Cardiovascular Protection by Sodium Glucose Cotransporter 2 Inhibitors: Potential Mechanisms

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Cardiovascular Protection by Sodium Glucose Cotransporter 2 Inhibitors: Potential Mechanisms

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ABSTRACT

The mechanism of action of empagliflozin in reducing the risk of adverse cardiovascular outcomes vs placebo in patients with type 2 diabetes mellitus and a high risk of cardiovascular disease in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME) trial is currently unknown. An antiatherosclerotic effect is considered unlikely given the speed of the observed decrease in cardiovascular mortality. Hemodynamic effects, such as reductions in blood pressure and intravascular volume, and involving osmotic diuresis, may provide a more plausible explanation. Metabolic effects, such as cardiac fuel energetics, and hormonal effects, such as increased glucagon release, may also contribute to the results observed during EMPA-REG OUTCOME. This review discusses the main hypotheses suggested to date.

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Data from the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME) trial demonstrated that patients with type 2 diabetes mellitus (T2DM) and a high risk of cardiovascular disease who were randomized to receive empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, on top of standard of care had reduced risk of a primary outcome event (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) relative to those randomized to receive placebo.[1] Notably, the primary outcome benefit was driven by a significant reduction in cardiovascular death; empagliflozin treatment also resulted in a reduced rate of hospitalization for heart failure.[2] Please see the EMPA-REG OUTCOME results discussed in the article on cardioprotection in T2DM by Lüscher and Paneni.[3] It had been thought previously that the effect of empagliflozin on reducing hyperglycemia (and other cardiovascular risk factors) would influence cardiovascular events via an impact on atherosclerosis.[4] However, the benefit of empagliflozin treatment reported in EMPA-REG OUTCOME was observed earlier than would be expected from any effect on atherosclerosis. In addition, the reduction in the occurrence of heart failure hospitalization observed in the study had not been anticipated. It should be noted that no imaging studies or substudies of specific patient populations were carried out during EMPA-REG OUTCOME, and biomarkers (eg, B-type natriuretic peptide, troponin T) were not measured; thus, the characterization of cardiac status in the study population may be limited, particularly with regard to the presence of subclinical heart failure, silent ischemia, or diabetic cardiomyopathy.[5]

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The benefits of empagliflozin observed during EMPA-REG OUTCOME were not limited to cardioprotection, as an improvement in microvascular outcomes driven by renal events was also reported with empagliflozin treatment.[6] It is possible that different mechanisms may have accounted for the cardiac benefits vs those observed in the kidney, and that multiple mechanisms may have contributed to the overall effect. Please see the article by Wanner[7] that discusses potential renal protective mechanisms associated with SGLT2 inhibitors. Briefly, these include reduced hyperglycemia, improved blood pressure control, reduced body weight, and decreases in glomerular hyperfiltration and intraglomerular pressure.[8,9] It is important to note the link between cardiovascular and renal dysfunction in that chronic kidney disease is an independent risk factor for cardiovascular disease and all-cause mortality.[10-12] This has been confirmed in patients with diabetes.[13,14] Potential pathogenic mechanisms of cardiovascular dysfunction in chronic kidney disease include endothelial dysfunction and progression of atherosclerosis, with the presence of a generalized inflammatory state (ie, elevated levels of inflammatory markers) and activation of the renin-angiotensin-aldosterone system (RAAS) contributing via enhanced production of reactive oxygen species.[15] Abnormal hemostasis associated with chronic kidney disease may also contribute to cardiovascular events.[16]

The main question regarding EMPA-REG OUTCOME is that if empagliflozin did not act via an antiatherosclerotic effect, what mechanism was involved? There has been considerable speculation about possible explanations. The current hypotheses are discussed below and are grouped into metabolic effects, hemodynamic effects, hormonal effects, and other potential mechanisms. A summary of possible mechanisms of action to explain cardiac protection with empagliflozin in EMPA-REG OUTCOME is presented in **Figure 1**.

SYSTEMIC METABOLIC EFFECTS

Several metabolic variables were modified by empagliflozin during EMPA-REG OUTCOME[1]; however, the change in each of these factors recorded during the study is unlikely to account for the results observed.

Glucose Control

There are several reasons why the changes in cardiovascular outcomes observed in EMPA-REG OUTCOME are likely to be independent of long-term improvements in glucose lowering (ie, reduced glycated hemoglobin [HbA1c]) following empagliflozin treatment. First, the placebo-subtracted difference in HbA1c during EMPA-REG OUTCOME was modest (~0.3%-0.4%)[17,18] and similar to that reported during the dipeptidyl peptidase-4 inhibitor cardiovascular outcome trials, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53[19]), Examination of Cardiovascular Outcomes with Alogliptin vs Standard of Care (EXAMINE[20]), and Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS[21]), all of which had a neutral effect on cardiovascular outcomes.[17] Second, separation of the cardiovascular event curves for the empagliflozin and placebo groups in EMPA-REG OUTCOME occurred early in the study (ie, after several weeks) and continued to study end, whereas previous studies demonstrated a reduction in cardiovascular events related to glucose control only after many years of follow-up.[18,22-24] Third, hyperglycemia is a weak risk factor for cardiovascular disease, as evidenced by numerous previous studies.[18,22,25]

Body Weight and Visceral Adiposity

Urinary glucose excretion caused by SGLT2 inhibition results in loss of calories and decreased body weight, which is due predominantly to a reduction in body fat.[26-28] Increasing adiposity is known to independently contribute to increased cardiovascular disease risk in diabetes.[29] Weight loss also contributes, in part, to the blood pressure reduction and lipid changes observed with SGLT2 inhibitor therapy. However, although not impossible, it is unlikely that the modest weight loss observed in the empagliflozin treatment groups during EMPA-REG OUTCOME (~2 kg) contributed to the reduced cardiovascular mortality that occurred so early in the study.[18]

Uric Acid

During EMPA-REG OUTCOME, empagliflozin was associated with small reductions in plasma uric acid concentrations when compared with placebo.[1] Similar findings have been reported in clinical trials of other SGLT2 inhibitors[30-32]; however, the clinical significance of this observation in terms of cardiovascular risk is unclear. Increased plasma uric acid concentration may be associated with increased risk of cardiovascular disease, although this increase in uric acid could simply reflect changes in renal function (ie, decreasing filtration capacity).[33]

Plasma Lipids

Small increases in the concentration of both low-density lipoprotein cholesterol and high-density lipoprotein cholesterol were observed in the empagliflozin group during EMPA-REG OUTCOME,[1] and similar changes have been reported in other SGLT2 inhibitor clinical trials.[30-32] It has been suggested that increased plasma lipid levels could be due to hemoconcentration caused by SGLT2 inhibitor treatment.[34] The significance of these changes, in terms of cardiovascular risk, is currently unclear.

GLUCOTOXICITY

The issue of glucotoxicity has not received much clinical attention in recent years, presumably because of the previous failure to achieve a reduction in cardiovascular disease with other glucose-lowering agents; however, the data from

EMPA-REG OUTCOME may encourage renewed interest in this topic. Hyperglycemia causes tissue damage through several major metabolic pathways (**Figure 2**[35]), leading to the overproduction of superoxide in the mitochondria.[36] Hyperglycemia is associated with increased β-O-linkage of N-acetylglucosamine (O-GlcNAc), known as O-GlcNAcylation,[37] which is a dynamic posttranslational modification of cellular and nuclear proteins that occurs in all cells, including cardiovascular tissue.[38] An increase in the level of O-GlcNAc is implicated as a pathogenic contributor to glucose toxicity and insulin resistance,[38] and may be associated with diabetic cardiac dysfunction.[37] Chronic hyperglycemia has also been shown to alter energy metabolism in the heart, with changes occurring in mitochondrial function associated with decreased contractile performance in the heart tissue of patients with diabetes prior to the onset of clinical cardiac dysfunction or cardiomyopathy.[39] Although speculative, decreasing chronic hyperglycemia by promoting urinary glucose excretion (via SGLT2 inhibition) could reduce the cardiac effects of glucotoxicity, thus reducing the risk of heart failure in these high-risk T2DM patients. Glucose clamp studies (so-called because blood glucose is held or "clamped" at a certain concentration) have shown that improvements in peripheral insulin sensitivity, as well as in pancreatic β-cell function, can occur following a reduction in glucotoxicity. In patients with T2DM, empagliflozin (25 mg once daily for 14 days) was associated with improvements in β-cell function, measured as insulin secretion/insulin resistance index, and a significant increase in glucose sensitivity during the hyperglycemic clamp stage.[40] A glucose clamp study using a diabetic mouse model also reported improved insulin sensitivity when empagliflozin was given either as monotherapy or in combination with linagliptin.[41] Additionally, a metabolic study in patients with T2DM confirmed that lowering elevated blood glucose levels with empagliflozin reduced glucose toxicity and improved β-cell function.[42] This study also demonstrated that insulin sensitivity of tissue glucose uptake was improved.[42] A recent glucose clamp study of dapagliflozin in T2DM patients also reported improved insulin sensitivity.[43] Given the direct link between insulin resistance and accelerated cardiovascular disease,[44,45] reduced insulin resistance could be expected to have positive effects on cardiovascular outcomes.

The directional effects on glucose fluxes associated with SGLT2 inhibition would not be observed with insulin, incretins, thiazolidinediones, or sulfonylureas because these

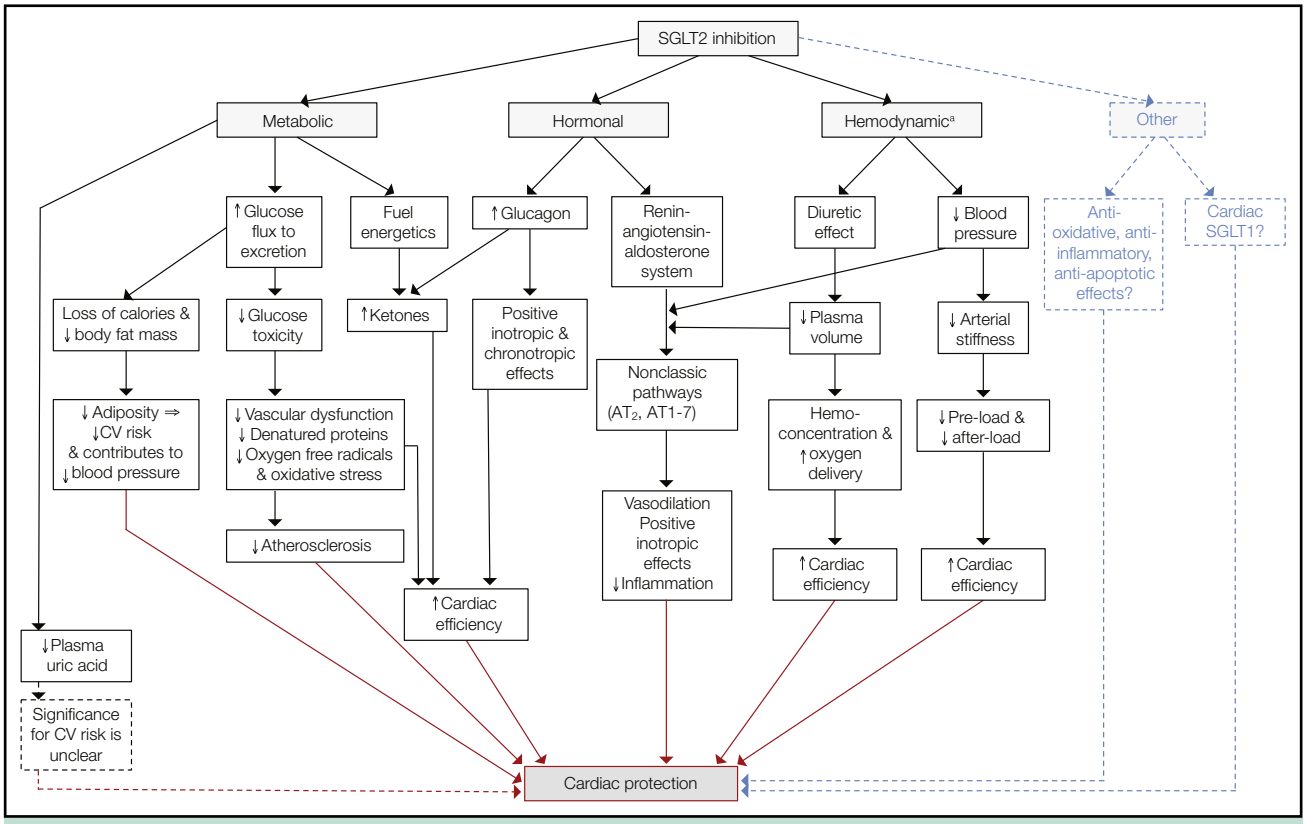

Figure 1 Summary of possible cardiac protection mechanisms in EMPA-REG OUTCOME. [a]Hemodynamic changes affecting the kidney are not shown, although they may impact on cardiac function; renal protection mechanisms are presented in Wanner's review.[7] AT_2 = type 2 angiotensin II receptor pathway; AT1-7 = angiotensin 1-7 activation; CV = cardiovascular; SGLT = sodium glucose cotransporter.

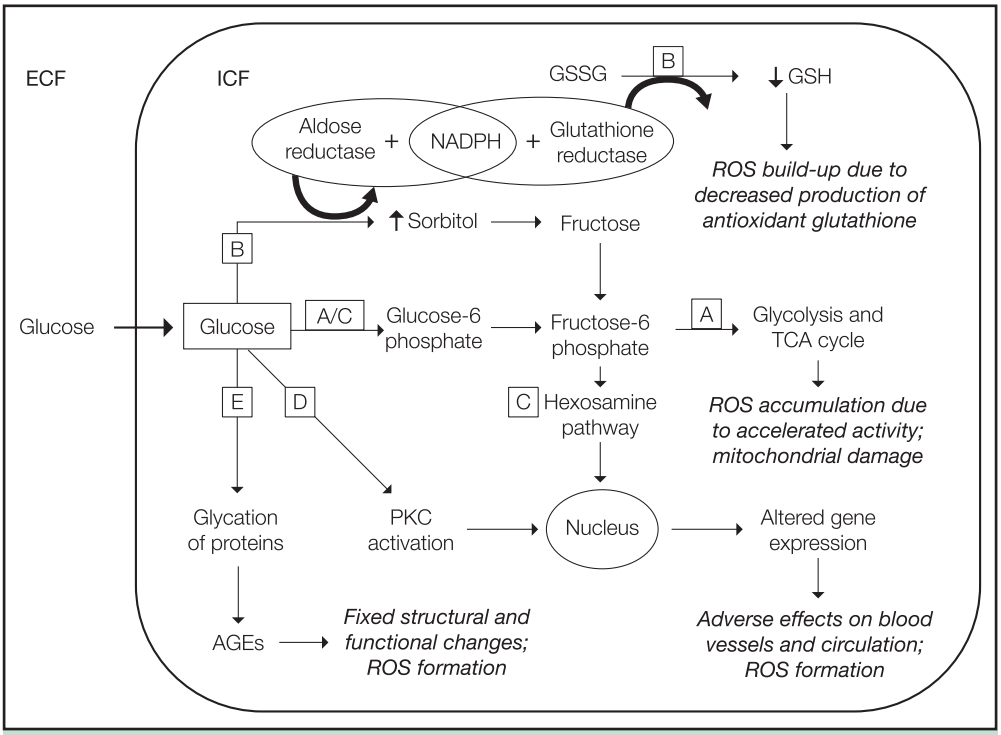

Figure 2 Metabolic pathways of tissue damage resulting from glucotoxicity. Glucose toxicity occurs through several mechanisms that begin when hyperglycemia leads to an increase in the intracellular glucose level: A, increased glucose oxidation promotes the generation of superoxide; B, production of sorbitol from excess glucose is increased, depleting NADPH and thereby limiting production of the antioxidant glutathione; C, some of the excess glucose converted to fructose-6 phosphate enters the hexosamine pathway, whose products can affect gene expression, with adverse clinical consequences; excessive activity in the main energy pathway (the TCA cycle) also promotes ROS formation; D, activation of PKC signaling likewise results in the expression of factors that promote ROS formation and have detrimental effects on vessels and circulation; E, glycation, or direct binding of glucose or its metabolites to proteins, produces structural changes that constitute an enduring cellular "memory" of the effects of hyperglycemia. AGE = advanced glycation end product; ECF = extracellular fluid; GSSG = oxidized glutathione (which is reduced to the antioxidant GSH form); ICF = intracellular fluid; NADPH = nicotinamide adenine dinucleotide phosphate (a key reducing agent in metabolic processes); PKC = protein kinase C (an intracellular signaling and regulatory system); ROS = reactive oxygen species; TCA = tricarboxylic acid (the TCA cycle is the main aerobic pathway). From:[35] Campos C. Chronic hyperglycemia and glucose toxicity: pathology and clinical sequelae. *Postgrad Med*. 2012;124:90-97. Reprinted by permission of the publisher Taylor & Francis Ltd, http://www.tandfonline.com.

agents all act by stimulating tissue glucose uptake. If recent data that indicate metformin acts mainly in the intestine are correct,[46] this would suggest that metformin (which is generally considered cardioprotective[47]) may also act to relieve glucose toxicity, albeit to a lesser extent than SGLT2 inhibitors, by a mechanism that is not yet understood.

Decreases in glucose flux associated with SGLT2 inhibitors could also modulate inflammatory processes that may contribute to cardiovascular disease. For example, inflammatory M1 macrophages preferentially utilize glucose through the glycolysis pathway. Thus, SGLT2 inhibitor treatment could act to dampen the inflammatory response, possibly affecting processes in vascular endothelial cells that could contribute to a reduced risk of cardiovascular disease.

CARDIAC FUEL ENERGETICS

In diabetic cardiomyopathy, a condition for which clinical interest and understanding have increased over recent years, the myocardium is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valvular disease, or congenital heart disease.[48] Metabolic abnormalities associated with diabetes (eg, hyperglycemia, hyperinsulinemia, lipotoxicity) promote the development of restrictive diabetic cardiomyopathy, also known as heart failure with preserved left ventricular ejection fraction, which is more prevalent in obese patients with T2DM.[49] The features of heart failure in diabetes are reviewed in the article by Lehrke and Marx.[50] The main source of energy (~95%) for the normal adult myocardium is derived

from mitochondrial oxidative metabolism and the remainder is obtained from glycolysis, the metabolism of glucose into pyruvate.[51] The heart can utilize different energy sources and the normal fuels are fatty acids or glucose, although lactate, amino acids, and ketones may be used to a lesser degree. Diabetic cardiomyopathy is characterized by increased fatty acid uptake and oxidation, with decreased glucose oxidation, causing changes in cardiac mitochondrial energy metabolism that contribute to contractile dysfunction and decreased cardiac efficiency.[52] During the development of heart failure, however, the capacity of the heart to utilize fatty acids is reduced and there is an increased reliance on glycolysis.[51] In the setting of T2DM with heart failure, where there is restricted fuel availability and low energetic reserve, ketone bodies act as a "super fuel" by releasing energy more efficiently than fatty acids or glucose.[53] Metabolic studies have confirmed that the hypertrophied and failing heart shifts to using ketone bodies as an alternate fuel source,[51,54] independent of the presence of diabetes.[54]

It has been demonstrated that SGLT2 inhibitors can shift whole-body metabolism from glucose to fatty acid oxidation,[42,43] and this could have beneficial effects for failing hearts.[55] Thus, it is possible that empagliflozin treatment during EMPA-REG OUTCOME may have caused changes in metabolism by increasing hepatic synthesis of ketones, making the ketone body β-hydroxybutyrate available as a metabolic substrate for the heart (and the kidney).[18,53,56] Increased cardiac efficiency, facilitated by the utilization of ketones,[53,56] could work together with increased oxygen delivery from SGLT2 inhibitor-associated hemoconcentration[56] and a reduced cardiac load resulting from decreases in blood volume and blood pressure.[56]

Because this fuel energetics hypothesis was generated in response to the results from EMPA-REG OUTCOME, and as ketones were not measured during the study, there are no data available to support or refute this hypothesis. Further research is thus required, including relevant clinical studies and investigation of the effect of empagliflozin on muscle ketone oxidation rates.[57,58] Moreover, caution is needed regarding other approaches that would increase blood ketone levels, such as the ketogenic diet, as the question of whether cardiovascular risk reduction associated with empagliflozin treatment derives, even in part, from increased levels of ketones is entirely speculative at present. Lastly, in addition to being a circulating energy source, ketones have an important role in cellular and epigenetic signaling[59,60] and act as nongenomic antioxidants,[61,62] effects that could potentially contribute to reducing cardiovascular disease.

HEMODYNAMIC EFFECTS

One of the most widely proposed explanations for the cardiovascular benefits seen in EMPA-REG OUTCOME is a hemodynamic effect related to reductions in blood pressure and intravascular volume, and involving osmotic diuresis.[18,22,63] This is an appealing hypothesis, because volume contraction and reduction in arterial stiffness[64] are expected to occur with SGLT2 inhibitor therapy. It would be predicted that, in patients with impaired cardiac function, reducing the preload and afterload of the heart, as well as hemoconcentration enhancing oxygen release to the tissues, could give the rapid results observed.[65] Contrary to this hypothesis, however, is the observation that the effect of empagliflozin was seen consistently in patients without heart failure at baseline,[2] although as previously mentioned, it is possible that many patients had undiagnosed or asymptomatic left ventricular systolic/diastolic dysfunction.[2,5] It has also been proposed that the effect of empagliflozin therapy on heart failure risk could have been exaggerated by increased use of thiazolidinediones in the placebo arm during the study.[63] However, this drug class was received by only 2.9% of patients in the placebo arm, vs 1.2% of those in the empagliflozin arms post baseline, and there was no difference in thiazolidinedione use between groups at baseline (4.3% for placebo vs 4.2% for empagliflozin) in EMPA-REG OUTCOME.[1] Initial results of a mediation analysis (investigation of a variable that explains a relation or provides a causal link between other variables) suggested that volume reduction, though measured indirectly via hematocrit, was likely to be a factor contributing to the study results.[66]

Blood Pressure

A decrease in systolic/diastolic blood pressure of 5/2 mm Hg was recorded during EMPA-REG OUTCOME,[18] and was not associated with increased heart rate.[1] It was suggested that this reduction in blood pressure could have played a role in explaining the EMPA-REG OUTCOME study results.[67] The study investigators concurred,[68] but pointed out that similar benefits were not yielded from previous studies[69,70] in which blood pressure was lowered beyond the mean baseline level of that in EMPA-REG OUTCOME patients (135/77 mm Hg).[68] They also stated that the divergence of the empagliflozin vs placebo event curves occurred much earlier in EMPA-REG OUTCOME than typically observed in clinical trials of blood pressure-lowering agents.[68] Furthermore, blood pressure reduction would be expected to have a greater effect on stroke reduction than other cardiovascular outcomes,[18,70] whereas in EMPA-REG OUTCOME there was no reduction in the rate of nonfatal stroke with empagliflozin treatment.[1] Blood pressure was treated according to standard of care, which included specific relative risk targets; however, the study protocol did not specify a treat-to-target obligation for investigators. In retrospect, this would have allowed the contribution of blood pressure to the study outcomes to be more clearly determined. Empagliflozin has also been shown to reduce arterial stiffness in patients with type 1 diabetes mellitus (T1DM), which may contribute to the blood pressure-lowering effects associated with SGLT2 inhibition,[64] and could be a factor in achieving the results from EMPA-REG OUTCOME. Given the relationship between chronic kidney disease and cardiovascular disease in diabetes, the blood pressure changes observed during EMPA-REG OUTCOME could be surrogate markers for

other renal effects of empagliflozin treatment that may act upon the heart.

Diuretic Effects

The diuretic potential of empagliflozin has been discussed as a possible contributory mechanism to explain the reduction in heart failure hospitalizations observed during EMPA-REG OUTCOME[71]; however, several caveats should be considered.[65] The most commonly used diuretic medications produce similar or greater decreases in intravascular volume and net sodium balance, but have not been associated with reduced cardiovascular death (per previous studies), and have had a far more modest effect on the risk of hospitalization for heart failure[72] vs that observed in EMPA-REG OUTCOME.[65] However, SGLT2 inhibitors differ from loop and thiazide diuretics in that: 1) SGLT2 inhibitors do not lead to reflex sympathetic nervous system activation (ie, no observed increase in heart rate despite blood pressure lowering); 2) thiazide diuretics act on the distal tubule, whereas SGLT2 inhibitors act on the proximal tubule (ie, proximal to the macula densa) and cause increased urinary sodium and chloride delivery to the juxtaglomerular apparatus[65,73]; and 3) thiazide and loop diuretics are known to cause hyperglycemia and hyperuricemia, whereas SGLT2 inhibitors are known to have a positive effect on blood glucose and uric acid. It has been suggested that these effects of SGLT2 inhibition reinstate tubuloglomerular feedback, resulting in afferent arteriolar vasoconstriction and decreased glomerular filtration (ie, decreased hyperfiltration) by reducing intraglomerular pressure.[73] Increased delivery of sodium and chloride to the macula densa during SGLT2 inhibitor treatment may influence other neurohormonal factors, such as local RAAS inhibition, and this may result in reduced levels of aldosterone and decreased sympathetic nerve activity — either or both of which could reduce the risk of cardiovascular death and heart failure.[65]

The sodium excretion (natriuresis) associated with empagliflozin could also contribute to the benefits seen in EMPA-REG OUTCOME; it could be the main cause of volume contraction and could also be sustained over time.[65,74,75] The diuretic action of empagliflozin via both glucose and sodium excretion, in addition to improvements in renal arteriolar responses, may also explain the observed reduction in risk of renal disease progression and slowing of renal function deterioration.[76]

HORMONAL EFFECTS

Glucagon

An increase in glucagon levels is generally perceived negatively in the context of T2DM because of its effect on increasing blood glucose levels; however, new perspectives on the role of glucagon in the maintenance of heart and kidney function could alter our understanding.[77] As demonstrated more than 45 years ago, glucagon has long been recognized as having a key role in the regulation of myocardial glucose utilization; it also modulates cardiac function with positive inotropic and chronotropic effects.[78]

Empagliflozin treatment increases blood glucagon levels (and endogenous glucose production).[42] Increased blood glucagon levels associated with SGLT2 inhibitor treatment may be due to increased glucosuria (ie, glucose excretion), combined with a recently reported direct effect on glucagon-secreting pancreatic α-cells.[79] An increase in glucagon levels has been proposed as a possible contributor to the reduced cardiovascular risk observed in EMPA-REG OUTCOME, particularly when considering its inotropic effects in the context of heart failure.[77] Conversely, evidence from animal and human research suggests that glucagon has an adverse effect on myocardial function, and it has been suggested that increases in glucagon levels are unlikely to account for the observed cardiovascular benefits of empagliflozin.[18] The impact of these changes in glucagon levels on cardiovascular risk remains to be more clearly determined.

RAAS

Previous SGLT2 inhibitor studies in T1DM[73,80] and T2DM[81] found that RAAS activity was slightly increased, although within the normal range.[82] This may be interpreted as a compensatory response to volume contraction, natriuresis, and decreased blood pressure.[82] However, SGLT2 inhibition leads to a hemodynamic effect consistent with afferent vasoconstriction rather than the efferent vasodilation associated with RAAS inhibition.[80] Furthermore, reduced arterial stiffness observed in patients with T1DM following empagliflozin treatment has been reported to be unrelated to nitric oxide and systemic RAAS activity.[64] Regarding EMPA-REG OUTCOME, it has been suggested that empagliflozin may act via the nonclassic RAAS pathways.[83] RAAS activation, caused by reduced intravascular volume and blood pressure during empagliflozin treatment, could stimulate the type 1 angiotensin II receptor, which is central in the pathogenesis of cardiovascular disease, thus potentially exacerbating any underlying disease.[84] However, during the EMPA-REG OUTCOME study, 81% of patients received angiotensin-converting enzyme inhibitors or type 1 angiotensin II receptor blockers. Empagliflozin could therefore have had additive cardioprotective effects via activation of the type 2 angiotensin II receptor pathway and angiotensin 1-7 activation, which cause responses such as vasodilation, anti-inflammatory effects, and positive inotropic effects.[83]

Erythropoietin

Increased hematocrit has been reported during treatment with SGLT2 inhibitors,[85] and was observed with empagliflozin treatment during EMPA-REG OUTCOME.[1] Elevation of hematocrit has generally been assumed to be related to hemoconcentration associated with the diuretic effect of SGLT2 inhibitors; however, it may also be linked to

increased erythropoietin (EPO) secretion.[81,86] It has been suggested that elevated hematocrit may be a surrogate marker for the recovery of tubulointerstitial function associated with SGLT2 inhibitor therapy.[86] In addition, low-dose EPO was reported to improve myocardial function in a mouse model of heart failure.[87] Thus, it would be of interest to further investigate EPO levels in patients treated with SGLT2 inhibitors.

OTHER POTENTIAL MECHANISMS

Other properties of SGLT2 inhibitors that have been shown in experimental models include antioxidative, anti-inflammatory, and antiapoptotic effects, and it is conceivable that these attributes may have contributed to the overall effects observed in EMPA-REG OUTCOME.[65] Empagliflozin may also have a direct effect on the heart via Na^+-mediated electrophysiological changes or via SGLT1 (which is expressed therein), as SGLT2 inhibitors also bind to SGLT1 receptors to some extent; however, this is considered unlikely given the relatively high specificity of SGLT2 inhibitors for SGLT2 (inhibitor concentration at half-maximal response, IC_{50} [nM]: empagliflozin 3.1 for SGLT2 and 8300 for SGLT1; dapagliflozin 1.2 for SGLT2 and 1400 for SGLT1; canagliflozin 2.7 for SGLT2 and 710 for SGLT1).[88]

ARE CARDIOVASCULAR PROTECTIVE EFFECTS SPECIFIC TO EMPAGLIFLOZIN?

As empagliflozin is one of several SGLT2 inhibitor agents currently marketed, clinicians may speculate whether the results reported during EMPA-REG OUTCOME are specific to empagliflozin or represent a class effect of SGLT2 inhibitors. The results of cardiovascular outcome trials (CVOTs) with other SGLT2 inhibitors are keenly awaited: CVOTs are ongoing for agents marketed (canagliflozin and dapagliflozin) or intended to be marketed (ertugliflozin) in the US.[4] Interestingly, following publication of the EMPA-REG OUTCOME results, the ertugliflozin study was expanded to recruit additional patients (from 3900 to 8000) and to specify cardiovascular death or hospitalization for heart failure as a secondary endpoint.[44] Noninferiority CVOTs are a requirement of the Food and Drug Administration for drugs for which regulatory approval is sought in the US; thus, CVOTs are not required for SGLT2 inhibitors marketed entirely outside of the US (eg, ipragliflozin, luseogliflozin, tofogliflozin), and no CVOTs are known to be planned or underway for these agents.

It is important to bear in mind that a drug class effect must be demonstrated and cannot simply be assumed to be present. Data from CVOTs of the glucagon-like peptide-1 receptor agonists lixisenatide and liraglutide revealed different results from those reported in EMPA-REG OUTCOME regarding cardiovascular endpoints, as well as different results from each other.[89,90] The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA), a lixisenatide CVOT, had neutral results,[89] whereas the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER), a liraglutide CVOT, reported a significant 13% relative risk reduction in the primary endpoint, which was a composite of the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.[90] Thus, ELIXA and LEADER show that agents from the same drug class may be different with respect to cardiovascular outcomes. These results could, however, be due to differences between the drugs (eg, lixisenatide is shorter acting and structurally dissimilar to liraglutide),[90] or the trial designs for ELIXA and LEADER (eg, median follow-up was 25 months and 45 months [3.8 years] for ELIXA and LEADER, respectively, and changes in cardiovascular outcomes with liraglutide were not seen in LEADER until around 12 months of follow-up). Other explanatory factors could include differences in potency of the individual drugs, doses used, study populations, and the statistical power of each study.

Similarly, differences among the designs of the various SGLT2 inhibitor CVOTs, and among the individual SGLT2 inhibitor agents used within the trials, may or may not become relevant once the respective data are published and can be compared with those from EMPA-REG OUTCOME. Hypothetically, an SGLT2 inhibitor class effect on cardiovascular outcomes might be expected if the associated mechanism is related to SGLT2 inhibition, although there may be differences among the individual drugs within the class (eg, target specificity, drug metabolism, and pharmacokinetic profiles). It is possible that empagliflozin acts on cardiovascular outcomes via a mechanism unrelated to SGLT2 inhibition, although this appears less likely given the various avenues of research based on the known mechanisms. Considering the available clinical trial evidence, the only conclusion that can be made at present is that although the causal mechanism may or may not be specific to empagliflozin, it is the only SGLT2 inhibitor currently proven to reduce the rate of cardiovascular events in patients with T2DM and high cardiovascular risk.

CONCLUSIONS

In the first publication of the results of EMPA-REG OUTCOME, the investigators stressed that this was not a mechanistic study, and was designed to test the effects of empagliflozin treatment rather than how the agent worked. All the mechanisms proposed to date to explain the results of EMPA-REG OUTCOME are speculative, albeit based on the known effects of SGLT2 inhibitors and the changes observed during this study. In the initial discussion of the results, the EMPA-REG OUTCOME study investigators speculated that the mechanism was probably multidimensional. It is also possible that the rapid response observed in the study could be explained by one mechanism and the long-term effects could involve separate mechanisms. Therefore, the results are likely explained by a combination of the mechanisms described above. There remains an

intriguing possibility that an as-yet unidentified action may also be uncovered. Our attempt to understand the mechanisms involved in the EMPA-REG OUTCOME results is not just an academic exercise, but may generate new areas of research regarding new uses of empagliflozin, and identify the patients most likely to experience the greatest benefits from this agent.

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