



# Antihypertensive effects of SGLT2 inhibitors; a letter to the editor on new concepts

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## ABSTRACT

SGLT2 inhibitors, primarily used to treat diabetes, have shown potential antihypertensive effects by reducing blood pressure through mechanisms like natriuresis, diuresis, and weight loss. These medications may also improve arterial stiffness and reduce inflammation, impacting to their blood pressure-lowering properties.

**Keywords:** SGLT2 inhibitors, Chronic kidney disease, Hypertension, Cardiovascular events, Heart failure, Natriuresis, Type 2 diabetes mellitus, Aldosterone, Sodium–glucose cotransporter 2 inhibitors

### *Implication for health policy/practice/research/medical education:*

Sodium–glucose cotransporter 2 inhibitors are a promising new class of antihypertensive agents with pleiotropic cardiorenal protective effects, making them a valuable addition to the treatment of hypertension in high-risk populations.

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## Introduction

Sodium–glucose cotransporter 2 (SGLT2) inhibitors appear to be a promising new class of antihypertensive agents, with a magnitude of effect comparable to low-dose hydrochlorothiazide (1). SGLT2 inhibitors (SGLT2i) have been shown to have blood pressure (BP) lowering effects in patients with type 2 diabetes, chronic kidney disease (CKD), and resistant hypertension (2). A previous study also showed that the BP-lowering effects of SGLT2i were more pronounced in non-obese patients compared to obese patients with type 2 diabetes and CKD. It is possible that the residual risk of obesity may limit the BP reduction of SGLT2 inhibitors in obese patients by ineffective improvement in insulin resistance or incomplete inhibition of sympathetic nervous system hyperactivation (3). The BP-lowering effect is dose-independent (1). However, SGLT2i should be considered as an adjuvant to first-line antihypertensive regimens in patients with T2DM and hypertension (2). In this study we sought to discuss the potential effectiveness of SGLT2i in the treatment of hypertension.

## Molecular mechanisms of antihypertensive effects of SGLT2i

SGLT2 inhibitors increase glucose excretion in the urine,

leading to osmotic diuresis and natriuresis. This results in a reduction in blood volume and subsequently lowers BP. SGLT2 inhibitors also have been shown to reduce arterial stiffness, which is a key factor in the development of hypertension. Moreover, SGLT2 inhibitors have been found to improve endothelial function, which plays a role in regulating BP. Additionally, SGLT2 inhibitors have been shown to reduce sympathetic nervous system activity, which can contribute to hypertension. Furthermore, SGLT2 inhibitors have been shown to modulate the renin-angiotensin-aldosterone system, leading to a decrease in angiotensin II levels and aldosterone secretion, both of which can contribute to hypertension. Other mechanisms consisted of reducing insulin, leptin, and blood glucose levels, across with improving insulin resistance and hyperinsulinemia. Previous investigations showed improving anemia following treatment by SGLT2i, could reduce carotid body activation. Treatment with these agents will be accompanied by reducing sodium volume and protein-bound uremic toxins, inhibiting activation of the anteroventral third ventricle region of the hypothalamus. Recent studies showed an inhibition of the crosstalk between inflammation and oxidative stress, reducing production of reactive oxygen species and pro-inflammatory mediators (4). In fact, activation of

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AMPK, inhibition of NHE1, and upregulation of SIRT1, will attenuate the pathological cardiac remodeling too (4). SGLT2 inhibitors have been found to have pleiotropic effects, including anti-inflammatory and antioxidant properties, which may contribute to their cardiorenal protective effects (5). These agents have been detected to reduce the risk of cardiovascular events, hospitalization for heart failure, and the progression of kidney disease in patients with type 2 diabetes and established cardiovascular disease or kidney disease too(5). Likewise, SGLT2 inhibitors have been found to reduce albuminuria, which is a marker of kidney damage and a predictor of kidney disease progression (6). Similarly, SGLT2 inhibitors have been associated with changes in lipid metabolism, which may contribute to their cardioprotective effects (6). One of the interesting effects of SGLT2 inhibitors is reduction in fat mass (7,8), which could be another explanation for anti-hypertensive efficacy of this class.

#### Potential side effects of SGLT2 inhibitors for hypertension

SGLT2 inhibitors are associated with an increased risk of urinary tract infections and genital mycotic infections (9). Due to their diuretic effect, SGLT2 inhibitors can lead to dehydration and low BP, especially when used in combination with other antihypertensive medications (9,10). SGLT2 inhibitors may also increase the risk of hypoglycemia, particularly in patients taking concomitant antidiabetic medications like insulin or sulfonylureas (10). Besides, SGLT2 inhibitors can cause imbalances in electrolytes such as potassium, sodium, and magnesium, which may lead to adverse effects like muscle cramps or cardiac arrhythmias (9). In addition, there have been reports of acute kidney injury associated with the use of SGLT2 inhibitors, particularly in patients with underlying kidney disease or dehydration (9-12). Meanwhile, SGLT2 inhibitors have been linked to an increased risk of euglycemic diabetic ketoacidosis, a serious condition characterized by high levels of ketones in the blood (13). Finally, few studies suggest a potential association between SGLT2 inhibitors and an increased risk of bone fractures, although the evidence is not conclusive (14).

#### Conclusion

The antihypertensive effects of SGLT2i are mediated by several molecular mechanisms consisting of osmotic and natriuretic diuresis in the early stages of treatment, leading to decreased circulating plasma volume. Suppression of sympathetic nervous system activity in the long term is also another potential mechanism of antihypertensive efficacy of SGLT2i. The BP-lowering effect appears to be a dose-independent class effect. It should remember that SGLT2i should be considered as an adjuvant antihypertensive therapy.

#### Authors' contribution

**Conceptualization:** Rahime Eskandarian.

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#### Conflicts of interest

The authors declare that they have no competing interests.

#### Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

#### Ethical issues

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