Invited review

Changing the Landscape of Hypertension Management With SGLT2i

Ines Bilić Ćurčić [1,2], Vjera Ninčević [3], Silvija Canecki Varžić [2,4], Ivana Prpić Križevac [2,4], Jasminka Milas Ahić [2,5], Ivica Mihaljević [6,7]

1 Department of Pharmacology, Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Croatia
2 Clinic for Internal Medicine, University Hospital Center Osijek, Croatia
3 Department of Pharmacology and Biochemistry, Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Croatia
4 Department of Internal Medicine, Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Croatia
5 Department of Pathophysiology, Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Croatia
6 Clinical Institute of Nuclear Medicine and Radiation Protection, University Hospital Center Osijek, Croatia
7 Department of Nuclear Medicine and Oncology, Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Croatia

*Corresponding author: Ines Bilić Ćurčić, ibcurcic@gmail.com

Abstract

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are a newer class of drugs that have primarily been used in the treatment of type 2 diabetes. However, as new findings from clinical trials have become available, their indication has been expanded to include treatment of heart failure and chronic kidney disease without the presence of diabetes. The pathophysiological mechanisms of extraglycemic effects of SGLT2i are still being unraveled, but one of the most prominent consequences is a decrease in blood pressure, which has implications for hemodynamics and arterial stiffness. Recent findings indicate that this class of drugs has a beneficial effect on lowering nocturnal blood pressure (BP), with special importance in type 2 diabetes (DMT2), since unregulated nocturnal hypertension is associated with an increased incidence of cardiovascular (CV) events. In this mini-review, we have summarized current knowledge about the effects of SGLT2i on blood pressure, including office, home, and ambulatory BP, and potential implications for treatment of hypertension in diabetic and non-diabetic individuals, with positive effects on cardiorenal outcomes.

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Introduction

SGLT2i are a class of newer therapeutic agents in diabetes treatment with proven cardiorenal benefits, which reduce the risk of cardiac failure and death from cardiovascular disease (CVD) and slow the progression of diabetic kidney disease [1–5]. This class of agents is therefore recommended for diabetes treatment in high-risk patients with heart failure, CVD or kidney disease, based on recent guidelines [6]. In addition, their role in the treatment of heart failure and kidney disease independent of the presence of diabetes has also been recognized recently [7, 8].

Possible mechanisms responsible for cardiorenal benefits are numerous, including positive effects on hemodynamic parameters, reduction of arterial stiffness, improvement of chronic inflammation, metabolic fuel switching, along with traditional mechanisms, such as lowering of blood glucose and reduction of blood pressure and body weight [9–12].

Diabetic patients have a specific 24-hour BP profile with a non-dipper pattern of nighttime BP likely caused by increased circulating volume [13–16]. The presence of nocturnal hypertension is more common in patients with diabetes compared to those without it [17–19] and is associated with higher mortality rates [20]. Likewise, the frequency of masked hypertension is relatively high in diabetic patients, ranging from 27% to 47% [21–24], and it is one of the independent predictors of CVD [24]. Recognizing and treating masked hypertension in patients with DMT2 is imperative, and out-of-office BP measurement using home BP monitoring (HBPM) or ambulatory BP monitoring (ABPM) is therefore recommended in the diagnosis of hypertension (HTN) [25–27].

Effects of SGLT2i on BP measurements

SGLT2i agents, such as empagliflozin [28–34], canagliflozin [35–39], ertugliflozin [40–42] and dapagliflozin [43–47], have been shown to lower office blood pressure in patients with DMT2 and HTN in a number of studies. According to several published meta-analyses, marked reductions in systolic BP (SBP) ranged from -2.45 mmHg to -4.45 mmHg compared to active comparators, with diastolic BP (DBP) reductions from -1.46 mmHg to -2.01 mmHg [48, 49]. Changes in BP with empagliflozin and existing antihypertensive therapy were examined in the SACRA (Sodium-Glucose Cotransporter-2 [SGLT2] Inhibitor and Angiotensin Receptor Blocker [ARB] Combination Therapy in Patients With Diabetes and Uncontrolled Nocturnal Hypertension) study. The study included Japanese patients with type 2 diabetes and poorly controlled nocturnal hypertension who were receiving standard antihypertensive therapy and were randomized to the empagliflozin or the placebo group. Clinic BP, 24-hour ABPM and morning home BP was monitored, while the primary endpoint was change from baseline in nighttime BP (ABPM). At 12 weeks, empagliflozin significantly reduced daytime, 24-hour, morning home, and clinic SBP (-9.5, -7.7, -7.5, and -8.6 mmHg, respectively). Body weight and glycosylated hemoglobin reductions between groups were significant, albeit minor (-1.3 kg and -0.33 percent, respectively). In addition, marked reductions in N-terminal pro-B-type natriuretic peptide levels were observed in the empagliflozin versus the placebo group (12.1%; P = 0.013); reductions were likewise observed in atrial natriuretic peptide levels (9.7%; P = 0.019) [50]. However, there was no statistically significant reduction in overnight BP compared to the placebo group, with a drop in nighttime SBP of 6.3 mmHg from the baseline. Given that a 5-mmHg decrease in mean overnight SBP has been linked to a 20% reduction in CVD risk [51], the nighttime BP reduction observed with empagliflozin could have clinical importance regardless of the lack of statistical significance.

As previously mentioned, 24-hour ambulatory BP is a better predictor of CV risk than office BP [20, 24]. A recently published meta-analysis including randomized, double-blind, placebo-controlled trials reporting 24-hour ABPM data demonstrated the lowering effect of SGLT2i on ambulatory systolic and diastolic BP by 3.76 mmHg (95 percent CI, 4.23 to 2.34; I2 = 0.99) and 1.83 mmHg (95 percent CI, 2.35 to 1.31; I2 = 0.76),

respectively, over a 24-hour period. There were also significant reductions in systolic and diastolic BP during the day and at night, independent of body weight change [52].

Another meta-analysis examining the effects of SGLT2i inhibition on ambulatory BP aimed to assess the relationship between dose and ambulatory BP response to SGLT2 inhibition and to compare it to low-dose hydrochlorothiazide. According to this meta-analysis, in 24-hour ABPM, SGLT2 inhibitors caused an average reduction of 3.62/1.70 mmHg in systolic/diastolic BP, which is equivalent to the BP-lowering efficacy of low-dose hydrochlorothiazide, regardless of the SGLT2 inhibitor dose. However, SGLT2 inhibition reduced blood pressure more effectively during the day than at night [53]. In a post-hoc analysis of the EMPA-REG BP trial, empagliflozin was found to lower nocturnal BP more than daytime BP in patients with DMT2 and a non-dipper HTN profile [54].

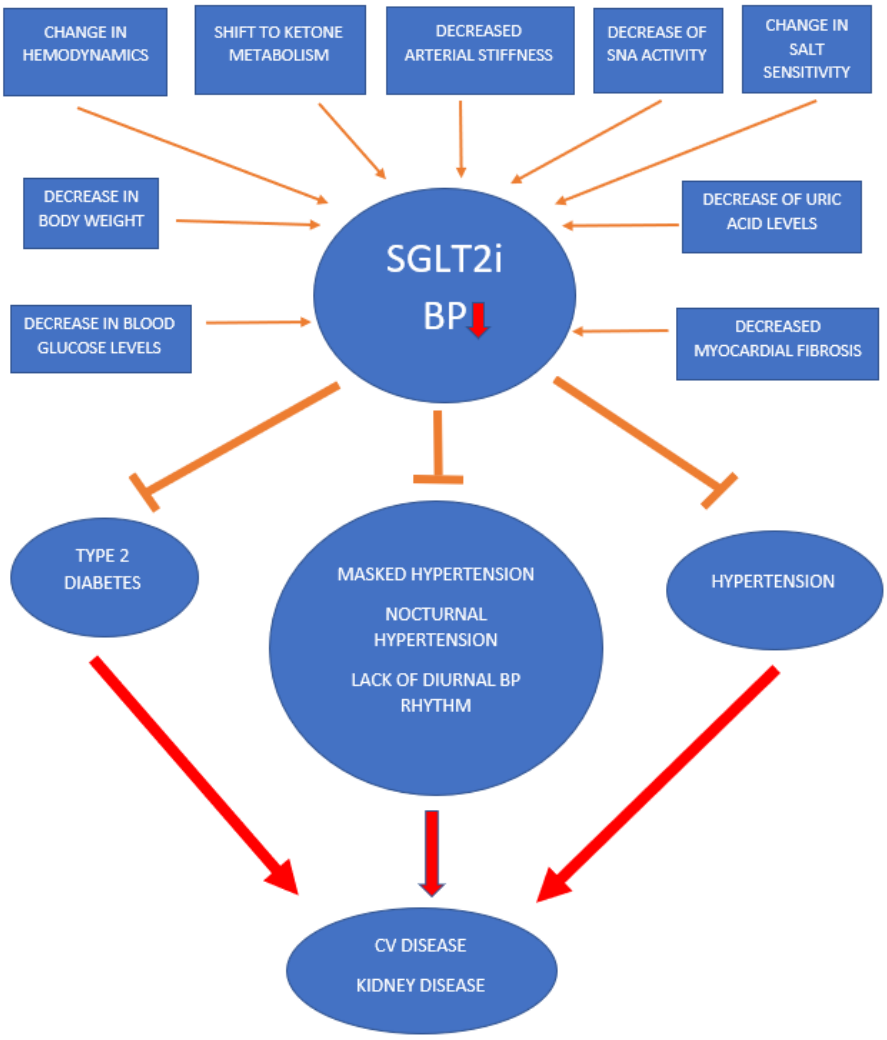

Figure 1. Pathophysiological mechanisms involved in blood pressure-lowering effects of SGLT2i and their role in preventing CV and kidney disease

The presently published data regarding the effects of SGLT2i on home BP are limited to the Japanese population. In addition to the results of the previously mentioned SACRA study, which showed a lowering effect of empagliflozin on morning home BP [50], the results of the SHIFT-J study demonstrated a beneficial effect of canagliflozin on nocturnal, morning and evening home SBP (-5.23, -6.82, -8.74, respectively) compared to the control group of patients with uncontrolled DMT2 and nocturnal BP [55]. In addition, beneficial effects of dapagliflozin on morning, evening and nocturnal home SBP (-8.32; -9.57 and -2.38 ± 7.82 mmHg, respectively)

were reported in Japanese patients with DMT2 [56].

Based on the available evidence, we can conclude that the drop in 24-hour ambulatory BP seen with SGLT2 inhibitors is a class effect and is comparable to low-dose hydrochlorothiazide. Likewise, it seems that SGLT2i have a significant BP-lowering effect at night, suggesting that these drugs have the potential to repair altered circadian BP rhythms in hypertensive patients with DMT2, thus improving cardiovascular and kidney outcomes (Figure 1).

Proposed mechanisms of SGLT2 inhibition on blood pressure

The effect of SGLT2i on lowering blood pressure could be explained by several mechanisms involving changes in hemodynamics due to a decrease in effective circulating volume caused by diuresis and natriuresis, reduction in body weight and uric acid levels, antihyperglycemic effects, shifting metabolic fuel from glucose to ketones, inhibition of sympathetic nervous system activity, change in arterial stiffness and switching of salt-sensitive to non-salt sensitive BP phenotype due to osmotic diuresis [11, 57, 58] (Figure 1).

Microvascular and macrovascular dysfunction leading to increased arterial stiffness is common in diabetic patients [59, 60], meaning that an increase in blood pressure and blood pressure variability cannot be attenuated in these patients' major arteries and are instead conveyed to atherosclerotic plaque sites in the periphery. As a result, the combination of HTN and DMT2 creates hemodynamic stress that predisposes patients to the development of CVD [61–63]. According to preclinical evidence, improvements in arterial stiffness and endothelial function may contribute to the CV advantages of SGLT2i therapy [64]. This is supported by evidence obtained in clinical trials, suggesting that currently available SGLT2i medications reduce arterial stiffness in individuals with DMT2 [65–68]. Furthermore, dapagliflozin also reduced cardiac fibrosis in infarcted rat hearts by controlling macrophage polarization via STAT3 signaling, as well as by altering epicardial fat tissue distribution and cytokine and adipokine secretion [69–71].

Clinical evidence of beneficial effects of SGLT2i on cardiorenal outcomes

Large cardiovascular outcome trials (CVOT) have shown the beneficial effects of SGLT2i on improving CV outcomes, largely due to reduction in hospitalizations caused by heart failure and, in some studies, decreasing mortality. In the EMPA-REG OUTCOME trial, empagliflozin significantly reduced the occurrence of primary endpoint events (3-point major cardiovascular event (MACE) consisting of non-fatal myocardial infarction, non-fatal stroke and CV death) compared to placebo, with significantly lower rates of CV death, hospitalization for heart failure (HF) and death from any cause [1]. Similar results were obtained in the CANVAS trial [2], which examined the cardiovascular safety of canagliflozin, demonstrating a reduction in 3-point MACE, but no effect on CV death, as opposed to the EMPA-REG OUTCOME trial. Dapagliflozin, on the other hand, reduced the risk of HF, but had no effect on atherosclerotic CVD, as shown in the DECLARE-TIMI 58 trial [3].

According to available evidence, the protective effect of SGLT2i on 3-point MACE is limited to patients with previously existing CVD, while class benefits exist for HF regardless of CVD presence [72]. Furthermore, in patients with DMT2 and chronic kidney disease (CKD) (eGFR 60 mL/min/1.73 m2), a favorable effect on HF and 3-point MACE has been confirmed [73]. Recently, results from two large-scale studies were published, demonstrating improved outcomes in patients with HF with reduced ejection fraction (HFrEF) treated with dapagliflozin and empagliflozin (DAPA-HF and EMPEROR-Reduced, respectively) independent of the presence of diabetes [7, 8].

Based on the evidence obtained in the above trials, the guidelines of the European Society of Cardiology (ESC) propose SGLT2i and/or

glucagon-like peptide-1 receptor agonists (GLP-1 RA) as the treatment of choice for patients with diabetes and proven CVD or risk thereof, which is contrary to the common practice of using metformin as the first choice for DMT2 treatment [6].

Nearly all patients included in the CREDENCE study, which examined the effect of canagliflozin on renal outcomes, were treated with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), with eGFR from 30 to 90 ml per minute [74]. The experiment was halted early due to favorable interim analysis results, showing that the relative risk of composite renal outcomes was reduced by 34%, while the relative risk of end-stage renal disease was reduced by 32%. These findings reveal that renoprotection was accomplished across the whole range of eGFR levels, re-establishing the nephroprotective effect regardless of baseline renal function.

The probability of dialysis, transplantation, or death due to kidney disease (hard renal outcomes) was considerably reduced in individuals treated with SGLT2i, as was recently validated in a meta-analysis of all studies using SGLT2i in diabetic patients [72]. Because of their reduced antihyperglycemic efficacy, SGLT2i were previously not recommended for diabetic patients with eGFR of less than 45 ml/min per 1.73 m2 [75, 76]. Such restrictions became debatable after the evidence of renoprotective effects emerged in the mentioned trials [77]. This was confirmed in the latest clinical trials involving diabetic and non-diabetic patients with heart failure and preserved ejection fraction [7, 8], demonstrating improvement of hard renal outcomes in the lower specter of eGFR, 30 and 20 mL/min/1.73 m2 in the EMPEROR-Reduced and DAPA-HF trials, respectively. The final proof that the renoprotective effect is independent of the antihyperglycemic effect was provided by the DAPA-CKD study, which indicated that dapagliflozin reduced renal events in patients with CKD with or without DM treated with maximum tolerated doses of ACE inhibitor/ARB [78]. Beneficial effects were observed on non-CV and all-cause mortality.

Conclusions

The effects of SGLT2i on blood pressure also appear to be largely responsible for the beneficial effects of this class of drugs on cardiorenal outcomes. They play a particularly important role in the control of nocturnal blood pressure, which is associated with increased CV risk, especially in patients with DMT2. Thus, the use of SGLT2i in patients with DMT2 and hypertension is certainly justified regardless of glycemic control in order to reduce the risk of CV and renal complications and improve the patient's quality of life. The extent to which the effects of SGLT2 inhibition on blood pressure are responsible for reduction of risk of heart failure, cardiovascular and renal disease in non-diabetic individuals with arterial hypertension remains a question to be answered.

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Competing interests. None to declare.

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[1] **Author contribution.** Acquisition of data: Bilić Ćurčić I, Ninčević V
Administrative, technical or logistic support: Bilić Ćurčić I, Canecki Varžić S, Prpić Križevac I
Analysis and interpretation of data: Bilić Ćurčić I, Ninčević V
Conception and design: Bilić Ćurčić I, Canecki Varžić S, Prpić Križevac I
Critical revision of the article for important intellectual content: Bilić Ćurčić I, Milas Ahić J
Drafting of the article: Bilić Ćurčić I, Ninčević V, Canecki Varžić S
Final approval of the article: Bilić Ćurčić I, Prpić Križevac I, Mihaljević I
Obtaining funding: Canecki Varžić S, Prpić Križevac I, Milas Ahić J, Mihaljević I