Sodium Glucose Co-transporter 2 Inhibitors and Heart Failure

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Sodium-glucose co-transporter 2 (SGLT2) receptors are primarily located in the proximal convoluted tubule of the nephron. These receptors are responsible for almost 90% to 95% of tubular reabsorption of the glucose in the nephron. In patients with diabetes mellitus, due to upregulation of SGLT2 receptors, glucose reabsorption is further increased. The Food and Drug Administration approved SGLT2 inhibitors, such as canagliflozin, empagliflozin, dapagliflozin, and ertugliflozin, for the treatment of type 2 diabetes. In addition to their positive effect on blood glucose, additional cardioprotective and renoprotective functions have been demonstrated in major trials such as EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI-58, and CREDENCE. Unlike other antihyperglycemic drugs, reduction in hospitalization for heart failure (HF) was also seen as a class effect with this group, mechanisms of which are probably multifactorial. Subgroup analysis from these major trials indicated a reduction in progression of nephropathy and HF readmission with SGLT2 inhibitors. Although this unique property of canagliflozin was further analyzed in the CREDENCE trial, similar trials for empagliflozin (EMPERIAL-Reduced and EMPERIAL-Preserved) and dapagliflozin (DAPA-HF) are currently underway. Recently released phase III results from DAPA-HF trial indicate that dapagliflozin shows significant reduction in death due to cardiovascular causes and hospitalization in HF compared with the placebo, in both diabetics and nondiabetics. In this review article, the authors attempt to explore the possible underlying molecular mechanisms and data from existing trials pertaining to the HF related outcomes associated with SGLT2 inhibitors. **(Am J Cardiol 2019;124:1790−1796)**

Diabetes mellitus (DM) is a prominent risk factor for cardiovascular disease (CVD) in both men and women.[1] According to the 2014 World Health Organization (WHO) data, the global prevalence of DM in adults stands at 422 million, a drastic rise from 108 million recorded in 1980. Another census indicated that DM related complications were the major cause of death 1.6 million adults in 2015.[2] Additionally, diabetic women and men have a five-fold and 2.4-fold higher risk, of developing heart failure (HF) respectively, as compared with their nondiabetic counterparts.[3] The US Food and Drug Administration (FDA) now requires all new diabetic drugs to demonstrate an absence of unacceptable CVD risk. HF has not been a component of the popularly used composite end point for cardiovascular outcomes studies, namely major atherosclerotic cardiovascular events or MACE (composite of CVD death, nonfatal myocardial infarction [MI], and nonfatal stroke). However, the higher rate of HF as compared with MI in several major diabetic trials warrants a closer look at the causal relation of antidiabetic drugs with specific HF related outcomes including hospital readmission.

Different Classes of Antihyperglycemic Agents and HF Outcomes

Although treatment of DM with oral antihyperglycemic agents improves the CVD morbidity and mortality by treating an important risk factor, many of the drugs in the diabetic toolbox have been known to worsen CVD related outcomes. Amongst the older agents, metformin is known to have a positive impact on CVD mortality. The data on sulfonylureas has been conflicting with some reports indicating a higher incidence of HF in patients treated with these drugs.[4] Similarly, rosiglitazone, a member of thiazolidinedione class, has been associated with higher all-cause mortality and an increased risk of stroke and HF.[5] Out of newer classes, glucagon-like peptide 1 or GLP-1 analogue exenatide has been linked with a substantial decline in risk of CVD and hospitalization in individuals with type 2

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diabetes.[6] In contrast, dipeptidyl peptidase 4 enzyme inhibitor saxagliptin, which acts through a mechanism of action related to GLP-1 analogues, paradoxically increases the risk of HF-related hospitalization.[7] In this context, the newest class of drugs sodium-glucose co-transporter 2 (SGLT2) inhibitors is a promising class of oral antihyperglycemic agents that have noted a favorable outcome, especially in HF.

Molecular Mechanisms and Nonglycemic Pharmacology of SGLT-2 Inhibitors Contributing to HF Outcomes

Antihyperglycemic Effects

SGLT2 receptors are present on the brush border epithelium of the proximal convoluted tubule and are responsible for approximately 90% of renal glucose reabsorption in the renal tubules.[8] In diabetic patients, the upregulation of SGLT2 gene coupled with reduced urinary excretion of glucose result in a poorer glycemic control.[9] SGLT2 inhibitors, thus, increase the urinary excretion of glucose, thereby reducing plasma glucose level as shown in Figure 1.

At present, the FDA has approved four SGLT2 inhibitors: canagliflozin, dapagliflozin, empagliflozin and ertugliflozin.[10] A basic summary of pharmacology of these drugs is represented in Table 1. These are available either as single-ingredient product or in combination with other antihyperglycemic agents.

Cardioprotective and Renoprotective Mechanisms of SGLT2 Inhibitors Specific to HF

SGLT2 inhibitors have a direct nonglycemic renoprotective function that was first documented in the experimental Otsuka Long-Evans Tokushima Fatty rat model. Rats with inhibited SGLT2 activity had lower renin−angiotensin aldosterone system activation, which in turn led to reduced expression of antioxidant enzymes and decreased inflammation in the tubular interstitium.[11] Hemodynamically, SGLT2 blockade is associated with reduced intraglomerular pressure, causing attenuated hyperfiltration and subsequently, tubular hypertrophy. The caloric deficit created by the loss of glucose is reflected in weight loss, which further boosts protection provided to the kidneys by this class of drugs.[12]

By virtue of its favorable effects on the hemodynamic of the glomerulus, SGLT2 inhibitors are able to reduce albuminuria and uric acid levels. A change in the systolic blood pressure is likely a consequence of natriuresis, osmotic diuresis, and weight loss associated with this class of medication.[13] Additionally, SGLT2 inhibitors decrease the single nephron glomerular filtration rate (GFR) by inducing afferent arteriolar constriction, which leads to reduced intraglomerular pressure.[14]

Canagliflozin has shown significant reduction in epicardial fat thickness at 100 mg dose over 3 months in a small study conducted in Japan. Although similar effect is yet to be investigated by other drugs of the class, this is significant as the epicardial adipose thickness directly correlates with

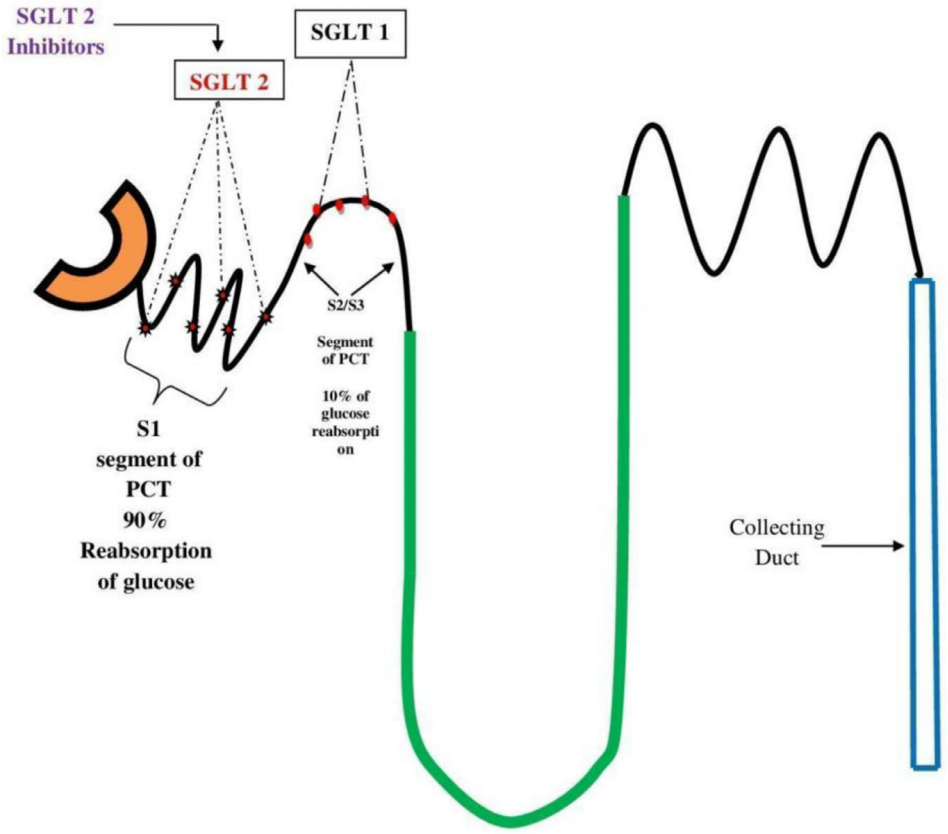

Figure 1. Mechanism of action of SGLT2 inhibitors. PCT = proximal convoluted tubule; SGLT = sodium glucose co-transporter 2.

Table 1
Pharmacology of important FDA approved members of SGLT2 class[10]

Drug	Daily dosage (mg)	Plasma half-life (hours)	Oral bioavailability	Metabolism and elimination
Dapagliflozin	5-10	12.9	78%	Hepatic and renal UGT1A9
Canagliflozin	100-300	10.6-13.1	65%	UGT1A9 and 2B4
Empagliflozin	10-25	10.6-13.1	Not measured	UGT1A3, UGT1A8, UGT1A and UGT2B7
Ertugliflozin	5-15	11-17	70%-90%	UGT1A9, UGT2B7

UGT = uridine diphosphate-glucuronosyltransferase.

the presence of atherogenic cytokines in the body and a reduction in epicardial adipose thickness will likely reduce the risk of CAD.[15]

The benefits of SGLT2 inhibitors may potentially be linked to its action on SGLT1 receptor as well. SGLT1 receptors are predominantly expressed in the small intestinal mucosa, the straight segment of the PCT, and ischemic and hypertrophied human cardiac tissues. In the kidney, these channels are responsible for reabsorption of glucose that has escaped reabsorption by SGLT2 channels present upstream.[16]

An interesting pathophysiology of HF is the elevated levels of intracellular Na^+ and Ca^{2+} and reduced levels of mitochondrial Ca^{2+}. Canagliflozin selectively inhibits Na^+/H^+ exchanger-1 in the cardiomyocytes, decreasing systolic, and diastolic Ca^{2+} overload. Empagliflozin, in contrast, acts by increasing mitochondrial Ca^{2+}, which is essential for energy production.[17] These effects may, in part, explain the diabetic cardiomyopathy benefit, noted with this class of drugs.

Empagliflozin, in particular, has other unique mechanisms through which it positively affects the cardiovascular physiology. At the molecular level, empagliflozin counteracts the upregulation of certain profibrotic and prohypertrophic proteins such as epithelial sodium channel and myocardial serum/glucocorticoid regulated kinase 1, thus preventing myocardial fibrosis.[18] As opposed to mechanism of diuresis shown by diuretics, SGLT2 inhibitors selectively remove fluid from the interstitial space instead of intravascular compartment, causing greater electrolyte-free water clearance and improved organ perfusion without affecting blood volume. This concept of differential column regulation was first suggested by Hallow et al in the context of empagliflozin in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial.[19]

The cardioprotective and renoprotective mechanisms are possibly linked to HF benefits seen with this class of drugs summarized in Table 2.

Table 2
Cardioprotective and renoprotective mechanisms resulting in HF benefits of SGLT2 inhibitors

Cardioprotective mechanisms	• Reduction in SBP • Weight loss • Canagliflozin has been associated with reduction in epicardial adipose thickness
HF-specific mechanisms	• Differential column regulation − reduces interstitial fluid through renal clearance instead of intravascular volume, thus maintaining organ perfusion • *Canagliflozin:* • Selectively inhibits NHE1 in the cardiomyocytes, decreasing systolic and diastolic Ca^{2+} overload • *Empagliflozin:* • Acts by increasing mitochondrial Ca^{2+} which is essential for energy production • Counteracts the upregulation of certain profibrotic and prohypertrophic proteins thus preventing myocardial fibrosis
Renoprotective mechanisms	• Lower RAAS activation causing reduction in tubular inflammation • Induce afferent arteriolar constriction • Reduced intraglomerular pressure and tubular hypertrophy • Reduced albuminuria • Weight loss

SGLT2 Inhibitors and Improved HF Outcomes: In-Vitro and Animal Data

In the rat models, empagliflozin has been shown to inactivate the endoplasmic reticulum stress pathway, a key process in the development of diabetic cardiomyopathy.[20] Empagliflozin also helps preserve the calcium handling and growth signaling pathways in the cardiomyocytes, leading to improved diastolic function in mice with type 2 diabetes.[21]

Lipodystrophic seipin knockout mice develop hypertrophic cardiomyopathy with hyperglycemia. Treatment of DM in these mice with dapagliflozin has shown to prevent the development of cardiomyopathy.[22] Dapagliflozin also attenuates activation of the inflammasome and prevents inflammatory cytokine production and apoptosis. It is also known to attenuate fibrosis, in a manner independent of glucose lowering, preventing deterioration of left ventricular ejection fraction in mice with type 2 diabetes.[23] Dapagliflozin treatment favorably affects glucose and fat metabolism in streptozotocin-induced diabetic mice.[24] In addition, treatment with dapagliflozin partially reverses atherosclerosis, inhibits macrophage infiltration, and stabilizes plaques. These effects are thought to be secondary to the reduced production of IL-1β, IL-18, NLRP3 protein, and mitochondrial reactive oxygen species in the aortic tissues.[25] The existing data on benefits of SGLT2 inhibitors on HF in animal models is summarized in Table 3.

HF-Related Outcomes from Major CVD Outcomes Trials

Several major trials exploring the CV benefits of SGLT2 inhibitors, with an emphasis on HF outcome, have come out in the recent years and are discussed below.

Table 3
In-vitro and animal data pertinent to HF outcomes with SGLT2 inhibitors

Dapagliflozin	• Prevents development of hypertrophic cardiomyopathy in diabetic mice models • Reduces activation of inflammasome and apoptosis • Prevents deterioration of LVEF in diabetic mice by reducing cardiac fibrosis • Partially reverses atherosclerosis by reducing atherogenic cytokine production in aorta in diabetic mice
Empagliflozin	• Inactivate the endoplasmic reticulum stress pathway in rat models • Preserve calcium handling and growth signalling pathways in diabetic mice

The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients(EMPA-REG OUTCOME)

The EMPA-REG OUTCOME[26] trial was a multicentric, double-blinded, randomized, placebo-controlled trial aimed at studying the effect of empagliflozin on MACE in 7,020 patients with type 2 DM and a high risk of CVD events, over a median period of 3.1 years. The primary end point of the trial was a composite of nonfatal MI (excluding silent MI), nonfatal stroke, and death from CVD causes, which was reported in 10.5% patients in the empagliflozin group compared with 12.1% in the placebo group (HR 0.86, CI 0.74 to 0.99, p value for noninferiority <0.001, p value for superiority 0.04). The empagliflozin group demonstrated a statistically significant lower incidence of CVD death (Absolute Risk Reduction 2.2%, Relative Risk Reduction 38%), HF-related admission (Absolute Risk Reduction 1.4%, Relative Risk Reduction 35%) and all-cause mortality (Absolute Risk Reduction 2.6%, Relative Risk Reduction 32%). Although there was no difference in the incidence of nonfatal MI or stroke between the 2 groups, the reduction in CVD mortality and HF-related admission was notably lower in patient subgroups with or without baseline HF. The diagnosis of HF at baseline was based on investigators' reports and since the HF diagnosis was not quantified, it remains an important limitation of the trial.[27] In a recent subgroup analysis, it was noted that the reduction in the risk of cardiovascular death, all-cause mortality, MACE and hospitalization for HF were consistent across the range of patients with existing cardiovascular risks such as previous MI and stroke.[28] In another post-hoc analysis, when the effect of empagliflozin on renal outcome was analyzed, it was found that empagliflozin was associated with a reduction in the incidence of nephropathy or worsening of pre-existing renal disease by 43% in the HF group when compared with the placebo group. Additionally, the progression to macroalbuminuria decreased by 50% in those patients being treated with empagliflozin versus those on placebo.[29]

After its initial approval as an adjunctive antihyperglycemic therapy in 2014, the FDA in 2016 extended the empagliflozin approval to CVD risk reduction in DM patients based on the cardioprotective benefits of the drug evident at preliminary stages itself in the EMPA-REG OUTCOME trial. In fact, the separation of the event curves for CVD mortality between empagliflozin and placebo was noted within 6 to 12 weeks of treatment initiation, not adequately explained by a possible antiatherosclerotic mechanism.[8] To further elaborate the benefits of this drug on HF, 2 sister trials are currently underway to specifically study the effect of empagliflozin on chronic stable HF (with preserved and reduced ejection fraction, respectively), irrespective of diabetic status. The trials aim to assess the change in exercise tolerance with empagliflozin by assessing the 6-minute walk test and secondarily evaluate symptomatic improvement of HF.[30]

The Canagliflozin Cardiovascular Assessment Study

This was a randomized, multicentric, double-blinded, placebo-controlled trial designed to assess the cardiovascular and renal safety and efficacy of canagliflozin in type 2 DM patients and high CVD risk. Designed originally in 2009 to evaluate only cardiovascular outcomes of canagliflozin, it was expanded to include data from a related sister trial called the CANVAS-R trial,[31] initiated in 2014, to finally jointly publish in 2017. In total, 10,142 participants were randomly assigned to canagliflozin and placebo and followed for a mean of 188.2 weeks. As compared with the placebo group (31.5 participants per 1000 patient-years), the canagliflozin group (26.9 participants per 1000 patient-years) demonstrated a significantly lower risk of primary end point of MACE (hazard ratio [HR] 0.86, confidence interval [CI] 0.75 to 0.97 and p <0.001 for noninferiority, p 0.02 for superiority). In a subsequent subgroup analysis, those patients with a baseline history of HF showed greater benefits for CVD death and HF readmission, when compared with patients without HF (16.3 vs 20.8 per 1000 patient-years, HR 0.78, CI 0.67 to 0.91).[32]

Following the results of the secondary endpoints of the CANVAS trial that included progression of albuminuria and renal composite endpoint, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation or the CREDENCE trial was designed to further evaluate the effect of the drug on renal function. Enrolling 4401 type 2 DM patients with pre-existing chronic kidney disease, the trial aimed to study the primary endpoint of renal composite (end stage renal disease, rise in serum creatinine by two times and death from either renal or cardiovascular cause) over a median of 2.62 years. The results indicated a 30% relative risk reduction of primary endpoint in the group treated with canagliflozin as compared to placebo (HR 0.70, CI 0.59 to 0.82, p = 0.00001).[33] In a post-hoc analysis of the CREDENCE trial, it was concluded that patients with type 2DM and chronic kidney disease had significantly lower risk of MACE when treated with canagliflozin as compared to placebo (HR 0.80, CI 0.67 to 0.95; p = 0.01).[34]

The Dapagliflozin Effect on Cardiovascular Events −Thrombolysis in Myocardial Infarction 58

Similar in design to the previous trials, the Dapagliflozin Effect on Cardiovascular Events−Thrombolysis in Myocardial Infarction 58[35] trial was a multicentric, randomized, double-blinded, placebo-controlled trial aimed at evaluating the cardiovascular safety (defined by the primary end point

of MACE) and efficacy (defined by the primary end point of MACE and composite of CVD death and HF-related hospitalization) of dapagliflozin. Seventeen thousand one hundred and sixty patients with type 2 DM with either pre-existing CVD or with presence of risk factors for CVD were included in the trial and followed up for a median period of 4.2 years. Although the incidence of MACE was similar in both dapagliflozin and placebo group, the trial demonstrated that dapagliflozin significantly reduced the rate of HF hospitalization and cardiovascular death in patients with and without established atherosclerosis when compared with the placebo group (4.9% vs 5.8%, HR 0.83, CI 0.73 to 0.95, $p = 0.005$). In a subgroup analysis, dapagliflozin was shown to reduce CVD death and hospitalization due to HF more in patients with HFrEF than in patients with HFpEF.[36] In another subgroup analysis, the dapagliflozin group showed reduced rate of progression of renal disease as defined by fall in eGFR by a minimum of 40%, incidence of end-stage renal disease and death from renal causes.[37]

The results of this pivotal trial laid the foundation for another trial called the Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure trial which aimed to study 4,744 patients with existing chronic HF (left ventricular ejection fraction ≤40%) with or without DM and eGFR ≥30 ml/min randomized to either dapagliflozin or placebo. The primary end point of this trial was the composite of HF-related hospitalization, urgent visits or CVD death, which was successfully achieved very recently and the full results will be presented at the upcoming European Society of Cardiology Congress in Paris, France. The trial indicates that dapagliflozin indeed has significant HF benefits, including in nondiabetics, and thus opens the possibility of expanding the scope of use of SGLT2 inhibitors beyond DM management.[38]

Caveats With SGLT2 Inhibitors and HF Outcomes

HFpEF is the most common phenotype of HF in DM patients. Although data from multiple clinical trials has demonstrated improved HF-related outcomes with SGLT2 inhibitors in type II diabetic patients, there is ambiguity regarding the maximal efficacy of these agents pertaining to HF phenotypes (reduced vs preserved ejection fraction and the stage of HF). Notwithstanding the favorable epidemiologic and clinical trial data, further edification of these agents' mechanistic impact assessed with echocardiographic parameters, such as diastolic function, left ventricular ejection fraction, strain, right ventricular function, and pulmonary pressure, the WHO functional capacity and invasive hemodynamic is awaited. Additionally, assessment of serum biomarkers of inflammation and HF is warranted.

An approximately twofold increased risk in lower limb amputations was observed with canagliflozin treatment in the CANVAS and CANVAS-R trials following which the FDA issued a "black box warning" against the drug labels. However, the higher amputation risk was not observed with 2 other molecules of the class. The common adverse events with this group are the risk of frequent urinary tract infection whereas other rarer side effects include euglycemic diabetic ketoacidosis, Fournier's gangrene and fracture.[39,40]

Table 4
Key points of SGLT2 inhibitors in HF

1. A number of renoprotective and cardioprotective effects of this class of drugs are linked to HF benefits
2. Reduction in HF-related admission was seen as a class effect of SGLT2 inhibitors
3. Data is emerging supporting long-term cardiovascular benefits, specifically HF, in patients with and without DM
4. EMPA-REG, CANVAS and DECLARE-TIMI are the 3 major cardiovascular trials examining MACE as primary outcome with drugs of this class
5. Subgroup analysis showed that HF benefits extended to patients with previous cardiovascular events
6. More trials examining the direct effect of SGLT2 inhibitors on HF are currently underway, including EMPERIAL-Reduced and EMPERIAL-Preserved
7. DAPA-HF results indicate a possible expanding role of SGLT2 inhibitors in nondiabetic patients with HFrEF

Hence, it is important for physicians to keep in mind the contraindications of this class of medications and the prompt identification of adverse events.

Summary

The cardioprotective benefits of SGLT2 inhibitors were noted at the very initial stage of the cardiovascular outcome trials. The reduction in the risk of hospitalizations for HF occurred early after initiation of therapy and the event curve separation related to this outcome was noted in the initial few weeks after therapy itself. This class effect is consistent across all 3 SGLT2 inhibitors. Besides the diuretic like effect and the beneficial effects on calcium handling, SGLT2 inhibitors also decrease blood pressure and body weight. The incidence of the progressive nephropathy and proteinuria in diabetics and the need for renal replacement therapy was significantly decreased by both empagliflozin and canagliflozin. Large randomized controlled trials are required in the future to address more HF specific outcomes like mortality benefit, improvement in left ventricular remodeling, diastolic function, right ventricular function, WHO functional class, 6-minute walk test, and serum biomarkers before a widespread usage of SGLT2 inhibitors in HF patients could be advocated. A number of trials such as EMPERIAL-Preserved and EMPERIAL-Reduced are presently underway to answer some of these questions. The results of Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure, in contrast, that are yet to be published or formally presented in a meeting were released and indicated that dapagliflozin showed significant reduction in endpoints of cardiovascular death and HF exacerbation requiring hospitalization in both diabetics and nondiabetics when compared with placebo. The key points of this review article are mentioned in Table 4. The possible inclusion of SGLT2 inhibitors in the toolbox of HF treatment could be an exciting new beginning for better outcome management for this disease.

Disclosures

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1. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, Mitch W, Smith SC Jr, Sowers JR. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation* 1999;100:1134–1146.
2. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet* 2016; 387:1513–1530.
3. Fonarow GC. Diabetes medications and heart failure. *Circulation* 2014;130:1565–1567.
4. Azoulay L, Suissa S. Sulfonylureas and the risks of cardiovascular events and death: a methodological meta-regression analysis of the observational studies. *Diabetes Care* 2017;40:706–714.
5. Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, Ali F, Sholley C, Worrall C, Kelman JA. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. *JAMA* 2010;304:411–418.
6. Mentz RJ, Thompson VP, Aguilar D, Choi J, Gustavson SM, Iqbal N, Kong AP, Öhman P, Sattar N, Scott RS, Wong YW, Holman RR, Hernandez AF. Effects of once-weekly exenatide on clinical outcomes in patients with preexisting cardiovascular disease. *Circulation* 2018;138:2576–2578.
7. Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, Udell JA, Mosenzon O, Im K, Umez-Eronini AA, Pollack PS, Hirshberg B, Frederich R, Lewis BS, McGuire DK, Davidson J, Steg PG, Bhatt DL. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. *Circulation* 2014;130:1579–1588.
8. Perreault L. EMPA-REG OUTCOME: the endocrinologist's point of view. *Am J Med* 2017;130:51–56.
9. Zou H, Zhou B, Xu G. SGLT2 inhibitors: a novel choice for the combination therapy in diabetic kidney disease. *Cardiovasc Diabetol* 2017;16:65.
10. Hsia DS, Grove O, Cefalu WT. An update on SGLT2 inhibitors for the treatment of diabetes mellitus. *Curr Opin Endocrinol Diabetes Obes* 2017;24:73–79.
11. Cherney DZ, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, Fagan NM, Woerle HJ, Johansen OE, Broedl UC, von Eynatten M. Renal hemodynamic effect of Sodium−glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation* 2014;129: 587–597.
12. Panchapakesan U, Pegg K, Gross S, Komala MG, Mudaliar H, Forbes J, Pollock C, Mather A. Effects of SGLT2 inhibition in human kidney proximal tubular cells−renoprotection in diabetic nephropathy? *PLoS ONE* 2013;8:e54442.
13. Briasoulis A, Al Dhaybi O, Bakris GL. SGLT2 inhibitors and mechanisms of hypertension. *Curr Cardiol Rep* 2018;20:1.
14. Vallon V, Blantz RC, Thomson S. Glomerular hyperfiltration and the salt paradox in early [corrected] type 1 diabetes mellitus: a tubulo-centric view. *J Am Soc Nephrol* 2003;14:530–537.
15. Yagi S, Hirata Y, Ise T, Kusunose K, Yamada H, Fukuda D, Salim HM, Maimaituxun G, Nishio S, Takagawa Y, Hama S, Matsuura T, Yamaguchi K, Tobiume T, Soeki T, Wakatsuki T, Aihara KI, Akaike M, Shimabukuro M, Sata M. Canagliflozin reduces epicardial fat in patients with type 2 diabetes mellitus. *Diabetol Metab Syndr* 2017;9:78.
16. Di Franco A, Cantini G, Tani A, Coppini R, Zecchi-Orlandini S, Raimondi L, Luconi M, Mannucci E. Sodium-dependent glucose transporters (SGLT) in human ischemic heart: a new potential pharmacological target. *Int J Cardiol* 2017;243:86–90.
17. Kates AM, Herrero P, Dence C, Soto P, Srinivasan M, Delano DG, Ehsani A, Gropler RJ. Impact of aging on substrate metabolism by the human heart. *J Am Coll Cardiol* 2003;41:293–299.
18. Habibi J, Aroor AR, Sowers JR, Jia G, Hayden MR, Garro M, Barron B, Mayoux E, Rector RS, Whaley-Connell A, DeMarco VG. Sodium glucose transporter 2 (SGLT2) inhibition with empagliflozin improves cardiac diastolic function in a female rodent model of diabetes. *Cardiovasc Diabetol* 2017;16:9.
19. Hallow KM, Helmlinger G, Greasley PJ, McMurray JJV, Boulton DW. Why do SGLT2 inhibitors reduce heart failure hospitalization? A differential volume regulation hypothesis. *Diabetes Obesity Metab* 2018;20:479–487.
20. Zhou Y, Wu W. The sodium-glucose co-transporter 2 inhibitor, empagliflozin, protects against diabetic cardiomyopathy by inhibition of the endoplasmic reticulum stress pathway. *Cell Physiol Biochem* 2017;41: 2503–2512.
21. Hammoudi N, Jeong D, Singh R, Farhat A, Komajda M, Mayoux E, Hajjar R, Lebeche D. Empagliflozin improves left ventricular diastolic dysfunction in a genetic model of type 2 diabetes. *Cardiovasc Drugs Ther* 2017;31:233–246.
22. Joubert M, Jagu B, Montaigne D, Marechal X, Tesse A, Ayer A, Dollet L, Le May C, Toumaniantz G, Manrique A, Charpentier F, Staels B, Magré J, Cariou B, Prieur X. The sodium-glucose cotransporter 2 inhibitor dapagliflozin prevents cardiomyopathy in a diabetic lipodystrophic mouse model. *Diabetes* 2017;66:1030–1040.
23. Ye Y, Bajaj M, Yang HC, Perez-Polo JR, Birnbaum Y. 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* 2017;31:119–132.
24. Terasaki M, Hiromura M, Mori Y, Kohashi K, Nagashima M, Kushima H, Watanabe T, Hirano T. Amelioration of hyperglycemia with a sodium-glucose cotransporter 2 inhibitor prevents macrophage-driven atherosclerosis through macrophage foam cell formation suppression in type 1 and type 2 diabetic mice. *PLoS One* 2015;10:e0143396.
25. Leng W, Ouyang X, Lei X, Wu M, Chen L, Wu Q, Deng W, Liang Z. The SGLT-2 inhibitor dapagliflozin has a therapeutic effect on atherosclerosis in diabetic ApoE(−/−) mice. *Mediators Inflamm* 2016;2016: e6305735.
26. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE, EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; 373:2117–2128.
27. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE, EMPA-REG OUTCOME® trial investigators. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. *Eur Heart J* 2016; 37:1526–1534.
28. Fitchett D, Inzucchi SE, Cannon CP, McGuire DK, Scirica BM, Johansen OE, Sambevski S, Kaspers S, Pfarr E, George JT, Zinman B. Empagliflozin reduced mortality and hospitalization for heart failure across the spectrum of cardiovascular risk in the EMPA-REG OUTCOME Trial. *Circulation* 2019;139:1384–1395.
29. Butler J, Zannad F, Fitchett D, Zinman B, Koitka-Weber A, von Eynatten M, Zwiener I, George J, Brueckmann M, Cheung AK, Wanner C. Empagliflozin improves kidney outcomes in patients with or without heart failure. *Circ Heart Fail* 2019;12:e005875.
30. Abraham WT, Ponikowski P, Brueckmann M, Zeller C, Macesic H, Peil B, Brun M, Ustyugova A, Jamal W, Salsali A, Lindenfeld J, Anker SD. Rationale and design of the EMPERIAL-Preserved and EMPERIAL-Reduced trials of empagliflozin in patients with chronic heart failure. *Eur J Heart Fail* 2019;21:932–942.
31. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; 377:644–657.
32. Rådholm K, Figtree G, Perkovic V, Solomon SD, Mahaffey KW, de Zeeuw D, Fulcher G, Barrett TD, Shaw W, Desai M, Matthews DR, Neal B. Canagliflozin and heart failure in type 2 diabetes mellitus. *Circulation* 2018;138:458–468.
33. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;380:2295–2306.
34. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;380:2295–2306.
35. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;380:347–357.
36. Kato ET, Silverman MG, Mosenzon O, Zelniker TA, Cahn A, Furtado RHM, Kuder J, Murphy SA, Bhatt DL, Leiter LA, McGuire DK,

Wilding JPH, Bonaca MP, Ruff CT, Desai AS, Goto S, Johansson PA, Gause-Nilsson I, Johanson P, Langkilde AM, Raz I, Sabatine MS, Wiviott SD. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. *Circulation* 2019;139:2528–2536.

37. Mosenzon O, Wiviott SD, Cahn A, Rozenberg A, Yanuv I, Goodrich EL, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. *Lancet Diabetes Endocrinol* 2019;7:606–617.
38. McMurray JJV, DeMets DL, Inzucchi SE, Kober L, Kosiborod MN, Langkilde AM, et al. A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). *Eur J Heart Fail* 2019;21:665–675.
39. Puckrin R, Saltiel MP, Reynier P, Azoulay L, Yu OHY, Filion KB. SGLT-2 inhibitors and the risk of infections: a systematic review and meta-analysis of randomized controlled trials. *Acta Diabetol* 2018;55:503–514.
40. Erondu N, Desai M, Ways K, Meininger G. Diabetic ketoacidosis and related events in the canagliflozin type 2 diabetes clinical program. *Diabetes Care* 2015;38:1680–1686.