



Blood Pressure Reduction: An Added Benefit of Sodium–Glucose Cotransporter 2 Inhibitors in Patients With Type 2 Diabetes

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Sodium–glucose cotransporter 2 (SGLT2) inhibitors are a newly approved class of glucose-lowering medications with a novel mechanism of action. These agents increase glycosuria, which leads to improved glucose control. They also produce an osmotic diuresis that, in part, contributes to blood pressure reduction and calorie loss secondary to glycosuria leading to weight loss (1,2).

A recent review of SGLT2 inhibitors focuses on the blood pressure–lowering effects of the two approved glucose-lowering agents, dapagliflozin and canagliflozin (3). While not approved as antihypertensive agents, they may potentially aid in lowering blood pressure in patients with diabetes. A review of studies in both hypertensive and normotensive patients with type 2 diabetes demonstrates a 4–10 mmHg reduction of systolic blood pressure (3).

In this issue of *Diabetes Care*, Tikkanen et al. (4) investigate the effectiveness and safety of the newest agent in this class, empagliflozin, on blood pressure using 24-h ambulatory blood pressure monitoring. This study randomized over 800 subjects with type 2 diabetes, mean age of 60 years, and good kidney function (i.e., a mean estimated glomerular filtration rate [eGFR] of 84 mL/min/1.73 m²). These subjects either were normotensive (<140/90 mmHg) or had stage 1 hypertension (≥140/90 < 160/99 mmHg).

They were randomized to either empagliflozin 10 mg daily, empagliflozin 25 mg daily, or placebo. The primary end point was the change in HbA_{1c} over the 12-week study. The coprimary end point was change in mean 24-h systolic blood pressure for which the study was 90% powered to see a 4 mmHg difference from placebo. The authors demonstrated a significant reduction in 24-h systolic and diastolic blood pressures, 4/2 mmHg lower than placebo at the 25 mg dose of empagliflozin.

The use of 24-h ambulatory blood pressure monitoring in the study by Tikkanen et al. is important and distinctive as it is the gold standard for assessing blood pressure (5). Moreover, it is the largest study to date to assess blood pressure lowering during both day and night with the use of SGLT2 inhibitors. Ambulatory blood pressure is recommended in the U.K. for evaluating all new patients with hypertension by the National Institute for Health and Care Excellence guidelines (5). Given the hypothesis of the study and its specific aim, it would have been more compelling if it stratified patients by level of eGFR (i.e., >45, <60, and >60 mL/min/1.73 m²) to assess the spectrum of blood pressure lowering across stages of kidney disease as was done with canagliflozin (6). This would have required substantially more

subjects, however. Additionally, the study could have been powered for a blood pressure end point; however, this class of drugs is not approved as a blood pressure–lowering agent.

The exact mechanism of blood pressure lowering with these agents is not completely understood; however, proposed mechanisms are listed in Table 1. Blood pressure reduction by these agents is assumed to be related to its osmotic diuretic effect, although they have very slight natriuretic effects much less than low-dose thiazide diuretics. It is curious that if osmotic diuresis was the sole mechanism, then the antihypertensive effect would wane as kidney function decreases; however, this is not the case (3). Similar levels of blood pressure reduction are seen in people with eGFR of 45 mL/min/1.73 m² as those with 85 mL/min/1.73 m². Also, there is no

Table 1—Proposed mechanisms for antihypertensive action of SGLT2 inhibitors

Osmotic diuresis
Weight loss after a week or so
Mild natriuresis
Possible indirect effects on nitric oxide release secondary to reduced oxidant stress by better glycemic control*

*Observation from preliminary studies in a couple of patients.

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reported hyponatremia with these agents, suggesting their blood pressure lowering is not related to sodium loss (1). Last, while weight loss has been postulated as a contributing mechanism for blood pressure lowering, it is unlikely as the blood pressure-lowering effect is seen much earlier than any significant weight loss (3).

An investigation by Cherney et al. (7) studied patients with type 1 diabetes treated with empagliflozin 25 mg daily for 8 weeks. This study demonstrated significant blood pressure reductions and there was an assessment of changes in arterial stiffness and sympathetic nervous system activity. The subjects had measurements of radial artery and carotid waveforms, augmentation index, heart rate, and aortic pulse wave velocity. During euglycemic clamp conditions, there was a significant reduction in systolic blood pressure, radial augmentation index, carotid augmentation index, and aortic augmentation index in subjects treated with empagliflozin 25 mg daily. The augmentation index is commonly accepted as a measure of central aortic pressure enhancement by a reflected pulse wave and is a predictor of adverse cardiovascular events. It is defined as a ratio calculated from the blood pressure waveform; the greater the augmentation, the greater the arterial stiffness. There were no significant changes in the measurements of sympathetic nervous system activity.

SGLT2 inhibitors are a unique class of medications that not only improve glucose control but also have a demonstrated impact on reducing cardiovascular risk factors (i.e., high blood pressure and excessive weight). The long-term effects of these agents on blood pressure and overall cardiovascular and kidney disease are being assessed in ongoing cardiovascular and chronic kidney disease outcome trials that should be completed within the next 3 to 5 years.

The data from the study by Tikkanen et al. (4), taken together with previous studies of other agents in the class, demonstrate that SGLT2 inhibitors not only lower glucose but also have other salutary effects (i.e., blood pressure-lowering and weight-reducing effects). Moreover, they are safe as they are not associated with hypoglycemia except when used with sulfonyleureas or insulin. Future studies should perhaps focus on use of these agents as antihypertensive agents and hence a potential substitute for diuretics to avoid adverse metabolic effects in patients with diabetes. It is important to treat all associated components of the abnormal metabolic profile in patients with diabetes to optimally reduce the risk of cardiovascular disease. These agents are a powerful new tool for the diabetologist and clinician in general. They should be considered for use in patients with type 2 diabetes with hypertension, where indicated. Patients should be warned of the

potential side effects including polyuria, orthostatic hypotension, hypoglycemia, and genital infections. Patients on diuretics may need dose reductions to avoid some of these adverse effects.

Duality of Interest. G.L.B. is a consultant for AbbVie, Janssen, Boehringer Ingelheim/Lilly, Medtronic, Relypsa, Bayer, Novartis, and GlaxoSmithKline. No other potential conflicts of interest relevant to this article were reported.

References

1. Plosker GL. Canagliflozin: a review of its use in patients with type 2 diabetes mellitus. *Drugs* 2014;74:807–824
2. Plosker GL. Dapagliflozin: a review of its use in patients with type 2 diabetes. *Drugs* 2014;74:2191–2209
3. Oliva RV, Bakris GL. Blood pressure effects of sodium-glucose co-transport 2 (SGLT2) inhibitors. *J Am Soc Hypertens* 2014;8:330–339
4. Tikkanen I, Narko K, Zeller C, et al.; EMPA-REG BP Investigators. Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension. *Diabetes Care* 2015;38:420–428
5. McManus RJ, Caulfield M, Williams B; National Institute for Health and Clinical Excellence. NICE hypertension guideline 2011: evidence based evolution. *BMJ* 2012;344:e181
6. Yamout H, Perkovic V, Davies M, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes and stage 3 nephropathy. *Am J Nephrol* 2014;40:64–74
7. Cherney DZ, Perkins BA, Soleymanlou N, et al. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. *Cardiovasc Diabetol* 2014;13:28