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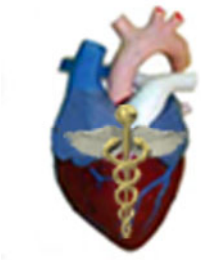

January 2020 • Volume 15 • No 1 (57)

ISSN: 1792-7919 e-ISSN: 1792-7927

URL: www.rhythmos.gr / http://rhythmos.info.tm

EDITORIAL

Use of Sodium–Glucose Cotransporter 2 (SGLT-2) Inhibitors Beyond Diabetes: On the Verge of a Paradigm Shift?

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Abstract

The sodium–glucose co-transporter 2 (SGLT2) inhibitors have proven effective in glycemia control in patients with type 2 diabetes (T2D) by increasing urinary glucose excretion. However, the beneficial effects of SGLT2 inhibition extend beyond glycemic control, with new studies demonstrating beneficial effects that lead to improved cardiovascular (CV) (cardioprotection) and renal outcomes (renoprotection) in patients with T2D. Pivotal CV outcomes trials have demonstrated a 27-35% reduction in heart failure (HF) hospitalizations in patients with T2D. Importantly, a variety of pleiotropic effects of these new agents have been identified that include, but are not limited to, anti-atherosclerotic, anti-inflammatory, and anti-oxidant effects, decreased vascular stiffness and improved endothelial function, weight loss, reduction in sympathetic activity and in cardiac arrhythmogenesis. Ongoing studies are investigating these actions in patients with and without diabetes. Such results, if positive, may lead to a paradigm shift in the management of CV, renal and even other diseases beyond diabetes. ***Rhythmos 2020;15(1):1-5***.

Key Words: diabetes; SGLT-2 inhibitors; gliflozins; empagliflozin; canagliflozin; dapagliflozin; cardiovascular outcomes; heart failure; cardioprotection; renoprotection; pleiotropic effects

Abbreviations: CKD = chronic kidney disease; CV = cardiovascular; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; SGLT2 = sodium–glucose co-transporter 2; T2D = type 2 diabetes (mellitus)

Introduction

The sodium–glucose co-transporter 2 (SGLT2) inhibitors (gliflozins), empagliflozin, canagliflozin, dapagliflozin, ertugliflozin (all four FDA approved), and sotagliflozin (only EU approved) have proven to be effective in glycemia control in patients with type 2 diabetes (T2D).[1] SGLT2 inhibition increases urinary glucose excretion, decreasing blood glucose levels. [2]

However, the beneficial effects of SGLT2 inhibition extend beyond glycemic control, with new studies demonstrating that inhibition of renal glucose reabsorption

reduces blood pressure, ameliorates glucotoxicity and confers hemodynamic effects that lead to improved cardiovascular (CV) and renal outcomes in patients with T2D.[3-5] Pivotal CV outcomes trials (EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58) for the first three agents have demonstrated 13-38% relative risk reduction in CV-related deaths vs placebo (empagliflozin, canagliflozin), and a 27-35% reduction in heart failure (HF) hospitalizations (empagliflozin, canagliflozin, dapagliflozin).[6-8]

These pleiotropic effects extend to a wide spectrum of actions that include weight loss induced initially by osmotic diuresis and later by reduction of fat mass; improved vascular stiffness and endothelial function; reduction in sympathetic activity and other effects discussed below and also mentioned in Table 1.

Cardioprotective Effects

Improved CV Outcomes. The SGLT2 inhibitor empagliflozin reduced CV mortality by 38% and HF hospitalizations by 35% in diabetic patients.[6] Canagliflozin reduced CV mortality by 13%, while it reduced the rate of hospitalization for HF by 33%.[7] Dapagliflozin conferred a 17% lower rate of CV death or hospitalization for HF, which reflected a 27% lower rate of hospitalization for HF.[8] A recent meta-analysis of 42 trials with a total of 61,076 patients with T2D showed that compared with the control treatment, SGLT2 inhibitor treatment was associated with a reduction in the incidence of major adverse CV events (odds ratio-OR=0.86, P<.0001), myocardial infarction (OR=0.86, P=0.001), CV mortality (OR=0.74, P<0.0001) and all-cause mortality (OR=0.85, P<0.0001).[9]

Heart Failure. As mentioned, pivotal CV outcomes trials (EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58) demonstrated a 27-35% reduction in HF hospitalizations in patients with T2D.[6-8] A recent meta-analysis of the results in patients included in randomized controlled trials (RCTs) (N=34,322), observational studies (N=15,36,339), and both (N=15,70,661) demonstrated a significant decrease in HF hospitalizations (OR 0.70, 0.64, 0.66, respectively, all p=0.000) with SGLT-2 inhibitors compared to placebo or other anti-diabetes drugs in T2DM.[10] A significant benefit in HF hospitalizations (OR 0.68, p=0.000) is also observed in patients with established HF (N=3891) in sub-group meta-analysis of RCTs.

Importantly, a most recent report of the DAPA-HF trial, which included patients with NYHA II-IV HF with reduced (≤40%) ejection fraction (HFrEF), randomized to dapagliflozin (n=2373) or placebo (n=2371), indicated that over a median of 18.2 months, the primary outcome, a composite of HF or CV death, was reduced by dapagliflozin by 26% (P<0.001), a first worsening HF event by 30%, CV death by 18% and total death by 17%.[4] Findings in patients with diabetes were similar to those in patients without diabetes. The frequency of adverse events related to volume depletion, renal dysfunction, and hypoglycemia did not differ between treatment groups.

According to the recent results of the DEFINE-HF trial, in patients with HFrEF, use of dapagliflozin over 12 weeks did not affect mean NT-proBNP but increased the proportion of patients experiencing clinically meaningful improvements in HF-related health status or natriuretic peptides.[11] Results were consistent among patients with or without T2D. The authors concluded that benefits of dapagliflozin on clinically meaningful HF measures appear to extend to patients without diabetes. Similarly, the DAPA-HF trial showed that among patients with HFrEF, the risk of worsening HF or death from CV causes was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of T2D.[4]

Several mechanisms have been put forward to explain the benefits of SGLT-2 inhibitors in diabetic patients with HF, which also raise the possibility of using these drugs as therapies not only in the prevention of HF, but also for the treatment of patients with established HF regardless of the presence or absence of diabetes.[12, 13] Ongoing dedicated HF trials will further shed light on the merits of SGLT-2Is in patients with established HF with or without T2D.

Ischemia/Myocardial infarction. As mentioned, a recent meta-analysis of 42 trials (N=61,076) showed that compared with the control, SGLT2 inhibitor treatment in diabetic patients was associated with a reduction in myocardial infarction by 14% (P=0.001). [9]

A cytoprotective effect, including protection against myocardial ischemia/reperfusion injury has been suggested by animal studies. Langendorff-perfused hearts, from diabetic and nondiabetic rats, fed long-term for 4 weeks with canagliflozin, had lower infarct sizes.[5] By contrast, direct treatment of isolated nondiabetic rat hearts with canagliflozin, solubilized in the isolated Langendorff perfusion buffer, had no impact on infarct size. This latter study demonstrates that the infarct-sparing effect of long-term treatment with canagliflozin results from either a glucose-independent effect or up-regulation of cardiac prosurvival pathways. These results further suggest that SGLT2 inhibitors could be repurposed as novel cardioprotective interventions in high-risk CV patients irrespective of diabetic status.

Renoprotective effects

The results of studies in non-diabetic chronic kidney disease (CKD) models suggest that SGLT2 inhibitors

could also have a direct beneficial effect on the kidney, which would be independent of the glycemic and blood pressure control.[3] Canagliflozin 100 or 300 mg/d, compared with glimepiride, slowed the progression of renal disease over 2 years in patients with T2D; importantly, canagliflozin conferred renoprotective effects independently of its glycemic effects.[14]

The renoprotective effects of SGLT2 can also be ascribed to natriuresis resulting from inhibition of sodium and glucose reabsorption.[3] An increased sodium delivery to the macula densa activates the tubuloglomerular feedback that leads to afferent arteriole vasoconstriction and a reduction in intraglomerular pressure. Interestingly, a pattern of change in renal function similar to that observed with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) has been demonstrated for SGLT2 inhibitors, where a short-term initial decrease of glomerular filtration rate is followed by stabilization over time, which appears to be reversible upon discontinuation of the drug.[15] Other plausible mechanisms that have been proposed to contribute to renoprotection conferred by SGLT2 inhibitors are blood pressure lowering, weight loss, amelioration of the volume overload and glycemic control itself. However, it is still not clear whether these drugs also exert direct protective effects on the kidney.

Reduction of Sympathetic Overactivity

It has been suggested that SGLT2 inhibitors reduce central sympathetic overactivity, probably by suppressing renal afferent signaling to the brain.[16] An attenuation of sympathetic activity is deduced as no rise of heart rate is detected despite reductions in blood pressure and plasma volume. This effect has been demonstrated in experimental and clinical data, shown to occur in key target organs such as the heart and the kidneys.[17]

Weight Loss

Several studies support the concept that SGLT2 inhibitors can be effective as adjuvant weight loss therapy when given together with agents that reduce food intake.[18] In overweight and obese subjects without diabetes, canagliflozin significantly reduced body weight compared with placebo and was generally well tolerated.[19]

Pleiotropic Effects and Potential Mechanisms of Cardiovascular and Renal Protection

As mentioned, several pleiotropic effects on the heart, kidney, vessels, autonomic nervous system, and elsewhere and various potential mechanisms have been suggested to explain the cardioprotective and renoprotective effects of SGLT-2 inhibitors (Table 1). [1, 20, 21] Among others, anti-atherosclerotic, anti-inflammatory, and anti-oxidant effects, decreased vascular stiffness and improved endothelial function have been proposed.[22] Hemodynamic effects involving reduction in blood pressure and afterload, natriuresis-related intravascular volume contraction, and an osmotic diuresis have also been considered as potential mechanisms for the beneficial effects in patients with heart failure.[23] SGLT2 inhibitors can also inhibit cardiac sodium-hydrogen exchanger (isoform 1) leading to improvement in cardiac injury and reduction of infarct size, hypertrophy, and fibrosis independently of their effects on sodium reabsorption or blood pressure; they can also inhibit renal sodium-hydrogen exchanger (isoform 3) leading to reduction of sodium reabsorption in the proximal tubule.[24] Other factors that may be involved in CV protection may relate to plasma volume contraction–mediated decreases in myocardial stretch contributing to reduced cardiac arrhythmogenesis, several metabolic effects (such as improved cardiac mitochondrial function and fuel energetics, decrease in body weight, decrease in uric acid and triglycerides and an increase in HDL cholesterol), and hormonal effects, such as increased glucagon release.[25] An experimental study indicated that empagliflozin causes direct pleiotropic effects on the myocardium by improving diastolic stiffness and hence diastolic function; these effects were independent of diabetic conditions. [26] As mentioned, a reduction of sympathetic overactivity by SGLT-2 inhibitors has also been suggested as a cardioprotective mechanism.[16] Nevertheless, significant knowledge gaps remain in this field which investigators are now beginning to explore; ongoing and future trials may aid in this direction.

With regards to the renoprotective effects of SGLT-2 inhibitors, several beneficial actions have been enlisted; blood pressure lowering even in the presence of CKD, reduced endothelial dysfunction and arterial stiffness; improved metabolic profile (decrease in weight and HbA1C); improved oxygenation of tubular cells and increased hematocrit; decreased albuminuria; optimized intravascular volume; decreased intraglomerular pressure; improved CV function that maintains renal perfusion. [27]

Side-Effects

In the context of an emerging widespread optimism often reaching enthusiasm about the potential of these new antihyperglycemic agents with their pleiotropic effects demonstrated beyond their glycemic effects, one needs to be vigilant about their potential side-effects.[28, 29] These harmful effects include euglycemic keto-acidosis which is a life-threatening condition requiring urgent hospitalization; acute kidney injury has also been reported; serious urinary tract infections may occur, as well as genital

mycotic infections; an increased risk for lower limb amputation has been observed in patients receiving canagliflozin; these agents may increase the risk of hypoglycemia when used in combination with insulin or an insulin secretagogue; dose-related increases in LDL-cholesterol have also been encountered.[28, 29]

Table 1. ***Pleiotropic Effects of SGLT-2 Inhibitors Beyond the Anti-Hyperglycemic Effects***

- BP/afterload reduction by natriuresis and osmotic diuresis and consequent plasma volume reduction
- Improved CV function maintains renal perfusion
- BP lowering even in the presence of CKD
- Decrease in intraglomerular pressure thus attenuating albuminuria
- Anti-atherogenic effects
- Cytoprotective effect, including protection against myocardial ischemia/reperfusion injury
- Anti-inflammatory / anti-oxidant / anti-fibrotic effects
- Improved endothelial function/Reduced arterial stiffness
- Inhibition of sodium-hydrogen exchanger isoform 3 in heart/vasculature and isoform 1 in kidney leading to attenuation of cardiac injury, hypertrophy, and fibrosis independently of their effects on sodium reabsorption or BP
- Metabolic effects: decreased triglycerides/uric acid/HbA1C, increased HDL, weight loss
- Improved mitochondrial function and fuel energetics
- Reduced arrhythmogenesis
- Hormonal effects: increased glucagon release
- Increased erythropoietin levels with increase in hematocrit improving O2 transport to heart and kidneys
- Reduced SNS activity

BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; SGLT-2 = sodium–glucose co-transporter 2; SNS = sympathetic nervous system

Ongoing and Future Trials

Heart Failure. The ***EMPA-TROPISM*** RCT is comparing the efficacy and safety of empagliflozin in non-diabetic HF patients.[30] The ***Empire HF*** trial will elucidate the effects and modes of action of empagliflozin in HFrEF patients with and without T2DM.[31]

The EMPEROR trials will study the empagliflozin also in patients with HF without diabetes. The ***EMPEROR-Reduced*** trial is enrolling ≈3600 patients with HFrEF (ejection fraction ≤ 40%), half of whom are expected not to have diabetes.[32] The ***EMPEROR-Preserved*** trial is enrolling ≈5750 patients with HF with preserved ejection fraction (HFpEF) (ejection fraction >40%), with and without diabetes.[33] The ***EMPERIAL-Preserved*** and ***EMPERIAL-Reduced*** are RCTs designed to investigate the effects of empagliflozin on exercise capacity and patient-reported outcomes in patients with chronic stable HFpEF and HFrEF, respectively. [34]

Coronary Artery Disease. The ***EMMY*** trial will test empagliflozin in patients with myocardial infarction regardless of their diabetic status. The EMMY trial will therefore explore the concept of SGLT2 inhibition to improve cardiac remodeling, pre-and after-load reduction and cardiac metabolism regardless of its antidiabetic effects.[35]

Chronic Kidney Disease (CKD). The ***EMPA-REIN*** trial will examine the acute and chronic renal effects of empagliflozin in healthy volunteers.[36] The ***DAPA-CKD*** trial will determine the efficacy and safety of dapagliflozin 10 mg/d to delay the progression of kidney disease in patients with both diabetic and nondiabetic CKD.[27] The ***DIAMOND*** trial will study the effects of dapagliflozin in non-diabetic patients with proteinuria

Current clinical trial data do not support the use of SGLT-2 inhibitors in patients with eGFR <30 ml/min/1.73 m^2. Ongoing trials considering patients with CKD stage 4 include ***EMPA-KIDNEY*** (empagliflozin), ***SCORED*** (Sotagliflozin; NCT03315143), and ***SOLOIST-WHF*** (Sotagliflozin; NCT03521934).[37]

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