103] Ramirez-Correa GA, Jin W, Wang Z, et al. O-linked GlcNAc modification of cardiac myofilament proteins: a novel

- regulator of myocardial contractile function. *Circ Res* 2008;103:1354–8.
- [104] Ramirez-Correa GA, Ma J, Slawson C, et al. Removal of Abnormal Myofilament O-GlcNAcylation Restores Ca²⁺ Sensitivity in Diabetic Cardiac Muscle. *Diabetes* 2015;64:3573–87.
- [105] Erickson JR, Pereira L, Wang L, et al. Diabetic hyperglycaemia activates CaMKII and arrhythmias by O-linked glycosylation. *Nature* 2013;502:372–6.
- [106] Ren J, Gintant GA, Miller RE, Davidoff AJ. High extracellular glucose impairs cardiac E-C coupling in a glycosylation-dependent manner. *Am J Physiol* 1997;273:H2876–83.
- [107] Jourdon P, Feuvray D. Calcium and potassium currents in ventricular myocytes isolated from diabetic rats. *J Physiol* 1993;470:411–29.
- [108] Shimoni Y, Firek L, Severson D, Giles W. Short-term diabetes alters K⁺ currents in rat ventricular myocytes. *Circ Res* 1994;74:620–8.
- [109] Yu P, Hu L, Xie J, et al. O-GlcNAcylation of cardiac Nav1.5 contributes to the development of arrhythmias in diabetic hearts. *Int J Cardiol* 2018;260:74–81.
- [110] Chong WH, Yanoff LB, Andraca-Carrera E, Thanh Hai M. Assessing the Safety of Glucose-Lowering Drugs - A New Focus for the FDA. *N Engl J Med* 2020;383:1199–202.
- [111] Eurich DT, Weir DL, Majumdar SR, et al. Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: systematic review of observational studies involving 34,000 patients. *Circ Heart Fail* 2013;6:395–402.
- [112] Hippisley-Cox J, Coupland C. Diabetes treatments and risk of heart failure, cardiovascular disease, and all cause mortality: cohort study in primary care. *BMJ* 2016;354:i3477.
- [113] Roumie CL, Min JY, D'Agostino McGowan L, et al. Comparative safety of sulfonylurea and metformin monotherapy on the risk of heart failure: a cohort study. *J Am Heart Assoc* 2017;6:e005379.
- [114] Nassif M, Kosiborod M. Effect of glucose-lowering therapies on heart failure. *Nat Rev Cardiol* 2018;15:282–91.
- [115] Zannad F, Cannon CP, Cushman WC, et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. *Lancet* 2015;385:2067–76.
- [116] McGuire DK, Van de Werf F, Armstrong PW, et al. Association between sitagliptin use and heart failure hospitalization and related outcomes in Type 2 Diabetes Mellitus: secondary analysis of a randomized clinical trial. *JAMA Cardiol* 2016;1:126–35.
- [117] Scirica BM, Braunwald E, Raz I, et al. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. *Circulation* 2015;132:e198.
- [118] Rosenstock J, Allison D, Birkenfeld AL, et al. Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults With Type 2 Diabetes Uncontrolled With Metformin Alone or With Sulfonylurea: The PIONEER 3 Randomized Clinical Trial. *JAMA* 2019;321:1466–80.
- [119] Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in Type 2 diabetes. *N Engl J Med* 2016;375:311–22.
- [120] Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;375:1834–44.
- [121] Husain M, Donsmark M, Bain SC. Oral Semaglutide and Cardiovascular Outcomes in Type 2 Diabetes. Reply. *N Engl J Med* 2019;381:2076–7.
- [122] Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 2019;394:121–30.
- [123] Margulies KB, McNulty SE, Cappola TP. Lack of benefit for liraglutide in heart failure-reply. *JAMA* 2016;316:2429–30.
- [124] Jorsal A, Kistorp C, Holmager P, et al. Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE)-a multicentre, double-blind, randomised, placebo-controlled trial. *Eur J Heart Fail* 2017;19:69–77.
- [125] Vijayakumar S, Vaduganathan M, Butler J. Glucose-lowering therapies and heart failure in Type 2 diabetes mellitus: mechanistic links, clinical data, and future directions. *Circulation* 2018;137:1060–73.
- [126] Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in Type 2 diabetes. *N Engl J Med* 2015;373:2117–28.
- [127] Neal B, Perkovic V, Matthews DR. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* 2017;377:2099.
- [128] Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in Type 2 Diabetes. *N Engl J Med* 2019;380:347–57.
- [129] Kosiborod M, Cavender MA, Fu AZ, et al. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL Study (comparative effectiveness of cardiovascular outcomes in new users of sodium-glucose cotransporter-2 Inhibitors). *Circulation* 2017;136:249–59.
- [130] Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;383:1413–24.
- [131] McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2019;381:1995–2008.
- [132] Savarese G, Cosentino F. The interaction between dapagliflozin and blood pressure in heart failure: new evidence dissipating concerns. *Eur Heart J* 2020;41:3419–20.
- [133] Hollenberg SM, Warner Stevenson L, Ahmad T, et al. 2019 ACC Expert Consensus Decision Pathway on risk assessment, management, and clinical trajectory of patients hospitalized with heart failure: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol* 2019;74:1966–2011.
- [134] Lopaschuk GD, Verma S. Mechanisms of cardiovascular benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors: a state-of-the-art review. *JACC Basic Transl Sci* 2020;5:632–44.
- [135] Scheen AJ. About the Belgian experience with SGLT2 inhibitors. *Med des Mal Metab* 2020;14:320–30.