INDIAN SOCIETY OF HYPERTENSION
World Hypertension League
CURRENT MEDICAL CONCEPTS
HTNJ
CrossMark

Review Article

Sodium-glucose Co-transporter 2 Inhibitors and Blood Pressure Reduction among Patients with Diabetes, Cardiovascular Disease, Chronic Kidney Disease

Jefferson L. Triozzi[1], Sankar D. Navaneethan[2], L. Parker Gregg[2], Addison A. Taylor[1]

[1]Department of Medicine, Baylor College of Medicine, Houston, Texas, United States. [2]Department of Nephrology, Baylor College of Medicine, Houston, Texas, United States

Abstract

The remarkable reductions in cardiovascular events and the blunting of the decline in kidney function observed in clinical trials of patients with diabetes, cardiovascular disease, and/or chronic kidney disease treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors are accompanied by a modest reduction in systolic (2–5 mm Hg) and diastolic (0.5–2.5 mm Hg) blood pressure. Blood pressure reduction occurs across a spectrum of blood pressure elevations, possibly including those with resistant hypertension, many of whom are already taking a variety of antihypertensive drugs. SGLT2 inhibitors appear to lower blood pressure to a greater extent in hypertensive Black and Asian individuals than White individuals. Mechanisms by which SGLT2 inhibitors likely contribute to blood pressure reduction and other cardiovascular and kidney benefits involve a variety of neuroendocrine, kidney, and hemodynamic systems. Some of these components include osmotic diuresis and natriuresis with a consequent decline in both interstitial and intravascular volume, weight reduction, a reduction in arterial stiffness, cardiac ventricular remodeling, loss of salt sensitivity, a decrease in uric acid concentrations, and a complicated interaction with the renin-angiotensin-aldosterone and sympathetic nervous systems. This review will provide an update on mechanisms purported to contribute to blood pressure reduction and the cardiovascular and kidney benefits observed with this the class of agents.

Key words: Blood pressure, cardiovascular disease, chronic kidney disease, diabetes, SGLT2 inhibitors

Introduction

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are primarily indicated as antihyperglycemic agents for patients with diabetes mellitus, with substantial data supporting cardiovascular and kidney benefits.[1] SGLT2 inhibitors also reduce blood pressure regardless of the presence of diabetes. Hypertension is an established risk factor cardiovascular disease, kidney disease, and death.[2] There are numerous mechanisms by which SGLT2 inhibitors affect blood pressure, but their potential use as antihypertensive agents is unclear.[3] In this review, we summarize pharmacological and clinical data that inform the role of SGLT2 inhibitors in blood pressure reduction among patients with and without diabetes.

A Review of Clinical Trials

Blood pressure reduction appears to be a class effect of SGLT2 inhibitors [Table 1].[4] A meta-analysis of SGLT2 inhibitor trials based on seated clinic blood pressure measurements demonstrated a mean systolic and diastolic blood pressure reduction of 3.8 mg Hg and 1.6 mm Hg, respectively.[5] Similarly, a meta-analysis of SGLT2 inhibitor trials based on 24-h ambulatory blood pressure monitoring demonstrated a mean systolic and diastolic blood pressure reduction of 3.8 mm Hg and 1.8 mm Hg, respectively.[6] In initial cardiovascular outcome trials, SGLT2 inhibitors improved cardiovascular outcomes and reduced blood pressure among patients with diabetes. In subsequent dedicated chronic kidney disease and heart failure

Address for correspondence:
Addison A. Taylor, Department of Medicine, Baylor College of Medicine, Houston, Taxes, United States.
E-mail: ataylor@bcm.edu

Received: 30-04-2021; Accepted: 04-05-2021
doi: 10.15713/ins.johtn.0219

Increasent Nature Science Publishers

Table 1: Selected randomized controlled trials of SGLT2 inhibitors among patients with diabetes, cardiovascular disease, and chronic kidney disease

Trial	Intervention	*n*=	Baseline DM (%)	Baseline blood pressure (mean±SD mm Hg)	Baseline antihypertensive agents reported (%)	Blood pressure observations
EMPA-REG OUTCOME	empagliflozin	7,020	100	SBP 135.3±16.9, DBP 76.6±9.7	RAAS inhibitor 81.0, BB 65.2, MRA 6.5, diuretic 43.7, CCB 32.6, renin inhibitor 0.6, Other 8.2	Mean SBP/DBP at the end of study was 131.3/75.1 mm Hg. There was no significant effect on the primary outcome/death from CV causes among subgroups with SBP ≥140 versus <140 mmHg or DBP ≥90 versus <90 mm Hg
CANVAS	canagliflozin	10,142	100	SBP 136.6±15.8, DBP 77.7±9.7	RAAS inhibitor 80, BB 53.5, diuretic 44.3	Significant reduction in blood pressure versus placebo of SBP 3.93 mm Hg (4.30–3.56) and DBP 1.39 mm Hg (1.61–1.17), *P*<0.001 (mean difference [95% CI]). There was no significant effect on the primary outcome among subgroups with SBP ≥140 versus <140 mmHg or DBP ≥90 versus <90 mm Hg
DECLARE-TIMI 58	dapagliflozin	17,160	100	SBP 135.1±15.3	RAAS inhibitor 81.3, BB 52.4, diuretic 40.6	Significant reduction in blood pressure versus placebo of SBP 2.7 mm Hg (2.4–3.0) and DBP 0.7 mm Hg (0.6–0.9) (least squared mean difference [95% CI])
DAPA-HF	dapagliflozin	4,744	41.8	SBP 122.0±16.3	RAAS inhibitor 84.5, ARB + neprolysin inhibitor 10.5, BB 96, MRA 71.5, diuretic 93.4	Significant reduction in blood pressure versus placebo from baseline to 2 weeks of SBP 2.54 mm Hg (3.33–1.76), *P*<0.001 (placebo-corrected reduction [95% CI])
EMPEROR-REDUCED	empagliflozin	3,730	49.8	SBP 122.6±15.9	RAAS inhibitor 70.5, ARB + neprolysin inhibitor 18.3, BB 94.7, MRA 70.1	Non-significant reduction in blood pressure versus placebo of SBP 0.7 mm Hg (1.8–0.4) [absolute reduction (95% CI)].
CREDENCE	canagliflozin	4,401	100	SBP 140.0±15.6, DBP 78.3±9.4	RAAS inhibitor 99.9, BB 40.2, diuretic 46.7	Significant reduction in blood pressure versus placebo of SBP 3.30 mm Hg (2.73–3.87) and DBP 0.95 mm Hg (0.61–1.28) (mean difference [95% CI])
DAPA-CKD	dapagliflozin	4,304	67.5	SBP 136.7±17.5, DBP 77.5±10.7	RAAS inhibitor 98.4, diuretic 43.1	The primary outcome was statistically significant among both subgroups with SBP ≤130 mm Hg 0.44 (0.31–0.63) and >130 mm Hg 0.68 (0.56–0.84) (hazard ratio [95% CI])

DM: Diabetes mellitus, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SD: Standard deviation, CI: Confidence interval, RAAS: Renin-angiotensin-aldosterone system, ARB: Angiotensin receptor blockers, BB: Beta-blocker, CCB: Calcium channel blocker, MRA: Mineralocorticoid receptor antagonist

trials, SGLT2 inhibitors improved outcomes and reduced blood pressure among patients with and without diabetes. The extent to which blood pressure reduction accounts for cardiovascular and kidney benefits is unclear. A large meta-analysis of 40 clinical trials was statistically underpowered to identify an association between blood pressure reduction and cardiovascular outcomes.[7]

Cardiovascular outcome trials

Cardiovascular outcome trials enrolled patients with Type 2 diabetes and varying baseline cardiovascular disease, kidney disease, and hypertension. EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) demonstrated a reduction of the primary composite cardiovascular outcome of cardiovascular death, non-fatal myocardial infarction, or nonfatal stroke among patients with established atherosclerotic cardiovascular disease.[8] Approximately 95% of patients enrolled in EMPA-REG OUTCOME received baseline antihypertensive therapy. Although EMPA-REG OUTCOME did not include a pre-specified blood pressure endpoint, a post-trail analysis demonstrated an decrease of systolic blood pressure by approximately 3–5 mm Hg regardless of baseline systolic blood pressure or the presence of heart failure.[9] CANVAS (Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes) and DECLARE-TIMI 58 (Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes) enrolled patients with type 2 diabetes and either established atherosclerotic cardiovascular disease or high cardiovascular risk, including hypertension.[10,11] CANVAS demonstrated a reduction in the primary composite cardiovascular outcome and a mean reduction in systolic and diastolic blood pressure versus placebo of 3.93 mm Hg and 1.39 mm Hg, respectively. DECLARE-TIMI

58 demonstrated cardiovascular safety without a reduction in the primary composite cardiovascular outcome (although a significant reduction in hospitalization for heart failure was observed) and a mean reduction in systolic and diastolic blood pressure versus placebo was 2.7 and 0.7 mm Hg, respectively.

Heart failure

The primary composite cardiovascular outcomes in the cardiovascular outcome trials were driven by reduced heart failure events. In the subsequent heart failure trials, a marginal blood pressure reduction was observed. EMPEROR-REDUCED (Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure) similarly demonstrated a reduction in cardiovascular death or hospitalization for heart failure regardless of baseline diabetes.[12] EMPEROR-REDUCED reported a 0.7 mm Hg difference in systolic blood pressure reduction versus placebo that was not statistically significant. DAPA-HF (Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction) enrolled patients with and without diabetes and there was a significant reduction in systolic blood pressure versus placebo at 2 weeks in a secondary analysis.[13] Blood pressure reduction is associated with reduced risk of acute decompensated heart failure but low blood pressure is associated with increased mortality among patients with heart failure.[14] Both trials excluded patients with baseline hypotension. SGLT2 inhibitor-mediated blood pressure reduction may reflect broader hemodynamic changes related to improved heart failure outcomes.

Chronic kidney disease

Promising secondary microvascular outcomes in the cardiovascular outcome trials prompted dedicated SGLT2 inhibitor clinical trials among patients with chronic kidney disease. It was expected that pharmacological effects of SGLT2 inhibitors would attenuate with reduced kidney function given their target of action in the proximal tubule.[15] However, SGLT2 inhibitors improved clinically meaningful kidney outcomes and reduced blood pressure among patients with advanced kidney disease. CREDENCE (Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy), a seminal kidney outcomes study, enrolled patients with type 2 diabetes, an estimated glomerular filtration rate (eGFR) 30–90 mL/min/1.73 m^2, and urine albumin to creatinine ratio >300–5000 mg/g.[16] In CREDENCE, canagliflozin reduced the primary composite kidney outcome by 33% and decreased the rate of diabetic kidney disease progression by 2.74 mL/min/1.73 m^2/year among a cohort receiving maximally titrated angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy. Mean reduction of systolic and diastolic blood pressure versus placebo was 3.30 mm Hg and 0.95 mm Hg, respectively. Similarly, DAPA-CKD (Dapagliflozin and Prevention of Adverse outcomes in Chronic Kidney Disease) investigated a primary composite kidney outcome among patients with chronic kidney disease, including one-third without diabetes. Dapagliflozin yielded a clinically and statistically significant reduction of the primary composite kidney outcome. A reduction in blood pressure was also observed, with a similar effect on patients with or without diabetes. A pooled analysis of five empagliflozin trials also demonstrated systolic blood pressure reduction with SGLT2 inhibitors in patients with advanced chronic kidney disease.[17] It was suggested that increased salt-sensitivity in patients with chronic kidney disease allows for a persistent antihypertensive effect despite reduced kidney function.[18]

Pharmacology of SGLT2 Inhibitors

The SGLT2 reabsorbs 90% of freely filtered glucose in the proximal tubule of the nephron. Glucose reabsorption in the kidney is an active process in using sodium gradients generated by the Na^+-K^+-ATPase. Thus, inhibition of sodium and glucose reabsorption in the proximal tubule produces natriuresis and glucosuria. It is speculated that SGLT2 inhibitors lead to other systemic anti-inflammatory, metabolic, and hemodynamic changes.[19] The effect of SGLT2 inhibition on blood pressure is multifactorial, but most likely involves extracellular fluid volume reduction, interaction with the renin-angiotensin-aldosterone system (RAAS), interaction with the sympathetic nervous system, and changes in vascular compliance.

Extracellular fluid volume reduction

SGLT2 inhibitors cause osmotic diuresis and reduce circulating blood volume. Natriuresis is related to direct inhibition of the sodium-glucose cotransporter and partially by inhibition of the Na^+-H^+ exchanger 3 (NHE3).[20] A pre-specified analysis of the EMPA-HEART trial (Effect of Empagliflozin on Left Ventricular Mass in Patients With Type 2 Diabetes Mellitus and Coronary Artery Disease) measured extracellular fluid volume by cardiac magnetic resonance among patients with Type 2 diabetes mellitus and coronary artery disease. This analysis indeed demonstrated a reduction in extracellular fluid volume over 24-week follow-up suggesting that SGLT2 inhibitors are effective diuretics.[21] It is unlikely that extracellular fluid volume reduction accounts entirely for blood pressure reduction. Whereas glucosuria persists throughout SGLT2 inhibitor therapy, natriuresis may attenuate over time. A placebo-controlled randomized clinical of canagliflozin measured changes in plasma volume among patients with type 2 diabetes. A modest initial increase in urine volume approximately 160 mL per 24 h decreased to approximately 50 mL per 24 h by week 12.[22] This suggests compensatory changes in the distal nephron adapt to increase sodium reabsorption following SGLT2 inhibition.

Interaction with RAAS

RAAS activation is a primary mediator of hypertension, chronic inflammation, and oxidative stress. The interaction between SGLT2 inhibition and RAAS is complex. In mice models, SGLT2 inhibition is effective for angiotensin II-mediated hypertension. Angiotensin II is a primary RAAS end-product causing vasoconstriction,

increased secretion of antidiuretic hormone and aldosterone, and intraglomerular hypertension. In addition, observational data suggest that the uricosuric effect of SGLT2 inhibition mitigates RAAS activation and improves cardiovascular and kidney events.[23] On the other hand, SGLT2 inhibition may initially activate the RAAS as a response to osmotic diuresis and changes in extracellular fluid volume. Some studies have demonstrated increased markers of RAAS related to SGLT2 inhibition. In a preclinical model, SGLT2 inhibitor increased intrarenal and systemic plasma renin activity in mice with and without diabetes, although no changes in renal angiotensin II were observed.[24]

Interaction with the sympathetic nervous system

Sympathetic nervous system activation both contributes to hypertension and exacerbates endothelial dysfunction and the progression of cardiovascular and kidney disease.[25] SGLT2 inhibition may exert cardiovascular events and blood pressure reduction through inhibition of sympathetic nervous activity.[24] Sympathetic nervous system activation both contributes to hypertension and exacerbates endothelial dysfunction and the progression of cardiovascular and kidney disease.[25] There are interactions between sympathetic nervous system activity and SGLT2 expression in the kidney. A sympatholytic effect of SGLT2 inhibitors may explain the phenomenon of blood pressure reduction without a change in pulse rate. In a preclinical model, norepinephrine increased SGLT2 expression in the proximal tubule *in vitro*. Treatment with dapagliflozin reduced markers of sympathetic nervous system activation in both the heart and the kidney.[26] In a follow-up study of hypertensive mice, the authors suggest "cross-talk" between SGLT2 inhibitor expression and renal innervation.[27]

Arterial stiffness

SGLT2 inhibitors may increase vascular compliance. Arterial stiffness may contribute to afterload and cardiac workload. Renal vascular stiffness may also be related to kidney injury. In a small randomized controlled trial among patients with Type 1 diabetes and normal blood pressure, empagliflozin was associated with reduced indices of arterial stiffness. The authors reported no difference in heart rate variability or sympathetic nervous activity measured through adrenergic biomarkers.[28] A smaller *post hoc* analysis including two cohorts from five empagliflozin trials assessed markers of arterial stiffness and vascular resistance in addition to blood pressure.[29] A separate study found no change in arterial stiffness using cardio-ankle vascular index.[30] It is unclear how indices of arterial stiffness used in these studies are themselves influenced by blood pressure.

Interpreting the Role of SGLT2 Inhibitors in Blood Pressure Reduction

SGLT2 inhibitor-mediated blood pressure reduction is observed across clinical trials, irrespective of baseline hemoglobin A1c, kidney function, or cardiovascular disease. The role of SGLT2 inhibitors in blood pressure reduction will also depend on baseline blood pressure, circadian blood pressure patterns, race, and combination with other antihypertensive agents.

Baseline blood pressure

Patients with higher baseline blood pressure have a greater response to antihypertensive agents and greater cardiovascular disease risk reduction. Thus far, SGLT2 inhibitor-mediated blood pressure reduction data are derived from patients with well-controlled baseline blood pressure. In large cardiovascular and kidney trials, for example, baseline systolic blood pressure averages around 135 mm Hg. More studies of patients with difficult-to-control or resistant hypertension are needed to clarify the role of SGLT2 inhibitors as antihypertensive agents and whether there are differences in the effect of individual SGLT2 inhibitors on blood pressure. Based on their potential mechanisms of action, SGLT2 inhibitors may be useful in resistant hypertension, which is often characterized by RAAS activation, sodium and fluid retention, and impaired renal-pressure natriuresis.[31] A *post hoc* analysis of EMPA-REG OUTCOME identified 22% of enrolled patients taking three or more antihypertensive agents at baseline, which the authors labeled presumed resistant hypertension. In this study, empagliflozin demonstrated significant reduction in blood pressure throughout the follow-up period regardless of presence or absence of apparent resistant hypertension.[32]

Circadian patterns

Although SGLT2 inhibitors demonstrate a greater absolute blood pressure reduction during the day than at night, their efficacy in treating nocturnal hypertension may reduce cardiovascular disease risk. Nocturnal hypertension and non-dipper nocturnal blood pressure patterns are associated with increased cardiovascular risk.[32] In pre-clinical models, SGLT2 inhibition restored rats with nocturnal hypertension to a more physiologic dipper profile.[34] The SACRA Study (24 h Blood Pressure–Lowering Effect of a Sodium-Glucose Cotransporter 2 Inhibitor in Patients With Diabetes and Uncontrolled Nocturnal Hypertension) similarly reported nighttime blood pressure reduction among patients taking empagliflozin with adequate glycemic control but poorly controlled nocturnal hypertension.[35] In the EMPA-HEART trial, empagliflozin demonstrated a significant reduction in ambulatory blood pressure both during the day and night. In addition to blood pressure reduction, empagliflozin was associated with reduced left ventricular mass, a predictor of adverse cardiovascular events and heart failure.[36]

Race

Race is thought to be an important factor in hypertension pathogenesis, response to antihypertensive agents, and clinical outcomes. Pooled ambulatory blood pressure monitoring data suggest a greater antihypertensive response to SGLT2 inhibitors among Black and Asian than White individuals.[37] Thus far, the

reasons behind these differences are largely speculative and based on information we have gleaned from other antihypertensive agents. A salt-sensitive, low-renin hypertension phenotype is prevalent in Asian and Black populations. Consequently, these patients may have greater sensitivity to antihypertensive agents that reduce both sodium and volume, like SGLT2 inhibitors. Racial predispositions toward nocturnal hypertension may also affect blood pressure response to SGLT2 inhibitors. Morning hypertension is more common in non-Western populations, and SGLT2 inhibitor studies among Asian patients with nocturnal hypertension are promising. Notably, Black patients were largely underrepresented in seminal SGLT2 inhibitor clinical trials. In a smaller study with 166 participants, Ferdinand *et al*. investigated the efficacy of empagliflozin compared to placebo among Black patients with Type 2 diabetes and hypertension.[38] The study included a primary glycemic control endpoint and multiple secondary blood pressure endpoints but no cardiovascular outcomes were reported. Mean ambulatory systolic blood pressure was 146 mm Hg and one-third was receiving three or more antihypertensive medications. Empagliflozin significantly reduced 24-h ambulatory systolic blood pressure versus placebo at 12 and 24 weeks by 8.39 mm Hg and 5.21 mm Hg, respectively. Enrolling diverse study populations in future clinical trials are imperative to better understand the role of SGLT2 inhibition in blood pressure reduction.

Combination with other antihypertensive agents

SGLT2 inhibitor study populations have prevalent use of other antihypertensive agents, particularly RAAS blockade. SGLT2 inhibition may have synergism with RAAS blockade, a cornerstone of management for patients with diabetes, chronic kidney disease, or heart failure. On the single-nephron level, SGLT2 inhibitors and RAAS inhibitors have complementary effects on glomerular hypertension. SGLT2 inhibitors primarily decrease glomerular pressures through afferent arteriolar vasoconstriction, and RAAS blockers decrease glomerular pressures through efferent arteriolar vasodilation. Both agents cause anticipated hemodynamically mediated drops in eGFR in addition to reduced blood pressure. Whereas a 30% change in eGFR is permitted after initiating ACE inhibitors or ARBs, it is uncertain what degree of eGFR is tolerable with SGLT2 inhibitors in combination with RAAS blockade. A meta-analysis of eight randomized controlled trials, specific analysis of SGLT2 inhibition and RAAS inhibition in combination was not associated with increased adverse events related to kidney function when compared to either placebo or RAAS inhibition.[39] SGLT2 inhibitors may have similar antihypertensive efficacy as thiazide diuretics.[40] However, SGLT2 inhibitors may demonstrate less blood pressure reduction when used in combination with diuretics. Weber *et al*. reported that the antihypertensive effect was greater among patients receiving beta-blockade or calcium channel-blockade at baseline than those receiving a thiazide diuretic.[41] In this trial, patients were already receiving RAAS inhibitors in addition to at least one other agent.

Safety

The most common adverse events associated with SGLT2 inhibitors are genital mycotic infections. Euglycemic ketoacidosis, acute kidney injury, fracture, and amputation are less common.[42] Risks associated with blood pressure reduction are rare. SGLT2 inhibitors did not increase the risk of orthostatic hypotension in an analysis of 19 randomized clinical trials.[5] In the EMPA-REG BP study (Empagliflozin Reduces Blood Pressure in Patients With Type 2 Diabetes and Hypertension), a Phase 3 study that preceded EMPA-REG OUTCOME, only one out of 825 patients experienced a drug-related hypotension complication.[43] This is surprising given the high base rate of autonomic dysfunction and predilection for orthostatic hypotension among patients with diabetes. We also note a lack of increase in heart rate with SGLT2 inhibitor-mediated blood pressure reduction, a phenomenon associated with orthostatic hypotension. Some speculate that blood pressure reduction, dehydration, and falls could increase the risk of fractures and amputations.[44] An increased risk of fracture and amputation in the CANVAS trial was ultimately not seen in follow-up studies or meta-analyses.[45] Although elderly patients may be at higher risk, a *post hoc* analysis of elderly patients from the SARCA study did not identify hypotension or other adverse events in patients ≥75 years.[46] Finally, the reduction of blood pressure and fall in extracellular fluid volume raised concern for kidney injury among susceptible patients. In general, the drop in eGFR after initiation of SGLT2 inhibitors is associated with decreased acute kidney injury, implicating a hemodynamic phenomenon rather than glomerular, or tubular injury.[47]

Conclusion

SGLT2 inhibitors modestly lower blood pressure in patients with and without diabetes, but at this time, there is insubstantial evidence to support the use of SGLT2 inhibitors as an antihypertensive agent *per se*. Blood pressure reduction alone cannot account for the multiple cardiovascular and kidney benefits observed in SGLT2 inhibitor trials. SGLT2 inhibitors likely have multiple systemic mechanisms of action, including impact on extracellular volume, RAAS, the sympathetic nervous system, and arterial stiffness, which may all contribute to antihypertensive effect. Regardless of specific antihypertensive mechanisms or the degree of the antihypertensive effect, clinical data supporting substantial reductions in cardiovascular disease, kidney disease, and death among patients with and without diabetes strongly supports the use of SGLT2 inhibitors for many patients.

References

1. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, *et al*. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in Type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;393:31-9.

2. Messerli FH, Williams B, Ritz E. Essential hypertension. Lancet 2007;370:591-603.
3. Verma S, McMurray JJ. SGLT2 inhibitors and mechanisms of cardiovascular benefit: A state-of-the-art review. Diabetologia 2018;61:2108-17.
4. Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in Type 2 diabetes mellitus: Systematic review and network meta-analysis. Diabetes Obes Metab 2016;18:783-94.
5. Baker WL, Smyth LR, Riche DM, Bourret EM, Chamberlin KW, White WB. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: A systematic review and meta-analysis. J Am Soc Hypertens 2014;8:262-75.e9.
6. Baker WL, Buckley LF, Kelly MS, Bucheit JD, Parod ED, Brown R, *et al*. Effects of sodium-glucose cotransporter 2 inhibitors on 24-hour ambulatory blood pressure: A systematic review and meta-analysis. J Am Heart Assoc 2017;6:005686.
7. Benham JL, Booth JE, Sigal RJ, Daskalopoulou SS, Leung AA, Rabi DM. Systematic review and meta-analysis: SGLT2 inhibitors, blood pressure and cardiovascular outcomes. IJC Hear Vasc 2021;33:100725.
8. Steiner S. Empagliflozin, cardiovascular outcomes, and mortality in Type 2 diabetes. Zeitschrift Fur Gefassmedizin 2016;13:17-8.
9. Böhm M, Fitchett D, Ofstad AP, Brueckmann M, Kaspers S, George JT, *et al*. Heart failure and renal outcomes according to baseline and achieved blood pressure in patients with Type 2 diabetes: Results from EMPA-REG OUTCOME. J Hypertens 2020;38:1829-40.
10. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, *et al*. Canagliflozin and cardiovascular and renal events in Type 2 diabetes. N Engl J Med 2017;377:644-57.
11. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, *et al*. Dapagliflozin and cardiovascular outcomes in Type 2 diabetes. N Engl J Med 2019;380:347-57.
12. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, *et al*. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383:1413-24.
13. Serenelli M, Böhm M, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, *et al*. Effect of dapagliflozin according to baseline systolic blood pressure in the dapagliflozin and prevention of adverse outcomes in heart failure trial (DAPA-HF). Eur Heart J 2020;41:3402-18.
14. Upadhya B, Rocco M, Lewis CE, Oparil S, Lovato LC, Cushman WC, *et al*. Effect of intensive blood pressure treatment on heart failure events in the systolic blood pressure reduction intervention trial. Circ Heart Fail 2017;10:e003613.
15. Wilcox CS. Antihypertensive and renal mechanisms of SGLT2 (sodium-glucose linked transporter 2) inhibitors. Hypertension 2020;75:894-901.
16. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJ, Charytan DM, *et al*. Canagliflozin and renal outcomes in Type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295-306.
17. Cherney DZ, Cooper ME, Tikkanen I, Pfarr E, Johansen OE, Woerle HJ, *et al*. Pooled analysis of Phase III trials indicate contrasting influences of renal function on blood pressure, body weight, and HbA1c reductions with empagliflozin. Kidney Int 2018;93:231-44.
18. Meng L, Fu B, Zhang T, Han Z, Yang M. Salt sensitivity of blood pressure in non-dialysis patients with chronic kidney disease. Ren Fail 2014;36:345-50.
19. Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: Cardiovascular and kidney effects, potential mechanisms, and clinical applications. Circulation 2016;134:752-72.
20. Onishi A, Fu Y, Patel R, Darshi M, Crespo-Masip M, Huang W, *et al*. A role for tubular Na+/H+ exchanger NHE3 in the natriuretic effect of the SGLT2 inhibitor empagliflozin. Am J Physiol 2020;319:F712-28.
21. Mason T, Coelho-Filho OR, Verma S, Chowdhury B, Zuo F, Quan A, *et al*. Empagliflozin reduces myocardial extracellular volume in patients with Type 2 diabetes and coronary artery disease. JACC Cardiovasc Imaging 2021;S1936-878X(20)30939-6.
22. Sha S, Polidori D, Heise T, Natarajan J, Farrell K, Wang SS, *et al*. Effect of the sodium glucose co-transporter 2 inhibitor canagliflozin on plasma volume in patients with Type 2 diabetes mellitus. Diabetes Obes Metab 2014;16:1087-95.
23. Lytvyn Y, Škrtić M, Yang GK, Yip PM, Perkins BA, Cherney DZ. Glycosuria-mediated urinary uric acid excretion in patients with uncomplicated Type 1 diabetes mellitus. Am J Physiol 2015;308:F77-83.
24. Scheen AJ. Effect of SGLT2 inhibitors on the sympathetic nervous system and blood pressure. Curr Cardiol Rep 2019;21:1-10.
25. Gamboa A, Figueroa R, Paranjape SY, Farley G, Diedrich A, Biaggioni I. Autonomic blockade reverses endothelial dysfunction in obesity-associated hypertension. Hypertension 2016;68:1004-10.
26. Matthews VB, Elliot RH, Rudnicka C, Hricova J, Herat L, Schlaich MP. Role of the sympathetic nervous system in regulation of the sodium glucose cotransporter 2. J Hypertens 2017;35:2059-68.
27. Herat LY, Magno AL, Rudnicka C, Hricova J, Carnagarin R, Ward NC, *et al*. SGLT2 inhibitor-induced sympathoinhibition: A novel mechanism for cardiorenal protection. JACC Basic Transl Sci 2020;5:169-79.
28. Cherney DZ, Perkins BA, Soleymanlou N, Har R, Fagan N, Johansen OE, *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.
29. Chilton R, Tikkanen I, Cannon CP, Crowe S, Woerle HJ, Broedl UC, *et al*. Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with Type 2 diabetes. Diabetes Obes Metab 2015;17:1180-93.
30. Kario K, Okada K, Murata M, Suzuki D, Yamagiwa K, Abe Y, *et al*. Effects of luseogliflozin on arterial properties in patients with Type 2 diabetes mellitus: The multicenter, exploratory LUSCAR study. J Clin Hypertens 2020;22:1585-93.
31. Hwang AY, Dietrich E, Pepine CJ, Smith SM. Resistant hypertension: Mechanisms and treatment. Curr Hypertens Rep 2017;19:1-11.
32. Ferreira JP, Fitchett D, Ofstad AP, Kraus BJ, Wanner C, Zwiener I, *et al*. Empagliflozin for patients with presumed resistant hypertension: A post hoc analysis of the EMPA-REG OUTCOME trial. Am J Hypertens 2020;33:1092-101.
33. Kario K. Hypertension: Benefits of strict blood-pressure lowering in hypertension. Nat Rev Cardiol 2016;13:125-6.
34. Takeshige Y, Fujisawa Y, Rahman A, Kittikulsuth W, Nakano D, Mori H, *et al*. A sodium-glucose co-transporter 2 inhibitor empagliflozin prevents abnormality of circadian rhythm of blood pressure in salt-treated obese rats. Hypertens Res 2016;39:415-22.

35. Kario K, Okada K, Kato M, Nishizawa M, Yoshida T, Asano T, *et al*. Twenty-four-hour blood pressure-lowering effect of a sodium-glucose cotransporter 2 inhibitor in patients with diabetes and uncontrolled nocturnal hypertension: Results from the randomized, placebo-controlled SACRA study. Circulation 2019;139:2089-97.
36. Verma S, Mazer CD, Yan AT, Mason T, Garg V, Teoh H, *et al*. Effect of empagliflozin on left ventricular mass in patients with Type 2 diabetes mellitus and coronary artery disease: The EMPA-HEART cardiolink-6 randomized clinical trial. Circulation 2019;140:1693-702.
37. Kario K, Ferdinand KC, O'Keefe JH. Control of 24-hour blood pressure with SGLT2 inhibitors to prevent cardiovascular disease. Prog Cardiovasc Dis 2020;63:249-62.
38. Ferdinand KC, Izzo JL, Lee J, Meng L, George J, Salsali A, *et al*. Antihyperglycemic and blood pressure effects of empagliflozin in black patients with Type 2 diabetes mellitus and hypertension. Circulation 2019;139:2098-109.
39. Cai Y, Shi W, Xu G. The efficacy and safety of SGLT2 inhibitors combined with ACEI/ARBs in the treatment of Type 2 diabetes mellitus: A meta-analysis of randomized controlled studies. Expert Opin Drug Saf 2020;19:1497-504.
40. Georgianos PI, Agarwal R. Ambulatory blood pressure reduction with SGLT-2 inhibitors: Dose-response meta-analysis and comparative evaluation with low-dose hydrochlorothiazide. Diabetes Care 2019;42:693-700.
41. Weber MA, Mansfield TA, Cain VA, Iqbal N, Parikh S, Ptaszynska A. Blood pressure and glycaemic effects of dapagliflozin versus placebo in patients with Type 2 diabetes on combination antihypertensive therapy: A randomised, double-blind, placebo-controlled, phase 3 study. Lancet Diabetes Endocrinol 2016;4:211-20.
42. Lupsa BC, Inzucchi SE. Use of SGLT2 inhibitors in Type 2 diabetes: Weighing the risks and benefits. Diabetologia 2018;61:2118-25.
43. Tikkanen I, Narko K, Zeller C, Green A, Salsali A, Broedl UC, *et al*. Empagliflozin reduces blood pressure in patients with Type 2 diabetes and hypertension. Diabetes Care 2015;38:420-8.
44. Cheng L, Li YY, Hu W, Bai F, Hao HR, Yu WN, *et al*. Risk of bone fracture associated with sodium-glucose cotransporter-2 inhibitor treatment: A meta-analysis of randomized controlled trials. Diabetes Metab 2019;45:436-45.
45. Inzucchi SE, Iliev H, Pfarr E, Zinman B. Empagliflozin and assessment of lower-limb amputations in the EMPA-REG OUTCOME trial. Diabetes Care 2018;41:e4-5.
46. Okada K, Hoshide S, Kato M, Kanegae H, Ishibashi S, Kario K. Safety and efficacy of empagliflozin in elderly Japanese patients with Type 2 diabetes mellitus: A post hoc analysis of data from the SACRA study. J Clin Hypertens 2021;23:860-9.
47. Barnett AH, Mithal A, Manassie J, Jones R, Rattunde H, Woerle HJ, *et al*. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with Type 2 diabetes and chronic kidney disease: A randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2014;2:369-84.

How to cite this article: Triozzi JL, Navaneethan SD, Gregg LP, Taylor AA. Sodium-glucose Co-transporter 2 Inhibitors and Blood Pressure Reduction among Patients with Diabetes, Cardiovascular Disease, Chronic Kidney Disease. Hypertens 2021;7(1): 39-45.

Source of support: S.D.N. is supported by research funding from the Department of Veterans Affairs Health Services Research & Development (1I01HX002917-01A1) and a grant from the National Institutes of Health (NIDDK-R01DK101500). This work was also supported in part by the Center for Innovations grant (CIN 13-413), Michael E. DeBakey VA Medical Center, Houston, TX. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or Veterans Administration, **Conflicts of interest:** S.D.N., L.P.G., and A.A.T. are employees of the US Department of Veterans Affairs. The interpretation and reporting of these data are the responsibility of the authors and in no way should be viewed as official policy or interpretation of the Department of Veterans Affairs or the US government. S.D.N. reports personal fees from Bayer, personal fees from Boehringer-Ingelheim, personal fees from REATA, personal fees from Tricida, and grants from Keryx, outside the submitted work. All remaining authors have nothing to disclose.