Sodium-glucose cotransporter 2 inhibitors (SGLT2i): their role in cardiometabolic risk management

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Abstract

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a novel category of oral antidiabetic drugs that suppress renal glucose reabsorption and increase renal glucose excretion, thus lowering plasma glucose levels. This unique mechanism of SGLT2i action is insulin independent, thus improving glycemic control without promoting hypoglycemia in the absence of exogenously administered insulin.

The present narrative review addresses the impact of SGLT2i on several cardiovascular (CV) risk factors, including fasting and postprandial plasma glucose levels, lipids, blood pressure, body weight, serum uric acid and arterial stiffness. These drugs may also favorably modulate cardiac and renal function via their effects on inflammation, oxidative stress, diuresis, fluid and sodium retention, myocardial function, vascular resistance and 'fuel' metabolism. In the EMPA-REG OUTCOME study, the first published large CV outcome SGLT2i trial, empagliflozin significantly reduced the primary composite outcome (i.e. CV death, nonfatal myocardial infarction or stroke) and all-cause death as well as hospitalization for heart failure. In addition, empagliflozin was associated with a slower progression of kidney disease and lower rates of clinically relevant renal events than was placebo when added to standard care in patients at high CV risk. Ongoing CV outcome trials involving other SGLT2i will help establish whether the reported CV and microvascular risk benefits are compound-specific or drug class effects.

Key words: dapagliflozin, empagliflozin, canagliflozin, sodium-glucose cotransporter 2 inhibitors, cardiovascular risk factors, cardiovascular outcome trials, renoprotection, microvascular complications

Introduction

Kidneys and glucose homeostasis

The role of the kidneys in glucose homeostasis is pivotal. Overall, 160 to 180 g of glucose are filtered daily in healthy individuals, the majority of which (approximately 90%) is reabsorbed within the early proximal tubules by the high-capacity, low-affinity sodium-glucose cotransporter 2 (SGLT2) system [1,2]. Glucose is then released into the circulation via glucose transporters 2 (GLUT2). More glucose is reabsorbed by the high-affinity, low-capacity SGLT1 in the distal proximal tubules, subsequently released into the circulation by GLUT1 [1,2]. Furthermore, SGLT1 is essential for intestinal glucose/galactose uptake from the lumen into enterocytes [3].

In diabetes, a state characterized by hyperglycemia, glucose filtered in the glomerulus surpasses the tubular maximum capacity of glucose reabsorption (T_m), leading to glycosuria. Interestingly, tubular glucose reabsorption is increased in patients with diabetes by up to 20% probably due to an increased expression and activity of SGLTs and GLUTs [1,2]. This may represent an initial adaptive mechanism of the kidneys to inhibit renal glucose loss. However, the final result is the maintenance and gradual exacerbation of hyperglycemia. Therefore, the kidneys were recognized early as organs involved in the pathophysiology of type 2 diabetes mellitus (T2DM) along with the pancreas, muscle, liver, brain, gastrointestinal tract and adipose tissue [4; Mitrakou].

SGLT2 inhibitors: mechanism of action, efficacy and safety

Targeting SGLT2 to ameliorate renal glucose reabsorption in individuals with diabetes led to the development of the SGLT2 inhibitors (SGLT2i) that showed

efficacy in animal and human studies with regard to improving insulin sensitivity and β-cell function [5]. SGLT2i were eventually introduced as a novel category of oral antidiabetic drugs that increase glucose excretion by the kidneys resulting in lower plasma glucose levels [6; Hasan et al]. Compared with other oral antidiabetic drugs, SGLT2i have a unique mechanism of action via the kidneys which is glucose-dependent but insulin independent, thus improving glycemic control without promoting hypoglycemia in the absence of exogenously administered insulin [7].

According to current guidelines, SGLT2i may be used as monotherapy (in the presence of contraindications or intolerance to metformin) or in combination with all other antidiabetic dugs, as well as with insulin, in patients with T2DM [8]. In the UK, The National Institute for Health and Care Excellence (NICE) has recommended the use of approved SGLT2i in combination with metformin (as a dual therapy regimen), only if a sulfonylurea is not tolerated or contraindicated and the patient is at a significant risk of hypoglycemia and/or its consequences [9].

There are side effects associated with the use of SGLT2i; these are mainly mild and transient, including higher rates of urogenital infections, mild-to-moderate dehydration and orthostatic hypotension [10]. Bone fractures have been related to the use of canagliflozin [11] but a recent meta-analysis found no significant association between fracture risk and treatment with SGLT2i in T2DM patients [12]. Furthermore, there were several cases of diabetic acute kidney injury and euglycemic diabetic ketoacidosis reported in patients on SGLT2i, but these were mainly attributed to individual patient characteristics predisposing to such metabolic abnormalities (e.g. acute illness, recently decreased insulin dose, severe dehydration. malnutrition or concomitant disease and drug treatments) [13,14]. This risk is especially high in patients with type 1 DM (T1DM); some cases involved T1DM patients that were

wrongly diagnosed as T2DM and thus treated with SGLT2i. However, most cases of normoglycemic diabetic ketoacidosis were confirmed when insulin-treated individuals with T1DM were exposed to SGLT2i thus inappropriately lowering their insulin dose. It should be noted that SGLT2i have not been approved for use in T1DM patients. [13,14]. Furthermore, impaired renal function may minimize their glucose-lowering efficacy and this is why these agents should be used early in the course of diabetes and not in the presence of moderate-to-severe kidney impairment, defined as estimated glomerular filtration rate (eGFR) < 45 (mL/min/1.73m^2) [15].

To-date, 3 different SGLT2i (i.e. dapagliflozin, canagliflozin and empagliflozin) are approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for T2DM treatment; tofogliflozin, ipragliflozin and luseogliflozin are also approved in Japan [16]. There are other SGLT2i in the pipeline (e.g. remogliflozin, sergliflozin, ertugliflozin and sotagliflozin) [17]. Sotagliflozin is a strong dual SGLT1/SGLT2 inhibitor under development [18]. Canagliflozin may also inhibit SGLT1 [Lehmann A et al 2016]. Intestinal SGLT1 inhibition may lead to beneficial metabolic effects such as delay and decrease in glucose excursion after the ingestion of carbohydrates as well as increase in peptide YY and glucagon-like peptide-1 (GLP-1) secretion [Lehmann A et al 2016 see above]. However, this mechanism of action may also be linked to adverse gastrointestinal events. These effects should be further investigated.

Apart from their efficacy as glucose lowering agents, SGLT2i were shown to exert pleiotropic benefits on CV risk factors such as body weight, blood pressure (BP) and lipids [19].

Aims of the present narrative review

The present review addresses the putative associations between SGLT2i and several CV and microvascular risk factors, as well as their effects on cardiac and renal function. We also elaborate on the potential clinical implications of CV outcome trials with SGLT2i following the results of the EMPA-REG OUTCOME trial and in anticipation of additional results from ongoing CV outcome trials with other drugs in that class.

SGLT2i and CV risk factors

Glucose (fasting and postprandial)

Postprandial glucose levels are a critical determinant of glucose homeostasis and they increase early in the pathophysiology of the hyperglycemia continuum leading to clinical diabetes. 'Prediabetes', a state of dysglycemia chiefly characterized by impaired glucose tolerance in both the fasting and postprandial state, has been related to increased CV risk compared the risk of normoglycemic individuals [20]. In T2DM, excursions of postprandial glucose levels are even higher than in prediabetes and alleviating them may play a much more important role in achieving optimal glycemic control [Fysekidis M et al 2014; 21]. Furthermore, postprandial hyperglycemia has been independently associated with elevated CV risk in individuals either with or without diagnosed diabetes. [21].

Both fasting and postprandial glucose levels were significantly reduced in T2DM patients following treatment with SGLT2i, namely dapagliflozin [22], canagliflozin [23], empagliflozin [24,25], tofogliflozin [26], ipragliflozin [27] and luseogliflozin [28]. Furthermore, these drugs had also led to significantly decreased HbA1c [29-35].

Sergliflozin was shown to significantly improve fasting and postprandial glucose as well as HbA1c levels only in animal models [36] but not in human studies [37]. Ertugliflozin significantly reduced fasting glucose and HbA1c in T2DM patients [38]; no reports are available regarding its effect on postprandial glucose levels. Interestingly, sotagliflozin was reported to decrease HbA1c as effectively as the other SGLT2i in T2DM patients, despite a weaker effect on urinary glucose excretion [35]. Improvement in fasting glucose levels and HbA1c were also linked to remogliflozin therapy in T2DM patients [39] but data are limited.

Glycemic variability (GV), characterized by aberrant glucose fluctuations, has been positively associated with CV morbidity, diabetic microvascular complications and mortality as reported in a recent meta-analysis [40]., independently of HbA1c levels. Targeting GV has lond been recognized as most useful in treating T2DM patients in terms of both hyperglycemia management and risk reduction of vascular complications [41]. In this context, luseogliflozin has reportedly reduced glucose fluctuations in a randomized controlled trial in T2DM patients [42]. However, data are lacking with regard to other SGLT2i in that context. Interestingly, there are scarce data from few studies in T1DM patients showing improvement in GV with both dapagliflozin and empagliflozin [43,44].

Body weight and other markers of obesity

Meta-analyses found a significant reduction in body weight following treatment of T2DM patients with dapagliflozin (effect size -2.10 kg, 95% CI -2.32 to -1.88) [45], canagliflozin (weighted mean difference -2.81 kg, 95%CI -3.26 to -2.37) [46] and empagliflozin (weighted mean difference -1.84 kg, 95% CI -2.30 to -1.38 kg) [47].

Similarly, decrease in body weight has been reported for tofogliflozin [48], ipragliflozin [49], luseogliflozin [50], ertugliflozin [38], remogliflozin [51] and sotagliflozin [52] in studies with T2DM patients. In contrast, sergliflozin led to weight loss in healthy overweight/obese volunteers [53], whereas data on T2DM patients are lacking.

Dapagliflozin [54] and canagliflozin [55] were also associated with a decrease in body mass index (BMI). Higher baseline BMI was associated with greater reduction in HbA1c levels in T2DM patients treated with SGLT2i, as reported in a meta-analysis [56]. Reduction in waist circumference was also seen following dapagliflozin [57,58], canagliflozin [58] and empagliflozin [24] treatment in T2DM patients.

Apart from visceral fat, abnormal peri- and intra-organ fat deposition has been linked to increased CV risk [59-61]. Dapagliflozin and empagliflozin reduced visceral adiposity and total body fat in T2DM patients [Liakos et al; 58,62]. Similarly, canagliflozin-related body weight loss observed in T2DM individuals was mainly due to reduction in total fat mass [55]. Ipragliflozin was also shown to decrease visceral adipose tissue in animal studies [63] as well as in T2DM Japanese patients [64,65].

Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) frequently co-exist with T2DM, further increasing CV risk [66-70]. Empagliflozin attenuated the histological features of NASH in mice [71]. Treatment with canagliflozin had also been associated with reduced liver weight in experimental studies [72]. Ipragliflozin improved hepatic steatosis independently of weight reduction in mice and liver function tests in T2DM patients [73]. Tofogliflozin therapy was shown to reduce liver weight and triglyceride content in animal models [74], accompanied by accelerated lipolysis in the adipose tissue [75]. Furthermore,

remogliflozin improved liver weight and triglyceride content as well as liver function tests in mice [76]. Similar benefits were observed in rodents treated with luseogliflozin [77].

Blood Pressure (BP)

Dapagliflozin, canagliflozin and empagliflozin were shown to significantly lower BP in various meta-analyses [47,78,79]. Treatment with tofogliflozin, ipragliflozin, luseogliflozin or sotagliflozin were also associated with decreased BP in studies with T2DM patients [34, 80-82]. A trend towards BP lowering was observed in patients with T2DM on remogliflozin [39], whereas ertugliflozin was only linked to lower systolic BP (SBP) [38]. More studies are needed to establish the effects of these SGLT2i on BP levels in large patient cohorts.

Dapagliflozin-induced BP reduction was greater in T2DM patients on β-blockers or calcium channel blockers compared with those on thiazide diuretics [83]. In another study [84], dapagliflozin treatment was significantly associated with decreased 24h ambulatory SBP in hypertensive T2DM patients on renin-angiotensin system blockers. Similar effects were reported for canagliflozin in T2DM patients with hypertension on either an angiotensin II receptor blocker (ARB) or an angiotensin-converting enzyme (ACE) inhibitor, with or without β-blockers, calcium channel blockers or diuretics (with the exception of loop diuretics) [85]. In the EMPA-REG BP trial, T2DM participants with hypertension in the empagliflozin arm were shown to exhibit significantly reduced 24h ambulatory SBP and diastolic BP (DBP) levels [86]. Furthermore, in a subgroup analysis of the EMPA-REG BP trial, empagliflozin-related mean 24h SBP lowering was greater in patients with stage 2 or stage 3 chronic

kidney disease [defined as eGFR 60 to < 90 or 30 to < 60 ml/min/1.73m^2, respectively] compared with patients with normal kidney function (eGFR ≥ 90 ml/min/1.73m^2) [87]. These findings highlight the presence of physiological pathways other than glycosuria contributing to BP lowering in patients on empagliflozin. In this context and apart from diuresis and weight loss, SGLT2i may promote nephron remodeling [88] and exert direct vascular effects resulting in decreased vascular resistance and attenuated arterial stiffness (see below) [89]. Ertugliflozin treatment was also associated with reduced mean 24h SBP in hypertensive T2DM patients, but only daytime (and not nighttime) SBP was consistently decreased [38].

Non-dipping (i.e. <10% reduction in the asleep compared with the awake mean BP) is frequently observed in T2DM patients and is associated with a higher CV risk [90]. In this context, dapagliflozin was found to convert BP pattern from that of "non-dipper" to "dipper" in T2DM [91]. Luseogliflozin was also shown to exert a similar effect on the BP pattern, converting it from "non-dipper" to "dipper" in an animal study [92]. Furthermore, empagliflozin treatment has been associated with reduced mean 24h SBP in both "dipper" and "non-dipper" T2DM patients [93]. In the EMPA-REG BP trial, greater reduction in mean day BP and mean night SBP was observed with empagliflozin (both 10 and 25 mg/day doses) compared with placebo, whereas mean night DBP was significantly reduced only in those patients on empagliflozin 25 mg [86]. Overall, empagliflozin-induced daytime BP lowering was more pronounced than night BP reductions.

It should be noted that the observed 24h BP lowering effect of SGLT2i is independent of antihypertensive drug use, although the degree of reduction might be preferentially affected by certain BP lowering medications. [89]. Furthermore, this clinically meaningful BP reduction occurs without concomitant increase in heart rate [94,95]. In

the EMPA-REG OUTCOME trial (see below), the risk of nonfatal stroke was non-significantly higher in the empagliflozin group compared with placebo [96]. However, it should be noted that most strokes occurred during the post-treatment phase and this may be at least partly explained by the above mentioned empagliflozin-induced effects on BP.

Arterial stiffness

Increased arterial stiffness is associated with increased CV risk and frequently co-exists with both T1DM and T2DM [97-100]. SGLT2i have been associated with decreased arterial stiffness [101]. In this context, empagliflozin was shown to improve arterial stiffness in both animal [102] and human studies in T1DM and T2DM patients [103,104]. The decrease in CV events in empagliflozin-treated individuals in the EMPAREG OUTCOME trial (see below) [96] cannot be explained solely by the observed reduction in brachial artery BP. Furthermore, this BP lowering may underestimate central aortic pressure and provides no information about aortic stiffness, both of which are independent predictors of CV mortality and LV function. Therefore, SGLT2i may have small actions on arterial stiffness but it is likely that their beneficial effects relate to multiple beneficial actions.

Apart from SGLT2i, other antidiabetic drugs may improve arterial stiffness; for example, metformin [Wu CF et al 2015], pioglitazone [Ohira M et al 2014] and dipeptidyl peptidase (DPP) 4 inhibitors (vildagliptin and sitagliptin) [Duvnjak L et al 2016]. However, conflicting data exist [Koren S et al 2012; Zografou I et al 2015; Kiyici S et al 2009]. Other drugs such as antihypertensive (such as ACE inhibitors,

ARBs and β-blockers) and hypolipidemic (including statins and ezetimibe) were reported to improve arterial stiffness [105-108].

Subclinical atherosclerosis

Currently, no data exist with regard to the effects of SGLT2i on subclinical atherosclerosis, as assessed by carotid intima-media thickness, ankle-branchial index or coronary calcium score. Future research should evaluate such associations. However, it should be noted that the very rapid onset of empagliflozin-induced CV benefits reported in the EMPA-REG OUTCOME trial (i.e. within 3 months; see below) point against a mechanism based on anti-atherosclerotic effects [109].

Flow-mediated dilatation

To-date, there are no data on the effects of SGLT2i on this marker of atherosclerosis.

Lipids (fasting and postprandial)

SGLT2i may exert modest beneficial effects on lipids, especially on the components of atherogenic dyslipidemia such as high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG), whereas adversely affecting low-density lipoprotein cholesterol (LDL-C) levels [110]. In this context, dapagliflozin, canagliflozin and empagliflozin were associated with significant increases in HDL-C and LDL-C levels, and decreases in TG levels and LDL/HDL ratio in T2DM patients [111-115]. Ipragliflozin was also shown to associate with raised HDL-C and decreased TGs in T2DM patients [65]. In another study, sotagliflozin therapy was linked to significantly reduced TGs [82].

However, not all studies found significant changes in lipids following SGLT2i therapy [116,117] and a recent meta-analysis reported that only HDL-C was significantly increased by SGLT2i [56].

With regard to putative pathophysiological mechanisms involved, it should be noted that, via promoting glycosuria, SGLT2i lead to a progressive shift in utilizing fatty substrates for energy metabolism, thus favoring ketogenesis [118]. In this context, empagliflozin was shown to significantly reduce the expression of the hepatic LDL receptor as well as LDL-C catabolism in hamsters, resulting in increased LDL-C levels [119]. Empagliflozin has also been associated with decreased intestinal absorption of cholesterol, thus enhancing cholesterol fecal excretion [119]. It is also thought that HDL-C is increased due to visceral fat reduction and TGs are reduced due to gluconeogenesis, improved glycemic control and weight loss [65]. Furthermore, baseline LDL-C levels may affect the magnitude of the association between LDL-C and SGLT2 I therapy. In this context, canagliflozin decreased LDL-C levels in T2DM patients with baseline LDL-C ≥120 mg/dL, whereas slightly increased them (without exceeding 120 mg/dL) in those with baseline LDL-C <120 mg/dL [120]. Apart from the quantitative traits, the qualitative features of LDL-C also appears to matter. Small dense LDL particles are more atherogenic [121-124]. Hypolipidemic drugs including statins, fibrates and ezetimibe as well as antidiabetic agents (such as pioglitazone and liraglutide) may decrease sdLDL [125-129]. However, similar data on the potential effects of SGLT2i on sdLDL are currently lacking. Finally, postprandial lipemia (PPL) is also implicated in increased CV risk [130-132]. Similar to sdLDL, there are hypolipidemic (statins, fibrates, ezetimibe) and antidiabetic drugs [metformin, pioglitazone, DPP4 inhibitors and liraglutide] that can improve PPL [133-136]. Currently, no data on the potential impact of SGLT2i therapy

on PPL exist. Overall, further research is needed to establish the associations between SGLT2i and lipoprotein metabolism and whether the small increases in LDL-C induced by SGLT2i are clinically meaningful, especially in long term treatment. Any such small increase may be negated by a decrease in the more atherogenic sdLDL as a consequence of lowering TG and raising HDL-C levels Dense LDL panel ref]. Furthermore, SGLT2i may improve PPL because lower TG levels are less likely to be associated with PPL [PPL panel ref].

Serum uric acid (SUA)

Hyperuricemia is linked to increased CV risk [137-140]. Dapagliflozin, canagliflozin, empagliflozin, ipragliflozin and luseogliflozin have been shown to associate with lower SUA levels [28,101,141-143]. This effect represents one of the possible mechanisms of CV risk reduction following SGLT2i therapy. Of note, several other drugs including hypoglycemic (such as metformin and pioglitazone), antihypertensive (such as renin-angiotensin system blockers) and lipid-reducing agents (mainly statins) may decrease SUA concentrations [144,145]. These data should be taken into consideration by physicians when selecting an individual therapeutic strategy in daily practice, as well as in interpreting data from CV outcome trials.

Inflammation and oxidative stress

Data on the effects of SGLT2i on markers of inflammation and oxidative stress mainly stem from experimental studies. Dapagliflozin improved inflammatory markers [including osteopontin, monocyte chemoattractant protein (MCP)-1 and transforming growth factor-β] and oxidative stress in animal diabetic models [146].

Inflammatory and oxidative status biomarkers as well as glucotoxicity and apoptosis of pancreatic β-cells were also shown to decrease by empagliflozin in diabetic rats [147,148]. Similar beneficial effects were observed in cultured human tubular cells following tofogliflozin exposure [149]. Furthermore, ipragliflozin decreased markers of oxidative stress and inflammation [such as C reactive protein (CRP), interleukin-6 and tumor necrosis factor (TNF)-α] in animal models of both T1DM and T2DM [150,151]. In a similar fashion, remogliflozin decreased levels of TNF-α, MCP-1 and oxidative stress in obese mice [76].

Only dapagliflozin treatment was associated with reduced CRP levels in T2DM patients [152]. Data on other SGLT2i are currently lacking.

SGLT2i and renal function

In a prespecified analysis of the EMPA-REG OUTCOME trial focusing on renal microvascular outcomes, empagliflozin significantly reduced the rate of incident or worsening of nephropathy, progression to macroalbuminuria, doubling of serum creatinine level and initiation of renal-replacement therapy compared with placebo [171]. Furthermore, eGFR was slightly decreased during the first month of treatment with empagliflozin, remained stable over time and increased after the cessation of the study drug [171]. In contrast, eGFR was continuously reduced in the placebo group during the same time periods. An initial small and transient lowering of eGFR followed by an increase at baseline values and then stabilization has also been observed for dapagliflozin [172]. It should be noted that HbA1c, SBP and weight reductions induced by dapagliflozin were similar in different eGFR subgroups as was CV risk lowering in empagliflozin-treated T2DM patients [96,173]. In contrast,

greater HbA1c reductions were observed in T2DM patients with higher baseline eGFR on canagliflozin [174]; decreases in SBP were similar in different eGFR subgroups. Furthermore, luseogliflozin-induced fasting glucose lowering effects were not affected by baseline eGFR in T2DM patients, but its impact on postprandial glucose was attenuated in those patients with mild-to-moderately reduced renal function [175]. Sotagliflozin exhibited similar efficacy in decreasing fasting and postprandial glucose levels independently of baseline eGFR [176].

SGLT2i have been reported to exert beneficial renal effects [177]. In this context, dapagliflozin reduced albuminuria in T2DM patients with hypertension or renal impairment [178,179]. Canagliflozin and empagliflozin decreased urinary albumin-to-creatinine ratio in T2DM patients [180,181]. It should be noted that there are ongoing long-term trials with dapagliflozin and canagliflozin exploring renal endpoints (NCT02547935, NCT01989754, NCT02065791).

With regard to pathophysiological mechanisms, SGLT2i were shown to improve inflammation and oxidative stress in the kidneys. Dapagliflozin treatment was associated with decreased markers of oxidative stress and inflammation in proximal tubular epithelial cells of diabetic mice [146]. Tubular injury, inflammation, oxidative stress and fibrosis were reduced following empagliflozin administration in diabetic rats [182]. In cultured human tubular cells, tofogliflozin suppressed the oxidant, proinflammatory and proapoptotic effects of high glucose exposure [149]. Other potential nephroprotective actions of SGLT2 inhibitors include reduced glomerular hyperfiltration as well as systemic and intraglomerular pressure [6]. Briefly, these drugs decrease sodium reabsorption in proximal tubules, thus increasing sodium delivery from distal tubules to macula densa [183]. These effects lead to vasoconstriction in the afferent arteriole and subsequently to reduction in glomerular

hyperfiltration [183]. These renal benefits of SGLT2i are observed in the early stages of renal impairment, thus potentially protecting against the progression of renal dysfunction [6].

SGLT-2i and CV outcome trials

The EMPA-REG OUTCOME Trial was the first randomized, placebo-controlled, double-blind CV outcome trial with a SGLT2 inhibitor to be completed and published [96]. This study evaluated the efficacy of empagliflozin (10 or 25 mg once-daily) *vs* placebo on CV events in 7,020 T2DM patients at high CV risk (median follow-up: 3.1 years). Empagliflozin was associated with a significant reduction in the primary composite outcome [i.e. CV death, nonfatal myocardial infarction (MI) or nonfatal stroke] compared with placebo [hazard ratio (HR), 0.86; 95% confidence interval (CI), 0.74 to 0.99; $p < 0.001$ for non-inferiority and $p = 0.04$ for superiority) [96]. This difference in the primary outcome between empagliflozin and placebo group was driven by a significant decrease in CV mortality, whereas the risk of nonfatal MI was non-significantly lower and the risk of nonfatal stroke was non-significantly higher in the empagliflozin group compared with placebo. Furthermore, empagliflozin resulted in a significantly lower risk of CV death (HR, 0.62; 95% CI, 0.49 to 0.77; $p < 0.001$), total mortality (HR, 0.68; 95% CI, 0.57 to 0.82; $p < 0.001$) and hospitalization for HF (HR, 0.65; 95% CI, 0.50 to 0.85; $p = 0.002$) compared with placebo [96]. These CV benefits became manifest as early as 1 month following randomization and were maintained throughout the trial.

In the EMPA-REG OUTCOME trial, empagliflozin also led to small reductions in BP (with no increase in heart rate), weight, waist circumference and SUA levels, as well

as to small increases in LDL-C and HDL-C. It should be noted that the empagliflozin-induced benefits were observed in T2DM patients treated with renin-angiotensin system blockers, statins and acetylsalicylic acid in whom BP and dyslipidemia were well-treated.

The results of the CANagliflozin cardioVascular Assessment Study (CANVAS) (https://clinicaltrials.gov/ct2/show/results/NCT01032629) and the multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58) (https://clinicaltrials.gov/ct2/show/NCT01730534) when available, will establish whether benefits on CV risk and heart failure (HF) are compound-specific or drug class effects.

It should be noted that dapagliflozin was associated with a non-significant reduction in the risk of major adverse CV events (MACE) in a recent meta-analysis [153]; the benefit was even greater with regard to the risk for MI and hospitalization for HF. In another recent meta-analysis, SGLT2i were found to significantly decrease the risk of MACE, HF, CV and total mortality; a non-significant trend towards an increase in the risk of stroke was also found, whereas the risk for MI was either significantly or insignificantly reduced [154,155]. However, we need to wait for the results of the large CV outcome trials (i.e. DECLARE and CANVAS) before reaching definite conclusions.

SGLT2i and heart failure (HF)

HF frequently develops in the course of T2DM [156]. Diabetic patients with HF have worse biochemical changes, cardiac function and higher mortality compared with HF patients without diabetes [157]. T2DM patients also have an increased risk of

hospitalization for HF [158]. Poor glycemic control is also associated with worse cardiac function and prognosis in diabetic patients with HF [157]. Therefore, it is important to evaluate the effect of antidiabetic drugs on HF. In this context, sulfonylureas and pioglitazone have been shown to increase the risk for HF [158]. The use of metformin is discouraged in patients with HF, primarily due to the risk of lactic acidosis that may be increased in the presence of HF [158]. However, there are data supporting the safety of metformin administration in HF patients [159] as well as improved HF outcomes following its use [160].

In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR-TIMI 53) trial, among T2DM patients with established CV disease or multiple CV risk factors, significantly more patients in the saxagliptin group were hospitalized for HF compared with the placebo group [161]. The EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome (EXAMINE) trial evaluated CV effects of alogliptin in T2DM patients with an acute coronary syndrome [162]. In a *post-hoc* analysis of the EXAMINE trial, a non-significant trend towards an increased risk for HF hospitalization was reported for alogliptin [163]. In contrast, sitagliptin was not associated with an increased HF hospitalization rate in T2DM patients with established CV disease as reported in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) study [164]. Previous and recent meta-analyses report that DPP4 inhibitors may increase the risk of HF hospitalization [154,165,166]. GLP-1 receptor agonists have not been linked to the risk of HF development or hospitalization [167]. Of note, in the recently published Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, there were non-significant fewer hospitalizations for HF among

patients in the liraglutide group than in the placebo group [168]. In the same study, liraglutide was associated with a significantly lower rate of nonfatal MI, nonfatal stroke, CV and all-cause death [168].

SGLT2i may beneficially affect HF development and outcomes as they can decrease BP and excess body fluid. In this context, a recent meta-analysis found a significant reduction in the rate of HF hospitalization in T2DM patients on dapagliflozin compared with controls [153]. This benefit was non-significant in the elderly T2DM patients with CV disease and hypertension [153]. With regard to canagliflozin, the ongoing CANDLE trial will evaluate the safety and non-inferiority of canagliflozin compared with glimepiride, a sulfonylurea, in T2DM patients with chronic HF [169]. In the EMPA-REG OUTCOME study, empagliflozin was shown to significantly reduce CV and all-cause mortality as well as hospitalization for HF in T2DM patients at high CV risk [96]. In a further analysis of the EMPA-REG OUTCOME trial, the reductions in the risk of HF hospitalization, CV death and all-cause mortality with empagliflozin were consistent in patients with and without HF at baseline [109]. These outcomes were 2- to 6- fold higher in T2DM patients with HF at baseline compared with those without HF at baseline [109].

Among the other SGLT2i, there are data only for ipragliflozin; ipragliflozin was safe and well-tolerated in T2DM patients with HF [170. Therefore, there is a need for further clinical trials to evaluate the effect of different SGLT2i on the risk for HF prevalence and outcome. In this context, the results of the ongoing CV outcome trials with dapagliflozin and canagliflozin will provide more information on this issue.

Potential mechanisms mediating the cardiorenal benefits of SGLT2i

As mentioned above, SGLT2i beneficially affect several CV risk factors including glucose, weight, BP and lipids. Furthermore, in the EMPA-REG OUTCOME trial, empagliflozin significantly reduced CV and all-cause death as well as HF hospitalization [96]. As the empagliflozin-induced CV benefits were observed very early (at 1 month) and were sustained throughout the trial, they are unlikely to be attributed to an effect on atherosclerosis regression [109]. Although the mechanisms behind these CV effects of empagliflozin are unknown, several possibilities have been proposed such as improvements in glucose, insulin and SUA levels, osmotic diuresis, fluid and sodium retention as well as reductions in BP, body weight, visceral fat, vascular resistance and arterial stiffness [109]. These mechanisms are probably all involved in producing benefits but the impressive empagliflozin-induced reduction in CV mortality and HF hospitalization seen in the EMPA-REG OUTCOME study, seem to be mainly attributed to hemodynamic parameters such as BP and extracellular volume decreases, leading to reduced cardiac pre- and afterload [114,184]. Furthermore, it has been recently suggested that myocardial/renal function may be improved by a empagliflozin-induced shift in myocardial and renal fuel metabolism from glucose and fat oxidation toward ketone bodies, an energy-efficient super fuel, thus better explaining the remarkable cardiorenal benefits seen with empagliflozin [185]. However, further research is needed to assess this mechanism of fuel energetics.

Direct effects of SGLT2i on the myocardium have also been reported. In this context, dapagliflozin affected Ca(2+) transport in ventricular myocytes from diabetic rats, thus partly explaining its negative inotropic action [186]. Protection against arrhythmias, myocardial hypertrophy, fibrosis and ischemia, may represent potential

cardioprotective mechanisms of SGLT2i [184]. Dapagliflozin and empagliflozin did not prolong the QT interval [187,188].

Conclusions

Treatment with SGLT2i may exert multiple beneficial effects on several CV risk factors, including fasting and postprandial glucose, fasting lipids, BP, body weight, SUA and arterial stiffness. This class of drugs may also exert cardio- and reno-protection via their effects on inflammation, oxidative stress, diuresis, fluid and sodium retention, myocardial function, vascular resistance and fuel metabolism. The EMPA-REG OUTCOME study was the first published large CV SGLT2i outcome trial reporting that empagliflozin significantly reduced CV and all-cause death as well as HF hospitalization. Further research is needed to establish the exact mechanisms mediating this impressive CV risk reduction by empagliflozin. Furthermore, ongoing CV studies with other SGLT2i will prove whether benefits on CV risk and HF are compound specific or drug class effects.

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