Concurrent diabetes and heart failure: interplay and novel therapeutic approaches

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Short title: The interplay between diabetes and heart failure

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Abstract:

Diabetes mellitus increases the risk of developing heart failure, and the co-existence of both diseases worsens cardiovascular outcomes, hospitalization and the progression of heart failure. Despite current advancements on therapeutic strategies to manage hyperglycemia, the likelihood of developing diabetes-induced heart failure is still significant, especially with the accelerating global prevalence of diabetes and an ageing population. This raises the likelihood of other contributing mechanisms beyond hyperglycemia in predisposing diabetic patients to cardiovascular disease risk. There has been considerable interest in understanding the alterations in cardiac structure and function in the diabetic patients, collectively termed as "diabetic cardiomyopathy". However, the factors that contribute to the development of diabetic cardiomyopathies is not fully understood. This review summarizes the main characteristics of diabetic cardiomyopathies, and the basic mechanisms that contribute to its occurrence. This includes perturbations in insulin resistance, fuel preference, reactive oxygen species generation, inflammation, cell death pathways, neurohormonal mechanisms, advanced glycated end-products accumulation, lipotoxicity, glucotoxicity, and posttranslational modifications in the heart of the diabetic. This review also discusses the impact of antihyperglycemic therapies on the development of heart failure, as well as how current heart failure therapies influence glycemic control in diabetic patients. We also highlight the current knowledge gaps in understanding how diabetes induces heart failure.

Introduction:

Cardiovascular disease (CVD) is the leading cause of death and complications in diabetic patients worldwide [1-6], the prevalence of which is increasing despite therapeutic and pharmacological advances [5, 7]. Diabetes mellitus, a metabolic disorder characterized by hyperglycemia resulting from insulin deficiency (type 1) or resistance (type 2) [11] is a major independent risk factor in the development of heart failure[8, 12, 13], and is becoming a global epidemic with increasing prevalence [14-17]. There are 2 main types of diabetes mellitus: type 1 and type 2; gestational diabetes mellitus is also part of this category but is not a major focus of this review. Type 1 diabetes mellitus, also called insulin-dependent diabetes, is an autoimmune disease where pancreatic beta cells are destroyed, and therefore, the body is unable to produce insulin [18]. Type 2 diabetes mellitus, also called non-insulin-dependent diabetes, is characterized by a deficit in the function of insulin produced by pancreatic beta cells; this is also referred to as insulin resistance. Type 2 diabetes is the more common form of diabetes, and factors such as age, obesity, diet, and pre-existing hypertension affect its development and its risk of development. Therefore, due to either the elimination of insulin secretion or the reduction in insulin function, blood glucose levels are, as a result, elevated, leading to chronic hyperglycemia if left untreated. The Framingham Study was one of the first epidemiological studies to show an increased risk of heart failure in patients with diabetes mellitus [13, 19, 20], with other clinical trials supporting this conclusion (see [21, 22] for reviews). The presence of both diabetes and heart failure in individuals leads to poor cardiovascular outcomes [5, 6, 23-26]. Diabetic patients have higher mortality from coronary artery disease than non-diabetics

[27] and show a worse prognosis [28, 29], which may be associated with increased atherosclerosis [27], and can lead to ischemic heart failure [30]. Heart failure is the major adverse cardiovascular outcome in diabetic patients [20]. Poor glycemic control is associated with increased risk of heart failure in individuals with type 2 diabetes [31], indicated by elevated hemoglobin A_{1C} levels, an index of glycemic control [32]. Therefore, it is critical to mediate and treat cardiovascular conditions in diabetic patients. The prevention and treatment of cardiovascular disease and heart failure remains a considerable challenge in the treatment and management of diabetes mellitus.

Diabetic cardiomyopathy is a condition characterized by ventricular dysfunction and hypertrophy in diabetic patients independent of hypertension, ischemia, or coronary artery disease [33]. The term originated from a Rubler et al. study that identified diabetic patients with congestive heart failure without the aforementioned risk factors or other causes. Noninvasive studies show impaired diastolic and systolic function [34-37], especially with the presence of hypertension. Multiple mechanisms contribute to the development of heart failure in diabetic individuals , including increased inflammation [38] and oxidative stress [39, 40], changes in cardiac myocardial energy metabolism [41-43], cardiac lipotoxicity [44-47], impaired cardiomyocyte calcium handling, and apoptosis [48, 49]. Diabetic cardiomyopathy may progress to either heart failure with preserved ejection fraction (HFpEF), where there is diastolic dysfunction [50, 51], or heart failure with reduced ejection fraction (HFrEF), where there is systolic dysfunction [8, 52, 53]. Each phenotype can be distinguished by the various mechanisms involved in contributing to it. Hypertrophy [54-56], insulin resistance [57], and lipotoxicity [58, 59] have been shown to contribute to the development of HFpEF, while

oxidative stress [60], fibrosis [61, 62], and autoimmunity caused cardiomyocyte cell death [63] are involved in contributing to HFrEF. Coronary deposition of advanced glycation end-products is involved in both phenotypes [64]. Diastolic dysfunction, which is part of the diagnosis of HFpEF [50, 51, 65], can precede the heart to develop HFpEF alongside comorbidities of impaired coronary vasculature and endothelial function, and hypertrophy [66, 67]. Although diastolic dysfunction is mostly predominant in diabetic cardiomyopathy, systolic dysfunction may also occur in later stages of diabetic cardiomyopathy, which can contribute to the development of HFrEF [52, 53]. Studies have demonstrated a metabolic link between the 2 heart failure phonotypes whereby abnormal mitochondrial function and oxidative stress can lead from a HFpEF phenotype into a HFrEF phenotype by mediating cardiac hypertrophy, inflammation, fibrosis, and further endothelial cell damage, which has adverse consequences on systolic function, and ultimately more severe manifestations of diabetes and heart failure [54, 68-77].

The aim of this review is to highlight the changes that occur in diabetic cardiomyopathy, alongside the mechanisms involved its development and progression. The effect of antihyperglycemic drugs on heart failure risk in diabetic individuals, and heart failure drugs on glycemic control will also be discussed, as well as novel therapeutic approaches.

Structural and functional characteristics of the failing heart in diabetics

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The failing heart in the context of diabetes is characterized by multiple alterations including impairments in diastolic and subsequent systolic function [34-36, 50], cardiac hypertrophy and fibrosis [99] and impaired coronary microvascular perfusion [100].

Diastolic and systolic dysfunction: Heart failure in diabetes is characterized by cardiac dysfunction, with diastolic dysfunction as a hallmark of the failing myocardium in diabetics [34, 101]. Echocardiography and doppler imaging assessments of diastolic dysfunction [102], have shown that left ventricular (LV) dysfunction is manifested in type 2 diabetic patients through altered LV filling [103], abnormal LV relaxation [34, 104, 105], reduced LV end diastolic volume [106], and LV chamber stiffness [107]. Studies in type 1 diabetics demonstrate abnormalities in LV diastolic filling [35, 108, 109], lower E to A ratios, prolonged isovolumetric relaxation times [35], and reduction in end-systolic volumes [36]. Thus, there is no single parameter to indicate and quantify diastolic dysfunction . Moreover, Attali *et al.* showed in both type 1 and 2 diabetic patients that abnormalities in diastolic function, including increased isovolumetric relaxation time and impaired LV compliance, were not related to additional factors such as age, sex, duration of diabetes, or presence of other complications [110]. Impaired diastolic function has also been shown in type 1 diabetic children [36, 111]. Additionally, the presence of hypertension can aggravate diastolic dysfunction , as demonstrated through further and severe impairment of LV relaxation and abnormal LV filling [50]. Speckle tracking echocardiography has emerged as a novel beneficial diagnostic method for early detection of LV dysfunction in diabetes, therefore being useful to detect LV abnormalities [112]. This method has been shown to overcome some of the limitations of transthoracic doppler imaging [113] and can be an equally, if not

better, powerful approach to assessing myocardial velocities and strain [113-115]. Studies have shown it's usefulness through examining LV strain in hypertensive and type 2 diabetic patients [116], and LV rotational mechanics in hypertensive type 2 mellitus diabetic patients [112]. This echocardiography method has also been utilized in animal models of diabetes, namely assessing systolic strain and contractile function in db/db mice by Li et al. [117] and assessing cardiac dysfunction in rat models of type 1 and type 2 diabetes mellitus by Matyas et al. [118].

Experimental evidence in animals complements these observations in human studies, showing a decrease in end-diastolic volume in alloxan diabetic dogs [119], a reduced E and A transmitral flow in *db/db* mice [120]; and an increased isovolumetric relaxation time and increased LV end-diastolic pressure in streptozotocin induced non-insulin dependent rats compared to controls [121]. Additionally, Otsuka Long-Evans Tokushima fatty rats show increased deceleration time [122].

Systolic dysfunction is also present in diabetic cardiomyopathy, although in both human and animal studies it has been shown to take longer to develop and usually occurs after diastolic dysfunction [36, 120]. In human studies, this manifests mainly as a reduction in ejection fraction [123, 124], along with increased LV end-systolic volume [123] and reduced fractional shortening [125]. The Strong Heart Study showed systolic dysfunction to occur, as evidenced by lower LV fractional shortening and decreased stress corrected midwall shortening in diabetic patients [126]. Animal studies are consistent with this, demonstrating impaired systolic function through lower peak-developed pressures [121], +dP/dt, peak

emptying rates [127], peak filling rates, fractional shortening [128], and systolic blood pressure in streptozotocin induced diabetic rats.

Impaired diastolic function is either associated with normal systolic function [50, 104, 105, 129, 130] or can precede systolic dysfunction [36]. In support of this, Raev *et al*. showed diastolic damage and abnormalities to be more prevalent than systolic damage and abnormalities in type 1 diabetic patients, while systolic dysfunction occurred much later in the progression of diabetes [36]. However, Fang *et al.* believe the use of less sensitive techniques to measure systolic dysfunction accounts for the reason behind studies demonstrating diastolic dysfunction with normal systolic function .

Cardiac hypertrophy: Diabetic cardiomyopathy is often associated with left ventricular hypertrophy [99]. The Strong Heart Study showed an independent association between diabetes and cardiac hypertrophy [126]. Increased myocardial wall thickness can be seen in type 1 and 2 diabetes, alongside ventricular dysfunction [105, 126, 131]. Additionally, myocardial hypertrophy is linked to adverse cardiovascular outcomes, including being a predictor of cardiovascular death [132, 133]. The Framingham study demonstrated that increased LV mass is associated with increased risk of cardiovascular outcomes of mobility and mortality [133]. Moreover, Solomon *et al.* observed a slightly greater wall thickness in diabetic patients alongside decreased ventricle size, which they believe may be associated with higher filling pressures and diastolic dysfunction [134]. These findings have been confirmed in animal studies showing an increase in LV mass alongside impaired LV relaxation and increased chamber stiffness [121]. The observed LV hypertrophy

in diabetics may precede the onset of systolic dysfunction , and can additionally be used as a diagnostic indicator in the development of heart failure in diabetics [135].

Cardiac fibrosis: Myocardial fibrosis and collagen accumulation can manifest as a major structural alteration in the setting of diabetes [136, 137], which can lead to myocardial damage and heart failure [138-141]. Multiple human studies demonstrate the presence of fibrosis in the left ventricle, alongside collagen accumulation in the interstitial and perivascular region of diabetic patients [99, 136, 142]. This cardiac fibrosis is associated with cardiac dysfunction [55, 140], and may lead to worsened cardiac outcomes including developing congestive heart failure [55, 139, 143].

Increased cardiac fibrosis in diabetes is supported by animal studies, where multiple mechanisms may be responsible for the cardiac fibrosis observed in diabetes. Otsuka Long-Evans Tokushima Fatty rats, a model of type 2 diabetes, show increased myocardial collagen content that is associated with impaired diastolic function through prolonged deceleration times and decreased early filling wave peak velocities [122]. Streptozotocin-induced diabetic rats have increased collagen and interstitial fibrosis due to oxidative stress, alongside decreased cardiac contractility [144, 145]. Additionally, streptozotocin-induced diabetic mice show a time dependent increase in LV collagen content, alongside impaired diastolic and systolic function [138]. This is suggested to be due to reduced matrix metalloproteinase 2 (MMP2) levels. Spiro *et al*. also showed an increase in type IV collagen in the myocardium of diabetic rats [146]. The increase in cardiac collagen in diabetes may be due to increased transforming growth factor–B1 (TGF-B1)

receptor II expression [71, 122, 147]. Another factor that can mediate this collagen accumulation and fibrosis development in diabetes is the myocardial accumulation of advanced glycosylation end products (AGEs) [148, 149] which will be discussed in more detail in a subsequent section of this review.

Impaired coronary microvascular perfusion: Abnormalities in coronary artery function and circulation are highly prevalent in diabetes [150], which may predispose the diabetic myocardium to cardiac damage and disease, including ischemia due to impaired blood circulation and flow [150, 151]. Coronary flow reserve (CFR) is reduced in both type 1 and 2 diabetic patients [100, 152], along with a reduction in coronary vasodilation [153] due to reduced nitric oxide (NO) production [154, 155]. Marciano *et al.* showed that type 2 diabetic patients without coronary artery disease have impaired coronary microvascular function, demonstrated by a lower CPT-CF ratio (cold pressure test to coronary flow), compared to non-diabetic individuals [156]. Additionally, Bagi *et al.* showed enhanced superoxide production and decreased NO production, leading to reduced coronary dilation in coronary arterioles isolated from *db/db* mice [157]. Hyperglycemia may be a cause for this, as shown by an association between CFR and HBA1c levels [158]. Additionally, Durante *et al.* showed lower coronary flows in diabetic BB rats in response to stimulation by noradrenaline, calcium, or tachycardia [159]. Coronary microvascular perfusion may be further impaired by the presence of hypertension-induced vascular lesions [160]. A reduction in coronary capillary density in the diabetic myocardium has also been observed, due to lower angiogenesis as a result of decreased vascular endothelial growth factor (VEGF) expression [161-163]. VEGF and VEGF receptor mRNA and protein expression were shown

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to be significantly decreased in diabetic and insulin-resistant non-diabetic rats [161, 162], and was accompanied by decreased myocardial perfusion and LV dysfunction [162]. Together, this suggests that structural abnormalities occur alongside functional abnormalities in the coronary microvasculature in diabetes. However, it is not clear which precedes the other, as some studies suggest structural changes in coronary arterial vasculature may be involved in causing further cardiac dysfunction [164] and also concurrently progress as diabetic cardiomyopathy progresses [162, 165]. Additionally, Giordano et al. showed that VEGF is a critical determinant of cardiac function as a VEGF knockout mouse model resulted in contractile dysfunction [166]. Therefore, further studies need to be done to fully elucidate the interplay in sequence of events between abnormalities in coronary capillary density and cardiac function.

Additionally, impaired coronary flow reserve and vasodilation may be an early marker of atherosclerosis, which can lead to progressive deterioration of the myocardium [151] and an increase in the risk of cardiovascular disease [152] and ischemia [153]. Impaired vasodilation in diabetes [155], which may also be due to NO production inhibition due to hyperglycemia [167] through the generation of oxygen-derived free radicals [168], can also lead to arterial atherosclerosis . Therefore, this abnormal coronary flow may greatly increase the risk and likelihood of myocardial ischemia [153, 159, 169].

Underlying mechanisms contributing to the development of diabetic cardiomyopathy

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Insulin resistance: Insulin resistance is one of the early contributing factors to the development of diabetic cardiomyopathy[170]. The decreased efficacy of insulin to lower blood glucose levels occurs as a result of hyperinsulinemia-mediated excessive insulin receptor signaling or downregulation of insulin receptor signaling. This insulin resistance contributes to a number of adverse changes in the heart that include alterations in cardiac energy metabolism, increased inflammation and hypertrophy, lipotoxicity, glucotoxicity, alterations in mitochondrial function and ROS production, accumulation of advanced glycation products and O-GlcNAcylation, alterations in cardiac cardiomyocyte Ca^{2+}-handling, systemic hyperglycemia and hyperlipidaemia[171], and neurohormonal changes (all of which are discussed below).

It is important to note that cardiac insulin resistance precedes the development of cardiac dysfunction and heart failure. A study in mice with heart failure developed diastolic dysfunction at 2 weeks and systolic dysfunction at 3 weeks. Notably, the decline in function was preceded by significant cardiac insulin resistance which was determined via serial and direct measurements of insulin-stimulated glucose metabolism in isolated working hearts [43]. These findings are supported by epidemiological studies that also found that insulin resistance is a predictor, rather than a biomarker, of heart failure. In a study of 1187 elderly men that did not have congestive heart failure, the epidemiological study between 1990 and 1995 found that insulin resistance significantly increased the risk and predicted congestive heart failure [172]. Another study in 431 50-year-old men with a 20-year follow-up, patients that developed heart failure at age 70 presented increased

plasma proinsulin at age 50, signifying that insulin resistance preceded cardiac dysfunction [173].

Insulin signaling begins with insulin binding to the insulin receptor, resulting in activation of the insulin receptor substrate-1/2, PI3K/PKB (Akt) activation, GLUT4 translocation to the cell membrane, stimulation of mitochondrial glucose oxidation, and inhibition of fatty acid oxidation [174]. Cardiac muscle biopsies from type 2 diabetic patients have depressed PI3K/PKB signaling and decreased GLUT4 expression[175]. In addition to decreased translocation of GLUT4, impaired PI3K engagement and stimulation of Akt also occur, due to increased phosphorylation of the serine residue on IRS-1/2[176].

Activation of forkhead box-containing proteins regulates insulin signaling, leading to insulin resistance. FoxO proteins are elevated in mice with high-fat diet-induced diabetes, which downregulates IRS1, consequently leading to decreased Akt signaling, insulin resistance and the development of diabetic cardiomyopathy[177]. Also important in the regulation of insulin signaling, and is perturbed in diabetic cardiomyopathy, is the E3 ubiquitin ligase – mitsugumin 53 [178]. In support of this, cardiac-specific overexpression of mitsugumin 53 in mice results in severe diabetic cardiomyopathy and insulin resistance, due to degradation of the insulin receptor and IRS-1. Mitsugumin 53 overexpression is involved in transcriptionally upregulating PPARα, contributing to lipid accumulation[179]. This accumulation of lipid intermediates (diacylglycerol and ceramides) contributes to the development of insulin resistance[180,181]. Conversely, decreasing

myocardial levels of ceramide and diacylglycerol is accompanied by improvements in insulin sensitivity and myocardial glucose utilization[182].

Altered cardiac energy metabolism: The heart has a very high energy demand despite having very low ATP stores (ATP levels effectively turnover in the heart every 5-10 seconds)[183]. The heart has the ability to continually generate large amounts of ATP from various energy substrates, including fatty acids, glucose, lactate, ketone bodies and amino acids, regardless of workload, nutritional status, and hormonal status [183, 184]. However, this metabolic flexibility is impaired in many forms of heart disease, including diabetic cardiomyopathy[183]. Insulin resistance results in an increase in myocardial fatty acid oxidation rates in diabetic cardiomyopathy and impaired glucose oxidation rates (Figure 1) [185-187]. This increases myocardial oxygen consumption, decreases cardiac efficiency and strongly correlates with impaired cardiac contraction and diastolic function [41, 42, 84, 188, 189].

Multiple mechanisms contribute to the increased reliance of the heart on fatty acid use during diabetes. The first such mechanism is increased supply of fatty acids to the heart. The lack of insulin suppressive action on adipose tissue results in the release of fatty acids from adipocyte to the circulation, leading to elevation of blood plasma free fatty acid levels. Fatty acid delivery and uptake to the heart is also increased in diabetes, due to an increase in cardiac myocyte lipoprotein lipase activity and increases in sarcolemmal CD36 protein expression, respectively [190, 191]. The increased uptake of fatty acids across the sarcolemma is facilitated by at least three proteins, namely, CD36, FA transport

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protein (FATP), and FA binding protein plasma membrane (FABPpm) [192]. In STZ-induced type 1 diabetic rats and type 2 *db/db* mice an upregulation of CD36 and FABPpm protein expression occurs [193, 194]. While CD36 alone accounts for more than half of the total fatty acid taken up by cardiomyocytes [195], both its expression and membrane localizations are increased in diabetes[193, 195].

Activation of transcription regulators such as peroxisome proliferator-activated receptors (PPARs) can promote expression of genes that facilities fatty acid uptake, storage and oxidation in the heart [196-198]. Myocardial PPARα expression is increased in type 2 diabetes, and mice lacking PPARα are protected from the development of diabetic cardiomyopathy [41, 199]. In contrast, a recent study found no differences in the risk of cardiac dysfunction between wildtype and PPARα deficient mice subjected to a low dose of streptozotocin (STZ) [200]. The discrepancy in the findings could be due to the different methodology followed for inducing Type 1 diabetes (1 single injection of high STZ dose vs. 5 daily injections of lower dose) and/or the different time points of cardiac function assessment (6 weeks vs 9-12 weeks post-STZ administration). Interestingly, it has been shown that PPARα/γ alterations may contribute to cardiac dysfunction independent of changes in fatty acid oxidation or lipid storage in non-diabetic animals [201, 202].

One effect of increased PPARα in diabetes is an increase in mitochondrial carnitine palmitoyltransferase I (CPT-1) expression, a key enzyme involved in mitochondrial uptake and oxidation of fatty acids [203]. In addition, perturbations in CPT-1 regulation also occur in diabetes. CPT-1 is inhibited by malonyl CoA produced from acetyl CoA by acetyl CoA

carboxylase (ACC) [204]. Activation of AMP-activated protein kinase (AMPK) in diabetes inhibits ACC activity . Decreased ACC activity with parallel increases in malonyl-CoA decarboxylase activity [205] decreases malonyl CoA levels, resulting in decreased inhibition of CPT1 and accelerated fatty acid oxidation rates Figure 1) [206-208] . Post-translational modification of fatty acid oxidative enzymes also occurs in diabetes, resulting in an increase in fatty acid oxidation [209]. Increased acetylation of major fatty acid metabolic enzymes due to decreased SIRT3 also leads to up-regulation of fatty acid oxidation and impaired glucose metabolism in the heart [210-212]. In addition to increases in myocardial fatty acid oxidation, an increase in myocardial triacylglycerol content is seen in diabetics [213]. Increased myocardial uptake of fatty acids leads to the increased accumulation of lipids and their intermediate metabolites, such as long and short fatty acyl-CoAs, diacylglycerol [196, 214]. However, studies on the turnover of endogenous fatty acid in hearts from diabetic animals have generated variable results. We have shown an increased myocardial lipolysis rate in diabetic hearts irrespective of exogenous fatty acid concentration while endogenous synthesis rate remains unaffected [213]. This is further supported by a ^{13}C-NMR isotopic enrichment study in diabetic rat hearts [215]. In contrast, others reported reduced or unchanged lipolysis and increased synthesis in the hearts of diabetics in the presence of high levels of exogenous free fatty acids [216, 217]. On the other hand, decreased levels of myocardial phospholipids is seen in diabetes together with impaired synthesis [218]. While the precise contribution of altered phospholipid metabolism is less clear in diabetes, various studies have suggested the etiologic role of phospholipid (membrane lipid) metabolic dysregulation in lipotoxic cardiomyopathy and other forms of myocardial dysfunction [219, 220].

In contrast to the increased myocardial uptake and oxidation of fatty acids seen in diabetes, myocardial glucose transport, glycolysis and glucose oxidation are decreased in diabetes [221-224]. Total myocardial GLUT4 and GLUT1 expression are decreased in diabetes [225]. Decreased myocardial glycogen content along with a reduced myocardial glycogen synthesis rate and impaired glycogen synthase enzyme activity is also reported in hearts of diabetics [226-228]. Insulin deficiency or resistance compromises the glucose transport and utilization in the heart. Also, the presence of excess fatty acid derivatives, such as fatty acyl CoA, diacylglycerol, and ceramide, leads to the inhibition of insulin signaling in the heart [229, 230]. In addition to decreased glucose transport, inhibition of cardiac phosphofructokinase (PFK-1), the rate limiting enzyme in glycolysis, is seen in diabetes [231, 232]. PFK-1 is inhibited allosterically by high levels of citrate, high ATP levels, and increases in NADH, that are derived from increased fatty acid oxidation. Glucose oxidation is also decreased, due in part to increases in fatty acid oxidation, which inhibits the rate limiting enzyme of glucose oxidation - pyruvate dehydrogenase (PDH) [187, 221, 233]. PPAR-α activation also suppresses glucose uptake and utilization by increasing the expression of pyruvate dehydrogenase kinase 4 (PDK-4), which inhibits PDH [47, 234].

Similar trends of fatty acid and glucose metabolic shifts have been also observed in type 1 and 2 diabetic patients [59, 235-238]. In ^{31}P and ^{1}H magnetic resonance spectroscopy studies, a significant reduction in myocardial glucose utilization accompanied by reduced myocardial energetics (phosphocreatine to ATP ratio (PCr/ATP) and increased myocardial fatty acid metabolism and triacylglycerol content is seen in type 2 diabetic

patients [236, 237]. The increased rates of myocardial fatty acid oxidation persist even after insulin treatment in human type 2 diabetic patients [235]. The levels of circulating free fatty acids is also negatively correlated with altered PCr/ATP ratios in patients with diabetes [239]. Earlier studies recognized myocardial PCr/ATP ratios as a predictor of cardiovascular mortality in patients with dilated cardiomyopathy [240]. Likewise, increased myocardial fatty acid utilization with a concomitant decrease in glucose utilization is seen in type 1 diabetic patients [59, 238].

Since fatty acids and glucose are the two important fuels for the heart, their balanced use is critical for maintaining normal contractile function. As a result, the decreased "metabolic flexibility" and increased reliance of the heart on fatty acid as source of energy is associated with impaired myocardial function in diabetes [222, 241-244]. Enhanced fatty acid oxidation increases myocardial O_2 consumption and decreases cardiac efficiency [245]. Enhanced fatty acid oxidation also alters the mitochondrial NADH to NAD^+ ratio and acetyl CoA levels which can further modify several intracellular signaling processes[210]. Although evidence suggests a detrimental effect of increased fatty acid oxidation on heart function in diabetes, there are still opposing views on the role of glucose and fatty acid alterations and pathologic significance in non-diabetic heart failure. Relatively few studies have combined diabetes and heart failure to study the impact of energy metabolism in the hearts during diabetes. By combining high fat feeding with pressure overload hypertrophy in mice we observed a marked decrease in insulin-stimulated glucose oxidation that was associated with both diastolic and systolic dysfunction [246, 247]. Furthermore, nutritional

strategies that increase insulin-stimulated glucose oxidation are accompanied by a decreased severity of heart failure [246, 247].

The contribution of alterations in the use of other fuels such as ketone bodies and branched chain amino acids (BCAAs) is increasingly being recognized in heart failure pathogenesis [248-250]. While ketone oxidation is increased in HFrEF and may be an adaptive process to maintain energy production [250, 251], in diabetes myocardial ketone oxidation is impaired, and may result in a decrease in metabolic flexibility and a decrease in energy production in the heart [252, 253]. A decrease in BCAA oxidation in insulin resistant hearts also contributes to an impaired insulin signaling and a decrease in insulin-stimulated glucose oxidation [254-256].

Cardiac lipotoxicity and glucotoxicity: Under normal circumstances, the uptake and oxidation of fatty acids are finely regulated resulting in only little myocardial lipid storage. However, in diabetes a persistent elevation in circulating free fatty acids supplies the heart with excess fatty acids and promote accumulation of lipids in the cardiomyocytes (cardiac lipotoxicity) (Figure 2) [257, 258]. The causative role of excess lipid accumulation in diabetic cardiomyopathy has been demonstrated using genetic or pharmacological approaches that modify uptake or oxidation of fatty acids. For instance, mice with cardiac specific overexpression of PPAR-α exhibit increased uptake and utilization fatty acid and typical features of diabetic cardiomyopathy, including ventricular hypertrophy and systolic dysfunction[47]. Recently, an increased activity of lipoprotein lipase (LPL) as shown in epicardial adipose tissue from type 2 diabetic patients [259]. Interestingly, elevated activity

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of LPL was associated with increased epicardial adipose tissue volume, suggesting increased fatty acids uptake. Of interest, deletion of CD36 or cardiac LpL rescues mice from a lipotoxic-induced cardiomyopathy caused by PPARα overexpression [260, 261].

In contrast, overexpression of CD36, FATP1, or acyl CoA synthetase results in lipotoxocity [262, 263]. This lipotoxicity correlates with diastolic dysfunction and other pathophysiological findings related to diabetic cardiomyopathy [264, 265]. Despite their contributing role in inducing cardiac lipotoxicity in diabetes, PPARα agonists (fibrates) are still in use clinically to treat hypertriglyceridemia [266]. In theory, lipotoxicity could arise either due to increased uptake or decreased oxidation. However, studies on pharmacological inhibition of FA oxidation or genetic manipulation of fatty acid oxidation enzymes revealed that decreased fatty acid oxidation does not actually lead to lipid accumulation [267]. It has been hypothesized that the reduction in oxidative function may inhibit the uptake of fatty acid by feedback mechanism[268].

In addition to fatty acid overload, cardiac lipotoxicity is also dependent on the type of fatty acids or lipids accumulated [268]. Ceramide is one fatty acid derivative strongly associated with cardiac lipotoxicity. Inhibition of ceramide synthesis, either by deletion of serine palmitoyltransferase or pharmacologically by myriocin, results in significant metabolic and structural changes to the heart. Decreasing cardiac ceramide levels decreases heart weight, pyruvate dehydrogenase kinase 4 (PDK4) expression, fatty acid oxidation rates and left ventricular diameter, while improving glucose oxidation [269, 270]. Diacylglycerol (DAG) is another lipid derivative associated with cardiac lipotoxicity. Increased levels of

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DAG in in the heart is associated with biochemical changes and macrovascular remodeling, indicating its possible role in the development of diabetic complications [271]. Increased levels of both ceramide and DAG can also activate and facilitate the translocation of protein kinase C (PKC) to the cell membrane [271, 272]. Activation of PKC by excess lipids impairs β-adrenergic signaling in the heart by phosphorylating its receptor [273, 274]. Phosphorylation of the β-adrenergic receptor leads to its desensitization, resulting in reduced myocardial contractility in response to catecholamines [275]. Increased PKC activity and its translocation to the cell membrane can also attenuate insulin signaling. Previous studies have shown that PKC can phosphorylate insulin receptor substrate 1 at its serine residue and blocks insulin stimulated tyrosine phosphorylation and downstream Akt signaling [276, 277].

On the other hand, although triacylglycerol is the most abundant lipid that accumulates in the heart, studies suggest that its accumulation is not associated with toxic effects in the heart [278, 279]. Overall, these data demonstrate that excess fatty acid storage and utilization in the heart are detrimental to heart function, although the mechanistic link between lipid accumulation and cardiomyopathy development are not clearly defined.

In contrast to lipotoxicity, less is known about glucotoxicity. Although myocardial glucose transporters are down regulated in diabetes, the heart can be still exposed to excess glucose. The increased extracellular glucose concentration results in the build-up of a glucose gradient for its transporter across the sarcolemma by mass action [280]. As myocardial glucose oxidation is inhibited in diabetes [187, 221, 281], the increased glucose flux

can lead to the accumulation of glycolysis intermediates and products. This imbalance can drive the diversion of glycolytic intermediates into pathological pathways in diabetes including protein kinase C stimulation, the hexosamine pathway, the polyol pathway, and the formation of advanced glycation end products [280, 282]. Increased glucose uptake in GLUT4 transgenic mice also contributes to mitochondrial dysfunction via O-GlcNAcylation of the transcription factor ST1 and many electron transport chain subunits [283].

Impaired mitochondrial function: The impact of heart failure and diabetes on mitochondrial bioenergetics has long been established. Perturbations in mitochondrial oxidative metabolism and mitochondrial ROS generation occur in both heart failure and diabetes [83, 284-286]. The reduction in cardiac function and efficiency along with impaired cardiac mitochondrial bioenergetics in obesity and diabetes is due to, at least in part, the excessive reliance on fatty acid oxidation and increased uncoupling protein content in these hearts, that contribute to reactive oxygen species (ROS) production [246, 287]. Many studies have proposed that ROS overload is a major culprit of diabetic cardiomyopathy [288-291]. Mitochondria are a major source of ROS production, and increased fatty acid oxidation can promote ROS production [83, 246, 287, 292-294]. Excessive cardiac ROS production induces inflammation and activates many crucial mediators of pathological signaling cascades [295-302], such as protein kinase C (PKC), apoptosis signal-regulating kinase-1 (Ask1), p38 mitogen activated protein kinase (p38-MAPK), NH2-terminal Jun kinases (JNK), and JAK-STAT. Activation of these signaling cascades can contribute to

the complications of diabetic cardiomyopathy [303, 304]. Furthermore, a recent study demonstrated that enhanced activity of Krüppel-like factor-5 (KLF5) is linked to an increase in oxidative stress in diabetic cardiomyopathy [200]. This occurs through an upregulation in the expression of NOX4 via direct binding to the NOX4 promoter [200]. The accumulation of ROS, increased ceramide production and low mitochondrial abundance contributes to impaired cardiac function in the hearts of the diabetics [200].

There have been many studies that have looked at the efficacy of antioxidants in managing diabetic cardiomyopathy [305-312]. Antioxidants can mitigate ROS-mediated mitochondrial uncoupling, a characteristic of diabetic cardiomyopathy, in animal studies [313, 314]. Similarly, antioxidants are protective against mitochondrial ROS in the failing heart [315-317]. Additionally, preclinical trials specifically targeting mitochondrial ROS respiratory complexes have been positive [318-320], but further clinical trials are necessary to confirm the efficacy of mitochondrial ROS scavenger under the contexts of both general heart failure and diabetic cardiomyopathy. Additionally, the use of Nrf2 activator and NOX inhibitor have shown to be effective in animal models[321, 322], and calorie restriction can lower ROS production and UCP expression in Type II diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats [299, 323]. Unfortunately, human clinical trials have failed to replicate these observations from animal models [324-327].

Inflammation and hypertrophy: Diabetes leads to increases in intramyocardial inflammation, characterized by increases in cell adhesion molecules (ICAM-1, VCAM-1) and increased macrophage infiltration resulting in the release of inflammatory cytokines

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(IL-1β, IL-6, IL-18, TGF-β1, TNF-α) [291]. Plasma concentrations of the cytokine acute-phase mediators, TNF-α and IL-6, are increased in the circulation in settings of impaired glucose tolerance, and thus, inflammation has been shown to be predictive for type 2 diabetes [328-330]. This is due to an excess level of glucose and free fatty acids stressing both pancreatic islet cells and adipocytes, resulting in the release of pro-inflammatory cytokines and chemokines into the circulation that promote inflammation in other tissues such as the heart [331]. Plasma TNF-α and IL-6 levels are increased and are associated with left ventricular diastolic dysfunction in patients with diabetes[332].

Systemic and local inflammation leads to fibrosis in the myocardium as well as hypertrophy and apoptosis at the level of the cardiomyocytes [333]. An upregulation of inflammatory signaling results in macrophage infiltration, cardiomyocyte apoptosis, hypertrophy and a profibrotic response via extracellular matrix remodeling – all of which lead to impaired cardiac contractility and diabetic cardiomyopathy [334-336]. Macrophage and lymphocyte infiltration into the cardiac cell are followed by secretion of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β, TGFβ, interferon-γ), which leads to adverse cardiac remodeling.

Due to systemic accumulation of advanced glycation end products, angiotensin II and lipotoxicity, an increase in toll-like receptor 4 (TLR4) and tumor necrosis factor receptor 1 (TNFR1) occurs in diabetes, leading to secretion of pro-inflammatory cytokines and subsequent cardiomyocyte death, hypertrophy, metabolic imbalances, contractile dysfunction, oxidative stress and mitochondrial dysfunction [336, 337]. More specifically, high

mobility group protein B1 (HMGB1) mediates lipopolysaccharide binding to and activation of TLR4, resulting in downstream activation of nuclear factor-KB (NF-KB) and the NLRP3 inflammasome [338]. Activation of the pleiotropic transcription factor, NF-KB, results in the transcription of genes that are pro-inflammatory (MCP-1, COX-2, VCAM-1), pro-hypertrophic (ANP, myosins) and pro-fibrosis (TGFβ, collagens, FN) [339, 340].

Hypertrophy follows inflammation in the heart of diabetics, since cytokines can induce cardiomyocyte hypertrophy[336, 341-343]. The pro-inflammatory cytokine TNF-α can activate the JNK and AKT/NF-κB pathway to promote cardiomyocyte hypertrophy[344]. Activation of the NF-κB pathway can also result in cardiomyocyte growth [345]. IL-1β, through IGF-1 downstream release from cardiac fibroblasts promotes cardiomyocyte hypertrophy [346]. Furthermore, IL-6 also contributes to cardiomyocyte hypertrophy through activation of the CaMKII and gp130 pathways which then activates the STAT3 pathway[347]. Lastly, TGF-β can activate the TAK1-MKK3/6-p38MAPK pathway and PKC-ATF2 to promote cardiomyocyte hypertrophy [348, 349].

Myocardial inflammation can also lead to cardiomyocyte apoptosis which subsequently contributes to cardiac remodeling. TNF-α activates both extrinsic and intrinsic apoptotic pathways, as well as NF-κB, to promote cardiomyocyte death [350, 351]. Additionally, through NO synthase activation or CHOP, IL-1β promotes apoptosis in cardiomyocytes[352]. The NLRP3 inflammasome also induces apoptosis via caspase-1 activation [353]. The inflammasome produces active caspase 1, that when activated results in cleavage of pro-interleukin-1β and pro-interleukin-18 and the production of active cytokines. In rats with

high-fat diet and streptozotocin-induced diabetic cardiomyopathy, silencing of the NLRP3 inflammasome decreases the levels of IL-1β, and this observation is mirrored when silencing CMKLR1, a G-protein-coupled receptor for chemerin. Concurrent silencing of both NLRP3 and CMKLR1 potentiates the decrease in mature IL-1β, as well as the levels of pyroptosis, underlining the important role the NLRP3 inflammasome and chemerin/CMKLR1 axis plays in mediating inflammation and pyroptosis in the setting of diabetic cardiomyopathy [354].

Myocardial inflammation not only results in the secretion of cytokines but also pro-fibrotic factors that activate fibroblasts and promotes cardiac fibrosis[341]. TGF-β, a major cardiac pro-fibrotic cytokine, activates fibroblasts which results in the production of extracellular matrix proteins, increases collagen production, and decreases extracellular matrix degradation [334]. Furthermore, IL-6 can suppress mir-29 and promote cardiac fibroblast proliferation and collagen production[355]. TNF-α also similarly promotes cardiac fibrosis through WISP1 activation [356].

Myocardial inflammation can also impair cardiac energy metabolism as IL-6 has been shown to impair myocardial glucose metabolism via SOCS3-dependent inhibition of IRS-1 [357]. Furthermore, NF-κB activation by TNF-α can inhibit PGC-1α and consequently, increase glucose metabolism via downregulation of PDK4 [358, 359].

Inflammation can also result in endothelial and microvascular damage, resulting in myocardial ischemia and contributing to diastolic and systolic dysfunction in diabetic

cardiomyopathy [291, 341, 360]. Furthermore, inflammation promotes ROS generation and downregulates SERCA2 (via IL-1β and IL-6), resulting in impaired Ca^{2+} handling and ultimately, diastolic dysfunction [361]. Myocardial inflammation can also depress cardiac contractility as TNF-α, IL-6, IL-1β and IL-2 exert negative inotropic effects on the heart [362]. Interestingly, a study in Zucker diabetic fatty rats treated with a β2-adrenergic receptor agonist decreased pro-inflammatory and pro-fibrotic responses in the heart and kidneys [363]. β-arrestin can bind to the β2-adrenergic receptor and promote internalization, subsequently promoting desensitization. While this may imply a negative role in the setting of diabetic cardiomyopathy, β-arrestins have previously been reported to inhibit NF-κB activity via IκBα. As such, inhibition of NF-κB in the setting of diabetes via β-arrestin and modulation of inflammatory mediators via sympathetic nervous system regulation may offer an alternative therapeutic strategy for diabetic cardiomyopathy. Further studies that investigate the interplay between β-arrestin and NF-κB in the setting of diabetic cardiomyopathy are warranted.

Hyperinsulinemia, via increased pancreatic production of insulin, follows insulin resistance in order to compensate for impaired cellular insulin actions. An excess of insulin can contribute to cardiomyocyte hypertrophy by acutely stimulating growth via the P13K/Akt-1 pathway .

Cardiac stiffness: Impairments in insulin signaling due to insulin resistance result in decreased GLUT4 translocation to the membrane and impaired PI3K/Akt signaling which

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results in decreased Ca^{2+}-ATPase activity, consequently increasing intracellular Ca^{2+} levels contributing to cardiac stiffness and diastolic dysfunction[176].

PI3K/Akt can activate endothelial NO synthase (eNOS), which results in an increase in NO that subsequently increases coronary vasodilation[176]. However, insulin resistance decreases activation of eNOS and consequently decreases NO levels [86]. Decreased NO results in impaired coronary microcirculation, due to impairments in coronary vascular smooth muscle cell relaxation [364, 365]. Therefore, insulin resistance alongside hyperinsulinemia can contribute to cardiac stiffness and diastolic dysfunction.

Advanced glycation end products: Diabetes-induced chronic hyperglycemia significantly increases the formation of advanced glycation end products (AGE) in the heart[366]. Protein glycation occurs after prolonged exposure to high concentrations of glucose, where amino groups of proteins bond non-enzymatically to glucose [367]. A correlation exists between formation of glycosylated tissue proteins in the heart and the period of hyperglycemia [368]. Compared to non-diabetics pathologies, hearts from diabetic patients also show a higher abundance of AGE formation in the myocardium [369]. A high abundance of AGEs also occurs in small intramyocardial arteries of the hearts of diabetic patients [370]. This suggests that diabetes can exaggerate AGE formation and increase the susceptibility of myocardial vasculature to glycation [366]. Formation of collagen cross-linking is a major determinant in the development of diabetic cardiomyopathy. Of relevance, an association between AGEs formation and decreased cardiac collagen solubility, and increased collagen III gene and protein expression, is seen in diabetes [371,

[372]. AGE-induced increases in cross-linked collagen may lead to myocardium and arterial wall stiffness and eventually atherosclerotic plaque formation [373]. Moreover, AGEs are also linked with other pathological pathways in diabetic cardiomyopathy, including oxidative stress [374, 375] and impaired Na^+/K^+-ATPase activity [376]. Chronic hyperglycemia increases both formation of AGE and expression of AGE receptors (RAGE), which in turn induces oxidative stress by activating transcription factor NFk-β [377]. A strong association has been observed between increased RAGE elicited by diabetes and LV contractile dysfunction typical of diabetes cardiomyopathy, which is rescued by RAGE gene knockdown or blocking [378, 379].

Hexosamine biosynthesis pathway O-GlcNAcylation (O-GlcNAc): O-GlcNAc is a posttranslational modification that is responsible for regulating the activity of proteins [380]. This process is initiated when N-acetylglucosamine (GlcNAc) is attached to a serine or a threonine residue of a peptide via an O-linkage (O-GlcNAc). The substrate for O-GlcNAc is uridine diphosphate-N-acetylglucosamine (UDP-GlcNAc), which is synthesized via the hexosamine biosynthetic pathway (HBP). It has been estimated that 5% of intracellular glucose contributes to the HBP[381], although this has been debated as to whether it is an accurate estimation for cardiomyocytes [382, 383]. Nevertheless, O-GlcNAc levels are closely related to glucose availability [380]. Glucose, after entering the cell is converted to fructose-6-phosphate (F6P) by hexokinase and isomerase. F6P is further processed to uridine diphosphate-N-acetylglucosamine (UDP-GlcNAc) by 4 enzymatic reactions. UDP-GlcNAc is the substrate for O-GlcNAc transferase (OGT), which is responsible for

catalyzing O-GlcNAc to targeted proteins. Similar to other posttranslational modifications, O-GlcNAc is a highly dynamic and reversible process, with the removal of O-GlcNAc from targeted proteins being accomplished by O-GlcNAcases [384].

O-GlcNAc has been proposed to occur in the nucleus, cytoplasm, and mitochondria[380], as opposed to other types of glycosylation which can take place in the extracellular matrix[385]. Chronic activation of the HBP is often associated with diabetic cardiomyopathy[386], as evidenced by increases in both gene expression and protein levels of GFAT in the myocardium of diabetic patients [387, 388]. Genetic modulation of OGA to a truncated, less effective form can exacerbate O-GlcNAc, inducing a higher chance of developing diabetes [389, 390]. Vascular dysfunction is a common feature of diabetes, and such dysfunction can be attributed to excess O-GlcNAc of proteins, such as transcription factor Sp1 and eNOS [391, 392]. Both protein levels and activity of OGT are elevated in rat aortic smooth muscle cells subjected to hyperglycemia. Additionally, excessive O-GlcNAc can lead to improper Ca^{2+} handling [393]. One specific target of O-GlcNAc is phospholamban, a protein regulating the function of SERCA2. Impairment of the function of phospholamban prevents the normal Ca^{2+} pumping after excitation from SERCA2, leading to improper contraction of heart muscle. The level of O-GlcNAc on cardiac proteins is carefully regulated by changes in OGT and OGA activity [394, 395]. O-GlcNAc may also affect complexes I, III, IV involved in mitochondrial respiration [394, 396]. O-GlcNAc may also impact ketone body metabolism by downregulating β-hydroxybutyrate dehydrogenase mRNA levels as well as succinyl-CoA:3-oxoacid CoA transferase protein

levels [253]. Of interest, ketone oxidation is decreased in the myocardium of diabetic mice [281].

An increasing body of evidence suggests an increase in O-GlcNAcylation levels in diabetic cardiomyopathy. Cardiac β1-adrenoceptors (β1AR) can be modified by O-GlcNAcylation, and its signaling transduction negatively correlates with its O-GlcNAcylation level in adult rat cardiomyocytes [404]. While circulating levels of N-terminal proteolytic fragment of histone deacetylase 4 (HDAC4) have been shown to be elevated in patients with diabetes, O-GlcNAcylation of HDAC4 is cardioprotective in a mouse model of diabetes [405]. This cardioprotection is associated with a reduction in pathological Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) signaling [405]. O-GlcNAcylation also plays a role in regulating autophagy by modifying the synaptosomal associated protein 29 (SNAP29) [406]. Increased O-GlcNAcylation of SNAP29 inhibits autophagic flux and causes further deterioration of cardiac diastolic dysfunction in STZ-induced diabetic rats [406]. Furthermore, O-GlcNAcylation can modulate ionic homeostasis by targeting the activity of a number of ion channels. For example, acute hyperglycemia can enhance K^+ channel recovery via CaMKIIδ-S^{280} O-GlcNAcylation [407]. Hyperglycemia also increases O-GlcNAcylation of $Na_{v1.5}$, which lead to the abnormal expression and distribution of $Na_{v1.5}$, loss of function of the sodium channel, and prolongation of the PR/QT interval in the hearts of diabetics [408]. In patients with T2D, increased O-GlcNAcylation is linked to the dynamic of glucose-induced impairment of endothelial nitric oxide synthase activation in endothelial cells that could contribute to vascular dysfunction in T2D [409].

Cardiac cell death pathways: Three main pathways are involved in cell death, apoptosis, necrosis, and autophagy [87]. A controlled rate of apoptosis and autophagy is necessary for removing unwanted cells [291]. However, in diabetes, cardiac cell death occurs at an accelerated rate[410-412]. This is due to both a hyperactivated cellular death pathway and an impaired cellular defense mechanism [413]. Cardiac apoptosis is elevated in diabetes [291, 305, 414, 415], which is important since an apoptotic rate as low as 0.023% is sufficient to induce lethal cardiomyopathy [415]. There are two main pathways of apoptosis: intrinsic or extrinsic . Intrinsic pathways can be initiated by various kinds of mitochondrial insult [87, 416, 417]. After formation of a mitochondrial permeability transition pore (mPTP), cytochrome C leaks into the cytoplasm and assemble with Apaf-1, ATP, and procaspase-9, forming apoptosome[418, 419]. The final product activates the effector caspase: caspase-3, which will go on to cleave target proteins[420, 421]. Additionally, p53 is able to sense damage of DNA strands and upregulate the transcription of two essential proteins: Bax and Fas[422]. Bax is a pro-apoptotic protein that resides on the mitochondrial membrane[423], whereas Fas contributes to the extrinsic cellular death pathway. Fas will act on death receptors located on cellular membrane[424]. Soluble extracellular protein, such as tumor necrosis factor-α (TNF-α) could also bind to death receptors[425]. Ligand binding initiates the assembly of multiprotein complex termed the death-inducing signaling complex (DISC), which recruits procaspase-8[426]. Such movement results in procaspase-8 activation [427, 428]. Caspase-8 cleaves Bid, leading to the formation of the active form, truncated-Bid (T-Bid) [429], that is pro-apoptotic by assisting the leak of cytochrome C into the cytoplasm. There is still debate regarding the relative contribution of apoptosis versus

necrosis to cardiomyocyte cell death in dilated cardiomyopathy [430]. It has been reported that necrotic cardiomyocytes are more dominant compared to apoptotic cells in dilated cardiomyopathy and severe aortic stenosis [431, 432]. In line with this, irreversible opening of the mitochondrial permeability transition pore (mPTP) also induces cell necrosis by ATP depletion, although it potentially triggers apoptosis via outer membrane rupture and cytochrome c release into the cytosol. Whether cardiomyocyte cell death by ischemia-induced mPTP opening has a significant contribution to cardiomyocyte loss and subsequent interstitial fibrosis in diabetic hearts warrants further investigation.

The cellular death pathways described above are altered in diabetic cardiomyopathy (Figure 3) . Direct exposure of high levels of glucose in myoblast H9c2 cells induces significant apoptotic cell death. The observations of hyperglycemia increases caspase 3 activation and cytochrome C release in cardiac cells are consistent with previous findings where high levels of glucose elevated the expression of Bax and its translocation from cytosol to mitochondria-enriched heavy membrane fraction in vascular endothelial cells[433]. On the other hand, the use of caspase-3 specific inhibitor, Ac-DEVD-cmk, can suppress hyperglycemia induced apoptosis[433, 434]. Additionally, up-regulation of p53 in myocytes, due to hyperglycemia, occur at very early stages in the development of diabetic cardiomyopathy[435], whereas attenuation of p53 transcriptional activity by IGF-1 prevents myocardial apoptosis in diabetic mice[436]. Besides high glucose, exposure to high levels of palmitate can also increase mitochondrial cytochrome C release, caspase-3 activation, followed by apoptotic cell death[437]. The formation of ROS and reactive nitrogen species (RNS) in the heart is another critical mediator of diabetes-induced myocardial cell death

[438]. Both ROS and RNS may be involved in many aspects of the cell death pathway, such as activation of caspase 3, the PKC pathway, release of cytochrome C and death receptor activation [434, 439, 440]. The antioxidant, metallothionein (MT), can ameliorate this hyperglycemia-induced myocardial cell death [40].

Unlike apoptosis, the role of autophagy in diabetic heart is still controversial. With some evidence suggesting that the induction of autophagy may convey protective effects [441], other studies proposed that excessive autophagy may accelerate the process to heart failure [442]. Autophagy is believed to be impaired in diabetic heart. One major regulator of autophagy is insulin and impaired insulin signaling stimulates myocardial autophagy[442, 443]. Given that many different animal models have not shown the blunted myocardial autophagy in diabetes [444-446], it is surprising that there has not been any approved treatment that targets autophagy specifically. However, some available medicines, such as metformin, rapamycin and resveratrol [447-449], have been found to promote autophagy indirectly, in addition to their main mechanism of action. Recently, Mst1 (macrophage stimulating 1) was found to be responsible for dictating the cardiomyocyte toward either apoptosis or autophagy in diabetes [450].

Study suggested that mitochondria-dependent, calcium overload-induced necrosis might contribute to the progression of heart failure [453]. Although necrosis has been suggested to be a passive and unregulated form of cell death, targeting the pathways of necrosis has potential for treating cardio-cerebrovascular injury [454]. Regulated necrosis can be

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classified into many categories, including but not limited to pyroptosis and ferroptosis.

Both forms have been proposed to correlate with diabetic cardiomyopathy development.

Pyroptosis is characterized by formation of plasma membrane pores and extracellular

release of inflammatory cytokines . High glucose promoted cardiomyocytes pyroptosis by

increasing ROS production[455]. Elevated level of pyroptosis also induces cell death via the

miR-214-3p/caspase-1/TGF-β1 pathway in diabetic mice [456]. Among the many protective

actions exerted by metformin, inhibition of pyroptosis by suppressing the mTOR pathway

via AMPK activation, may decrease pyroptosis-induced cell death in diabetic

cardiomyopathy[457]. Therefore, therapies targeting pyroptosis may be an effective

approach. On the other hand, ferroptosis is a newly discovered form of cell death, which

can be initiated by either iron overload or oxidative stress [458]. Of interest, hydrogen sulfide

is an endogenous gaseous signaling molecule that is capable of inhibiting ferroptosis.

One recent study proposed that treatment with the ferroptosis inhibitor ferrostatin-1 can

prevent hyperglycemia-induced ferroptosis [459].

Alterations in cardiac Ca^{2+} handling: One of the early perturbations in Ca^{2+}

homeostasis in diabetic cardiomyopathy that precedes LV dysfunction is a slow decay of

the Ca^{2+} transient [460-463]. Possible mechanisms that contribute to the occurrence of these

disarrangements in Ca^{2+} handling include perturbations in the activity of SERCA2a [465, 466], as well as malfunctions in Ca^{2+} handling proteins due to posttranslational

modifications, namely AGEs [467], O-GlcNacylation [468] and carbonylation [305, 469]. Impaired

Ca^{2+} handling between the sarcoplasmic reticulum and the mitochondria and alterations in Ca^{2+} influx and efflux to/from the cytosol and extracellular tissue and reduced activity of phospholamban and ryanodine receptors also contribute to the Ca^{2+} mishandling in diabetic cardiomyopathies [461, 470-472]. Ca^{2+} reuptake via SERCA2a is impaired in hearts from diabetic rats [473-475] and ob/ob mice [476, 477]. Interestingly, overexpression of SERCA2a improves Ca^{2+} handling in animal models of diabetic cardiomyopathy [478]. A recent study also demonstrated that insulin resistance impairs SERCA2a activity and cardiac function via inhibiting protein kinase B/striated muscle preferentially expressed protein kinase (SPEG) signaling [479]. It has also been shown that oxidative stress in the hearts of diabetics could contribution to the development of diabetic cardiomyopathy via impairing SERCA2a activity [480], and that enhancing SERCA2a activity is associated with improve cardiac function in the hearts of diabetics [479-481].

Diabetes is also accompanied by alterations in contractile proteins that are associated with the changes in contractile function in the diabetic heart [136, 482, 483]. The decrease in contractile function in the diabetic heart is also positively liked to the decrease in cardiac ATPase activity [472, 484, 485]. Along with the disturbances in cardiac ATPase proteins, it has also been shown that there are disturbances in isomyosin distribution and shifts from V_1 to V_3 in the diabetic heart [486-488]. There are also decreases in Ca^{2+} sensitivity along with troponin T-band shift in the diabetic heart [489, 490].

Neurohormonal mechanisms: The role of the renin-angiotensin-aldosterone system and endothelin-1 system in the pathophysiology of both heart failure and diabetes has

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long been recognized [491-493]. Diabetes is accompanied by an upregulation of the renin-angiotensin-aldosterone pathway that causes an increase in afterload, an important contributor to cardiac remodeling in diabetic cardiomyopathy . Consistent with this, a number of animal studies have shown that inhibiting activity of the renin-angiotensin-aldosterone system limits the progression of diabetic cardiomyopathy [492, 494, 495]. As a result, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor antagonists are recommended to treat heart failure in diabetic and non-diabetic patients [496]. Moreover, diabetes is also associated with alterations in systemic autonomic function and perturbations in cardiac rhythm [497, 498]. Despite the detrimental effect of these irregularities in the neurohormonal system, there are no therapeutic approaches presently used to target this system in the setting of diabetic cardiomyopathy.

Changes in cardiac gene regulation: In diabetic cardiomyopathy there is differential expression of several genes involved in inflammation, fibrosis, insulin signaling, cell death and metabolism (Figure 4) [499, 500]. The advancements in microarray technology facilitates extensive gene expression profiling to uncover genetic mechanisms of diabetic cardiomyopathy and its therapeutic implication. Genes that are often dysregulated in diabetic cardiomyopathy are discussed in the respective section and are summarized in Figure 4.

Studies both in type 1 and type 2 diabetes have shown abnormal cytosolic Ca^{2+} homeostasis and decreased SERCA2a expression in cardiomyocytes along with diminished contractile function [501]. This is important in the development of diabetic

cardiomyopathy, as SERCA2a gene transfer or overexpression can reduce diabetes-related contractile dysfunction, hypertrophy, and can differentially modulate the expression of genes involved in insulin signaling, glucose metabolism and cardiac remodeling [502]. Genes involved in inflammation and immune response are also affected by diabetic cardiomyopathy. For instance, IL6 and STAT3 genes are upregulated in patients with diabetic cardiomyopathy. On the other hand, downregulation of SOCS3 (Suppressor of cytokine signaling 3) is observed in diabetic cardiomyopathy patients compared to healthy controls [503].

Mitofusin 1 and 2 (Mfn1 and Mfn2) are mitochondrial dynamics proteins that controls fusion of the mitochondrial outer membrane [504]. In *db/db* diabetic mice hearts, Mfn2 is down-regulated and contributes to an imbalance in mitochondrial dynamics. On the other hand, Mfn2 overexpression relieves diabetic cardiomyopathy by promoting mitochondrial fusion [505].

Activation of PPAR-α expression, a transcription regulator, also occurs in diabetic cardiomyopathy [47, 506]. Importantly, over expression of PPAR-α activates genes involved in cardiac fatty acid utilization, while suppressing genes in glucose metabolic pathways. This suggests that dysregulation of PPAR-α expression contributes to the metabolic derangements observed in diabetic cardiomyopathy [47]. Increased mitochondrial biogenesis has also been implicated in diabetic cardiomyopathy, and PPAR*α*-dependent activation of PGC-1*α* may be a key driver of mitochondrial biogenic response in diabetic cardiomyopathy [506]. An increase in PGC-1*α* gene expression occurs in hearts of *db/db*

mice [41]. In addition, the up-regulation of PPARα-dependent PGC-1α is associated with increased expression of proteins of the mitochondrial electron transport chain and oxidative phosphorylation such as nuclear receptors families NRF-1 and NRF-2 and mtDNA transcription and replication (mtTFA) [506].

Recently, changes in the levels of non-coding RNAs have been recognized as important mediators of altered gene expression. The largest portion of the genome consists of non-coding RNAs. Although they are not directly transcribed to protein products, these RNAs regulate the transcription and post-transcriptional processing of many proteins. These regulatory RNAs consist of microRNAs (miRNA), long non-coding RNAs (lncRNA) and circular RNAs (circRNAs) [507]. Over 4,500 lncRNA genes, and 2,000 microRNA genes has been identified in human genome alone [508]. Although the function of the majority of non-coding RNAs are still unknown, mounting evidence suggests that these molecules play a significant role in a number of diseases processes and many of them are dysregulated in diabetic cardiomyopathy [499, 500, 509, 510]. Thus, their differential expression and role in diabetic cardiomyopathy pathogenesis is being actively investigated, partly because they may be potential biomarkers and therapeutic tools to treat diabetic cardiomyopathies.

LncRNAs are noncoding RNAs longer than 200 nucleotides in length. In addition to regulating other RNA functions, lncRNAs play an important role in epigenetic regulation by interacting with histone modifiers or chromatin remodelers or DNA [511]. These lncRNAs also forms nucleic acid-protein complexes thereby regulating the activity or localization of these proteins or serves as a precursor for other miRNAs and circRNAs [512]. Differential

expression of lncRNAs has been reported in diabetic cardiomyopathy and their abnormal expression has a role in promoting or inhibiting the development of diabetes. In diabetic cardiomyopathy there are significant alterations of a large number of lncRNAs that control apoptosis [513-515], fibrosis [516] and inflammation [513, 517]. Detailed data on lncRNA changes and their function are summarized in Table 1.

Alterations in many microRNAs (miRNAs) are also linked to changes in gene expression patterns in diabetic cardiomyopathy. MiRNAs are short non-coding RNAs that regulate gene expression by binding to the 3' untranslated region of target messenger RNAs (mRNAs) [426]. Upon binding, miRNAs repress gene expression by destabilizing or degrading the target mRNAs. To date, over 2650 mature miRNAs have been identified in humans that are implicated in various diseases [427]. The role of various miRNAs in mediating diabetic cardiomyopathies have been studied broadly and is summarized in Table 1. Of importance, these studies have suggested the contribution of specific miRNAs to hypertrophic [518-522], fibrotic [523-525], apoptotic [526-529], inflammatory and oxidative stress [525, 530-532] changes in diabetic cardiomyopathy.

Circular RNAs (circRNAs) are produced during the processing of pre-mRNA [508]. They are involved in the regulation of pre-mRNA splicing and RNA polymerase II [533, 534]. Analysis of the circRNA expression profiles in diabetic cardiomyopathy has shown differential regulation of several circRNAs in tissues from *db/db* mice hearts [535]. Upregulation of these

circRNAs has also been shown in association with myocardial fibrosis [536-538] and pyroptosis [539].

Epigenetics mediated dysregulation of gene expression also contributes to the development of diabetic cardiomyopathies. Modification of histone proteins by lysine acetylation is a major epigenetic mechanism that regulates expression of many genes. For instance, increased acetylation of cardiac histone H3 leads to increased mRNA expression of multiple cardiomyopathy-related genes, together with cardiomyocyte hypertrophy, in diabetic mice [540]. Increased acetylation of histone H3 and H4 in diabetes also leads to the recruitment of inflammatory genes promoters, including TNF-α and COX-2 [541]. Augmented histone acetylation at promoter regions of natriuretic peptide genes is also associated with increased expressions of ANP and BNP in the heart of diabetics [542]. Diabetes specific alterations in DNA methylation is also associated with altered in the phenotype of the heart in diabetes [543]. This suggests that diabetes-associated epigenetic modification may be an independent risk factor for diabetic cardiomyopathy.

The effect of antihyperglycemic drugs on diabetic cardiomyopathy severity

Although anti-hyperglycemic drugs significantly improve glycemic control in diabetic patients, use of these therapies does not necessarily equate to a reduced risk of developing heart failure [544, 545]. This highlights that lowering blood glucose alone is not sufficient to prevent diabetic cardiomyopathy development [545]. However, a number of anti-

hyperglycemic drugs can alter the course of cardiovascular complications in the diabetic (Table 2). The impacts of these therapies on glucose and fatty acid oxidation are also summarized in Figure 5.

Metformin: Metformin is a first-line therapy in the majority of type 2 diabetic patients. In addition to its primary role in lowering blood glucose, beneficial effects of metformin have been shown on stimulating insulin action, decreasing inflammation [546], and improving myocardial energy metabolism [547, 548]. However, its effect on heart failure development remains uncertain. Some studies indicated that metformin is contraindicated in diabetic patients with heart failure due to lactic acidosis [549]. A recent systematic review of 9 RCTs studies that examined metformin on heart failure related outcomes in patients with or without diabetes suggest some beneficial effects of metformin, but the overall evidence were not strong enough to make a solid conclusion about metformin decreasing heart failure severity [550]. Other studies have suggested that metformin therapy does not decrease the risk of heart failure development [551, 552].

Sulfonylureas: Sulfonylureas, especially older generation ones, increase the risk of adverse events in type 2 diabetic patients and are associated with a greater prevalence of hypoglycemia [553, 554]. A meta-analysis of 115 selected trials showed that sulfonylureas are associated with increased mortality, although major adverse cardiovascular events (MACE) did not appear to be affected [555]. Another meta-analysis investigating the association of metformin and sulfonylureas on both all-cause and cardiovascular mortality in type 2 diabetic patients, showed that combination therapy resulted in an increase in

relative risk for cardiovascular hospitalization, as well as fatal and nonfatal events[556].

Similarly, a retrospective cohort analysis investigating the addition of insulin or a

sulfonylurea in diabetic patients suggests that sulfonylureas increase the risk of non-fatal

cardiovascular outcomes and all-cause mortality [557]. This was also seen in a metformin

and sulfonylurea combination therapy study of type 2 diabetic patients, in which patients

newly treated with sulfonylureas possessed a higher risk for adverse cardiovascular

events [558]. Recently, a meta-regression analysis of 18 studies on the risk of

cardiovascular events associated with sulfonylureas found that there was an increased

risk of cardiovascular mortality and events with sulfonylurea treatment [559]. In a network

meta-analysis, 167,327 patients were studied to evaluate the risk of cardiovascular

events with different sulfonylureas. Gliclazide and glimepiride were shown to have a lower

risk of both cardiovascular-related mortality and all-cause mortality versus glibenclamide

[560]. Therefore, differences in the risk of mortality exist within the class of sulfonylureas.

This is further reinforced by a cohort study of patients with type 2 diabetes on

monotherapy with sulfonylureas, where glyburide and glimepiride did not increase the risk

of adverse cardiovascular events versus glicazide, glipizide and tolbutamide[561].

Thiazolidinediones (TZDs): TZDs are known to cause fluid retention and as such, can

increase the risk of congestive heart failure [562]. In the Pioglitazone Clinical Trial In

Macrovascular Events (PROACTIVE) study, patients with type 2 diabetes and a history

of macrovascular disease were randomized to receive pioglitazone or placebo[563].

Pioglitazone increased heart failure hospitalization, although this was associated with less

cardiac ischemic events [563]. The Diabetes Reduction Assessment With Ramipril and

Rosiglitazone Medication (DREAM) study, consisting of patients with impaired fasting glucose/glucose tolerance and no known cardiovascular disease, found that while rosiglitazone reduced diabetes and the development of renal disease, it increased new-onset heart failure [564]. In the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes (RECORD) trial, a multi-centre open-label study with type 2 diabetic patients, rosiglitazone increased the risk of heart failure or hospitalization by over 2-fold [565]. As such, rosiglitazone increases the risk of heart failure and alongside other TZDs, contain serious warnings regarding the increase in fluid retention and risk of congestive heart failure [562].

Glitazars: A dual PPARα and γ agonist designed to concurrently treat hyperlipidemia and hyperglycemia, glitazars combine the beneficial effects of agonizing both peroxisome proliferator-activated receptors. However, glitazars present a paradox and while addressing diabetic concerns with hyperlipidemia and hyperlycemia, they have been shown to worsen congestive heart failure in diabetic patients [566, 567]. Specifically, muraglitazar increases major adverse cardiovascular events, congestive heart failure and death in a review of several clinical trials that included 3725 patients [568]. Another glitazar, aleglitazar, while presenting effective anti-diabetic effects, also increases the risk of heart failure [569]. As such, concurrent agonism of PPARα and γ results in cardiac dysfunction, which may be due to inhibition of PGC1α and mitochondrial biogenesis [570].

GLP-1 receptor agonists: GLP-1 agonists improve glycemic control in diabetics by mimicking GLP-1 action [571-573]. These include Exenatide, a partial structural analogue of

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GLP-1, , with other GLP-1 analogues including liraglutide, lixisenatide [574], and semaglutide [575]. Some of these GLP-1 analogues have efficacy in mediating heart failure risk in diabetics, as shown by results of multiple phase III/IV large scale double-blind randomized clinical trials. The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) Trial showed that exenatide in type 2 patients with cardiovascular risk did not increase their overall risk and that the incidence of major adverse cardiovascular events was not worsened [576]. The Evaluation of Cardiovascular Outcomes in Patients with Type 2 Diabetes after Acute Coronary Syndrome during Treatment with Lixisenatide (ELIXA) Trial showed similar results, where lixisenatide treatment showed no effect on major adverse cardiovascular events (MACE) in type 2 diabetic patients who had a recent acute coronary event [577]. In contrast, the Liraglutide Effect and Action in Diabetes (LEADER) trial showed a lower risk of MACE, including the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in type 2 diabetic patients with high cardiovascular risk [578]. Additionally, the Trial to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) showed a significantly lower rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in type 2 diabetic patients with high cardiovascular risk [578]. However, the results of the Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) Trial showed no improved post-hospitalization clinical stability with liraglutide in recently hospitalized patients with established heart failure and reduced ejection fraction [579]. Examination of the effect of liraglutide on ventricular function in stable chronic heart failure patients with and without diabetes also showed that liraglutide did not improve LVEF or systolic function, and was associated with an increase in heart rate

and more serious cardiac adverse events [580]. Combined, this calls into question the benefits of liraglutide use in preventing diabetic cardiomyopathies.

DPP4 inhibitors: Incretins-based therapy has emerged as a novel treatment approach for diabetes management, with the inhibition of dipeptidyl peptidase 4 (DPP4) being used to prevent the cleavage and inactivation of GLP-1 [581]. DPP-4 inhibitors increase insulin secretion from pancreatic B-cells, thereby improving insulin tolerance and glucose control [582-584]. Current DPP4 inhibitors include vildagliptin, sitagliptin, and saxagliptin and are similar in their efficacy in lowering HBA1C levels [585] and improving glucose tolerance in diabetes [586-589]. Despite the efficacy of DPP4 inhibitors in improving glycemic control, the efficacy of DPP4 inhibitors in improving heart failure outcomes in diabetics remains unclear. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)-Thrombosis in Myocardial Infarction (TIMI) 53 trial (SAVOR-TIMI53) showed a significant increase in the rate of hospitalization for heart failure in type 2 diabetic patients treated with saxagliptin [590]. However, the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial showed non-inferiority of alogliptin to placebo on major cardiovascular events in diabetic patients with recent acute coronary syndrome [591, 592]. Moreover, the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) showed that sitagliptin neither improved or decreased rates of cardiovascular events such as death, myocardial infarction, stroke, or hospitalization for heart failure in type 2 diabetics with pre-existing cardiovascular disease [593, 594]. Other studies support the results of EXAMINE and TECOS trials [595-598]. although results from meta-analyses demonstrate conflicting evidence for the

effect of DPP4 inhibitors on mediating cardiovascular disease [599-601]. Animals studies have also shown conflicting results on the efficacy of DPP4 inhibitors on cardiovascular disease. Sitagliptin treatment decreased LV passive stiffness and improved global LV performance in an obese type 2 diabetic mice [602]. However, long term treatment of vildagliptin showed no cardioprotective effects on cardiac function, remodeling, or infarct size in Sprague-Dawley rats subjected to myocardial infarction induced by coronary ligation [603]. Combined, these studies suggest minimal beneficial effects of DPP4 inhibitors in reducing the risk of heart failure in diabetics, and support that certain DPP4 inhibitors may be safe in patients. However, the cardiovascular safety and efficacy of DPP4 inhibitors needs to be further elucidated.

SGLT2 inhibitors: Sodium glucose co-transporter 2 inhibitors (SGLT2i) prevent glucose reabsorption in the proximal tubules of the kidney, therefore increasing its secretion into the urine and improving glycemic control [604-606]. Three SGLT2i approved for clinical use include empagliflozin, dapagliflozin, and canagliflozin. Recently, large-scale clinical trials have shown cardioprotective benefits independent of its antihyperglycemic effect in both type 2 diabetic and non-diabetic patients [607-612]. The results of the Empaglifozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOMES) showed a lower occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, and a reduction in overall mortality and heart failure hospitalization in empagliflozin treated type 2 diabetics patients with cardiovascular risk compared to placebo [607]. The Canagliflozin Cardiovascular Assessment Study (CANVAS) and Dapagliflozin effect on Cardiovascular Events-Thrombolysis in

Myocardial Infarction 58 (DECLARE-TIMI58) trials supported the results of the EMPA-REG OUTCOMES study. The CANVAS trial showed a lower risk of cardiovascular events in type 2 diabetic patients with an elevated risk of cardiovascular disease [612], while the DECLARE-TIMI58 trial showed a reduction in cardiovascular death and heart failure hospitalization in type 2 diabetic patients with or at high risk of cardiovascular disease, although it did not reduce the rate of MACE [611]. Interestingly, the Dapagliflozin and Prevention of Adverse-Outcome in Heart Failure (DAPA-HF) trial showed a reduction of in the risk of mortality and heart failure reduction in patients with heart failure and reduced ejection fraction with or without type 2 diabetes [609]. These results are supported by the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) trial [610]. Combined, evidence from clinical trials show a safety and efficacy of SGLT2i as a therapeutic strategy to manage diabetes and associated cardiovascular disease, heart failure, and their risk.

Studies in animal models have also demonstrated cardiovascular benefits supporting the results from the major clinical trials. Empagliflozin improves cardiac contractility, by fractional area change, and improves microvascular function in *ob/ob*^{-/-} mice [613]. Additionally, empagliflozin treatment attenuates cardiac fibrosis and improves hemodynamics in hypertensive rat heart failure [614]. However, despite these beneficial cardiac outcomes, the exact mechanism of the cardioprotective effects of SGLT2i are unknown [615]. Multiple mechanisms have been proposed including diuresis/natriuresis, improved cardiac energy metabolism [281], reduction of inflammation [616], and prevention of ischemia reperfusion injury [617] to name a few key mechanisms. Further studies are

needed to fully elucidate a mechanism to explain the observed cardioprotective effects of SGLT2i in the diabetic and nondiabetic failing heart.

Insulin: While insulin is the first-line therapy to treat T1D, it is only used to manage T2D patients when oral hypoglycemic drugs and lifestyle do not establish glycemic control. It has been suggested that heart failure prevalence and cardiovascular mortality is increased in patient with T2D who receive insulin [618]. Evaluation of the impact of insulin therapy on cardiovascular disease in diabetic patients has been the focus of a number of recent clinical trials. For example, the ORIGIN trial (Outcome Reduction With Initial Glargine Intervention) investigated glargine's impact compared to standard care in T2D patients with high cardiovascular risk. The trial data were neutral, and the rates of incident cardiovascular outcomes were similar in the insulin-glargine and standard-care [619]. In addition, the DEVOTE trial (A Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Subjects With Type 2 Diabetes at High Risk of Cardiovascular Events) compared the cardiovascular safety of degludec, ultralong acting insulin, to insulin glargine in patients with T2D and high cardiovascular risk. The study showed that degludec was noninferior to glargine concerning the incidence of major cardiovascular events [620]. While enhancing circulating insulin levels can restore cardiac insulin sensitivity in the failing heart, enhancing cardiac efficiency and reducing cardiovascular mortality, prospective studies that aim to access this possibility directly are currently lacking.

The effect of heart failure drugs on glycemic control

Renin-Aldosterone-Angiotensin inhibitors: ACE inhibitors have been shown to improve insulin resistance and glucose intolerance via increases in GLUT4 translocation (Table 3) [621]. Diabetic mice treated with the ACE inhibitor temocapril show decreases in plasma glucose and insulin levels, increases in skeletal muscle glucose uptake and increases in translocation of GLUT4 to the plasma membrane [621]. In a single blind, cross-over design study in type 2 diabetic patients that had arterial hypertension, the ACE inhibitor captopril increased insulin sensitivity and improved glycemic control [622]. Captopril treatment of diabetic patients also improves glucose control [623]. However, while ACE inhibitor therapy improves glycemic control effects, a case-control study in diabetic patients found that ACE inhibitors are associated with an increase in hospitalization for severe hypoglycemia [624].

Lipid-lowering agents: Statins have a propensity to induce hyperglycemia and have been shown to cause glucose intolerance in both animals and humans. For instance, diabetic rats treated with atorvastatin or simvastatin exhibit hyperglycemia and glucose intolerance [625]. In a meta-analysis of 9 trials of patients treated with statins, mean HbA_{1C} was higher by 0.12%, indicative of a modestly increased risk for diabetes with statin treatment [626]. In another meta-analysis that investigated the effect of statin therapy on HbA_{1C} levels as well as fasting plasma glucose, statins increased HbA_{1C} [627]. Specifically, pitavastatin improved glycemic control while atorvastatin worsened glycemic control [627]. This diabetogenic effect was also recapitulated in a national health screening cohort of non-diabetic individuals taking statins, showing that greater adherence to the use of

statins, specifically atorvastatin, rosuvastatin, pitavastatin and simvastatin, results in increases in fasting glucose levels[628].

ß-blockers: β-adrenergic stimulation promotes insulin and glucagon release while α-adrenergic stimulation inhibits insulin and glucagon secretion . Therefore β-adrenergic receptor antagonism inhibits insulin release and may worsen glycemic control especially during hypoglycemia. The selectivity of the ß-blocker yields distinct metabolic effects and certain ß-blockers can exacerbate hypoglycemic episodes by delaying glucose recover time [629, 630]. A retrospective study that monitored glucose in patients receiving either carvedilol or a selective second-generation ß-blocker (metoprolol or atenolol) found that ß-blockers, specifically metoprolol or atenolol, increase the odds of hypoglycemia in these hospitalized patients [631]. In hypertensive diabetic patients, treatment with propranolol or metoprolol results in mean blood sugar increases of 1.0-1.5 mM [629, 632]. A randomized, double-blind parallel-group trial in patients with diabetes and hypertension showed that metoprolol increases mean HbA_{1C}, but insulin sensitivity is improved with carvedilol treatment[633]. Third generation non-selective β-blockers (carvedilol) possess insulin-sensitizing properties and improve glycemic control, while second generation $β_1$-selective (metoprolol) antagonism worsens glycemic control [634]. To underline the distinct benefits between β-blockers, non-vasodilating β-blockers (metoprolol, propranolol and atenolol) have been shown to worsen glycemic control while vasodilating β-blockers (carvedilol, labetalol, nebivolol) improve glucose profiles .

Aldosterone Antagonists: Enhanced activity of the aldosterone signaling has been implicated in the development of diabetes-induced heart failure via triggering fibrosis and insulin resistance. Treatment of dilated cardiomyopathy patients with the aldosterone antagonist spironolactone resulted in a reduced collagen accumulation in the heart and improved LV function [635]. Likewise, antagonizing aldosterone can improve diastolic function and limit fibrosis in patients with hypertensive cardiomyopathy [636] and metabolic syndrome [637]. Of interest is that eplerenone is shown to limit biomarkers of inflammation and insulin resistance in patients with HIV [638]. Aldosterone antagonists have also shown promising effects by reducing apoptosis and improving diastolic function in murine models of diabetic cardiomyopathy [639-641]. The impact of aldosterone antagonism on diastolic function, cardiac insulin resistance and inflammation in patient with diabetes-induced heart failure is yet to be determine.

Concluding remarks

The pathophysiology of diabetes can affect the heart through multiple mechanisms that cause structural, metabolic, and functional remodeling, leading to a well-acknowledged condition called diabetic cardiomyopathy. Diabetes-induced perturbations in insulin resistance, fuel preference, reactive oxygen species generation, inflammation, cell death pathways, neurohormonal mechanisms, advanced glycated end-products accumulation, lipotoxicity, glucotoxicity and posttranslational modifications contribute to the development of diabetic cardiomyopathies. Targeting these pathways is a potential therapeutic approach to lessening the likelihood of developing diabetic cardiomyopathies.

A number of antidiabetic therapies can also prevent diabetic cardiomyopathy and reverse cardiac dysfunction. These advancements will help achieve personalized treatment for diabetic patients by achieving glycemic control and managing comorbidities and limiting cardiovascular disease. Better clarity of the mechanisms involved in diabetic cardiomyopathy should lead to better therapeutics approaches to treat patients with diabetes and heart failure.

Conflict of Interest: None

References:

1. Organization WH. Noncommunicable diseases country profiles 2018. 2018.
2. Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, Abbastabar H, Abd-Allah L, Abdela J, Abdelalim A, Abdollahpour I, Abdulkader RS, Abebe HT, Abebe M, Abebe Z, Abejie AN, Abera SF, Abil OZ, Abraha HN, Abrham AR, Abu-Raddad LJ, Accrombessi MMK, Acharya D, Adamu AA, Adebayo O, Adedoyin RA, Adekanmbi V, Adookunboh O, Adhena BM, Adib MG, Admasie A, Afshin A, Agarwal G, Agesa KM, Agrawal A, Agrawal S, Ahmadi A, Ahmadi M, Ahmed MB, Ahmed S, Aichour AN, Aichour I, Aichour MTF, Akbari ME, Akinyeniti RO, Akseer N, Al-Aly Z, Al-Eyadhy A, Al-Raddadi RM, Alandab F, Alam K, Alam T, Alebel A, Alene KA, Alijanzadeh M, Alizadeh-Navaei R, Aljunid SM, Alkerwi A, Alla F, Allebeck P, Alonso J, Altirkawi K, Alvis-Guzman N, Amare AT, Aminde LN, Amini E, Ammar W, Amoako YA, Anber NH, Andrei CL, Androudi S, Animut MD, Anjomshoa M, Ansari H, Aniha MG, Antonio CAT, Anwari P, Aremu O, Arnlov J, Arora A, Arora M, Artaman A, Aryal KK, Asayesh H, Asfaw ET, Ataro Z, Atique S, Atre SR, Ausloos M, Avokpaho EFGA, Awasthi A, Quintattilla BPA, Ayele Y, Ayer R, Azzopardi PS, Babazadeh A, Bacha U, Badali H, Badawi A, Bali AG, Ballesteros KE, Banach M, Banerjee K, Bannick MS, Banoub JAM, Barboza MA, Barker-Collo SL, Barnighausen TW, Barquera S, Barrero L, Bassat Q, Base S, Baune BT, Baynes HW, Bazargan-Hejazi S, Beth N, Beghi E, Behzadifar M, Behzadifar M, Bejot Y, Bekele BB, Belaciew AB, Belay E, Belay YA, Bell ML, Bello AK, Bennett DA, Bensenor IM, Berman AF, Bernabe E, Bernstein RS, Bertolacci GJ, Beuran M, Beyranvand T, Bhalla A, Bhattarai S, Bhaumik S, Bhutta ZA, Biadgo B, Biehl MH, Bijani A, Bikbov B, Bilano V, Bililign N, Bin Sayeed MS, Bisanzio D, Biswas T, Blacker BF, Basara BB, Borschmann R, Bosetti C, Bozorgmehr K, Brady OJ, Brant LC, Brayne C, Brazinova A, Breitborde NJK, Brenner H, Briant PS, Britton G, Brugha T, Busse R, Butt ZA, Callender CSKH, Campos-Nonato IR, Rincon JCC, Cano J, Car M, Cardenas R, Carreras G, Carrero JJ, Carter A, Carvalho F, Castaneda-Orjuela CA, Rivas JC, Castle CD, Castro C, Castro F, Catala-Lopez F, Cerin E, Chaiah Y, Chang JC, Chanson FJ, Chaturvedi P, Chiang PPC, Chimed-Ochir O, Chisumpa VH, Chitheet A, Chowdhury R, Christensen H, Christopher DJ, Chiang SC, Cicuttini FM, Ciobanu LG, Cirillo M, Cohen AJ, Cooper LT, Cortesi PA, Cortinovis M, Cousin E, Cowie BC, Criqui MH, Cromwell EA, Crowe CS, Crump JA, Cunningham M, Daba AK, Dadi AF, Dandona L, Dandona R, Dang AK, Dargan PI, Daryani A, Das SK, Das Gupta R, Das Neves J, Dasa TT, Dash AP, Davis AC, Weaver ND, Davitoiu DV, Davletov K, De La Hoz FP, De Neve JW, Degefa MG, Degenhardt L, Degfie TT, Deiparine S, Demoz GT, Demtsu BB, Denova-Gutierrez E, Deribe K, Dervenis N, Jarlais DCD, Dessie GA, Dey S, Dhannaratne SD, Dicker D, Dinberu MT, Ding EL, Dirac MA, Djalalinia S, Dokova K, Ter Doku D, Donnelly CA, Dorsey ER, Doshi PP, Douwes-Schultz D, Doyle KE, Driscoll TR, Dubey M, Dubljanin E, Duken EE, Duncan BB, Duraes AR, Ebrahimi H, Ebrahimpour S, Edessa D, Edvardsson D, Eggen AE, El Bcheraoui C, Zaki ME, El-Khatib Z, Elkout H, Eltinsel CL, Endres M, Endries AY, Er B, Erskine HE, Eshrati B, Eskandarieh

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S, Esmaeili R, Esteghamati A, Fakhar M, Fakhim H, Faramarzi M, Fareed M, Farhadi F, Faninha CSES, Faro A, Farvid MS, Farzadfar F, Farzaei MH, Feign VL, Feigl AB, Fentahun N, Eereshtehnejad SM, Fernandes E, Fernandes JC, Ferrari AJ, Feyissa GT, Filip I, Finegold S, Fischer F, Eitzmaurice C, Foigt NA, Foreman KJ, Fornari C, Frank TD, Fukumoto T, Fuller JE, Fullman N, Furst T, Furtado JM, Futran ND, Gallus S, Garcia-Basteiro AL, Garcia-Gordillo MA, Gardner WM, Gebre AK, Gebrehiwol TT, Gebremedhin AT, Gebremichael B, Gebremichael TG, Gelano TF, Geleijinse JM, Genova-Maleras R, Geramo YCD, Gething PW, Gezae KE, Ghadami MR, Ghadimi R, Falavarjani KG, Ghasemi-Kasman M, Ghimire M, Gibney KB, Gill PS, Gill TK, Gillum RF, Ginawi IA, Giroud M, Giussani G, Goenka S, Goldberg EM, Goli S, Gomez-Dantes H, Gona PN, Gopalani SV, Gorman TM, Goto A, Goulart AC, Gnedovskaya EV, Grada A, Grosso G, Gugnani HC, Guimaraes ALS, Gun N, Gupta PC, Gupta R, Gupta R, Gupta T, Gutierrez RA, Gyawali B, Haagsma JA, Hafezi-Nejad N, Hagos TB, Hailegiyorgis TT, Hailu GB, Haj-Mirzaian A, Haj-Mirzaian A, Hamadeh RR, Hamidi S, Handal MJ, Hankey GJ, Harb HL, Harikrishnan S, Haro JM, Hasan M, Hassankhani H, Hassen HY, Havmoeller R, Hay RJ, Hay SI, He Y, Hedayatizadeh-Omran A, Hegazy MI, Heibati B, Heidari M, Hendrie D, Henok A, Henry NJ, Herteliu C, Heydarpour F, Heydarpour P, Heydarpour S, Hibstu DT, Hoek HW, Hole MK, Red EH, Hoogar P, Hosgood HD, Hosseini SM, Hosseinzadeh M, Hostiuc M, Hostiuc S, Hotez PJ, Hoy DC, Hsiao T, Hu G, Huang JJ, Husseini A, Hussen MM, Hutfless S, Idrisov B, Ilesanmi OS, Iqbal U, Irvani SSN, Irvine CMS, Islam N, Islam SMS, Islami F, Jacobsen KH, Jahangiry L, Jahanmehr N, Jain SK, Jakovlievic M, Jalu MT, James SL, Javanbakht M, Jayatilleke AU, Jeemon P, Jenkins KJ, Jha RP, Jha V, Johnson CO, Johnson SC, Jonas JB, Joshi A, Jozwiak JJ, Jungari SB, Jurisson M, Kabir Z, Kadel R, Kahsay A, Kalani R, Karami M, Matin BK, Karch A, Karerna C, Karimi-Sari H, Kasaeian A, Kassa DH, Kassa GM, Kassa TD, Kassebaum NJ, Katikireddi SV, Kaul A, Kazemi Z, Karyani AK, Kazi DS, Kefale AT, Keiyoro PN, Kemp GR, Kengne AP, Keren A, Kesavachandran CN, Khader YS, Khafaei B, Khafaie MA, Khajavi A, Khalid N, Khalil IA, Khan EA, Khan MS, Khan MA, Khang YH, Khater MM, Khoja AT, Khosravi A, Khosravi MH, Khubchandani J, Kiadaliri AA, Kibret GD, Kidanemariam ZT, Kiirithio DN, Kim D, Kim YE, Kim YJ, Kimokoti RW, Kinfu Y, Kisa A, Kissimova-Skarbek K, Kivimaki M, Knudsen AKS, Kocarnik JM, Kochhar S, Kokubo Y, Kolola T, Kopec JA, Koul PA, Koyanagi A, Kravchenko MA, Krishan K, Defo BK, Bicer BK, Kumar GA, Kumar M, Kumar P, Kutz MJ, Kuzin I, Kyu HH, Lad DP, Lad SD, Lafranconi A, Lal DK, Lalloo R, Lallukka T, Lam JO, Lami FH, Lansingh VC, Lansky S, Larson HJ, Latifi A, Lau KMM, Lazarus JV, Lebedev G, Lee PH, Leigh J, Leili M, Leshargie CT, Li SS, Li YC, Liang J, Lim LL, Lim SS, Limenih MA, Linn S, Liu SW, Liu Y, Lodha R, Lansdale C, Lopez AD, Lorkowski S, Lotufo PA, Lozano R, Lunevicius R, Ma S, Macarayan ERK, Mackay MT, MacLachlan JH, Maddison ER, Nadotto F, Abd El Razek HM, Abd El Razek MM, Maghavani DP, Majdan M, Majdzadeh R, Majeed A, Malekzadeh R, Malta DC, Manda AL, Mandarano LG, Manguerra H, Mansournia MA, Mapoma CC, Marami D, Maravilla JC, Marcenes W, Marczak L, Marks A, Marks GB, Martinez G, Martins-Melo FR, Martopullo I, Marz W, Marron MB, Masci JR, Lylassenburg BB, Mathur MR, Mathur P, Matzopoulos R, Maulik PK, Mazidi M, McAlinden C,

McGrath JJ, McKee M, McMahon BJ, Mehata S, Mehndiratta MM, Mehrotra R, Mehta KM, Mehta V, Mekonnen TC, Melese A, Melku M, Memiah PTN, Memish ZA, Mendoza W, Mengistu DT, Mengistu G, Mensah GA, Mereta ST, Meretoja A, Meretoja TJ, Meshovic T, Mezgebe HB, Miazgowski B, Miazgowski T, Millear AI, Miller TR, Katherine M, Petrie M, Mini GK, Mirabi P, Mirarefin M, Mirica A, Mirrakhimov EM, Misganaw AT, Mitiku H, Moazen B, Mohammad KA, Mohammad M, Mohammadifard N, Mohammed MA, Mohammed S, Mohan V, Mokdad AH, Molokhia M, Monasta L, Moradi G, Moradi-Lakeh M, Moradinazar M, Moraga P, Morawska L, Velasquez IM, Morgado-Da-Costa J, Morrison SD, Moschos MM, Mouodi S, Mousavi SM, Muchie KE, Mueller UO, Mukhopadhyay S, Muller K, Mumford JE, Musa J, Musa KI, Mustafa G, Muthupandian S, Nachega JB, Nagel G, Naheed A, Nahvijou A, Naik G, Nair S, Najafi F, Naldi L, Nam HS, Nangia V, Nansseu JR, Nascirnento BR, Natarajan G, Nearnati N, Negoi I, Negoi RI, Nettpane S, Newton CRJ, Ngalesoni FN, Ngunjiri JW, Nguyen AQ, Nguyen G, Nguyen HT, Nguyen LT, Nguyen LH, Nguyen M, Nguyen TH, Nichols E, Ningnun DNA, Nirayo YL, Nixon MR, Nolutshungu N, Nomura S, Norhelin OF, Noroozi M, Norrving B, Noubiap JJ, Nouri HR, Shiadeh MN, Nowroozi MR, Nyasulu PS, Odell CM, Ofori-Asenso R, Ogbo FA, Oh IH, Oladimeji O, Olagunju AT, Olivares PR, Olsen HE, Olusanya BO, Olusanya JO, Ong KL, Ong SKS, Oren E, Orpana HM, Ortiz A, Ortiz JR, Otstavnov SS, Overland S, Owolabi MO, Ozdemir R, Mahesh PA, Pacella R, Pakhale S, Pakhare AP, Pakpour AH, Pana A, Panda-Jonas S, Pandian JD, Parisi A, Park EK, Parry CDH, Parsian H, Patel S, Pati S, Patton GC, Paturi VR, Paulson KR, Pereira A, Pereira DM, Perico N, Pesudovs K, Petzold M, Phillips MR, Piel FB, Pigott DM, Pillay JD, Pirsaheb M, Pishgar F, Polinder S, Postma MJ, Pourshams A, Poustchi H, Pujar A, Prakash S, Prasad N, Purcell CA, Qorbani M, Quintana H, Quistberg DA, Rade KW, Radfah A, Rafay A, Rafiei A, Rahim F, Rahimi K, Rahimi-Movaghar A, Rahman M, Rahman MHU, Rahman MA, Rai RK, Rajsic S, Ram U, Ranabhat CL, Ranjan P, Rao PC, Rawaf DL, Rawaf S, Razo-Garcia C, Reddy KS, Reiner RC, Reitsma MB, Remuzzi G, Renzaho AMN, Resnikoff S, Rezaei S, Rezaeian S, Rezai MS, Riahi SM, Ribeiro ALP, Rios-Blancas MJ, Roba KT, Roberts NLS, Robinson SR, Roever L, Ronfani L, Roshandel G, Rostami A, Rothenbacher D, Roy A, Rubagotti E, Sachdev PS, Saddik B, Sadeghi E, Safari H, Safdarian M, Safi S, Safiri S, Sagar R, Sahebkar A, Sahraian MA, Salam N, Salama JS, Salamati P, Saldanha RD, Saleem Z, Salimi Y, Salvi SS, Salz I, Sambala EZ, Samy AM, Sanabria J, Sanchez-Nino MD, Santomauro DF, Santos IS, Santos JV, Milicevic MMS, Jose BPS, Sarker AR, Sarmiento-Suarez R, Sarrafzadegan N, Sartorius B, Sarvi S, Sathian B, Satpathy M, Sawant AR, Sawhney M, Saxena S, Sayyah M, Schaeffher E, Schmidt MI, Schneider IJC, Schottker B, Schutte AE, Schwebel DC, Schwendicke F, Scott JG, Sekerija M, Sepanlou SG, Servan-Mori E, Seyedmousavi S, Shabaninejad H, Shackelford KA, Shafieesabet A, Shahbazi M, Shaheen AA, Shaikh MA, Shams-Beyranvand M, Shamsi M, Shamsizadeh M, Sharafi K, Sharif M, Sharif-Alhoseini M, Sharma R, She J, Sheikh A, Shi PL, Shiferaw MS, Shigematsu M, Shiri R, Shirkoohi R, Shiue I, Shokraneh F, Shrine MG, Si S, Siabani S, Siddiqi TJ, Sigfusdottir ID, Sigurvinsdottir R, Silberberg DH, Silva DAS, Silva JP, Da Silva NT, Silveira DBA, Singh JA, Singh NP, Singh PK, Singh V, Sinha DN, Sliwa K, Smith

M, Sobaih BH, Sobhani S, Solangwi E, Soneji SS, Soofi M, Sorensen RJD, Soriano JB, Soyiri IN, Sposato LA, Sreeramareddy CF, Srinivasan V, Stanaway JD, Starodubov VI, Stathopoulou V, Stein DJ, Steiner C, Stewart LG, Stokes MA, Subart ML, Sudaryanto A, Sufiyan MB, Sur PJ, Sutradhar I, Sykes BL, Sylaja PN, Sylte DO, Szoeke CEI, Tabares-Seisdedos R, Tabuchi T, Tadakamadla SK, Takahashi K, Tandon N, Tassew SG, Taveira N, Tehrani-Banihashemi A, Tekalign TG, Tekle MG, Temsah MH, Temsah O, Terkawi AS, Teshale MY, Tesserna B, Tessema GA, Thankappan KR, Thirinavukkarasu S, Thomas N, Thrift AG, Thurston GD, Tilahun B, To QG, Tobe-Gai R, Tonellli M, Topor-Madry R, Torre AE, Tortajada-Cirbes M, Touvier M, Tovani-Palone MR, Tran BX, Tran KB, Tripathi S, Troeger CE, Truelsen TC, Truong NT, Tsadik AG, Tsoi D, Car LT, Tuzcu EM, Tyrovolas S, Ukwaja KN, Whiff I, Undurraga EA, Updike RL, Usman MS, Uthman OA, Uzun SB, Vaduganathan M, Vaezi A, Vaidya G, Valdez PR, Varavikova E, Vasankari TJ, Venketasubramanian N, Villafaina S, Violante FS, Vladimirov SK, Vlassov V, Vollset SE, Vos T, Wagner GR, Wagnew FS, Waheed Y, Wallin MT, Watson JL, Wang YP, Wang YP, Wassie MM, Weiderpass E, Weintraub RG, Weldegebreal E, Weldegwergs KG, Werdecker A, Werkneh AA, West TE, Westerman R, Whiteford HA, Widecka J, Wilner LB, Wilson S, Winkler AS, Wiysonge CS, Wolfe CDA, Wu SL, Wu YC, Wyper GMA, Xavier D, Xu GL, Yadgir S, Yadollahpour A, Jabbari SHY, Yakob B, Yan LJL, Yano Y, Yaseri M, Yasin YJ, Yentur GK, Yeshaneh A, Yimer EM, Yip P, Yirsaw BD, Yisma E, Yonemoto N, Yonga G, Yoon SJ, Yotebieng M, Younis MZ, Yousefifard M, Yu CH, Zadnik V, Zaidi Z, Bin Zaman S, Zamani M, Zare Z, Zeleke AJ, Zenebe ZM, Zhang AL, Zhang K, Zhou MG, Zodpey S, Zuhlke LJ, Naghavi N, Murray CJL, Collaborotors GCD. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;**392**:1736-1788.

3.   Tancredi M, Rosengren A, Svensson AM, Kosiborod M, Pivodic A, Gudbjoornsdottir S, Wedel H, Clements M, Dahlqvist S, Lind M. Excess Mortality among Persons with Type 2 Diabetes. *N Engl J Med* 2015;**373**:1720-1732.

4.   Kiss Z, Rokszin G, Abonyi-Toth Z, Jermendy G, Kempler P, Aradi D, Wittmann I. Dissimilar impact of type 2 diabetes on cardiovascular outcomes according to age categories: a nationwide population study from Hungary. *Cardiovasc Diabetol* 2018;**17**:107.

5.   Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Jordan LC, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, O'Flaherty M, Pandey A, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Spartano NL, Stokes A, Tirschwell DL, Tsao CW, Turakhia MP, VanWagner LB, Wilkins JT, Wong SS, Virani SS, American Heart Association Council on E, Prevention Statistics C, Stroke Statistics S. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circ* 2019;**139**:e56-e528.

6. Dagenais GR, Leong DP, Rangarajan S, Lanas F, Lopez-Jaramillo P, Gupta R, Diaz R, Avezum A, Oliveira GBF, Wielgosz A, Parambath SR, Mony P, Alhabib KF, Temizhan A, Ismail N, Chifamba J, Yeates K, Khatib R, Rahman O, Zatonska K, Kazmi K, Wei L, Zhu J, Rosengren A, Vijayakumar K, Kaur M, Mohan V, Yusufali A, Kelishadi R, Teo KK, Joseph P, Yusuf S. Variations in common diseases, hospital admissions, and deaths in middle-aged adults in 21 countries from five continents (PURE): a prospective cohort study. *Lancet* 2020;**395**:785-794.

7. Low Wang CC, Hess CN, Hiatt WR, Goldfine AB. Clinical Update: Cardiovascular Disease in Diabetes Mellitus: Atherosclerotic Cardiovascular Disease and Heart Failure in Type 2 Diabetes Mellitus - Mechanisms, Management, and Clinical Considerations. *Circ* 2016;**133**:2459-2502.

8. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL. 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-e239.

9. Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. *Int J Cardiol* 2014;**171**:368-376.

10. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. *Nat Rev Cardiol* 2016;**13**:368-378.

11. Association AD. Screening for diabetes. *Diabetes Care* 2002;**25**:s21-s24.

12. Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham study. *JAMA* 1979;**241**:2035-2038.

13. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol* 1993;**22**:6A-13A.

14. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, Malanda B. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract* 2018;**138**:271-281.

15. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, Colagiuri S, Guariguata L, Motala AA, Ogurtsova K, Shaw JE, Bright D, Williams R, Committee IDFDA. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. *Diabetes Res Clin Pract* 2019;**157**:107843.

16. Amos AF, McCarty DJ, Zimmet P. The rising global burden of diabetes and its complications: estimates and projections to the year 2010. *Diabet Med* 1997;**14 Suppl 5**:S1-85.

17. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. *Diabetes Care* 1998;**21**:1414-1431.

18. American Diabetes A. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2020. *Diabetes Care* 2020;**43**:S98-S110.

19. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol* 1974;**34**:29-34.

20. Kannel W, McGee D. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. *Diabetes Care* 1979;**2**:120-126.

21. Gottdiener JS, Arnold AM, Aurigemma GP, Polak JF, Tracy RP, Kitzman DW, Gardin JM, Rutledge JE, Boineau RC. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. *J Am Coll Cardiol* 2000;**35**:1628-1637.

22. Bell DSH. Heart failure - The frequent, forgotten, and often fatal complication of diabetes. *Diabetes Care* 2003;**26**:2433-2441.

23. 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**:105-111.

24. Das SR, Drazner MH, Yancy CW, Stevenson LW, Gersh BJ, Dries DL. Effects of diabetes mellitus and ischemic heart disease on the progression from asymptomatic left ventricular dysfunction to symptomatic heart failure: a retrospective analysis from the Studies of Left Ventricular Dysfunction (SOLVD) Prevention trial. *Am Heart J* 2004;**148**:883-888.

25. De Groote P, Lamblin N, Mouquet F, Plichon D, McFadden E, Van Belle E, Bauters C. Impact of diabetes mellitus on long-term survival in patients with congestive heart failure. *Eur Heart J* 2004;**25**:656-662.

26. Collaboration ERF. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011;**364**:829-841.

27. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998;**339**:229-234.

28. Smith JW, Marcus FI, Serokman R. Prognosis of patients with diabetes mellitus after acute myocardial infarction. *Am J Cardiol* 1984;**54**:718-721.

29. Malmberg K, Ryden L. Myocardial infarction in patients with diabetes mellitus. *Eur Heart J* 1988;**9**:259-264.

30. Janand-Delenne B, Savin B, Habib G, Bory M, Vague P, Lassmann-Vague V. Silent myocardial ischemia in patients with diabetes: who to screen. *Diabetes Care* 1999;**22**:1396-1400.

31. Laakso M. Glycemic control and the risk for coronary heart disease in patients with non-insulin-dependent diabetes mellitus. The Finnish studies. *Ann Intern Med* 1996;**124**:127-130.

32. Iribarren C, Karter AJ, Go AS, Ferrara A, Liu JY, Sidney S, Selby JV. Glycemic control and heart failure among adult patients with diabetes. *Circ* 2001;**103**:2668-2673.

33. 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.

34. Di Bonito P, Cuomo S, Moio N, Sibilio G, Sabatini D, Quattrin S, Capaldo B. Diastolic dysfunction in patients with non-insulin-dependent diabetes mellitus of short duration. *Diabet Med* 1996;**13**:321-324.

35. Schannwell CM, Schneppenheim M, Perings S, Plehn G, Strauer BE. Left ventricular diastolic dysfunction as an early manifestation of diabetic cardiomyopathy. *Cardiology* 2002;**98**:33-39.

36. Raev DC. Which left ventricular function is impaired earlier in the evolution of diabetic cardiomyopathy?: an echocardiographic study of young type I diabetic patients. *Diabetes Care* 1994;**17**:633-639.

37. Zhang H, Zhang Y, Li Z, Liu C, Hou R, Zhu S, Ma N, Zhou L, Liu Y. Left ventricular radial systolic dysfunction in diabetic patients assessed by myocardial acceleration derived from velocity vector imaging. *J Ultrasound Med* 2012;**31**:1179-1186.

38. Shimizu I, Yoshida Y, Katsuno T, Tateno K, Okada S, Moriya J, Yokoyama M, Nojima A, Ito T, Zechner R. p53-induced adipose tissue inflammation is critically involved in the development of insulin resistance in heart failure. *Cell Metab* 2012;**15**:51-64.

39. Wold LE, Ceylan-Isik AF, Fang CX, Yang X, Li SY, Sreejayan N, Privratsky JR, Ren J. Metallothionein alleviates cardiac dysfunction in streptozotocin-induced diabetes: role of Ca2+ cycling proteins, NADPH oxidase, poly(ADP-Ribose) polymerase and myosin heavy chain isozyme. *Free Radic Biol Med* 2006;**40**:1419-1429.

40. Cai L, Wang Y, Zhou G, Chen T, Song Y, Li X, Kang YJ. Attenuation by metallothionein of early cardiac cell death via suppression of mitochondrial oxidative stress results in a prevention of diabetic cardiomyopathy. *J Am Coll Cardiol* 2006;**48**:1688-1697.

41. Buchanan J, Mazumder PK, Hu P, Chakrabarti G, Roberts MW, Yun UJ, Cooksey RC, Litwin SE, Abel ED. Reduced cardiac efficiency and altered substrate metabolism precedes the onset of hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity. *Endocrinol* 2005;**146**:5341-5349.

42. Mazumder PK, O'Neill BT, Roberts MW, Buchanan J, Yun UJ, Cooksey RC, Boudina S, Abel ED. Impaired cardiac efficiency and increased fatty acid oxidation in insulin-resistant ob/ob mouse hearts. *Diabetes* 2004;**53**:2366-2374.

43. Zhang L, Jaswal JS, Ussher JR, Sankaralingam S, Wagg C, Zaugg M, Lopaschuk GD. Cardiac insulin-resistance and decreased mitochondrial energy production precede the development of systolic heart failure after pressure-overload hypertrophy. *Circ Heart Fail* 2013;**6**:1039-1048.

44. Chun L, Junlin Z, Aimin W, Niansheng L, Benmei C, Minxiang L. Inhibition of ceramide synthesis reverses endothelial dysfunction and atherosclerosis in streptozotocin-induced diabetic rats. *Diabetes Res Clin Pract* 2011;**93**:77-85.

45. Rask-Madsen C, Li Q, Freund B, Feather D, Abramov R, Wu IH, Chen K, Yamamoto-Hiraoka J, Goldenbogen J, Sotiropoulos KB, Clermont A, Geraldes P, Dall'Osso C, Wagers AJ, Huang PL, Rekhter M, Scalia R, Kahn CR, King GL. Loss of insulin signaling in vascular endothelial cells accelerates atherosclerosis in apolipoprotein E null mice. *Cell Metab* 2010;**11**:379-389.

46. Zhou YT, Grayburn P, Karim A, Shimabukuro M, Higa M, Baetens D, Orci L, Unger RH. Lipotoxic heart disease in obese rats: implications for human obesity. *Proc Natl Acad Sci U S A* 2000;**97**:1784-1789.

47. Finck BN, Lehman JJ, Leone TC, Welch MJ, Bennett MJ, Kovacs A, Han X, Gross RW, Kozak R, Lopaschuk GD, Kelly DP. The cardiac phenotype induced by PPARalpha overexpression mimics that caused by diabetes mellitus. *J Clin Invest* 2002;**109**:121-130.

48. Zhao X-Y, Hu S-J, Li J, Mou Y, Chen B-P, Xia Q. Decreased cardiac sarcoplasmic reticulum Ca 2+-ATPase activity contributes to cardiac dysfunction in streptozotocin-induced diabetic rats. *J Physiol Biochem* 2006;**62**:1.

49. Trost SU, Belke DD, Bluhm WF, Meyer M, Swanson E, Dillmann WH. Overexpression of the sarcoplasmic reticulum Ca2+-ATPase improves myocardial contractility in diabetic cardiomyopathy. *Diabetes* 2002;**51**:1166-1171.

50. Liu JE, Palmieri V, Roman MJ, Bella JN, Fabsitz R, Howard BV, Welty TK, Lee ET, Devereux RB. The impact of diabetes on left ventricular filling pattern in normotensive and hypertensive adults: the Strong Heart Study. *J Am Coll Cardiol* 2001;**37**:1943-1949.

51. Vasan RS, Levy D. Defining diastolic heart failure: a call for standardized diagnostic criteria. *Circ* 2000;**101**:2118-2121.

52. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, Hochadel M, Komajda M, Lassus J, Lopez-Sendon JL, Ponikowski P, Tavazzi L, EuroHeart Survey I, Heart Failure Association ESoC. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J* 2006;**27**:2725-2736.

53. Maisch B, Alter P, Pankuweit S. Diabetic cardiomyopathy-fact or fiction? *Herz* 2011;**36**:102-114.

54. van Heerebeek L, Hamdani N, Falcao-Pires I, Leite-Moreira AF, Begieneman MP, Bronzwaer JG, van der Velden J, Stienen GJ, Laarman GJ, Somsen A, Verheugt FW, Niessen HW, Paulus WJ. Low myocardial protein kinase G activity in heart failure with preserved ejection fraction. *Circ* 2012;**126**:830-839.

55. Falcao-Pires I, Hamdani N, Borbely A, Gavina C, Schalkwijk CG, van der Velden J, van Heerebeek L, Stienen GJM, Niessen HWM, Leite-Moreira AF, Paulus WJ. Diabetes Mellitus Worsens Diastolic Left Ventricular Dysfunction in Aortic Stenosis Through Altered Myocardial Structure and Cardiomyocyte Stiffness. *Circ* 2011;**124**:1151-1159.

56. Montaigne D, Marechal X, Coisne A, Debry N, Modine T, Fayad G, Potelle C, El Arid J-M, Mouton S, Sebti Y. Myocardial contractile dysfunction is associated with impaired mitochondrial function and dynamics in type 2 diabetic but not in obese patients. *Circ* 2014;**130**:554-564.

57. Savji N, Meijers WC, Bartz TM, Bhambhani V, Cushman M, Nayor M, Kizer JR, Sarma A, Blaha MJ, Gansevoort RT, Gardin JM, Hillege HL, Ji F, Kop WJ, Lau ES, Lee DS, Sadreyev R, van Gilst WH, Wang TJ, Zanni MV, Vasan RS, Allen NB, Psaty BM, van der Harst P, Levy D, Larson M, Shah SJ, de Boer RA, Gottdiener JS, Ho JE. The Association of Obesity and Cardiometabolic Traits With Incident HFpEF and HFrEF. *JACC Heart Fail* 2018;**6**:701-709.

58. Rijzewijk LJ, van der Meer RW, Smit JW, Diamant M, Bax JJ, Hammer S, Romijn JA, de Roos A, Lamb HJ. Myocardial steatosis is an independent predictor of diastolic dysfunction in type 2 diabetes mellitus. *J Am Coll Cardiol* 2008;**52**:1793-1799.

59. Herrero P, Peterson LR, McGill JB, Matthew S, Lesniak D, Dence C, Gropler RJ. Increased myocardial fatty acid metabolism in patients with type 1 diabetes mellitus. *J Am Coll Cardiol* 2006;**47**:598-604.

60. Witman MA, Fjeldstad AS, McDaniel J, Ives SJ, Zhao J, Barrett-O'Keefe Z, Nativi JN, Stehlik J, Wray DW, Richardson RS. Vascular function and the role of oxidative stress in heart failure, heart transplant, and beyond. *Hypertension* 2012;**60**:659-668.

61. Li F, Xu M, Fan Y, Wang Y, Song Y, Cui X, Fu M, Qi B, Han X, Zhou J, Ge J. Diffuse myocardial fibrosis and the prognosis of heart failure with reduced ejection fraction in Chinese patients: a cohort study. *Int J Cardiovasc Imaging* 2020;**36**:671-689.

62. Aoki T, Fukumoto Y, Sugimura K, Oikawa M, Satoh K, Nakano M, Nakayama M, Shimokawa H. Prognostic Impact of Myocardial Interstitial Fibrosis in Non-Ischemic Heart Failure - Comparison Between Preserved and Reduced Ejection Fraction Heart Failure. *Circ J* 2011;**75**:2605-2613.

63. Gottumukkala RV, Lv H, Cornivelli L, Wagers AJ, Kwong RY, Bronson R, Stewart GC, Schulze PC, Chutkow W, Wolpert HA, Lee RT, Lipes MA. Myocardial infarction triggers chronic cardiac autoimmunity in type 1 diabetes. *Sci Transl Med* 2012;**4**:138ra180.

64. Campbell DJ, Somaratne JB, Jenkins AJ, Prior DL, Yii M, Kenny JF, Newcomb AE, Schalkwijk CG, Black MJ, Kelly DJ. Impact of type 2 diabetes and the metabolic syndrome on myocardial structure and microvasculature of men with coronary artery disease. *Cardiovasc Diabetol* 2011;**10**:80.

65. Tschope C, Lam CS. Diastolic heart failure: What we still don't know. Looking for new concepts, diagnostic approaches, and the role of comorbidities. *Herz* 2012;**37**:875-879.

66. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. *Circ* 2003;**107**:714-720.

67. Elesber AA, Redfield MM, Rihal CS, Prasad A, Lavi S, Lennon R, Mathew V, Lerman LO, Lerman A. Coronary endothelial dysfunction and hyperlipidemia are independently associated with diastolic dysfunction in humans. *Am Heart J* 2007;**153**:1081-1087.

68. Amir O, Paz H, Rogowski O, Barshai M, Sagiv M, Shnizer S, Reznick AZ, Amir RE. Serum oxidative stress level correlates with clinical parameters in chronic systolic heart failure patients. *Clin Cardiol* 2009;**32**:199-203.

69. Chaanine AH, Joyce LD, Stulak JM, Maltais S, Joyce DL, Dearani JA, Klaus K, Nair KS, Hajjar RJ, Redfield MM. Mitochondrial Morphology, Dynamics, and Function in Human Pressure Overload or Ischemic Heart Disease With Preserved or Reduced Ejection Fraction. *Circ Heart Fail* 2019;**12**:e005131.

70. Gottdiener JS, McClelland RL, Marshall R, Shemanski L, Furberg CD, Kitzman DW, Cushman M, Polak J, Gardin JM, Gersh BJ, Aurigemma GP, Manolio TA. Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function. The Cardiovascular Health Study. *Ann Intern Med* 2002;**137**:631-639.

71. Westermann D, Rutschow S, Jager S, Linderer A, Anker S, Riad A, Unger T, Schultheiss HP, Pauschinger M, Tschope C. Contributions of inflammation and cardiac matrix metalloproteinase activity to cardiac failure in diabetic cardiomyopathy: the role of angiotensin type 1 receptor antagonism. *Diabetes* 2007;**56**:641-646.

72. Mancia G, Bombelli M, Facchetti R, Madotto F, Corrao G, Trevano FQ, Giannattasio C, Grassi G, Sega R. Long-term risk of diabetes, hypertension and

left ventricular hypertrophy associated with the metabolic syndrome in a general population. *J Hypertens* 2008;**26**:1602-1611.

73. Roy C, Slimani A, de Meester C, Amzulescu M, Pasquet A, Vancraeynest D, Beauloye C, Vanoverschelde JL, Gerber BL, Pouleur AC. Associations and prognostic significance of diffuse myocardial fibrosis by cardiovascular magnetic resonance in heart failure with preserved ejection fraction. *J Cardiovasc Magn Reson* 2018;**20**:55.

74. Kodama S, Fujihara K, Horikawa C, Sato T, Iwanaga M, Yamada T, Kato K, Watanabe K, Shimano H, Izumi T, Sone H. Diabetes mellitus and risk of new-onset and recurrent heart failure: a systematic review and meta-analysis. *ESC Heart Fail* 2020;**7**:2146-2174.

75. Targher G, Dauriz M, Laroche C, Temporelli PL, Hassanein M, Seferovic PM, Drozdz J, Ferrari R, Anker S, Coats A, Filippatos G, Crespo-Leiro MG, Mebazaa A, Piepoli MF, Maggioni AP, Tavazzi L, investigators E-HHL-TR. In-hospital and 1-year mortality associated with diabetes in patients with acute heart failure: results from the ESC-HFA Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017;**19**:54-65.

76. MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, Solomon SD, Granger CB, Swedberg K, Yusuf S, Pfeffer MA, McMurray JJ, Investigators C. 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**:1377-1385.

77. Barasch E, Gottdiener JS, Aurigemma G, Kitzman DW, Han J, Kop WJ, Tracy RP. Association between elevated fibrosis markers and heart failure in the elderly: the cardiovascular health study. *Circ Heart Fail* 2009;**2**:303-310.

78. Hayat SA, Patel B, Khattar RS, Malik RA. Diabetic cardiomyopathy: mechanisms, diagnosis and treatment. *Clin Sci (Lond)* 2004;**107**:539-557.

79. Fang ZY, Prins JB, Marwick TH. Diabetic cardiomyopathy: evidence, mechanisms, and therapeutic implications. *Endocr Rev* 2004;**25**:543-567.

80. Bell DS. Diabetic cardiomyopathy. A unique entity or a complication of coronary artery disease? *Diabetes Care* 1995;**18**:708-714.

81. Wold LE, Ceylan-Isik AF, Ren J. Oxidative stress and stress signaling: menace of diabetic cardiomyopathy. *Acta Pharmacol Sin* 2005;**26**:908-917.

82. Lopaschuk GD. Metabolic abnormalities in the diabetic heart. *Heart Fail Rev* 2002;**7**:149-159.

83. Fukushima A, Lopaschuk GD. Cardiac fatty acid oxidation in heart failure associated with obesity and diabetes. *Biochim Biophys Acta* 2016;**1861**:1525-1534.

84. Karwi Q, Lopaschuk GD. Energy metabolism in patients with diabetes and heart failure. *Heart Metab* 2019:32-36.

85. Symons JD, Abel ED. Lipotoxicity contributes to endothelial dysfunction: a focus on the contribution from ceramide. *Rev Endocr Metab Disord* 2013;**14**:59-68.

86. Falcao-Pires I, Leite-Moreira AF. Diabetic cardiomyopathy: understanding the molecular and cellular basis to progress in diagnosis and treatment. *Heart Fail Rev* 2012;**17**:325-344.

87. Frustaci A, Kajstura J, Chimenti C, Jakoniuk I, Leri A, Maseri A, Nadal-Ginard B, Anversa P. Myocardial cell death in human diabetes. *Circ Res* 2000;**87**:1123-1132.

88. Seferovic PM, Paulus WJ. Clinical diabetic cardiomyopathy: a two-faced disease with restrictive and dilated phenotypes. *Eur Heart J* 2015;**36**:1718-1727, 1727a-1727c.

89. Selvin E, Lazo M, Chen Y, Shen L, Rubin J, McEvoy JW, Hoogeveen RC, Sharrett AR, Ballantyne CM, Coresh J. Diabetes mellitus, prediabetes, and incidence of subclinical myocardial damage. *Circ* 2014;**130**:1374-1382.

90. Hamdani N, Bishu KG, von Frieling-Salewsky M, Redfield MM, Linke WA. Deranged myofilament phosphorylation and function in experimental heart failure with preserved ejection fraction. *Cardiovasc Res* 2013;**97**:464-471.

91. Bahrami H, Bluemke DA, Kronmal R, Bertoni AG, Lloyd-Jones DM, Shahar E, Szklo M, Lima JA. Novel metabolic risk factors for incident heart failure and their relationship with obesity: the MESA (Multi-Ethnic Study of Atherosclerosis) study. *J Am Coll Cardiol* 2008;**51**:1775-1783.

92. Nakamura M, Liu T, Husain S, Zhai P, Warren JS, Hsu CP, Matsuda T, Phiel CJ, Cox JE, Tian B, Li H, Sadoshima J. Glycogen Synthase Kinase-3alpha Promotes Fatty Acid Uptake and Lipotoxic Cardiomyopathy. *Cell Metab* 2019;**29**:1119-1134 e1112.

93. Tsutsui H, Kinugawa S, Matsushima S. Oxidative stress and heart failure. *Am J Physiol Heart Circ Physiol* 2011;**301**:H2181-2190.

94. Jia G, Hill MA, Sowers JR. Diabetic Cardiomyopathy: An Update of Mechanisms Contributing to This Clinical Entity. *Circ Res* 2018;**122**:624-638.

95. Hamblin M, Friedman DB, Hill S, Caprioli RM, Smith HM, Hill MF. Alterations in the diabetic myocardial proteome coupled with increased myocardial oxidative stress underlies diabetic cardiomyopathy. *J Mol Cell Cardiol* 2007;**42**:884-895.

96. Hegab Z, Gibbons S, Neyses L, Mamas MA. Role of advanced glycation end products in cardiovascular disease. *World J Cardiol* 2012;**4**:90-102.

97. Meagher P, Adam M, Civitarese R, Bugyei-Twum A, Connelly KA. Heart Failure With Preserved Ejection Fraction in Diabetes: Mechanisms and Management. *Can J Cardiol* 2018;**34**:632-643.

98. Dei Cas A, Fonarow GC, Gheorghiade M, Butler J. Concomitant diabetes mellitus and heart failure. *Curr Probl Cardiol* 2015;**40**:7-43.

99. Nunoda S, Genda A, Sugihara N, Nakayama A, Mizuno S, Takeda R. Quantitative approach to the histopathology of the biopsied right ventricular myocardium in patients with diabetes mellitus. *Heart Vessels* 1985;**1**:43-47.

100. Di Carli MF, Janisse J, Grunberger G, Ager J. Role of chronic hyperglycemia in the pathogenesis of coronary microvascular dysfunction in diabetes. *J Am Coll Cardiol* 2003;**41**:1387-1393.

101. 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**:300-305.

102. Shapiro LM. Echocardiographic features of impaired ventricular function in diabetes mellitus. *Br Heart J* 1982;**47**:439-444.

103. 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**:870-875.

104. Galderisi M. Diastolic dysfunction and diabetic cardiomyopathy: evaluation by Doppler echocardiography. *J Am Coll Cardiol* 2006;**48**:1548-1551.

105. Park JW, Ziegler AG, Janka HU, Doering W, Mehnert H. Left ventricular relaxation and filling pattern in diabetic heart muscle disease: an echocardiographic study. *Klin Wochenschr* 1988;**66**:773-778.

106. Bouchard A, Sanz N, Botvinick EH, Phillips N, Heilbron D, Byrd BF, Karam JH, Schiller NB. Noninvasive Assessment of Cardiomyopathy in Normotensive Diabetic-Patients between 20 and 50 Years Old. *Am J Med* 1989;**87**:160-166.

107. Shimizu M, Sugihara N, Kita Y, Shimizu K, Shibayama S, Takeda R. Increase in left ventricular chamber stiffness in patients with non-insulin dependent diabetes mellitus. *Jpn Circ J* 1991;**55**:657-664.

108. Giampietro O, Di Bello V, Matteucci E, Talarico L, Ruberti F, Boldrini E, Giorgi D, Giusti C. Erythrocyte Na+/H+ exchange and preclinical abnormalities of the left ventricular diastolic function in normotensive type 1 (insulin-dependent) diabetic patients. *Acta Diabetol* 1997;**34**:223-229.

109. Ruddy TD, Shumak SL, Liu PP, Barnie A, Seawright SJ, McLaughlin PR, Zinman B. The relationship of cardiac diastolic dysfunction to concurrent hormonal and metabolic status in type I diabetes mellitus. *J Clin Endocrinol Metab* 1988;**66**:113-118.

110. Attali JR, Sachs RN, Valensi P, Palsky D, Tellier P, Vulpillat M, Lanfranchi J, Sebaoun J. Asymptomatic diabetic cardiomyopathy: a noninvasive study. *Diabetes Res Clin Pract* 1988;**4**:183-190.

111. Cerutti F, Vigo A, Sacchetti C, Bessone A, Barattia G, Morello M, Casalucci D, Gastaldi L. Evaluation of left ventricular diastolic function in insulin dependent diabetic children by M-mode and Doppler echocardiography. *Panminerva Med* 1994;**36**:109-114.

112. Gokdeniz T, Kalaycioglu E, Aykan AC, Gul I, Boyaci F, Gursoy MO. Effects of non-dipper blood pressure pattern on left ventricular rotational mechanics in hypertensive patients with type 2 diabetes mellitus: a speckle tracking study. *Int J Cardiovasc Imaging* 2014;**30**:57-65.

113. Blessberger H, Binder T. NON-invasive imaging: Two dimensional speckle tracking echocardiography: basic principles. *Heart* 2010;**96**:716-722.

114. Bauer M, Cheng S, Jain M, Ngoy S, Theodoropoulos C, Trujillo A, Lin FC, Liao R. Echocardiographic speckle-tracking based strain imaging for rapid cardiovascular phenotyping in mice. *Circ Res* 2011;**108**:908-916.

115. Biswas M, Sudhakar S, Nanda NC, Buckberg G, Pradhan M, Roomi AU, Gorissen W, Houle H. Two- and three-dimensional speckle tracking echocardiography: clinical applications and future directions. *Echocardiography* 2013;**30**:88-105.

116. Mondillo S, Cameli M, Caputo ML, Lisi M, Palmerini E, Padeletti M, Ballo P. Early detection of left atrial strain abnormalities by speckle-tracking in hypertensive and diabetic patients with normal left atrial size. *J Am Soc Echocardiogr* 2011;**24**:898-908.

117. Li RJ, Yang J, Yang Y, Ma N, Jiang B, Sun QW, Li YJ. Speckle tracking echocardiography in the diagnosis of early left ventricular systolic dysfunction in type II diabetic mice. *BMC Cardiovasc Disord* 2014;**14**:141.

118. Matyas C, Kovacs A, Nemeth BT, Olah A, Braun S, Tokodi M, Barta BA, Benke K, Ruppert M, Lakatos BK, Merkely B, Radovits T. Comparison of speckle-tracking echocardiography with invasive hemodynamics for the detection of characteristic cardiac dysfunction in type-1 and type-2 diabetic rat models. *Cardiovasc Diabetol* 2018;**17**:13.

119. Regan TJ, Ettinger PO, Khan MI, Jesrani MU, Lyons MM, Oldewurtel HA, Weber M. Altered Myocardial-Function and Metabolism in Chronic Diabetes-Mellitus without Ischemia in Dogs. *Circ Res* 1974;**35**:222-237.

120. Semeniuk LM, Kryski AJ, Severson DL. Echocardiographic assessment of cardiac function in diabetic db/db and transgenic db/db-hGLUT4 mice. *Am J Physiol Heart Circ Physiol* 2002;**283**:H976-982.

121. Joffe, II, Travers KE, Perreault-Micale CL, Hampton T, Katz SE, Morgan JP, Douglas PS. Abnormal cardiac function in the streptozotocin-induced non-insulin-dependent diabetic rat: noninvasive assessment with doppler echocardiography and contribution of the nitric oxide pathway. *J Am Coll Cardiol* 1999;**34**:2111-2119.

122. Mizushige K, Yao L, Noma T, Kiyomoto H, Yu Y, Hosomi N, Ohmori K, Matsuo H. Alteration in left ventricular diastolic filling and accumulation of myocardial collagen at insulin-resistant prediabetic stage of a type II diabetic rat model. *Circ* 2000;**101**:899-907.

123. Friedman NE, Levitsky LL, Edidin DV, Vitullo DA, Lacina SJ, Chiemmongkoltip P. Echocardiographic evidence for impaired myocardial performance in children with type I diabetes mellitus. *Am J Med* 1982;**73**:846-850.

124. Iwasaka T, Takahashi N, Nakamura S, Sugiura T, Tarumi N, Kimura Y, Okubo N, Taniguchi H, Matsui Y, Inada M. Residual left ventricular pump function after acute myocardial infarction in NIDDM patients. *Diabetes Care* 1992;**15**:1522-1526.

125. Shapiro LM, Howat AP, Calter MM. Left ventricular function in diabetes mellitus. I: Methodology, and prevalence and spectrum of abnormalities. *Br Heart J* 1981;**45**:122-128.

126. Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Lee ET, Welty TK, Fabsitz RR, Robbins D, Rhoades ER, Howard BV. Impact of diabetes on cardiac structure and function: the strong heart study. *Circ* 2000;**101**:2271-2276.

127. Hoit BD, Castro C, Bultron G, Knight S, Matlib MA. Noninvasive evaluation of cardiac dysfunction by echocardiography in streptozotocin-induced diabetic rats. *J Card Fail* 1999;**5**:324-333.

128. Hayashi K, Okumura K, Matsui H, Murase K, Kamiya H, Saburi Y, Numaguchi Y, Toki Y, Hayakawa T. Involvement of 1,2-diacylglycerol in improvement of heart function by etomoxir in diabetic rats. *Life Sci* 2001;**68**:1515-1526.

129. Rajan S, Gokhale SM. Cardiovascular Function in Patients with Insulin-Dependent Diabetes Mellitus: A Study Using Noninvasive Methods. *Ann N Y Acad Sci* 2002;**958**:425-430.

130. 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.

131. Carugo S, Giannattasio C, Calchera I, Paleari F, Gorgoglione MG, Grappiolo A, Gamba P, Rovaris G, Failla M, Mancia G. Progression of functional and structural cardiac alterations in young normotensive uncomplicated patients with type 1 diabetes mellitus. *J Hypertens* 2001;**19**:1675-1680.

132. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 1991;**114**:345-352.

133. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990;**322**:1561-1566.

134. Solomon SD, Sutton MSJ, Lamas GA, Plappert T, Rouleau JL, Skali H, Moyé L, Braunwald E, Pfeffer MA. Ventricular remodeling does not accompany the development of heart failure in diabetic patients after myocardial infarction. *Circ* 2002;**106**:1251-1255.

135. Paulus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007;**28**:2539-2550.

136. Regan TJ, Lyons MM, Ahmed SS, Levinson GE, Oldewurtel HA, Ahmad MR, Haider B. Evidence for cardiomyopathy in familial diabetes mellitus. *J Clin Invest* 1977;**60**:884-899.

137. Kawaguchi M, Techigawara M, Ishihata T, Asakura T, Saito F, Maehara K, Maruyama Y. A comparison of ultrastructural changes on endomyocardial biopsy specimens obtained from patients with diabetes mellitus with and without hypertension. *Heart Vessels* 1997;**12**:267-274.

138. Van Linthout S, Seeland U, Riad A, Eckhardt O, Hohl M, Dhayat N, Richter U, Fischer JW, Bohm M, Pauschinger M, Schultheiss HP, Tschope C. Reduced MMP-2 activity contributes to cardiac fibrosis in experimental diabetic cardiomyopathy. *Basic Res Cardiol* 2008;**103**:319-327.

139. van Hoeven KH, Factor SM. A comparison of the pathological spectrum of hypertensive, diabetic, and hypertensive-diabetic heart disease. *Circ* 1990;**82**:848-855.

140. Polyakova V, Hein S, Kostin S, Ziegelhoeffer T, Schaper J. Matrix metalloproteinases and their tissue inhibitors in pressure-overloaded human myocardium during heart failure progression. *J Am Coll Cardiol* 2004;**44**:1609-1618.

141. 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**:124-130.

142. Shimizu M, Umeda K, Sugihara N, Yoshio H, Ino H, Takeda R, Okada Y, Nakanishi I. Collagen remodelling in myocardia of patients with diabetes. *J Clin Pathol* 1993;**46**:32-36.

143. Lovic D, Erdine S, Catakoglu AB. How to estimate left ventricular hypertrophy in hypertensive patients. *Anatolian Journal of Cardiology* 2014;**14**:389-395.

144. Aragno M, Mastrocola R, Alloatti G, Vercellinatto I, Bardini P, Geuna S, Catalano MG, Danni O, Boccuzzi G. Oxidative stress triggers cardiac fibrosis in the heart of diabetic rats. *Endocrinol* 2008;**149**:380-388.

145. Riva E, Andreoni G, Bianchi R, Latini R, Luvara G, Jeremic G, Traquandi C, Tuccinardi L. Changes in diastolic function and collagen content in normotensive and hypertensive rats with long-term streptozotocin-induced diabetes. *Pharmacol Res* 1998;**37**:233-240.

146. Spiro MJ, Kumar BRR, Crowley TJ. Myocardial Glycoproteins in Diabetes - Type-Vi Collagen Is a Major Pas-Reactive Extracellular-Matrix Protein. *J Mol Cell Cardiol* 1992;**24**:397-410.

147. Lee AA, Dillmann WH, McCulloch AD, Villarreal FJ. Angiotensin II stimulates the autocrine production of transforming growth factor-β1 in adult rat cardiac fibroblasts. *J Mol Cell Cardiol* 1995;**27**:2347-2357.

148. Asif M, Egan J, Vasan S, Jyothirmayi GN, Masurekar MR, Lopez S, Williams C, Torres RL, Wagle D, Ulrich P, Cerami A, Brines M, Regan TJ. An advanced glycation endproduct cross-link breaker can reverse age-related increases in myocardial stiffness. *Proc Natl Acad Sci U S A* 2000;**97**:2809-2813.

149. Tang M, Zhong M, Shang Y, Lin H, Deng J, Jiang H, Lu H, Zhang Y, Zhang W. Differential regulation of collagen types I and III expression in cardiac fibroblasts by AGEs through TRB3/MAPK signaling pathway. *Cell Mol Life Sci* 2008;**65**:2924-2932.

150. Strauer BE, Motz W, Vogt M, Schwartzkopff B. Impaired coronary flow reserve in NIDDM: a possible role for diabetic cardiopathy in humans. *Diabetes* 1997;**46 Suppl 2**:S119-124.

151. Nitenberg A, Valensi P, Sachs R, Dali M, Aptecar E, Attali JR. Impairment of coronary vascular reserve and ACh-induced coronary vasodilation in diabetic patients with angiographically normal coronary arteries and normal left ventricular systolic function. *Diabetes* 1993;**42**:1017-1025.

152. Pitkänen O-P, Nuutila P, Raitakari OT, Rönnemaa T, Koskinen PJ, Iida H, Lehtimäki TJ, Laine HK, Takala T, Viikari JS. Coronary flow reserve is reduced in young men with IDDM. *Diabetes* 1998;**47**:248-254.

153. Nahser Jr PJ, Brown RE, Oskarsson H, Winniford MD, Rossen JD. Maximal coronary flow reserve and metabolic coronary vasodilation in patients with diabetes mellitus. *Circ* 1995;**91**:635-640.

154. Okon EB, Chung AW, Rauniyar P, Padilla E, Tejerina T, McManus BM, Luo H, van Breemen C. Compromised arterial function in human type 2 diabetic patients. *Diabetes* 2005;**54**:2415-2423.

155. Williams SB, Cusco JA, Roddy MA, Johnstone MT, Creager MA. Impaired nitric oxide-mediated vasodilation in patients with non-insulin-dependent diabetes mellitus. *J Am Coll Cardiol* 1996;**27**:567-574.

156. Marciano C, Galderisi M, Gargiulo P, Acampa W, D'Amore C, Esposito R, Capasso E, Savarese G, Casaretti L, Lo Iudice F, Esposito G, Rengo G, Leosco D, Cuocolo A, Perrone-Filardi P. Effects of type 2 diabetes mellitus on coronary microvascular

function and myocardial perfusion in patients without obstructive coronary artery disease. *Eur J Nucl Med Mol Imag* 2012;**39**:1199-1206.

157. Bagi Z, Koller A, Kaley G. Superoxide-NO interaction decreases flow- and agonist-induced dilations of coronary arterioles in Type 2 diabetes mellitus. *Am J Physiol Heart Circ Physiol* 2003;**285**:H1404-1410.

158. Yokoyama I, Momomura S, Ohtake T, Yonekura K, Nishikawa J, Sasaki Y, Omata M. Reduced myocardial flow reserve in non-insulin-dependent diabetes mellitus. *J Am Coll Cardiol* 1997;**30**:1472-1477.

159. Durante W, Sunahara FA, Sen AK. Effect of diabetes on metabolic coronary dilatation in the rat. *Cardiovasc Res* 1989;**23**:40-45.

160. Candido R, Jandeleit-Dahm KA, Cao Z, Nesteroff SP, Burns WC, Twigg SM, Dilley RJ, Cooper ME, Allen TJ. Prevention of accelerated atherosclerosis by angiotensin-converting enzyme inhibition in diabetic apolipoprotein E-deficient mice. *Circ* 2002;**106**:246-253.

161. Chou E, Suzuma I, Way KJ, Opland D, Clermont AC, Naruse K, Suzuma K, Bowling NL, Vlahos CJ, Aiello LP, King GL. Decreased cardiac expression of vascular endothelial growth factor and its receptors in insulin-resistant and diabetic States: a possible explanation for impaired collateral formation in cardiac tissue. *Circ* 2002;**105**:373-379.

162. Yoon YS, Uchida S, Masuo O, Cejna M, Park JS, Gwon HC, Kirchmair R, Bahlman F, Walter D, Curry C, Hanley A, Isner JM, Losordo DW. Progressive attenuation of myocardial vascular endothelial growth factor expression is a seminal event in diabetic cardiomyopathy - Restoration of microvascular homeostasis and recovery of cardiac function in diabetic cardiomyopathy after replenishment of local vascular endothelial growth factor. *Circ* 2005;**111**:2073-2085.

163. Khazaei M, Fallahzadeh AR, Sharifi MR, Afsharmoghaddam N, Javanmard SH, Salehi E. Effects of diabetes on myocardial capillary density and serum angiogenesis biomarkers in male rats. *Clinics (Sao Paulo)* 2011;**66**:1419-1424.

164. Neglia D, Parodi O, Gallopin M, Sambuceti G, Giorgetti A, Pratali L, Salvadori P, Michelassi C, Lunardi M, Pelosi G, Marzilli M, Labbate A. Myocardial Blood-Flow Response to Pacing Tachycardia and to Dipyridamole Infusion in Patients with Dilated Cardiomyopathy without Overt Heart-Failure - a Quantitative Assessment by Positron Emission Tomography. *Circ* 1995;**92**:796-804.

165. Yarom R, Zirkin H, Stammler G, Rose AG. Human coronary microvessels in diabetes and ischaemia. Morphometric study of autopsy material. *J Pathol* 1992;**166**:265-270.

166. Giordano FJ, Gerber HP, Williams SP, VanBruggen N, Bunting S, Ruiz-Lozano P, Gu YS, Nath AK, Huang Y, Hickey R, Dalton N, Peterson KL, Ross J, Chien KR, Ferrara N. A cardiac myocyte vascular endothelial growth factor paracrine pathway is required to maintain cardiac function. *Proc Natl Acad Sci U S A* 2001;**98**:5780-5785.

167. Angulo J, Rodriguez-Manas L, Peiro C, Neira M, Marin J, Sanchez-Ferrer CF. Impairment of nitric oxide-mediated relaxations in anaesthetized autoperfused streptozotocin-induced diabetic rats. *Naunyn Schmiedebergs Arch Pharmacol* 1998;**358**:529-537.

168. Tesfamariam B, Cohen RA. Free radicals mediate endothelial cell dysfunction caused by elevated glucose. *Am J Physiol* 1992;**263**:H321-326.

169. Wong ND, Rozanski A, Gransar H, Miranda-Peats R, Kang XP, Hayes S, Shaw L, Friedman J, Polk D, Berman DS. Metabolic syndrome and diabetes are associated with an increased likelihood of inducible myocardial ischemia among patients with subclinical atherosclerosis. *Diabetes Care* 2005;**28**:1445-1450.

170. Goyal BR, Mehta AA. Diabetic cardiomyopathy: pathophysiological mechanisms and cardiac dysfuntion. *Hum Exp Toxicol* 2013;**32**:571-590.

171. Bornfeldt KE, Tabas I. Insulin resistance, hyperglycemia, and atherosclerosis. *Cell Metab* 2011;**14**:575-585.

172. Ingelsson E, Sundstrom J, Arnlov J, Zethelius B, Lind L. Insulin resistance and risk of congestive heart failure. *JAMA* 2005;**294**:334-341.

173. Arnlov J, Lind L, Zethelius B, Andren B, Hales CN, Vessby B, Lithell H. Several factors associated with the insulin resistance syndrome are predictors of left ventricular systolic dysfunction in a male population after 20 years of follow-up. *Am Heart J* 2001;**142**:720-724.

174. Karwi QG, Jorg AR, Lopaschuk GD. Allosteric, transcriptional and post-translational control of mitochondrial energy metabolism. *Biochem J* 2019;**476**:1695-1712.

175. Cook SA, Varela-Carver A, Mongillo M, Kleinert C, Khan MT, Leccisotti L, Strickland N, Matsui T, Das S, Rosenzweig A, Punjabi P, Camici PG. Abnormal myocardial insulin signalling in type 2 diabetes and left-ventricular dysfunction. *Eur Heart J* 2010;**31**:100-111.

176. Jia G, DeMarco VG, Sowers JR. Insulin resistance and hyperinsulinaemia in diabetic cardiomyopathy. *Nat Rev Endocrinol* 2016;**12**:144-153.

177. Battiprolu PK, Hojayev B, Jiang N, Wang ZV, Luo X, Iglewski M, Shelton JM, Gerard RD, Rothermel BA, Gillette TG, Lavandero S, Hill JA. Metabolic stress-induced activation of FoxO1 triggers diabetic cardiomyopathy in mice. *J Clin Invest* 2012;**122**:1109-1118.

178. Song R, Peng W, Zhang Y, Lv F, Wu HK, Guo J, Cao Y, Pi Y, Zhang X, Jin L, Zhang M, Jiang P, Liu F, Meng S, Zhang X, Jiang P, Cao CM, Xiao RP. Central role of E3 ubiquitin ligase MG53 in insulin resistance and metabolic disorders. *Nature* 2013;**494**:375-379.

179. Liu F, Song R, Feng Y, Guo J, Chen Y, Zhang Y, Chen T, Wang Y, Huang Y, Li CY, Cao C, Zhang Y, Hu X, Xiao RP. Upregulation of MG53 induces diabetic cardiomyopathy through transcriptional activation of peroxisome proliferation-activated receptor alpha. *Circ* 2015;**131**:795-804.

180. Zhang L, Ussher JR, Oka T, Cadete VJ, Wagg C, Lopaschuk GD. Cardiac diacylglycerol accumulation in high fat-fed mice is associated with impaired insulin-stimulated glucose oxidation. *Cardiovasc Res* 2011;**89**:148-156.

181. Ussher JR, Koves TR, Cadete VJ, Zhang L, Jaswal JS, Swyrd SJ, Lopaschuk DG, Proctor SD, Keung W, Muoio DM, Lopaschuk GD. Inhibition of de novo ceramide synthesis reverses diet-induced insulin resistance and enhances whole-body oxygen consumption. *Diabetes* 2010;**59**:2453-2464.

182. Ussher JR, Folmes CD, Keung W, Fillmore N, Jaswal JS, Cadete VJ, Beker DL, Lam VH, Zhang L, Lopaschuk GD. Inhibition of serine palmitoyl transferase I

reduces cardiac ceramide levels and increases glycolysis rates following diet-induced insulin resistance. *PLoS One* 2012;**7**:e37703.

183. Lopaschuk GD. Metabolic Modulators in Heart Disease: Past, Present, and Future. *Can J Cardiol* 2017;**33**:838-849.

184. Karwi QG, Uddin GM, Ho KL, Lopaschuk GD. Loss of Metabolic Flexibility in the Failing Heart. *Front Cardiovasc Med* 2018;**5**:68.

185. Greenwell AA, Gopal K, Ussher JR. Myocardial Energy Metabolism in Non-ischemic Cardiomyopathy. *Front Physiol* 2020;**11**:570421.

186. Ussher JR, Lopaschuk GD. Cardiac insulin resistance: it's sweeter than you think. *Endocrinol* 2013;**154**:2575-2578.

187. Lopaschuk GD, Russell JC. Myocardial function and energy substrate metabolism in the insulin-resistant JCR:LA corpulent rat. *J Appl Physiol* 1985;**71**:1302-1308.

188. Kota SK, Kota SK, Jammula S, Panda S, Modi KD. Effect of diabetes on alteration of metabolism in cardiac myocytes: therapeutic implications. *Diabetes Technol Ther* 2011;**13**:1155-1160.

189. How OJ, Aasum E, Severson DL, Chan WY, Essop MF, Larsen TS. Increased myocardial oxygen consumption reduces cardiac efficiency in diabetic mice. *Diabetes* 2006;**55**:466-473.

190. Ouwens DM, Diamant M, Fodor M, Habets DDJ, Pelsers M, El Hasnaoui M, Dang ZC, van den Brom CE, Vlasblom R, Rietdijk A, Boer C, Coort SLM, Glatz JFC, Luiken J. Cardiac contractile dysfunction in insulin-resistant rats fed a high-fat diet is associated with elevated CD36-mediated fatty acid uptake and esterification. *Diabetologia* 2007;**50**:1938-1948.

191. Sambandam N, Abrahani MA, St Pierre E, Al-Atar O, Cam MC, Rodrigues B. Localization of lipoprotein lipase in the diabetic heart: regulation by acute changes in insulin. *Arterioscler Thromb Vasc Biol* 1999;**19**:1526-1534.

192. Luiken JJ, Turcotte LP, Bonen A. Protein-mediated palmitate uptake and expression of fatty acid transport proteins in heart giant vesicles. *J Lipid Res* 1999;**40**:1007-1016.

193. Luiken JJ, Arumugam Y, Bell RC, Calles-Escandon J, Tandon NN, Glatz JF, Bonen A. Changes in fatty acid transport and transporters are related to the severity of insulin deficiency. *Am J Physiol Endocrinol Metab* 2002;**283**:E612-621.

194. Carley AN, Atkinson LL, Bonen A, Harper ME, Kunnathu S, Lopaschuk GD, Severson DL. Mechanisms responsible for enhanced fatty acid utilization by perfused hearts from type 2 diabetic db/db mice. *Arch Physiol Biochem* 2007;**113**:65-75.

195. Kim TT, Dyck JR. The role of CD36 in the regulation of myocardial lipid metabolism. *Biochim Biophys Acta* 2016;**1861**:1450-1460.

196. An D, Rodrigues B. Role of changes in cardiac metabolism in development of diabetic cardiomyopathy. *Am J Physiol Heart Circ Physiol* 2006;**291**:H1489-1506.

197. Karwi QG, Jörg AR, Lopaschuk GD. Allosteric, transcriptional and post-translational control of mitochondrial energy metabolism. *Biochem J* 2019;**476**:1695-1712.

198. Varma U, Koutsifeli P, Benson VL, Mellor KM, Delbridge LMD. Molecular mechanisms of cardiac pathology in diabetes - Experimental insights. *Biochim Biophys Acta Mol Basis Dis* 2018;**1864**:1949-1959.

199. Finck BN, Han X, Courtois M, Aimond F, Nerbonne JM, Kovacs A, Gross RW, Kelly DP. A critical role for PPARalpha-mediated lipotoxicity in the pathogenesis of diabetic cardiomyopathy: modulation by dietary fat content. *Proc Natl Acad Sci U S A* 2003;**100**:1226-1231.

200. Kyriazis ID, Hoffman M, Gaignebet L, Lucchese AM, Markopoulou E, Palioura D, Wang C, Bannister TD, Christofidou-Solomidou M, Oka SI, Sadoshima J, Koch WJ, Goldberg IJ, Yang VW, Bialkowska AB, Kararigas G, Drosatos K. KLF5 Is Induced by FOXO1 and Causes Oxidative Stress and Diabetic Cardiomyopathy. *Circ Res* 2021;**128**:335-357.

201. Kalliora C, Kyriazis ID, Oka SI, Lieu MJ, Yue Y, Area-Gomez E, Pol CJ, Tian Y, Mizushima W, Chin A, Scerbo D, Schulze PC, Civelek M, Sadoshima J, Madesh M, Goldberg IJ, Drosatos K. Dual peroxisome-proliferator-activated-receptor-alpha/gamma activation inhibits SIRT1-PGC1alpha axis and causes cardiac dysfunction. *JCI Insight* 2019;**5**.

202. Son NH, Yu S, Tuinei J, Arai K, Hamai H, Homma S, Shulman GI, Abel ED, Goldberg IJ. PPARgamma-induced cardiolipotoxicity in mice is ameliorated by PPARalpha deficiency despite increases in fatty acid oxidation. *J Clin Invest* 2010;**120**:3443-3454.

203. Song S, Attia RR, Connaughton S, Niesen MI, Ness GC, Elam MB, Hori RT, Cook GA, Park EA. Peroxisome proliferator activated receptor alpha (PPARalpha) and PPAR gamma coactivator (PGC-1alpha) induce carnitine palmitoyltransferase IA (CPT-1A) via independent gene elements. *Mol Cell Endocrinol* 2010;**325**:54-63.

204. Rasmussen BB, Holmback UC, Volpi E, Morio-Liondore B, Paddon-Jones D, Wolfe RR. Malonyl coenzyme A and the regulation of functional carnitine palmitoyltransferase-1 activity and fat oxidation in human skeletal muscle. *J Clin Invest* 2002;**110**:1687-1693.

205. Sakamoto J, Barr RL, Kavanagh KM, Lopaschuk GD. Contribution of malonyl-CoA decarboxylase to the high fatty acid oxidation rates seen in the diabetic heart. *American Journal of Physiology-Heart and Circulatory Physiology* 2000;**278**:H1196-H1204.

206. Saddik M, Gamble J, Witters LA, Lopaschuk GD. Acetyl-CoA carboxylase regulation of fatty acid oxidation in the heart. *J Biol Chem* 1993;**268**:25836-25845.

207. Dyck JR, Lopaschuk GD. Glucose metabolism, H+ production and Na+/H+-exchanger mRNA levels in ischemic hearts from diabetic rats. Cardiac Metabolism in Health and Disease: Springer, 1998:85-93.

208. Sakamoto J, Barr RL, Kavanagh KM, Lopaschuk GD. Contribution of malonyl-CoA decarboxylase to the high fatty acid oxidation rates seen in the diabetic heart. *Am J Physiol Heart Circ Physiol* 2000;**278**:H1196-1204.

209. Wende AR. Post-translational modifications of the cardiac proteome in diabetes and heart failure. *Proteomics Clin Appl* 2016;**10**:25-38.

210. Fukushima A, Lopaschuk GD. Acetylation control of cardiac fatty acid beta-oxidation and energy metabolism in obesity, diabetes, and heart failure. *Biochim Biophys Acta* 2016;**1862**:2211-2220.

211. Vadvalkar SS, Baily CN, Matsuzaki S, West M, Tesiram YA, Humphries KM. Metabolic inflexibility and protein lysine acetylation in heart mitochondria of a chronic model of type 1 diabetes. *Biochem J* 2013;**449**:253-261.

212. Sun Y, Tian Z, Liu N, Zhang L, Gao Z, Sun X, Yu M, Wu J, Yang F, Zhao Y, Ren H, Chen H, Zhao D, Wang Y, Dong S, Xu C, Lu F, Zhang W. Exogenous H2S switches cardiac energy substrate metabolism by regulating SIRT3 expression in db/db mice. *J Mol Med (Berl)* 2018;**96**:281-299.

213. Saddik M, Lopaschuk GD. Triacylglycerol turnover in isolated working hearts of acutely diabetic rats. *Can J Physiol Pharmacol* 1994;**72**:1110-1119.

214. Borisov AB, Ushakov AV, Zagorulko AK, Novikov NY, Selivanova KF, Edwards CA, Russell MW. Intracardiac lipid accumulation, lipoatrophy of muscle cells and expansion of myocardial infarction in type 2 diabetic patients. *Micron* 2008;**39**:944-951.

215. O'Donnell JM, Zampino M, Alpert NM, Fasano MJ, Geenen DL, Lewandowski ED. Accelerated triacylglycerol turnover kinetics in hearts of diabetic rats include evidence for compartmented lipid storage. *Am J Physiol Endocrinol Metab* 2006;**290**:E448-455.

216. Paulson DJ, Crass MF, 3rd. Endogenous triacylglycerol metabolism in diabetic heart. *Am J Physiol* 1982;**242**:H1084-1094.

217. Larsen TS, Severson DL. Influence of exogenous fatty acids and ketone bodies on rates of lipolysis in isolated ventricular myocytes from normal and diabetic rats. *Can J Physiol Pharmacol* 1990;**68**:1177-1182.

218. Chauhan UP, Singh VN. Myocardial phospholipid metabolism in alloxan diabetic rats. *Life Sci* 1978;**22**:1771-1776.

219. Lim HY, Wang W, Wessells RJ, Ocorr K, Bodmer R. Phospholipid homeostasis regulates lipid metabolism and cardiac function through SREBP signaling in Drosophila. *Genes Dev* 2011;**25**:189-200.

220. Ovide-Bordeaux S, Bescond-Jacquet A, Grynberg A. Cardiac mitochondrial alterations induced by insulin deficiency and hyperinsulinaemia in rats: targeting membrane homeostasis with trimetazidine. *Clin Exp Pharmacol Physiol* 2005;**32**:1061-1070.

221. Wall SR, Lopaschuk GD. Glucose oxidation rates in fatty acid-perfused isolated working hearts from diabetic rats. *Biochim Biophys Acta* 1989;**1006**:97-103.

222. Nicholl TA, Lopaschuk GD, McNeill JH. Effects of free fatty acids and dichloroacetate on isolated working diabetic rat heart. *Am J Physiol* 1991;**261**:H1053-1059.

223. Garvey WT, Hardin D, Juhaszova M, Dominguez JH. Effects of diabetes on myocardial glucose transport system in rats: implications for diabetic cardiomyopathy. *Am J Physiol* 1993;**264**:H837-844.

224. Hu L, Qiu C, Wang X, Xu M, Shao X, Wang Y. The association between diabetes mellitus and reduction in myocardial glucose uptake: a population-based (18)F-FDG PET/CT study. *BMC Cardiovasc Disord* 2018;**18**:203.

225. Camps M, Castello A, Munoz P, Monfar M, Testar X, Palacin M, Zorzano A. Effect of diabetes and fasting on GLUT-4 (muscle/fat) glucose-transporter expression in insulin-sensitive tissues. Heterogeneous response in heart, red and white muscle. *Biochem J* 1992;**282 (Pt 3)**:765-772.

226. Laughlin MR, Petit WA, Jr., Shulman RG, Barrett EJ. Measurement of myocardial glycogen synthesis in diabetic and fasted rats. *Am J Physiol* 1990;**258**:E184-190.

227. Das I. Studies on glycogen metabolism in normal and diabetic rat heart in vivo. *Can J Biochem* 1973;**51**:637-641.

228. Nakao M, Matsubara T, Sakamoto N. Effects of diabetes on cardiac glycogen metabolism in rats. *Heart Vessels* 1993;**8**:171-175.

229. Yu C, Chen Y, Cline GW, Zhang D, Zong H, Wang Y, Bergeron R, Kim JK, Cushman SW, Cooney GJ, Atcheson B, White MF, Kraegen EW, Shulman GI. Mechanism by which fatty acids inhibit insulin activation of insulin receptor substrate-1 (IRS-1)-associated phosphatidylinositol 3-kinase activity in muscle. *J Biol Chem* 2002;**277**:50230-50236.

230. Ellis BA, Poynten A, Lowy AJ, Furler SM, Chisholm DJ, Kraegen EW, Cooney GJ. Long-chain acyl-CoA esters as indicators of lipid metabolism and insulin sensitivity in rat and human muscle. *Am J Physiol Endocrinol Metab* 2000;**279**:E554-560.

231. Bockus LB, Matsuzaki S, Vadvalkar SS, Young ZT, Giorgione JR, Newhardt MF, Kinter M, Humphries KM. Cardiac Insulin Signaling Regulates Glycolysis Through Phosphofructokinase 2 Content and Activity. *J Am Heart Assoc* 2017;**6**:e007159.

232. Da Silva D, Ausina P, Alencar EM, Coelho WS, Zancan P, Sola-Penna M. Metformin reverses hexokinase and phosphofructokinase downregulation and intracellular distribution in the heart of diabetic mice. *IUBMB Life* 2012;**64**:766-774.

233. Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet* 1963;**1**:785-789.

234. Dewald O, Sharma S, Adrogue J, Salazar R, Duerr GD, Crapo JD, Entman ML, Taegtmeyer H. Downregulation of peroxisome proliferator-activated receptor-alpha gene expression in a mouse model of ischemic cardiomyopathy is dependent on reactive oxygen species and prevents lipotoxicity. *Circ* 2005;**112**:407-415.

235. Mather KJ, Hutchins GD, Perry K, Territo W, Chisholm R, Acton A, Glick-Wilson B, Considine RV, Moberly S, DeGrado TR. Assessment of myocardial metabolic flexibility and work efficiency in human type 2 diabetes using 16-[18F]fluoro-4-thiapalmitate, a novel PET fatty acid tracer. *Am J Physiol Endocrinol Metab* 2016;**310**:E452-460.

236. Rider OJ, Apps A, Miller J, Lau JYC, Lewis AJM, Peterzan MA, Dodd MS, Lau AZ, Trumper C, Gallagher FA, Grist JT, Brindle KM, Neubauer S, Tyler DJ. Noninvasive In Vivo Assessment of Cardiac Metabolism in the Healthy and Diabetic Human Heart Using Hyperpolarized (13)C MRI. *Circ Res* 2020;**126**:725-736.

237. Rijzewijk LJ, van der Meer RW, Lamb HJ, de Jong HW, Lubberink M, Romijn JA, Bax JJ, de Roos A, Twisk JW, Heine RJ, Lammertsma AA, Smit JW, Diamant M. Altered myocardial substrate metabolism and decreased diastolic function in nonischemic human diabetic cardiomyopathy: studies with cardiac positron emission tomography and magnetic resonance imaging. *J Am Coll Cardiol* 2009;**54**:1524-1532.

238. Doria A, Nosadini R, Avogaro A, Fioretto P, Crepaldi G. Myocardial metabolism in type 1 diabetic patients without coronary artery disease. *Diabet Med* 1991;**8 Spec No**:S104-107.

239. Scheuermann-Freestone M, Madsen PL, Manners D, Blamire AM, Buckingham RE, Styles P, Radda GK, Neubauer S, Clarke K. Abnormal cardiac and skeletal muscle energy metabolism in patients with type 2 diabetes. *Circ* 2003;**107**:3040-3046.

240. Neubauer S, Horn M, Cramer M, Harre K, Newell JB, Peters W, Pabst T, Ertl G, Hahn D, Ingwall JS, Kochsiek K. Myocardial phosphocreatine-to-ATP ratio is a predictor of mortality in patients with dilated cardiomyopathy. *Circ* 1997;**96**:2190-2196.

241. Ritchie RH, Abel ED. Basic Mechanisms of Diabetic Heart Disease. *Circ Res* 2020;**126**:1501-1525.

242. Mereweather LJ, Montes Aparicio CN, Heather LC. Positioning Metabolism as a Central Player in the Diabetic Heart. *Journal of Lipid and Atherosclerosis* 2020;**9**:92-109.

243. van den Brom CE, Huisman MC, Vlasblom R, Boontje NM, Duijst S, Lubberink M, Molthoff CF, Lammertsma AA, van der Velden J, Boer C, Ouwens DM, Diamant M. Altered myocardial substrate metabolism is associated with myocardial dysfunction in early diabetic cardiomyopathy in rats: studies using positron emission tomography. *Cardiovasc Diabetol* 2009;**8**:39.

244. Lopaschuk GD, Spafford M. Response of isolated working hearts to fatty acids and carnitine palmitoyltransferase I inhibition during reduction of coronary flow in acutely and chronically diabetic rats. *Circ Res* 1989;**65**:378-387.

245. Lopaschuk GD, Saddik M, Barr R, Huang L, Barker CC, Muzyka RA. Effects of high levels of fatty acids on functional recovery of ischemic hearts from diabetic rats. *American Journal of Physiology-Endocrinology and Metabolism* 2006;**263**:E1046-E1053.

246. Karwi QG, Zhang L, Altamimi TR, Wagg CS, Patel V, Uddin GM, Joerg AR, Padwal RS, Johnstone DE, Sharma A, Oudit GY, Lopaschuk GD. Weight loss enhances cardiac energy metabolism and function in heart failure associated with obesity. *Diabetes Obes Metab* 2019;**21**:1944-1955.

247. Sankaralingam S, Abo Alrob O, Zhang L, Jaswal JS, Wagg CS, Fukushima A, Padwal RS, Johnstone DE, Sharma AM, Lopaschuk GD. Lowering body weight in obese mice with diastolic heart failure improves cardiac insulin sensitivity and function: implications for the obesity paradox. *Diabetes* 2015;**64**:1643-1657.

248. Sun H, Olson KC, Gao C, Prosdocimo DA, Zhou M, Wang Z, Jeyaraj D, Youn JY, Ren S, Liu Y, Rau CD, Shah S, Ilkayeva O, Gui WJ, William NS, Wynn RM, Newgard CB, Cai H, Xiao X, Chuang DT, Schulze PC, Lynch C, Jain MK, Wang Y. Catabolic Defect of Branched-Chain Amino Acids Promotes Heart Failure. *Circ* 2016;**133**:2038-2049.

249. Du X, Li Y, Wang Y, You H, Hui P, Zheng Y, Du J. Increased branched-chain amino acid levels are associated with long-term adverse cardiovascular events in patients with STEMI and acute heart failure. *Life Sci* 2018;**209**:167-172.

250. Lopaschuk GD, Karwi QG, Ho KL, Pherwani S, Ketema EB. Ketone metabolism in the failing heart. *Biochim Biophys Acta Mol Cell Biol Lipids* 2020;**1865**:158813.

251. Voros G, Ector J, Garweg C, Droogne W, Van Cleemput J, Peersman N, Vermeersch P, Janssens S. Increased Cardiac Uptake of Ketone Bodies and Free

Fatty Acids in Human Heart Failure and Hypertrophic Left Ventricular Remodeling. *Circ Heart Fail* 2018;**11**:e004953.

252. 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**:632-644.

253. Brahma MK, Ha CM, Pepin ME, Mia S, Sun Z, Chatham JC, Habegger KM, Abel ED, Paterson AJ, Young ME, Wende AR. Increased Glucose Availability Attenuates Myocardial Ketone Body Utilization. *J Am Heart Assoc* 2020;**9**:e013039.

254. Fillmore N, Wagg CS, Zhang LY, Fukushima A, Lopaschuk GD. Cardiac branched-chain amino acid oxidation is reduced during insulin resistance in the heart. *American Journal of Physiology-Endocrinology and Metabolism* 2018;**315**:E1046-E1052.

255. Uddin GM, Zhang L, Shah S, Fukushima A, Wagg CS, Gopal K, Al Batran R, Pherwani S, Ho KL, Boisvenue J, Karwi QG, Altamimi T, Wishart DS, Dyck JRB, Ussher JR, Oudit GY, Lopaschuk GD. Impaired branched chain amino acid oxidation contributes to cardiac insulin resistance in heart failure. *Cardiovasc Diabetol* 2019;**18**:86.

256. Karwi QG, Zhang L, Wagg CS, Wang W, Ghandi M, Thai D, Yan H, Ussher JR, Oudit GY, Lopaschuk GD. Targeting the glucagon receptor improves cardiac function and enhances insulin sensitivity following a myocardial infarction. *Cardiovasc Diabetol* 2019;**18**:1.

257. Marfella R, Di Filippo C, Portoghese M, Barbieri M, Ferraraccio F, Siniscalchi M, Cacciapuoti F, Rossi F, D'Amico M, Paolisso G. Myocardial lipid accumulation in patients with pressure-overloaded heart and metabolic syndrome. *J Lipid Res* 2009;**50**:2314-2323.

258. McGavock JM, Lingvay I, Zib I, Tillery T, Salas N, Unger R, Levine BD, Raskin P, Victor RG, Szczepaniak LS. Cardiac steatosis in diabetes mellitus: a 1H-magnetic resonance spectroscopy study. *Circ* 2007;**116**:1170-1175.

259. Barchuk M, Schreier L, Lopez G, Cevey A, Baldi J, Fernandez Tome MDC, Goren N, Rubio M, Miksztowicz V, Berg G. Glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1 and angiopoietin-like protein 4 are associated with the increase of lipoprotein lipase activity in epicardial adipose tissue from diabetic patients. *Atherosclerosis* 2019;**288**:51-59.

260. Yang J, Sambandam N, Han X, Gross RW, Courtois M, Kovacs A, Febbraio M, Finck BN, Kelly DP. CD36 deficiency rescues lipotoxic cardiomyopathy. *Circ Res* 2007;**100**:1208-1217.

261. Duncan JG, Bharadwaj KG, Fong JL, Mitra R, Sambandam N, Courtois MR, Lavine KJ, Goldberg IJ, Kelly DP. Rescue of cardiomyopathy in peroxisome proliferator-activated receptor-alpha transgenic mice by deletion of lipoprotein lipase identifies sources of cardiac lipids and peroxisome proliferator-activated receptor-alpha activators. *Circ* 2010;**121**:426-435.

262. Bastie CC, Hajri T, Drover VA, Grimaldi PA, Abumrad NA. CD36 in myocytes channels fatty acids to a lipase-accessible triglyceride pool that is related to cell lipid and insulin responsiveness. *Diabetes* 2004;**53**:2209-2216.

263. Febbraio M, Guy E, Coburn C, Knapp FF, Beets AL, Abumrad NA, Silverstein RL. The impact of overexpression and deficiency of fatty acid translocase (FAT)/CD36. *Mol Cell Biochem* 2002;**239**:193-197.

264. Chiu HC, Kovacs A, Blanton RM, Han X, Courtois M, Weinheimer CJ, Yamada KA, Brunet S, Xu H, Nerbonne JM, Welch MJ, Fettig NM, Sharp TL, Sambandam N, Olson KM, Ory DS, Schaffer JE. Transgenic expression of fatty acid transport protein 1 in the heart causes lipotoxic cardiomyopathy. *Circ Res* 2005;**96**:225-233.

265. Zlobine I, Gopal K, Ussher JR. Lipotoxicity in obesity and diabetes-related cardiac dysfunction. *Biochim Biophys Acta* 2016;**1861**:1555-1568.

266. Takada I, Makishima M. Peroxisome proliferator-activated receptor agonists and antagonists: a patent review (2014-present). *Expert Opin Ther Pat* 2020;**30**:1-13.

267. Dyck JR, Hopkins TA, Bonnet S, Michelakis ED, Young ME, Watanabe M, Kawase Y, Jishage K, Lopaschuk GD. Absence of malonyl coenzyme A decarboxylase in mice increases cardiac glucose oxidation and protects the heart from ischemic injury. *Circ* 2006;**114**:1721-1728.

268. Goldberg IJ, Trent CM, Schulze PC. Lipid metabolism and toxicity in the heart. *Cell Metab* 2012;**15**:805-812.

269. Park TS, Hu YY, Noh HL, Drosatos K, Okajima K, Buchanan J, Tuinei J, Homma S, Jiang XC, Abel ED, Goldberg IJ. Ceramide is a cardiotoxin in lipotoxic cardiomyopathy. *J Lipid Res* 2008;**49**:2101-2112.

270. Ussher JR, Folmes CD, Keung W, Fillmore N, Jaswal JS, Cadete VJ, Beker DL, Lam VH, Zhang L, Lopaschuk GD. Inhibition of serine palmitoyl transferase I reduces cardiac ceramide levels and increases glycolysis rates following diet-induced insulin resistance. *PLoS One* 2012;**7**:22.

271. Inoguchi T, Battan R, Handler E, Sportsman JR, Heath W, King GL. Preferential elevation of protein kinase C isoform beta II and diacylglycerol levels in the aorta and heart of diabetic rats: differential reversibility to glycemic control by islet cell transplantation. *Proc Natl Acad Sci U S A* 1992;**89**:11059-11063.

272. Wang G, Silva J, Krishnamurthy K, Tran E, Condie BG, Bieberich E. Direct binding to ceramide activates protein kinase Czeta before the formation of a pro-apoptotic complex with PAR-4 in differentiating stem cells. *J Biol Chem* 2005;**280**:26415-26424.

273. Chuang TT, LeVine H, 3rd, De Blasi A. Phosphorylation and activation of beta-adrenergic receptor kinase by protein kinase C. *J Biol Chem* 1995;**270**:18660-18665.

274. Drosatos K, Bharadwaj KG, Lymperopoulos A, Ikeda S, Khan R, Hu Y, Agarwal R, Yu S, Jiang H, Steinberg SF, Blaner WS, Koch WJ, Goldberg IJ. Cardiomyocyte lipids impair beta-adrenergic receptor function via PKC activation. *Am J Physiol Endocrinol Metab* 2011;**300**:E489-499.

275. Koch WJ, Rockman HA, Samama P, Hamilton RA, Bond RA, Milano CA, Lefkowitz RJ. Cardiac function in mice overexpressing the beta-adrenergic receptor kinase or a beta ARK inhibitor. *Science* 1995;**268**:1350-1353.

276. Itani SI, Zhou Q, Pories WJ, MacDonald KG, Dohm GL. Involvement of protein kinase C in human skeletal muscle insulin resistance and obesity. *Diabetes* 2000;**49**:1353-1358.

277. Li Y, Soos TJ, Li X, Wu J, Degennaro M, Sun X, Littman DR, Birnbaum MJ, Polakiewicz RD. Protein kinase C Theta inhibits insulin signaling by phosphorylating IRS1 at Ser(1101). *J Biol Chem* 2004;**279**:45304-45307.

278. Suzuki J, Ueno M, Uno M, Hirose Y, Zenimaru Y, Takahashi S, Osuga J, Ishibashi S, Takahashi M, Hirose M, Yamada M, Kraemer FB, Miyamori I. Effects of hormone-sensitive lipase disruption on cardiac energy metabolism in response to fasting and refeeding. *Am J Physiol Endocrinol Metab* 2009;**297**:E1115-1124.

279. Listenberger LL, Han X, Lewis SE, Cases S, Farese RV, Jr., Ory DS, Schaffer JE. Triglyceride accumulation protects against fatty acid-induced lipotoxicity. *Proc Natl Acad Sci U S A* 2003;**100**:3077-3082.

280. Isfort M, Stevens SC, Schaffer S, Jong CJ, Wold LE. Metabolic dysfunction in diabetic cardiomyopathy. *Heart Fail Rev* 2014;**19**:35-48.

281. Verma S, Rawat S, Ho KL, Wagg CS, Zhang LY, Teoh H, Dyck JE, Uddin GM, Oudit GY, Mayoux E, Lehrke M, Marx N, Lopaschuk GD. Empagliflozin Increases Cardiac Energy Production in Diabetes Novel Translational Insights Into the Heart Failure Benefits of SGLT2 Inhibitors. *Jacc-Basic to Translational Science* 2018;**3**:576-587.

282. Amaral N, Okonko DO. Metabolic abnormalities of the heart in type II diabetes. *Diab Vasc Dis Res* 2015;**12**:239-248.

283. Wende AR, Schell JC, Ha CM, Pepin ME, Khalimonchuk O, Schwertz H, Pereira RO, Brahma MK, Tuinei J, Contreras-Ferrat A, Wang L, Andrizzi CA, Olsen CD, Bradley WE, Dell'Italia LJ, Dillmann WH, Litwin SE, Abel ED. Maintaining Myocardial Glucose Utilization in Diabetic Cardiomyopathy Accelerates Mitochondrial Dysfunction. *Diabetes* 2020;**69**:2094-2111.

284. Bugger H, Pfeil K. Mitochondrial ROS in myocardial ischemia reperfusion and remodeling. *Biochim Biophys Acta Mol Basis Dis* 2020;**1866**:165768.

285. Song M, Chen Y, Gong G, Murphy E, Rabinovitch PS, Dorn GW, 2nd. Super-suppression of mitochondrial reactive oxygen species signaling impairs compensatory autophagy in primary mitophagic cardiomyopathy. *Circ Res* 2014;**115**:348-353.

286. Newsholme P, Haber EP, Hirabara SM, Rebelato EL, Procopio J, Morgan D, Oliveira-Emilio HC, Carpinelli AR, Curi R. Diabetes associated cell stress and dysfunction: role of mitochondrial and non-mitochondrial ROS production and activity. *J Physiol* 2007;**583**:9-24.

287. Boudina S, Sena S, Theobald H, Sheng X, Wright JJ, Hu XX, Aziz S, Johnson JI, Bugger H, Zaha VG, Abel ED. Mitochondrial energetics in the heart in obesity-related diabetes: direct evidence for increased uncoupled respiration and activation of uncoupling proteins. *Diabetes* 2007;**56**:2457-2466.

288. Nishikawa T, Edelstein D, Du XL, Yamagishi S, Matsumura T, Kaneda Y, Yorek MA, Beebe D, Oates PJ, Hammes HP, Giardino I, Brownlee M. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. *Nature* 2000;**404**:787-790.

289. Teshima Y, Takahashi N, Nishio S, Saito S, Kondo H, Fukui A, Aoki K, Yufu K, Nakagawa M, Saikawa T. Production of reactive oxygen species in the diabetic heart. Roles of mitochondria and NADPH oxidase. *Circ J* 2014;**78**:300-306.

290. Wilson AJ, Gill EK, Abudalo RA, Edgar KS, Watson CJ, Grieve DJ. Reactive oxygen species signalling in the diabetic heart: emerging prospect for therapeutic targeting. *Heart* 2018;**104**:293-299.

291. Bugger H, Abel ED. Molecular mechanisms of diabetic cardiomyopathy. *Diabetologia* 2014;**57**:660-671.

292. Kaludercic N, Di Lisa F. Mitochondrial ROS Formation in the Pathogenesis of Diabetic Cardiomyopathy. *Front Cardiovasc Med* 2020;**7**:12.

293. Brookes PS, Yoon Y, Robotham JL, Anders MW, Sheu SS. Calcium, ATP, and ROS: a mitochondrial love-hate triangle. *Am J Physiol Cell Physiol* 2004;**287**:C817-833.

294. Yan J, Young ME, Cui L, Lopaschuk GD, Liao R, Tian R. Increased Glucose Uptake and Oxidation in Mouse Hearts Prevent High Fatty Acid Oxidation but Cause Cardiac Dysfunction in Diet-Induced Obesity. *Circ* 2009;**119**:2818-U2131.

295. Santos CX, Raza S, Shah AM. Redox signaling in the cardiomyocyte: From physiology to failure. *Int J Biochem Cell Biol* 2016;**74**:145-151.

296. Sharma A, Tate M, Mathew G, Vince JE, Ritchie RH, de Haan JB. Oxidative Stress and NLRP3-Inflammasome Activity as Significant Drivers of Diabetic Cardiovascular Complications: Therapeutic Implications. *Front Physiol* 2018;**9**:114.

297. Ge Q, Zhao L, Ren XM, Ye P, Hu ZY. LCZ696, an angiotensin receptor-neprilysin inhibitor, ameliorates diabetic cardiomyopathy by inhibiting inflammation, oxidative stress and apoptosis. *Exp Biol Med (Maywood)* 2019;**244**:1028-1039.

298. Luo W, Jin Y, Wu G, Zhu W, Qian Y, Zhang Y, Li J, Zhu A, Liang G. Blockage of ROS and MAPKs-mediated inflammation via restoring SIRT1 by a new compound LF10 prevents type 1 diabetic cardiomyopathy. *Toxicol Appl Pharmacol* 2019;**370**:24-35.

299. Eid RA, Alkhateeb MA, El-Kott AF, Eleawa SM, Zaki MSA, Alaboodi SA, Salem Al-Shudiefat AA, Aldera H, Alnamar NM, Alassiri M, Khalil MA. A high-fat diet rich in corn oil induces cardiac fibrosis in rats by activating JAK2/STAT3 and subsequent activation of ANG II/TGF-1beta/Smad3 pathway: The role of ROS and IL-6 trans-signaling. *J Food Biochem* 2019;**43**:e12952.

300. Yang Y-C, Tsai C-Y, Chen C-L, Kuo C-H, Hou C-W, Cheng S-Y, Aneja R, Huang C-Y, Kuo W-W. Pkcδ activation is involved in ROS-mediated mitochondrial dysfunction and apoptosis in cardiomyocytes Exposed to advanced glycation end products (ages). *Aging Dis* 2018;**9**:647.

301. Liu Q, Wang S, Cai L. Diabetic cardiomyopathy and its mechanisms: Role of oxidative stress and damage. *J Diabetes Investig* 2014;**5**:623-634.

302. Ritchie RH, Love JE, Huynh K, Bernardo BC, Henstridge DC, Kiriazis H, Tham YK, Sapra G, Qin C, Cemerlang N, Boey EJ, Jandeleit-Dahm K, Du XJ, McMullen JR. Enhanced phosphoinositide 3-kinase(p110alpha) activity prevents diabetes-induced cardiomyopathy and superoxide generation in a mouse model of diabetes. *Diabetologia* 2012;**55**:3369-3381.

303. Joseph LC, Barca E, Subramanyam P, Komrowski M, Pajvani U, Colecraft HM, Hirano M, Morrow JP. Inhibition of NAPDH Oxidase 2 (NOX2) Prevents Oxidative Stress and Mitochondrial Abnormalities Caused by Saturated Fat in Cardiomyocytes. *PLoS One* 2016;**11**:e0145750.

304. Wang S, Ding L, Ji H, Xu Z, Liu Q, Zheng Y. The Role of p38 MAPK in the Development of Diabetic Cardiomyopathy. *Int J Mol Sci* 2016;**17**:1037.

305. Huynh K, Bernardo BC, McMullen JR, Ritchie RH. Diabetic cardiomyopathy: mechanisms and new treatment strategies targeting antioxidant signaling pathways. *Pharmacol Ther* 2014;**142**:375-415.

306. Rajesh M, Mukhopadhyay P, Batkai S, Mukhopadhyay B, Patel V, Hasko G, Szabo C, Mabley JG, Liaudet L, Pacher P. Xanthine oxidase inhibitor allopurinol attenuates the development of diabetic cardiomyopathy. *J Cell Mol Med* 2009;**13**:2330-2341.

307. Huynh K, Kiriazis H, Du XJ, Love JE, Gray SP, Jandeleit-Dahm KA, McMullen JR, Ritchie RH. Targeting the upregulation of reactive oxygen species subsequent to hyperglycemia prevents type 1 diabetic cardiomyopathy in mice. *Free Radic Biol Med* 2013;**60**:307-317.

308. De Blasio MJ, Huynh K, Qin C, Rosli S, Kiriazis H, Ayer A, Cemerlang N, Stocker R, Du XJ, McMullen JR, Ritchie RH. Therapeutic targeting of oxidative stress with coenzyme Q10 counteracts exaggerated diabetic cardiomyopathy in a mouse model of diabetes with diminished PI3K(p110alpha) signaling. *Free Radic Biol Med* 2015;**87**:137-147.

309. Heart Outcomes Prevention Evaluation Study I, Yusuf S, Dagenais G, Pogue J, Bosch J, Sleight P. Vitamin E supplementation and cardiovascular events in high-risk patients. *N Engl J Med* 2000;**342**:154-160.

310. Sairam T, Patel AN, Subrahmanian M, Gopalan R, Pogwizd SM, Ramalingam S, Sankaran R, Rajasekaran NS. Evidence for a hyper-reductive redox in a sub-set of heart failure patients. *J Transl Med* 2018;**16**:130.

311. Ilkun O, Wilde N, Tuinei J, Pires KM, Zhu Y, Bugger H, Soto J, Wayment B, Olsen C, Litwin SE, Abel ED. Antioxidant treatment normalizes mitochondrial energetics and myocardial insulin sensitivity independently of changes in systemic metabolic homeostasis in a mouse model of the metabolic syndrome. *J Mol Cell Cardiol* 2015;**85**:104-116.

312. Dietl A, Maack C. Targeting Mitochondrial Calcium Handling and Reactive Oxygen Species in Heart Failure. *Curr Heart Fail Rep* 2017;**14**:338-349.

313. Boudina S, Bugger H, Sena S, O'Neill BT, Zaha VG, Ilkun O, Wright JJ, Mazumder PK, Palfreyman E, Tidwell TJ, Theobald H, Khalimonchuk O, Wayment B, Sheng X, Rodnick KJ, Centini R, Chen D, Litwin SE, Weimer BE, Abel ED. Contribution of impaired myocardial insulin signaling to mitochondrial dysfunction and oxidative stress in the heart. *Circ* 2009;**119**:1272-1283.

314. Ma W, Guo W, Shang F, Li Y, Li W, Liu J, Ma C, Teng J. Bakuchiol Alleviates Hyperglycemia-Induced Diabetic Cardiomyopathy by Reducing Myocardial Oxidative Stress via Activating the SIRT1/Nrf2 Signaling Pathway. *Oxid Med Cell Longev* 2020;**2020**:3732718.

315. Dai DF, Chen T, Szeto H, Nieves-Cintron M, Kutyavin V, Santana LF, Rabinovitch PS. Mitochondrial targeted antioxidant Peptide ameliorates hypertensive cardiomyopathy. *J Am Coll Cardiol* 2011;**58**:73-82.

316. Dai DF, Hsieh EJ, Chen T, Menendez LG, Basisty NB, Tsai L, Beyer RP, Crispin DA, Shulman NJ, Szeto HH, Tian R, MacCoss MJ, Rabinovitch PS. Global proteomics and pathway analysis of pressure-overload-induced heart failure and

its attenuation by mitochondrial-targeted peptides. *Circ Heart Fail* 2013;**6**:1067-1076.

317. Karwi QG, Bornbaum J, Boengler K, Torregrossa R, Whiteman M, Wood ME, Schulz R, Baxter GF. AP39, a mitochondria-targeting hydrogen sulfide (H2 S) donor, protects against myocardial reperfusion injury independently of salvage kinase signalling. *Br J Pharmacol* 2017;**174**:287-301.

318. Gu J, Cheng Y, Wu H, Kong L, Wang S, Xu Z, Zhang Z, Tan Y, Keller BB, Zhou H, Wang Y, Xu Z, Cai L. Metallothionein Is Downstream of Nrf2 and Partially Mediates Sulforaphane Prevention of Diabetic Cardiomyopathy. *Diabetes* 2017;**66**:529-542.

319. Wang JQ, Wang SD, Wang WN, Chen J, Zhang ZG, Zheng Q, Liu Q, Cai L. Protection against diabetic cardiomyopathy is achieved using a combination of sulforaphane and zinc in type 1 diabetic OVE26 mice. *Journal of Cellular and Molecular Medicine* 2019;**23**:6319-6330.

320. Minamiyama Y, Bito Y, Takemura S, Takahashi Y, Kodai S, Mizuguchi S, Nishikawa Y, Suehiro S, Okada S. Calorie restriction improves cardiovascular risk factors via reduction of mitochondrial reactive oxygen species in type II diabetic rats. *J Pharmacol Exp Ther* 2007;**320**:535-543.

321. Tian C, Gao L, Zhang A, Hackfort BT, Zucker IH. Therapeutic Effects of Nrf2 Activation by Bardoxolone Methyl in Chronic Heart Failure. *J Pharmacol Exp Ther* 2019;**371**:642-651.

322. Usui M, Matsuoka H, Miyazaki H, Ueda S, Okuda S, Imaizumi T. Increased endogenous nitric oxide synthase inhibitor in patients with congestive heart failure. *Life Sci* 1998;**62**:2425-2430.

323. Ge ZD, Lian QQ, Mao XW, Xia ZY. Current Status and Challenges of NRF2 as a Potential Therapeutic Target for Diabetic Cardiomyopathy. *Int Heart J* 2019;**60**:512-520.

324. Yang H, Xu W, Zhou Z, Liu J, Li X, Chen L, Weng J, Yu Z. Curcumin attenuates urinary excretion of albumin in type II diabetic patients with enhancing nuclear factor erythroid-derived 2-like 2 (Nrf2) system and repressing inflammatory signaling efficacies. *Exp Clin Endocrinol Diabetes* 2015;**123**:360-367.

325. Cheng D, Li W, Wang L, Lin T, Poiani G, Wassef A, Hudlikar R, Ondar P, Brunetti L, Kong AN. Pharmacokinetics, Pharmacodynamics, and PKPD Modeling of Curcumin in Regulating Antioxidant and Epigenetic Gene Expression in Healthy Human Volunteers. *Mol Pharm* 2019;**16**:1881-1889.

326. Bhaumik S, Jyothi MD, Khar A. Differential modulation of nitric oxide production by curcumin in host macrophages and NK cells. *FEBS Lett* 2000;**483**:78-82.

327. Jung KK, Lee HS, Cho JY, Shin WC, Rhee MH, Kim TG, Kang JH, Kim SH, Hong S, Kang SY. Inhibitory effect of curcumin on nitric oxide production from lipopolysaccharide-activated primary microglia. *Life Sci* 2006;**79**:2022-2031.

328. Kado S, Nagase T, Nagata N. Circulating levels of interleukin-6, its soluble receptor and interleukin-6/interleukin-6 receptor complexes in patients with type 2 diabetes mellitus. *Acta Diabetol* 1999;**36**:67-72.

329. Muller S, Martin S, Koenig W, Hanifi-Moghaddam P, Rathmann W, Haastert B, Giani G, Illig T, Thorand B, Kolb H. Impaired glucose tolerance is associated with

increased serum concentrations of interleukin 6 and co-regulated acute-phase proteins but not TNF-alpha or its receptors. *Diabetologia* 2002;**45**:805-812.

330. Pickup JC, Chusney GD, Thomas SM, Burt D. Plasma interleukin-6, tumour necrosis factor alpha and blood cytokine production in type 2 diabetes. *Life Sci* 2000;**67**:291-300.

331. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. *Nat Rev Immunol* 2011;**11**:98-107.

332. Dinh W, Futh R, Nickl W, Krahn T, Ellinghaus P, Scheffold T, Bansemir L, Bufe A, Barroso MC, Lankisch M. Elevated plasma levels of TNF-alpha and interleukin-6 in patients with diastolic dysfunction and glucose metabolism disorders. *Cardiovasc Diabetol* 2009;**8**:58.

333. 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**:339-351.

334. Frieler RA, Mortensen RM. Immune cell and other noncardiomyocyte regulation of cardiac hypertrophy and remodeling. *Circ* 2015;**131**:1019-1030.

335. Mann DL. Innate immunity and the failing heart: the cytokine hypothesis revisited. *Circ Res* 2015;**116**:1254-1268.

336. Tan Y, Zhang Z, Zheng C, Wintergerst KA, Keller BB, Cai L. Mechanisms of diabetic cardiomyopathy and potential therapeutic strategies: preclinical and clinical evidence. *Nat Rev Cardiol* 2020;**17**:585-607.

337. Ha T, Li Y, Hua F, Ma J, Gao X, Kelley J, Zhao A, Haddad GE, Williams DL, William Browder I, Kao RL, Li C. Reduced cardiac hypertrophy in toll-like receptor 4-deficient mice following pressure overload. *Cardiovasc Res* 2005;**68**:224-234.

338. Tao A, Song J, Lan T, Xu X, Kvietys P, Kao R, Martin C, Rui T. Cardiomyocyte-fibroblast interaction contributes to diabetic cardiomyopathy in mice: Role of HMGB1/TLR4/IL-33 axis. *Biochim Biophys Acta* 2015;**1852**:2075-2085.

339. Lorenzo O, Picatoste B, Ares-Carrasco S, Ramirez E, Egido J, Tunon J. Potential role of nuclear factor kappaB in diabetic cardiomyopathy. *Mediators Inflamm* 2011;**2011**:652097.

340. Gordon JW, Shaw JA, Kirshenbaum LA. Multiple facets of NF-kappaB in the heart: to be or not to NF-kappaB. *Circ Res* 2011;**108**:1122-1132.

341. Frati G, Schirone L, Chimenti I, Yee D, Biondi-Zoccai G, Volpe M, Sciarretta S. An overview of the inflammatory signalling mechanisms in the myocardium underlying the development of diabetic cardiomyopathy. *Cardiovasc Res* 2017;**113**:378-388.

342. Varga ZV, Giricz Z, Liaudet L, Hasko G, Ferdinandy P, Pacher P. Interplay of oxidative, nitrosative/nitrative stress, inflammation, cell death and autophagy in diabetic cardiomyopathy. *Biochim Biophys Acta* 2015;**1852**:232-242.

343. Palomer X, Salvado L, Barroso E, Vazquez-Carrera M. An overview of the crosstalk between inflammatory processes and metabolic dysregulation during diabetic cardiomyopathy. *Int J Cardiol* 2013;**168**:3160-3172.

344. Condorelli G, Morisco C, Latronico MV, Claudio PP, Dent P, Tsichlis P, Condorelli G, Frati G, Drusco A, Croce CM, Napoli C. TNF-alpha signal transduction in rat neonatal cardiac myocytes: definition of pathways generating from the TNF-alpha receptor. *FASEB J* 2002;**16**:1732-1737.

345. Kawano S, Kubota T, Monden Y, Kawamura N, Tsutsui H, Takeshita A, Sunagawa K. Blockade of NF-kappaB ameliorates myocardial hypertrophy in response to chronic infusion of angiotensin II. *Cardiovasc Res* 2005;**67**:689-698.

346. Honsho S, Nishikawa S, Amano K, Zen K, Adachi Y, Kishita E, Matsui A, Katsume A, Yamaguchi S, Nishikawa K, Isoda K, Riches DW, Matoba S, Okigaki M, Matsubara H. Pressure-mediated hypertrophy and mechanical stretch induces IL-1 release and subsequent IGF-1 generation to maintain compensative hypertrophy by affecting Akt and JNK pathways. *Circ Res* 2009;**105**:1149-1158.

347. Zhao L, Cheng G, Jin R, Afzal MR, Samanta A, Xuan YT, Girgis M, Elias HK, Zhu Y, Davani A, Yang Y, Chen X, Ye S, Wang OL, Chen L, Hauptman J, Vincent RJ, Dawn B. Deletion of Interleukin-6 Attenuates Pressure Overload-Induced Left Ventricular Hypertrophy and Dysfunction. *Circ Res* 2016;**118**:1918-1929.

348. Matsumoto-Ida M, Takimoto Y, Aoyama T, Akao M, Takeda T, Kita T. Activation of TGF-beta1-TAK1-p38 MAPK pathway in spared cardiomyocytes is involved in left ventricular remodeling after myocardial infarction in rats. *Am J Physiol Heart Circ Physiol* 2006;**290**:H709-715.

349. Lim JY, Park SJ, Hwang HY, Park EJ, Nam JH, Kim J, Park SI. TGF-beta1 induces cardiac hypertrophic responses via PKC-dependent ATF-2 activation. *J Mol Cell Cardiol* 2005;**39**:627-636.

350. Haudek SB, Taffet GE, Schneider MD, Mann DL. TNF provokes cardiomyocyte apoptosis and cardiac remodeling through activation of multiple cell death pathways. *J Clin Invest* 2007;**117**:2692-2701.

351. Kawamura N, Kubota T, Kawano S, Monden Y, Feldman AM, Tsutsui H, Takeshita A, Sunagawa K. Blockade of NF-kappaB improves cardiac function and survival without affecting inflammation in TNF-alpha-induced cardiomyopathy. *Cardiovasc Res* 2005;**66**:520-529.

352. Liu Z, Zhao N, Zhu H, Zhu S, Pan S, Xu J, Zhang X, Zhang Y, Wang J. Circulating interleukin-1beta promotes endoplasmic reticulum stress-induced myocytes apoptosis in diabetic cardiomyopathy via interleukin-1 receptor-associated kinase-2. *Cardiovasc Diabetol* 2015;**14**:125.

353. Mezzaroma E, Toldo S, Farkas D, Seropian IM, Van Tassell BW, Salloum FN, Kannan HR, Menna AC, Voelkel NF, Abbate A. The inflammasome promotes adverse cardiac remodeling following acute myocardial infarction in the mouse. *Proc Natl Acad Sci U S A* 2011;**108**:19725-19730.

354. Xie Y, Huang Y, Ling X, Qin H, Wang M, Luo B. Chemerin/CMKLR1 Axis Promotes Inflammation and Pyroptosis by Activating NLRP3 Inflammasome in Diabetic Cardiomyopathy Rat. *Front Physiol* 2020;**11**:381.

355. Zhang Y, Wang JH, Zhang YY, Wang YZ, Wang J, Zhao Y, Jin XX, Xue GL, Li PH, Sun YL, Huang QH, Song XT, Zhang ZR, Gao X, Yang BF, Du ZM, Pan ZW. Deletion of interleukin-6 alleviated interstitial fibrosis in streptozotocin-induced diabetic cardiomyopathy of mice through affecting TGFbeta1 and miR-29 pathways. *Sci Rep* 2016;**6**:23010.

356. Venkatachalam K, Venkatesan B, Valente AJ, Melby PC, Nandish S, Reusch JE, Clark RA, Chandrasekar B. WISP1, a pro-mitogenic, pro-survival factor, mediates tumor necrosis factor-alpha (TNF-alpha)-stimulated cardiac fibroblast proliferation

but inhibits TNF-alpha-induced cardiomyocyte death. *J Biol Chem* 2009;**284**:14414-14427.

357. Ko HJ, Zhang Z, Jung DY, Jun JY, Ma Z, Jones KE, Chan SY, Kim JK. Nutrient stress activates inflammation and reduces glucose metabolism by suppressing AMP-activated protein kinase in the heart. *Diabetes* 2009;**58**:2536-2546.

358. Palomer X, Alvarez-Guardia D, Rodriguez-Calvo R, Coll T, Laguna JC, Davidson MM, Chan TO, Feldman AM, Vazquez-Carrera M. TNF-alpha reduces PGC-1alpha expression through NF-kappaB and p38 MAPK leading to increased glucose oxidation in a human cardiac cell model. *Cardiovasc Res* 2009;**81**:703-712.

359. Alvarez-Guardia D, Palomer X, Coll T, Davidson MM, Chan TO, Feldman AM, Laguna JC, Vazquez-Carrera M. The p65 subunit of NF-kappaB binds to PGC-1alpha, linking inflammation and metabolic disturbances in cardiac cells. *Cardiovasc Res* 2010;**87**:449-458.

360. Bajpai A, Tilley DG. The Role of Leukocytes in Diabetic Cardiomyopathy. *Front Physiol* 2018;**9**:1547.

361. Thaik CM, Calderone A, Takahashi N, Colucci WS. Interleukin-1 beta modulates the growth and phenotype of neonatal rat cardiac myocytes. *J Clin Invest* 1995;**96**:1093-1099.

362. Finkel MS, Oddis CV, Jacob TD, Watkins SC, Hattler BG, Simmons RL. Negative inotropic effects of cytokines on the heart mediated by nitric oxide. *Science* 1992;**257**:387-389.

363. Noh H, Yu MR, Kim HJ, Lee JH, Park BW, Wu IH, Matsumoto M, King GL. Beta 2-adrenergic receptor agonists are novel regulators of macrophage activation in diabetic renal and cardiovascular complications. *Kidney Int* 2017;**92**:101-113.

364. Zhou X, Ma L, Habibi J, Whaley-Connell A, Hayden MR, Tilmon RD, Brown AN, Kim JA, Demarco VG, Sowers JR. Nebivolol improves diastolic dysfunction and myocardial remodeling through reductions in oxidative stress in the Zucker obese rat. *Hypertension* 2010;**55**:880-888.

365. Hayden MR, Habibi J, Joginpally T, Karuparthi PR, Sowers JR. Ultrastructure Study of Transgenic Ren2 Rat Aorta - Part 1: Endothelium and Intima. *Cardiorenal Med* 2012;**2**:66-82.

366. Nozynski J, Zakliczynski M, Konecka-Mrowka D, Przybylski R, Zembala M, Zielinska T, Mrowka A, Lange D, Zembala-Nozynska E, Nikiel B, Mlynarczyk-Liszka J. Advanced glycation end-products in myocardium-supported vessels: effects of heart failure and diabetes mellitus. *J Heart Lung Transplant* 2011;**30**:558-564.

367. Bodiga VL, Eda SR, Bodiga S. Advanced glycation end products: role in pathology of diabetic cardiomyopathy. *Heart Fail Rev* 2014;**19**:49-63.

368. Kumari K, Sahib MK. Susceptibility of different rat tissues to non-enzymatic protein glycosylation in experimental diabetes. *Indian J Exp Biol* 1993;**31**:194-195.

369. Nożyński J, Zakliczyński M, Konecka-Mrowka D, Zielinska T, Zakliczynska H, Nikiel B, Mlynarczyk-Liszka J, Mrowka A, Zembala-Nozynska E, Pijet M, Rdzanowska K, Lange D, Przybylski R, Zembala M. Advanced glycation end product accumulation in the cardiomyocytes of heart failure patients with and without diabetes. *Ann Transplant* 2012;**17**:53-61.

370. Schalkwijk CG, Baidoshvili A, Stehouwer CD, van Hinsbergh VW, Niessen HW. Increased accumulation of the glycoxidation product Nepsilon-(carboxymethyl)lysine in hearts of diabetic patients: generation and characterisation of a monoclonal anti-CML antibody. *Biochim Biophys Acta* 2004;**1636**:82-89.

371. Candido R, Forbes JM, Thomas MC, Thallas V, Dean RG, Burns WC, Tikellis C, Ritchie RH, Twigg SM, Cooper ME, Burrell LM. A breaker of advanced glycation end products attenuates diabetes-induced myocardial structural changes. *Circ Res* 2003;**92**:785-792.

372. Liu J, Masurekar MR, Vatner DE, Jyothirmayi GN, Regan TJ, Vatner SF, Meggs LG, Malhotra A. Glycation end-product cross-link breaker reduces collagen and improves cardiac function in aging diabetic heart. *Am J Physiol Heart Circ Physiol* 2003;**285**:H2587-2591.

373. Yilmaz S, Canpolat U, Aydogdu S, Abboud HE. Diabetic Cardiomyopathy; Summary of 41 Years. *Korean Circ J* 2015;**45**:266-272.

374. Ko SY, Chang SS, Lin IH, Chen HI. Suppression of antioxidant Nrf-2 and downstream pathway in H9c2 cells by advanced glycation end products (AGEs) via ERK phosphorylation. *Biochimie* 2015;**118**:8-14.

375. Hou J, Zheng D, Fung G, Deng H, Chen L, Liang J, Jiang Y, Hu Y. Mangiferin suppressed advanced glycation end products (AGEs) through NF-κB deactivation and displayed anti-inflammatory effects in streptozotocin and high fat diet-diabetic cardiomyopathy rats. *Can J Physiol Pharmacol* 2016;**94**:332-340.

376. Yuan Q, Zhou QY, Liu D, Yu L, Zhan L, Li XJ, Peng HY, Zhang XL, Yuan XC. Advanced glycation end-products impair Na(+)/K(+)-ATPase activity in diabetic cardiomyopathy: role of the adenosine monophosphate-activated protein kinase/sirtuin 1 pathway. *Clin Exp Pharmacol Physiol* 2014;**41**:127-133.

377. Aragno M, Mastrocola R, Medana C, Catalano MG, Vercellinatto I, Danni O, Boccuzzi G. Oxidative stress-dependent impairment of cardiac-specific transcription factors in experimental diabetes. *Endocrinol* 2006;**147**:5967-5974.

378. Ma H, Li SY, Xu P, Babcock SA, Dolence EK, Brownlee M, Li J, Ren J. Advanced glycation endproduct (AGE) accumulation and AGE receptor (RAGE) up-regulation contribute to the onset of diabetic cardiomyopathy. *J Cell Mol Med* 2009;**13**:1751-1764.

379. Nielsen JM, Kristiansen SB, Norregaard R, Andersen CL, Denner L, Nielsen TT, Flyvbjerg A, Botker HE. Blockage of receptor for advanced glycation end products prevents development of cardiac dysfunction in db/db type 2 diabetic mice. *Eur J Heart Fail* 2009;**11**:638-647.

380. Torres CR, Hart GW. Topography and polypeptide distribution of terminal N-acetylglucosamine residues on the surfaces of intact lymphocytes. Evidence for O-linked GlcNAc. *J Biol Chem* 1984;**259**:3308-3317.

381. Marshall S, Bacote V, Traxinger RR. Discovery of a metabolic pathway mediating glucose-induced desensitization of the glucose transport system. Role of hexosamine biosynthesis in the induction of insulin resistance. *J Biol Chem* 1991;**266**:4706-4712.

382. Gibb AA, Lorkiewicz PK, Zheng Y-T, Zhang X, Bhatnagar A, Jones SP, Hill BG. Integration of flux measurements to resolve changes in anabolic and catabolic metabolism in cardiac myocytes. *Biochem J* 2017;**474**:2785-2801.

383. Olson AK, Bouchard B, Zhu WZ, Chatham JC, Des Rosiers C. First characterization of glucose flux through the hexosamine biosynthesis pathway (HBP) in ex vivo mouse heart. *J Biol Chem* 2020;**295**:2018-2033.

384. Hart GW, Slawson C, Ramirez-Correa G, Lagerlof O. Cross Talk Between O-GlcNAcylation and Phosphorylation: Roles in Signaling, Transcription, and Chronic Disease. *Annual Review of Biochemistry, Vol 80* 2011;**80**:825-858.

385. Snow CM, Senior A, Gerace L. Monoclonal antibodies identify a group of nuclear pore complex glycoproteins. *J Cell Biol* 1987;**104**:1143-1156.

386. Chatham JC, Young ME, Zhang JH. Reprint of: Role of O-linked N-acetylglucosamine (O-GlcNAc) modification of proteins in diabetic cardiovascular complications. *Curr Opin Pharmacol* 2020;**54**:209-220.

387. Prakoso D, Kiriazis H, Tate M, Qian H, Deo M, Parry L, Gregorevic P, Du X, Chatham J, De Blasio M. 5213 Manipulation of cardiac O-GlcNAc modification alters cardiac function and remodelling in the setting of diabetic cardiomyopathy. *Eur Heart J* 2018;**39**:ehy566. 5213.

388. Erickson JR, Pereira L, Wang L, Han G, Ferguson A, Dao K, Copeland RJ, Despa F, Hart GW, Ripplinger CM, Bers DM. Diabetic hyperglycaemia activates CaMKII and arrhythmias by O-linked glycosylation. *Nature* 2013;**502**:372-376.

389. Lehman DM, Fu D-J, Freeman AB, Hunt KJ, Leach RJ, Johnson-Pais T, Hamlington J, Dyer TD, Arya R, Abboud H. A single nucleotide polymorphism in mgea5 encoding o-glcnac–selective n-acetyl-β-d glucosaminidase is associated with type 2 diabetes in mexican americans. *Diabetes* 2005;**54**:1214-1221.

390. Duggirala R, Blangero J, Almasy L, Dyer TD, Williams KL, Leach RJ, O'Connell P, Stern MP. Linkage of type 2 diabetes mellitus and of age at onset to a genetic location on chromosome 10q in Mexican Americans. *Am J Hum Genet* 1999;**64**:1127-1140.

391. Han I, Kudlow JE. Reduced O glycosylation of Sp1 is associated with increased proteasome susceptibility. *Molecular and Cellular Biology* 1997;**17**:2550-2558.

392. Du XL, Edelstein D, Dimmeler S, Ju QD, Sui C, Brownlee M. Hyperglycemia inhibits endothelial nitric oxide synthase activity by posttranslational modification at the Akt site. *J Clin Invest* 2001;**108**:1341-1348.

393. Akimoto Y, Kreppel LK, Hirano H, Hart GW. Hyperglycemia and the O-GlcNAc transferase in rat aortic smooth muscle cells: elevated expression and altered patterns of O-GlcNAcylation. *Arch Biochem Biophys* 2001;**389**:166-175.

394. Ma J, Banerjee P, Whelan SA, Liu T, Wei AC, Ramirez-Correa G, McComb ME, Costello CE, O'Rourke B, Murphy A, Hart GW. Comparative Proteomics Reveals Dysregulated Mitochondrial O-GlcNAcylation in Diabetic Hearts. *J Proteome Res* 2016;**15**:2254-2264.

395. Ramirez-Correa GA, Ma J, Slawson C, Zeidan Q, Lugo-Fagundo NS, Xu M, Shen X, Gao WD, Caceres V, Chakir K, DeVine L, Cole RN, Marchionni L, Paolocci N, Hart GW, Murphy AM. Removal of Abnormal Myofilament O-GlcNAcylation Restores Ca2+ Sensitivity in Diabetic Cardiac Muscle. *Diabetes* 2015;**64**:3573-3587.

396. Banerjee PS, Ma J, Hart GW. Diabetes-associated dysregulation of O-GlcNAcylation in rat cardiac mitochondria. *Proc Natl Acad Sci U S A* 2015;**112**:6050-6055.

397. Giaccari A, Morviducci L, Zorretta D, Sbraccia P, Leonetti F, Caiola S, Buongiorno A, Bonadonna RC, Tamburrano G. In vivo effects of glucosamine on insulin secretion and insulin sensitivity in the rat: possible relevance to the maladaptive responses to chronic hyperglycaemia. *Diabetologia* 1995;**38**:518-524.

398. Robinson KA, Weinstein ML, Lindenmayer GE, Buse MG. Effects of diabetes and hyperglycemia on the hexosamine synthesis pathway in rat muscle and liver. *Diabetes* 1995;**44**:1438-1446.

399. Liu K, Paterson AJ, Chin E, Kudlow JE. Glucose stimulates protein modification by O-linked GlcNAc in pancreatic beta cells: linkage of O-linked GlcNAc to beta cell death. *Proc Natl Acad Sci U S A* 2000;**97**:2820-2825.

400. Hanover JA, Lai Z, Lee G, Lubas WA, Sato SM. Elevated O-linked N-acetylglucosamine metabolism in pancreatic beta-cells. *Arch Biochem Biophys* 1999;**362**:38-45.

401. Andrali SS, Qian Q, Ozcan S. Glucose mediates the translocation of NeuroD1 by O-linked glycosylation. *J Biol Chem* 2007;**282**:15589-15596.

402. Hebert LF, Jr., Daniels MC, Zhou J, Crook ED, Turner RL, Simmons ST, Neidigh JL, Zhu JS, Baron AD, McClain DA. Overexpression of glutamine:fructose-6-phosphate amidotransferase in transgenic mice leads to insulin resistance. *J Clin Invest* 1996;**98**:930-936.

403. McClain DA, Lubas WA, Cooksey RC, Hazel M, Parker GJ, Love DC, Hanover JA. Altered glycan-dependent signaling induces insulin resistance and hyperleptinemia. *Proc Natl Acad Sci U S A* 2002;**99**:10695-10699.

404. Cao H, Hu Y, Zhu X, Yao N, Gu J, Wang Y, Zhu W. O-GlcNAc transferase affects the signal transduction of beta1 adrenoceptor in adult rat cardiomyocytes by increasing the O-GlcNAcylation of beta1 adrenoceptor. *Biochem Biophys Res Commun* 2020;**528**:71-77.

405. Kronlage M, Dewenter M, Grosso J, Fleming T, Oehl U, Lehmann LH, Falcao-Pires I, Leite-Moreira AF, Volk N, Grone HJ, Muller OJ, Sickmann A, Katus HA, Backs J. O-GlcNAcylation of Histone Deacetylase 4 Protects the Diabetic Heart From Failure. *Circ* 2019;**140**:580-594.

406. Huang L, Yuan P, Yu P, Kong Q, Xu Z, Yan X, Shen Y, Yang J, Wan R, Hong K, Tang Y, Hu J. O-GlcNAc-modified SNAP29 inhibits autophagy-mediated degradation via the disturbed SNAP29-STX17-VAMP8 complex and exacerbates myocardial injury in type I diabetic rats. *Int J Mol Med* 2018;**42**:3278-3290.

407. Hegyi B, Borst JM, Bailey LRJ, Shen EY, Lucena AJ, Navedo MF, Bossuyt J, Bers DM. Hyperglycemia regulates cardiac K(+) channels via O-GlcNAc-CaMKII and NOX2-ROS-PKC pathways. *Basic Res Cardiol* 2020;**115**:71.

408. Yu P, Hu L, Xie J, Chen S, Huang L, Xu Z, Liu X, Zhou Q, Yuan P, Yan X, Jin J, Shen Y, Zhu W, Fu L, Chen Q, Yu J, Hu J, Cao Q, Wan R, Hong K. O-GlcNAcylation of cardiac Nav1.5 contributes to the development of arrhythmias in diabetic hearts. *Int J Cardiol* 2018;**260**:74-81.

409. Masaki N, Feng B, Breton-Romero R, Inagaki E, Weisbrod RM, Fetterman JL, Hamburg NM. O-GlcNAcylation Mediates Glucose-Induced Alterations in

Endothelial Cell Phenotype in Human Diabetes Mellitus. *J Am Heart Assoc* 2020;**9**:e014046.

410. Riehle C, Bauersachs J. Of mice and men: models and mechanisms of diabetic cardiomyopathy. *Basic Res Cardiol* 2019;**114**:2.

411. Ritchie RH, Abel ED. Basic mechanisms of diabetic heart disease. *Circulation research* 2020;**126**:1501-1525.

412. Selvin E, Lazo M, Chen Y, Shen L, Rubin J, McEvoy JW, Hoogeveen RC, Sharrett AR, Ballantyne CM, Coresh J. Diabetes mellitus, prediabetes, and incidence of subclinical myocardial damage. *Circulation* 2014;**130**:1374-1382.

413. Hou N, Mai Y, Qiu X, Yuan W, Li Y, Luo C, Liu Y, Zhang G, Zhao G, Luo JD. Carvacrol Attenuates Diabetic Cardiomyopathy by Modulating the PI3K/AKT/GLUT4 Pathway in Diabetic Mice. *Front Pharmacol* 2019;**10**:998.

414. Olivetti G, Abbi R, Quaini F, Kajstura J, Cheng W, Nitahara JA, Quaini E, Di Loreto C, Beltrami CA, Krajewski S, Reed JC, Anversa P. Apoptosis in the failing human heart. *N Engl J Med* 1997;**336**:1131-1141.

415. Wencker D, Chandra M, Nguyen K, Miao W, Garantziotis S, Factor SM, Shirani J, Armstrong RC, Kitsis RN. A mechanistic role for cardiac myocyte apoptosis in heart failure. *J Clin Invest* 2003;**111**:1497-1504.

416. von Harsdorf R, Li PF, Dietz R. Signaling pathways in reactive oxygen species-induced cardiomyocyte apoptosis. *Circ* 1999;**99**:2934-2941.

417. Xu J, Wang G, Wang Y, Liu Q, Xu W, Tan Y, Cai L. Diabetes- and angiotensin II-induced cardiac endoplasmic reticulum stress and cell death: metallothionein protection. *J Cell Mol Med* 2009;**13**:1499-1512.

418. Zou H, Henzel WJ, Liu X, Lutschg A, Wang X. Apaf-1, a human protein homologous to C. elegans CED-4, participates in cytochrome c-dependent activation of caspase-3. *Cell* 1997;**90**:405-413.

419. Li P, Nijhawan D, Budihardjo I, Srinivasula SM, Ahmad M, Alnemri ES, Wang X. Cytochrome c and dATP-dependent formation of Apaf-1/caspase-9 complex initiates an apoptotic protease cascade. *Cell* 1997;**91**:479-489.

420. Stennicke HR, Deveraux QL, Humke EW, Reed JC, Dixit VM, Salvesen GS. Caspase-9 can be activated without proteolytic processing. *J Biol Chem* 1999;**274**:8359-8362.

421. Renatus M, Stennicke HR, Scott FL, Liddington RC, Salvesen GS. Dimer formation drives the activation of the cell death protease caspase 9. *Proc Natl Acad Sci U S A* 2001;**98**:14250-14255.

422. Toshiyuki M, Reed JC. Tumor suppressor p53 is a direct transcriptional activator of the human bax gene. *Cell* 1995;**80**:293-299.

423. Oltval ZN, Milliman CL, Korsmeyer SJ. Bcl-2 heterodimerizes in vivo with a conserved homolog, Bax, that accelerates programed cell death. *Cell* 1993;**74**:609-619.

424. Siegel RM, Frederiksen JK, Zacharias DA, Chan FK, Johnson M, Lynch D, Tsien RY, Lenardo MJ. Fas preassociation required for apoptosis signaling and dominant inhibition by pathogenic mutations. *Science* 2000;**288**:2354-2357.

425. Haudek SB, Taffet GE, Schneider MD, Mann DL. TNF provokes cardiomyocyte apoptosis and cardiac remodeling through activation of multiple cell death pathways. *The Journal of clinical investigation* 2007;**117**:2692-2701.

426. Kischkel FC, Hellbardt S, Behrmann I, Germer M, Pawlita M, Krammer PH, Peter ME. Cytotoxicity-dependent APO-1 (Fas/CD95)-associated proteins form a death-inducing signaling complex (DISC) with the receptor. *EMBO J* 1995;**14**:5579-5588.

427. Boldin MP, Goncharov TM, Goltsev YV, Wallach D. Involvement of MACH, a novel MORT1/FADD-interacting protease, in Fas/APO-1- and TNF receptor-induced cell death. *Cell* 1996;**85**:803-815.

428. Boatright KM, Renatus M, Scott FL, Sperandio S, Shin H, Pedersen IM, Ricci JE, Edris WA, Sutherlin DP, Green DR, Salvesen GS. A unified model for apical caspase activation. *Mol Cell* 2003;**11**:529-541.

429. Luo X, Budihardjo I, Zou H, Slaughter C, Wang X. Bid, a Bcl2 interacting protein, mediates cytochrome c release from mitochondria in response to activation of cell surface death receptors. *Cell* 1998;**94**:481-490.

430. Takemura G, Kanoh M, Minatoguchi S, Fujiwara H. Cardiomyocyte apoptosis in the failing heart--a critical review from definition and classification of cell death. *Int J Cardiol* 2013;**167**:2373-2386.

431. Kostin S, Pool L, Elsasser A, Hein S, Drexler HC, Arnon E, Hayakawa Y, Zimmermann R, Bauer E, Klovekorn WP, Schaper J. Myocytes die by multiple mechanisms in failing human hearts. *Circ Res* 2003;**92**:715-724.

432. Hein S, Arnon E, Kostin S, Schonburg M, Elsasser A, Polyakova V, Bauer EP, Klovekorn WP, Schaper J. Progression from compensated hypertrophy to failure in the pressure-overloaded human heart: structural deterioration and compensatory mechanisms. *Circ* 2003;**107**:984-991.

433. Nakagami H, Morishita R, Yamamoto K, Yoshimura SI, Taniyama Y, Aoki M, Matsubara H, Kim S, Kaneda Y, Ogihara T. Phosphorylation of p38 mitogen-activated protein kinase downstream of bax-caspase-3 pathway leads to cell death induced by high D-glucose in human endothelial cells. *Diabetes* 2001;**50**:1472-1481.

434. 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**:1938-1948.

435. Monkemann H, De Vriese AS, Blom HJ, Kluijtmans LA, Heil SG, Schild HH, Golubnitschaja O. Early molecular events in the development of the diabetic cardiomyopathy. *Amino Acids* 2002;**23**:331-336.

436. Kajstura J, Fiordaliso F, Andreoli AM, Li B, Chimenti S, Medow MS, Limana F, Nadal-Ginard B, Leri A, Anversa P. IGF-1 overexpression inhibits the development of diabetic cardiomyopathy and angiotensin II-mediated oxidative stress. *Diabetes* 2001;**50**:1414-1424.

437. Sparagna GC, Hickson-Bick DL, Buja LM, McMillin JB. A metabolic role for mitochondria in palmitate-induced cardiac myocyte apoptosis. *Am J Physiol Heart Circ Physiol* 2000;**279**:H2124-2132.

438. Ohkuwa T, Sato Y, Naoi M. Hydroxyl radical formation in diabetic rats induced by streptozotocin. *Life Sci* 1995;**56**:1789-1798.

439. Shizukuda Y, Reyland ME, Buttrick PM. Protein kinase C-delta modulates apoptosis induced by hyperglycemia in adult ventricular myocytes. *Am J Physiol Heart Circ Physiol* 2002;**282**:H1625-1634.

440. Bryant D, Becker L, Richardson J, Shelton J, Franco F, Peshock R, Thompson M, Giroir B. Cardiac failure in transgenic mice with myocardial expression of tumor necrosis factor-alpha. *Circ* 1998;**97**:1375-1381.

441. Sciarretta S, Maejima Y, Zablocki D, Sadoshima J. The Role of Autophagy in the Heart. *Annu Rev Physiol* 2018;**80**:1-26.

442. Riehle C, Wende AR, Sena S, Pires KM, Pereira RO, Zhu Y, Bugger H, Frank D, Bevins J, Chen D, Perry CN, Dong XC, Valdez S, Rech M, Sheng X, Weimer BC, Gottlieb RA, White MF, Abel ED. Insulin receptor substrate signaling suppresses neonatal autophagy in the heart. *J Clin Invest* 2013;**123**:5319-5333.

443. Pires KM, Torres NS, Buffolo M, Gunville R, Schaaf C, Davis K, Selzman CH, Gottlieb RA, Boudina S. Suppression of Cardiac Autophagy by Hyperinsulinemia in Insulin Receptor-Deficient Hearts Is Mediated by Insulin-Like Growth Factor Receptor Signaling. *Antioxidants & Redox Signaling* 2019;**31**:444-457.

444. Xie ZL, Lau K, Eby B, Lozano P, He CY, Pennington B, Li HL, Rathi S, Dong YZ, Tian R, Kem D, Zou MH. Improvement of Cardiac Functions by Chronic Metformin Treatment Is Associated With Enhanced Cardiac Autophagy in Diabetic OVE26 Mice. *Diabetes* 2011;**60**:1770-1778.

445. Pires KM, Buffolo M, Schaaf C, Symons JD, Cox J, Abel ED, Selzman CH, Boudina S. Activation of IGF-1 receptors and Akt signaling by systemic hyperinsulinemia contributes to cardiac hypertrophy but does not regulate cardiac autophagy in obese diabetic mice. *J Mol Cell Cardiol* 2017;**113**:39-50.

446. Zhao Y, Zhang L, Qiao Y, Zhou X, Wu G, Wang L, Peng Y, Dong X, Huang H, Si L, Zhang X, Zhang L, Li J, Wang W, Zhou L, Gao X. Heme oxygenase-1 prevents cardiac dysfunction in streptozotocin-diabetic mice by reducing inflammation, oxidative stress, apoptosis and enhancing autophagy. *PLoS One* 2013;**8**:e75927.

447. Xie Z, He C, Zou MH. AMP-activated protein kinase modulates cardiac autophagy in diabetic cardiomyopathy. *Autophagy* 2011;**7**:1254-1255.

448. Das A, Durrant D, Koka S, Salloum FN, Xi L, Kukreja RC. Mammalian target of rapamycin (mTOR) inhibition with rapamycin improves cardiac function in type 2 diabetic mice: potential role of attenuated oxidative stress and altered contractile protein expression. *J Biol Chem* 2014;**289**:4145-4160.

449. Morselli E, Maiuri MC, Markaki M, Megalou E, Pasparaki A, Palikaras K, Criollo A, Galluzzi L, Malik SA, Vitale I. Caloric restriction and resveratrol promote longevity through the Sirtuin-1-dependent induction of autophagy. *Cell Death Dis* 2010;**1**:e10.

450. Zhang M, Zhang L, Hu J, Lin J, Wang T, Duan Y, Man W, Feng J, Sun L, Jia H, Li C, Zhang R, Wang H, Sun D. MST1 coordinately regulates autophagy and apoptosis in diabetic cardiomyopathy in mice. *Diabetologia* 2016;**59**:2435-2447.

451. Cai L, Kang YJ. Cell death and diabetic cardiomyopathy. *Cardiovasc Toxicol* 2003;**3**:219-228.

452. Cai L, Kang YJ. Oxidative stress and diabetic cardiomyopathy: a brief review. *Cardiovasc Toxicol* 2001;**1**:181-193.

453. Nakayama H, Chen X, Baines CP, Klevitsky R, Zhang X, Zhang H, Jaleel N, Chua BH, Hewett TE, Robbins J, Houser SR, Molkentin JD. Ca2+- and mitochondrial-dependent cardiomyocyte necrosis as a primary mediator of heart failure. *J Clin Invest* 2007;**117**:2431-2444.

454. Lu LQ, Tian J, Luo XJ, Peng J. Targeting the pathways of regulated necrosis: a potential strategy for alleviation of cardio-cerebrovascular injury. *Cell Mol Life Sci* 2021;**78**:63-78.

455. Wang X, Pan J, Liu H, Zhang M, Liu D, Lu L, Tian J, Liu M, Jin T, An F. AIM2 gene silencing attenuates diabetic cardiomyopathy in type 2 diabetic rat model. *Life Sci* 2019;**221**:249-258.

456. Yang F, Qin Y, Lv J, Wang Y, Che H, Chen X, Jiang Y, Li A, Sun X, Yue E, Ren L, Li Y, Bai Y, Wang L. Silencing long non-coding RNA Kcnq1ot1 alleviates pyroptosis and fibrosis in diabetic cardiomyopathy. *Cell Death Dis* 2018;**9**:1000.

457. Yang F, Qin Y, Wang Y, Meng S, Xian H, Che H, Lv J, Li Y, Yu Y, Bai Y, Wang L. Metformin Inhibits the NLRP3 Inflammasome via AMPK/mTOR-dependent Effects in Diabetic Cardiomyopathy. *Int J Biol Sci* 2019;**15**:1010-1019.

458. Xie Y, Hou W, Song X, Yu Y, Huang J, Sun X, Kang R, Tang D. Ferroptosis: process and function. *Cell Death Differ* 2016;**23**:369-379.

459. Kar S, Shahshahan H, Mishra PK. Hydrogen Sulfide Protects the Heart Against Ferroptotic Cell Death in Diabetic Cardiomyopathy. Circ Res: Am Heart Assoc, 2020:A501-A501.

460. Lagadic-Gossmann D, Buckler KJ, Le Prigent K, Feuvray D. Altered Ca2+ handling in ventricular myocytes isolated from diabetic rats. *Am J Physiol* 1996;**270**:H1529-1537.

461. Belke DD, Swanson EA, Dillmann WH. Decreased sarcoplasmic reticulum activity and contractility in diabetic db/db mouse heart. *Diabetes* 2004;**53**:3201-3208.

462. Ren J, Davidoff AJ. Diabetes rapidly induces contractile dysfunctions in isolated ventricular myocytes. *Am J Physiol* 1997;**272**:H148-158.

463. Davidoff AJ, Davidson MB, Carmody MW, Davis ME, Ren J. Diabetic cardiomyocyte dysfunction and myocyte insulin resistance: role of glucose-induced PKC activity. *Mol Cell Biochem* 2004;**262**:155-163.

464. Lacombe VA, Viatchenko-Karpinski S, Terentyev D, Sridhar A, Emani S, Bonagura JD, Feldman DS, Gyorke S, Carnes CA. Mechanisms of impaired calcium handling underlying subclinical diastolic dysfunction in diabetes. *Am J Physiol Regul Integr Comp Physiol* 2007;**293**:R1787-1797.

465. Zhou H, Yue Y, Wang J, Ma Q, Chen Y. Melatonin therapy for diabetic cardiomyopathy: A mechanism involving Syk-mitochondrial complex I-SERCA pathway. *Cell Signal* 2018;**47**:88-100.

466. Miki T, Yuda S, Kouzu H, Miura T. Diabetic cardiomyopathy: pathophysiology and clinical features. *Heart Fail Rev* 2013;**18**:149-166.

467. Papadaki M, Holewinski RJ, Previs SB, Martin TG, Stachowski MJ, Li A, Blair CA, Moravec CS, Van Eyk JE, Campbell KS, Warshaw DM, Kirk JA. Diabetes with heart failure increases methylglyoxal modifications in the sarcomere, which inhibit function. *JCI Insight* 2018;**3**.

468. Hu Y, Belke D, Suarez J, Swanson E, Clark R, Hoshijima M, Dillmann WH. Adenovirus-mediated overexpression of O-GlcNAcase improves contractile function in the diabetic heart. *Circ Res* 2005;**96**:1006-1013.

469. Shao CH, Capek HL, Patel KP, Wang M, Tang K, DeSouza C, Nagai R, Mayhan W, Periasamy M, Bidasee KR. Carbonylation contributes to SERCA2a activity loss

and diastolic dysfunction in a rat model of type 1 diabetes. *Diabetes* 2011;**60**:947-959.

470. Kranstuber AL, Del Rio C, Biesiadecki BJ, Hamlin RL, Ottobre J, Gyorke S, Lacombe VA. Advanced glycation end product cross-link breaker attenuates diabetes-induced cardiac dysfunction by improving sarcoplasmic reticulum calcium handling. *Front Physiol* 2012;**3**:292.

471. Bidasee KR, Zhang Y, Shao CH, Wang M, Patel KP, Dincer UD, Besch HR, Jr. Diabetes increases formation of advanced glycation end products on Sarco(endo)plasmic reticulum Ca2+-ATPase. *Diabetes* 2004;**53**:463-473.

472. Pierce GN, Dhalla NS. Cardiac myofibrillar ATPase activity in diabetic rats. *J Mol Cell Cardiol* 1981;**13**:1063-1069.

473. Penpargkul S, Fein F, Sonnenblick EH, Scheuer J. Depressed cardiac sarcoplasmic reticular function from diabetic rats. *J Mol Cell Cardiol* 1981;**13**:303-309.

474. Lopaschuk GD, Tahiliani AG, Vadlamudi RV, Katz S, McNeill JH. Cardiac sarcoplasmic reticulum function in insulin- or carnitine-treated diabetic rats. *Am J Physiol* 1983;**245**:H969-976.

475. Lopaschuk GD, Katz S, McNeill JH. The effect of alloxan- and streptozotocin-induced diabetes on calcium transport in rat cardiac sarcoplasmic reticulum. The possible involvement of long chain acylcarnitines. *Can J Physiol Pharmacol* 1983;**61**:439-448.

476. Fauconnier J, Lanner JT, Zhang SJ, Tavi P, Bruton JD, Katz A, Westerblad H. Insulin and inositol 1,4,5-trisphosphate trigger abnormal cytosolic Ca2+ transients and reveal mitochondrial Ca2+ handling defects in cardiomyocytes of ob/ob mice. *Diabetes* 2005;**54**:2375-2381.

477. Li SY, Yang X, Ceylan-Isik AF, Du M, Sreejayan N, Ren J. Cardiac contractile dysfunction in Lep/Lep obesity is accompanied by NADPH oxidase activation, oxidative modification of sarco(endo)plasmic reticulum Ca2+-ATPase and myosin heavy chain isozyme switch. *Diabetologia* 2006;**49**:1434-1446.

478. Trost SU, Belke DD, Bluhm WF, Meyer M, Swanson E, Dillmann WH. Overexpression of the sarcoplasmic reticulum Ca(2+)-ATPase improves myocardial contractility in diabetic cardiomyopathy. *Diabetes* 2002;**51**:1166-1171.

479. Quan C, Du Q, Li M, Wang R, Ouyang Q, Su S, Zhu S, Chen Q, Sheng Y, Chen L, Wang H, Campbell DG, MacKintosh C, Yang Z, Ouyang K, Wang HY, Chen S. A PKB-SPEG signaling nexus links insulin resistance with diabetic cardiomyopathy by regulating calcium homeostasis. *Nat Commun* 2020;**11**:2186.

480. Shah S, Akhtar MS, Hassan MQ, Akhtar M, Paudel YN, Najmi AK. EGFR tyrosine kinase inhibition decreases cardiac remodeling and SERCA2a/NCX1 depletion in streptozotocin induced cardiomyopathy in C57/BL6 mice. *Life Sci* 2018;**210**:29-39.

481. Akhtar MS, Pillai KK, Hassan MQ, Dhyani N, Ismail MV, Najmi AK. Levosimendan reduces myocardial damage and improves cardiodynamics in streptozotocin induced diabetic cardiomyopathy via SERCA2a/NCX1 pathway. *Life Sci* 2016;**153**:55-65.

482. Fein FS, Kornstein LB, Strobeck JE, Capasso JM, Sonnenblick EH. Altered myocardial mechanics in diabetic rats. *Circ Res* 1980;**47**:922-933.

483. REGAN TJ, ETTINGER PO, KHAN MI, JESRANI MU, LYONS MM, OLDEWURTEL HA, WEBER M. Altered Myocardial Function and Metabolism in Chronic Diabetes Mellitus without Ischemia in Dogs. *Circulation Research* 1974;**35**:222-237.

484. Garber DW, Neely JR. Decreased myocardial function and myosin ATPase in hearts from diabetic rats. *Am J Physiol* 1983;**244**:H586-591.

485. Garber DW, Everett AW, Neely JR. Cardiac function and myosin ATPase in diabetic rats treated with insulin, T3, and T4. *Am J Physiol* 1983;**244**:H592-598.

486. Malhotra A, Mordes JP, McDermott L, Schaible TF. Abnormal cardiac biochemistry in spontaneously diabetic Bio-Breeding/Worcester rat. *Am J Physiol* 1985;**249**:H1051-1055.

487. Dillmann WH. Diabetes mellitus induces changes in cardiac myosin of the rat. *Diabetes* 1980;**29**:579-582.

488. Dillmann WH. Influence of thyroid hormone administration on myosin ATPase activity and myosin isoenzyme distribution in the heart of diabetic rats. *Metabolism* 1982;**31**:199-204.

489. Akella AB, Ding XL, Cheng R, Gulati J. Diminished Ca2+ sensitivity of skinned cardiac muscle contractility coincident with troponin T-band shifts in the diabetic rat. *Circ Res* 1995;**76**:600-606.

490. 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**:H1656-1663.

491. Wang Y, Fan PS, Kahaleh B. Association between enhanced type I collagen expression and epigenetic repression of the FLI1 gene in scleroderma fibroblasts. *Arthritis Rheum* 2006;**54**:2271-2279.

492. Singh VP, Le B, Khode R, Baker KM, Kumar R. Intracellular angiotensin II production in diabetic rats is correlated with cardiomyocyte apoptosis, oxidative stress, and cardiac fibrosis. *Diabetes* 2008;**57**:3297-3306.

493. Miller JA. Impact of hyperglycemia on the renin angiotensin system in early human type 1 diabetes mellitus. *J Am Soc Nephrol* 1999;**10**:1778-1785.

494. Verma S, Arikawa E, McNeill JH. Long-term endothelin receptor blockade improves cardiovascular function in diabetes. *Am J Hypertens* 2001;**14**:679-687.

495. Jia G, Habibi J, Bostick BP, Ma L, DeMarco VG, Aroor AR, Hayden MR, Whaley-Connell AT, Sowers JR. Uric acid promotes left ventricular diastolic dysfunction in mice fed a Western diet. *Hypertension* 2015;**65**:531-539.

496. Tate M, Grieve DJ, Ritchie RH. Are targeted therapies for diabetic cardiomyopathy on the horizon? *Clin Sci (Lond)* 2017;**131**:897-915.

497. Pappachan JM, Sebastian J, Bino BC, Jayaprakash K, Vijayakumar K, Sujathan P, Adinegara LA. Cardiac autonomic neuropathy in diabetes mellitus: prevalence, risk factors and utility of corrected QT interval in the ECG for its diagnosis. *Postgrad Med J* 2008;**84**:205-210.

498. Voulgari C, Pagoni S, Vinik A, Poirier P. Exercise improves cardiac autonomic function in obesity and diabetes. *Metabolism* 2013;**62**:609-621.

499. Pant T, Dhanasekaran A, Bai X, Zhao M, Thorp EB, Forbess JM, Bosnjak ZJ, Ge ZD. Genome-wide differential expression profiling of lncRNAs and mRNAs associated with early diabetic cardiomyopathy. *Sci Rep* 2019;**9**:15345.

500. Chavali V, Tyagi SC, Mishra PK. Differential expression of dicer, miRNAs, and inflammatory markers in diabetic Ins2+/- Akita hearts. *Cell Biochem Biophys* 2014;**68**:25-35.
501. Dillmann WH. Diabetic Cardiomyopathy. *Circ Res* 2019;**124**:1160-1162.
502. Karakikes I, Kim M, Hadri L, Sakata S, Sun Y, Zhang W, Chemaly ER, Hajjar RJ, Lebeche D. Gene remodeling in type 2 diabetic cardiomyopathy and its phenotypic rescue with SERCA2a. *PLoS One* 2009;**4**:e6474.
503. Li N, Wu H, Geng R, Tang Q. Identification of Core Gene Biomarkers in Patients with Diabetic Cardiomyopathy. *Dis Markers* 2018;**2018**:6025061.
504. Gollmer J, Zirlik A, Bugger H. Mitochondrial Mechanisms in Diabetic Cardiomyopathy. *Diabetes Metab J* 2020;**44**:33-53.
505. Hu L, Ding M, Tang D, Gao E, Li C, Wang K, Qi B, Qiu J, Zhao H, Chang P, Fu F, Li Y. Targeting mitochondrial dynamics by regulating Mfn2 for therapeutic intervention in diabetic cardiomyopathy. *Theranostics* 2019;**9**:3687-3706.
506. Duncan JG, Fong JL, Medeiros DM, Finck BN, Kelly DP. Insulin-resistant heart exhibits a mitochondrial biogenic response driven by the peroxisome proliferator-activated receptor-alpha/PGC-1alpha gene regulatory pathway. *Circ* 2007;**115**:909-917.
507. Beermann J, Piccoli MT, Viereck J, Thum T. Non-coding RNAs in Development and Disease: Background, Mechanisms, and Therapeutic Approaches. *Physiol Rev* 2016;**96**:1297-1325.
508. Seal RL, Chen LL, Griffiths-Jones S, Lowe TM, Mathews MB, O'Reilly D, Pierce AJ, Stadler PF, Ulitsky I, Wolin SL, Bruford EA. A guide to naming human non-coding RNA genes. *EMBO J* 2020;**39**:e103777.
509. Zhang W, Xu W, Feng Y, Zhou X. Non-coding RNA involvement in the pathogenesis of diabetic cardiomyopathy. *J Cell Mol Med* 2019;**23**:5859-5867.
510. de Gonzalo-Calvo D, Kenneweg F, Bang C, Toro R, van der Meer RW, Rijzewijk LJ, Smit JW, Lamb HJ, Llorente-Cortes V, Thum T. Circulating long-non coding RNAs as biomarkers of left ventricular diastolic function and remodelling in patients with well-controlled type 2 diabetes. *Sci Rep* 2016;**6**:37354.
511. Li D, Kular L, Vij M, Herter EK, Li X, Wang A, Chu T, Toma MA, Zhang L, Liapi E, Mota A, Blomqvist L, Gallais Serezal I, Rollman O, Wikstrom JD, Bienko M, Berglund D, Stahle M, Sommar P, Jagodic M, Landen NX. Human skin long noncoding RNA WAKMAR1 regulates wound healing by enhancing keratinocyte migration. *Proc Natl Acad Sci U S A* 2019;**116**:9443-9452.
512. Wang P, Xue Y, Han Y, Lin L, Wu C, Xu S, Jiang Z, Xu J, Liu Q, Cao X. The STAT3-binding long noncoding RNA lnc-DC controls human dendritic cell differentiation. *Science* 2014;**344**:310-313.
513. Gao L, Wang XF, Guo S, Xiao LL, Liang C, Wang Z, Li YP, Liu YZ, Yao R, Liu Y, Zhang YZ. LncRNA HOTAIR functions as a competing endogenous RNA to upregulate SIRT1 by sponging miR-34a in diabetic cardiomyopathy. *J Cell Physiol* 2019;**234**:4944-4958.
514. Zhou X, Zhang W, Jin MC, Chen JC, Xu WT, Kong XQ. lncRNA MIAT functions as a competing endogenous RNA to upregulate DAPK2 by sponging miR-22-3p in diabetic cardiomyopathy. *Cell Death Dis* 2017;**8**:321.

515. Zhuo C, Jiang R, Lin X, Shao M. LncRNA H19 inhibits autophagy by epigenetically silencing of DIRAS3 in diabetic cardiomyopathy. *Oncotarget* 2017;**8**:1429-1437.

516. Feng B, Chen S, Chakrabarti S. Long Noncoding RNA Zfas1 in Diabetic Cardiomyopathy. Am Diabetes Assoc, 2018.

517. Li X, Wang H, Yao B, Xu W, Chen J, Zhou X. lncRNA H19/miR-675 axis regulates cardiomyocyte apoptosis by targeting VDAC1 in diabetic cardiomyopathy. *Sci Rep* 2016;**6**:36340.

518. Raut SK, Singh GB, Rastogi B, Saikia UN, Mittal A, Dogra N, Singh S, Prasad R, Khullar M. miR-30c and miR-181a synergistically modulate p53-p21 pathway in diabetes induced cardiac hypertrophy. *Mol Cell Biochem* 2016;**417**:191-203.

519. Feng B, Chen S, George B, Feng Q, Chakrabarti S. miR133a regulates cardiomyocyte hypertrophy in diabetes. *Diabetes Metab Res Rev* 2010;**26**:40-49.

520. Duan Y, Zhou B, Su H, Liu Y, Du C. miR-150 regulates high glucose-induced cardiomyocyte hypertrophy by targeting the transcriptional co-activator p300. *Exp Cell Res* 2013;**319**:173-184.

521. Shen E, Diao X, Wang X, Chen R, Hu B. MicroRNAs involved in the mitogen-activated protein kinase cascades pathway during glucose-induced cardiomyocyte hypertrophy. *Am J Pathol* 2011;**179**:639-650.

522. Kuwabara Y, Horie T, Baba O, Watanabe S, Nishiga M, Usami S, Izuhara M, Nakao T, Nishino T, Otsu K, Kita T, Kimura T, Ono K. MicroRNA-451 Exacerbates Lipotoxicity in Cardiac Myocytes and High-Fat Diet-Induced Cardiac Hypertrophy in Mice Through Suppression of the LKB1/AMPK Pathway. *Circ Res* 2015;**116**:279-U217.

523. Chen S, Puthanveetil P, Feng B, Matkovich SJ, Dorn GW, 2nd, Chakrabarti S. Cardiac miR-133a overexpression prevents early cardiac fibrosis in diabetes. *J Cell Mol Med* 2014;**18**:415-421.

524. Rawal S, Munasinghe PE, Nagesh PT, Lew JKS, Jones GT, Williams MJA, Davis P, Bunton D, Galvin IF, Manning P, Lamberts RR, Katare R. Down-regulation of miR-15a/b accelerates fibrotic remodelling in the Type 2 diabetic human and mouse heart. *Clin Sci (Lond)* 2017;**131**:847-863.

525. Feng B, Chen S, Gordon AD, Chakrabarti S. miR-146a mediates inflammatory changes and fibrosis in the heart in diabetes. *J Mol Cell Cardiol* 2017;**105**:70-76.

526. Moore A, Shindikar A, Fomison-Nurse I, Riu F, Munasinghe PE, Ram TP, Saxena P, Coffey S, Bunton RW, Galvin IF, Williams MJ, Emanueli C, Madeddu P, Katare R. Rapid onset of cardiomyopathy in STZ-induced female diabetic mice involves the downregulation of pro-survival Pim-1. *Cardiovasc Diabetol* 2014;**13**:68.

527. Zheng D, Ma J, Yu Y, Li M, Ni R, Wang G, Chen R, Li J, Fan GC, Lacefield JC, Peng T. Silencing of miR-195 reduces diabetic cardiomyopathy in C57BL/6 mice. *Diabetologia* 2015;**58**:1949-1958.

528. Qiao Y, Zhao Y, Liu Y, Ma N, Wang C, Zou J, Liu Z, Zhou Z, Han D, He J, Sun Q, Liu Y, Xu C, Du Z, Huang H. miR-483-3p regulates hyperglycaemia-induced cardiomyocyte apoptosis in transgenic mice. *Biochem Biophys Res Commun* 2016;**477**:541-547.

529. Arnold N, Koppula PR, Gul R, Luck C, Pulakat L. Regulation of cardiac expression of the diabetic marker microRNA miR-29. *PLoS One* 2014;**9**:e103284.

530. Yildirim SS, Akman D, Catalucci D, Turan B. Relationship Between Downregulation of miRNAs and Increase of Oxidative Stress in the Development of Diabetic Cardiac Dysfunction: Junctin as a Target Protein of miR-1. *Cell Biochem Biophys* 2013;**67**:1397-1408.

531. Yu M, Liu Y, Zhang B, Shi Y, Cui L, Zhao X. Inhibiting microRNA-144 abates oxidative stress and reduces apoptosis in hearts of streptozotocin-induced diabetic mice. *Cardiovasc Pathol* 2015;**24**:375-381.

532. Reddy MA, Jin W, Villeneuve L, Wang M, Lanting L, Todorov I, Kato M, Natarajan R. Pro-inflammatory role of microrna-200 in vascular smooth muscle cells from diabetic mice. *Arterioscler Thromb Vasc Biol* 2012;**32**:721-729.

533. Ashwal-Fluss R, Meyer M, Pamudurti NR, Ivanov A, Bartok O, Hanan M, Evantal N, Memczak S, Rajewsky N, Kadener S. circRNA biogenesis competes with pre-mRNA splicing. *Mol Cell* 2014;**56**:55-66.

534. Li Z, Huang C, Bao C, Chen L, Lin M, Wang X, Zhong G, Yu B, Hu W, Dai L, Zhu P, Chang Z, Wu Q, Zhao Y, Jia Y, Xu P, Liu H, Shan G. Exon-intron circular RNAs regulate transcription in the nucleus. *Nat Struct Mol Biol* 2015;**22**:256-264.

535. Dong SZ, Tu CY, Ye X, Li LL, Zhang MC, Xue AM, Chen SH, Zhao ZQ, Cong B, Lin JY, Shen YW. Expression profiling of circular RNAs and their potential role in early-stage diabetic cardiomyopathy. *Mol Med Report* 2020;**22**:1958-1968.

536. Tang N, Jiang S, Yang Y, Liu S, Ponnusamy M, Xin H, Yu T. Noncoding RNAs as therapeutic targets in atherosclerosis with diabetes mellitus. *Cardiovasc Ther* 2018;**36**:e12436.

537. Zhou B, Yu JW. A novel identified circular RNA, circRNA_010567, promotes myocardial fibrosis via suppressing miR-141 by targeting TGF-beta1. *Biochem Biophys Res Commun* 2017;**487**:769-775.

538. Wang W, Zhang S, Xu L, Feng Y, Wu X, Zhang M, Yu Z, Zhou X. Involvement of circHIPK3 in the pathogenesis of diabetic cardiomyopathy in mice. *Diabetologia* 2021;**64**:681-692.

539. Yang F, Li A, Qin Y, Che H, Wang Y, Lv J, Li Y, Li H, Yue E, Ding X, Yu Y, Bai Y, Wang L. A Novel Circular RNA Mediates Pyroptosis of Diabetic Cardiomyopathy by Functioning as a Competing Endogenous RNA. *Mol Ther Nucleic Acids* 2019;**17**:636-643.

540. Gaikwad AB, Sayyed SG, Lichtnekert J, Tikoo K, Anders HJ. Renal failure increases cardiac histone h3 acetylation, dimethylation, and phosphorylation and the induction of cardiomyopathy-related genes in type 2 diabetes. *Am J Pathol* 2010;**176**:1079-1083.

541. Miao F, Gonzalo IG, Lanting L, Natarajan R. In vivo chromatin remodeling events leading to inflammatory gene transcription under diabetic conditions. *J Biol Chem* 2004;**279**:18091-18097.

542. Malek V, Sharma N, Gaikwad AB. Histone Acetylation Regulates Natriuretic Peptides and Neprilysin Gene Expressions in Diabetic Cardiomyopathy and Nephropathy. *Curr Mol Pharmacol* 2019;**12**:61-71.

543. Uchihashi M, Hoshino A, Okawa Y, Ariyoshi M, Kaimoto S, Tateishi S, Ono K, Yamanaka R, Hato D, Fushimura Y, Honda S, Fukai K, Higuchi Y, Ogata T, Iwai-Kanai E, Matoba S. Cardiac-Specific Bdh1 Overexpression Ameliorates Oxidative

Stress and Cardiac Remodeling in Pressure Overload-Induced Heart Failure. *Circ Heart Fail* 2017;**10**:e004417.

544. van den Berge JC, Constantinescu AA, Boiten HJ, van Domburg RT, Deckers JW, Akkerhuis KM. Short- and Long-term Prognosis of Patients With Acute Heart Failure With and Without Diabetes: Changes Over the Last Three Decades. *Diabetes Care* 2018;**41**:143-149.

545. Kenny HC, Abel ED. Heart Failure in Type 2 Diabetes Mellitus. *Circ Res* 2019;**124**:121-141.

546. Cameron AR, Morrison VL, Levin D, Mohan M, Forteath C, Beall C, McNeilly AD, Balfour DJ, Savinko T, Wong AK, Viollet B, Sakamoto K, Fagerholm SC, Foretz M, Lang CC, Rena G. Anti-Inflammatory Effects of Metformin Irrespective of Diabetes Status. *Circ Res* 2016;**119**:652-665.

547. Dziubak A, Wojcicka G, Wojtak A, Beltowski J. Metabolic Effects of Metformin in the Failing Heart. *Int J Mol Sci* 2018;**19**:2869.

548. El Messaoudi S, Rongen GA, de Boer RA, Riksen NP. The cardioprotective effects of metformin. *Curr Opin Lipidol* 2011;**22**:445-453.

549. Eurich DT, Tsuyuki RT, Majumdar SR, McAlister FA, Lewanczuk R, Shibata MC, Johnson JA. Metformin treatment in diabetes and heart failure: when academic equipoise meets clinical reality. *Trials* 2009;**10**:1745-6215.

550. Dludla PV, Nyambuya TM, Johnson R, Silvestri S, Orlando P, Mazibuko-Mbeje SE, Gabuza KB, Mxinwa V, Mokgalaboni K, Tiano L, Muller CJF, Louw J, Nkambule BB. Metformin and heart failure-related outcomes in patients with or without diabetes: a systematic review of randomized controlled trials. *Heart Fail Rev* 2020.

551. Weir DL, Abrahamowicz M, Beauchamp ME, Eurich DT. Acute vs cumulative benefits of metformin use in patients with type 2 diabetes and heart failure. *Diabetes Obesity & Metabolism* 2018;**20**:2653-2660.

552. Retwinski A, Kosmalski M, Crespo-Leiro M, Maggioni A, Opolski G, Ponikowski P, Polonski L, Jankowska E, Drzewoski J, Drozdz J. The influence of metformin and the presence of type 2 diabetes mellitus on mortality and hospitalisation in patients with heart failure. *Kardiol Pol* 2018;**76**:1336-1343.

553. Pantalone KM, Kattan MW, Yu C, Wells BJ, Arrigain S, Jain A, Atreja A, Zimmerman RS. The risk of developing coronary artery disease or congestive heart failure, and overall mortality, in type 2 diabetic patients receiving rosiglitazone, pioglitazone, metformin, or sulfonylureas: a retrospective analysis. *Acta Diabetol* 2009;**46**:145-154.

554. Sola D, Rossi L, Schianca GP, Maffioli P, Bigliocca M, Mella R, Corliano F, Fra GP, Bartoli E, Derosa G. Sulfonylureas and their use in clinical practice. *Arch Med Sci* 2015;**11**:840-848.

555. Monami M, Genovese S, Mannucci E. Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab* 2013;**15**:938-953.

556. Rao AD, Kuhadiya N, Reynolds K, Fonseca VA. Is the combination of sulfonylureas and metformin associated with an increased risk of cardiovascular disease or all-cause mortality?: a meta-analysis of observational studies. *Diabetes Care* 2008;**31**:1672-1678.

557. Roumie CL, Greevy RA, Grijalva CG, Hung AM, Liu X, Murff HJ, Elasy TA, Griffin MR. Association between intensification of metformin treatment with insulin vs sulfonylureas and cardiovascular events and all-cause mortality among patients with diabetes. *JAMA* 2014;**311**:2288-2296.

558. Evans JM, Ogston SA, Emslie-Smith A, Morris AD. Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with sulfonylureas and metformin. *Diabetologia* 2006;**49**:930-936.

559. Azoulay L, Suissa S. Sulfonylureas and the Risks of Cardiovascular Events and Death: A Methodological Meta-Regression Analysis of the Observational Studies. *Diabetes Care* 2017;**40**:706-714.

560. Simpson SH, Lee J, Choi S, Vandermeer B, Abdelmoneim AS, Featherstone TR. Mortality risk among sulfonylureas: a systematic review and network meta-analysis. *Lancet Diabetes & Endocrinology* 2015;**3**:43-51.

561. Douros A, Yin H, Yu OHY, Filion KB, Azoulay L, Suissa S. Pharmacologic Differences of Sulfonylureas and the Risk of Adverse Cardiovascular and Hypoglycemic Events. *Diabetes Care* 2017;**40**:1506-1513.

562. Diabetes Canada Clinical Practice Guidelines Expert C, Connelly KA, Gilbert RE, Liu P. Treatment of Diabetes in People With Heart Failure. *Can J Diabetes* 2018;**42 Suppl 1**:S196-S200.

563. Charbonnel B, Dormandy J, Erdmann E, Massi-Benedetti M, Skene A, Group PRS. The prospective pioglitazone clinical trial in macrovascular events (PROactive): can pioglitazone reduce cardiovascular events in diabetes? Study design and baseline characteristics of 5238 patients. *Diabetes Care* 2004;**27**:1647-1653.

564. Investigators DT, Dagenais GR, Gerstein HC, Holman R, Budaj A, Escalante A, Hedner T, Keltai M, Lonn E, McFarlane S, McQueen M, Teo K, Sheridan P, Bosch J, Pogue J, Yusuf S. Effects of ramipril and rosiglitazone on cardiovascular and renal outcomes in people with impaired glucose tolerance or impaired fasting glucose: results of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial. *Diabetes Care* 2008;**31**:1007-1014.

565. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJ, Team RS. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* 2009;**373**:2125-2135.

566. Kendall DM, Rubin CJ, Mohideen P, Ledeine JM, Belder R, Gross J, Norwood P, O'Mahony M, Sall K, Sloan G, Roberts A, Fiedorek FT, DeFronzo RA. Improvement of glycemic control, triglycerides, and HDL cholesterol levels with muraglitazar, a dual (alpha/gamma) peroxisome proliferator-activated receptor activator, in patients with type 2 diabetes inadequately controlled with metformin monotherapy: A double-blind, randomized, pioglitazone-comparative study. *Diabetes Care* 2006;**29**:1016-1023.

567. Kalliora C, Drosatos K. The Glitazars Paradox: Cardiotoxicity of the Metabolically Beneficial Dual PPARalpha and PPARgamma Activation. *J Cardiovasc Pharmacol* 2020;**76**:514-526.

568. Nissen SE, Wolski K, Topol EJ. Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. *JAMA* 2005;**294**:2581-2586.

569. Lincoff AM, Tardif JC, Schwartz GG, Nicholls SJ, Ryden L, Neal B, Malmberg K, Wedel H, Buse JB, Henry RR, Weichert A, Cannata R, Svensson A, Volz D, Grobbee DE, AleCardio I. Effect of aleglitazar on cardiovascular outcomes after acute coronary syndrome in patients with type 2 diabetes mellitus: the AleCardio randomized clinical trial. *JAMA* 2014;**311**:1515-1525.

570. Kalliora C, Kyriazis ID, Oka SI, Lieu MJ, Yue Y, Area-Gomez E, Pol CJ, Tian Y, Mizushima W, Chin A, Scerbo D, Schulze PC, Civelek M, Sadoshima J, Madesh M, Goldberg IJ, Drosatos K. Dual peroxisome-proliferator-activated-receptor-alpha/gamma activation inhibits SIRT1-PGC1alpha axis and causes cardiac dysfunction. *JCI Insight* 2019;**5**.

571. Hui H, Farilla L, Merkel P, Perfetti R. The short half-life of glucagon-like peptide-1 in plasma does not reflect its long-lasting beneficial effects. *European journal of endocrinology* 2002;**146**:863-869.

572. Rachman J, Barrow BA, Levy JC, Turner RC. Near-normalisation of diurnal glucose concentrations by continuous administration of glucagon-like peptide-1 (GLP-1) in subjects with NIDDM. *Diabetologia* 1997;**40**:205-211.

573. Mojsov S, Weir G, Habener J. Insulinotropin: glucagon-like peptide I (7-37) co-encoded in the glucagon gene is a potent stimulator of insulin release in the perfused rat pancreas. *J Clin Invest* 1987;**79**:616-619.

574. Ussher JR, Drucker DJ. Cardiovascular biology of the incretin system. *Endocr Rev* 2012;**33**:187-215.

575. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsboll T, Investigators S-. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2016;**375**:1834-1844.

576. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, Chan JC, Choi J, Gustavson SM, Iqbal N, Maggioni AP, Marso SP, Ohman P, Pagidipati NJ, Poulter N, Ramachandran A, Zinman B, Hernandez AF, Group ES. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2017;**377**:1228-1239.

577. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Kober LV, Lawson FC, Ping L, Wei X, Lewis EF, Maggioni AP, McMurray JJ, Probstfield JL, Riddle MC, Solomon SD, Tardif JC, Investigators E. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *N Engl J Med* 2015;**373**:2247-2257.

578. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB, Committee LS, Investigators LT. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2016;**375**:311-322.

579. Margulies KB, Hernandez AF, Redfield MM, Givertz MM, Oliveira GH, Cole R, Mann DL, Whellan DJ, Kiernan MS, Felker GM, McNulty SE, Anstrom KJ, Shah MR, Braunwald E, Cappola TP, Res NHFC. Effects of Liraglutide on Clinical Stability Among Patients With Advanced Heart Failure and Reduced Ejection

Fraction A Randomized Clinical Trial. *Jama-Journal of the American Medical Association* 2016;**316**:500-508.

580. Jorsal A, Kistorp C, Holmager P, Tougaard RS, Nielsen R, Hänselmann A, Nilsson B, Møller JE, Hjort J, Rasmussen J. 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.

581. Mentlein R, Gallwitz B, Schmidt WE. Dipeptidyl-peptidase IV hydrolyses gastric inhibitory polypeptide, glucagon‑like peptide‑1 (7–36) amide, peptide histidine methionine and is responsible for their degradation in human serum. *Eur J Biochem* 1993;**214**:829-835.

582. Deacon CF, Hughes TE, Holst JJ. Dipeptidyl peptidase IV inhibition potentiates the insulinotropic effect of glucagon-like peptide 1 in the anesthetized pig. *Diabetes* 1998;**47**:764-769.

583. Ahren B, Holst JJ, Martensson H, Balkan B. Improved glucose tolerance and insulin secretion by inhibition of dipeptidyl peptidase IV in mice. *Eur J Pharmacol* 2000;**404**:239-245.

584. Gutzwiller JP, Goke B, Drewe J, Hildebrand P, Ketterer S, Handschin D, Winterhalder R, Conen D, Beglinger C. Glucagon-like peptide-1: a potent regulator of food intake in humans. *Gut* 1999;**44**:81-86.

585. Dicker D. DPP-4 inhibitors: impact on glycemic control and cardiovascular risk factors. *Diabetes Care* 2011;**34 Suppl 2**:S276-278.

586. Burkey BF, Li X, Bolognese L, Balkan B, Mone M, Russell M, Hughes TE, Wang PR. Acute and chronic effects of the incretin enhancer vildagliptin in insulin-resistant rats. *J Pharmacol Exp Ther* 2005;**315**:688-695.

587. Ahren B, Simonsson E, Larsson H, Landin-Olsson M, Torgeirsson H, Jansson PA, Sandqvist M, Bavenholm P, Efendic S, Eriksson JW, Dickinson S, Holmes D. Inhibition of dipeptidyl peptidase IV improves metabolic control over a 4-week study period in type 2 diabetes. *Diabetes Care* 2002;**25**:869-875.

588. Ahren B, Landin-Olsson M, Jansson PA, Svensson M, Holmes D, Schweizer A. Inhibition of dipeptidyl peptidase-4 reduces glycemia, sustains insulin levels, and reduces glucagon levels in type 2 diabetes. *J Clin Endocrinol Metab* 2004;**89**:2078-2084.

589. Ristic S, Byiers S, Foley J, Holmes D. Improved glycaemic control with dipeptidyl peptidase-4 inhibition in patients with type 2 diabetes: vildagliptin (LAF237) dose response. *Diabetes Obes Metab* 2005;**7**:692-698.

590. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I, Committee S-TS, Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;**369**:1317-1326.

591. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Cushman WC, Zannad F,

Investigators E. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013;**369**:1327-1335.

592. White WB, Kupfer S, Zannad F, Mehta CR, Wilson CA, Lei L, Bakris GL, Nissen SE, Cushman WC, Heller SR, Bergenstal RM, Fleck PR, Cannon CP, Investigators E. Cardiovascular Mortality in Patients With Type 2 Diabetes and Recent Acute Coronary Syndromes From the EXAMINE Trial. *Diabetes Care* 2016;**39**:1267-1273.

593. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, Lachin JM, McGuire DK, Pencina MJ, Standl E, Stein PP, Suryawanshi S, Van de Werf F, Peterson ED, Holman RR, Group TS. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2015;**373**:232-242.

594. Fisher M. Series: Cardiovascular outcome trials for diabetes drugs Sitagliptin and TECOS. *Br J Diabetes* 2020;**20**:55-57.

595. Oyama J, Murohara T, Kitakaze M, Ishizu T, Sato Y, Kitagawa K, Kamiya H, Ajioka M, Ishihara M, Dai K, Nanasato M, Sata M, Maemura K, Tomiyama H, Higashi Y, Kaku K, Yamada H, Matsuhisa M, Yamashita K, Bando YK, Kashihara N, Ueda S, Inoue T, Tanaka A, Node K, Investigators PS. The Effect of Sitagliptin on Carotid Artery Atherosclerosis in Type 2 Diabetes: The PROLOGUE Randomized Controlled Trial. *PLoS Med* 2016;**13**:e1002051.

596. Ou SM, Chen HT, Kuo SC, Chen TJ, Shih CJ, Chen YT. Dipeptidyl peptidase-4 inhibitors and cardiovascular risks in patients with pre-existing heart failure. *Heart* 2017;**103**:414-420.

597. Sato A, Yoshihisa A, Kanno Y, Takiguchi M, Miura S, Shimizu T, Nakamura Y, Yamauchi H, Owada T, Sato T, Suzuki S, Oikawa M, Yamaki T, Sugimoto K, Kunii H, Nakazato K, Suzuki H, Saitoh SI, Takeishi Y. Associations of dipeptidyl peptidase-4 inhibitors with mortality in hospitalized heart failure patients with diabetes mellitus. *ESC Heart Fail* 2016;**3**:77-85.

598. Giorda CB, Picariello R, Tartaglino B, Marafetti L, Di Noi F, Alessiato A, Costa G, Gnavi R. Hospitalisation for heart failure and mortality associated with dipeptidyl peptidase 4 (DPP-4) inhibitor use in an unselected population of subjects with type 2 diabetes: a nested case-control study. *Bmj Open* 2015;**5**.

599. Monami M, Dicembrini I, Martelli D, Mannucci E. Safety of dipeptidyl peptidase-4 inhibitors: a meta-analysis of randomized clinical trials. *Curr Med Res Opin* 2011;**27 Suppl 3**:57-64.

600. Clifton P. Do dipeptidyl peptidase IV (DPP-IV) inhibitors cause heart failure? *Clin Ther* 2014;**36**:2072-2079.

601. Wu S, Hopper I, Skiba M, Krum H. Dipeptidyl peptidase-4 inhibitors and cardiovascular outcomes: meta-analysis of randomized clinical trials with 55,141 participants. *Cardiovasc Ther* 2014;**32**:147-158.

602. Hamdani N, Hervent AS, Vandekerckhove L, Matheeussen V, Demolder M, Baerts L, De Meester I, Linke WA, Paulus WJ, De Keulenaer G. Left ventricular diastolic dysfunction and myocardial stiffness in diabetic mice is attenuated by inhibition of dipeptidyl peptidase 4. *Cardiovasc Res* 2014;**104**:423-431.

603. Yin M, Sillje HH, Meissner M, van Gilst WH, de Boer RA. Early and late effects of the DPP-4 inhibitor vildagliptin in a rat model of post-myocardial infarction heart failure. *Cardiovasc Diabetol* 2011;**10**:85.

604. Gallo LA, Wright EM, Vallon V. Probing SGLT2 as a therapeutic target for diabetes: Basic physiology and consequences. *Diab Vasc Dis Res* 2015;**12**:78-89.

605. Hattersley AT, Thorens B. Type 2 Diabetes, SGLT2 Inhibitors, and Glucose Secretion. *N Engl J Med* 2015;**373**:974-976.

606. Vallon V, Thomson SC. Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. *Diabetologia* 2017;**60**:215-225.

607. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE, Investigators E-RO. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015;**373**:2117-2128.

608. Radholm K, Figtree G, Perkovic V, Solomon SD, Mahaffey KW, de Zeeuw D, Fulcher G, Barrett TD, Shaw W, Desai M, Matthews DR, Neal B. Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus: Results From the CANVAS Program. *Circ* 2018;**138**:458-468.

609. McMurray JJV, DeMets DL, Inzucchi SE, Kober L, Kosiborod MN, Langkilde AM, Martinez FA, Bengtsson O, Ponikowski P, Sabatine MS, Sjostrand M, Solomon SD, Committees D-H, Investigators. A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). *Eur J Heart Fail* 2019;**21**:665-675.

610. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Bohm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F, Investigators EM-RT. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med* 2020;**383**:1413-1424.

611. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;**380**:347-357.

612. Neal B, Perkovic V, Mahaffey KW, De Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**:644-657.

613. Adingupu DD, Gopel SO, Gronros J, Behrendt M, Sotak M, Miliotis T, Dahlqvist U, Gan LM, Jonsson-Rylander AC. SGLT2 inhibition with empagliflozin improves coronary microvascular function and cardiac contractility in prediabetic ob/ob(-/-) mice. *Cardiovasc Diabetol* 2019;**18**:16.

614. Lee HC, Shiou YL, Jhuo SJ, Chang CY, Liu PL, Jhuang WJ, Dai ZK, Chen WY, Chen YF, Lee AS. The sodium-glucose co-transporter 2 inhibitor empagliflozin attenuates cardiac fibrosis and improves ventricular hemodynamics in hypertensive heart failure rats. *Cardiovasc Diabetol* 2019;**18**:45.

615. Lopaschuk GD, Verma S. Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors: a state-of-the-art review. *Basic to Translational Science* 2020;**5**:632-644.

616. Lee TM, Chang NC, Lin SZ. Dapagliflozin, a selective SGLT2 Inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts. *Free Radic Biol Med* 2017;**104**:298-310.

617. Lim VG, Bell RM, Arjun S, Kolatsi-Joannou M, Long DA, Yellon DM. SGLT2 Inhibitor, Canagliflozin, Attenuates Myocardial Infarction in the Diabetic and Nondiabetic Heart. *JACC Basic Transl Sci* 2019;**4**:15-26.

618. 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.

619. Investigators OT, Gerstein HC, Bosch J, Dagenais GR, Diaz R, Jung H, Maggioni AP, Pogue J, Probstfield J, Ramachandran A, Riddle MC, Ryden LE, Yusuf S. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* 2012;**367**:319-328.

620. Marso SP, McGuire DK, Zinman B, Poulter NR, Emerson SS, Pieber TR, Pratley RE, Haahr PM, Lange M, Brown-Frandsen K, Moses A, Skibsted S, Kvist K, Buse JB, Group DS. Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes. *N Engl J Med* 2017;**377**:723-732.

621. Shiuchi T, Cui TX, Wu L, Nakagami H, Takeda-Matsubara Y, Iwai M, Horiuchi M. ACE inhibitor improves insulin resistance in diabetic mouse via bradykinin and NO. *Hypertension* 2002;**40**:329-334.

622. Torlone E, Britta M, Rambotti AM, Perriello G, Santeusanio F, Brunetti P, Bolli GB. Improved insulin action and glycemic control after long-term angiotensin-converting enzyme inhibition in subjects with arterial hypertension and type II diabetes. *Diabetes Care* 1993;**16**:1347-1355.

623. Alkharouf J, Nalinikumari K, Corry D, Tuck M. Long-term effects of the angiotensin converting enzyme inhibitor captopril on metabolic control in non-insulin-dependent diabetes mellitus. *Am J Hypertens* 1993;**6**:337-343.

624. Morris AD, Boyle DI, McMahon AD, Pearce H, Evans JM, Newton RW, Jung RT, MacDonald TM. ACE inhibitor use is associated with hospitalization for severe hypoglycemia in patients with diabetes. DARTS/MEMO Collaboration. Diabetes Audit and Research in Tayside, Scotland. Medicines Monitoring Unit. *Diabetes Care* 1997;**20**:1363-1367.

625. Seshadri S, Rapaka N, Prajapati B, Mandaliya D, Patel S, Muggalla CS, Kapadia B, Babu PP, Misra P, Saxena U. Statins exacerbate glucose intolerance and hyperglycemia in a high sucrose fed rodent model. *Sci Rep* 2019;**9**:8825.

626. Erqou S, Lee CC, Adler AI. Statins and glycaemic control in individuals with diabetes: a systematic review and meta-analysis. *Diabetologia* 2014;**57**:2444-2452.

627. Cui JY, Zhou RR, Han S, Wang TS, Wang LQ, Xie XH. Statin therapy on glycemic control in type 2 diabetic patients: A network meta-analysis. *J Clin Pharm Ther* 2018;**43**:556-570.

628. Kim J, Lee HS, Lee KY. Effect of statins on fasting glucose in non-diabetic individuals: nationwide population-based health examination in Korea. *Cardiovasc Diabetol* 2018;**17**:155.

629. Struthers AD, Murphy MB, Dollery CT. Glucose tolerance during antihypertensive therapy in patients with diabetes mellitus. *Hypertension* 1985;**7**:II95-101.

630. Vue MH, Setter SM. Drug-Induced Glucose Alterations Part 1: Drug-Induced Hypoglycemia. *Diabetes Spectr* 2011;**24**:171-177.

631. Dungan K, Merrill J, Long C, Binkley P. Effect of beta blocker use and type on hypoglycemia risk among hospitalized insulin requiring patients. *Cardiovasc Diabetol* 2019;**18**:163.

632. Wright AD, Barber SG, Kendall MJ, Poole PH. Beta-adrenoceptor-blocking drugs and blood sugar control in diabetes mellitus. *Br Med J* 1979;**1**:159-161.

633. Bakris GL, Fonseca V, Katholi RE, McGill JB, Messerli FH, Phillips RA, Raskin P, Wright JT, Jr., Oakes R, Lukas MA, Anderson KM, Bell DS, Investigators G. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA* 2004;**292**:2227-2236.

634. Sirenko Y. Effect of Beta - Blockers on Insulin Resistance in Patients with Hypertension and Metabolic Syndrome after 6 Months of Treatment. *J Endocrinol Diabetes* 2017;**4**:1-11.

635. Izawa H, Murohara T, Nagata K, Isobe S, Asano H, Amano T, Ichihara S, Kato T, Ohshima S, Murase Y, Iino S, Obata K, Noda A, Okumura K, Yokota M. Mineralocorticoid receptor antagonism ameliorates left ventricular diastolic dysfunction and myocardial fibrosis in mildly symptomatic patients with idiopathic dilated cardiomyopathy: a pilot study. *Circ* 2005;**112**:2940-2945.

636. Mottram PM, Haluska B, Leano R, Cowley D, Stowasser M, Marwick TH. Effect of aldosterone antagonism on myocardial dysfunction in hypertensive patients with diastolic heart failure. *Circ* 2004;**110**:558-565.

637. Kosmala W, Przewlocka-Kosmala M, Szczepanik-Osadnik H, Mysiak A, O'Moore-Sullivan T, Marwick TH. A randomized study of the beneficial effects of aldosterone antagonism on LV function, structure, and fibrosis markers in metabolic syndrome. *JACC Cardiovasc Imaging* 2011;**4**:1239-1249.

638. Srinivasa S, Fitch KV, Wong K, O'Malley TK, Maehler P, Branch KL, Looby SE, Burdo TH, Martinez-Salazar EL, Torriani M, Lyons SH, Weiss J, Feldpausch M, Stanley TL, Adler GK, Grinspoon SK. Randomized, Placebo-Controlled Trial to Evaluate Effects of Eplerenone on Metabolic and Inflammatory Indices in HIV. *J Clin Endocrinol Metab* 2018;**103**:2376-2384.

639. Nagatomo Y, Meguro T, Ito H, Koide K, Anzai T, Fukuda K, Ogawa S, Yoshikawa T. Significance of AT1 receptor independent activation of mineralocorticoid receptor in murine diabetic cardiomyopathy. *PLoS One* 2014;**9**:e93145.

640. Ramirez E, Klett-Mingo M, Ares-Carrasco S, Picatoste B, Ferrarini A, Ruperez FJ, Caro-Vadillo A, Barbas C, Egido J, Tunon J, Lorenzo O. Eplerenone attenuated cardiac steatosis, apoptosis and diastolic dysfunction in experimental type-II diabetes. *Cardiovasc Diabetol* 2013;**12**:172.

641. Liu W, Gong W, He M, Liu Y, Yang Y, Wang M, Wu M, Guo S, Yu Y, Wang X, Sun F, Li Y, Zhou L, Qin S, Zhang Z. Spironolactone Protects against Diabetic

Cardiomyopathy in Streptozotocin-Induced Diabetic Rats. *J Diabetes Res* 2018;**2018**:9232065.

642. Zhang M, Gu H, Xu W, Zhou X. Down-regulation of lncRNA MALAT1 reduces cardiomyocyte apoptosis and improves left ventricular function in diabetic rats. Int J Cardiol. 2016 Jan 15;203:214-6. doi: 10.1016/j.ijcard.2015.10.136. Epub 2015 Oct 19.

643. Zheng D, Zhang Y, Hu Y, Guan J, Xu L, Xiao W, Zhong Q, Ren C, Lu J, Liang J, Hou J. Long noncoding RNA Crnde attenuates cardiac fibrosis via Smad3-Crnde negative feedback in diabetic cardiomyopathy. FEBS J., 2019.

644. Zhao F, Li B, Wei YZ, Zhou B, Wang H, Chen M, Gan XD, Wang ZH, Xiong SX. MicroRNA-34a regulates high glucose-induced apoptosis in H9c2 cardiomyocytes. *J Huazhong Univ Sci Technolog Med Sci* 2013;**33**:834-839.

645. Chen C, Yang SL, Li HP, Yin ZW, Fan JH, Zhao YR, Gong W, Yan MW, Wang DW. Mir30c Is Involved in Diabetic Cardiomyopathy through Regulation of Cardiac Autophagy via BECN1. *Molecular Therapy-Nucleic Acids* 2017;**7**:127-139.

646. Li X, Du N, Zhang Q, Li J, Chen X, Liu X, Hu Y, Qin W, Shen N, Xu C, Fang Z, Wei Y, Wang R, Du Z, Zhang Y, Lu Y. MicroRNA-30d regulates cardiomyocyte pyroptosis by directly targeting foxo3a in diabetic cardiomyopathy. *Cell Death Dis* 2014;**5**:e1479.

647. Baseler WA, Thapa D, Jagannathan R, Dabkowski ER, Croston TL, Hollander JM. miR-141 as a regulator of the mitochondrial phosphate carrier (Slc25a3) in the type 1 diabetic heart. *Am J Physiol: Cell Physiol* 2012;**303**:C1244-C1251.

648. Panguluri SK, Tur J, Chapalamadugu KC, Katnik C, Cuevas J, Tipparaju SM. MicroRNA-301a mediated regulation of Kv4.2 in diabetes: identification of key modulators. *PLoS One* 2013;**8**:e60545.

649. Yi F, Shang YG, Li B, Dai SL, Wu W, Cheng L, Wang XC. MicroRNA-193-5p modulates angiogenesis through IGF2 in type 2 diabetic cardiomyopathy. *Biochem Biophys Res Commun* 2017;**491**:876-882.

650. Bergmark BA, Bhatt DL, McGuire DK, Cahn A, Mosenzon O, Steg PG, Im K, Kanevsky E, Gurmu Y, Raz I, Braunwald E, Scirica BM, I S-TSC. Metformin Use and Clinical Outcomes Among Patients With Diabetes Mellitus With or Without Heart Failure or Kidney Dysfunction Observations From the SAVOR-TIMI 53 Trial. *Circ* 2019;**140**:1004-1014.

651. Bromage DI, Godec TR, Pujades-Rodriguez M, Gonzalez-Izquierdo A, Denaxas S, Hemingway H, Yellon DM. Metformin use and cardiovascular outcomes after acute myocardial infarction in patients with type 2 diabetes: a cohort study. *Cardiovasc Diabetol* 2019;**18**:019-0972.

652. Yang Z, Wang M, Zhang Y, Cai F, Jiang B, Zha W, Yu W. Metformin Ameliorates Diabetic Cardiomyopathy by Activating the PK2/PKR Pathway. *Front Physiol* 2020;**11**:425.

653. Halabi A, Sen J, Huynh Q, Marwick TH. Metformin treatment in heart failure with preserved ejection fraction: a systematic review and meta-regression analysis. *Cardiovasc Diabetol* 2020;**19**:124.

654. Ye YM, Keyes KT, Zhang CF, Perez-Polo JR, Lin Y, Birnbaum Y. The myocardial infarct size-limiting effect of sitagliptin is PKA-dependent, whereas the protective

effect of pioglitazone is partially dependent on PKA. *American Journal of Physiology: Heart and Circulatory Physiology* 2010;**298**:H1454-H1465.

655. Liu Q, Anderson C, Broyde A, Polizzi C, Fernandez R, Baron A, Parkes DG. Glucagon-like peptide-1 and the exenatide analogue AC3174 improve cardiac function, cardiac remodeling, and survival in rats with chronic heart failure. *Cardiovasc Diabetol* 2010;**9**:76.

656. Sonne DP, Engstrom T, Treiman M. Protective effects of GLP-1 analogues exendin-4 and GLP-1(9-36) amide against ischemia-reperfusion injury in rat heart. *Regul Pept* 2008;**146**:243-249.

657. Noyan-Ashraf MH, Momen MA, Ban K, Sadi AM, Zhou YQ, Riazi AM, Baggio LL, Henkelman RM, Husain M, Drucker DJ. GLP-1R agonist liraglutide activates cytoprotective pathways and improves outcomes after experimental myocardial infarction in mice. *Diabetes* 2009;**58**:975-983.

658. Kim JA, Wei Y, Sowers JR. Role of mitochondrial dysfunction in insulin resistance. *Circ Res* 2008;**102**:401-414.

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Figure legends

Figure 1: Energy metabolic changes in a healthy setting versus diabetic cardiomyopathy. In the healthy heart, approximately 60% of the heart's energy comes from the oxidation of fatty acids, followed by approximately 5% by glycolysis and 25% from glucose oxidation, and 10% by ketone oxidation. However, in diabetic cardiomyopathy, due to systemic and local changes in energy substrate concentrations as well as insulin resistance, the metabolic protein machinery is perturbed and subsequently, the heart's overall energy metabolic profile is impaired. As such, diabetic cardiomyopathy results in an increase in fatty acid oxidation, decreased glucose metabolism and decreased ketone oxidation.

Figure 2: The different stages of diabetic cardiomyopathy. HFpEF, heart failure with preserved ejection fraction; HFrEF heart failure with reduced ejection fraction; HF, heart failure; AGEs, advanced glycation end products.

Figure 3: Mechanisms that contribute to diabetes-induced heart failure. While the exact pathophysiology of the diabetic-induced heart failure still not fully defined, there are a number of mechanisms that play important roles in its occurrence. This includes mitochondrial dysfunction, cardiac insulin resistance and impaired cardiac insulin signaling pathway, perturbed fuel use, low ATP levels, inflammation, advanced glycation end products, O-GlcNAcylation, cell death, neurohormonal mechanism, contractile

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proteins dysfunction, oxidative stress, gene reprogramming, lipotoxicity, glucose toxicity and perturbed Ca^{2+} handling.

Figure 4: Gene expression dysregulation in diabetic cardiomyopathy. CD36: cluster of differentiation 36; PPARα: Peroxisome proliferator-activated receptor; FABP: fatty-acid-binding proteins; GLUT1: glucose transpoter 1; GLUT4: glucose transporter 4; PDK: pyruvate dehydrogenase kinase; MG53: mitsugumin 53; ANP: atrial natriuretic peptide; NF-kB: nuclear factor kappa B; TGF-β1: transforming growth factor beta 1; MMP2: matrix metalloproteinase-2; Mst1: macrophage Stimulating 1; SERCA2a: sarcoplasmic-endoplasmic reticulum Ca2+ ATPase 2a; MCP-1: monocyte chemoattractant protein-1; VCAM-1: vascular cell adhesion molecule 1; TNFα: tumor necrosis factor; SOCS3: suppressor of cytokine signaling-3; COL1A1: collagen type 1 alpha1.

Figure 5. Summary figure of various antihyperglycemic drugs and their mode of action in the context of the heart. Fatty acid, glucose and ketone body metabolism are represented in this figure with the key modes of homeostasis regulation presented. SGLT2 inhibitors inhibit SGLT2 in the proximal tubules and thus, prevent renal glucose reabsorption, promote glycosuria, decreased insulin release, increased hepatic ketogenesis and increased circulating blood ketone levels. These increased circulating ketones can subsequently modulate cardiac ketone oxidation rates. Metformin's mode of action is not well understood, although it does stimulate AMPK which inhibits ACC, decreases malonyl-CoA levels and increases fatty acid metabolism. DPP4 inhibitors prevent DPP4 from inactivating GLP-1, and thus increase GLP-1 levels to potentiate

insulin secretion from pancreatic beta cells. GLP-1 receptor agonists similarly increase GLP-1 levels to increase insulin secretion. Sulfonylureas bind to SUR1, and consequently the K-ATP channel closes, depolarizing the pancreatic islet cell and increasing intracellular calcium levels to promote secretion of insulin. Lastly, TZDs have widespread actions in the body but here we focus on its role in promoting glucose metabolism and improving insulin sensitivity via binding to PPARγ and promoting the transcription of genes involved in glucose uptake and metabolism.

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Table 1: Alterations in miRNA, LncRNA, CircRNA and their role in diabetic cardiomyopathy

Non-coding RNAs	Subclasses	Status	Study setting	Altered proteins /RNAs	Pathological Pathways involved	Reference
HOTAIR	lncRNA	Downregulated	STZ induced diabetic mice, H9c2 cardiomyocytes	SIRT1	Apoptosis & inflammation	[513]
MALAT1)	lncRNA	Upregulated	STZ- induced diabetic rats	-	Apoptosis	[642]
MIAT	lncRNA	Upregulated	STZ induced diabetic rats, neonatal cardiomyocytes	miR-22-3p	Apoptosis	[514]
Crnde	lncRNA	Downregulated	STZ induced diabetic mice, mouse neonatal cardiac fibroblasts	Smad3	Fibrosis	[643]
LncRNA H19	lncRNA	Downregulated	STZ-induced diabetic rats, neonatal cardiomyocytes	VDAC1 , miR-675, EZH2 & DIRAS3	Autophagy& apoptosis	[515, 517]
Zfas1	lncRNA	Upregulated	STZ-induced diabetic mice, H9c2 cardiomyocytes	miR-9 , FN mRNA, Col1&4	Fibrosis	[516]
miR-1	miRNA	Upregulated	STZ induced diabetic rats	Junctin	Oxidative stress	[530]
miR-30c, miR-181a	miRNA	Down regulated	Diabetic patients, diabetic rats, and H9c2 cardiomyocytes	p53, p21, ANP	Hypertrophy & apoptosis	[518]

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miRNA133a	miRNA	Downregulated	STZ-induced diabetic mice, neonatal rat cardiomyocytes	ANP, BNP, MEF2A and MEF2C	Hypertrophy	[519]
miR-133a	miRNA	Downregulated	STZ-induced diabetic mice	TGF-β1, fibronectin (FN1) and COL4A1	Fibrosis	[523]
miR-150	miRNA	Downregulated	STZ induced diabetic rats, neonatal rat cardiomyocytes	p300	Hypertrophy	[520]
miR-373	miRNA	Down regulated	Diabetic mice , neonatal rat cardiomyocytes	MAPK signaling (ERK1/2, JNK, and p38)	Hypertrophy	[521]
miRNA-1, miRNA-208a	miRNA	upregulated	STZ-induced diabetic mice, diabetic patients	pro-survival Pim-1 & Caspase-3	Apoptosis	[526]
miR-451	miRNA	Upregulated	type 2 diabetic mice, neonatal rat cardiac myocytes	Calcium-binding protein 39 (Cab39)	Hypertrophy and contractile	[522]
miR-195, miR-34a	miRNA	Upregulated	STZ induced diabetic mice	BCL-2? H9c2 cells	Apoptosis	[527, 644]
miR-144	miRNA	Upregulated	STZ-induced diabetic mice	Nuclear factor erythroid-2-related factor 2 (Nrf2)	Oxidative stress	[531]
miR-483-3p	miRNA	Upregulated	STZ-induced diabetic mice, H9c2 cardiomyocyte	Insulin growth factor 1 (IGF1)	Apoptosis	[528]

miR30c	miRNA	Down regulated	Type 2 db/db mice, H9c2 cardiomyocytes	BECN1	Autophagy	[645]
miR-30d	miRNA	Up regulated	STZ-induced diabetic rats, neonatal rat cardiomyocytes	Caspase-1, IL-1β and IL-18 & Foxo3a	Pyroptosis	[646]
miR-15a/b	miRNA	down-regulated	Type 2 diabetic patients, type 2 db/db mice HL-1 cardiomyocytes	(TGFβR1) and connective tissue growth factor (CTGF)	Fibrosis	[524]
miR-29	miRNA	dysregulated	Zucker diabetic fatty (ZDF) rats, HL-1 cardiomyocytes	Myeloid Cell Leukemia 1(MCL-1)	Apoptosis	[529]
miR-200b	miRNA		STZ-induced diabetic mice			
miR-200	miRNA	Upregulated	db/db mice	cyclooxygenase-2	Inflammation	[532]
miR-141	miRNA	Upregulated	STZ-induced diabetes,HL-1 cells	mitochondrial phosphate carrier (Slc25a3)	Mitochondrial ATP production.	[647]
miR-146a	miRNA	downregulated	STZ-induced diabetes	L6, TNFα, IL-1β, MCP-1, NF-κB, Col1α1, Col4α1	Fibrosis & inflammation	[525]

miR-301	miRNA	Upregulated	Type 2 db/db mice ,H9C2 cells	Voltage-gated potassium channel (Kv4.2)	Action potential	[648]
miR-193-5p	miRNA	Upregulated	Myocardial microvascular endothelial cells of type 2 diabetic Goto-Kakizaki (GK) rats	IGF2	Angiogenesis	[649]
circRNA_010567	crcRNA	Upregulated	db/db mice, cardiacfibroblasts	TGF-β1	Fibrosis	[537]
circHIPK3	circRNA	Upregulated	STZ induced diabetic mice	*Col1α1* and *Col3α1*	Fibrosis	[538]
circ_0076631	circRNA	Upregulated	Type 2 diabetic patients, AC16 cardiomyocyte	Caspase 1	Pyroptosis	[539]

lncRNA: long non-coding RNA; miRNA: micro-RNA; circRNA: circular-RNA; STZ: Streptozotocin; VDAC1; voltage-dependent anion channel 1; EZH2: enhancer of zeste homolog 2; FN: fibronectin; Col 1&4: collagen type 1& 4; ANP: atrial natriuretic peptide; B-type natriuretic peptide; MEF2A: myocyte enhancer factor 2A; TGF-β1: transforming growth factor-beta 1; MAPK: mitogen-activated protein kinase; ERK1: extracellular signal‑regulated protein kinase 1; JNK: jun N-terminal kinase; BECN1: IL-1β: interleukin-1β; IL-1β: interleukin-18; GFβR1: transforming growth factor beta receptor I; CTGF: connective tissue growth factor; IL-6: interleukin-6; TNFα: tumor necrosis factor-alpha; MCP-1: monocyte chemoattractant protein-1; Col1α1:collagen type I alpha 1; Col4α1: collagen type IV alpha 1; IGF2: insulin-like growth factor 2; Col3α1: collagen type III alpha 1

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Table 2: The effects of different classes of anti-diabetes drugs on the cardiovascular system and the development of diabetic cardiomyopathy

Class of the therapy	Biological target of each drug class	Study characteristics	Main findings	References
Metformin	Unknown	Systematic review randomized clinical trials (RCTs)	-Improved cardiovascular outcomes in early stage of diabetes -No beneficial effects after hospitalization or in those with overt CVD	550
		Post hoc analysis of SAVOR-TIMI 53 Trial (Saxagliptin and Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus	No effect on CVD end points in patients with prior heart failure and kidney disease	650
		Prospective cohort study	Increased risk of CVD and death in patients with T2DM at the time of first AMI May be beneficial in Post-AMI	651
		Experimental DCM (both *in vivo & in vitro*)	improved cardiac function and alleviation of apoptosis	652
		Systematic review and meta-regression analysis	Reduced mortality in patients with HFpEF	653
		Observational study	Has no effect on the risk of HF-related exacerbation	551
Sulfonylureas				
		Retrospective analysis of 20,450 type 2 diabetic patients	Increased risk of adverse cardiovascular events with sulfonylureas	553
Sulfonylureas	Stimulate insulin release from the pancreas	Meta-analysis of 115 randomized clinical trials	Increased mortality and risk of stroke with sulfonylureas in type 2 diabetics	555
		Meta-analysis of 9 observational studies	Combination therapy with sulfonylureas and metformin increased the relative risk of	556

			cardiovascular mortality and hospitalization	
		Retrospective cohort analysis of 1787,341 diabetic patients	Sulfonylureas increased the risk of non-fatal cardiovascular outcomes and all-cause mortality	557
		Retrospective cohort analysis of 5,730 patients with type 2 diabetes	Increased risk of adverse cardiovascular outcomes with sulfonylurea treatment or combination therapy of sulfonylurea + metformin	558
		Meta-regression analysis of 18 studies	Increased risk of cardiovascular mortality and events with sulfonylurea treatment	559
Glicazide and glimepiride vs. glibenclamide		Network meta-analysis of 167, 327 patients	Gliclazide and glimepiride lowered the risk of cardiovascular-related mortality and all-cause mortality than glibenclamide.	560
Non-specific, long-acting sulfonylureas (glyburide, glimepiride)		Retrospective cohort analysis of 17,604 sulfonylurea initiators	Does not increase myocardial infarction, ischemic stroke, cardiovascular deaths or all-cause mortality	561
Short-acting sulfonylureas (glicazide, glipizide, tolbutamide)			Increases myocardial infarction, ischemic stroke, cardiovascular deaths or all-cause mortality	
Thiazolidinediones				
Pioglitazone	Bind avidly to peroxisome proliferator-activated receptor gamma in adipocytes to promote adipogenesis and fatty acid uptake	5238 type 2 diabetic patients treated with either pioglitazone or placebo for 4 years	Pioglitazone increases the percent of heart failure hospitalizations but associated with decreased cardiac ischemic events	563
Rosiglitazone		5,269 subjects with impaired glycemic control treated with ramipril, rosiglitazone or placebo	Rosiglitazone increased new-onset heart failure despite decrease diabetes	564
		4447 type 2 diabetic patients on metformin or sulfonylurea monotherapy received either	Rosiglitazone increased the risk of heart failure or hospitalization	565

		rosiglitazone or a combination of metformin and sulfonylurea		
Dipeptidyl-peptidase 4 (DPP4) inhibitors				
Saxagliptin		Type 2 diabetic patients who had a history of, or were at risk for cardiovascular events received saxagliptin or placebo and followed individuals for 2 years	Saxagliptin increased the rate of hospitalization for heart failure in type 2 diabetic patients, with no effect on any other outcomes including rate of ischemic events, myocardial infarction, or death	590
Alogliptin	Block the action of Dipeptidyl-peptidase 4 (DPP4) on incretins	Type 2 diabetic patients with a recent acute coronary syndrome (either an acute myocardial infarction or unstable angina requiring hospitalization within the previous 15 to 90 days), received either alogliptin or placebo and were followed individuals for 40 months	Alogliptin was non-inferior to placebo on major adverse cardiovascular events (MACE - rates of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke)	591
Sitagliptin		Type 2 diabetic patients with pre-existing cardiovascular disease received either Sitagliptin or placebo and were followed for 3 years	Sitagliptin neither improved or decreased rates of cardiovascular events such as death, myocardial infarction, stroke, or hospitalization for heart failure	593
Sitagliptin		Type 2 diabetes received either sitagliptin or conventional therapy and were followed for 2 years	Sitagliptin did not have any additional effects on the progression of carotid IMT in participants with type 2 diabetes; no significant	595

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			differences between groups	
DDP-4 Inhibitors		Identified patients from Taiwan's National Health Insurance Research who were diagnosed with type 2 diabetes mellitus (T2DM) and had previous history of HF between 2009 and 2013 who did and did not use DPP-4 inhibitors.	The risks of all-cause mortality, and mortality from the combination of MI and stroke, and ischemic stroke were lower for patients receiving DPP-4 inhibitors than for those who did not receive this treatment. The risk of hospitalization for heart failure had no significant differences between groups.	596
DPP-4 inhibitors		Analysis of heart failure patients with diabetes mellitus who were hospitalized due to their heart failure and discharged from Fukushima Medical University between 2009 and 2013, and either did or did not take DPP4 inhibitors	DPP-4 inhibitor use was associated with low cardiac and all-cause mortality in heart failure patients with diabetes mellitus hospitalized for heart failure	597
DPP-4 inhibitors		A meta-analysis of randomized clinical trials to determine the effect of DPP4 inhibitors on the incidence of MACE, cancer, and pancreatitis	DPP-4 inhibitor use may be associated with a possible protection from cardiovascular events	599
DPP-4 inhibitors		A systematic review of articles with the search terms _DPP-IV inhibitors_ and _heart failure_ in full papers and abstracts published since October 2013	DPP-4 inhibitor use may increase the risk of hospitalization for heart failure, should be used with caution especially in patients with a history of CVD and heart failure	600
DPP-4 inhibitors		A meta-analysis of clinical trials assessing the effects of DPP-4 inhibitors in	DPP-4 inhibitors have a no significant effects on both all-cause and cardiovascular mortality; there is a statistically	601

		participants with type 2 diabetes mellitus	significant increase in heart failure hospitalizations with DPP-4 inhibitors in comparison with placebo or other hypoglycemic agents	
Sitagliptin		Male CD-1 mice received sitagliptin prior to 30 min myocardial ischemia and 4 h reperfusion	Sitagliptin limited myocardial infarct size post myocardial ischemia and reperfusion	654
Sitagliptin		db/db mice received either sitagliptin or vehicle for 8 weeks	Sitagliptin decreased LV passive stiffness and improved global LV performance	602
Vildagliptin		Sprague-Dawley rats pretreated with either vildagliptin or vehicle then subjected to coronary ligation to induce MI	Vildagliptin showed no cardioprotective effects on cardiac function, remodeling, or infarct size	603
Glucagon-like peptide 1 (GLP-1) receptor agonists				
Exenatide	Mimic the action of incretin on insulin release from the pancreas	Patients with type 2 diabetes, with or without previous cardiovascular disease received either exenatide or placebo and were followed for 3 years	Exenatide showed no significant differences in the incidence of major adverse cardiovascular events	576
Lixisenatide		Type 2 diabetes who had had a myocardial infarction or who had been hospitalized for unstable angina within the previous 180 days received either lixisenatide or placebo and were followed for 2 years	Lixisenatide treatment showed no significant effect on major adverse cardiovascular events (MACE) between type 2 diabetic patients who had a recent acute coronary event	577

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Liraglutide		Patients with type 2 diabetes and high cardiovascular risk; individuals received either liraglutide or placebo and were followed up for 3 years	Liraglutide treatment demonstrated a lower risk of MACE, including the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	578
Semaglutide		Type 2 diabetic patients received either semaglutide or placebo for 104 weeks	Semaglutide lowered the rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	575
Liraglutide		Patients with established heart failure and reduced LVEF who were recently hospitalized received either liraglutide or placebo and were followed for 180 days	Liraglutide showed no improved post-hospitalization clinical stability with Liraglutide in recently hospitalized patients with established heart failure and reduced ejection fraction	579
Liraglutide		Diabetic and nondiabetic patients with reduced left ventricular ejection fraction received either liraglutide or placebo for 24 weeks	Liraglutide did not improve LVEF or systolic function, and was associated with an increase in heart rate and more serious cardiac adverse events	580
		Male Sprague-Dawley rats received either exenatide analog AC3174 or vehicle two weeks post-MI for 11 weeks	Exenatide analog, AC3174, improved cardiac function, morphology and survival	655
Exendin-4		Male Sprague-Dawley rats heart received either exendin-4 or GLP-1(9-36) amide, the primary endogenous metabolite of GLP-1, following 45 minutes ischemia	Exendin treatment administered at reperfusion reduced infarct size and improved mechanical performance in isolated Sprague Dawley rat hearts during ischemia-reperfusion	656

		prior to 120 minutes reperfusion		
Liraglutide		Male C57BL/6 mice received liraglutide for 1 week prior to a permanent surgical ligation of the left anterior descending artery	Liraglutide treatment decreased infarct size, and improved cardiac output 4 weeks post ischemia in mice	657
sodium-glucose transport protein 2 (SGLT2) inhibitors				
Empagliflozin	Inhibit sodium-glucose transport protein 2 in the kidney and prevent the kidneys from reabsorbing glucose back into the blood	Patients with type 2 diabetes at high risk for cardiovascular events; individuals received either empagliflozin or placebo once daily and were followed up for around 3 years	Empagliflozin treatment showed a lower occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, and a reduction in overall mortality and heart failure hospitalization in type 2 diabetics patients with cardiovascular risk compared to placebo	607
Canagliflozin		Patients with type 2 diabetes and an elevated risk of cardiovascular disease; individuals received either canagliflozin or vehicle and were followed for 188 weeks	Canagliflozin showed a lower risk of cardiovascular events	612
Dapagliflozin		Patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease; individuals received ither dapagliflozin or placebo and were followed for 4 years	Dapagliflozin showed a reduction in cardiovascular death and heart failure hospitalization	611
Dapagliflozin		Patients with heart failure and reduced ejection fraction	Dapagliflozin reduced the risk of mortality and heart failure reduction in	609

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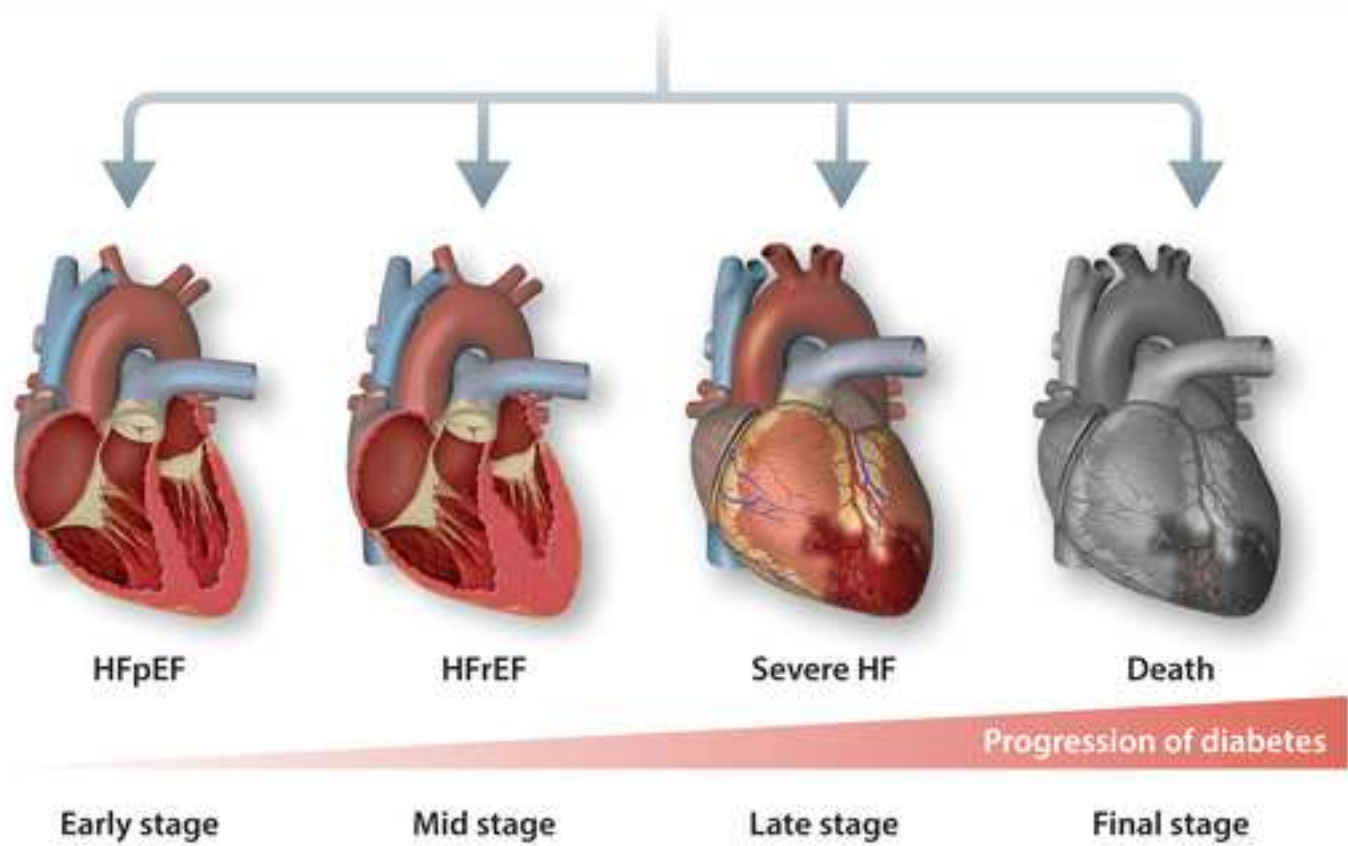|				
		with or without type 2 diabetes; individuals received either dapagliflozin or placebo and were followed for around 18 months	patients with heart failure and reduced ejection fraction with or without type 2 diabetes	
Empagliflozin		Patients with class II, III, or IV heart failure and an ejection fraction of 40% or less; individuals received empagliflozin or placebo and were followed for 16 months	Individuals receiving empagliflozin had a lower risk of cardiovascular death or hospitalization for heart failure than those receiving placebo, regardless of the presence or absence of diabetes	610
Empagliflozin		ob/ob$^{-/-}$ mice received empagliflozin for 10 weeks	Empagliflozin improved cardiac contractility, by fractional area change, and improved microvascular function after 10 weeks of treatment compared to controls	613
Empagliflozin		Spontaneous hypertensive rats (SHR) fed with high fat diet received empagliflozin for 12 weeks	Empagliflozin attenuated cardiac fibrosis and improved hemodynamics in in a hypertensive rat heart failure model	614
Insulin				
Insulin	Enhances glucose uptake and oxidation	12,537 people with cardiovascular risk factors plus impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes to receive insulin or standard care	Rates of incident cardiovascular outcomes were similar in the insulin-glargine and standard-care	619
		7637 patients with type 2 diabetes to receive either insulin degludec or insulin glargine	Degludec was noninferior to glargine concerning the incidence of major cardiovascular events	620

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Table 3: The effects of different classes of heart failure therapies on glycemic control and diabetic cardiomyopathy

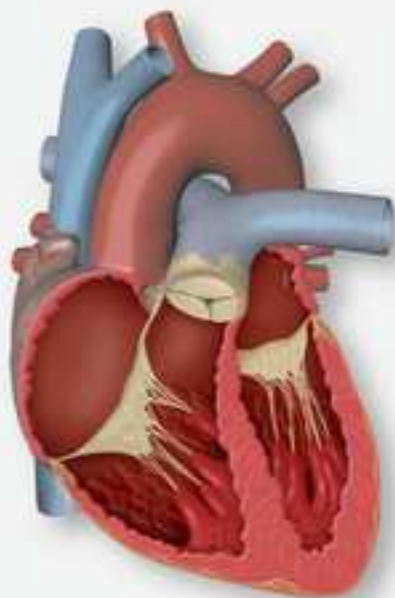| Class of the therapy	Biological target of each drug class	Study characteristics	Main findings	References
Renin-Aldosterone-Angiotensin System inhibitors				
Renin-Aldosterone-Angiotensin System inhibitors	Reduce sodium and water retention	Case-control study of 6,649 diabetic patients using ACE inhibitors	Increased the hospitalization for severe hypoglycemia	[624]
Temocapril		Diabetic mice treated with temocapril for 14 days	Temocapril decreased improved glycemic control	[621]
Captopril		Single blind, cross-over study with 16 type 2 diabetic patients treated with captopril or placebo for two 3-month treatment periods	Captopril improved glycemic control and insulin sensitivity in postprandial conditions	[622]
		130 diabetic patients treated with captopril for 4 months	Captopril improved glucose control	[623]
Lipid-lowering agents				
Lipid-lowering agents	Inhibitor of HMG-CoA reductase, the enzyme that catalyses the first step of cholesterol synthesis	Meta-analysis of 9 trials	Statins increase HbA1c levels	[626]
		Meta-analysis of 23 trials	Statins increase HbA1c levels	[627]
Pitavastatin		Meta-analysis of 23 trials	Improved glycemic control	[627]
Atorvastatin		Meta-analysis of 23 trials	Worsened glycemic control	[627]
Atorvastatin, rosuvastatin, pitavastatin and simvastatin		National health screening cohort of 379,865 non-diabetic individuals	Statins increase fasting glucose levels	[658]

		taking statins for 11 years		
ß-receptor blockers				
Atenolol, metoprolol	Reduce sympathetic output in the heart	Retrospective study of patients receiving either carvedilol or a selective second-generation beta-blocker (metoprolol or atenolol)	Metoprolol or atenolol increased hypoglycemia	631
Propranolol, metoprolol		20 hypertensive diabetic patients receiving propranolol or metoprolol	Propranolol or metoprolol increased mean blood sugar levels	632
Second generation ß$_1$-selective-blockers (Metoprolol)		Randomized, double-blind parallel-group trial with 1235 diabetic patients treated with carvedilol or metoprolol	Metoprolol increased HbA$_{1C}$	633
Third generation non-selective ß-blockers (Carvedilol)		Randomized, double-blind parallel-group trial with 1235 diabetic patients treated with carvedilol or metoprolol	Carvedilol improved insulin sensitivity	633
Aldosterone antagonists				
Spironolactone	Reduce sodium and water retention	25 dilated cardiomyopathy patients with a New York Heart Association functional class of I or II were examined before and after treatment with spironolactone for 12 months	Spironolactone reduced collagen accumulation in the heart and improved LV function	635
		30 medically treated ambulatory hypertensive patients with	Spironolactone improved diastolic function and limited fibrosis	636

		diastolic dysfunction and without ischemia were randomized to spironolactone or placebo for 6 months		
		Eighty patients with metabolic syndrome treated with angiotensin II inhibition, were randomized to spironolactone or placebo for 6 months	Spironolactone improved diastolic function and limited fibrosis	637

- Mitochondrial dysfunction
- Insulin resistance
- Impaired insulin signaling
- Hyperglycemia
- ROS generation
- Inflammation
- Fibrosis
- Hypertrophy

- Dyslipidemia
- Perturbed Ca^{2+} handling
- Contractile protein dysfunction
- Autophagy
- Lipotoxicity
- Glucotoxicity
- Cell Death
- O-GlcNAcylation

- AGEs
- Neurohormonal mechanisms
- Ischemia
- Hypertension
- Renal Failure
- Microangiopathy
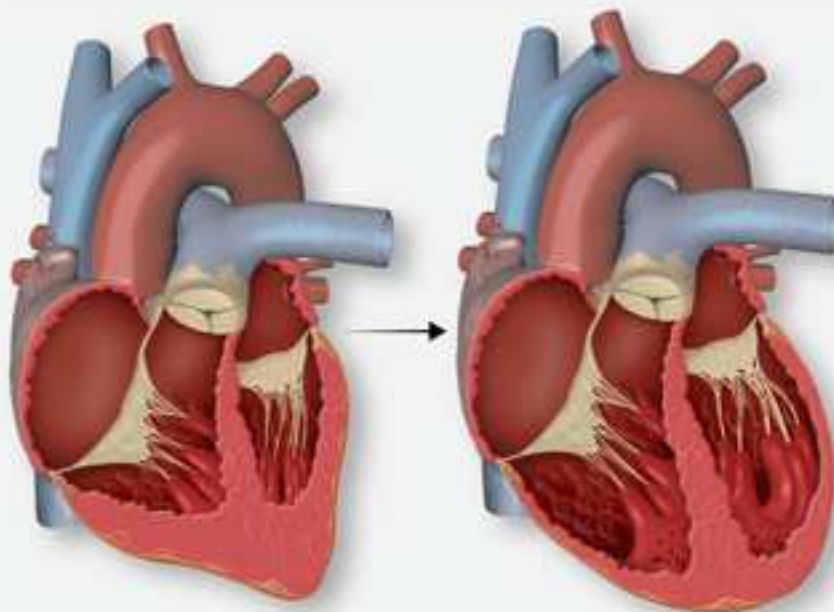- Coronary artery disease
- Macroangiopathy

HFpEF

HFrEF

Severe HF

Death

Progression of diabetes

Early stage

Mid stage

Late stage

Final stage

Healthy heart

- 60% Fatty acid oxidation
- 5% Glycolysis
- 25% Glucose oxidation
- 25% Ketone oxidation

Diabetic cardiomyopathy

- ↑ Fatty acid oxidation
- ↓ Glycolysis
- ↓ Glucose oxidation
- ↓ Ketone oxidation

The diabetic cardiomyopathy puzzle

Calcium dysregulation
↓ SERCA2a

Inflammation
↑ MCP-1   ↑ NTFα
↑ COX-2   ↓ SOCS3
↑ VCAM-1

Altered metabolism
↑ CD-36   ↓ GLUT1
↑ PPARα   ↓ GLUT4
↑ FABP   ↑ PDK

Cell death
↑ Bax
↑ Fas
↑ Mst1

Hypertrophy
↑ ANP
↑ PPARa
↑ NF-Kβ

Diabetic cardiomyopathy

Insulin resistance
↑ FOXO proteins
↑ MG53

Fibrosis
↑ TGF-B1   ↑ collagen IV
↑ MMP2   ↑ COL1A1