**Commentary**

# The Cardiovascular and Blood Pressure Effects and Safety of the SGLT2 Inhibitors

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## Abstract

The Sodium-Glucose Cotransporter2 (SGLT2) inhibitors are a novel class of drugs for the treatment of Type2 Diabetes Mellitus (T2DM), and members of this class (canaglifloxin, dapaglifloxin, and empaglifloxin) have been approved by the FDA for the treatment of T2DM. These drugs are effective by the lowering of blood glucose and HbA1c in patients with Type2 DM through inhibition of glucose reabsorption from the proximal renal tubule of the kidney. In addition, they lower Blood Pressure (BP) and body weight and have demonstrated beneficial cardiovascular effects. However, their use has been associated with several cases of leg and toe amputations and acute kidney injury according to analysis of data by the FDA. These are preliminary warnings for physicians and their use of has not been stopped for more confirmatory reports. The SGLT2 inhibitors present a significant addition to our armamentarium for the treatment of Type2 DM, since treatment with the currently available drugs is suboptimal. These promising beneficial cardiovascular and blood pressure effects have been derived from short-term clinical trials. Hopefully, the ongoing long-term clinical outcomes studies will provide the needed information about the log-term benefits and safety of these drugs.

## Introduction

Type 2 diabetes mellitus is an independent risk factor for Cardiovascular Disease (CVD) and hypertension and patients with Type2 DM has a two-to four fold risk in developing CVD than non-diabetic persons [1]. For very long time, management of Type2 DM was focused on controlling blood glucose, since hyperglycemia has been associated with increased cardiovascular risk [2,3], but aggressive blood glucose control has not produced the expected beneficial cardiovascular effects, but rather an in increase in cardiovascular complications, possibly due to metabolic or hyperglycemic memory of blood vessels [2,4-6]. However, the treatment of chronic hyperglycemia with the use of traditional antihyperglycemic drugs has not clearly shown a reduction of cardiovascular events [1]. The discovery and marketing of new drugs that lower blood glucose independently of insulin action have shown promising results in reducing Cardiovascular Disease (CVD) and Blood Pressure (BP) by recent studies [7,8]. This new class of drugs exerts their effects through inhibition of Sodium-Glucose Cotransporter2 (SGLT2) in the proximal renal tubule and interferes with glucose reabsorption [9]. The renal glucose loss leads to decease in blood glucose and energy loss leading to reduction in body weight. However, besides their promising antidiabetic and cardiovascular and BP effects, there are some warning signs of serious adverse effects investigated by the Food and Drug Administration (FDA). There are 3 SGLT2 inhibitors approved and marketed in the US, canaglifloxin, dapaglifloxin, and empaglifloxin (table 1), and their beneficial cardiovascular and blood pressure effects together with their adverse effects, will be discussed in this commentary.

### The role of kidney in glucose homeostasis

The kidney plays an important role in glucose homeostasis through glomerular glucose filtration, proximal tubule reabsorption, and endogenous glucose production. Renal gluconeogenesis localized in the proximal tubule, is particularly important for glucose homeostasis during times of fasting, and in type 2 diabetic subjects, the kidney produces equal amounts of glucose as the liver (40 $\mu$g *vs.* 47 $\mu$g/kg min). Under normal conditions, the kidneys filter 160-180 g of glucose/day, and it is all reabsorbed and returned to circulation. The reabsorption of glucose from the glomerular filtrate occurs through the Sodium-Glucose Co-Transporters2 (SGLT2) and the inhibition of its absorption by the SGLT2 inhibitors results in 44% decrease of filtered glucose causing a 70 g glucose loss through the kidneys leading to reduction in blood glucose levels and HbA1c independent of insulin action. This glucose loss accounts for 200-300 loss of calories/day resulting in eventual weight loss of 2-3 kg [9,10].

### Cardiovascular and blood pressure effects of SGLT 2 inhibitors

Several randomized, placebo-controlled trials have shown that the SGLT2 inhibitors exert

**Table 1:** Biological characteristics of SGLT2 inhibitors approved by FDA and EMA.

|  | Canaglifloxin | Dapaglifloxin | Empaglifloxin |
|---|---|---|---|
| FDA approval | 29 March 2013 | 8 January 2014 | 1 August 2014 |
| EMA approval | 15 November 2013 | 12 November 2012 | 22 May 2014 |
| Selectivity Ratio | | | |
| SGLT 2:SGLT1 | 414:1 | 1200:1 | 2500:1 |
| Dosology (mg) | 100 and 300 | 5 and 10 | 10 and 25 |
| Half life (hours) | 12-15 | 17 | 10-19 |
| Tmax (hours) | 2.8-4.0 | 1.5 | 1.5 |

EMA = European Medicines Agency.

significant antidiabetic as well as cardiovascular and BP protective effects. Although there are no clinical outcomes trials available at present, the beneficial effects of these agents on several cardiovascular risk factors, like DM, insulin resistance, obesity, waist circumference, abdominal and total fat, including BP, promise positive cardiovascular outcomes.

**Blood pressure effects:** The BP lowering effects of SGLT2 inhibitors have been reported by several clinical trials and reviews (table 2). In placebo-controlled studies by Weir, et al. [11], canaglifloxin given in daily doses of 100 and 300 mg in 2313 type 2 diabetic hypertensive subjects, resulted in significant reductions of both Systolic BP (SBP) and Diastolic BP (DBP). Compared with placebo, canaglifloxin reduced the SBP and DBP by 4.3 and 2.5 mmHg, respectively for the 100 mg dose, and by 5.0 and 2.4 mmHg, respectively for the 300 mg dose, compared to placebo of –0.3 and –0.9 mmHg, respectively for the total population. In patients with a baseline BP ≥140/90 mmHg, the SBP and DBP reductions for the 100 mg dose were 12.8 and 5.9 mmHg, respectively, and for the 300 mg dose were 14.2 and 9.0 mmHg, respectively. In this study, a larger number of patients reached SBP <140 mmHg (67.1%, 69.9%, and 44.8%) for canaglfloxin 100 mg, 300 mg, and placebo, respectively. The drug was well tolerated including osmotic diuresis, which was mild and did not result in dehydration or orthostatic hypotension. In another similar study by Townsend, et al. [12], canaglifloxin administration in 171 diabetic hypertensive patients produced similar BP reductions (table 2). Mean 24-hour SBP reduction by Ambulatory BP Monitoring (ABPM) was 4.5 mmHg and 3.3 mmHg after placebo subtraction, whereas the mean DBP reduction was 2.2 mmHg and 1.9 mmHg after placebo subtraction for 100 mg dose. For the 300 mg dose, the mean 24-hour SBP by ABPM was 6.2 mmHg, and 4.9 mmHg after placebo subtraction, whereas the DBP was 3.2 mmHg, and 2.9 mmHg after placebo subtraction. There was also, significant weight reduction of 1.3 kg

and 1.7 kg (placebo subtracted) for the 100 and 300 mg dose (<0.01), respectively. Reductions in BP have also, been reported by Tikkanen, et al. [13], in a randomized, double-blind, placebo-controlled study of 825 type 2 diabetic hypertensive patients. In this study, empaglifloxin 10 mg/day reduced the SBP by ABPM by 3.4 mmHg and the DBP by 1.04 mmHg, whereas the SBP and DBP were reduced by 4.2 and 1.4 mmHg, respectively for the 25 mg dose. The results were very similar with office BP measurements. There was also, significant weight reduction noted, of 1.68 and 2.16 kg (p < 0.01) for the 10 and 25 mg dose, respectively. No serious adverse events were reported. Significant BP reductions have also, been reported by Baker, et al. [14], from a large review and meta-analysis of 12,960 hypertensive type2 diabetic patients treated with different SGLT2 inhibitors [14]. In this review, the weighted mean difference from baseline in SBP was –4.0 mmHg, and the weighted mean difference in the DBP from baseline was –1.6 mmHg. In addition, significant reduction in body weight of 1.74 kg (95% CI –2.03 to –1.45) was also, noted. No serious adverse effects were reported.

**Cardiovascular effects:** Several short-term studies have reported beneficial cardiovascular effects with the SGLT2 inhibitors. One major meta-analysis of 25 trials [15], compared canaglifloxin and dapaglifloxin with placebo or an active comparator, and showed a decrease in cardiovascular death, myocardial infarction (MI), stroke, and hospitalizations for unstable angina, HR 0.89 (95% CI 0.70-1.14). These results are consistent with those reported by the FDA from the analysis of 21 phase 2b/3 trials for the approval of dapaglifloxin [16]. In this analysis, 178 cardiovascular events occurred in 9339 patients, HR 0.81 (95% CI 0.59-1.09). In addition, in a recent report by Zinman, et al. [7], 7020 type 2 diabetic subjects with established CVD were randomized to placebo or empaglifloxin 10 or 25 mg/day and were followed for a median duration of 3.1 years. The primary composite outcome of death from CVD, nonfatal MI, or nonfatal stroke, occurred in 12.1% in the placebo group and in 10.5% in the empaglifloxin, pooled analysis group, HR 0.86 (95% CI 0.74-0.90) ( p < 0.001) for non-inferiority and (p = 0.04) for superiority. Compared with placebo, empaglifloxin treatment resulted in a lower risk of CVD death (3.7% vs. 5.9%), HR 0.62 (95% CI 0.49-0.77, p< 0.001, a relative risk reduction of 38%), death from any cause 5.7% vs. 8.3% for empaglifloxin vs. placebo, HR 0.68 (95% CI 0.57-0.82, p < 0.001), and hospitalizations for heart failure, (2.7% vs. 4.1%, for empaglifloxin vs. placebo, respectively), a 35% risk reduction, HR 0.65 (95% CI 0.50-0.85, p = 0.002). However, there was no between-group difference in the secondary outcome that included the primary outcome plus hospitalization for unstable angina. There were significant reductions in HbA1c, body weight, BP, and uric acid levels, with no increase in heart rate. Also, a simulated study by Dziuba, et al. [17], using the

**Table 2:** Blood pressure effects of different SGLT2 inhibitors in patients with type2 diabetes.

| Author | Patients (n) | Age (yrs) | F-U (weeks) | SGLT2 (name) | Dose (mg) | BSBP (mmHg) | BDBP (mmHg) | ΔSBP (mmHg) | ΔDBP (mmHg) |
|---|---|---|---|---|---|---|---|---|---|
| Weir | 2313 | 56 | 26 | Cana | 100 | 129 | 78 | -4.3 | -2.5 |
|  |  |  |  | " | 300 | " | " | -5 | -2.4 |
|  |  |  |  | Pl | 0 | " | " | -0.3 | -0.6 |
| Townsend | 171 | 57 | 6 | Cana | 100 | 140 | 79 | -4.5 | -3.8 |
|  |  |  |  | " | 300 | " | " | -6.2 | -3.2 |
| Tikkanen | 825 | 60 | 12 | Empa | 10 | 132 | 75 | -3.4 | -1 |
|  |  |  |  | " | 25 | " | " | -4.2 | -1.4 |
|  |  |  |  | Pl | 0 | " | " | 0.5 | 0.3 |
| Baker | 12,960 | 55 | 4-52 | SGLT2 | Diff | 130 | 78 | -4 | -1.6 |

F-U = Follow-Up, BSBP = Baseline Systolic Blood Pressure, BDBP = Baseline Diastolic Blood Pressure, Cana = Canaglifloxin, Empa = Empaglifloxin, Diff = Different drug doses for SGLT2s.

Archimedes model, showed that dapaglifloxin 10 mg/day added to standard of care, predicted a 20-year relative risk reduction of MI, stroke, cardiovascular death, and all-cause death of 13.8%, 9.1%, 9.6%, and 5%, respectively. This projection is realistic based on the fact that these agents reduce several cardiovascular risk factors, like hyperglycemia, insulin resistance, body weight, waist circumference, visceral obesity, total body fat, and BP.

**Worrisome side effects:** Besides the beneficial antidiabetic, cardiovascular and BP effects of the SGLT2 inhibitors, there are some warning signs of possible serious side effects reported by the FDA from an interim analysis of data from several studies with the use of SGLT2 inhibitors. From the analysis of canaglifloxin studies (CANVAS), there were several cases of leg and toe amputations 7/1000 patients treated with canaglifloxin 100 mg/day and 5/1000 patients treated with canaglifloxin 300 mg/day [18]. In addition, the FDA has issued warnings about acute kidney injury with canaglifloxin and dapaglifloxin [19]. From March 2013, when canaglifloxin was approved for the treatment of type 2 DM, till October 2015, the FDA received 101 post marketing reports of acute kidney injury from the use of canaglifloxin. Since these reports were voluntary from doctors treating patients with type 2 DM, the FDA suspects that the number could be higher. Other possible side effects from the use of these drugs, is their predisposition for the development of ketoacidosis [20]. Hopefully, when the following long-term outcomes studies are completed, will provide the needed information regarding their overall benefits and risks. (a) CANVAS, NCT01032629, (b) CANVAS-R, NCT01989754, (c) CREDENCE, NCT020655791, and (d) DECLARE-TIMI 58, NCT11730534 [15].

## Discussion

The short-term clinical trials performed with the SGLT2 inhibitors have shown that they produce moderate reductions in BP and incidence of cardiovascular complications. In the future, the magnitude of the cardiovascular protection can be projected from their effects on hyperglycemia, BP, and body weight. Based on meta-analyses of clinical trials, a 0.8% reduction of HbA1c could result in 8% reduction of cardiovascular risk [21]. Likewise, a mean decrease in SBP as low as 2 mmHg, could result in 7% ischemic heart disease reduction [22]. Jointly, these effects would be expected to reduce IHD by about 15%. This reduction could be even higher since the decrease in SBP was 4-5 mmHg with the SGLT2 inhibitors (table 2). Cardiovascular benefits associated with weight reduction are likely to act through changes in BP and glucose levels or possibly through other independent mechanisms and will, possibly, add to the cardiovascular beneficial effects of SGLT2 inhibitors. While there are already available multiple pharmacological compounds to treat Type2 DM, control of hyperglycemia remains suboptimal for most, and premature death and disability affects many patients [23]. However, the potential cardiovascular benefits of the SGLT2 inhibitors must be balanced against their adverse effects. Recent interim analyses by the FDA of data from clinical trials with the SGLT2 inhibitors have shown some worrisome adverse effects. These analyses showed an increased incidence of leg and toe amputations, acute kidney injury and ketoacidosis [18-20], besides urinary tract infections and hypovolemia. SGLT2 inhibitors have shown an increase in the blood levels of phosphate through renal reabsorption leading to increase in PTH secretion and PTH blood levels. This combination leads to decrease in 1,25 dihydroxyvitamin D levels, bone resorption and

the development of bone fractures [24]. The diabetic ketoacidosis is developed when SGLT2 inhibitors are combined with insulin. In this case, the insulin dose is often decreased to avoid hypoglycemia. The lower dose of insulin may then, not be sufficient to suppress the lipolysis and the development of ketoacidosis. In addition, SGLT2 inhibitors decrease the renal secretion of ketone bodies and consequently, increase their blood levels [20]. The kidney injury could result from hypovolemia, decreased BP and the administration of drugs like angiotensin converting enzyme inhibitors, angiotensin receptor blockers or diuretics. Therefore, doctors should follow their patients very closely and watch for decreased urine output, increased levels of serum creatinine, edema of the legs and leg tenderness. If the ongoing long-term studies do not demonstrate a significant cardiovascular protection and overall safety, then the balance of benefits and risks might be viewed differently. Hopefully the ongoing long-term clinical outcomes trials will provide the needed information.

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