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ANTIHYPERTENSIVE AGENTS: MECHANISMS OF DRUG ACTION (MICHAEL E. ERNST, SECTION EDITOR)

Blood Pressure Lowering and Sodium-Glucose Co-transporter 2 Inhibitors (SGLT2is): More Than Osmotic Diuresis

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Abstract

Purpose of Review This is an update of data regarding changes in blood pressure using sodium-glucose co-transporter 2 inhibitors (SGLT2i) for the treatment of diabetes. The mechanism of blood pressure lowering by SGLT2i was thought to be due to their osmotic diuretic effects. New data, however, has emerged from meta-analyses and studies of people with impaired kidney function demonstrating similar or greater magnitudes of blood pressure reduction in the absence of significant glycosuria. Potential additional mechanisms are proposed and reviewed.

Recent Findings Two separate meta-analyses in over 10,000 participants combined demonstrate an average of 4/2 mmHg reduction in blood pressure by SGLT2i. This includes consistency between measurements of in-office and ambulatory blood pressure monitoring. This reduction extends to decreases in nocturnal blood pressure of 2.6 mmHg systolic pressure. These reductions in blood pressure by SGLT2i are also present when added to ongoing treatment with ACE inhibitors or ARBs. In one study, dapagliflozin, when added to a regimen of a renin-angiotensin-aldosterone system (RAAS) antagonist and a diuretic, further lowered in-office systolic pressure by 2.4 mmHg. In contrast, when prescribed to those on a RAAS antagonist plus a calcium channel blocker or RAAS antagonist plus a beta blocker, systolic pressure decreased 5.4 mmHg. Lastly, post hoc analyses of major cardiovascular outcome trials across the spectrum of estimated glomerular filtration rates from 30 to 80 ml/min/1.73 m2 demonstrated similar magnitudes of BP reduction in spite of far less reduction in glucosuria among those with advanced kidney disease. Moreover, recent data implicate the potential for increased ketones associated with SGLT2i contributing to blood pressure lowering in advanced-stage kidney disease.

Summary SGLT2i are well established to lower blood pressure. Their mechanism appears to be multifactorial and has a hemodynamic as well as metabolic component contributing to this reduction.

Keywords Hypertension · Diabetes · Sodium-glucose transporter

Introduction

Since 2000, a raft of antihyperglycemic therapies for type 2 diabetes mellitus (DM2) has entered the market. Such agents, from ultra-long-acting insulin preparations to glucagon-like peptide 1 (GLP-1) and dipeptidyl peptidase-4 (DPP-4) inhibitors, while new, are not novel as they are mechanistically similar to historical classes such as biguanides, sulfonylureas, thiazolidinediones, and meglitinides [1]. In contradistinction, the recent introduction of sodium-glucose co-transporter 2 inhibitors (SGLT2is) has ushered in a new era of pharmacologic agents, a class diverging from the targeting of the historical trinity of enhancing beta-cell activity, insulin sensitivity, and tissue glucose uptake and embracing the renal axis of glucose homeostasis [2]. These agents are not only singular in their mechanism of action but also their extra-glycemic (pleiotropic) effects on reducing cardiovascular risk and chronic kidney disease (CKD) progression.

This article is part of the Topical Collection on *Antihypertensive Agents: Mechanisms of Drug Action*

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Effects on Blood Pressure Lowering

As a class, meta-analyses have consistently shown SGLT2is to provide sustained reductions in both systolic and diastolic blood pressure (BP) whether measured by in-office or ambulatory blood pressure monitoring (ABPM). In a meta-analysis of 8100 individuals with diabetes abstracted from 21 randomized, placebo-controlled trials, treatment with empagliflozin, canagliflozin, or dapagliflozin for up to 1 year produced a 3.8/1.4 mmHg decline in-office-measured BP [3]. A separate meta-analysis of 2100 people with diabetes drawn from 6 randomized, placebo-controlled trials studied for up to 12 weeks found reductions in BP of 3.8/1.8 mmHg when measured by 24-h ABPM. Moreover, reductions in daytime pressure were greater than those realized overnight (4.3 vs. 2.6 mmHg systolic). Of note, other studies have consistently and reproducibly demonstrated nocturnal drops in BP [4, 5•]. No association between baseline values and the magnitude of BP reduction was noted in either study; a dose-response relationship vis-à-vis antihypertensive effect was also not detected [3, 6]. In sum, the magnitude of antihypertensive effect appears to be consonant across agents and posology [5•]. Only head-to-head trials with BP-specific endpoints will allow for definitive conclusions to be drawn.

Of consequence, the data has been abstracted from trials whose primary outcome was that of glycemic control. While changes in BP have since come to represent an endpoint of interest, the participant's intra-trial antihypertensive regimen was not prespecified. This is noteworthy because the antihypertensive magnitude of SGLT2is appears to vary as a function of the subject's concomitant antihypertensive regimen. For example, when dapagliflozin was added to a regimen of a renin-angiotensin-aldosterone system (RAAS) antagonist and a diuretic, in-office systolic pressure fell by 2.4 mmHg. In contrast, when prescribed to those on a RAAS antagonist plus a calcium channel blocker or RAAS antagonist plus a beta blocker, systolic pressure decreased by 5.4 mmHg [7•].

Mechanism of BP Lowering Effect

At present, there is no unifying theory as to the mechanism by which SGLT2is lower BP among those without and with CKD. Nascent enthusiasm for a comprehensive mechanism explained by the class's diuretic and weight-reducing effects has been tempered by conflicting trial data. Hypotheses espousing favorable changes in vascular resistance or the neurohormonal network have been inconclusive. Current lines of inquisition suggest the ketogenic properties of SGLT2is may help explain the reduced rates of heart failure and antihypertensive effects independent of the level of kidney function [8•, 9].

Early theories and evidence championed an osmotic and natriuretic mechanism. This hypothesis was not only an extension of historical theories but had a strong physiologic basis [10]. However, studies supporting this conjecture were performed in populations with normal kidney function, i.e., estimated glomerular filtration rates (eGFR) well above 60 mL/min/1.73m^2, thereby limiting its broad applicability [11–13]. Among those with preserved kidney function, the osmotic diuretic effect of glucosuria (with some element of natriuresis) can partially account for the antihypertensive effects of these agents. The results of a randomized, placebo-controlled, double-blind trial of 75 hypertensive type 2 diabetics without kidney disease support this argument. After 12 weeks of either 10 mg (full dose) dapagliflozin or 25 mg hydrochlorothiazide daily, 24-h ambulatory BP fell by 3.3- and 6.6-mmHg systolic, respectively. Weight and renal function declined in both arms; plasma renin and aldosterone levels rose. The authors posit that the diuretic-like properties of dapagliflozin induce a volume-contracted state with favorable effects on weight and hemodynamic status. The heightened levels of renin and aldosterone reflect a compensatory response to this decrease in effective circulating volume. Of note, changes in serum sodium and potassium levels were not provided [14]. A separate double-blind, placebo-controlled trial of dapagliflozin specifically tested the magnitude of its antihypertensive effects when used as the third agent in patients for both glycemic and BP control. The researchers found that dapagliflozin 10 mg lowered in-office systolic BP by 4.3 mmHg, but when used in combination with another antihypertensive, its antihypertensive effects were more pronounced when the initial antihypertensive regimen did not include a diuretic. The authors suggest this data supports the role of SGLT2is as diuretic-like agents capable of reducing BP among those who have volume-mediated hypertensive [7•].

Further support for this antihypertensive volume argument is drawn from the manufacturers of canagliflozin who caution that it "causes intravascular volume contraction." "Symptomatic hypotension can occur in elderly patients as well as patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system." This suggests a diuretic-like effect given that older people and those on RAAS blockade are particularly prone to hypotension as a result of volume depletion [15].

BP Lowering Effects in CKD

Unfortunately, more recent evidence suggests the "osmotic diuresis" paradigm to be overly simplistic. If SGLT2is are considered a subclass of diuretics, then they too should provoke hypokalemia, hypomagnesemia, and hyperuricemia [16]. Instead, aggregated data from four randomized, placebo-controlled trials comprising 2300 patients with type 2 diabetes exposed to canagliflozin for 26 weeks found hyperkalemia and hypermagnesemia to be the defining electrolyte abnormalities [17]. Moreover, a subsequent

Table 1 Effect of empagliflozin on metabolic and hemodynamic parameters by CKD stage (adapted from ref. 21). Note the differences in HBA1c and systolic BP lowering (italics) between stages 1 and 3

CKD stage	eGFR (mL/min/1.73m^2)	HbA1c, % (95% CI)	Weight, kg (95% CI)	Systolic BP, mmHg (95% CI)
1	*≥ 90*	*− 0.84 (− 0.95 to − 0.72)*	− 1.9 (− 2.3 to − 1.5)	*− 3.2 (− 4.9 to − 1.5)*
2	60–90	− 0.60 (− 0.70 to − 0.51)	− 2.0 (− 2.3 to − 1.7)	− 4.0 (− 5.4 to − 2.6)
3	*30–60*	*− 0.38 (− 0.52 to − 0.24)*	− 1.4 (− 1.8 to − 0.9)	*− 5.5 (− 7.6 to − 3.4)*

publication found SGLT2i therapy to be associated with lower, rather than higher, levels of serum uric acid [18]. Finally, the compensatory increase in sympathetic tone accompanying diuretic therapy is absent in SGLT2i-treated patients [19].

The premise of osmotic diuresis and sodium loss is predicated on intact kidney function. Thus, declines in BP should not be observed in people who have minimal reductions in blood glucose (e.g., those with an eGFR well below 60 mL/min/1.73m^2). Moreover, trials including individuals with CKD have confirmed lesser improvements in glycosylated hemoglobin (HgA1c) concentration than those experienced by individuals with an eGFR greater than 60 mL/min/1.73m^2 [20]. Surprisingly, despite a lack of improvement in glycemic parameters, even among participants with advanced diabetic nephropathy (eGFR as low as 23 mL/min/1.73m^2), BP declined to a similar degree as those with preserved kidney function [21••]. These results would serve to reject the prevailing theory that the osmotic and natriuretic properties of SGLT2is are solely responsible for BP reduction [22].

These observations have been reproduced with all three SGLT2is indicating a class effect, predominantly among those with stage 3 CKD. In a post hoc subgroup analysis of patients with diabetic nephropathy from several studies, those with eGFR of 40–45 mL/min/1.73m^2 demonstrated similar levels of BP reduction with minimal improvements in glycemic control [20]. After exposing 270 patients with diabetic nephropathy (mean eGFR 40 mL/min/1.73m^2) to canagliflozin or placebo for 26 weeks, weight and in-office systolic BP decreased as expected (by 1.4–1.6 kg and 5.8–6.1/1.2–2.1 mmHg, respectively) among SGLT2i-treated participants [23]. However, HgA1c decreased by only 0.3%, approximately half that observed in patients with diabetes but without CKD [24].

After a post hoc stratification of empagliflozin-treated patients by CKD stage, Cherney and colleagues documented consistent changes in weight and BP across CKD stages 1–4 (Table 1). The quartile with the lowest eGFR had the smallest improvement in blood sugar [21••]. While intriguing, the above observations were generated in a post hoc fashion lessening their value. The soon to be released CREDENCE trial should, therefore, carry considerable weight in helping delineate the magnitude of BP reduction in people with stage 3 CKD. It will prospectively evaluate the effects of canagliflozin on CKD progression and cardiovascular mortality in a cohort with advanced kidney disease, i.e., eGFR down to 30 mL/min/1.73m^2 [25•].

Ancillary Factors Contributing to BP Reduction

Given that the osmotic diuresis hypothesis does not fully explain BP lowering across the spectrum of kidney function, alternate pathways have been proposed. Weight loss, while a clear mediator, can account for no more than 40% of the BP effect of SGLT2is [26, 27]. Based on our current understanding, neurohormonal pathways play a lesser role in SGLT2i BP modulation. An 8-week course of empagliflozin in patients with type 1 diabetes failed to lower hormonal constituents of the RAAS or effect nitric oxide [28, 29]. While neurogenic elements contribute to essential hypertension and diuretics result in an increase in sympathetic tone, parallel findings in SGLT2i-treated patients are absent. For example, empagliflozin failed to raise heart rate, muscle sympathetic nerve activity (e.g., burst frequency or incidence), or serum catecholamines despite reductions in BP and weight [19, 30].

Conclusions

We propose that an integrated effect of both hemodynamic and metabolic changes accounts for the spectrum of BP reduction. The ketogenic hypothesis is of considerable value, not only to explain the benefit of heart failure risk but also benefits to the vasculature and kidneys. SGLT2is are associated with low-level ketosis and can in the right setting cause ketoacidosis. This may partially explain the class's antihypertensive effect [8•, 31]. While states of prolonged fasting have been known to mobilize free fatty acids and promote hepatic ketone production in order to satisfy the body's metabolic requirements, basic science experiments suggest ketone bodies, specifically β-hydroxybutyrate, may contribute to BP homeostasis [9]. In a Dahl salt-sensitive rat model of hypertension, sodium administration elevated BP and was associated with a reduction in ketones. However, when β-hydroxybutyrate was co-administered with a salt-rich diet, BP fell within hours [32••]. The recognition of this alternate role of β-hydroxybutyrate could help explain the hypotensive effects of SGLT2is in the absence of urinary glucose wasting and needs to be properly studied.

Compliance with Ethical Standards

Conflict of Interest Dr. Bakris reports grants from Janssen, Bayer, Vascular Dynamics, and NovoNordisk, and personal fees from Merck, outside the submitted work. Dr. Sternlicht declares no conflicts of interest relevant to this manuscript.

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