AMPK is associated with the beneficial effects of antidiabetic agents on cardiovascular diseases

Qingguo Lu1,2, Xuan Li2, Jia Liu2,3, Xiaodong Sun2,4, Thomas Rousselle2, Di Ren2, Nanwei Tong1 and Ji Li2

1Department of Endocrinology and Metabolism, West China Hospital of Sichuan University, 610041 Chengdu, China; 2Department of Physiology and Biophysics, Mississippi Center for Heart Research, University of Mississippi Medical Center, 39216 Jackson, MS, U.S.A.; 3Department of Geriatrics, The First Hospital of Jilin University, 130021 Changchun, China; 4Department of Endocrinology, Affiliated Hospital of Weifang Medical University, 261000 Weifang, China

Correspondence: Ji Li (jli3@umc.edu)

Diabetics have higher morbidity and mortality in cardiovascular disease (CVD). A variety of antidiabetic agents are available for clinical choice. Cardiovascular (CV) safety assessment of these agents is crucial in addition to hypoglycemic effect before clinical prescription. Adenosine 5′-monophosphate-activated protein kinase (AMPK) is an important cell energy sensor, which plays an important role in regulating myocardial energy metabolism, reducing ischemia and ischemia/reperfusion (I/R) injury, improving heart failure (HF) and ventricular remodeling, ameliorating vascular endothelial dysfunction, antichronic inflammation, anti-apoptosis, and regulating autophagy. In this review, we summarized the effects of antidiabetic agents to CVD according to basic and clinical research evidence and put emphasis on whether these agents can play roles in CV system through AMPK-dependent signaling pathways. Metformin has displayed definite CV benefits related to AMPK. Sodium-glucose cotransporter 2 inhibitors also demonstrate sufficient clinical evidence for CV protection, but the mechanisms need further exploration. Glucagon-like peptide1 analogs, dipeptidyl peptidase-4 inhibitors, α-glucosidase inhibitors and thiazolidinediones also show some AMPK-dependent CV benefits. Sulfonylureas and meglitinides may be unfavorable to CV system. AMPK is becoming a promising target for the treatment of diabetes, metabolic syndrome and CVD. But there are still some questions to be answered.

Introduction

The prevalence of diabetes has been growing rapidly over the past 20 years. Number of diabetic patients of 20–79 years old worldwide is expected to increase to 439 million by 2030 [1]. Diabetes is considered as a significant risk factor for cardiovascular disease (CVD), the primary cause of mortality worldwide [2,3]. In 2012, about 1.5 million people died of diabetes in the world, of which about 80% were associated with myocardial infarction (MI) or stroke [4].

Diabetes treatment aims to control multiple risk factors, such as hyperglycemia, hyperlipidemia, and hypertension, etc., in order to decrease the incidence of CVD and other complications. A variety of antidiabetic agents are available clinically, for example: sulfonylureas and meglitinides, biguanides, α-glucosidase inhibitors (AGIs), thiazolidinediones (TZDs), glucagon-like peptide1 (GLP-1) analogs, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, insulin and insulin analogs, etc. Previously, cardiovascular (CV) safety was rarely assessed in large clinical trials before antidiabetic agents were approved for market, and the majority of data obtained originally from postmarketing clinical observations. In 2007, however, an amazing result of a meta-analysis from 42 randomized trials treated with rosiglitazone, one of TZDs, was reported by Nissen and Wolski [5], which showed a possible increased risk of MI and death from CVD when comparing to the control group. This result sparked long-standing debate, although no excess CVD risk was reported in the following studies [6]. Consequently, a guidance about requiring the evidence of CV safety of novel antidiabetic agents by the...
pharmaceutical industry before approval was released by the US Food and Drug Administration (US FDA) [7].

Diabetic CVD is caused by many pathophysiological processes, such as macroangiopathy, microangiopathy, metabolic abnormalities, chronic inflammation, and fibrosis [8,9]. Pathogenesis and protective molecular mechanisms of diabetic CVD have been the focus of research in recent years. Adenosine 5'-monophosphate-activated protein kinase (AMPK) is an important serine and threonine protein kinase with the structure of three subunits (α, β, γ), which plays crucial roles in cell energy metabolism [10]. Increasing the ratio between intracellular adenosine monophosphate (AMP) and adenosine triphosphate (ATP), such as during strenuous exercise, hypoxia or nutritional deficiency, could phosphorylate a threonine, the 172th amino acid of the α subunit, thereby activating AMPK [11]. In addition, liver kinase B1 (LKB1), calmodulin-dependent protein kinase β (CaMKKβ) and AMP kinase (AMPKK) can be employed as upstream molecules. After activation, AMPK shuts down pathways of ATP-consuming and switches on catabolic pathways of ATP-producing through downstream signaling and target molecules [12,13], regulates lipid and protein metabolism, fatty acid oxidation, glucose uptake, gluconeogenesis, and autophagy [12–15], etc. AMPK also plays an important role in reducing oxidative stress, regulating autophagy, and anti-apoptosis of cardiomyocytes [16,17].

Our research team and others have reported that AMPK played cardioprotective roles during ischemia by increasing glucose uptake and glucose transporter 4 (GLUT4) translocation [18], decreasing apoptosis, improving postischemic recovery and limiting MI [7,19]. Furthermore, our studies have also suggested that activated protein C could activate AMPK and protect the heart from ischemia/reperfusion (I/R) injury [20], and inhibit inflammatory responses during hypoxia/reoxygenation (H/R) by modulating a JNK-mediated nuclear factor κB (NF-κB) pathway [21].

Antidiabetic agents may affect the CV system through many molecular signaling pathways. In this review, we intend to summarize the literature and discuss whether commonly used antidiabetic agents can affect CVD through AMPK-related signaling and molecular pathways.

**Sulfonylureas and meglitinides**

Sulfonylureas act by binding to sulphonylurea receptor 1 (SUR1) of pancreatic β cells, and close the ATP-sensitive potassium channels (KATP), causing an augment of intracellular K⁺, triggering of membrane depolarization, opening of voltage-dependent Ca²⁺ channels, increasing intracellular Ca²⁺ influx, then inducing insulin secretion [22]. Glibenclamide, glipizide, gliclazide, and glimepiride are commonly used in clinical practice. Meglitinides, including repaglinide, nateglinide and mitiglinide, display a similar hypoglycemic mechanism (binding to SUR2) as sulfonylureas.

Concern exists regarding the CV safety of sulfonylureas [23]. In the UK Prospective Diabetes Study (UKPDS), CV mortality was similar in patients of chlorpropamide group and insulin group [24]. Glibenclamide has been associated with acute MI and mortality [25], as well as being associated with blocking the protective effects of postconditioning [26]. By contrast, gliclazide and repaglinide appear to be related a lower risk than other sulfonylureas [25, 27]. Multiple research has suggested that cardiotoxicity of sulfonylureas is associated to the closure of specific KATP channels expressed in the heart [28], which could worsen the myocardial injury. Some newer sulfonylureas may not inhibit myocardial protection. For example, gliclazide and glimepiride appear not to prevent the protective effect of ischemic preconditioning in animals [29] and humans [30].

Very little research can be retrieved on the relationship between sulfonylures and AMPK nor meglitinides and AMPK. Glibenclamide induced a dose-dependent increase of the AMP/ATP ratio by inhibiting complexes I, II, III [31], resulting in an increased AMPK phosphorylation in H9C2 cells. However, it profoundly changes cell metabolism in cardiomyocytes by impairing mitochondrial structure and function and induces irreversible damage beyond the benefits of AMPK activation. This may further explain the risk of CV events related to this drug. However, gliclazide can increase CaMKKβ and the phosphorylated AMPK levels in vascular smooth muscle cell (VSMC) and suppress platelet-derived growth factor (PDGF)-induced VSMC proliferation by the rising of intracellular Ca²⁺ concentration [32], which is beneficial for reducing CVD.

**Biguanides**

Biguanides were used for treatment of diabetes in humans in the 1920s [33] with several derivatives such as metformin, phenformin and buformin. Phenformin was withdrawn from the market in 1978 because of a rare but life-threatening side effect of lactic acidosis. Metformin is the most widely prescribed antidiabetic agent in individuals with type 2 diabetes (T2DM), which is the first-line oral therapy recommended by almost all guidelines, such as American Diabetes Association (ADA) [34], European Association of the Study of Diabetes (EASD) [35], and National Institute for Health and Care Excellence (NICE) [36], etc.
UKPDS [24] suggested that metformin reduced diabetes-related death by 42% and all-cause mortality by 36%. Similar results reported later from many clinical studies have shown CV protection and mortality reduction exerted by metformin appearing not to be dependent on its hypoglycemic effects [37–39]. Although the main antidiabetic effect of metformin was known as reducing hepatic glucose output and an increasing insulin-dependent peripheral glucose utilization [40,41], mainly by inhibiting gluconeogenesis [42], its molecular mechanism remained unclear until it was reported that it could activate AMPK in isolated hepatocytes [43]. Metformin inhibits complex I of the respiratory chain of the cell resulting in a decrease of the intracellular ATP concentration and an increase of the AMP/ATP ratio for the activation of AMPK [44–46], which is required for the CV protective effects of metformin [44,47]. Interestingly, there are also studies demonstrating that AMPK can be activated by metformin without changes in the AMP/ATP ratio [48,49] and metformin can also exert its beneficial metabolic effects on cardiomyocytes in an AMPK-independent manner [50].

Many studies suggest the pleiotropic effects of metformin mediated by activation of AMPK. We can summarize the effects of metformin on CVD through the AMPK pathways from the following aspects.

Energy metabolism of cardiomyocyte
Impaired energy metabolism exists in many kinds of heart disease. After activation by metformin, AMPK can phosphorylate acetyl-coenzyme A carboxylase (ACC) and inhibit its function, which reduces the production of malonyl-CoA and the inhibitory effect of AMPK on carnitine palmitoyl transferase 1 (CPT1), promoting the oxidation of fatty acids [51]. In addition, activation of AMPK by metformin increases glucose uptake by inducing GLUT4 recruitment to the plasma membrane [52,53], prevents GLUT4 endocytosis and increases the residence time of GLUT4 in the plasma membrane thus increasing glucose transport and catabolism [54].

Vascular endothelium and oxidative stress
The dysfunction of endothelial cells plays a crucial role in the occurrence and development of CVD. Metformin exerts an inhibitory effect to mitochondrial reactive oxygen species (ROS) production by selectively blocking the reverse electron flow through complex I of respiratory chain [55]. Multiple studies indicated that activated AMPK is beneficial to endothelial function by suppressing oxidative stress in endothelial cells [56,57].

Endothelial nitric oxide synthase (eNOS) has a protective function in the CV system, which is attributed to NO production regulating the vascular tone. Administration of metformin in vivo increases AMPK phosphorylation in the aorta of mice, resulting in increased NO synthesis, and bioavailability [58]. Metformin can also increase mitochondria-derived peroxynitrite ONOO\(^-\) to activate AMPK in c-Src/PI3K (phosphatidylinositol-3-kinases)-dependent manners in cultured bovine aortic endothelial cells [59]. A further study has demonstrated that AMPK activation by metformin increases the association between heat-shock protein 90 (Hsp90) and eNOS, which reduces eNOS-derived O\(^2-\) [60]. In addition to antioxidant stress, metformin also regulates endothelial cell energy metabolism. For example, AMPK activation by metformin increases fatty acid oxidation, which can alleviate endothelial lipotoxicity and improve endothelial function [61].

AMPK is considered as an important target for endothelial dysfunction and atherosclerosis. As an AMPK activator, metformin has great potential for promoting endothelial function to resist atherosclerosis [62]. Metformin’s CV beneficial effects of atherosclerosis prevention are mediated in part through its ability of inhibiting the oxidative stress-mediated accumulation of cholesterol via AMPK-SREBP2 (sterol regulatory element-binding protein 2)-LDLR (low-density lipoprotein receptor) axis in vascular cells [63].

Heart failure and ventricular remodeling
Diabetes has a higher risk of developing heart failure (HF). Diabetic cardiomyopathy [64] is a common cause of HF in diabetics. It is characterized with reduced cardiomyocyte contractile function and apoptosis, mitochondrial pathology and dysfunction, and myocardial interstitial fibrosis [65].

Previously, metformin is considered contraindicated in patients with HF due to increase the risk of lactic acidosis. However, growing evidence indicates that this contraindication could be revised [66–68]. Accordingly, FDA removed the HF contraindication on the drug label for metformin in 2006, although congestive HF remains in the label’s warning section [69].

It has also been demonstrated that metformin has multiple beneficial AMPK-mediated effects in HF [70,71]. Several animal studies showed that metformin could delay the process of cardiac remodeling and the development of HF
by a different pathway of AMPK activation [72]. Gundewar et al. [73] have carried out some experiments that metformin could significantly improve left ventricular (LV) function and survival by AMPK and its downstream mediators activation, peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α) and eNOS in a murine model of HF. Chronic administration of metformin to a dog model of cardiac pacing-induced HF attenuated the hemodynamic and structural changes by AMPK activation [74]. Moreover, chronic treatment with a low dose of metformin (100 mg/kg) exerts significant cardioprotection effect against HF of rat by activating the AMPK/eNOS pathway, as well as reducing circulating and myocardial levels of insulin, transforming growth factor beta 1 (TGF-β1), basic fibroblast growth factor (bFGF), and tumor necrosis factor α (TNFα) [75].

**Myocardial ischemia and I/R injury**

It has been tested that metformin and activated AMPK can play essential roles in the protection of myocardial ischemia and I/R injury by maintenance of the energy supply, and anti-oxidative stress [76]. Metformin (5 mM) in H9C2 cardiomyoblasts attenuated high glucose and H/R-induced cell injury, mitochondrial dysfunction, ROS over generation and inflammatory response through an AMPK/JNK-dependent signaling pathway [77]. A meta-analysis with 38 animals treated with metformin and 50 controls showed that the average infarct area at risk was reduced from 47.8 in the ischemia control group to 29.4 in the metformin group [78]. In the study of isolated rat hearts, during the first 15 min of reperfusion metformin reduced infarct area with approximately 40–50% [79] by increased AMPK phosphorylation. Yin et al. [69] have also shown the reduction of the infarct size by metformin through AMPK phosphorylation in rats independent of systemic glucose levels. Metformin can also prevent acute death of cells in cardiac allografts by mainly suppressing intrinsic apoptosis due to I/R injury incurred from the transplantation procedure by AMPK activation [80].

**Chronic myocardium inflammation**

Recent studies have indicated that metformin has a direct anti-inflammatory action by inhibition of NF-κB via AMPK-dependent and independent pathways [81]. AMPK activation by short-term administration of metformin and the subsequent suppression of Toll-like receptor 4 (TLR4) expression and activity can suppress inflammatory responses and protect the infarcted heart [82]. However, Soraya et al. found that low dose pre-treatment of metformin chronically could suppress TLR4 signaling, inhibit the release of inflammatory mediators, and reverse LV contractile dysfunction in the setting of MI in an AMPK-independent manner [83].

**Apoptosis**

Cardiomyocyte apoptosis is common in CVD and diabetic cardiomyopathy. Experimental evidence suggested that metformin reduced the production of pro-apoptotic proteins, increased the anti-apoptotic proteins, and attenuated the percentage of apoptotic cardiomyocytes [84]. High-fat-induced cardiomyocyte apoptosis was partly blunted by metformin associated with increased AMPK phosphorylation [85]. Doxorubicin, a chemotherapy medication used to treat some cancer, can cause cardiotoxicity, and cardiomyocyte apoptosis. Metformin protected adult mouse cardiomyocytes (HL-1 cells) from doxorubicin-induced oxidative stress and apoptosis by modulating the expression of the adiponectin system via AMPK-mediated signaling [86]. Another research suggested that cardioprotective effects of metformin are mediated by AMPK activation, protein kinase A (PKA), Src, and platelet-derived growth factor receptor (PDGFR) [87].

**Autophagy**

Autophagy is a self-degradative process that is important for balancing sources of energy at critical times in development and in response to nutrient stress [88]. Declined AMPK activity and the following reduction in cardiac autophagy are central to the development of diabetic cardiomyopathy. Metformin significantly improved mitochondrial respiration and ATP synthesis of cardiomyocytes by an underlying mechanism requiring the AMPK activation and its downstream mediators eNOS and PGC-1α [73]. Xie et al. [72] found that AMPK activated by metformin stimulates autophagy activity in cardiomyocytes by modulating Beclin1 and the tuberous sclerosis complex (TSC) mammalian target of rapamycin (mTOR) pathway in OVE26 mice. Meanwhile, a study in a murine model demonstrated that activation of Pink1-AMPK signaling by metformin rescued against phosphatase and tensin homolog (PTEN) deletion-induced changes in myocardial geometry, function, and autophagy [89].

Downstream molecular signaling pathways of AMPK activated by metformin for the protection of CV system are shown in Figure 1.
**α-Glucosidase inhibitors**

AGIs are a type of widely used hypoglycemic agents with the mechanism of delaying the absorption of carbohydrates from the upper part of small intestine and producing a lowering effect to postprandial blood glucose. Acarbose, miglitol, and voglibose are involved.

Some clinical and basic studies have provided evidence of CV protection of AGIs. Acarbose reportedly reduced the morbidity of hypertension, CV events [90], and silent MI [91]. It also slowed progression of intima-media thickening of individuals with impaired glucose tolerance (IGT), improved carotid plaque echogenicity in patients with acute coronary syndrome (ACS) [92,93], and reduces the risk of MI in T2DM patients [94]. Acarbose could also stabilize carotid plaque within 1 month of therapy in patients with ACS and T2DM [93]. In the reports of basic research, acarbose reduced MI size in animals by opening mitochondrial KATP channels [95]. Some reports have suggested that the absorbed miglitol suppressed neointimal thickening of the arterial wall in animals [96,97]. Voglibose significantly decreased infarct size of nondiabetic rabbits during 30 min of ischemia and 48 h of reperfusion condition [98] by up-regulating GLP-1 levels and activating the GLP-1 receptors, with downstream activation of Akt, eNOS, and the mitochondrial KATP channels.

Research of AGIs on CVD through AMPK pathway is rare. Acarbose could improve vascular inflammation by enhancing NO expression to suppress cell cycle progression and inhibiting VSMC proliferation through AMPK activation and Ras inhibition, thus preventing or slowing the development of atherosclerosis [99]. Miglitol inhibits endothelial cell injury and protects against DNA damage under intensive oxidative stress, which may be involved in the activation of AMPK in endothelial cells, with the result of increasing NO production and reduced intercellular cell adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) mRNA expression [100]. Mulberry 1-deoxynojirimycin (DNJ) can be considered as an AGI analog with the effect of inhibiting α-glucosidase in the small intestine [101,102]. Chan’s group has indicated the mechanisms by which mulberry leaf DNJ effectively inhibit proliferation and migration of VSMCs, including AMPK/RhoB activation and down-regulation of FAK *in vitro* study [103].

**Thiazolidinediones**

TZDs increase insulin sensitivity through binding of the so-called peroxisome proliferator-activated receptor γ (PPAR-γ) to activate downstream genes that are involved in glucose and fatty acid metabolism. Of the members in this family, troglitazone has been withdrawn from the market, but rosiglitazone and pioglitazone remain in use.
In clinical studies, the effects of rosiglitazone and pioglitazone on CVD display diversity. Previous meta-analysis suggested that rosiglitazone use is associated with the risk of MI and death from CVD, and also increase risk of fluid retention which may exacerbate HF [5,104]. In a retrospective, observational trial, rosiglitazone was related with an increased risk of stroke, HF, and a composite outcomes of acute myocardial infarction (AMI) [105]. However, the prospective Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial found that there is no adverse effect of rosiglitazone on the composite outcome of CV death or hospitalization but report an increased risk of hospitalization for congestive heart failure (CHF) in patients using rosiglitazone versus active comparator [6]. Rosiglitazone has beneficial CV effects of nondiabetics in basic research [106]. Other clinical studies [107] and a meta-analysis [108] have demonstrated that pioglitazone reduces CV complications in individuals of T2DM. Despite the FDA’s release of rosiglitazone use and prescription restrictions in 2013 due to later clinical trial evidence [109,110], patients with HF are still very cautious to use.

TZDs are ligands for the nuclear hormone receptor family member PPAR-γ [111]. Both rosiglitazone and pioglitazone have been proved to activate AMPK in intact cells [112,113] by stimulating the release and expression of circulating adiponectin from adipose tissue [114–116], or indirectly by enhancing the cellular AMP/ATP ratio, possibly via a similar mechanism with biguanides [117]. Our group conducted a series of studies on the role of TZDs and AMPK in the heart. The result demonstrated that by using rosiglitazone acutely under I/R stress, MI is decreased and postischemic cardiac function is improved by modulating AMPK, Akt, and JNK signaling mechanisms in the nondiabetic mouse heart [118].

Many studies have suggested that TZDs can attenuate myocardial hypertrophy mediated by AMPK. It has been shown that adiponectin stimulates the phosphorylation of AMPK and suppresses agonist-stimulated extracellular regulated protein kinases (ERK1/2) activation and hypertrophic response in cultured cardiomyocytes through activating AMPK signaling [119]. Antihypertrophic effect of pioglitazone is attributed to reduced ERK1/2 activation that is involved in the adiponectin-AMPK regulatory axis [120]. Administration of pioglitazone with long term delayed the development of LV hypertrophy and fibrosis as well as inhibited phosphorylation of mTOR and p70S6 kinase in the heart, which are likely attributable, at least in part, not only to the AMPK activation through stimulation of adiponectin secretion but also to the Akt signaling inhibition in the heart [121].

TZDs also plays an essential role in adjusting energy metabolism. Troglitazone could significantly increase glucose uptake and activated both AMPK and eNOS signaling in isolated papillary muscles [122]. Adiponectin stimulated by TZDs can bind to adiponectin receptor 1 (AdipoR1) and activate AMPK/ACC/CPT-1 pathway to enhance fatty acid β-oxidation in the heart, a pathway that is also regulated by PGC-1α and PPARα [123]. However, rosiglitazone does not always increase glucose and fatty acid metabolism in adiponectin/AMPK pathway. An interesting research showed that activation of PPAR-γ in the late-gestation sheep fetus, rosiglitazone may decrease cardiac metabolism (glucose uptake, fatty acid β-oxidation) and cardiomyocyte size by down-regulating AdipoR1, phospho-AMPK, phospho-ACC, and PGC-1α [124].

**Figure 2. Upstream signaling pathways of AMPK activation by antidiabetic agents**

Abbreviations: DPP4i, DPP-4 inhibitors; p-AMPK, phosphorylated AMPK; SGLT2i, sodium-glucose cotransporter 2 inhibitors.
GLP-1 analogs

GLP-1 is a type of incretin hormone that is secreted from L-cells of the small intestine in a glucose-dependent manner to stimulate insulin secretion, increase pancreatic β cell mass, and inhibits glucagon secretion and gastric emptying, thus reducing postprandial glycemia [125,126]. Due to rapid degradation by DPP-4, the half-life of endogenous GLP-1 is very short. Longer half-life synthetic analogs have been developed for clinical use as a new class of antidiabetic agents, such as: exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, and semaglutide, etc.

Several large clinical studies have revealed that GLP-1 analogs can reduce the risk of major adverse cardiovascular events (MACE), nonfatal MI, and CV death, etc., in T2DM [127–130]. GLP-1 analogs play CV protective roles mediated by GLP-1 receptor (GLP1R) in CV tissues, among which, activation of AMPK signaling pathway is still crucial. Considerable evidences demonstrate that GLP-1 protects the isolated mouse heart against I/R injury by AMPK pathway [131]. GLP-1 analogs have also been shown to exert direct cardioprotective effects of MI in murine models [132]. Liraglutide could increase AMPK phosphorylation in the hearts of obese mice with the similar effect to metformin [73]. A short-term treatment with a weight-neutral dose of liraglutide can reverse the molecular pathophysiology of obesity-induced heart disease in mice through a variety of putative mechanisms with a central role for AMPK [133]. GLP-1 analogs can also display the effect in balancing energy metabolism and maintaining heart function of diabetic models. Guo’s [134] study showed that exenatide treatment increased the level of phosphorylation of AMPK [133]. GLP-1 analogs can also improve endothelial dysfunction. Liraglutide plays an anti-inflammatory role to primary human aortic endothelial cells (HAECs) by causing a subsequent increase in intracellular calcium, CaMKKβ activity and AMPK activation [140]. Exenatide significantly improves coronary artery endothelial function of individuals with newly diagnosed T2DM. The improvement effect may be mediated by activation of the AMPK/Akt/eNOS pathway via a GLP-1R/cAMP-dependent mechanism [141].

DPP-4 inhibitors

DPP-4 inhibitors are a group of agents for treating T2DM [126]. They prevent the deactivation of the two endogenous incretin hormones, GLP-1 and glucose-dependent-insulinotropic-peptide (GIP), thus causing the accumulation of these hormones [142] to make these hormones play the role of antidiabetes. Sitagliptin, saxagliptin, vildagliptin, alogliptin, linagliptin, and trelagliptin are approved on market as DPP-4 inhibitors family members. Several large clinical studies have revealed that DPP-4 inhibitors can reduce the risk of CVD in type 2 diabetics compared with placebos [143–145].

It has been reported that DPP-4 inhibitors can limit infarct size in the nondiabetic mice [146] and isolated rat hearts [147]. Sitagliptin has been reported to play a protective role in CVD and atherosclerosis [148,149]. Sitagliptin can decrease the atherosclerotic lesion area by activating AMPK-mediated Akt signaling pathway in ApoE−/− mice while attenuating the phosphorylation of p38 and ERK1/2 and mitogen-activated protein kinase (MAPK), therefore, inhibiting inflammatory responses in the aorta, such as the release of monocyte chemoattractant protein 1 (MCP-1) and interleukin 6 (IL-6), and the expression of the VCAM-1 and serum P-selectin [150]. One study indicated that sitagliptin inhibits endothelin-1 (ET-1) expression in the aortic endothelium by suppressing the NF-κB/IκBα system through the activation of the AMPK pathway in diabetic rats, which demonstrated some of the vasoprotective properties of DPP-4 inhibitors in vivo [151]. In other studies, sitagliptin prevented hyperglycemia induced apoptosis via activation of AMPK in HUVECs and also attenuated myocardial apoptosis by activating LKB-1/AMPK/Akt signaling pathway and suppressing the activity of GSK-3β and p38α/MAPK in diabetic cardiomyopathy of rat [152].
However, Lenski’s group found that [153] sitagliptin treatment reduced the increased phosphorylation of AMPK and ACC in db/db^−/− mice, then reduced membrane translocation of GLUT4 in cardiomyocytes, thus prevented the metabolic alteration associated with the diabetes-obesity syndrome via AMPK and its downstream molecule in the myocardium.

**SGLT2 inhibitors**

SGLT2 inhibitors selectively inhibit SGLT2 of the renal proximal tubule, with a consequent decrease in renal tubular thresholds for glycosuria and increase in urinary excretion of glucose, reducing blood glucose independently of insulin. Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin of this family have been approved by FDA.

As the request of FDA, some clinical trials for CV risk assessments were conducted before market. EMPA REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in type 2 diabetes) demonstrated that empagliflozin exerts a 38% risk reduction in death from CV causes, 32% risk reduction death from any cause and 35% reduction on risk of hospitalization for HF [154]. CVD-REAL study has confirmed that the positive effects on HF of SGLT2 inhibitors can be considered a class effect, not only by empagliflozin [155]. CANVAS study for evaluating canagliflozin also showed similar CV protective effect [156]. FDA has approved a new indication for empagliflozin to reduce the risk of CVD death in adult patients with T2DM and CVD in December, 2016 [157].

After clinical analysis, the protective effect of SGLT2 inhibitors on heart may be related to lowering blood pressure, weight loss, decreasing serum uric acid level, osmotic diuresis, reducing volume load and hemodynamic changes, etc. Further molecular mechanism is still in the exploratory stage. At present, basic research are focusing on energy metabolism, inflammation, oxidative stress, myocardial fibrosis and electrolyte homeostasis [158]. SGLT2 inhibitors change the energy metabolism of the heart from glucose to fat [159–161] and slightly increase the ketone level [162], which is beneficial for cardiac energy supply during HF. Empagliflozin can significantly improve myocardial fibrosis in obese and diabetic mice [163,164], and also play the role of anti-oxidative stress and anti-apoptosis [165,166]. Meanwhile, empagliflozin can reduce infarct size after I/R [167], and improve diastolic function of the left ventricle in diabetic mice [168]. Dapagliflozin can delay the occurrence and progress of diabetic cardiomyopathy [169].

There are currently relatively few studies on SGLT2 inhibitors and AMPK. Canagliflozin activates AMPK human embryonic kidney (HEK-293) cells and hepatocytes by inhibiting complex I in the mitochondrial respiratory chain and increasing cellular AMP levels [170]. Clinically-relevant canagliflozin concentrations can directly inhibit endothelial pro-inflammatory chemokine/cytokine secretion by AMPK dependent and independent mechanisms without affecting early interleukin-1β (IL-1β) signaling [171]. Dapagliflozin decreases the activation of the NOD-like receptor family, pyrin domain containing 3/apoptosis-associated speck-like protein containing a CARD (NLRP3/ASC) inflammasome attenuated myocardial inflammation, fibrosis, apoptosis, and diabetic remodeling likely mediated through AMPK activation [164]. In another study, empagliflozin alleviated diabetic cardiac microvascular endothelial cell (CMEC) injury by inhibiting mitochondrial fission via the activation of AMPK-Drp1 (Dynamin-related protein 1) signaling pathways, preserved cardiac CMEC barrier function through suppressed mitochondrial ROS production and subsequently oxidative stress to inhibit CMEC senescence. So empagliflozin can be considered as a cardiac microvascular-protection agents to maintain cardiac circulatory function and structure upon hyperglycemic insult [172].

Our group is currently studying the molecular mechanisms underlying the cardioprotective effect of empagliflozin. Preliminary results show that a certain concentration of empagliflozin can enhance the contractility of isolated mice cardiomyocytes under the condition of intracellular hypoxia. At baseline, empagliflozin can phosphorylate AMPK in mice cardiomyocytes. In intracellular hypoxia state induced by sodium cyanide (NaCN), empagliflozin can prolong AMPK activation time of mice cardiomyocytes (unpublished data). The further molecular mechanisms of AMPK activation is still under exploration.

We summarized the upstream signal pathways of AMPK activated by antidiabetic agents in CV system in Figure 2.

**Perspectives**

We enumerate the CV safety of commonly used antidiabetic agents in clinical practice and summarize whether these drugs can affect CVD through AMPK-related signaling pathways in this review to help clinicians for selection of antidiabetic agents. The mechanism of metformin on activating AMPK is relatively clear, but it is still obscure for other antidiabetic agents. Therefore, further research is needed to find answers from the intricate AMPK signal transduction network. Given the benefits of AMPK activation for diabetes and CVD, AMPK is becoming a promising target for the treatment of diabetes, metabolic syndrome, and CVD. There are still some problems to be solved. First, AMPK has many subtypes, and the expression of each subunit is different among species and tissues, making it more difficult...
to translate AMPK activators from pre-clinical animal experiment to clinical trial. Second, AMPK is expressed in many organs and tissues of the whole body. Whether systemic activation caused by nonspecific AMPK agonists has adverse effects on some organs is unknown. Therefore, it is necessary to develop organ-specific AMPK agonists. Third, the AMPK signaling network is very complicated, and there are many cross-talk with other pathways. The effect of activating AMPK on other pathways also needs a lot of research to confirm. At last, what is the activation duration and degree of AMPK? It is also unknown whether excessive or prolonged activation will bring adverse effects. Therefore, there is still a long way to go on progressing AMPK from basic research to clinical application.

Competing interests
The authors declare that there are no competing interests associated with the manuscript.

Funding
The present study was supported by American Diabetes Association [grant number 1-17-IBS-296]; [grant numbers NIH R01AG049835, R01GM124108, P01HL051971 and P20GM104357].

Abbreviations
ACC, coenzyme A carboxylase; ACS, acute coronary syndrome; AdipoR, adiponectin receptor; AGI, α-glucosidase inhibitor; AMPK, adenosine 5′-monophosphate-activated protein kinase; CaMKK, calcineurin-dependent protein kinase kinase; CMEC, cardiac microvascular endothelial cell; CV, cardiovascular; CVD, cardiovascular disease; DNJ, deoxynojirimycin; DPP, dipeptidyl peptidase; ENOS, endothelial nitric oxide synthase; ERK, extracellular regulated protein kinase; GLP, glucagon-like peptide; GLUT, glucose transporter; GSK, glycogen synthase kinase; H/R, hypoxia/reoxygenization; I/R, ischemia/reperfusion; KATP, ATP-sensitive potassium channel; LDLR, low-density lipoprotein receptor; LKB, liver kinase B; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor κB; PGC, peroxisome proliferator-activated receptor γ coactivator 1-α; P3K, phosphatidylinositol-3-kinase; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SGLT, sodium-glucose cotransporter; SREBP2, sterol regulatory element-binding protein; T2DM, type 2 diabetes; TLR, Toll-like receptor; T2D, thiazolidinedione; UKPDS, UK Prospective Diabetes Study; VCAM, vascular cell adhesion molecule; VSMC, vascular smooth muscle cell.

References
1. Shaw, J.E., Sicree, R.A. and Zimmet, P.Z. (2010) Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res. Clin. Pract.* **87**, 4–14, https://doi.org/10.1016/j.diabres.2009.10.007
2. Mazzoni, T. (2010) Intensive glucose lowering and cardiovascular disease prevention in diabetes: reconciling the recent clinical trial data. *Circulation* **122**, 2021–2031, https://doi.org/10.1161/CIRCULATIONAHA.109.13350
3. Rawshani, A., Safar, N., Franzen, S. et al. (2018) Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. *Lancet* **392**, 477–486, https://doi.org/10.1016/S0140-6736(18)3196-X
4. Fox, C.S., Golden, S.H., Anderson, C. et al. (2015) Update on prevention of cardiovascular disease in adults with type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* **386**, 2764–2772, https://doi.org/10.1016/S0140-6736(15)00129-9
5. Nissen, S.E. and Wolski, K. (2007) Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N. Engl. J. Med.* **356**, 2457–2471, https://doi.org/10.1056/NEJMoA072761
6. Home, P.D., Pocock, S.J., Beck-Nielsen, H. et al. (2009) Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* **373**, 2125–2135, https://doi.org/10.1016/S0140-6736(09)60953-3
7. Ma, H., Wang, J., Thomas, D.P., et al. (2010) Impaired macrophage migration inhibitory factor-AMP-activated protein kinase activation and ischemic recovery in the senescent heart. *Circulation* **122**, 282–292, https://doi.org/10.1161/CIRCULATIONAHA.110.953208
8. Aces, E., Ural, D., Bildirici, U., Sahin, T. and Yilmaz, I. (2011) Diabetic cardiomyopathy. *Anadolu Kardiyol. Derg.* **11**, 732–737
9. Voulgari, C., Papadogiannis, D. and Tentolouris, N. (2010) Diabetic cardiomyopathy: from the pathophysiology of the cardiac myocytes to current diagnosis and management strategies. *Vasc. Health Risk Manag.* **6**, 883–903, https://doi.org/10.2147/VHRM.S11681
10. Hardie, D.G. (2004) The AMP-activated protein kinase pathway—new players upstream and downstream. *J. Cell Sci.* **117**, 5479–5487, https://doi.org/10.1242/jcs.01540
11. Hardie, D.G. and Carling, D. (1997) The AMP-activated protein kinase—fuel gauge of the mammalian cell? *Eur. J. Biochem.* **246**, 259–273, https://doi.org/10.1111/j.1432-1327.1997.tb2355.x
12. Ruderman, N.B., Carling, D., Prentki, M. and Cacicedo, J.M. (2013) AMPK, insulin resistance, and the metabolic syndrome. *J. Clin. Invest.* **123**, 2764–2772, https://doi.org/10.1172/JCI67227
13. Steinberg, G.R. and Kemp, B.E. (2009) AMPK in health and disease. *Physiol. Rev.* **89**, 1025–1078, https://doi.org/10.1152/physrev.00011.2008
14. Woods, A., Johnstone, S.R., Dickerson, K. et al. (2003) LKB1 is the upstream kinase in the AMP-activated protein kinase cascade. *Curr. Biol.* **13**, 2004–2008, https://doi.org/10.1016/j.cub.2003.10.031
15 Hurley, R.L., Anderson, K.A., Franzone, J.M., Kemp, B.E., Means, A.R. and Witters, L.A. (2005) The Ca2+-calmodulin-dependent protein kinase kinases are AMP-activated protein kinase kinases. J. Biol. Chem. 280, 29060–29066, https://doi.org/10.1074/jbc.M503824200

16 Bertrand, L., Ginion, A., Beauloye, C. et al. (2006) AMPK activation restores the stimulation of glucose uptake in an in vitro model of insulin-resistant cardiomyocytes via the activation of protein kinase B. Am. J. Physiol. Heart Circ. Physiol. 291, H239–H250, https://doi.org/10.1152/ajpheart.01269.2005

17 He, C., Zhu, H., Li, H., Zou, M.H. and Xie, Z. (2013) Dissociation of Bcl-2–Bcl-xI complex by activated AMPK enhances cardiac autophagy and protects against cardiomyocyte apoptosis in diabetes. Diabetes 62, 1270–1281, https://doi.org/10.2337/db12-0533

18 Miller, E.J., Li, J., Leng, L. et al. (2008) Macrophage migration inhibitory factor stimulates AMP-activated protein kinase in the ischaemic heart. Nature 451, 578–582, https://doi.org/10.1038/nature06504

19 Russell, R.R. 3rd, Li, J., Coven, D.L. et al. (2004) AMP-activated protein kinase mediates ischemic glucose uptake and prevents postischemic cardiac dysfunction, apoptosis, and injury. J. Clin. Invest. 114, 495–503, https://doi.org/10.1172/JCI19297

20 Wang, J., Yang, L., Rezaie, A.R. and Li, J. (2011) Activated protein C protects against myocardial ischemic/reperfusion injury through AMP-activated protein kinase signaling. J. Thorac. Haemost. 9, 1308–1317, https://doi.org/10.1111/j.1538-7836.2011.04331.x

21 Chen, X., Li, X., Zhang, W. et al. (2018) Activation of AMPK inhibits inflammatory response during hypoxia and reoxygenation through modulating JNK-mediated NF-kappaB pathway. Metabolism 83, 256–270, https://doi.org/10.1016/j.metabol.2018.03.004

22 Takahashi, H., Shibasaki, T., Park, J.H. et al. (2015) Role of Epac2A/Rap1 signaling in interplay between incretin and sulfonylurea in insulin secretion. Diabetes 64, 1262–1272, https://doi.org/10.2337/db14-0576

23 Klamm, A., Sarfert, P., Launhardt, V., Schulte, G., Schmiegel, W.H. and Nauck, M.A. (2000) Myocardial infarction in diabetic vs non-diabetic subjects. Survival and infarct size following therapy with sulfonylureas (glibenclamide). Eur. Heart J. 21, 220–229

24 (1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 352, 854–865, https://doi.org/10.1016/S0140-6736(98)07037-8

25 Schramm, T.K., Gislason, G.H., Vaag, A. et al. (2011) Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. Eur. Heart J. 32, 1900–1908, https://doi.org/10.1093/eurheartj/eht077

26 Yang, X.M., Proctor, J.B., Cui, L., Krieg, T., Downey, J.M. and Cohen, M.V. (2004) Multiple, brief coronary occlusions during early reperfusion protect rabbit hearts by targeting cell signaling pathways. J. Am. Coll. Cardiol. 44, 1103–1110, https://doi.org/10.1016/j.jacc.2004.05.060

27 Gribble, F.M. and Ashcroft, F.M. (2000) Sulfonylurea sensitivity of adenosine triphosphate-sensitive potassium channels from beta cells and extrapancreatic tissues. Metabolism 49, 3–6, https://doi.org/10.1053/meta.2000.17822

28 Brown, N.J. (2012) Cardiovascular effects of antidiabetic agents: focus on blood pressure effects of incretin-based therapies. J. Am. Soc. Hypertens. 6, 163–168, https://doi.org/10.1016/j.jash.2012.02.003

29 Maddock, H.L., Siedlecke, S.M. and Yellon, D.M. (2004) Myocardial protection from either ischaemic preconditioning or nicorandil is not blocked by gliclazide. Cardiovasc. Drugs Ther. 18, 113–119, https://doi.org/10.1023/B:CARD.0000290287.5316.5e

30 Lee, T.M. and Chou, T.F. (2003) Impairment of myocardial protection in type 2 diabetic patients. Cell. Physiol. Biochem. 43, 879–890, https://doi.org/10.1159/000481638

31 Salani, B., Ravera, S., Fabbri, P. et al. (2017) Glibenclamide mimics metabolic effects of metformin in H9c2 cells. Cell. Physiol. Biochem. 43, 879–890, https://doi.org/10.1159/000481638

32 Lee, K.Y., Kim, J.R. and Choi, H.C. (2018) Gliclazide, a KATP channel blocker, inhibits vascular smooth muscle cell proliferation through the CaMKKbeta-AMPK pathway. Vascul. Pharmacol. 102, 21–28, https://doi.org/10.1016/j.ypmph.2018.01.001

33 Hardie, D.G., Ross, F.A. and Hawley, S.A. (2012) AMP-activated protein kinase: a target for drugs both ancient and modern. Chem. Biol. 19, 1222–1236, https://doi.org/10.1016/j.chembiol.2012.08.019

34 American Diabetes A (2018) B. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2018. Diabetes Care 41, S73–S85

35 Nathan, D.M., Buse, J.B., Davidson, M.B. et al. (2009) Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 32, 193–203, https://doi.org/10.2337/dc08-9025

36 Adler, A.I., Shaw, E.J., Stokes, T., Ruiz, F. and Guideline Development G (2009) Newer agents for blood glucose control in type 2 diabetes: summary of NICE guidance. BMJ 338, b1668, https://doi.org/10.1136/bmj.b1668

37 Masoudi, F.A., Inzucchi, S.E., Wang, Y., Havranek, E.P., Foody, J.M. and Krumholz, H.M. (2005) Thiazolidinediones, metformin, and outcomes in older patients with diabetes and heart failure: an observational study. Circulation 111, 583–590, https://doi.org/10.1161/01.CIR.0000154542.13412.B1

38 Johnson, J.A., Majumdar, S.R., Simpson, S.H. and Toth, E.L. (2002) Decreased mortality associated with the use of metformin compared with sulfonylurea monotherapy in type 2 diabetes. Diabetes Care 25, 2244–2248, https://doi.org/10.2337/diacare.25.12.2244

39 Pantalone, K.M., Kattan, M.W., Yu, C. et al. (2010) The risk of overall mortality in patients with type 2 diabetes receiving glipizide, glyburide, or glimepiride monotherapy: a retrospective analysis. Diabetes Care 33, 1224–1229, https://doi.org/10.2337/dc10-0017

40 Kirpichnikov, D., McFarlane, S.I. and Sowers, J.R. (2002) Metformin: an update. Am. Intern. Med. 137, 25–33, https://doi.org/10.7326/0003-4819-137-1-20007020-00009

41 Cusi, K., Consoli, A. and DeFronzo, R.A. (1996) Metabolic effects of metformin on glucose and lactate metabolism in noninsulin-dependent diabetes mellitus. J. Clin. Endocrinol. Metab. 81, 4059–4067

42 Hundal, R.S., Krssak, M., Dufour, S. et al. (2000) Mechanism by which metformin reduces glucose production in type 2 diabetes. Diabetes 49, 2063–2069, https://doi.org/10.2337/diabetes.49.12.2063
43 Natali, A. and Ferrannini, E. (2006) Effects of metformin and thiazolidinediones on suppression of hepatic glucose production and stimulation of glucose uptake in type 2 diabetes: a systematic review. Diabetologia 49, 434–441, https://doi.org/10.1007/s00125-006-0141-7

44 Zhou, G., Myers, R., Li, Y. et al. (2001) Role of AMP-activated protein kinase in mechanism of metformin action. J. Clin. Invest. 108, 1167–1174, https://doi.org/10.1172/JCI13505

45 Owen, M.R., Dorain, E. and Halestrap, A.P. (2000) Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain. Biochem. J. 348, 613–618, https://doi.org/10.1016/S0006-291X(00)00037-4

46 El-Mir, M.Y., Nogueira, V., Fontaine, E., Averet, N., Rigoulet, M. and Le Verge, X. (2000) Dimethylbiguanide inhibits cell respiration via an indirect effect targeted on the respiratory chain complex I. J. Biol. Chem. 275, 223–228, https://doi.org/10.1074/jbc.275.1.223

47 Xie, Z., He, C. and Zou, M.H. (2011) AMP-activated protein kinase modulates cardiac autophagy in diabetic cardiomyopathy. Autophagy 7, 1254–1255, https://doi.org/10.4161/auto.7.10.16740

48 Hawley, S.A., Gadalla, A.E., Olsen, G.S. and Hardie, D.G. (2002) The antidiabetic drug metformin activates the AMP-activated protein kinase cascade via an adenosine nucleotide-independent mechanism. Diabetes 51, 2420–2425, https://doi.org/10.2337/diabetes.51.8.2420

49 Berghoef, I., Guo, L., Davis, M.A. et al. (2006) Metformin prevents alcohol-induced liver injury in the mouse: critical role of plasminogen activator inhibitor-1. Gastroenterology 130, 2099–2112, https://doi.org/10.1053/j.gastro.2006.03.020

50 Saeedi, R., Parsons, H.L., Wambolt, R.B. et al. (2008) Metabolic actions of metformin in the heart can occur by AMPK-independent mechanisms. Am. J. Physiol. Heart Circ. Physiol. 294, H2497–H2506, https://doi.org/10.1152/ajpheart.00873.2007

51 Ruderman, N.B., Saha, A.K. and Kraegen, E.W. (2003) Minireview: malonyl CoA, AMP-activated protein kinase, and adiposity. Endocrinology 144, 5166–5171, https://doi.org/10.1210/en.2003-0849

52 Kurth-Kraczek, E.J., Hirshman, M.F., Goodyear, L.J. and Winder, W.W. (1999) 5'-AMP-activated protein kinase is acutely activated in skeletal muscle. Diabetes 48, 1667–1671, https://doi.org/10.2337/diabetes.48.8.1667

53 Yang, J. and Holman, G.D. (2006) Long-term metformin treatment stimulates cardiomyocyte glucose transport through an AMP-activated protein kinase-dependent reduction in GLUT4 endocytosis. Endocrinology 147, 2728–2736, https://doi.org/10.1210/en.2006-0543

54 Zhang, L., He, H. and Balschi, J.A. (2007) Metformin and phenformin activate AMP-activated protein kinase in the heart by increasing cytosolic AMP concentration. Am. J. Physiol. Heart Circ. Physiol. 293, H457–H466, https://doi.org/10.1152/ajpheart.00002.2007

55 Sambe, T., Mason, R.P., Dawoud, H., Bhatt, D.L. and Malinski, T. (2018) Metformin treatment decreases nitroxidative stress, restores nitric oxide bioavailability and endothelial function beyond glucose control. Br. J. Pharmacol. 179, 149–156, https://doi.org/10.1111/brjp.13826

56 Sambe, T., Mason, R.P., Dawoud, H., Bhatt, D.L. and Malinski, T. (2018) Metformin treatment decreases nitroxidative stress, restores nitric oxide bioavailability and endothelial function beyond glucose control. Br. J. Pharmacol. 179, 149–156, https://doi.org/10.1111/brjp.13826

57 Kukudome, D., Nishikawa, T., Sonoda, K. et al. (2006) Activation of AMPK is associated with increased ATP production via an adenine nucleotide-independent mechanism. Diabetes 55, 120–127, https://doi.org/10.2337/db05-0943

58 Calvert, J.W., Gundewar, S., Jha, S. et al. (2006) Acute metformin therapy confers cardioprotection against myocardial infarction via AMPK-eNOS-mediated signaling. Diabetes 55, 679–689, https://doi.org/10.2337/db06-0849

59 Zou, M.H., Kirkpatrick, S.S., Davis, B.J. et al. (2004) Activation of the AMP-activated protein kinase by the anti-diabetic drug metformin in vivo. Role of mitochondrial reactive nitrogen species. J. Biol. Chem. 279, 43940–43951

60 McCarty, M.F. (2005) AMPK activation as a strategy for reversing the endothelial lipotoxicity underlying the increased vascular risk associated with insulin resistance syndrome. Med. Hypotheses 64, 1211–1215, https://doi.org/10.1016/j.mehy.2004.01.042

61 Gao, F., Chen, J. and Zhu, H. (2018) A potential strategy for treating atherosclerosis: improving endothelial function via AMP-activated protein kinase. Sci. China Life Sci. 61, 1024–1029, https://doi.org/10.1007/s11427-017-9285-1

62 Gopou, R., Panangipalli, S. and Kotamrajur, S. (2018) Metformin treatment prevents SREBP2-mediated cholesterol uptake and improves lipid homeostasis during oxidative stress-induced atherosclerosis. Free Radic. Biol. Med. 118, 85–97, https://doi.org/10.1016/j.freeradbiomed.2018.02.031

63 Picano, E. (2003) Diabetic cardiomyopathy: the importance of being early. J. Am. Coll. Cardiol. 42, 454–457, https://doi.org/10.1016/s0735-1097(03)00064-8

64 Boudina, S. and Abel, E.D. (2007) Diabetic cardiomyopathy revisited. Circulation 115, 3213–3223, https://doi.org/10.1161/CIRCULATIONAHA.106.679597

65 Khurana, R. and Malik, I.S. (2010) Metformin: safety in cardiac patients. Heart 96, 99–102

66 Inzucchi, S.E., Masoudi, F.A. and McGuire, D.K. (2007) Metformin in heart failure. Diabetes Care 30, e129, https://doi.org/10.2337/dcc07-0084

67 Bain, A., Varughese, G.S., Scarpello, J.H. and Hanna, F.W. (2007) Metformin, heart failure, and lactic acidosis: is metformin absolutely contraindicated? BMJ 335, 508–512, https://doi.org/10.1136/bmj.39255.669444.4E

68 Yin, M., van der Horst, I.C., van Melle, J.P. et al. (2011) Metformin improves cardiac function in a non-diabetic rat model of post-MI heart failure. Am. J. Physiol. Heart Circ. Physiol. 301, H459–H468, https://doi.org/10.1152/ajpheart.00054.2011

69 Kim, T.T. and Dyck, J.R. (2015) Is AMPK the savior of the failing heart? Trends Endocrinol. Metab. 26, 40–48, https://doi.org/10.1016/j.tem.2014.11.001

70 Varjabedian, L., Bourji, M., Pourafkari, L. and Nader, N.D. (2018) Cardioprotection by metformin: beneficial effects beyond glucose reduction. Am. J. Cardiovasc. Drugs 18, 181–193, https://doi.org/10.1007/s40256-018-0266-3
97 Wang, N., Minatoguchi, S., Chen, X. et al. (2004) Antidiabetic drug miglitol inhibits myocardial apoptosis involving decreased hydroxyl radical production and Bax expression in an ischemia/reperfusion rabbit heart. Br. J. Pharmacol. 142, 983–990, https://doi.org/10.1038/bj.0705863

98 Iwasa, M., Kobayashi, H., Yasuda, S. et al. (2010) Antidiabetic drug voglibose is protective against ischemia-reperfusion injury through glucagon-like peptide 1 receptors and the phosphoinositide-3-kinase-Akt-endothelial nitric oxide synthase pathway in rabbits. J. Cardiovasc. Pharmacol. 55, 625–634, https://doi.org/10.1097/FJC.0b013e3181cd240

99 Chan, K.C., Yu, M.H., Lin, M.C. et al. (2016) Pleiotropic effects of acarbose on atherosclerosis development in rabbits are mediated via upregulating AMPK signals. Sci. Rep. 6, 38642, https://doi.org/10.1038/srep38642

100 Aoki, C., Suzuki, K., Yanagi, K., Satoh, H., Niltani, M. and Aso, Y. (2012) Miglitol, an anti-diabetic drug, inhibits oxidative stress-induced apoptosis and mitochondrial ROS over-production in endothelial cells by enhancement of AMP-activated protein kinase. J. Pharmacol. Sci. 120, 121–128, https://doi.org/10.1254/jphs.12108FP

101 Kimura, T., Nakagawa, K., Kubota, H. et al. (2007) Food-grade mulberry powder enriched with 1-deoxynojirimycin suppresses the elevation of postprandial blood glucose in humans. J. Agric. Food Chem. 55, 5869–5874, https://doi.org/10.1021/jf062680g

102 Kojima, Y., Kimura, T., Nakagawa, K. et al. (2010) Effects of mulberry leaf extract rich in 1-deoxynojirimycin on blood lipid profiles in humans. J. Clin. Biochem. Nutr. 47, 155–161, https://doi.org/10.3164/jcn.10.53

103 Chan, K.C., Lin, M.C., Huang, C.N., Chang, W.C. and Wang, C.J. (2013) Mulberry 1-deoxynojirimycin pleiotropically inhibits glucose-stimulated vascular smooth muscle cell migration by activation of AMPK/RhoB and down-regulation of FAK. J. Agric. Food Chem. 61, 9867–9875, https://doi.org/10.1021/jf403636z

104 Lago, R.M., Singh, P.P. and Nesto, R.W. (2007) Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. Lancet 370, 1129–1136, https://doi.org/10.1016/S0140-6736(07)61514-1

105 Graham, D.J., Ouettel-Hellstrom, R., MacCordy, T.E. et al. (2010) Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. JAMA 304, 411–418, https://doi.org/10.1001/jama.2010.920

106 Wang, T.D., Chen, W.J., Lin, J.W., Chen, M.F. and Lee, Y.T. (2004) Effects of rosiglitazone on endothelial function, C-reactive protein, and components of the metabolic syndrome in nondiabetic patients with the metabolic syndrome. Am. J. Cardiol. 93, 362–365, https://doi.org/10.1016/j.amjcard.2003.10.022

107 Mazzone, Z., Meyer, P.M., Feinstein, S.B. et al. (2006) Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. JAMA 296, 2572–2581, https://doi.org/10.1001/jama.296.21.joc0158

108 Lincoff, A.M., Wolski, K., Nicholls, S.J. and Nissen, S.E. (2007) Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA 298, 1180–1188, https://doi.org/10.1001/jama.298.10.1180

109 Duckworth, W., Abrailo, C., Moritz, T. et al. (2009) Glucose control and vascular complications in veterans with type 2 diabetes. N. Engl. J. Med. 360, 129–139, https://doi.org/10.1056/NEJMo0908431

110 Hiatt, W.R., Kaul, S. and Smith, R.J. (2013) The cardiovascular safety of diabetes drugs—insights from the rosiglitazone experience. N. Engl. J. Med. 369, 1285–1287, https://doi.org/10.1056/NEJMtp1309610

111 Lehmann, J.M., Moore, L.B., Smith-Oliver, T.A., Wilkison, W.O., Willson, T.M. and Kliewer, S.A. (1995) An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). J. Biol. Chem. 270, 12953–12956, https://doi.org/10.1074/jbc.270.22.12953

112 Fryer, L.G., Parbu-Patel, A. and Carling, D. (2002) The anti-diabetic drugs rosiglitazone and metformin stimulate AMP-activated protein kinase through distinct signaling pathways. J. Biol. Chem. 277, 25226–25232, https://doi.org/10.1074/jbc.M202489200

113 Schneider, C.A., Ferrarini, E., Defronzo, R., Schimmenti, G., Yates, J. and Erdmann, E. (2008) Effect of pioglitazone on cardiovascular outcome in diabetes and chronic kidney disease. J. Am. Soc. Nephrol. 19, 182–187, https://doi.org/10.1681/ASN.2007060678

114 Ye, J.M., Dazmik, N., Hoy, A.J., Iglesias, M.A., Kemp, B. and Kraegen, E. (2006) Rosiglitazone treatment enhances acute AMP-activated protein kinase-mediated muscle and adipose tissue glucose uptake in high-fat-fed rats. Diabetes 55, 2797–2804, https://doi.org/10.2337/db05-1315

115 Tomas, E., Tsao, T.S., Saha, A.K. et al. (2002) Enhanced muscle fat oxidation and glucose transport by ACRP30 globular domain: acetyl-CoA carboxylase inhibition and AMP-activated protein kinase activation. Proc. Natl. Acad. Sci. U.S.A. 99, 16309–16313, https://doi.org/10.1073/pnas.222657499

116 Nawrocki, A.R., Rajala, M.W., Tomas, E. et al. (2006) Mice lacking adiponectin show decreased hepatic insulin sensitivity and reduced responsiveness to peroxisome proliferator-activated receptor gamma agonists. J. Biol. Chem. 281, 2654–2660, https://doi.org/10.1074/jbc.M505311200

117 Brunmair, B., Staniek, K., Gras, F. et al. (2004) Thiazolidinediones, like metformin, inhibit respiratory complex I: a common mechanism contributing to their antidiabetic actions. Diabetes 53, 1052–1059, https://doi.org/10.2337/diabetes.53.4.1052

118 Morrison, A., Yan, X., Tong, C. and Li, J. (2011) Acute rosiglitazone treatment is cardioprotective against ischemia-reperfusion injury by modulating AMPK, Akt, and JNK signaling in nondiabetic mice. Am. J. Physiol. Heart Circ. Physiol. 301, H895–H902, https://doi.org/10.1152/ajpheart.00137.2011

119 Shibata, R., Ouchi, N., Ito, M. et al. (2004) Adiponectin-mediated modulation of hypertrophic signals in the heart. Nat. Med. 10, 1384–1389, https://doi.org/10.1038/nm1137

120 Li, P., Shibata, R., Unno, K. et al. (2010) Evidence for the importance of adiponectin in the cardioprotective effects of pioglitazone. Hypertension 55, 69–75, https://doi.org/10.1161/HYPERTENSIONAHA.109.141655

121 Kato, M.F., Shibata, R., Obata, K. et al. (2008) Pioglitazone attenuates cardiac hypertrophy in rats with salt-sensitive hypertension: role of activation of AMP-activated protein kinase and inhibition of Akt. J. Hypertens. 26, 1669–1676, https://doi.org/10.1097/HJH.0b013e328302f0f7

122 Xiao, X., Su, G., Brown, S.N., Chen, L., Ren, J. and Zhao, P. (2010) Peroxisome proliferator-activated receptors gamma and alpha agonists stimulate cardiac glucose uptake via activation of AMP-activated protein kinase. J. Nutr. Biochem. 21, 621–626, https://doi.org/10.1016/j.jnutbio.2009.03.011
123 Vega, R.B., Huss, J.M. and Kelly, D.P. (2000) The coactivator PGC-1 cooperates with peroxisome proliferator-activated receptor alpha in transcriptional control of nuclear genes encoding mitochondrial fatty acid oxidation enzymes. Mol. Cell. Biol. 20, 1868–1876, https://doi.org/10.1128/MCB.20.5.1868-1876.2000

124 Liu, S., Hui, M., McMillen, I.C. et al. (2014) Exposure to rosiglitazone, a PPAR-gamma agonist, in late gestation reduces the abundance of factors regulating cardiac metabolism and cardiomyocyte size in the sheep fetus. Am. J. Physiol. Regul. Integr. Comp. Physiol. 306, R429–R437, https://doi.org/10.1152/ajpregu.00431.2013

125 Holst, J.J. (2007) The physiology of glucagon-like peptide 1. Physiol. Rev. 87, 1409–1439, https://doi.org/10.1152/physrev.00034.2006

126 Drucker, D.J. and Nauck, M.A. (2006) The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 368, 1696–1705, https://doi.org/10.1016/S0140-6736(06)69705-5

127 Marso, S.P., Daniels, G.H., Brown-Brandts, K. et al. (2016) Liraglutide and cardiovascular outcomes in type 2 diabetes. N. Engl. J. Med. 375, 311–322, https://doi.org/10.1056/NEJMoa1603827

128 Sivertsen, J., Rosenmeier, J., Holst, J.J. and Vilsboll, T. (2012) The effect of glucagon-like peptide 1 on cardiovascular risk. Nat. Rev. Cardiol. 9, 209–222, https://doi.org/10.1038/nrcardio.2011.211

129 Best, J.H., Hoogwerf, B.J., Herman, W.H. et al. (2011) Risk of cardiovascular disease events in patients with type 2 diabetes prescribed the glucagon-like peptide 1 (GLP-1) receptor agonist exenatide twice daily or other glucose-lowering therapies: a retrospective analysis of the LifeLink database. Diabetes Care 34, 90–95, https://doi.org/10.23736/dc10-1393

130 Horton, E.S., Silberman, C., Davis, K.L. and Berrila, R. (2010) Weight loss, glycemic control, and changes in cardiovascular biomarkers in patients with type 2 diabetes receiving incretin therapies or insulin in a large cohort study. Diabetes Care 33, 1759–1765, https://doi.org/10.2337/dc09-2062

131 Ban, K., Noyan-Ashraf, M.H., Hofer, J., Bolz, S.S., Drucker, D.J. and Husain, M. (2008) Cardioprotective and vasodilator actions of glucagon-like peptide 1 receptor are mediated through both glucagon-like peptide 1 receptor-dependent and -independent pathways. Circulation 117, 2340–2350, https://doi.org/10.1161/CIRCULATIONAHA.107.739938

132 Noyan-Ashraf, M.H., Momen, M.A., Ban, K. et al. (2009) GLP-1R agonist liraglutide activates cytoprotective pathways and improves outcomes after experimental myocardial infarction in mice. Diabetes 58, 975–983, https://doi.org/10.2337/db08-1193

133 Noyan-Ashraf, M.H., Shikatani, E.A., Schuiki, I. et al. (2013) A glucagon-like peptide-1 analog reverses the molecular pathology and cardiac dysfunction of a mouse model of obesity. Circulation 127, 72–85, https://doi.org/10.1161/CIRCULATIONAHA.112.091215

134 Guo, Z., Qi, W., Yu, Y., Du, S., Wu, J. and Liu, J. (2014) Effect of exenatide on the cardiac expression of adiponectin receptor 1 and NADPH oxidase subunits and heart function in streptozotocin-induced diabetic rats. Diabetol. Metab. Syndr. 6, 29, https://doi.org/10.1186/s13098-014-0070-3

135 Zhou, Y., He, X., Chen, Y., Huang, Y., Wu, L. and He, J. (2015) Exendin-4 attenuates cardiac hypertrophy via AMPK/mTOR signaling pathway activation. Biochem. Biophys. Res. Commun. 468, 394–399, https://doi.org/10.1016/j.bbrc.2015.09.179

136 Zhang, Y., Ling, Y., Yang, L. et al. (2017) Liraglutide relieves myocardial damage by promoting autophagy via AMPK-mTOR signaling pathway in zucker diabetic fatty rat. Mol. Cell. Endocrinol. 448, 98–107, https://doi.org/10.1016/j.mce.2017.03.029

137 Bialatte, M., Van Steenberga, A., Timmermans, A.D. et al. (2014) AMPK activation by glucagon-like peptide-1 prevents NADPH oxidase activation induced by hyperglycemia in adult cardiomyocytes. Am. J. Physiol. Heart Circ. Physiol. 307, H1120–H1133, https://doi.org/10.1152/ajpheart.00210.2014

138 Abbas, N.A.T. and Kabil, S.L. (2017) Liraglutide ameliorates cardiotoxicity induced by doxorubicin in rats through the Akt/GSK-3beta signaling pathway. Naunyn Schmiedebergs Arch. Pharmacol. 390, 1145–1153, https://doi.org/10.1007/s00210-017-1414-z

139 Inoue, T., Inoguchi, T., Sonoda, N. et al. (2015) GLP-1 analog liraglutide protects against cardiac steatosis, oxidative stress and apoptosis in streptozotocin-induced diabetic rats. Atherosclerosis 240, 250–259, https://doi.org/10.1016/j.atherosclerosis.2015.03.026

140 Krasner, N.M., Ido, Y., Ruderman, N.B. and Cacicedo, J.M. (2014) Glucagon-like peptide-1 (GLP-1) analog liraglutide inhibits endothelial cell inflammation through a calcium and AMPK dependent mechanism. PLoS ONE 9, e97554, https://doi.org/10.1371/journal.pone.0097554

141 Wei, R., Ma, S., Wang, C. et al. (2016) Exenatide exerts direct protective effects on endothelial cells through the AMPK/Akt/eNOS pathway in streptozotocin-induced diabetic rats. Am. J. Physiol. Endocrinol. Metab. 310, E947–E957, https://doi.org/10.1152/ajpendo.00400.2015

142 Zannad, F., Cannon, C.P., Cushman, W.C. et al. (2015) Heart failure and mortality outcomes in patients with type 2 diabetes taking alglutin vs placebo in EXAMINE: a multicentre, randomised, double-blind trial. Lancet 385, 2067–2076, https://doi.org/10.1016/S0140-6736(14)62225-X

143 Scianna, B.M., Bhatt, D.L., Braunwald, E. et al. (2013) Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N. Engl. J. Med. 369, 1317–1326, https://doi.org/10.1056/NEJMoa1307684

144 Green, J.B., Bethel, M.A., Armstrong, P.W. et al. (2015) Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N. Engl. J. Med. 373, 232–242, https://doi.org/10.1056/NEJMoa1501352

145 Ye, Y., Keyes, K.T., Zhang, C., Perez-Polo, J.R., Lin, Y. and Birnbaum, Y. (2010) The myocardial infarct size-limiting effect of sitagliptin is PKA-dependent, whereas the protective effect of pioglitazone is partially dependent on PKA. Am. J. Physiol. Heart Circ. Physiol. 298, H1454–H1465, https://doi.org/10.1152/ajpheart.00867.2009

146 Huisamen, B., Genis, A., Marais, E. and Lochner, A. (2011) Pre-treatment with a DPP-4 inhibitor is infarct sparing in hearts from obese, pre-diabetic rats. Cardiovasc. Drugs Ther 25, 13–20, https://doi.org/10.1007/s10557-010-6271-7

147 Vittone, F., Liberam, A., Vasic, D. et al. (2012) Sitagliptin reduces plaque macrophage content and stabilises arteriosclerotic lesions in Apoe (-/-) mice. Diabetologia 55, 2267–2275, https://doi.org/10.1007/s00125-012-2582-5

148 Shah, Z., Kappfrah, T., Deiulis, J.A. et al. (2011) Long-term dipeptidyl-peptidase 4 inhibition reduces atherosclerosis and inflammation via effects on monocyte recruitment and chemotaxis. Circulation 124, 2338–2349, https://doi.org/10.1161/CIRCULATIONAHA.111.014418

149 Zeng, Y., Li, C., Guan, M. et al. (2014) The DPP-4 inhibitor sitagliptin attenuates the progress of atherosclerosis in apolipoprotein-E-knockout mice via AMPK- and MAPK-dependent mechanisms. Cardiovasc. Diabetol. 13, 32, https://doi.org/10.1186/1475-2840-13-32
150 Tang, S.T., Su, H., Zhang, Q. et al. (2016) Sitagliptin inhibits endothelin-1 expression in the aortic endothelium of rats with streptozotocin-induced diabetes by suppressing the nuclear factor-kappaB/ikappaBalpha system through the activation of AMP-activated protein kinase. *Int. J. Mol. Med.* **37**, 1558–1566, https://doi.org/10.3892/ijmm.2016.2578

151 Wu, C., Hu, S., Wang, N. and Tian, J. (2017) Dipeptidyl peptidase4 inhibitor sitagliptin prevents high glucose-induced apoptosis via activation of AMP-activated protein kinase in endothelial cells. * Mol. Med. Rep.* **15**, 4346–4351, https://doi.org/10.3892/mmr.2017.6501

152 Al-Damry, N.T., Atlia, H.A., Al-Rasheed, N.M. et al. (2018) Sitagliptin attenuates myocardial apoptosis via activating LKB-1/AMPK/Akt pathway and suppressing the activity of GSK-3beta and p38alpha/MAPK in a rat model of diabetic cardiomyopathy. *Biomed. Pharmacother.* **107**, 347–358, https://doi.org/10.1016/j.biopha.2018.07.126

153 Lenski, M., Kazakov, A., Marx, N., Bohm, M. and Laufs, U. (2011) Effects of DPP-4 inhibition on cardiac metabolism and function in mice. *J. Mol. Cell Cardiol.* **51**, 906–918, https://doi.org/10.1016/j.yjmcc.2011.08.001

154 Zinman, B., Wanner, C., Lachin, J.M. et al. (2015) Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N. Engl. J. Med.* **373**, 2117–2128, https://doi.org/10.1056/NEJMoA1504720

155 Kosiborod, M., Cavender, M.A., Fu, A.Z. et al. (2017) Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors). *Circulation* **136**, 249–259, https://doi.org/10.1161/CIRCULATIONAHA.117.029190

156 Neal, B., Perkovic, V., Mahaffey, K.W. et al. (2017) Dapagliflozin, a selective SGLT2 Inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts. *Free Radic. Biol. Med.* **121**, 263–276, https://doi.org/10.1016/j.freeradbiomed.2017.01.035

157 Lopaschuk, G.D., Belke, D.D., Gamble, J., Itoi, T. and Schonekess, B.O. (1994) Regulation of fatty acid oxidation in the mammalian heart in health and disease. *Biochim. Biophys. Acta* **1213**, 263–276, https://doi.org/10.1016/0005-2760(94)90082-4

158 Bertero, E., Piras, R., Romano, L., Ameri, P. and Maack, C. (2018) Cardiac effects of SGLT2 inhibitors: the sodium hypothesis. *Cardiovasc. Res.* **114**, 12–18, https://doi.org/10.1093/cvr/cvx149

159 Merovci, A., Solis-Herrera, C., Daniele, G. et al. (2014) Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. *J. Clin. Invest.* **124**, 509–514, https://doi.org/10.1172/JCI70704

160 Ferrannini, E., Mark, M. and Mayoux, E. (2016) CV Protection in the EMPA-REG OUTCOME trial: a “Thrifty Substrate” hypothesis. *Diabetes Care* **39**, 1108–1114, https://doi.org/10.2337/dc16-0330

161 Ferrannini, E., Baldi, S., Fraschera, S. et al. (2016) Shift to fatty substrate utilization in response to sodium-glucose cotransporter 2 inhibition in subjects without diabetes and patients with type 2 diabetes. *Diabetes* **65**, 1190–1195, https://doi.org/10.2373/dbi.15-1356

162 Taylor, S.I., Blau, J.E. and Rother, K.I. (2015) SGLT2 Inhibitors May Predispose to Ketoacidosis. *J. Clin. Endocrinol. Metab.* **100**, 2849–2852, https://doi.org/10.1210/jc.2015-1884

163 Lee, T.M., Chang, N.C. and Lin, S.Z. (2017) Dapagliflozin, a selective SGLT2 Inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts. *Free Radic. Biol. Med.* **104**, 298–310, https://doi.org/10.1016/j.freeradbiomed.2017.01.035

164 Ye, Y., Bajaj, M., Yang, H.C., Perez-Polo, J.R. and Birnbaum, Y. (2017) SGLT-2 inhibition with dapagliflozin reduces the activation of the Nlrp3/ASC inflammasome and attenuates the development of diabetic cardiomyopathy in mice with type 2 diabetes. further augmentation of the effects with saxagliptin, a DPP4 inhibitor. *Cardiovasc. Drugs Ther.* **31**, 119–132, https://doi.org/10.1007/s10557-017-6725-2

165 Lin, B., Kobuchi, N., Hasegawa, Y. et al. (2014) Glucoregic control with empagliflozin, a novel selective SGLT2 inhibitor, ameliorates cardiovascular injury and cognitive dysfunction in obese and type 2 diabetic mice. *Cardiovasc. Diabetol.* **13**, 146, https://doi.org/10.1186/s12933-014-0148-1

166 Zhou, Y. and Wu, W. (2017) The sodium-glucose co-transporter 2 inhibitor, empagliflozin, protects against diabetic cardiomyopathy by inhibition of the endoplasmic reticulum stress pathway. *Cell. Physiol. Biochem.* **41**, 2503–2512, https://doi.org/10.1159/000475942

167 Andreoudou, I., Efentakis, P., Balafas, E. et al. (2017) Empagliflozin limits myocardial infarction in vivo and cell death in vitro: role of ST3A, mitochondria, and redox aspects. *Front. Physiol.* **8**, 1077, https://doi.org/10.3389/fphys.2017.01077

168 Hammoudi, N., Jeong, D., Singh, R. et al. (2017) Empagliflozin improves left ventricular diastolic dysfunction in a genetic model of type 2 diabetes. *Cardiovasc. Drugs Ther.* **31**, 233–246, https://doi.org/10.1007/s10557-017-6734-1

169 Joubert, M., Jaug, B., Montagne, D. et al. (2017) The sodium-glucose cotransporter 2 inhibitor dapagliflozin prevents cardiomyopathy in a diabetic lipodystrophic mouse model. *Diabetes* **66**, 1030–1040, https://doi.org/10.2337/db16-0733

170 Hawley, S.A., Ford, R.J., Smith, B.K. et al. (2016) The Na+-glucose cotransporter inhibitor canagliflozin activates AMPK by inhibiting mitochondrial function and increasing cellular AMP levels. *Diabetes* **65**, 2784–2794, https://doi.org/10.2337/db16-0058

171 Mancini, S.J., Boyd, D., Katwan, O.J. et al. (2018) Canagliflozin inhibits interleukin-1beta-stimulated cytokine and chemokine secretion in vascular endothelial cells by AMPK-activated protein kinase-dependent and -independent mechanisms. *Sci. Rep.* **8**, 5276, https://doi.org/10.1038/s41598-018-3420-4

172 Zhou, H., Wang, S., Zhu, P., Hu, S., Chen, Y. and Ren, J. (2018) Empagliflozin rescues diabetic myocardial microvascular injury via AMPK-mediated inhibition of mitochondrial fission. *Redox. Biol.* **15**, 335–346, https://doi.org/10.1016/j.redox.2017.12.019