

## NEWER THERAPEUTIC INSIGHTS

# Sodium-Glucose Co-transporter 2 Inhibitor: A Perspective on Cardiovascular Risk Reduction in Type 2 Diabetes Mellitus

<sup>1</sup>Gary E Sander, <sup>2</sup>Camilo Fernandez, <sup>3</sup>Philip J Kadowitz, <sup>4</sup>Thomas D Giles

## ABSTRACT

**Aim:** To provide a perspective on the effect of Sodium-glucose co-transporter 2 (SGLT2) inhibitors on cardiovascular (CV) risk reduction in type 2 diabetes mellitus (DM) patients.

**Background:** Sodium-glucose co-transporter 2 inhibitors have been introduced as hypoglycemic agents for the treatment of type 2 diabetes by the unique mechanism of inhibiting the SGLT2 protein-mediated uptake of glucose by the kidney, producing an osmotic diuresis and some degree of natriuresis. The Food and Drug Administration (FDA) has thus far approved three drugs of this class for the treatment of type 2 diabetes – empagliflozin, canagliflozin, and dapagliflozin.

**Review results:** During the clinical trials performed to establish efficacy in diabetes control, these drugs were found to exert a range of beneficial effects beyond glucose lowering. The most interesting of these has been a reduction in systolic blood pressure (SBP) by an average of 3 to 5 mm Hg and diastolic blood pressure (DBP) of 2 to 3 mm Hg. A larger and even more unexpected discovery was that empagliflozin reduced the primary outcome of death from CV causes and nonfatal myocardial infarctions and strokes from 12.1% in the placebo group to 10.5% in an empagliflozin group in a clinical trial enrolling high CV risk patients. Overall, there was a 30 to 40% reduction in heart failure hospitalizations (HFHs) and all-cause deaths, with the event reduction appearing within the first 6 months and persisting to the trial conclusion.

**Conclusion:** The mechanisms for the aforementioned impressive beneficial events remain unclear, but may involve improvements in such parameters as blood pressure, vascular volume, myocardial glucose availability, reduced arterial vascular stiffness, and improvements in autonomic nervous system function. At this time, all approved SGLT2 inhibitors appear similar in pharmacological actions. Clinical trials are now in progress – or under development – that will further explore the CV actions and outcomes of these drugs.

**Clinical significance:** This review may aid to unify the existing knowledge on SGLT2 inhibitors and CV risk reduction, and set the path for further research endeavors to clarify mechanisms of action associated with additional CV benefits.

**Keywords:** Blood pressure, Cardiovascular outcomes, Cardiovascular risk, Hypertension, SGLT2 inhibitors, Type 2 diabetes mellitus.

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## INTRODUCTION

Sodium-glucose co-transporters (SGLTs) are important mediators of glucose uptake across apical cell membranes. In the kidney SGLT2, and to a lesser extent SGLT1, account for more than 90% and nearly 3% respectively, of glucose reabsorption from the glomerular ultrafiltrate. Sodium-glucose co-transporters regulation has been reported to occur via cyclic adenosine monophosphate/protein kinase A, protein kinase C, glucagon-like peptide 2, insulin, leptin, signal transducer and activator of transcription-3 (STAT3), phosphoinositide-3 kinase (PI3K)/Akt, mitogen-activated protein kinases (MAPKs), nuclear factor-kappaB (NF-kappaB), with-no-K[Lys] kinases/STE20/SPS1-related proline/alanine-rich kinase (Wnk/SPAK) and regulatory solute carrier protein 1 (RS1) pathways.<sup>1</sup> Inhibitors of SGLT2 have been developed for the treatment of type 2 diabetes mellitus (DM) but have efficacy in type 1 diabetes as well.

Sodium-glucose co-transporter 2 may have increased the importance in DM. In cultured human exfoliated proximal tubular epithelial cells from diabetic patients, hyperglycemia increases proximal tubular reabsorption due to upregulation of SGLT2 expression, leading to secondary increases in sodium-glucose co-transport.<sup>2</sup> Sodium-glucose co-transporter 2 inhibition has been reported to reduce the hyperfiltration that results from SGLT2 upregulation in type 1 diabetic patients.<sup>3</sup> Thus, SGLT2 inhibition may target a specific molecular abnormality.

The SGLT2 inhibitors derive from the phlorizin group of compounds found in plants. They induce glycosuria by inhibition of glucose uptake in the kidney, and thus produce an osmotic diuresis; they may also cause a mild natriuresis. During clinical trials designed to demonstrate

<sup>1,3</sup>Professor, <sup>2</sup>Post-Doctoral Fellow, <sup>4</sup>Adjunct Professor

<sup>1,4</sup>Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana, USA

<sup>2</sup>Department of Medicine, Tulane University School of Medicine New Orleans, Louisiana, USA; HeartGEN Institute, Boston Massachusetts, USA

<sup>3</sup>Department of Pharmacology, Tulane University School of Medicine, New Orleans, Louisiana, USA

**Corresponding Author:** Thomas D Giles, Adjunct Professor Department of Medicine, Tulane University School of Medicine New Orleans, Louisiana, USA, e-mail: tgiles4@cox.net

the efficacy of these drugs in the treatment of diabetes, a number of additional benefits were observed. As will be discussed, these drugs have unexpectedly been found to reduce blood pressure (BP) and confer cardiovascular (CV) protection by mechanisms still not specifically defined. The risk factors beyond glucose reduction that have been shown to be modulated positively by SGLT2 inhibitors include BP, weight, visceral adiposity, hyperinsulinemia arterial stiffness, albuminuria, uric acid levels, and oxidative stress.<sup>4</sup>

These clinical findings suggest that it is now time to recognize that SGLT2 inhibitors may well be more than just another class of drugs to decrease blood glucose in patients with type 2 DM. Rather, the SGLT2 inhibitor class may well be recognized as drugs that lower BP and confer CV protection. Dapagliflozin, canagliflozin, and empagliflozin have been approved by the Food and Drug Administration (FDA). The other SGLT2 inhibitors still in clinical trials include ertugliflozin, ipragliflozin, remogliflozin, tofogliflozin. Table 1 lists some differences in the approved drugs: Luseogliflozin and sotagliflozin.

We will summarize clinical trial results that have demonstrated improvements in BP and overall CV event rates and then outline possible mechanisms by which SGLT2 inhibitors produce these effects, as well as describe the ongoing and planned clinical trials designed to further validate these early results.

## BLOOD PRESSURE REDUCTION BY SGLT2 INHIBITORS

The SGLT2 inhibitors have been shown in multiple reports to lower clinic systolic blood pressure (SBP) and diastolic blood pressure (DBP) in patients with type 2 DM. In particular, the reduction in SBP is more impressive. The effect on circadian patterns of BP measured by ambulatory blood pressure monitoring (ABPM) has also been established. As a general statement, the SGLT2 inhibitors reduce office SBP by 3 to 5 mm Hg and DBP by 2 to 3 mm Hg across all class members,<sup>5</sup> although greater reductions of 4 to 10 mm Hg have been described.<sup>6</sup> Corresponding clinically meaningful, significant BP lowering effects have been confirmed using 24-hour ABPM. These SGLT2 inhibitors reduce BP irrespective of the type of background antihypertensive medication.

**Table 1:** Characteristics of SGLT2 inhibitors

|                              | <i>Canagliflozin</i> | <i>Dapagliflozin</i> | <i>Empagliflozin</i> |
|------------------------------|----------------------|----------------------|----------------------|
| SGLT2 selectivity Over SGLT1 | 1:414                | 1:1,200              | >1:2,500             |
| Posology (tablets)           | 100 and 300 mg       | 5 and 10 mg          | 10 and 25 mg         |
| Half-life                    | 12–15 hour           | 17 hour              | 10–19 hour           |
| Absorption (peak)            | 2.8–4 hour           | 1.5 hour             | 1.5 hour             |

They also reduce BP independent of renal function; patients with glomerular filtration rates (eGFR) of 45 mL/minute/1.73,<sup>2</sup> and similarly to those with eGFR of 85 mL/minute/1.73.<sup>7</sup>

In perhaps the earliest large-scale comparison of SGLT2 inhibitors with placebo in 45 studies (n = 11,232), SGLT2 inhibitors reduced SBP (RR, –4.45 mm Hg, 95% confidence interval (CI), –5.73 to –3.18 mm Hg).<sup>8</sup> In a subsequent meta-analysis of 27 randomized controlled trials with 12,960 participants, SGLT2 inhibitors significantly reduced both SBP (weighted mean difference, –4.0 mm Hg; 95% CI, –4.4 to –3.5) and DBP (weighted mean difference, –1.6 mm Hg; 95% CI, –1.9 to –1.3) from baseline.<sup>9</sup> The SGLTs had no significant effect on the incidence of orthostatic hypotension (p > 0.05). In the most recent meta-analysis that included 38 studies with 23,997 subjects, it was reported that at highest doses, canagliflozin 300 mg reduced SBP by 1 to 3 mm Hg relative to dapagliflozin and empagliflozin.<sup>10</sup> Only canagliflozin had a significant dose/response relationship with SBP (p = 0.008).<sup>9</sup> Ertugliflozin is another SGLT2 inhibitor still undergoing preclinical testing. One-hundred and ninety four patients with type 2 DM and hypertension were administered ertugliflozin, hydrochlorothiazide, or placebo for 4 weeks and monitored by using ABPM.<sup>11</sup> Significant decreases in placebo-corrected 24-hour mean SBP (–3.0 to –4.0 mm Hg) were recorded for all doses of ertugliflozin vs an average of –3.2 mm Hg for hydrochlorothiazide. Daytime, but not night-time SBP, was consistently reduced. No notable changes in plasma renin activity or urinary aldosterone were reported.

## CARDIOVASCULAR OUTCOME TRIALS

The empagliflozin treatment in the EMPA-REG (empagliflozin, CV outcomes, and mortality in type 2 diabetes) OUTCOME trial was the first to examine and report major CV events (MACE) outcomes with an SGLT2 inhibitor.<sup>12</sup> A total of 7,020 high CV risk patients were treated for a median observation time of 3.1 years. The primary outcome of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke (MACE) occurred in 490 of 4,687 patients (10.5%) in the pooled empagliflozin group and in 282 of 2,333 patients (12.1%) in the placebo group (RR, 0.86; 95% CI; 0.74 to 0.99; p = 0.04 for superiority). Cardiovascular mortality (RR, 0.62, 95% CI, 0.49–0.77, p < 0.001) and all-cause mortality were reduced, but there was no significant benefit for overall MACE (RR, 0.86, 95% CI, 0.70–1.09, p = 0.22) and stroke (RR, 1.24, 95% CI, 0.92–1.67, p = 0.22). There were no significant between-group differences in the rates of myocardial infarction or stroke, but in the empagliflozin group there were significantly lower rates of death from CV causes (RR reduction

38, 3.7 vs 5.9% in the placebo group), hospitalization for heart failure (RR reduction 35, 2.7 and 4.1% respectively), and death from any cause (RR reduction 32, 5.7 and 8.3% respectively). There was no significant between-group difference in the key secondary outcome ( $p=0.08$  for superiority). However, there was a highly impressive 30 to 40% reductions in heart failure hospitalization (HFH) and CV and all-cause deaths in patients treated with empagliflozin. A very important observation was that event reduction occurred within the first 3 to 6 months, and was sustained up to the end of the trial.

Following the EMPA-REG OUTCOMES publication, an evaluation by meta-analysis of MACE reductions with SGLT2 inhibitors was reported that included data from six regulatory submissions (37,525 participants) and 57 published trials (33,385 participants), which provided data from testing with seven different SGLT2 inhibitors.<sup>13</sup> The SGLT2 inhibitors protected against the risk of MACE (RR, 0.84, 95% CI, 0.75–0.95;  $p=0.006$ ), CV death (RR 0.63, 95% CI, 0.51–0.77;  $p<0.0001$ ), heart failure (RR 0.65, 95% CI, 0.50–0.85;  $p=0.002$ ), and death from any cause (RR, 0.71, 95% CI, 0.61–0.83;  $p<0.0001$ ). No clear effect was apparent for nonfatal myocardial infarction (RR, 0.88, 95% CI, 0.72–1.07;  $p=0.18$ ) or angina (RR, 0.95, 95% CI, 0.73–1.23;  $p=0.70$ ), but an adverse effect for nonfatal stroke (RR, 1.30, 95% CI, 1.00–1.68;  $p=0.049$ ) was reported. There was no clear evidence that the individual drugs had different effects on MACE [all by I(2) statistic  $<43\%$ ]. Thus results appear consistent among multiple trials.

As impressive as the EMPA-REG OUTCOME and the meta-analyses findings are, a word of caution may be necessary, as outlined in a very thoughtful analysis of these results.<sup>14</sup> Most trials of hypoglycemic agents have failed to show dramatic reductions in CV outcomes, and these findings are novel and unexpected. A significant concern is a lack of understanding of the mechanism

driving the large reduction in CV events and total mortality in the absence of significant reductions in myocardial infarction and stroke. The rapid reduction in death rate within 6 months cannot be easily explained by the reported effects upon BP, weight, glucose, and uric acid, suggesting that the mechanism of event reduction remains uncertain.

## MECHANISMS FOR BENEFICIAL EFFECTS IN HYPERTENSION

As outlined earlier, the SGLT2 inhibitors have been reported to exert a number of significant that are potentially beneficial; however, the exact mechanism(s) by which SGLT2 inhibitors lower BP remains unclear. There has been speculation that it is due to a decrease in intravascular volume secondary to the osmotic diuresis produced by the drug. Systolic BP is dependent on both pulse volume and vascular stiffness (impedance to ejection). We have suggested that the transition to hypertension involves two pathways.<sup>15</sup> One pathway is initiated by increased activity of the sympathetic nervous system (SNS) and decreased activity of the parasympathetic nervous system (PNS). The other pathway shows an increase in vascular stiffness (Fig. 1). We also further suggested that the metabolic syndrome is a marker of the transitional phenotype of prehypertension. As described below, the SGLT2 inhibitor mechanisms for BP reduction may exert beneficial effects through multiple sites in these pathways.

### Autonomic Changes

Although BP is lowered by the SGLT2 inhibitors, heart rate and heart rate variability (HRV) are not changed. Thus, there must be either a decrease in SNS activity, an increase in PNS activity, or both. Also, there could be an effect on the baroreceptor as well as the SA node.

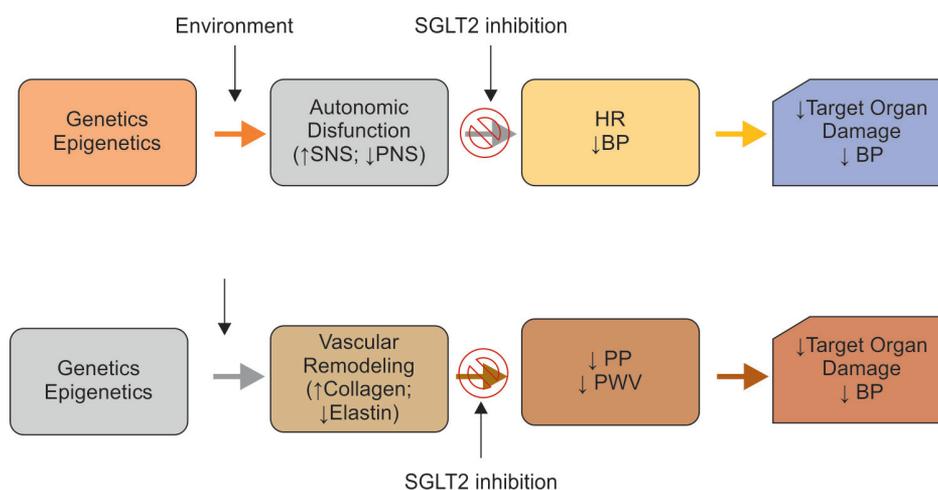


Fig. 1: Proposed pathway on the role of SGLT2 inhibition in the reduction of cardiovascular disease risk

## Decrease in Intravascular Volume

Blood pressure may possibly be lowered by a decrease in intravascular volume secondary to the osmotic diuresis produced by the glycosuria. However, if osmotic diuresis was the sole mechanism, then the BP lowering effect should wane as kidney function deteriorates, but this is not what has been reported.<sup>7</sup> Furthermore, orthostatic changes in BP following treatment with the SGLT2 inhibitors have not been prominent.

## Vascular Stiffness

Arterial stiffness is caused by salt as well as advanced glycation end-products, which result from nonenzymatic protein glycation to form irreversible cross-links between long-lived proteins, such as collagen (Zieman et al<sup>16</sup> and Safar et al<sup>17</sup>). In response to 8 weeks of empagliflozin administration during clamped euglycemia in normotensive type 1 diabetic subjects, SBP ( $111 \pm 9$  to  $109 \pm 9$  mm Hg,  $p=0.02$ ) and augmentation indices at the radial ( $-52\% \pm 16$  to  $-57\% \pm 17$ ,  $p=0.0001$ ), carotid ( $+1.3 \pm 1.7$  to  $-5.7 \pm 17.0\%$ ,  $p<0.0001$ ), and aortic positions ( $+0.1 \pm 13.4$  to  $-6.2 \pm 14.3\%$ ,  $p<0.0001$ ) declined significantly. Similar effects on arterial stiffness were observed during clamped hyperglycemia without changing BP under this condition. Carotid-radial pulse wave velocity decreased significantly under both glycemic conditions ( $p \leq 0.0001$ ), while declines in carotid-femoral pulse wave velocity were only significant during clamped hyperglycemia ( $5.7 \pm 1.1$  to  $5.2 \pm 0.9$  m/s,  $p=0.0017$ ). Heart rate variability, plasma noradrenaline, and plasma adrenaline remained unchanged under both clamped euglycemic and hyperglycemic conditions. The authors have suggested that underlying mechanisms may relate to pleiotropic actions of SGLT2 inhibition, including glucose lowering, antihypertensive, diuretic, and weight reduction effects, as well as unrelated pathways, such as modulation of vasoactive substances and decreases in anti-inflammatory mediators and oxidative stress.<sup>18</sup> New approaches to the treatment of hypertension are directed toward the possibility of reducing BP by altering collagen, elastin, and other components of connective tissue that participate in the process of arterial stiffening; such changes would reduce pulse pressure by reducing arterial stiffening.<sup>19</sup> The SGLT2 inhibitors may also improve endothelial function or vascular architecture – collagen, elastin, advanced glycation end-products, and other components of connective tissue that contribute to material stiffening.<sup>4</sup>

## Urinary Sodium, Weight Loss, Glucose, and Insulin Sensitivity

The SGLT2 may also have a favorable effect on vascular stiffness by increasing urinary sodium excretion. As we

have mentioned, increased sodium intake is associated with an increase in vascular stiffness.<sup>16</sup> Dapagliflozin treatment induces glucosuria and markedly lowers fasting plasma glucose. Insulin-mediated tissue glucose disposal increases by approximately 18% after 2 weeks of dapagliflozin treatment, while placebo-treated subjects had no change in insulin sensitivity. Surprisingly, following dapagliflozin treatment, endogenous glucose production increases substantially and is accompanied by an increase in fasting plasma glucagon concentration.<sup>20</sup> Dapagliflozin-induced SGLT2 inhibition for 12 weeks is further associated with reductions in 24-hour BP, body weight, glomerular filtration rate and possibly plasma volume, suggesting that dapagliflozin may have a diuretic-like capacity to lower BP in addition to beneficial effects on glycemic control.<sup>21</sup>

## Uric Acid, Lipids

Favorable changes occur in uric acid levels following treatment with SGLT2 inhibitors. Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) have been reported to increase and triglycerides to decrease, but the HDL-C/LDL-C ratio remains unchanged.<sup>8</sup> However, the changes are not substantial enough and occur too early to explain the benefit.

## Glucagon

The SGLT2 inhibitors have been reported to indirectly increase glucagon.<sup>20,22,23</sup> Physiological levels of glucagon produce an insulin-like increase in cardiac glucose utilization *in vivo* through activation of phosphoinositide 3-kinase (PI3K).<sup>24</sup> This has been hypothesized to explain cardiac outcomes, particularly in heart failure. However, SGLT2 has not yet been demonstrated in human hearts; SGLT1 has been reported to interfere with ischemia-reperfusion injury.<sup>25</sup>

## MECHANISMS FOR BENEFICIAL EFFECTS IN HEART FAILURE

As described earlier, empagliflozin treatment in the EMPA-OUTCOMES trial significantly lowered rates of death from CV causes relative to placebo (RR reduction 38, 3.7, *vs* 5.9%), hospitalization for heart failure (RR reduction 35, 2.7 *vs* 4.1), and death from any cause (RR reduction 32, 5.7 *vs* 8.3) but not the rate of myocardial infarction or stroke. The 30 to 40% reduction in HFH was unexpected and very impressive and deserves further comment. In addition to the possible role of increased glucagon in increasing myocardial glucose utilization discussed earlier, it has been suggested that benefit may result from positive effects on renal sodium and glucose handling, leading to both diuresis and improvements in

diabetes-related maladaptive renal arteriolar responses, effects likely to be beneficial in patients with clinical or subclinical cardiac dysfunction. The net result of these processes seems to be an improvement in cardiac systolic and diastolic function and, thereby, a lower risk of HFH and sudden cardiac death.<sup>26</sup>

### PLANNED CLINICAL TRIALS

Several CV outcome trials are in progress and will yield valuable information regarding the clinical use of the SGLT2 inhibitors.

#### ErtuglifloxinCVOT

ErtuglifloxinCVOT [efficacy and safety of ertugliflozin (MK-8835/PF-04971729) with sitagliptin in the treatment of participants with type 2 DM with inadequate glycemic control on diet and exercise] (MK-8835-017) has been completed but not yet reported.

#### CANDLE

CANDLE (safety of canagliflozin in diabetic patients with chronic heart failure: Randomized, noninferiority trial) (UMIN000017669) will further assess SGLT2 inhibitor effects on heart failure outcomes.<sup>27</sup> This trial will test the safety and noninferiority of canagliflozin compared with glimepiride in patients with type 2 DM and chronic heart failure. A total of 250 patients with type 2 diabetes who are drug-naïve or taking any antidiabetic agents and suffering from chronic heart failure with a New York Heart Association classification I to III will be randomized centrally into either canagliflozin or glimepiride groups, stratified by age (<65, ≥65 year), HbA1c level (<6.5, ≥6.5%), and left ventricular ejection fraction (<40, ≥40%). The primary endpoint is the percentage change from baseline in NT-proBNP after 24 weeks of treatment. The key secondary endpoints after 24 weeks of treatment are the change from baseline in glycemic control, blood pressure, body weight, lipid profile, quality of life score related to heart failure, and cardiac and renal function.

#### DECLARE-TIMI58

The DECLARE-TIMI58 (Dapagliflozin on the Incidence of Cardiovascular Events Multicenter Trial) (NCT01730534) will enroll 17,276 subjects to determine if dapagliflozin when added to a patients current antidiabetes therapy is effective in reducing MACE when compared with placebo; planned completion date is April 2019 (<https://clinicaltrials.gov/ct2/show/NCT01730534>).

### CONCLUSION

The SGLT2 inhibitors are proving to be effective drugs in diabetes management, but with added advantages

in BP reduction and overall CV risk reduction. This is particularly impressive with the realization that clinical trials have enrolled high CV risk patients. General enthusiasm over SGLT2 inhibitors is reflected in the current abundance of literature reports. There are now three drugs FDA approved, with at least four more in the pipeline. Thus there will be increasing interest in potential differences among these drugs, although no significant issues have separated empagliflozin, canagliflozin, and dapagliflozin. These drugs are approved only for the treatment of type 2 DM; it will prove interesting to follow treatment indications and guideline changes as they evolve. At present, it is still possible to utilize these drugs in the treatment of diabetic patients with comorbidities that can be favorably influenced by SGLT2 inhibitors to provide a “personalized” treatment regimen.

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