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Cardiovascular Protection by Sodium Glucose Cotransporter 2 Inhibitors: Potential Mechanisms

Bart Staels, PhD

Université Lille, INSERM, CHU Lille, Institut Pasteur de Lille, U1011-EGID, Lille, France.

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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Requests for reprints should be addressed to Bart Staels, PhD, Institut Pasteur de Lille, 1 rue du Professeur Calmette, BP 245, 59019 Lille, France.

E-mail address: Bart.Staels@pasteur-lille.fr

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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