CHAPTER 181

Empagliflozin: Potential Mechanisms of Cardiovascular Benefits

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T2DM individuals manifest a two- to threefold greater risk of CV events compared with nondiabetics, and CV mortality is responsible for 80% of the mortality. In T2DM patients without MI, risk of CV death is similar to individuals without diabetes with prior MI. Although hyperglycemia is the principal 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 in reducing CV risk. Metabolic syndrome with its cluster of obesity, insulin resistance, dyslipidemia, hypertension and its metabolic abnormalities are major CV risk factors even in individuals without diabetes, 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

Antihyperglycaemic agents like insulin, sulfonylureas, dipeptidyl peptidase inhibitors that lower plasma glucose without affecting other metabolic abnormalities associated with insulin resistance syndrome have not much effect in lowering CVD risk in T2DM especially when these agents are started late in the natural history of T2DM and atherosclerosis. Antidiabetic agents like metformin and pioglitazone and possibly GLP-1 RA that improve insulin sensitivity and have effects on lipids, blood pressure and weight have a favourable effect on CVD risk in T2DM independent of their glucose lowering effects. Newer strategies and therapies are needed for the treatment of T2DM to reduce the CVD risk.

The recently published BI 10773 (Empagliflozin, an SGLT2 inhibitor) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) study demonstrated that in T2DM patients with high CVD risk empagliflozin reduced the primary major adverse cardiac event end point (CV death, nonfatal myocardial infarction, nonfatal stroke) by 14%. This beneficial effect was driven by a 38% reduction in CV mortality with no significant decrease in nonfatal myocardial infarction or stroke. Empagliflozin also caused a 35% reduction in hospitalization for heart failure without affecting hospitalization for unstable angina. The potential mechanisms for these intriguing benefits is discussed.

METABOLIC EFFECTS OF SODIUM–GLUCOSE COTRANSPORTER 2 INHIBITORS

Sodium–glucose cotransporter 2 (SGLT2) inhibitors have insulin independent action. By inhibiting SGLT2 in the renal proximal tubule, they lower plasma glucose by producing glucosuria. In addition to lowering plasma glucose, they correct other 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. SGLT2 inhibition decreases sodium reabsorption in the proximal tubule and exerts diuretic/natriuretic effects. 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. 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; LDL/HDL cholesterol ratio remains unchanged. The mechanism by which SGLT2 inhibitors cause changes in lipid profile remains unknown. Weight loss partly explains the decrease in triglycerides and increase in HDL cholesterol. The mechanisms responsible for increased LDL cholesterol and its clinical significance requires further study. Insulin resistance per se contributes to the pathogenesis of atherosclerosis, independent of accompanying metabolic abnormalities, i.e. obesity, dyslipidemia dysglycemia or hypertension. Improving insulin sensitivity would be anticipated to reduce CV risk. Ghani et al have demonstrated that SGLT2 inhibitors by alleviating glucotoxicity improve insulin sensitivity. Two weeks of dapagliflozin treatment improved wholebody insulin-mediated glucose uptake by 20–25%, measured by euglycemic insulin clamp.

Because of the beneficial cardiometabolic/hemodynamic profile associated with SGLT2 inhibitor therapy, one might expect these drugs would lower CVD risk in T2DM, independent of their glucose-lowering effect.

THE EMPA-REG OUTCOME STUDY 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). Other surprising outcomes were: 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) 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, and 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 of 10 and 25 mg had a similar effect on outcome measures with no dose-response relationship.

POSSIBLE MECHANISMS OF CVD BENEFIT WITH EMPAGLIFLOZIN

Metabolic Actions

Reduction in HbA1c, Weight loss, increased fat oxidation, increased glucagon 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 an acute 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, 0.5to 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. Empagliflozin failed to reduce hospitalization from unstable angina (HR 0.97, P = 0.97). Because of 1) the lack of beneficial effect of empagliflozin on nonfatal stroke and nonfatal MI, 2) the absence of reduction in unstable angina, and 3) the rapidity of onset of decrease in CV mortality, it is not likely that decrease in MACE outcome in EMPA-REG OUTCOME study is due to slowing the atherosclerotic process by empagliflozin.

Glycemic Control

It is unlikely that empagliflozin reduced mortality in the EMPA-REG OUTCOME study by improving glucose control. Firstly hyperglycemia is weak risk factor for CVD. Intensive glycemic control failed to decrease CV events in the UK Prospective Diabetes Study (UKPDS), Action to Control Cardiovascular Risk inDiabetes (ACCORD) study, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study, and Veterans Affairs Diabetes Trial (VADT). Secondly, difference in HbA1c 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 and VADT 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.

Shift in Fuel Metabolism

SGLT2 inhibitors shift whole-body metabolism from glucose to fat oxidation as seen in 4 weeks of treatment with empagliflozin, reduced the respiratory quotient (RQ) during fasting state and during a mixed meal, glucose oxidation decreased by 60% and fat oxidation increased by 20%. The amount of oxygen required to generate the same amount of ATP is greater with fat than with glucose, therefore the shift from glucose to fat oxidation would increase myocardial oxygen demand, and would worsen myocardial ischemia in T2DM patients. Thus, increased myocardial fat oxidation caused by empagliflozin in the EMPA-REG OUTCOME study cannot explain the reduction in CV mortality caused by the drug.

Ketones

SGLT2 inhibitors cause a shift from glucose to fat oxidation. The end product of fatty acid oxidation is acetyl CoA, which can enter the tricarboxylic acid cycle or be converted to ketones, the latter being favored by SGLT2 inhibitor–induced stimulation of glucagon secretion. The rise in plasma ketone concentration is small (0.3–0.6 meq/L). Like free fatty acids, the amount of oxygen required to generate the same amount of ATP is greater with ketones compared with glucose. However, the heart avidly extracts and consumes ketone bodies and ketone body oxidation may improve cardiac muscle efficiency. Further studies will be required to examine whether the preferential oxidation of ketones by the heart provides an energetic benefit to the failing myocardium.

Uric Acid

SGLT2 inhibitors promote uric acid excretion and reduce plasma uric acid by 0.7% mg/Dl.

Increased uric acid levels are associated with increased CVD. Studies indicate that elevated uric acid 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. Reduction in plasma uric acid concentration also may contribute to slowing of diabetic nephropathy observed in the EMPA-REG OUTCOME study.

Glucagon

SGLT2 is expressed in pancreatic a-cells and plays an important role in regulating glucagon secretion. Empagliflozin causes a robust increase in plasma glucagon in T2DM patients. In experimental animals, glucagon receptor activation has detrimental effect on myocardial function and glucagon infusion in humans has no effect on left ventricular (LV) function. Thus, it is unlikely that increase in plasma glucagon contributed to

reduced CV mortality or hospitalization for heart failure by empagliflozin.

Weight Loss

SGLT2 inhibitors, cause caloric loss and decrease 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.

Direct Effect of Drug

SGLT2 is not expressed in cardiac myocytes, while SGLT1 is present in myocardial tissue. Therefore, possible partial SGLT1 inhibition by empagliflozin could affect cardiac function. However, most of the circulating drug is bound to plasma proteins and the expected plasma-free empagliflozin concentration in the EMPA-REG OUTCOME study would be very low, and not likely to affect SGLT1 function.

Further, if SGLT1 were inhibited by empagliflozin, myocardial function is expected to decline, not improve as seen with phlorizine a dual SGLT1/2 inhibitor. Direct myocardial effects by empagliflozin are unlikely to explain the beneficial effect of the drug on CV mortality.

Plasma Electrolyte Changes

SGLT2 inhibition produces negative sodium balance in the first 2–3 days after starting the drug without a change in plasma sodium concentration. This natriuresis may lead to sodium redistribution between the intra and extracellular compartments. In animal models of heart failure, increased intracellular sodium has been reported. Preclinical studies also have reported heart tissue remodelling 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. Small increases in serum potassium, magnesium and phosphate occur with SGLT2 inhibitors and are not contributory to CV benefit.

Blood Pressure

Most participants in the EMPAREG OUTCOME study were hypertensive, 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. This could contribute to the reduction in CV events in the study. However, in studies that examined the effect of blood pressure reduction on CV events, the decrease became evident only after 1year. Moreover, lowering blood pressure generally has a greater impact on stroke reduction than on other cardiac events. In the EMPA-REGOUTCOME study there was a small, nonsignificant, 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. Also 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. Results from the Conduit Artery Function Evaluation (CAFE) study showed reduction in central aortic blood pressure by perindopril and amlodipine was strongly associated with reduced CV events. If empagliflozin

caused a greater decrease in central aortic pressure than evident by the decrease in brachial artery blood pressure and reduced aortic stiffness, it could have greater impact on cardiac events and heart failure than on stroke. Consistent with this hypothesis, empagliflozin reduces aortic stiffness in subjects with diabetes, possibly by reducing oxidative stress or suppressing inflammation. Changes in nitric oxide and systemic renin-angiotensin aldosterone system (RAAS) activity were unrelated to the decline in aortic stiffness following empagliflozin therapy. Further, the diuretic effect of empagliflozin and the accompanying decrease in intravascular volume could further decrease central aortic pressure and produce an afterload reduction effect that improves LV function, reduces cardiac workload, and decreases myocardial oxygen demand. These hemodynamic effects of empagliflozin would be expected to reduce cardiac events, particularly in subjects with ischemic heart disease, impaired LV function, and congestive heart failure (CHF). Consistent with this scenario, participants with history of heart disease benefited most from empagliflozin treatment. Thus, it is possible that these hemodynamic effects of empagliflozin contributed to its beneficial CV effect, particularly in subjects with reduced LV function and CHF. Future studies examining the impact of SGLT2 inhibitors on central aortic and brachial artery blood pressure, aortic stiffness, and LV function will add insight about this hypothesis. Such hemodynamic effects of empagliflozin also could explain lack of relationship between empagliflozin dose and CV outcomes. As empagliflozin

10 mg produces near-maximal glucosuric, natriuretic, and blood pressure–lowering effects, the beneficial CV effect of 10 and 25 mg doses would be expected to be

similar. Last, 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. However, previous studies from suggest that increase in endogenous (hepatic) glucose production observed with SGLT2 inhibitors is mediated by stimulation of renal sympathetic nerves. If there was a generalized activation of the sympathetic nervous system, the heart rate would increase, not decrease, as seen in EMPAREG OUTCOME study. Further studies are needed to examine the effect of SGLT2 inhibitor therapy on the sympathetic nervous .system.

Table 1: Possible mechanisms that could contribute to the reduction of CV mortality by empagliflozin in the EMPA-REG OUTCOME study

Effect	Likelihood	Reason
Metabolic actions		
Lowered plasma glucose	Unlikely	Hyperglycemia weak CV risk factor benefit of HbA1c on CVD takes 10y
Increased fat oxidation	Unlikely	Increased oxygen demand per ATP generated
Increased plasma ketones	Unlikely	Increased oxygen demand per ATP generated
Increased plasma uric acid	Unlikely	Causal association with CVD not established
Increased plasma glucagon	Unlikely	Physiological increase in glucagon has no effect on CV function
Weight loss	Unlikely	Weight loss modest, contribute to long-term benefit in BP,CVD
Change in plasma electrolyte	Unlikely	No consistent changes observed
Hemodynamic actions		
Decrease in blood pressure	Likely	Rapid reduction in BP early CV benefit; proven CV protection
Diuretic effect and decrease ECVF	Likely	Rapid reduction ECFV- early CV benefit proven protect from CHF
Impaired arterial elasticity	Possible	Arterial stiffness CV risk factor; empa reduces arterial stiffness
Direct effect on the myocardium	Unlikely	No evidence
Decreased sympathetic tone	Possible	No increase in heart rate despite decrease in BP and ECFV

Cited from Ghani et al. SGLT2 Inhibitors and Cardiovascular Risk. Diabetes Care 2016;39: p 723

Empagliflozin reduced hospitalization from CHF by 35%. Possibly empagliflozin reduced CV mortality by improving survival specifically among patients with compromised LV function and/or clinically symptomatic CHF. A recent subanalysis showed that empagliflozin

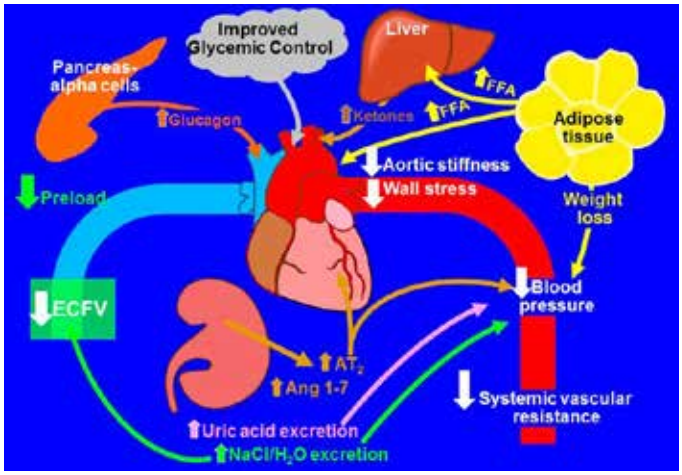

Fig. 1: Schematic representation of the possible metabolic and hemodynamic mechanisms via which empagliflozin reduced mortality and hospitalization for heart failure in the EMPA-REG OUTCOME study. Because of the rapidity of onset of these beneficial effects and the known CV benefits of blood pressure and volume reduction from previous trials with antihypertensive agents and diuretics, it is likely that the hemodynamic and volume-depleting actions play a pivotal role in the cardioprotective effects of empagliflozin. It seems less likely that the metabolic/ hormonal effects (shift from glucose to fat/ketone oxidation, reduced plasma uric acid concentration, weight loss, increased glucagon secretion, increased angiotensin [Ang] 1-7, and AT2 receptor activation) of empagliflozin therapy could play a role in the drug's cardioprotective effects. ECFV, extracellular fluid volume. Ghani et al.SGLT2 Inhibitors and Cardiovascular risk. Diabetes Care2016;39: p720.

similarly reduced CV mortality in subjects with/without heart failure at time of entry into EMPA-REG OUTCOME study. However, diagnosis of heart failure at baseline was based on self-reporting rather than on measured LV function. Further, subjects

who did not report a history of heart failure and developed heart failure during the study were placed in the category without heart failure. It is likely that many individuals who developed heart failure during the study

actually had heart failure at baseline and were misclassified. Last, the reduction in CV mortality became evident shortly after starting therapy. This time course is similar to the effect of spironolactone on survival in subjects with CHF. It is possible that the entire benefit of empagliflozin on CV mortality occurs secondary to the drug's unique action to simultaneously reduce both preload (reduction of plasma volume) and afterload (improved blood pressure and aortic stiffness) in patients with reduced LV function and heart failure Measurement of B-type natriuretic peptide can add insight about this hypothesis and help identify this high-risk population. Exploring this possibility would improve our understanding of how empagliflozin reduces CV mortality and would identify a subgroup of patients with diabetes and existing heart failure who would benefit most from SGLT2 inhibitor treatment.

Reduction in the intravascular volume by empagliflozin could lead to activation of the RAAS leading to an exacerbation of the underlying CVD by stimulating the type 1 angiotensin (AT1) receptor. However, 81% of patients with diabetes in the study were receiving ACE inhibitors or angiotensin receptor blockers. This would favour activation of the AT2 receptor and angiotensin 1-7 pathway, resulting in vasodilation; antiproliferation; antihypertrophy; antiarrhythmic, anti-inflammatory, positive inotropic effects; and reduction in microalbuminuria. Microalbuminuria is a known risk factor for CVD, although a direct causal association has not been established.

Atherosclerosis

Empagliflozin-treated subjects experienced 2 kg weight loss, 2 mg/dL increase in HDL cholesterol, and 5 mmHg decrease in systolic blood pressure compared with placebo-treated subjects.

These benefits expect to slow the atherosclerosis and reduce nonfatal CV events. However, nonfatal CV events (MI and stroke)were not affected by empagliflozin. However study duration was too short to observe impact of metabolic/hemodynamic effects on atherosclerosis-related events or antiatherosclerotic effect 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. An 11% and 7% increase in insulin and sulfonylurea use in the placebo group could cause weight gain, hypoglycemia and adverse CV outcomes in placebo group.

Although sodium–glucose cotransporter 2 inhibitors exert multiple metabolic benefits (decreases in HbA1c, body weight, and blood pressure and an increase in HDL cholesterol), all of which could reduce CVD risk, it is unlikely that the reduction in CV mortality can be explained by empagliflozin's metabolic effects. More likely, hemodynamic effects, specifically reduced blood pressure and decreased extracellular volume, are responsible for the reduction in CV mortality and heart failure hospitalization.

REFERENCES

1. Ghani MA, Prato et al SGLT2 Inhibitors and Cardiovascular Risk: Lessons learned from the EMPA-REG OUTCOME Study. Diabetes Care 2016;39:717-725.
2. Heerspink et al. SGLT2 Inhibitors in the Treatment of Diabetes: Cardiovascular and Kidney Effects, Potential Mechanisms and Clinical Applications. Circulation 2016.