Hypertension Research (2017) 40, 629–631

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COMMENTARY

Amelioration of arterial pressure lability: an unmissable target for diabetes management

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Hypertension Research (2017) **40,** 629–631; doi:10.1038/hr.2017.35; published online 16 March 2017

Impaired glycemic metabolism and hyperglycemia play major roles in diabetes pathophysiology. However, medical interventions in only glycemic changes do not fully prevent macrovascular complications or improve the prognosis of people with type 2 diabetes mellitus (T2DM). A multifactorial approach, including a healthy diet, exercise and comprehensive medical care of comorbidities, is therefore mandatory in order to improve survival.[1] Hypertension is an established major complication in people with T2DM, with increased levels of arterial pressure (AP) known to contribute to the development of cardiovascular disease (CVD) and worse mortality.[2–4] Hypertension may also cause systemic endothelial dysfunction leading to diabetes-related microvascular complications.[5] Accumulated evidence suggests that lowering the AP level in people with T2DM is effective for preventing the development of vascular complications and reducing mortality.[6,7] However, it remains controversial whether intensive treatment to lower AP is clinically beneficial compared with standard treatment.[8–10] These results indicate that clinicians should focus on the quality of antihypertensive treatment in addition to lowering AP.

'Variability' or 'lability' often has negative impacts on the pathophysiology of T2DM. Numerous experimental and clinical studies have demonstrated that abnormal glucose fluctuations cause increased production of reactive oxygen species (ROS) and endothelial dysfunction, and are associated with adverse clinical events, such as destabilization of coronary artery plaque and worse outcomes.[11–15] In addition to avoiding the risk of hypoglycemia, it is also clinically important to prevent steep postprandial glucose spikes and maintain an appropriate range of glucose levels, rather than merely decreasing the average levels of glycemic parameters.[16]

Recent studies have shown that impaired AP variability, including day-by-day (short-term) and visit-to-visit (long-term) variability, are strong predictors for CVD and mortality in people with or without diabetes.[17–20] Several clinical studies have examined the effects of AP variability on atherogenic changes. Nakano *et al.*[21] reported that visit-to-visit AP variability was associated negatively with endothelial function assessed by flow-mediated dilation, whereas Wu *et al.*[22] showed that systolic AP variability during nighttime in patients with diabetes showed an independent relationship with carotid intima–media thickness. A clinical association between increased short-term AP variability and impaired circadian rhythm of AP, with greater day-by-day changes in patients with T2DM has also been reported.[23] Interestingly, Takao *et al.*[24] found that both long-term AP and HbA1c variability in diabetes patients were significant predictors of prevalent CVD in a combined and additive manner, independent of the mean values of AP and HbA1c. These association and adverse impact on clinical outcomes suggest that therapeutic intervention in increased AP variability is a potential residual target in the daily care of diabetes. However, to date, there are only limited data available on the beneficial effects of anti-diabetes agents on AP variability.

Sodium glucose cotransporter 2 (SGLT2) inhibitors are a novel type of anti-diabetes agents, which lower plasma glucose levels by inhibiting glucose reuptake in the proximal renal tubule, which, in turn, increases urinary glucose excretion. In addition to the beneficial effects on a wide range of metabolic parameters associated with attenuation of glucotoxicity and caloric loss, osmotic diuresis in the proximal renal tubule also plays a key role in inducing the hemodynamic action.[25] These actions may have accounted for a major portion of the clinical benefits observed in the EMPA-REG OUTCOME trial of patients with T2DM with a high cardiovascular (CV) risk.[26] Among their multifactorial effects, the impact of SGLT2 inhibitors on AP modification has become a central focus of clinicians and researchers. It is well recognized that treatment with SGLT2 inhibitors leads to AP reduction without causing a compensatory increase in heart rate.[27,28] Although the mechanisms by which SGLT2 inhibitors reduce BP are not yet fully understood, several factors including reduced plasma volume, body weight loss and improved arterial stiffness are likely to be involved.[29,30] These beneficial actions of SGLT2 inhibitors may synergistically improve endothelial function and possibly attenuate arteriosclerosis via direct and indirect vascular pathways. Clinical trials to evaluate these effects of SGLT2 inhibitors are currently in progress.[31]

Recent animal studies have demonstrated that SGLT2 inhibitors successfully modulated the circadian rhythm of AP from a non-dipper to a dipper pattern.[32,33] In the current issue of *Hypertension Research*, Yoshikawa *et al.*[34] demonstrated clearly that treatment with a SGLT2 inhibitor at a non-depressor dose in streptozotocin-induced diabetes model rats attenuated AP lability in collaboration with inhibition of sympathetic activity and improvement of baroreflex sensitivity

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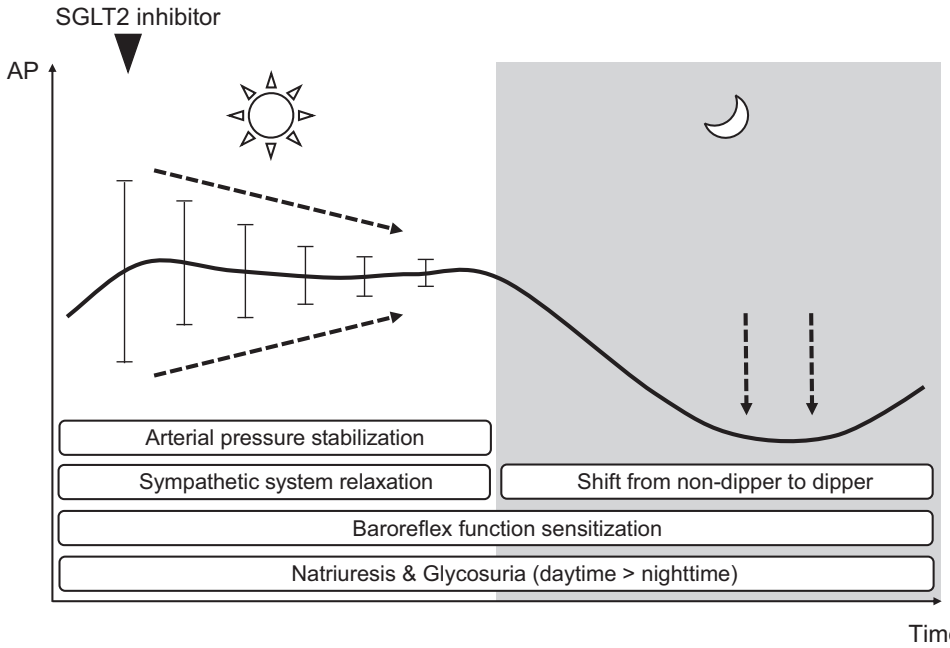

Figure 1 Anticipated actions of sodium glucose cotransporter 2 (SGLT2) inhibitor on arterial pressure (AP) properties during daytime and nighttime.

(BRS). Interestingly, a decrease in SGLT2 inhibitor-induced AP lability and sympathetic nerve relaxation were observed during the active phase. Consistent with this result, other studies demonstrated that lowering of AP was greater during daytime than nighttime.[28,35] Several physiological differences in the action of SGLT2 inhibitor during daytime or nighttime, such as glucose levels and renal perfusion, appear to contribute to the changes in AP.[25] On the other hand, BRS was refined during both the active and rest phases, possibly indicating a continuous beneficial effect, and may, in part, also have contributed to improved circadian rhythms of AP.[32,33] As stated by Yoshikawa *et al.*,[34] the precise mechanisms by which SGLT2 inhibitors improve these vascular properties have yet to be determined. However, we consider that these favorable actions of SGLT2 inhibitors on AP properties are likely to be effective for preventing the progression of vascular failure, thereby improving clinical outcomes in people with diabetes.

As expected, the current study showed a clear difference in hemodynamic properties between SGLT2 inhibitor and insulin treatments. Insulin treatment resulted in unwanted increases in body weight and heart rate during the active phase, AP lability and sympathetic activity, despite causing greater amelioration of glycemic parameters than SGLT2 inhibitors. A recent experimental study showed that insulin stimulation increased the expression levels of SGLT2 associated with excess ROS production in tubular cells.[36] Several published studies have also demonstrated that SGLT2 inhibitors reduce plasma insulin levels and attenuate insulin resistance indices.[37,38] This evidence and current results indicate that combination therapy with a SGLT2 inhibitor would be reasonable and more effective for improving glycemic parameters and hemodynamic control in insulin-treated patients with diabetes or hyperinsulinemia.[39]

Before the publication of the results of the EMPA-REG OUTCOME trial, Inzucchi *et al.*[29] anticipated that SGLT2 inhibitors could regulate several pathways associated with CV benefits. On the basis of a number of studies including the EMPA-REG OUTCOME trial, the majority of these pathways have now been clearly and directly verified. However, the impact of SGLT2 inhibitors on sympathetic regulation has only been evaluated using indirect findings such as heart rate stabilization and possible decreases in arrhythmia.[26] To the best of our knowledge, the current result is the first to show this effect using more sophisticated and direct methods than used previously. The concept recently proposed by Yoshikawa *et al.*[34] that SGLT2 inhibitors may mitigate AP lability in conjunction with regulation of sympathetic activity and BRS is likely to explain, in part, the potential of the beneficial outcomes associated with SGLT2 inhibitors (Figure 1). As discussed herein, the missing component of the mode of action of SGLT2 inhibitors on CV systems should be identified increasingly in the near future.

CONFLICT OF INTEREST

KN has received honorariums from Boehringer Ingelheim, Daiichi Sankyo, Astellas, MSD, Takeda, Mitsubishi Tanabe and Sanofi, and research grants from Sanwa Kagaku Kenkyusho, Astellas, Takeda, Boehringer Ingelheim, Bayer, Teijin and Mitsubishi Tanabe. The remaining author declares no conflict of interest.

ACKNOWLEDGEMENTS

The authors are grateful to Ms Aya Yamada for her assistance.

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