

## INTRODUCTION

T2DM individuals manifest a 2-3 times greater risk of CV events compared to non-diabetics, and CV mortality is responsible for ~70% of total mortality. In T2DM patients without MI, risk of CV death is similar to individuals without diabetes with prior MI.<sup>1</sup> Although hyperglycemia is a strong risk factor for microvascular complications, it is a weak risk factor for CV disease (CVD), and interventional studies focused on reducing plasma glucose in T2DM have only a minor effect to reduce CV risk.<sup>2-5</sup> Furthermore, it takes many years to observe the CV benefit associated with improved glycemic control.<sup>6,7</sup> Most T2DM individuals manifest insulin resistance (metabolic syndrome), which is associated with multiple metabolic abnormalities, i.e., obesity, dyslipidemia, and hypertension, all of which are CV risk factors. The molecular mechanisms responsible for insulin resistance directly contribute to the pathogenesis of atherosclerosis, independent of the associated metabolic abnormalities.<sup>8</sup> Thus, obese individuals without diabetes with the insulin resistance syndrome manifest a similarly increased risk for CVD compared with T2DM patients, supporting the concept that hyperglycemia is not a major determinant for the development of CVD in T2DM. Consequently, lowering blood pressure and improving lipid profile have a greater effect to reduce CVD risk than lowering plasma glucose concentration in T2DM.<sup>9</sup> Therefore, it is not surprising that antidiabetes agents, e.g. sulfonylureas,<sup>10</sup> insulin,<sup>11</sup> and DPP4-inhibitors (12-14), that lower plasma glucose without affecting other metabolic abnormalities associated with the insulin resistance syndrome have little beneficial effect to lower CVD risk in T2DM, especially when these agents are started late in the natural history of T2DM and atherosclerosis. Conversely, pioglitazone, which improves insulin sensitivity and multiple components of insulin resistance syndrome, i.e., blood pressure and lipids, exerts a favorable effect on CVD risk in T2DM individuals, independent of its glucose-lowering action.<sup>15</sup> In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive), pioglitazone lowered the main secondary end point (CV death, nonfatal MI, and stroke) by 16% ( $P = 0.025$ ).<sup>15</sup> While SGLT2-inhibitors can exert a beneficial effect on CV risk by having favorable effects on weight and blood pressure, and also other favorable hemodynamic effects.<sup>16</sup>

## MECHANISM OF ACTION OF SGLT2-INHIBITORS

Sodium-Glucose co Transporter 2 (SGLT2) inhibitors have a unique mechanism of action, which is independent

of insulin secretion and insulin action.<sup>16</sup> By inhibiting SGLT2 receptors in the renal proximal tubule, they lower plasma glucose by producing glucosuria. This unique mechanism of action, in addition to lowering plasma glucose, also corrects a number of metabolic and hemodynamic abnormalities that are risk factors for CVD. Urinary glucose loss produces negative caloric balance, resulting in a weight loss of 2–3 kg. Approximately two-thirds of the weight loss is fat, with subcutaneous and mesenteric fat loss contributing equally to the reduction in total body fat.<sup>17</sup>

SGLT2 inhibition decreases sodium reabsorption in the proximal tubule and exerts diuretic/natriuretic effect. SGLT2 inhibition also promotes urinary sodium excretion by causing osmotic diuresis. The result is a modest decrease in extracellular volume of ~5–10%. This natriuretic effect, combined with the more long-term reduction in body weight, contributes, in part, to decreases in systolic/diastolic blood pressure (4–5/1–2 mmHg), which is observed with all SGLT2 inhibitors.<sup>17</sup> Blood pressure reduction is not accompanied by an increase in heart rate and is independent of background antihypertensive therapy, suggesting that SGLT2 inhibition might reduce sympathetic tone or influence other hormonal factors that contribute to decreased blood pressure without increasing heart rate.

SGLT2 inhibitors cause a small increase in plasma LDL and HDL cholesterol and a decrease in plasma triglycerides;<sup>18</sup> LDL/HDL cholesterol ratio remains unchanged. The mechanism by which SGLT2 inhibitors cause these changes in lipid profile remains unknown. Weight loss can explain, in part, the decrease in triglycerides and increase in HDL cholesterol. The mechanism(s) responsible for increased LDL cholesterol and clinical significance of this increase requires further study.

T2DM individuals manifest moderate-to-severe insulin resistance. It has been suggested that insulin resistance per se contributes to the pathogenesis of atherosclerosis, independent of accompanying metabolic abnormalities, i.e., obesity, dyslipidemia, or hypertension. Thus, improving insulin sensitivity would be anticipated to reduce CV risk. Two weeks of dapagliflozin treatment improved whole-body insulin-mediated glucose uptake by 20–25%, measured with the euglycemic insulin clamp.<sup>16</sup>

Because of the beneficial cardiometabolic/hemodynamic profile associated with SGLT2 inhibitor therapy, one might expect that this class of drugs would lower CVD risk in

248 T2DM, independent of its glucose-lowering effect. Thus, the EMPA-REG OUTCOME study, which was required by U.S. Food and Drug Administration to establish CV safety, was powered not only for noninferiority compared to placebo but also for superiority.<sup>19</sup>

### EMPA-REG OUTCOME STUDY

The EMPA-REG OUTCOME study<sup>19</sup> is the first study to provide evidence that an antidiabetes agent decreases CV events. In 7,020 T2DM patients with established CVD, empagliflozin significantly reduced (hazard ratio [HR] 0.86 [95% CI 0.74–0.99],  $P = 0.04$ ) the primary major adverse cardiac event (MACE) outcome (CV death, nonfatal MI, nonfatal stroke). However, several outcomes were surprising. First, the primary outcome was driven by decreased CV mortality and a striking disconnect between the three MACE components was observed: 1) for nonfatal MI, HR (0.87) decreased slightly but not significantly ( $P = 0.22$ ); 2) for stroke, HR (1.24) increased slightly but not significantly ( $P = 0.22$ ); and 3), and for CV death, HR (0.62) decreased significantly by 38% ( $P = 0.001$ ). Second, unlike other interventions that reduce CV risk, e.g., lowering LDL cholesterol and blood pressure, separation between empagliflozin and placebo curves occurred very early (3 months), thus reduction in the primary outcome was evident 3 months after starting empagliflozin. Third, the beneficial effect of empagliflozin on mortality and hospitalization for heart failure widened progressively over the 3.1 years of treatment. Fourth, both empagliflozin doses (10 and 25 mg) had a similar effect on outcome measures with no dose-response relationship.

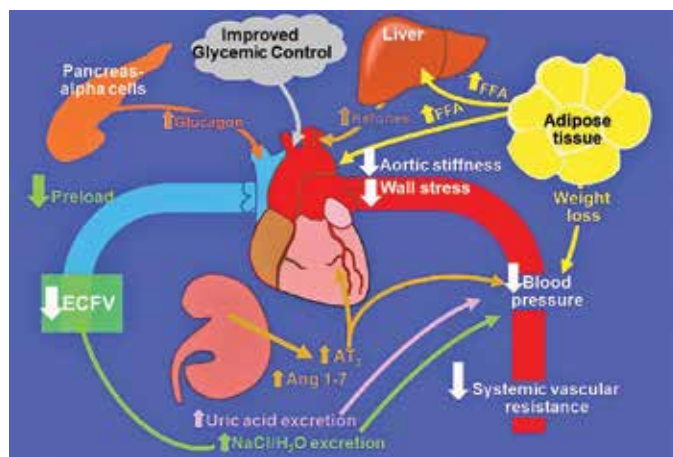
### POSSIBLE MECHANISMS FOR CARDIO-RENAL BENEFITS

1. **Metabolic Actions:** Inhibition of renal SGLT2 in T2DM exerts multiple metabolic effects (e.g., reduced HbA<sub>1c</sub>, weight loss, increase in fat oxidation, and increase in glucagon secretion) that can affect cardiac function and potentially influence CV mortality. Reduction in CV death without decrease in MI or stroke suggests that the beneficial effect of empagliflozin is to improve survival among patients experiencing a CV event rather than to slow the atherosclerotic process and prevent atherosclerotic events, i.e. MI and stroke. Reduction in CV death (5.9 to 3.6%,  $P < 0.001$ ) was observed across all diagnostic categories (sudden death, 1.6 to 1.1%; worsening heart failure, 0.8 to 0.2%; acute MI, 0.5 to 0.3%; stroke, 0.5 to 0.3%; other CV death, 2.4 to 1.6%). The latter category includes deaths not explained by other known causes. The majority of such cases result from acute MI and arrhythmias, and this category is not as diagnostically sound as the others.<sup>19</sup>
2. **Glycemic Control:** It is unlikely that empagliflozin reduced mortality in the EMPA-REG OUTCOME study by improving glucose control. First, hyperglycemia is weak risk factor for CVD. Intensive glycemic control failed to decrease CV events in the UK Prospective Diabetes Study (UKPDS),<sup>3</sup> Action to Control Cardiovascular Risk

in Diabetes (ACCORD) study,<sup>4</sup> Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) study,<sup>5</sup> and Veterans Affairs Diabetes Trial (VADT).<sup>6</sup> Second, the difference in HbA<sub>1c</sub> between empagliflozin and placebo groups was modest: 0.45% at 90 weeks and 0.28% at 204 weeks. Third, it took ~10 years in UKPDS<sup>7</sup> and VADT<sup>8</sup> to demonstrate a small (~10%), though significant, reduction in CV events by tight glycemic control, while the effect of empagliflozin on CV mortality was evident at 3 months and well established at 6 months.

3. **Weight Loss:** Glucosuria (~ 70 gm/day) produced by SGLT2 inhibitors, causes caloric loss (~ 280 Cals/day) and a decrease in body weight. In the EMPA-REG OUTCOME study, empagliflozin-treated subjects lost ~2 kg. Although possible, it is unlikely that this small amount of weight loss contributed to the reduction in CV mortality that was observed within 2–3 months after the start of empagliflozin.
4. **Effect on Blood Pressure?** Most of the participants in the EMPA-REG OUTCOME study were hypertensive and >90% received antihypertensive therapy, starting blood pressure was well controlled (135/77 mmHg). The decrease in systolic/diastolic blood pressure in the EMPA-REG OUTCOME study was ~5/2 mmHg, and was maintained throughout the 3.1-year study duration. Such a decrease in blood pressure could contribute to the reduction in CV events in the EMPA-REG OUTCOME study. However, in studies that examined the effect of blood pressure reduction on CV events, the decrease became evident only after 1 year. Moreover, lowering blood pressure generally has a greater impact on stroke reduction than on other cardiac events. In the EMPA-REG OUTCOME study there was a small, albeit non-significant, increase in nonfatal stroke. Thus, it is unlikely that the decrease in CV events in empagliflozin treated individuals can be explained solely by the decrease in brachial artery blood pressure. However, reduction in brachial artery blood pressure may underestimate central aortic pressure and provides no information about aortic stiffness, both of which are independent predictors of CV mortality and LV function. Also empagliflozin caused a 5/2 mmHg decrease in systolic/diastolic blood pressure without any increase in heart rate. This is consistent with the action of the drug to reduce sympathetic tone, which could have favorable effects on CV mortality. But further studies are needed to examine the effect of SGLT2 inhibitor therapy on the sympathetic nervous system.
5. **Effect to Slow Atherosclerosis?** Empagliflozin-treated subjects experienced ~2 kg weight loss, 2 mg% increase in HDL cholesterol, and 5 mmHg decrease in systolic blood pressure compared with placebo-treated subjects. These benefits

would be expected to slow the atherosclerotic process and reduce nonfatal CV events. However, nonfatal CV events (MI and stroke) were not affected by empagliflozin.<sup>19</sup> It is possible that the study duration was too short to observe the impact of these metabolic/hemodynamic effects on atherosclerosis-related events or that the anti-atherosclerotic effect of empagliflozin may have been obscured by the advanced atherosclerotic condition of the participants. It is also possible that the increase in plasma LDL, although small, negated some beneficial effect of empagliflozin on CV risk factors.



**Fig. 1: Schematic representation of the possible metabolic and hemodynamic mechanisms via which empagliflozin reduced CV mortality and hospitalization for heart failure in the EMPA-REG OUTCOME study.**

6. **Effect on Glucagon:** SGLT2 is expressed in pancreatic  $\alpha$ -cells and plays an important role in regulating glucagon secretion.<sup>20</sup> Dapagliflozin and empagliflozin cause a small increase in plasma glucagon in T2DM patients (Figure 1). In experimental animals, glucagon receptor activation exerts a detrimental effect on myocardial function, and glucagon infusion in humans has no effect on left ventricular (LV) function. Thus, it is unlikely that an increase in plasma glucagon contributed to reduced CV mortality or hospitalization for heart failure by empagliflozin.
7. **Effect on Uric Acid:** SGLT2 inhibitors promote uric acid excretion and reduce the plasma uric acid concentration by  $\sim 0.7\%$  mg/dL. Increased uric acid levels long have been associated with increased CVD,<sup>21</sup> but a causal link remains controversial. However, accumulating evidence in both humans and animals indicates that elevated plasma uric acid levels can cause hypertension, vascular damage, and impaired renal function. Although unlikely to explain the early reduction in CV mortality, the potential benefits of uric acid reduction to reduce blood pressure and prevent vascular damage may play a role in the progressive late separation in the mortality curves between empagliflozin and placebo. The reduction in plasma uric acid concentration also may contribute to the impressive slowing of diabetic nephropathy observed in the EMPA-REG Renal study.<sup>20</sup>
8. **Change in Plasma Electrolyte Concentration:** There is a negative sodium balance in the first 2–3 days after starting the drug without a change in plasma sodium concentration. What remains to be established is whether sodium redistribution between the intra- and extracellular compartments may have occurred as a result of the natriuretic effect of the drug. Preclinical studies also have reported heart tissue remodeling<sup>22</sup> after the administration of SGLT2 inhibitors in association with a marked reduction of interstitial fibrosis. The latter, however, requires time and is unlikely to explain the early deviation of curves for CV mortality and heart failure hospitalization. No consistent changes in plasma potassium, chloride,
9. **Shift in Fuel Metabolism:** SGLT2 inhibitors shift whole-body metabolism from glucose to fat oxidation<sup>27,28</sup> (Figure 1), and the end product of fatty acid oxidation is acetyl CoA, which either can enter the tricarboxylic acid cycle or be converted to Beta-OH Butyrate, which is a more efficient fuel (Super fuel) than fatty acids<sup>28</sup> (Figure 3). The rise in plasma ketone concentration is small (0.3–0.6 meq/L) and does not lead to ketosis. The heart avidly extracts and consumes Beta-OH Butyrate, resulting in improved cardiac muscle efficiency. This mechanism appears to be the most important and plausible in explaining the Cardio-renal benefits of empagliflozin. Further physiological and imaging studies will be required to examine whether the preferential oxidation of ketones by the heart<sup>27</sup> provides an energetic benefit to the failing myocardium.
10. **Direct Effect of the Drug:** SGLT2 is not expressed in cardiac myocytes, but SGLT1 is present in myocardial tissue. Thus partial SGLT1 inhibition by empagliflozin could affect cardiac function. However, half-maximal effective concentration for SGLT1 inhibition by empagliflozin is 8.3  $\mu\text{mol/L}$ , which is  $\sim 2,600$ -fold greater than for SGLT2, and the peak plasma empagliflozin concentration following the administration of 10 and 25 mg/day doses is only  $\sim 500$  and  $\sim 800$  nmol/L. Moreover, most of the circulating drug is bound to plasma proteins and free drug concentration is much lower. Therefore, the expected plasma-free

empagliflozin concentration in the EMPA-REG OUTCOME study would be very low, and it is very unlikely that the low circulating free empagliflozin level could have any effect on SGLT1 function. Further, if SGLT1 were inhibited by empagliflozin, myocardial function would be expected to decline, not improve. In short, direct myocardial effects by empagliflozin are unlikely to explain the beneficial effect of the drug on CV mortality.

### IS IT A CLASS EFFECT?

There are no significant differences in glucose lowering, body weight loss, and blood pressure reduction among the individual SGLT2 inhibitors. Using the Archimedes model, it has been predicted that, over a period of 20 years, patients with diabetes treated with dapagliflozin would experience a relative reduction of MI, stroke, CV death, and all-cause death. However, only well-designed CV intervention trials will provide a true answer to the question. The CANagliflozin cardioVascular Assessment Study (CANVAS),<sup>26</sup> is going to be completed in 2017 and DECLARE TIMI 58 study, going to be completed in 2019. These ongoing studies would examine the effect of canagliflozin and dapagliflozin, respectively, on CV outcomes, may help clarify whether the effect of empagliflozin<sup>19</sup> to reduce CV events is a class effect or represents a specific pharmacological effect of empagliflozin. It is impossible at this time to determine whether other SGLT2 inhibitors will exert similar reductions in CV death and CHF hospitalization. Populations with diabetes in CANVAS and DECLARE differ significantly from those in the EMPA-REG OUTCOME study. Approximately 60-70% of patients in CANVAS and ~40% in DECLARE had a prior CV event and the remaining participants qualified based on CV risk factor profile. Moreover, the sample size (4,339 patients) in CANVAS is relatively small compared with the EMPA-REG OUTCOME study. As the beneficial CV effects of empagliflozin most likely are mediated via its hemodynamic/volume depletion actions, one might expect other members of this class to have similar beneficial effects on CV events. However, because of different selection criteria in CANVAS and DECLARE, it is possible that a beneficial effect of canagliflozin and dapagliflozin to reduce CV mortality and CHF may not be observed even though the beneficial hemodynamic (and metabolic) effects of all three SGLT2 inhibitors are similar.

### ADVERSE EFFECTS

The most common adverse effect seen with SGLT2 inhibitors is an increase in infections of the genitourinary tract as well as female genital mycotic infections. These genitourinary infections are generally mild and can be managed conservatively. Dapagliflozin causes other side effects such as dehydration (probably because of polyuria) while canagliflozin is associated with polydipsia, constipation, nausea as well as polyuria. An imbalance in the frequency of bladder cancer was observed in clinical trials with dapagliflozin. Hence, dapagliflozin should

not be prescribed to patients with active bladder cancer or with a history of bladder cancer. With empagliflozin, headaches were a common adverse event.

The US FDA issued a drug safety communication in May 2015 that warned patients and healthcare professionals about the tendency of SGLT2 inhibitors to cause ketoacidosis. A review of the FDA Adverse Event Reporting System (FAERS) database showed that there were 73 cases of ketoacidosis from March, 2013 to May, 2015 in patients with type 1 and type 2 diabetes who were being treated with SGLT2 inhibitors. The communication also said that a review of the FAERS database from March 2013 to October 2014 also identified 19 cases of urosepsis and pyelonephritis that originated as urinary tract infections]. All the adverse effects are very uncommon and can be avoided by proper selection of the patient.

### FUTURE PERSPECTIVE

SGLT2-inhibitors exert multiple hemodynamic (reduction in plasma volume and decrease in blood pressure) and metabolic benefits (decreases in HbA<sub>1c</sub>, body weight, and an increase in HDL cholesterol). The results of the EMPA-REG OUTCOME study suggest that the beneficial effect of empagliflozin to lower CV mortality in T2DM patients most likely results from its hemodynamic rather than its metabolic effects, it is intriguing to examine the impact of the drug specifically in subjects with and without diabetes with reduced LV function (e.g., post-MI) and in subjects with existing CHF. At present the beneficial effect of empagliflozin on CV mortality and CHF hospitalization in these patient populations is likely to be quite robust, which may change the paradigm in the management of type 2 diabetes. Additional physiological and imaging studies are required to further examine this possibility.

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