Journal of
Cardiology & Cardiovascular Therapy
ISSN: 2474-7580

Juniper Publishers
key to the Researchers

Review Article
Volume 18 Issue 1 - December 2022
DOI: 10.19080/JOCCT.2022.18.555977

J Cardiol & Cardiovasc Ther

SGLT 2 Inhibitors and Hypertension: Mild but Effective. What can we expect ?

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Submission: November 30, 2022; **Published:** December 13, 2022

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Abstract

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a new class of medications used for the treatment of diabetes mellitus (DM). It has been shown that, in addition to a favorable metabolic effect, they significantly reduce atherosclerotic events, cardiovascular and total mortality, hospitalization duration in patients with heart failure and have a significant effect on reducing the progression of chronic kidney disease. It has been observed that in patients with diabetes mellitus, they lead to a reduction of blood pressure (BP). The aim of this article is to evaluate current knowledge about mechanisms of antihypertensive action and clinical benefits of SGLT2 inhibitors in reducing arterial blood pressure in patients with diabetes mellitus and arterial hypertension.

Keywords: SGLT 2 Inhibitors; Arterial Hypertension; Diabetes Mellitus

Introduction

In patients with metabolic diseases including insulin resistance, diabetes mellitus and cardiometabolic syndrome, there is an incresed prevalance of arterial hypertension. We find it in 50 to 80% of patients with DM [1]. Activation of the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system, mitochondrial dysfunction, oxidative stress, inflammation, abnormal release of extracellular vesicles that mediate cell to cell communication and contain appropriate micro RNA, gut microbiota dysregulation and renal sodium-glucose-co-transporter-2 (SGLT2) play a role in the development of arterial hypertension, insulin resistance and diabetes melitus [1]. SGLT2 is responsible for the reabsorption of about 90% of the filtered glucose in the proximal tubules and sodium absorption leading to an increase in blood pressure (BP). In the context of this mechanism, more than 10 years ago, the question arose whether SGLT2 inhibitors could affect the BP. It has been shown that their usage has a long-term effect on the BP.

Mechanisms of arterial pressure reduction with SGLT2 inhibitors

SGLT2 inhibitors are a newer generation of oral antihyperglycemic drugs with a unique insulin-independent mode of action [2]. Primarily, these drugs inhibit renal tubular glucose reabsorption, thereby decreasing blood glucose level without stimulating insulin. The exact mechanism(s) of antihypertensive action have not been clarified. It is assumed that the osmotic and diuretic effects of SGLT2 inhibitors are the basis, i.e. the inhibition of glucose and sodium reabsorption in the proximal tubules of the kidney. SGLT2 inhibition results in an increase in urinary sodium excretion by 30 to 60% [3]. In combination with a beta blocker or calcium channel blocker, the antihypertensive effect of SGLT2 inhibitors is greater than the effect of thiazide diuretics [4,5]. However, with the use of SGLT2 inhibitors, after a few weeks, the volume of urine returns to the basal level [6]. This indicates that diuresis and natriuresis are not the only mechanisms in BP reduction when using this group of drugs.

The finding that SGLT2 inhibitors reduce BP without a compensatory increase in heart rate and 6-hydroxydopamine leads to the assumption that SGLT2 inhibitors also suppress sympathetic nerve activity [7]. Reed assumed that local RAAS inhibition plays a role in the reduction of BP due to sodium delivery to the juxtaglomerular apparatus during SGLT2 blockade [8]. SGLT2 inhibitors increase endothelial nitric oxide bioavailability and affect endothelium-dependent vasodilation in patients with

diabetes mellitus. Also, they affect the proliferation, migration, differentiation, survival and aging of endothelial cells. Furthermore, they have a potent antioxidant and anti-inflammatory effect on endothelial cells. In addition to affecting contraction, they block the proliferation and migration of smooth muscle cells [9]. The above-mentioned effects, in addition to directly affecting the BP, in the long term contribute to the reduction of arterial stiffness, which is partly responsible for the increase of BP. In addition to affecting arterial stiffness, these drugs also lead to a decrease in central pressure in the aorta [10,11].

It is assumed that, in addition to the repair of endothelial function and reduction of oxidative stress, weight reduction, osmotic diuresis, contraction volume and changes in neurohumoral activation are responsible for this. In the regulation of BP, the role of SGLT2 inhibitors in reducing the level of uric acid, which can be attributed to the change in the activity of transporter 9 isoform 2 in glycosuria in the renal tubules, can not be ignored. Short-term studies have shown that the reduction of uric acid participates in the regulation of BP. The assumption that weight loss is a contributing mechanism in BP reduction has been questioned due to findings that BP reduction occurs before significant weight loss [12]. However, the long-term benefit of this mechanism in regulating BP and reducing cardiovascular risk is undeniable. Table 1 lists possible mechanisms by which SGLT2 inhibitors participate in the reduction of BP.

Table 1: Possible mechanisms of blood pressure reduction.

Volume depletion due to diuresis and natriuresis
Inhibition of sympathetic nervous system activity
Reduction in oxidative stress and improved endothelial function
Improvement of arterial stiffness
Uric acid reduction
Weight loss

Clinical data on the effectiveness of SGLT2 inhibitors in reducing arterial blood pressure

In the EMPA-REG BP study was examined the effect of empagliflozin on 24-hour ambulatory and ambulatory blood pressure [13]. It was shown that, after 12 weeks, empagliflozin in comparison with placebo when administered in a dose of 10 mg reduced the mean 24- hour systolic BP by -3.44 mmHg and when administered in a dose of 25 mg by -4.16 mmHg. The mean diastolic BP was reduced by -1.36 mmHg at the dose of 10 mg and by -1.36 mmHg at the dose of 25 mmHg. Changes in ambulatory values were consistent with those obtained by 24-hour ABPM. An additional analysis found that the effectiveness of empagliflozin in reducing BP was not affected by the number and type of antihypertensive drugs, and that increasing the dose of empagliflozin did not affect the effectiveness [14]. Post-hoc analysis of the EMPA-REG BP study found that empagliflozin more effectively reduced night BP values than daytime BP values in patients with diabetes mellitus and non-dipper pattern BP [15]. 132 Japanese patients with diabetes mellitus type 2 and uncontrolled nocturnal hypertension were included in the SACRA study [16]. The use of empagliflozin led to a reduction of daytime systolic BP by 11.7 mmHg and nighttime by 6.3 mmHg. The results of these two studies indicate the possibility of using this group of drugs in nocturnal hypertension. The effect of dapagliflozin on BP reduction was confirmed by the analysis of 13 controlled studies [17]. The studies investigated the effect of dapagliflozin on BP in normotensive (<140mmHg) and hypertensive (>140mmHg) patients with type 2 diabetes mellitus. Dapagliflozin was found to reduce systolic blood pressure by 3.6 mmHg and diastolic blood pressure by 1.2 mmHg in hypertensive patients and by 2.6 mmHg and 1.2 mmHg in normotensive diabetics compared to placebo. The addition of dapagliflozin to the RAAS blocker in patients with type 2 diabetes mellitus and hypertension, after 12 weeks, led to a reduction of ambulatory systolic BP by 10.4 mmHg and 24-hour ambulatory BP by 9.6 mmHg, and a greater number of patients achieved normalization of BP values than in the control group on placebo [18].

The influence of canagliflozin given in two different doses (100 and 300 mg) on the BP in patients with diabetes mellitus and arterial hypertension was also examined. After 6 weeks of treatment, canagliflozin given in a dose of 300 mg reduced the mean 24-hour value of MAP by 6.2 mmHg, while a less significant reduction in BP was recorded when a lower dose was used [19]. In the CREDENCE study, canagliflozin reduced systolic pressure by 3.5 mmHg very early, after 3 weeks, and reduced the need for other antihypertensive drugs [20]. The same study included patients with resistant hypertension, but not those treated with spironolactone, which compromised the conclusion. The mentioned data on the impact of individual SGLT2 inhibitors on the reduction of BP did not differ from those obtained by meta-analyses which confirmed a significant decrease in BP with this treatment modality [21,22]. One of the meta-analyses compared the impact of SGLT2 inhibitors and low doses of hydrochlorothiazide on ambulatory BP values [23]. It was found that SGLT2 inhibitors reduced the mean 24-hour values of systolic and diastolic BP by 3.62/1.7mmHg and that the efficacy was not affected by the dose of SGLT2 inhibitors, and that the efficacy was comparable to that of low- doses of hydrochlorothiazide.

Of practical importance are the findings that the antihypertensive effect of SGLT2 inhibitors is greater in patients with salt sensitivity and high BMI [24,25]. When using SGLT2 inhibitors, the degree of BP change depends on the basal BP values. Greater reduction of BP is in patients with higher basal values of BP [26]. The combination of an SGLT2 inhibitor with a thiazide diuretic or a loop of Henle diuretic did not lead to an additional reduction in BP. In addition to the evidence of similar antihypertensive potential, the fact that SGLT2 inhibitors, unlike thiazide diuretics, do not lead to hypokalemia and hypomagnesemia and prerenal hypovolemia should not be overlooked. Additive action in BP reduction is achieved with combinations of SGLT2 inhibitors

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with RAAS blockers, beta blockers and calcium channel blockers [27]. SGLT2 inhibitors are safe drugs. Hypoglycemia is practically absent, diabetic ketoacidosis is rarely seen. No cases of orthostatic hypotension were registered. The most common side effect when using these drugs is a bacterial or mycotic infection of the urinary tract. An increased risk of amputations was noted only with the use of canagliflozin in the CANVAS study [28]. The increased incidence of bone fractures requires more data to determine its significance.

Conclusion

Considering everything mentioned before, it is clear that the addition of SGLT2 inhibitors to other antihypertensives is justified in patients with diabetes mellitus type 2 and arterial hypertension on behalf of mild to moderate reduction of BP but also a downgrading the risk of cardiovascular and renal complications. New studies are needed to indicate the possible benefit of SGLT2 inhibitors in the treatment of arterial hypertension in non-diabetic patients.

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