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Direct cardiovascular impact of SGLT2 inhibitors: mechanisms and effects

Abdullah Kaplan[1] · Emna Abidi[1] · Ahmed El-Yazbi[1,2] · Ali Eid[1,3] · George W. Booz[4] · Fouad A. Zouein[1]

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Abstract
Diabetes is a global epidemic and a leading cause of death with more than 422 million patients worldwide out of whom around 392 million alone suffer from type 2 diabetes (T2D). Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are novel and effective drugs in managing glycemia of T2D patients. These inhibitors gained recent clinical and basic research attention due to their clinically observed cardiovascular protective effects. Although interest in the study of various SGLT isoforms and the effect of their inhibition on cardiovascular function extends over the past 20 years, an explanation of the effects observed clinically based on available experimental data is not forthcoming. The remarkable reduction in cardiovascular (CV) mortality (38%), major CV events (14%), hospitalization for heart failure (35%), and death from any cause (32%) observed over a period of 2.6 years in patients with T2D and high CV risk in the EMPA-REG OUTCOME trial involving the SGLT2 inhibitor empagliflozin (Empa) have raised the possibility that potential novel, more specific mechanisms of SGLT2 inhibition synergize with the known modest systemic improvements, such as glycemic, body weight, diuresis, and blood pressure control. Multiple studies investigated the direct impact of SGLT2i on the cardiovascular system with limited findings and the pathophysiological role of SGLTs in the heart. The direct impact of SGLT2i on cardiac homeostasis remains controversial, especially that SGLT1 isoform is the only form expressed in the capillaries and myocardium of human and rodent hearts. The direct impact of SGLT2i on the cardiovascular system along with potential lines of future research is summarized in this review.

Keywords SGLT2 inhibitors · Type 2 diabetes · Diabetic cardiomyopathy · EMPA-REG OUTCOME · Cardiovascular

Introduction

Diabetes is a chronic disease characterized by the inability of the body to either produce enough insulin or effectively employ the insulin it produces to control blood glucose levels [1]. Uncontrollable and sustained increase in blood glucose levels could seriously damage vital organs and systems such as the heart, kidneys, blood vessels, eyes, and nerves. Multiple complications such as coronary artery disease, stroke, nephropathy, neuropathy, and retinopathy are directly linked to long-term diabetes and negatively impact the lifespan of the diabetic population [2]. In 2012, diabetes was the 8th cause of death worldwide for both sexes with a total estimate of 3.7 million deaths, out of which 1.5 million were directly related to diabetes while the other 2.2 million deaths were linked to high blood glucose levels. According to the world health organization (WHO), the number of worldwide patients with diabetes increased between 1980 and 2014 from 108 million to 422 million with a prevalence of 8.5% among the adult population (WHO, Global report on diabetes, 2016). Diabetes is projected to become the 7th leading cause of death by 2030 [3]. Although long-known anti-diabetic drugs such as metformin, sulfonylureas, meglitinides, thiazolidinediones, and dipeptidyl-peptidase-4 inhibitors have been effective in lowering glucose levels independently or in combination therapy, they show no reduction in adverse cardiovascular outcomes

Abdullah Kaplan and Emna Abidi contributed equally to this work.

✉ Fouad A. Zouein
fouadzouein@outlook.com

[1] Department of Pharmacology and Toxicology, American University of Beirut & Medical Center, Riad El-Solh, Beirut 1107 2020, Lebanon

[2] Department of Pharmacology and Toxicology, Faculty of Pharmacy, Alexandria University, Alexandria, Egypt

[3] Department of Biological and Environmental Sciences, Qatar University, Doha, Qatar

[4] Department of Pharmacology and Toxicology, University of Mississippi Medical Center, School of Medicine, Jackson, MS, USA

and are associated with multiple side effects including hypoglycemia, weight gain, fluid retention, and increased risk of congestive heart failure [4–7]. SGLT2 inhibitors (SGLT2i) recently emerged as promising antidiabetic drugs with high therapeutic index and effectively lower blood glucose levels in type II diabetes (T2D) populations [8]. SGLT is a sodium-glucose cotransporter detected in two major isoforms, SGLT1 and SGLT2. The latter is mainly expressed in the lumen of the small intestine and kidneys and is involved in the absorption/reabsorption of glucose driven by the sodium gradient across the cell membrane [8, 9]. SGLT1 expression on the other hand was mainly detected in other tissues of the cardiovascular system (CV) including cardiac capillaries and cardiomyocytes of human and rodent heart, playing an important role in glucose uptake into the myocardium [9–12]. Emerging clinical evidence reports reduced negative CV outcomes with SGLT2 inhibitor therapy [13]. Yet, an equally interesting observation is the positive effect on BP reduction, arterial stiffness, vascular resistance, and microvascular remodeling [14–17]. Whether SGLT2 inhibition in T2D patients exerts any short- or long-term CV complications remain controversial. The clinical utility and the long-term CV outcomes of SGLT2i use in diabetic patients are subject to extensive research. Although experimental studies did not document SGLT2 expression in the heart, the positive impacts of SGLT2i on the heart are intriguing. The present review aims at exploring the potential mechanisms through which these drugs directly affect the CV system independently of their well-known systemic effects.

Diabetes and the emergence of SGLT2 inhibitors cardiovascular protection

Type 1 and type 2 diabetes are the most common types of diabetes. Type 1 diabetes (T1D), previously known as juvenile diabetes, accounts for 5 to 10% of diabetic cases and is characterized by abnormalities in sufficient insulin production with undefined mechanisms, mostly linked to both genetic and environmental factors [18]. In order to survive, T1D patients require a daily administration of insulin. T2D on the other hand is the most prevalent form of diabetes and constitutes 85 to 90% of all diabetic cases and results from the inability of the body to effectively use insulin [1, 19]. Unlike T1D, symptoms arising with T2D are less marked and mostly latent making diagnosis difficult and at later stages of the disease when serious complications emerge, unless high risk factors such as obesity are present [1].

Management of blood glucose levels in T2D patients presents a frequent and progressive challenge. As the most recent class of oral anti-hyperglycemic medications, SGLT2i provide a solution for a number of unmet clinical needs. Body weight, blood pressure (BP), and lipid reduction in addition to durable glycemic control were all much welcomed effects of the drug class in this patient cohort [20, 21]. Affecting metabolism independently of insulin without increasing hypoglycemic risk encouraged the use of SGLT2i in double or triple combination therapy with standard agents such as metformin and dipeptidyl peptidase-4 inhibitor, throughout the development of T2D [22].

Typically, the detrimental vascular phenotype with T2D was thought to be a consequence of hyperglycemia through multiple and complex pathways [23]. Thus, current practice for management of patients with T2D focuses on maintaining good control of blood glucose level with a glycosylated hemoglobin target (HbA1c) < 7% [24]. This recommendation stems from robust clinical evidence documenting a reduced rate of development of micro-vascular complications (i.e., diabetic neuropathy, retinopathy, nephropathy) with good glycemic control in T2D patients, which initiated during the interventional trial and was sustained for years throughout the post-trial period [25, 26]. Follow-up clinical studies showed that intensive glucose control at the time of T2D diagnosis not only protects against microvascular complications in early and post-trial stages, but also extends to protection from macrovascular complications (i.e., CAD, PAD), which emerge overtime and in the post-trial follow-up phase only [26]. This led to the emergence of the "Legacy Effect" or "Cardiovascular Metabolic Memory" concept whereby the extent of vascular damage is determined, not only by current glycemic control, but also by the history of blood glucose level management [27]. To date, no promising drug that target diabetes has proven effective in preventing adverse cardiac remodeling following cardiac injury such as myocardial infarction (MI), independently of glycemic control [28, 29]. However, emerging evidence supports a protective effect for certain anti-hyperglycemic drugs against CV complications in diabetic patients already receiving standard of care for glycemic control and cardiovascular disease (CVD) [30, 31]. An exciting aspect of SGLT2i therapeutic effect in T2D patients is potential direct cardioprotection independently of glycemic control. SGLT2i, empagliflozin (Empa), is the first drug to display significant cardioprotection in clinical trials with a clear reduction in CV mortality and hospitalization due to heart failure within the first 3 months of initiating the treatment [31]. Speculations on the basis of such effects included a role for the observed reduction of BP, body weight, and increased diuretic effects (see box for EMPA-REG Outcome Trial Summary) [32]. Canaglifolzin, another promising SGLT2i, was assessed for its cardiovascular safety and efficacy in patients with T2D and high CV risks in the CANVAS program which integrates both CANVAS and CANVAS-Renal trials. Observed effects on both CV and renal outcomes were comparable to EMPA-REG trial outcomes, yet with a difference in the degree of influence. Of note, heart failure

patients treated with canagliflozin showed a lower risk of hospitalization with no statistical significance [33]. Subgroup analysis of EMPA-REG Outcome trial revealed similar but significant findings by showing that Empa addition to standard care in T2D patients and high CVD risks reduced heart failure hospitalization and cardiovascular death to the same extent in the presence or absence of heart failure at baseline when compared to their relative placebo group. However, rate of hospitalization per 1000 patients per years was lower in patients without heart failure at baseline when compared to patients with heart failure at baseline [34]. Whether SGLT2i CV benefits is a class effect remains to be determined by the outcome of ongoing trials examining the effects of other SGLT2 inhibitor molecules and expected to report in 2019 [25].

EMPA-REG Outcome Trial Summary

Description and general outcomes

A multicenter, randomized, double-blind, placebo-controlled trial that aims to assess the CV protective effect of Empa in patients with T2D associated to a high risk for CV events.

➢ Compared to placebo, Empa showed better glycemic control and advanced management of T2D's deleterious effects on CV events (mortality among T2D patients with CVD).

Study characteristics

• 63.1 years old mean aged, 7028 patients;
• Empa 10 mg ($n = 2345$), 25 mg ($n = 2342$) per day
• Matching placebo ($n = 2333$)
• Enrollees characteristics: White 72%, Asian 22%, other 6%
• 57 % diagnosed with T2D > 10 years:
• History of MI: 47% multivessel disease and 47% CAD
• Antidiabetic therapy unchanged for 12 weeks prior to randomization

Inclusion criteria

• T2D with established CVD
• Age ≥ 18 years old
• HbA1c of ≥ 7.0% and ≤ 10% for patients on background therapy or HbA1c ≥ 7.0% and ≤ 9.0% for drug-naive patients
• BMI ≤ 45 kg/m^2
• GFR > 30 ml/min/1.73 m^2

General endpoints outcome¥

➢ 14% reduction in major CV events , 38% reductions in CV mortality, 35% reduction in heart failure hospitalization, 32% reduction of death from any cause.

Primary outcomes

↓ CV death (3.7 vs. 5.9%, $p < 0.001$)
↓ All MI (4.8 vs. 5.4%, $p = 0.23$)
↓ All stroke (3.5 vs. 3.0%, $p = 0.26$)

Secondary outcomes:

↓ Preload, afterload burden to heart, SBP, DBP
↓ Arterial stiffness
↓ CHF hospitalization or CV death(5.7 vs. 8.5%, $p < 0.001$)
↓ Coronary revascularization(7 vs. 8%, $p = 0.11$)
↓ BW, BV
↓ Oxidative stress
↓ Visceral adiposity
↓ Hyperinsulinemia
↓ HbA1c, albuminuria
↓ Uric acid level
↑ Glycosuria, fasting, and postmeal glucagon concentration
↑ Hematocrit (5% in absolute values, and 11% in percentage points)
↑ Ketonemia, natriuresis and osmotic diuresis

Results were similar for the two doses of empagliflozin vs. placebo; CV, cardiovascular; T2D, type 2 diabetes; CVD, cardiovascular disease; Empa, empagliglozin; MI, myocardial infarction; HbA1c, glycosylated hemoglobin; BMI, body mass index; GFR, glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHF, congestive heart failure; BW, body weight; BV, blood volume;

Nevertheless, considering that a significant proportion of T2D patients already show evidence of microvascular complications at the time of initial diagnosis of diabetes [35], a thorough examination of the underlying mechanism of SGLT2 inhibition-mediated cardioprotective effect is warranted. Identification of the target(s) for this "pleiotropic effect" is required to develop an understanding of their potential benefit and guide further research on rational and

justified use in patients. Herein, we will review some potential molecular mechanisms through which SGLT2i can facilitate this cardioprotective effect (Fig. 1).

The diabetic myocardium

Diabetes is associated with 2- to 4-fold increase in the risk for cardiovascular disease [36–38]. Seventy five to 80% of the deaths in patients with T2D are associated with a thrombotic event and ~ 70% of diabetic people > 65 years of age will die of some form of heart disease [37]. Prevalence of T2D or impaired glucose tolerance may be as high as 65% in MI patients, increasing the risk of mortality and congestive heart failure development [39, 40]. Heart failure is preceded by metabolic and mitochondrial dysfunction, oxidative stress, and cardiac myocytes death that are exacerbated in T2D patients with no defined mechanisms [36, 38]. To date, multiple studies emphasize the positive correlation between acute hyperglycemia and detrimental cardiac remodeling and prognosis post-MI [41–46]. Elevated plasma glucose on admission post-MI is a powerful prognostic tool for both in-hospital and long-term outcome in both diabetic and non-diabetic patients. In fact, there is positive correlation between plasma glucose level and mortality level post-MI, although the basis for the harmful effect of hyperglycemia is not understood [43, 44, 47]. A 4% increase in mortality is encountered for every 18 mg/dL increase in plasma glucose level [46]. Patients with and without established diabetes have comparable mortality rate when post-MI admission glucose levels are more than 200 mg/dL suggesting an acute glucose-mediated toxicity on the myocardium [46].

Mechanisms behind worsened cardiac remodeling post-injury in diabetic hearts remain unclear [48]. Hearts of diabetic patients are associated with contractile and relaxation dysfunction as well as an increased arrhythmia risk that are linked to autonomic neuropathy and sympatho-parasympathetic imbalance caused by parasympathetic denervation and sympathetic hyperinnervation [49–51]. In addition to the autonomic dysfunction, ion homeostasis and electrophysiological properties of the diabetic myocardium at the tissue level are also altered [52–55]. Metabolic aberrations, oxidative damage, and inflammation are also attributed to cardiac dysfunction in diabetic patients and further discussed in this review.

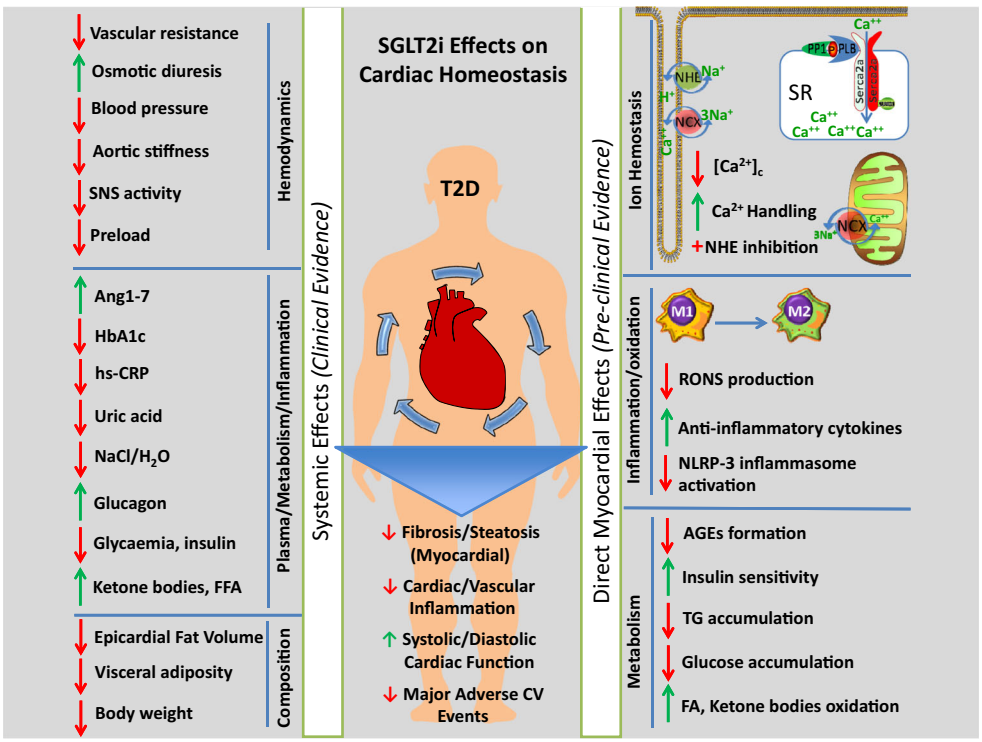

Fig. 1 SGLT2 inhibitors impact on cardiac homeostasis following systemic and direct myocardial effects. Together SGLT2 mediated systemic and direct myocardial effects potentiate cardioprotective outcomes in T2D patients. Ang1-7, angiotensin 1-7; HBA1c, glycosylated hemoglobin; hs-CRP, high sensitive C reactive protein; NaCl, sodium chloride; FFA, free fatty acids; SGLT, sodium/glucose cotransporter; T2D, type 2 diabetes; CV, cardiovascular; Ca^{2+}, calcium; Na^{2+}, sodium; NHE, cardiac Na^{+}/H^{+} exchanger; PP1, protein phosphatase 1; PLB, phospholamban; SERCA2a, sarcoplasmic/endoplasmic reticulum Ca(2+)ATPase 2a; $[Ca^{2+}]_c$, cardiac cytoplasmic Ca^{2+} concentration; M1, M1 macrophages; M2, M2 macrophage; RONS, reactive oxygen and nitrogen species; NLRP-3 inflammasome, nucleotide-binding domain leucine-rich repeat containing protein inflammasome; AGEs, advanced glycoxidation end products; TG, triglyceride; FA, fatty acids; SNS, sympathetic nervous system;

SGLT2 inhibitors and ion homeostasis of the diabetic myocardium

Myocardial Ca^{2+} and Na^+ homeostasis is critical for proper cardiac signal transduction, heart rhythm regulation, and cardiomyocyte energy production and respiration [56, 57]. Rapid and proper change of intracellular Ca^{2+} concentration is essential for cardiac myocytes contraction and relaxation and is normally regulated by ion exchangers and channels including L-type Ca^{2+} channels, ryanodine receptor, Na^+/Ca^{2+} exchanger (NCX), and sarcoplasmic-reticulum calcium ATPase 2a (SERCA2a) [56–58]. Na^+ homeostasis on the other hand is regulated mainly by NCX, Na^+/H^+ exchanger (NHE), and the Na^+/K^+ pump and directly affects myocardial Ca^{2+} dynamics [52, 59]. Both Ca^{2+} and Na^+ transport, handling and regulation are altered in the diabetic myocardium [52–55]. Altered Na^+ transport in diabetic heart is attributed to decreased Na^+/K^+ pump and NCX activities but enhanced NHE activity overloading the cytosol with Na^+ [55, 60–64]. Recent findings suggest an important role of SGLTi on ion homeostasis in T2D heart and a potential protective impact on T2D cardiac remodeling (Table 1). In a recent study, Lambert et al. found increased SGLT1 expression in failing hearts of T2D patients compared to controls, and linked Na^+ overload in T2D rat myocytes to increased SGLT1-mediated Na^+/glucose uptake [53]. Using dapagliflozin (Dapa), a selective SGLT2i, Hamouda et al. tested the electromechanical function of isolated ventricular myocytes of streptozotocin (STZ)-induced diabetic rats [73]. Their findings revealed a reduction in ventricular myocyte shortening and the amplitude of the intracellular Ca^{2+} transients in both STZ and control myocytes with greater effect in STZ myocytes, 5 min after Dapa exposure. The exact mechanism behind the negative inotropic effects is unclear but most probably is linked to alteration in the mechanisms of Ca^{2+} transport since together the myofilament sensitivity to Ca^{2+} and sarcoplasmic reticulum Ca^{2+} release were not altered by Dapa in both groups [73]. Indeed, in a very recent study, Baartscheer and colleagues confirmed the ion concentration alteration hypothesis [72]. Using Empa, another selective SGLT2i, ion homeostasis was tested on isolated ventricular myocytes from rabbits and rats in the presence of increased levels of extracellular glucose. Findings revealed that Empa decreased cardiac myocytes cytosolic Na^+ $[Na^+]c$ and cytosolic Ca^{2+} $[Ca^{2+}]c$ levels and increased myocytes' mitochondrial Ca^{2+} concentration by modulating NHE activity [72]. Although SGLT2 expression is not found in neither healthy nor pathological heart tissue [9, 75], Empa impact on ion homeostasis in cardiomyocytes has been linked to its potential direct interaction with NHE [72]. Data supporting this notion have been generated by using Cariporide, a well-known specific NHE inhibitor. Of note Cariporide attenuates intracellular Na^+ accumulation during ischemia and Ca^{2+} accumulation during both ischemia and reperfusion, mechanisms that are proven to be cardioprotective by limiting infarct expansion and border-zone extension [76–78]. Cardioprotective impact of Cariporide was confirmed clinically in patients with acute ischemic coronary event undergoing PTCA or CABG procedures attenuating adverse remodeling within both the infarcted and non-infarcted areas of the heart [76, 79–82]. Application of Cariporide in the presence of Empa had minimal effect on Empa-induced cytosolic Na^+ reduction and vice versa. Additionally, recovery of pH following acute acidic load was inhibited in the presence of Cariporide but strongly reduced with Empa [72]. These findings reinforce the potential direct NHE inhibition of Empa which is yet to be fully elucidated. In summary, decreasing intracellular Na^+ levels by inhibiting SGLT2 and attenuating NHE activity results in increased Ca^{2+} uptake into the mitochondria and efflux into the extracellular space probably through NCX activity, decreasing intracellular Ca^{2+} levels and subsequently, improving calcium handling between cardiac cycles. These direct effects on the myocardium correlate well with the reduction in sympathetic activity observed in SGLT2i-treated T2D patients and support the cardioprotective effects of SGLT2i in T2D-heart failure patients [83–85]. On a functional level, two studies recently emerged supporting diastolic function improvement in T2D mouse model following SGLT2 inhibition [70, 71]. In the first study, Empa treatment in T2D ob/ob mouse model showed an increase in the myocardium contractile reserve following dobutamine stress challenge along with an increase in calcium handling through enhancing SERCA2a activity and improving left ventricular (LV) maximum pressure and diastolic function parameters [70]. In T2D female db/db mouse model exposed to Empa treatment, diastolic function significantly improved as evidenced by decreased LV filling pressure and enhanced septal wall motion, all in absence of any changes in BP [71]. In addition to Ca^{2+} handling improvement, diastolic function enhancement was linked to the antifibrotic aspect of Empa treatment. Serum and glucocorticoid-regulated kinase 1 (SGK1)/Enac profibrotic signaling pathway and the associated myocardial interstitial fibrosis decreased in the presence of Empa [71]. Notably, SGK1 is highly expressed and activated in the diabetic heart in the presence of an excess of circulating glucose and is directly linked to cardiac pro-fibrotic/hypertrophic effects [86–88]

SGLT2 inhibitors and metabolic alteration of the diabetic myocardium

Under physiologic conditions, 95% of myocardial energy is supplied via mitochondrial oxidative metabolism. Free fatty acids (FFAs), glucose, lactate, ketone bodies, and amino acids are all involved in oxidative metabolism. However, most of the energy production is obtained from FFAs and glucose metabolism with a negligible contribution of other substrates

Table 1 A selective list of studies highlighting direct cardiovascular effects of SGLT2 inhibitors in rodents

Model	Study design¥	Heart/vasculature					Extra-CV effects	Ref
		Structural/functional	Ion homeostasis	Inflammation	Oxidative stress	Metabolism		
Non-diabetic rodents								
Non-diabetic male Wistar rats: Dapa: 0.1 mg/kg/day/4 W post-MI	Dapa effects on cardiac fibrosis attenuation post-MI in rats	↑ Maximal rate of LV+dp/dt and –dp/dt ↔ Infarct size, LVESD ↓ Myofibroblast α-SMA protein/mRNA levels ↓ Remote myocardial fibrosis	N/A	↓ M1 mRNA (IL-6, IL-1β, iNOS) levels ↑ M2 mRNA (CD206, IL-10) levels ↑ M2 (IL-10) protein levels ↑ M2/M1 ratio	↓ RONS ↑ STAT3 activation	N/A	↓ LgW/BW	[65]
T2D rodents								
C57BLKS/J-lepr^{db}/lepr^{db} 7 W-old T2D db/db mice: Empa: 0.03% of the standard diet for 1 W or 10 W	Empa effects on CV injury in T2D mice	1 W treatment N/A 10 W treatment ↓ Coronary arterial thickening ↓ Impairment of vascular endothelial function ↓ Cardiac interstitial and peri-coronary arterial fibrosis ↑ SNAP-induced vascular relaxation	1 W treatment ↑ Sodium excretion 10 W treatment ↔ Sodium excretion	1 W treatment N/A 10 W treatment ↓ Myocardial macrophage infiltration	1 W treatment N/A 10 W treatment ↓ Cardiac and aortic O_2^-	N/A	1 W treatment ↑ Water intake 10 W treatment ↔ Water intake ↑ Cognitive function ↑ Cerebral BDNF levels ↓ Cerebral oxidative damage ↓ Glomerular sclerosis index, M infiltration, and O_2^- levels	[66]
B0 old T2D SHRcp rats: Empa: 0.03% of the standard diet for 10 W	Empa effects on metabolic syndrome rats with prediabetes	1 W treatment N/A 10 W treatment ↓ LVM ↔ HR, ↓ Cardiac interstitial fibrosis	1 W treatment N/A ↓ Daily and 24 h Na^+ balance 10 W treatment ↔ Sodium balance	1 W treatment N/A 10 W treatment ↓ Cardiac interstitial macrophage infiltration	1 W treatment N/A 10 W treatment ↓ O_2^- levels	1 W treatment N/A 10 W treatment ↔Cardiac TG	1 W treatment N/A 10 W treatment ↑ 24-h water and food intake ↔SNS activity, 24-h locomotor activity, sBRG, and LW	[67]
4 W old C57BL6/J male mice HFHS induced obesity and insulin resistance + 2 months of 3 mg/kg of Empa	Empa chronic effects in diet-induced obesity and IR mice	N/A	N/A	↔ IL-1β levels	N/A	↓ Cardiac TG accumulation	↔ Food intake ↓ Efficiency of food intake* ↓ LW, steatosis, and TG ↓ Hepatic and renal NLRP3 expression, Caspase-1 activation, and IL-1β production	[68]
6 W old T2D lipodystrophic Bscl2$^{-/-}$ SKO mice: 1 mg/kg Dapa/day/8 W	Dapa effects on cardiomyopathy in T2D mice	↓ E/A, IVRT, and LVWT ↑ EF ↓ HW/BW ratio	↑ SERCA2a function	N/A	N/A	N/A	↔ Liver steatosis ↔ Insulin sensitivity	[69]
10 to 12 W old leptin-deficient T2D ob/ob male mice 10 mg/kg/day Empa mixed in diet for 6 W	Empa chronic effects on LV functions in T2D mice	↔ LVESD, LVEDD and morphology ↔ FS, EF, HR, and ESPVR ↔ HW/TL ratio ↓ Relaxation time, tau and EDPVR ↓Cardiac expression of Anf and β-Mhc ↔ Myocardial apoptotic and fibrotic states	↔ SERCA2a protein and mRNA levels ↑ pPLB and SERCA2a/PLB ratio ↓ PLB expression	N/A	N/A	N/A	N/A	[70]

Table 1 (continued)

Model	Study design[¥]	Heart/vasculature					Extra-CV effects	Ref
		Structural/functional	Ion homeostasis	Inflammation	Oxidative stress	Metabolism		
C57BLKS/J 8 W old female T2D db//db mice 10 mg/kg/day Empa mixed in diet for 6 W	Empa effects on reducing CVD events in T2D mice	↓ LVEDP, CO, SV, CSA, and myocardial fibrosis ↔ LA/Ao ratio, EF, FS, LVM, LVWT, LVEDD, and LVESD	↓ LV ENaC protein expression	↓ LV SGK1 protein expression	↔ LV AGEs and RAGEs	N/A	↔ ALT ↑ PW	[71]
In vitro studies								
Isolated ventricular CM from rabbits and rats: 1 μmol/l of Empa	Empa effects on CM ions handling in isolated rats and rabbits CM	N/A	↓ $[Na^+]c$, diastolic and systolic$[Ca^{2+}]c$	N/A	N/A	N/A	N/A	[72]
Isolated CM from 4 W old Wistar STZ-induced diabetic male rats: 1 μmol/l (10–6 M) Dapa for 5 min or 1–3 h	Dapa effects on ventricular CM shortening and intracellular Ca^{2+} transport in diabetic rats	5 min treatment ↓ CM shortening 1–3 h treatment ↔ CM shortening ↔ Myofilament sensitivity to Ca^{2+}	↓ Ca^{2+} transient amplitude, and Ltype Ca^{2+} current in CM ↔ SR Ca^{2+} release	N/A	N/A	N/A	N/A	[73]
Human PASMCs and isolated CA and PA from C57BL/6 T2D male mice In vivo chronic treatment of 30 mg/kg/day Canagliflozin for 4 W and ex vivo acute treatment with different doses tested for 20 min	Canagliflozin effects on vascular relaxation in T2D mice	In vivo ↔ SNP-induced PA dilation ↑ SNP-induced CA dilation Ex vivo 10 μmol/l 10 μmol/l ↓ SNP-induced PA dilation ↔ SNP-induced CA dilation 100 pmol/l ↑ SNP-induced PA dilation ↔ SNP-induced CA dilation	In vitro 10 μmol/l ↓ SNP-induced hyperpolarization in PASMCs by decreasing K+ channel activation	N/A	N/A	N/A	N/A	[74]

N/A, not available; ↑, increase; ↓, decrease; ↔, no changes; (−), inhibition; *Empa*, empagliflozin; *W*, week; *MI*, myocardial infarction; *LV*, left ventricle; *LVESD*, left ventricular end-systolic diameter; *α-SMA*, alpha-smooth muscle actin; *M1*, M1 macrophage phenotype; *M2*, M2 macrophage; *mRNA*, messenger RNA; *IL-10*, interleukin 10; *IL-6*, interleukin 6; *iNOS*, inducible nitric oxide synthases isoform; *CD206*, cluster of differentiation 206; *RONS*, reactive oxygen and nitrogen species; *STAT3*, signal transducer and activator of transcription 3; *LgW*, lungs weight; *BW* body weight; *T2D*, type 2 diabetes; *CV*, cardiovascular; *SNAP*, sodium nitroprusside; O_2^-, superoxide anion; *BDNF*, brain-derived neurotrophic factor; *LVM*, left ventricular mass; *HR*, heart rate; *SNS*, sympathetic nervous system; *sBRG*, spontaneous baroreceptor reflex gain; *LW*, liver weight; *IR*, insulin resistance; *, body weight gain divided by the food intake; *NLRP-3 inflammasome*, nucleotide-binding domain leucine-rich repeat containing protein inflammasome; *E/A*, early diastolic/late diastolic; *IVRT*, isovolumetric relaxation time; *LVWT*, end diastolic LV wall thickness; *EF*, ejection fraction; *HW/BW*, heart weight/body weight; *SERCA2a*, Ca^{2+}-ATPase; *LVEDD*, left ventricular end diastolic diameter; *ESPVR*, end-systolic pressure volume relationship; *EDPVR*, end-diastolic pressure-volume relationship; *FS*, fractional shortening; *TL*, tibia length; *Anf*, atrial natriuretic peptide/factor; *β-Mhc*, beta myosin heavy chain; *PLB*, phospholamban; *CVD*, cardiovascular disease; *LVEDP*, left ventricular end diastolic pressure; *CO*, cardiac output; *SV*, stroke volume; *LDd*, lumen diameters at end diastole; *LDs*, lumen diameters at end systole; *CSA*, cardiomyocytes cross sectional area; *ENaC*, epithelial sodium channel; *SGK1*, serum/glucocorticoid regulated kinase 1; *AGEs*, advanced glycoxidation end products; *RAGE*, receptor for advanced glycation endproducts; *ALT*, alanine transaminase; *PW*, pancreas weight; *CM*, cardiomyocytes; $[Na^+]_c$, cardiomyocytes cytoplasmic Na^+ concentration; $[Ca^{2+}]_c$, cardiomyocytes cytoplasmic Ca^{2+} concentration; *NHE*, cardiomyocytes Na^+/H^+ exchanger; $[Ca^{2+}]_m$, mitochondrial Ca^{2+} concentration; *SR*, sarcoplasm; *PASMCs*, human pulmonary artery smooth muscle cells; *PA*, pulmonary arteries; *CA*, coronary arteries; K^+, potassium ion

[¥] Results resented in this table are in comparison with T2D rodents same conditioning treatment

[89]. Myocardial metabolism can change depending on cardiac stress, substrate availability, and hormonal situation. Lipotoxicity, glucotoxicity, ketone bodies oxidation, and mitochondrial dysfunction are all associated with metabolic abnormalities of the diabetic myocardium. With T2D, insulin resistance increases lipolysis and subsequent fatty acid (FA) uptake and triglyceride (TG) storage into the myocardium [90]. Consequently, myocardial FA abundance amplifies the reliance on β-oxidation and FA storage while inhibiting pyruvate dehydrogenase (PDH) through PPARα-mediated PDK4 activation and subsequently inhibiting glucose oxidation, increasing the risk of myocardial steatosis and cytotoxicity [91–95]. Cardiac steatosis is considered a powerful predictor of cardiac dysfunction and cardiac remodeling and highly correlates with obese and T2D patients [96–101]. Inhibiting cardiac glucose oxidation raises cardiomyocytes glucose levels along with the risk of protein glycation and the formation of advanced glycation end-products (AGEs). Multiple metabolic pathways including pentose phosphate pathway (PPP), hexosamine biosynthesis pathway (HBP), and glycogeneic pathways are altered in this process, affecting the myocardium negatively [102–105]. AGEs formation is associated with cellular dysfunction via reactive oxygen species (ROS) production, and cross-linking with multiple macromolecules including SERCA, collagen, and ryanodine receptor leading to ventricular stiffness and dysfunction [106, 107]. LV dysfunction in T2D patients and rodents has also been linked to mitochondrial dysfunction [108–111]. Reduction in oxidative phosphorylation (OxPhos) limits ATP supply to the myocardium leading to systolic and diastolic impairment [110, 112–115]. Decreased OxPhos rate and increased FA oxidation will also increase ROS production due to high electron leakage in the mitochondrial respiratory chain. As expected, excessive ROS production amplifies T2D-mediated cardiac remodeling by inducing acute cellular damage and inflammatory responses [116, 117]. To date, the impact of SGLT2 inhibition on cardiac metabolic impairment has not been thoroughly investigated nor deciphered (Table 1). In their study, Joubert at al. used a unique non-obese mouse model of T2D known as the lipodystrophic *Bscl2*$^{-/-}$ (seipin knockout [SKO]) mouse to investigate the impact of SGLT2i on glucotoxicity in the absence of lipotoxicity [69]. SKO mice are characterized by an excessive increase in myocardial glucose uptake without lipid accumulation or lipotoxic features. Using Dapa as SGLT2 inhibitor and pioglitazone as insulin sensitizer, data revealed a more pronounced cardioprotective effect of Dapa-treated group compared to pioglitazone-treated group despite similar glucose lowering effects of both drugs [69]. This study supports direct cardioprotective effects of SGLT2i independently of glycemic control. In another study, the impact of SGLT2i on lipotoxicity was tested in a high-fat-high-sugar (HFHS) mouse model [68]. HFHS animals displayed T2D characteristics including high lipid deposition in both heart and liver along with hyperglycemia and insulin resistance. In addition to glycemic control, Empa treatment in HFHS group significantly mitigated myocardial and liver steatosis by reducing TG accumulation. Although Empa treatment significantly decreased TG plasma level with no effect on diet-induced increase of plasma total cholesterol and HDL-cholesterol levels, it is not clear whether the observed Empa effect on cardiac TG accumulation is also tissue-specific and requires further investigation [68, 118]. Metabolically, one possible explanation for SGLT2 inhibition-mediated cardioprotective effects is ketone bodies formation [13]. Ketone bodies are generated through FA metabolism in the liver with low plasma concentration under physiologic conditions [119]. With diabetes however, low plasma insulin, insulin resistance, lipolysis, and subsequent high FA levels accelerate ketone bodies formation and their importance as energy source for myocardium increases [120]. Multiple experimental studies showed that β-hydroxybutyrate, a ketone body, competes with FFA and glucose entry into cardiac mitochondrial metabolic oxidation with higher energy efficiency and lower myocardial oxygen consumption [121–123]. Unlike FFA oxidation, β-hydroxybutyrate generates less ROS and possesses antioxidants capacities which maintain mitochondrial integrity [124]. Additionally, ketone bodies increase mitochondrial biogenesis and exert anti-arrhythmic effects by stabilizing cell membrane potential [125]. In diet-induced obese diabetic rats, treatment with SGTL2i promotes lipolysis instead of glucose oxidation as a source of energy [126, 127]. SGLT2 inhibition also increased plasma ketone bodies levels in both experimental and clinical T2D along with shifting substrate usage from carbohydrates to lipids [126–131]. In summary, there is no clear understanding of how SGLT2i exert their cardioprotective effects through myocardial metabolism modulation. Evidence supports a direct effect of SGLT2i on reducing plasma glucose levels and shifting myocardial metabolism to FA and ketone bodies oxidation along with appropriate non-accumulative myocardial FA storage. Glucose lowering effects of antidiabetic drugs by itself induces lipolysis and ketone body formation as a compensatory mechanism [132]. SGLT2 inhibition however, improves lipolysis and limits TG accumulation in the liver and the myocardium [68]. Additionally, recent evidence has emerged showing an improvement in myocardial insulin sensitivity and glucose utilization following Empa treatment in a T2D ob/ob mouse model [70]. Improvement of myocardial insulin sensitivity could be linked to the significant decrease in epicardial fat volume (EFV) that was observed in T2D patients treated with SGLT2i [133, 134]. Of note, EFV accumulation highly correlates with cardio-metabolic risks including insulin resistance and inflammation [135, 136]. All the above findings suggest that reducing plasma glucose levels, improving myocardial insulin sensitivity and glucose utilization, along with directly lowering TG accumulation in the myocardium could allow ketone

bodies cardioprotective metabolism to dominate while limiting myocardial glucotoxic and lipotoxic effects. Investigating this concept with stronger evidence such as direct SGLT2 inhibiting effect on improving myocardial ketone bodies uptake and oxidation, increasing myocardial FA oxidation and subsequently lowering myocardial TG accumulation, and ultimately restoring pre-diabetic glucose-FA metabolic balance is warranted. However, a critical clinical complication known as euglycemic diabetic ketoacidosis (DKA) has emerged, not so infrequently, in individuals treated with SGLT2i. DKA has the potential of becoming a life-threatening condition due to systemic ketone bodies accumulation consequent to SGLT2 inhibition-dependent decrease in insulin secretion and subsequent increase in glucagon secretion and activation of lipolysis [137–139].

SGLT2 inhibition and oxidative inflammatory response with the diabetic cardiovascular system

Oxidative stress and chronic systemic inflammation are closely associated and long-known to play a key role in the pathogenesis of diabetes-induced CVD. They are crucial members of the vicious cycle of diabetes, which also includes hyperglycemia, insulin resistance, and dyslipidemia [140–144]. When it comes to oxidative stress and inflammation in the diabetic myocardium, investigations take into consideration the micro and macrovascular complications of diabetes and the direct impact on end-organ damage. Endothelial function by itself is vital for proper homeostasis of the body and its dysfunction is directly associated with multiple pathophysiological abnormalities including acute coronary syndrome and cardiomyopathy [145]. In the diabetic myocardium, oxidative stress plays a major role in promoting cardiac inflammation and fibrosis [146–148]. In fact, several studies have documented a significant reduction in cardiac pro-inflammatory and fibrotic markers upon treatment with antioxidants [143, 147, 149]. Conclusively, microvascular, macrovascular, and cardiac dysfunction with diabetes could not be evaluated as independent entities since they are functionally interconnected and directly affected by systemic oxidative stress and inflammation.

Effects on the myocardium

The impact of SGLT2 inhibition on the myocardial oxidative and inflammatory response has been investigated in multiple studies (Table 1). In a prediabetic rat model of metabolic syndrome, 10 weeks of treatment with Empa significantly reduced cardiomyocytes hypertrophy, interstitial fibrosis, and subcutaneous fat tissue despite no significant change in BP and autonomic function [67]. Reduction of cardiac oxidative stress and inflammation following Empa accounted for the observed direct cardioprotective effects [67]. In a T2D mouse model, administration of Empa to db/db mice for a 10-week period significantly improved cardiac and pericoronary arterial fibrosis, and myocardial macrophage infiltration with no impact on BP [66]. Findings were directly linked to significant reduction in cardiac superoxide production supporting the antioxidant capacities of SGLT2is [66]. In an attempt to better understand the impact of SGLT2 inhibition on cardiac inflammatory modulation, Dapa was tested on a MI rat model. Dapa administration over a period of 4 weeks post-MI resulted in significant decrease in reactive oxygen and nitrogen species (RONS) as early as 3 days post-MI followed by a significant decrease in myofibroblast infiltration and cardiac fibrosis, 28 days post-MI [65]. Those results were attributed to an enhanced M2 macrophage polarization and IL-10 anti-inflammatory cytokine upregulation through a RONS-attenuation-mediated STAT3 activation signaling pathway [65]. Of note, antioxidants are known to increase STAT3 activity during MI and to polarize, along with STAT3 activation, macrophages towards an M2 anti-inflammatory phenotype [150–153], supporting the role of SGLT2i as antioxidant and inflammatory modulators in the heart. Modulation of cardiac inflammation by SGLT2i was directly tested on nucleotide-binding domain leucine-rich repeat containing protein (NLRP)-3 inflammasome activation [154]. NLRP-3 inflammasome is an intracellular oligomer, which promotes the activation of the pro-inflammatory cytokines IL-1β and IL-18 and is directly involved in the pathogenesis of some metabolic disorders including obesity induced insulin resistance, diabetes mellitus, and atherosclerosis [154–157]. In T2D models, NLRP-3 inflammasome is upregulated in the myocardium and contribute to cardiac inflammation, fibrosis, and subsequent cardiac dysfunction and cardiomyopathy [158–162]. Dapa treatment in T2D ob/ob mice significantly reduced cardiac NLRP-3 inflammasome activation along with antifibrotic effects and overall improvement in LV ejection fraction and systolic function when compared to controls [163]. Observed non-functional effects were replicated in vitro, ruling out any glucose or hemodynamic-lowering dependent effects [163].

Effects on the vasculature

Early experiments with phlorizin, a natural product with non-selective SGLT inhibitory properties, revealed that inhibition of glucose entry into vascular smooth muscle cells via this transporter modulated both intracellular calcium levels and serotonin-mediated contractions [164]. Using phlorizin, SGLT was postulated to act as a glucose sensor in retinal pericytes whereby capillary tone and microvascular blood flow would be regulated based on extracellular glucose levels [165]. Attenuation of smooth muscle contraction by SGLT blockade was reported in lymphatic preparations as well and was linked to smooth muscle ion homeostasis [166]. Increasing vascular tone was attributed to the sodium component of the SGLT transport process driven by glucose,

whereby sodium entering the cell would later be exchanged for extracellular calcium via NCX activity and hence, the increased vascular tone [166]. A better-studied aspect of the effect of SGLT function on vascular tone is through its action on endothelial cells. Several lines of evidence implicated an enhanced SGLT activity in vascular endothelial cells under stress conditions [167]. SGLT inhibition by phlorizin ameliorated hypoxia-induced endothelial cell activation and production of vasoactive prostaglandins and platelet-activating factors [168]. Indeed, simulation of stroke conditions in vitro led to an increase in SGLT-mediated glucose transport, which upon inhibition in in vivo models of stroke was associated with a reduced brain infarct size and edema [169]. With regard to endothelium-dependent relaxation, acute exposure to glucose and insulin was associated with endothelial NO production attributed to sodium entry via SGLT and later exchange with extracellular calcium [170]. It followed that SGLT inhibition with phlorizin strongly attenuated endothelium-dependent NO-dependent vasodilation ex vivo [170]. Such an observation is contradictory to a proposed vasculoprotective effect for SGLT inhibitors in diabetic vascular disorders of which endothelium dysfunction is considered a hallmark. However, observed in vitro results with phlorizin are questionable for three major reasons: (1) phlorizin is not specific to SGLT and has broad off-target effects; (2) phlorizin could be hydrolyzed either chemically (as may occur in aqueous solutions) or enzymatically to phloretin, which inhibits most passive glucose transporters (GLUTs) and not just the SGLTs [171]; and (3) in vitro studies focus on acute and limited rather than chronic and systemic effects of the drugs. Chronic and systemic effects are essential in multifactorial diseases such as diabetes. A newer study examined the effect of chronic in vivo phlorizin treatment (10 weeks) on a diabetic mouse model [172]. Isolated aortas from the treated mice showed an improved endothelium-dependent relaxation compared to the untreated diabetic animals. This was attributed to an apparent reduction in oxidative stress and AGEs rather than direct vasoactive effects as hypothesized in acute in vitro studies. In an attempt to confirm these findings with more selective SGLT inhibitor drugs, a study compared ex vivo and in vivo treatment effects using chronic phlorizin and canagliflozin, a highly specific SGLT2 inhibitor, on mouse coronary arteries [74]. The authors found that, despite the observation that both SGLT inhibitors did not affect NO-dependent coronary relaxation ex vivo, arteries isolated from diabetic animals receiving 4-week canagliflozin treatment had improved relaxation compared to untreated diabetic cohorts. Of note though, in the latter study, the authors were not able to detect SGLT2 expression in mouse or human coronary vascular smooth muscle and endothelia to justify canagliflozin vasoactive action, which question the direct mechanisms behind SGLT2 inhibition on the vasculature. Recent studies with Empa and ipragliflozin, both novel selective and highly specific SGLT2i, fortified these findings [66, 173]. Empa significantly improved pericoronary arterial fibrosis, coronary arterial thickening, and vasodilation impairment following a 10-week treatment in T2D db/db mice. In this model, Empa protective effects were attributed to significant attenuation of oxidative stress in cardiovascular tissue [66]. Ipragliflozin was tested in STZ-induced diabetic mouse model on a 3-week administration timeframe. Findings of the ipragliflozin study revealed a protection against endothelial dysfunction via modulation of inflammation and attenuation of oxidative stress [173]. Taken together, the previous results indicate that the potential vasculoprotection associated with SGLT2i therapy is mediated by an indirect modulatory effect, and most probably through attenuating oxidative stress and inflammation, thus supporting their capacity in reversing the perivascular adipose inflammation associated with insulin resistance and diabetes [174, 175].

A significant body of literature underscores the role of inflammation in the vasculature and perivascular adipose tissue in diabetic vasculopathy [174]. A vascular anti-inflammatory role for SGLT2i is supported by recent evidence whereby the beneficial vascular effect of chronic oral SGLT2 inhibitor treatment was accompanied by a reduced vascular expression of inflammatory molecules, e.g., monocyte chemoattractant protein-1, vascular cell adhesion molecule-1, and intercellular adhesion molecule [173]. Dapa treatment was shown to decrease both visceral and sub-cutaneous adipose tissue mass in diabetic patients along with the decrease in high sensitivity C-reactive protein (hsCRP) serum levels, a well-known marker of inflammation in CVD [176, 177]. Nevertheless, SGLT2 inhibitor-mediated vasculoprotective effect through suppression of perivascular adipose inflammation remains to be examined systematically.

Protective mechanisms of SGLT2 inhibition in heart failure

Both, heart failure with preserved and reduced ejection fraction are debilitating complexed clinical syndromes that are often accompanied with comorbidities that directly affect patient's prognosis and clinical intervention [178, 179]. The alteration of cardiac stroke volume in heart failure could be related to three major affected mechanisms: preload, afterload, and myocardial contractility. Clinically heart failure patients treated with SGLT2i exhibited a lower risk of hospitalization when compared to placebo [33, 34]. SGLT2 inhibition may decrease preload through promoting osmotic diuresis which reduces volume overload in heart failure patients improving myocardial stretching mechanisms and contractility [180]. Recent studies revealed a reduction in blood pressure, arterial stiffness, and vascular resistance in T2D patients treated with Empa, effects that could decrease afterload and subsequently improve cardiac output in heart failure patients [16]. In

Table 2 A selective list of studies highlighting systemic effects of SGLT2 inhibitors in rodents

Model	Study design	Systemic effects					Ref
		Blood pressure	Body weight	Metabolism	Fat tissue	Kidney	
Non-diabetic rodents Non-diabetic male Wistar rats: Dapa: 0.1 mg/kg/day/4 W post-MI	Dapa effects on cardiac fibrosis attenuation post-MI in rats	N/A	↔	N/A	N/A	↑ Glucosuria ↑ UO	[65]
TD2 rodents C57BLKS/J-lepr^{db}/lepr^{db} 7 W old T2D db/db mice: Empa: 0.03% of the standard diet for 1 W or 10 W	Empa effects on CV injury in T2D mice	↔	1 W treatment ↓ 10 W treatment ↑	1 W treatment N/A 10 W treatment ↓ Plasma glucose level	N/A	1 W treatment ↑ 24-h glucose excretion and UO 10 W treatment ↓ 24-h glucose excretion and UO ↓ Albuminuria	[66]
20 W old SHRcp rats: Empa: 0.03% of the standard diet for 10 W	Empa effects on metabolic syndrome rats with prediabetes	↔ LF-SBP and LF/HF ratio of PI	1 W treatment ↔ ≥ 7 W treatment ↓	1 W treatment N/A 10 W treatment ↔Serum total cholesterol and FFA ↑ Plasma TG ↓ Non-fasting blood glucose and HbA1c	10 W treatment ↓ SF weight ↔ VF weight ↓ EFV and SF adipocyte size ↓ EFV and SF large adipocytes size proportion ↑ EFV and SF small adipocytes size proportion ↓ EFV oxidation ↔ SF oxidation ↔ EFV and SF adiponectin levels	1 W treatment ↑ Urinary glucose and Na^+ excretion and UO ↓ Cumulative 24-h water balance 1–10 W treatment ↑ Urinary glucose excretion and UO ↔ Urinary Na^+ excretion and water balance	[67]
4 W old C57BL6/J male mice HFHS induced obesity and insulin resistance + 2 months of 3 mg/kg of Empa	Empa chronic effects in diet-induced obesity and IR mice	N/A	↓ in gain	↔ Total and LDL cholesterol ↓ Glycemia and HOMA-IR levels ↑ Glucose tolerance	↓ VF	↓ ACR	[68]
6 W old T2D lipodystrophic Bscl2$^{-/-}$ SKO mice: 1 mg/kg Dapa/day/8 W	Dapa effects on cardiomyopathy in T2D mice	N/A	↔	↓ Plasma TG and glycemia ↓ OGlcNAcylated FOXO1 protein level	N/A	↑ Glycosuria	[69]
10 to 12 W old leptin-deficient T2D ob/ob male mice 10 mg/kg/day Empa mixed in diet for 6 W	Empa chronic effects on LV functions in T2D mice	N/A	↓	↓ Fasting glucose and HbA1c levels ↓ HOMA-IR index	N/A	↑ SGLT2 expression	[70]
C57BLKS/J 8W old female T2D db//db mice 10 mg/kg/day of Empa for 5 W	Empa effects on reducing CVD events in T2D mice	SBP and DBP ↔	N/A	↔ Plasma TG and cholesterol levels ↓ Fasting plasma Glucose and HbA1c	N/A	↑ Glycosuria	[71]
C57BL/6 T2D male mice 30 mg/kg/day Canagliflozin for 4 W	Cana effects on vascular relaxation in T2D mice	N/A	↑	↓Total and LDL cholesterol ↔ TG ↑ HDL ↓ LDL ↑ Glucose tolerance	N/A	N/A	[74]

N/A, not Available; ↑, increase; ↓, decrease; ↔, no changes; *W*, week; *T2D*, type 2 diabetes; *Empa*, empagliflozin; *MI*, myocardial infarction; *UO*, urine output; *CV*, cardiovascular; *LF-SBP*, low frequency systolic blood pressure; *LF*, low frequency; *HF*, high frequency; *PI*, pulse interval; *FFA*, free fatty acids; *TG*, triglycerides; *LV*, left ventricle; *HOMA-IR*, homeostasis model assessment of insulin resistance; *SF*, subcutaneous fat; *VF*, visceral fat; *EFV*, epicardial fat volume; *Na^+* , sodium; *ACR*, albumin-to-creatinine ratio; *CVD*, cardiovascular disease; *FOXO1*, Forkhead box protein O1; *LDL*, low-density lipoprotein; *HDL*, high-density lipoprotein; *SGLT*, sodium/glucose cotransporter; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure

¥ Results presented in this table are in comparison with T2D rodents same conditioning treatment

addition to the protective SGLT2 inhibition impact on multiple mechanisms preceding heart failure and diabetic cardiomyopathy development including metabolic impairment, mitochondrial dysfunction, calcium handling, inflammation, and oxidative stress, SGLT2i impact on BMI, a well-known heart failure risk factor, is also promising [13, 181, 182]. In fact, treatment with SGLT2 inhibitor results in approximately 2–3 kg reduction body weight over 24–52 weeks in diabetic patients most probably due to osmotic diuresis and caloric loss as well as other undefined mechanisms [13, 182, 183]. Although SGLT2i-mediated weight reduction is small, its combination with modest reduction in preload and afterload could synergistically improve cardiac workload and contractility [184].

Conclusions and future perspectives

To date, no antidiabetic drug showed the same CV benefit as SGLT2is did with diabetic patients. Although other antidiabetic drugs appeared to produce CV benefit when given to pre-diabetic patients, e.g., metformin [185] and pioglitazone [186], neither drug showed the same benefit in diabetic patients. Clinical data describing the cardiovascular benefits of SGLT2is in diabetic patients highlight the potential these drugs offer as future therapeutic tools to address cardiovascular deterioration in an impaired metabolic milieu. Recent studies showed that SGLT1, but not SGLT2, is found in the capillaries and myocytes of human and rodent hearts and upregulated in the myocardium of multiple pathological conditions including T2D, hypertrophy, heart failure, and infarcted hearts [9–12, 75]. SGLT1 effect in heart remains controversial as it has been directly linked to NOX2-mediated ROS production in cardiomyocytes but also shown to play a critical role in cardiac cell protection during the acute phase of ischemia-reperfusion injury by regulating cardiac energy metabolism [187–189]. These findings question whether the direct observed SGLT2 inhibition effects on the CV system are mediated through off-target effects such as SGLT1 upregulation or inhibition. To date, no data support the upregulation of SGLT1 in the heart following SGLT2 inhibition as a compensatory mechanism similarly to what is found in the kidneys and GI tract [190]. Although canagliflozin expressed a modest SGLT-1 inhibitory effect in the small intestine from the luminal side at clinical dosage, it did not affect SGLT-1 in the heart or the skeletal muscle [191]. Nonetheless, there is a consensus that SGLT2i direct effects on the myocardium (Table 1) are independent of SGLT2i-mediated systemic effects (Table 2), and together direct and systemic effects potentiate SGLT2 inhibition cardioprotective outcomes (Fig. 1). Several questions remain to be answered in terms of the exact mechanism of action upon chronic use, optimal timing of intervention, and whether structural and functional modifications of these molecules could serve to enhance the CV protective effect and thus, maximizing their therapeutic benefit. Finally, exploring the effects of these drugs in pre-diabetic or non-diabetic individuals with other forms of metabolic impairment and at high risk of CVD is also warranted.

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Compliance with ethical standards

Conflict of interest The authors confirm that there are no conflicts of interest or disclosure to make.

Abbreviations SGLT, sodium/glucose cotransporter; WHO, World Health Organization; Ca^{2+}, calcium; T2D, type 2 diabetes; CV, cardiovascular; Empa, empagliflozin; MI, myocardial infarction; CVD, cardiovascular disease; NHE, sodium hydrogen exchanger; NCX, sodium calcium exchanger; SERCA2a, sarcoplasmic-reticulum calcium ATPase 2a; Dapa, dapagliflozin; STZ, streptozotocin; [Na+]c, cytoplasmic Na^+ concentration; [Ca2+]c, cytoplasmic Ca^{2+} concentration; ob/ob, leptin-deficient homozygous T2D mouse model; LV, left ventricle; db/db, C57BLKS/J-$Lepr^{db}$/$Lepr^{db}$ T2D mouse model; SGK1, serum/glucocorticoid regulated kinase 1; FFAs, free fatty acids; TG, triglyceride; PDH, pyruvate dehydrogenase; PPARα, peroxisome proliferator-activated receptor alpha; PDK4, pyruvate dehydrogenase lipoamide kinase isozyme 4; AGEs, advanced glycation end products; PPP, pentose phosphate pathway; HBP, hexosamine biosynthesis pathway; ROS, reactive oxygen species; OxPhos, oxidative phosphorylation; ATP, adenosine triphosphate; SKO, lipodystrophic *Bscl2*$^{-/-}$ (seipin knockout [SKO]) T2D mouse model; HFHS, high-fat-high-sugar; EFV, epicardial fat volume; DKA, diabetic ketoacidosis; RONS, reactive oxygen and nitrogen species; NLRP, nucleotide binding domain leucine rich repeat containing protein; IL, interleukin; NO, nitric oxide; Phlor, phlorizin; Cana, canagliflozin; hsCRP, high sensitivity C-reactive protein

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