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REVIEW

Cardioprotective effects of SGLT2 inhibitors are possibly associated with normalization of the circadian rhythm of blood pressure

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Improvement in cardiovascular (CV) morbidity and mortality in the EMPA-REG OUTCOME study provides new insight into the therapeutic use of sodium-dependent glucose cotransporter 2 (SGLT2) inhibitors in patients with type 2 diabetes. Although SGLT2 inhibitors have several pleiotropic effects, the underlying mechanism responsible for their cardioprotective effects remains undetermined. In this regard, the absence of a nocturnal fall in blood pressure (BP), that is, non-dipping BP, is a common phenomenon in type 2 diabetes and has a crucial role in the pathogenesis of CV morbidity and mortality. In most clinical trials, SGLT2 inhibitors reduce both systolic BP (~3–5 mm Hg) and diastolic BP (~2 mm Hg) in patients with type 2 diabetes. In addition, recent clinical and animal studies have revealed that SGLT2 inhibitors enable the change in BP circadian rhythm from a non-dipper to a dipper type, which is possibly associated with the improvement in CV outcomes in patients with type 2 diabetes. In this review, recent data on the effect of SGLT2 inhibitors on the circadian rhythm of BP will be summarized. The possible underlying mechanisms responsible for the SGLT2 inhibitor-induced improvement in the circadian rhythm of BP will also be discussed.
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INTRODUCTION

The prevalence of cardiovascular disease (CVD) is greater among individuals with diabetes and obesity, which contributes to the major cause of mortality in these patients.[1] Moreover, hypertension is found in two-thirds of patients with diabetes and is a significant contributing factor that adds a further layer of complexity to CVD in these patients.[2] Therefore, several guidelines have emphasized the importance of blood pressure (BP) control to prevent the progression of cardiovascular (CV) complications in patients with type 2 diabetes.

Recently, the EMPA-REG OUTCOME study provided new insight into the management of CV complications using a selective sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor in patients with type 2 diabetes.[3] SGLT2 inhibition prevents the reabsorption of glucose from the S1 segment of the proximal tubules of the kidney and thereby increases the urinary excretion of glucose.[4] Although SGLT2 inhibitor-induced reduction in blood glucose levels occurs independently of β-cell functions and insulin,[5] the underlying mechanism by which an SGLT2 inhibitor improves CV outcomes in type 2 diabetes remains undetermined. Accumulating evidence suggests that SGLT2 inhibitors have pleiotropic effects, including reduced body weight and BP, and improved vascular stiffness and insulin sensitivity as well as diuretic effects.[6]

Advance in ambulatory BP monitoring and home BP measurement have demonstrated the variability of BP.[7–9] In healthy subjects, BP drops an average of 10–20% when transitioning from waking (active period) to sleeping (inactive period), and this phenomenon is referred to as dipper-type BP.[7] Subjects in whom the nocturnal drop in BP is blunted or $<10\%$ are referred to as having a non-dipper BP pattern.[9] The Ohasama study indicated that each 5% change in the decline in nocturnal systolic BP (SBP) and diastolic BP (DBP) was associated with an approximately 20% greater risk of CV mortality.[9] It has also been shown that diminished nocturnal decline in BP is an important determinant of CV mortality independently of overall BP during a 24-h period.[8,9]

Recent clinical studies have indicated that SGLT2 inhibitors improve nocturnal BP.[10,11] Thus the cardioprotective effects of SGLT2 inhibitors may be mediated by their effects on BP, especially their improvement of the circadian rhythm of BP. In this review, we summarize recent information regarding the effects of SGLT2 inhibitors on BP and its circadian rhythm. We also discuss the possible mechanisms underlying the SGLT2 inhibitor-induced improvement in the circadian rhythm of BP.

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HYPOTHESIS: IMPROVEMENT IN CV EVENTS MEDIATED BY AN SGLT2 INHIBITOR IS ASSOCIATED WITH BP CHANGES

The absence of physiological nocturnal dipping (non-dipping pattern) and an early morning BP surge confer a significantly worse prognosis in hypertensive patients with diabetes.[12,13] It has also been indicated that non-dipper hypertensive patients show a greater degree of insulin resistance and lower levels of adiponectin than do dipper hypertensive subjects.[14] Importantly, a significant correlation has been shown between a disrupted circadian rhythm of BP and CV events or mortality.[15–17] A meta-analysis that included data from 3468 patients from four prospective studies demonstrated that the dipping pattern and night–day BP ratio are significant and independent predictors of CV events and mortality in hypertensive patients without a history of major CVD.[18] Moreover, Fogari *et al.*[16] showed that the persistence of the non-dipper type of BP was associated with increased left ventricular hypertrophy and atherosclerotic CVD. It has also been shown that increases in CV morbidity and mortality are associated with a loss of the physiological circadian rhythm of BP in hypertensive patients with diabetes.[19,20]

SGLT2 inhibition and cardiovascular events in type 2 diabetes

Patients with type 2 diabetes commonly develop CVD, which is responsible for approximately 80% of the mortality in type 2 diabetics.[21] Although hyperglycemia is crucial for macrovascular complications to develop in diabetes, clinical studies have shown that intensive blood glucose control has little beneficial effect on CV morbidity and mortality in patients with type 2 diabetes.[22,23] Recently, the EMPA-REG OUTCOME study has shown that empagliflozin, an SGLT2 inhibitor, significantly reduces the primary composite outcome of CV events, which is driven by the 38% reduction in CV mortality.[3] Moreover, meta-analyses of major adverse CV events in type 2 diabetes in 11 292 patients treated with empagliflozin[24] and 9339 patients treated with dapagliflozin[25] have revealed that the administration of SGLT2 inhibitors was not associated with an increased risk of major adverse CV events but rather had the potential for beneficial CV effects on the population with major adverse CV events or with a history of CVD. Several prospective clinical trials are ongoing with canagliflozin (CANVAS)[26], dapagliflozin (Declare-TIMI 58[27] REFORM[28]) and ertugliflozin (VERTIS)[29] in patients with type 2 diabetes with either established or multiple high-risk factors for CVD. In db/db mice, empagliflozin ameliorated CV injury, including cardiac interstitial fibrosis and remodeling as well as vascular dysfunction.[30] These data are consistent with the hypothesis that an SGLT2 inhibitor has the potential to improve CV morbidity and mortality in subjects with type 2 diabetes.

SGLT2 inhibitors and BP

Several clinical trials have demonstrated that SGLT2 inhibitors, as either monotherapy or add-on therapy, are clearly associated with a significant reduction in BP in patients with type 2 diabetes. A recent network meta-analysis of 33 randomized control trials in 17 600 participants with type 2 diabetes showed a reduction in office seated SBP (maximum reduction of -4.9 mm Hg) and DBP (maximum reduction of -2.0 mm Hg) by SGLT2 inhibitors.[31]

Ambulatory BP measurement is better than office seated BP.[32] Moreover, ambulatory 24-h BP is a more significant predictor of CV events than conventional office seated BP in patients with type 2 diabetes.[33] It has been suggested that the circadian rhythm of BP is a possible target for treatment with SGLT2 inhibitors in patients with type 2 diabetes.[34] Tikkanen *et al.*[10] demonstrated a significant reduction in 24-h ambulatory SBP and DBP with either 10 mg (-3.44 and -1.36 mm Hg, respectively) or 25 mg (-4.16 and -1.72 mm Hg, respectively) empagliflozin for 12 weeks in hypertensive patients with type 2 diabetes. In a randomized, placebo-controlled, double-blind trial with 75 subjects with type 2 diabetes, 12 weeks of treatment with dapagliflozin (10 mg day^{-1}) caused a significant reduction in 24-h ambulatory BP (5.6 mm Hg), although the change was greater in daytime BP (8.8 mm Hg) and less in the nocturnal BP (1.9 mm Hg).[35] Amin *et al.*[36] showed that ertugliflozin consistently reduced ambulatory mean daytime, but not nocturnal, SBP. In a subgroup analysis of a phase III randomized trial of the EMPA-REG OUTCOME study, empagliflozin significantly reduced 24- h SBP in dipper (sleep-time mean SBP $\leqslant$ 90% of awake-time mean; $n=417$) and non-dipper (sleep-time mean SBP $>$ 90% of awake-time mean; $n=350$) hypertensive patients with type 2 diabetes.[37] Moreover, in a randomized, double-blind placebo-controlled phase III study, dapagliflozin consistently decreased 24-h ambulatory SBP, whereas greater reductions in daytime ambulatory SBP was shown in type 2 hypertensive diabetic patients who already received a β-blocker.[38] In a case report of a patient with type 2 diabetes, Mori *et al.*[11] showed that dapagliflozin caused decreases in both 24-h SBP and DBP from 131/87 to 127/83 mm Hg at day 14, with a particular decrease in nocturnal BP from 123/84 to 116/75 mm Hg (the nocturnal BP dip increased from 9.6% to 12.8%), respectively. These data suggest that dapagliflozin changed the circadian rhythm of BP from a non-dipper to dipper pattern in these patients with type 2 diabetes.

We have recently shown that empagliflozin administration changed the circadian rhythm of BP from a non-dipper to dipper profile in salt-treated, obese Otsuka Long Evans Tokushima Fatty (OLETF) rats.[39] In this study, 4 weeks of salt treatment elevated BP and abolished the differences in BP between dark and light periods, suggesting a non-dipper type of hypertension. Interestingly, 5-week treatment with empagliflozin (10 mg kg^{-1} day^{-1}) reduced BP with a normalization of the circadian rhythm of BP to a dipper pattern. Obesity, impaired glucose metabolism, insulin resistance and hypertension are common features of metabolic syndrome.[40,41] Furthermore, metabolic syndrome is also associated with the development of type 2 diabetes and CVD, as well as a disrupted circadian rhythm of BP.[42,43] In this regard, we have shown that 5-week treatment with luseogliflozin (10 mg kg^{-1} day^{-1}) not only blunted the development of hypertension but also restored the circadian rhythm of BP from a non-dipper to dipper type in SHR/NDmcr-cp (+/+) rats, a model of metabolic syndrome.[44] Taken together, these data strongly indicate that BP reduction by an SGLT2 inhibitor is associated with the restoration of a disrupted circadian rhythm of BP from a non-dipper to dipper pattern in hypertensive subjects with impaired glucose metabolism and insulin resistance.

POSSIBLE MECHANISMS UNDERLYING THE SGLT2 INHIBITOR-INDUCED NORMALIZATION OF THE BP DIPPING PATTERN

Body weight

Body weight gain is associated with impaired glucose homeostasis as well as BP regulation, including a disrupted circadian rhythm of BP.[45,46] Moreover, it has been shown that visceral fat accumulation is an independent risk factor for the disruption of the circadian rhythm of BP in Japanese patients.[47] Clinical studies have shown that treatment with SGLT2 inhibitors decreased body weight in subjects with type 2 diabetes.[35,48,49] Moreover, the SGLT2 inhibitor-induced reduction in body weight is associated with reduction in

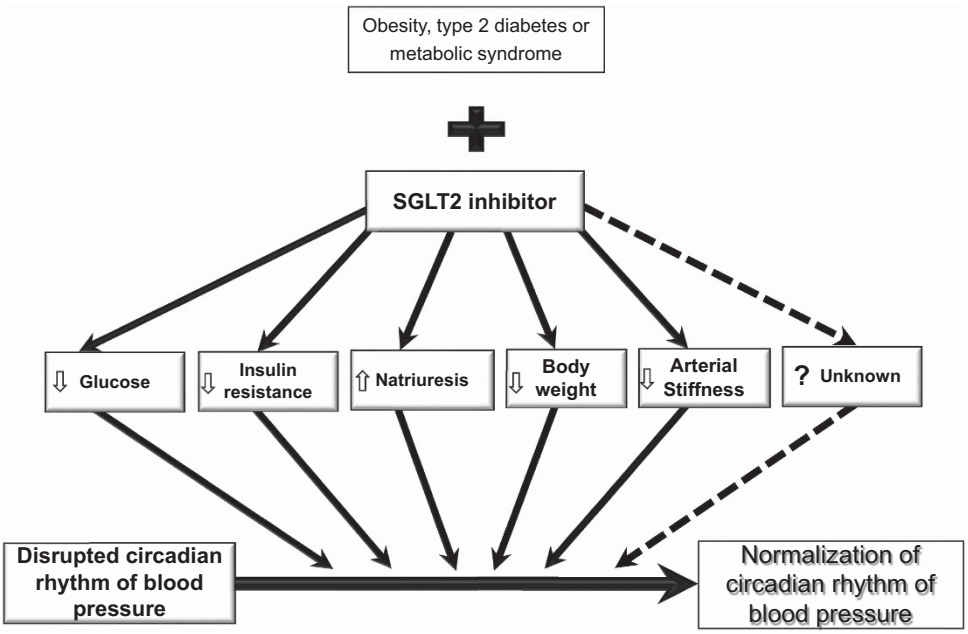

Figure 1 A schematic representation of possible underlying mechanisms that are involved in SGLT2 inhibitor-induced normalization of a dysregulated circadian rhythm of blood pressure.

body fat mass.[50,51] Therefore, it is possible that SGLT2 inhibitor-induced changes in body weight are accompanied by improvement in the circadian rhythm of BP in subjects with type 2 diabetes. However, it has been shown that the SGLT2 inhibitor-induced reduction in BP was not correlated with body weight changes.[51,52] Furthermore, BP reduction and BP circadian rhythm improvement were not associated with body weight reduction during treatment with SGLT2 inhibitors in obese animals.[39,44] Therefore, SGLT2 inhibitor-induced BP reduction and BP dipping pattern improvement may not be solely explained by body weight reduction.

Blood glucose

The prevalence of a non-dipping BP pattern was significantly higher in subjects with impaired glucose tolerance.[53] Glycated hemoglobin levels exhibited a strong association with the variability of nocturnal SBP and DBP in patients with type 2 diabetes.[54] However, the SGLT2 inhibitor-induced reduction in BP was not correlated with glycated hemoglobin levels.[51,52] Furthermore, the potential relationship between blood glucose levels and changes in the dipping pattern of BP has not been reported in diabetic patients whose blood sugar levels are controlled by any other antidiabetic drugs. Collectively, it seems unlikely that the improvement in circadian rhythm is mediated by blood sugar control.

Insulin sensitivity

Insulin induces BP elevation through multiple mechanisms, and insulin resistance has a pivotal role in the pathogenesis of type 2 diabetes mellitus with CV complications as well as a non-dipping pattern of BP.[5,55] Blood glucose control with an SGLT2 inhibitor is independently mediated by β-cell function and endogenous insulin.[5] It has been shown that treatment with an SGLT2 inhibitor improves insulin resistance in patients with type 2 diabetes.[56] Euglycemic insulin clamp test results have also indicated that dapagliflozin treatment for 2 weeks improved whole-body insulin-induced glucose uptake by 20–25%.[57] We also showed that treatment with SGLT2 inhibitors significantly improved insulin sensitivity in an oral glucose tolerance test in obese rats.[39,44] Thus it is possible that the improvement in insulin resistance contributes to BP reduction by an SGLT2 inhibitor. Further studies will be needed to determine the direct relationship between insulin resistance improvement and BP reduction during treatment with an SGLT2 inhibitor.

Natriuresis

Sodium retention has an important role in the development of hypertension in patients with diabetes[58] and metabolic syndrome[59] and contributes to the development of a disrupted circadian rhythm of BP.[60] Of note, a non-dipping pattern of BP can be transformed to a dipping pattern of BP by a sodium-restricted diet[61] or diuretics[62] in sodium-sensitive hypertensive patients. Lambers *et al.*[35] showed that dapagliflozin caused a 7% reduction in plasma volume in patients with type 2 diabetes, indicating a diuretic effect possibly owing to enhanced sodium excretion or to osmotic diuresis as a result of increased urinary glucose excretion. It has also been shown that urinary sodium excretion tended to be increased in the early period of canagliflozin administration in patients with type 2 diabetes.[63] These effects of an SGLT2 inhibitor are similar to those of diuretics such as chlorothiazide, which increases urinary sodium excretion for only a few days because of a compensatory mechanism against body fluid loss.[63] A case report of a patient with type 2 diabetes showed that a 2-week regimen of the SGLT2 inhibitor dapagliflozin changed the BP pattern from a non-dipper to a dipper type possibly resulting from the increased urinary excretion of sodium. In this study, the sodium excretion rate rose from 0.37% at day 0 to 0.68% at day 8, although this change was not statistically significant.[11]

In OLETF rats with type 2 diabetes that were treated with a high-salt diet, empagliflozin-induced changes in the dipping pattern of BP were associated with increased urinary sodium excretion.[39] Moreover, the SGLT2 inhibitor luseogliflozin-induced shifting of the

circadian rhythm of BP from a non-dipper to a dipper pattern was associated with increased urinary excretion of sodium in SHR/NDmcr-cp(+/+) rats with metabolic syndrome. In this study, luseogliflozin treatment caused a significantly negative sodium balance in comparison with the vehicle-treated animals, suggesting a reduction in sodium retention by treatment with an SGLT2 inhibitor.[44] Based on these data, it can be speculated that SGLT2 inhibitors induce natriuresis, which has an important role in the improvement in the circadian rhythm of BP in subjects with type 2 diabetes. Recent studies have suggested that sodium is accumulated in the muscle and skin in patients with hypertension[64] and heart failure,[65,66] which is attenuated by treatment with a diuretic.[66] Preliminary studies by Schmieder *et al.*[67] have shown that dapagliflozin treatment caused a significant decrease in the skin tissue content of sodium in type 2 diabetic patients. Therefore, it can be hypothesized that SGLT2 inhibition has the potential to decrease sodium levels in the extracellular space, which contributes to the improvement in the dipping pattern of BP and the associated cardiovascular mortality.

Arterial stiffness

The non-dipping type of BP is associated with increases in the index of arterial stiffness,[68] greater intima-media thickness in the carotid bifurcation and average intima-media thickness,[69] all of which are related to the risk of CVD.[70,71] Interestingly, empagliflozin significantly decreased carotid-radial/femoral pulse wave velocity in patients with type 1 diabetes, suggesting an improvement in arterial stiffness.[72] Furthermore, empagliflozin reduced the pulse and mean arterial pressures and caused a greater reduction in double product while inducing a trend of reduced ambulatory arterial stiffness index values in patients with type 2 diabetes.[73] These data suggest that SGLT2 inhibitors improve arterial stiffness and vascular resistance in patients with type 2 diabetes. However, no studies have investigated a possible contribution of arterial stiffness improvement to the normalization of BP circadian rhythm during treatment with an SGLT2 inhibitor.

Other mechanisms

It has been shown that non-dipping nocturnal BP is associated with urinary albumin excretion in patients with type 2 diabetes.[74] In the EMPA-REG OUTCOME trial, patients with type 2 diabetes who were treated with empagliflozin had a significantly lower risk of progression of microalbuminuria to macroalbuminuria.[75] Moreover, Cherney *et al.*[76] showed that, regardless of microalbuminuria or macroalbuminuria, empagliflozin caused a clinically meaningful reduction in the urinary albumin/creatinine ratio in patients with type 2 diabetes. A *post hoc* analysis of phase III clinical trials has shown that dapagliflozin effectively reduced albuminuria in hypertensive patients with type 2 diabetes who were treated with renin–angiotensin system inhibitors.[77] In diabetic Akita mice, empagliflozin reduced both albuminuria and glomerular hyperfiltration.[78] High levels of plasma triglycerides and low levels of high-density lipoprotein-cholesterol were also associated with non-dipper hypertension in subjects with metabolic abnormalities.[43] Several clinical studies have shown that SGLT2 inhibitors slightly but significantly decrease triglycerides.[3,79] Serum uric acid levels have also independently been associated with type 2 diabetes,[80] CVD[81] and non-dipper hypertension.[82] Recent clinical trials have demonstrated that SGLT2 inhibitors with either monotherapy[3,83] or add on therapy[79] reduced the levels of serum uric acid (~10–15%) in patients with type 2 diabetes. However, the specific contributions of reductions in urinary albumin excretion, triglycerides and serum uric acid to the normalization of BP circadian rhythm have not yet been investigated during treatment with an SGLT2 inhibitor.

CONCLUSIONS

Recent clinical trials have indicated that treatment with an SGLT2 inhibitor elicits beneficial outcomes in terms of CV events in patients with type 2 diabetes. Emerging data have also shown that SGLT2 inhibitors not only decrease BP but also improve a disrupted circadian rhythm of BP. Thus it can be postulated that the beneficial effects of SGLT2 inhibitors on CV events are associated with the improvement in BP circadian rhythm. However, further investigation should be undertaken to determine the precise mechanism involved (Figure 1).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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