Editorial

Empagliflozin: Not just a glorified diuretic

Mathew John

Department of Endocrinology and Diabetes, Providence Endocrine and Diabetes Specialty Centre, Trivandrum, Kerala, India

The EMPA-REG OUTCOME, the cardiovascular trial of empagliflozin randomized 7020 subjects with diabetes and prior cardiovascular disease to empagliflozin vs. standard of care. Subjects randomized to empagliflozin had significant reduction in primary composite endpoints of major adverse cardiovascular events (MACE) (cardiovascular death, nonfatal MI, nonfatal stroke) by 14% compared to placebo (HR= 0.86, 95% CI = 0.74-0.99, $P = 0.04$ for superiority).[1] Although various potential mechanisms of benefit were discussed, the most hailed is the "diuretic hypothesis."[2,3] This has led even to comments questioning if empagliflozin is a glorified diuretic or if the outcomes of this trial just represented an optimized diuretic regime.[4]

The "diuretic hypothesis"

The "diuretic hypothesis" for improved CV outcomes is based on certain assumptions. Subjects included in EMPA-REG OUTCOME were older subjects (mean age: 63 years) and had established cardiovascular disease. This makes them prone for heart failure.[1] The improvements in primary outcomes occurred quite early in the course of the trial (2-4 months).[1,2] The rapid time course of reduction of mortality favors ventricular offloading as a potential mechanism of action.[1,2] The improvements in blood pressure and weight reduction effectively contribute to the same. These improvements were seen very early in the course of the study and can be considered secondary to fluid loss.[1,5] Other potential benefits associated with empagliflozin like effects on ventricular remodeling, arterial stiffness, effects of retardation of atherosclerosis, and improved myocardial efficiency are mechanisms that may take longer periods to translate into clinical benefits.[2] This is again seen in lack of benefits of empagliflozin on nonfatal myocardial infarction (MI), fatal and nonfatal stroke, transient ischemic attacks, and coronary revascularization.[2]

Corresponding Author: Dr. Mathew John,
Department of Endocrinology and Diabetes, Providence Endocrine and Diabetes Specialty Centre, TC 1/2138, Murinjapalam, Trivandrum - 695 011, Kerala, India.
E-mail: drmathewjohn@yahoo.com

Against the "diuretic hypothesis"

In EMPA-REG OUTCOME study, around 10% of subjects in the placebo arm and empagliflozin arm had cardiac failure at baseline (as defined by standard MeDRA queries). As all subjects in the trial had a prior CV event or lesion, it is likely that these subjects were evaluated well before entry into the trial. This would mean that 90% of subjects did not have proven heart failure at baseline.[1] Analysis of EMPA-REG OUTCOME has shown that mortality benefits were much more pronounced in diabetic subjects *without* heart failure than in those with heart failure at baseline.[6] If the diuretic effects were the predominant mechanism, the opposite would have been the case.

There could be a concern that more subjects in the placebo arm had fluid retaining drugs (e.g., insulin and pioglitazone) and drugs with potential CV adverse effects (e.g., sulfonylurea) introduced for glycemic control postrandomization. It could also be argued in favor of "diuretic hypothesis" that these could have contributed to increased risk of heart failure in the subjects in placebo arm.[2] However, the data also show that there is an increased use of diuretics and mineralocorticoid receptor antagonists in the placebo arm which could have negated this effect.[1]

Favorable outcomes were found in CV mortality, all-cause mortality, hospitalization for heart failure, and primary composite of major adverse cardiac events.[1] A closer look at CV deaths shows that events other than death due to worsening heart failure, e.g., sudden cardiac death also were reduced. Around 40% of the mortality was due to other CV deaths (e.g., arrhythmias and pulmonary embolism) in both the arms. Even these were reduced in subjects using empagliflozin. No benefits were found in nonfatal MI, fatal and nonfatal stroke, transient ischemic attacks, and coronary revascularization.[1]

There is an increase in activity of renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system in heart failure. Trials of chronic heart failure have shown that significant mortality and morbidity benefits have

been provided by inhibitors of RAAS (angiotensin converting enzyme [ACE] inhibitors, angiotensin receptor blockers), beta blockers, and mineralocorticoid receptor antagonists (spironolactone, eplerenone).[7-11] The data with loop diuretics are less convincing.[12] Sodium Glucose Cotransporter 2 (SGLT2) inhibitors by virtue of natriuresis and volume depletion activate the systemic RAAS activity in studies of subjects with type 1 diabetes. However, the net effect is reduction in blood pressure as the elevated RAAS activity is balanced by the weight loss and natriuresis.[13] Subjects on ACE inhibitors in combination with SGLT2 inhibitors can have activation of nonclassical RAAS pathway. The nonclassical pathway results in the production of angiotensin (1–7) which has a vasodilatory, antiproliferative, anti-inflammatory, and antioxidative stress effect.[14] The favorable effect of eplerenone in Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) was shown in subjects with systolic heart failure with an ejection fraction of <40%. However, in a subgroup analysis, subjects with diabetes and heart failure did not meet the two primary endpoints: time to death from any cause and time to death from CV causes or first hospitalization for a CV event (including heart failure, recurrent acute MI, stroke, or ventricular arrhythmia).[10] Further, the effect size on primary end points were much larger with EMPA-REG OUTCOME than with EPHESUS. Randomized Aldactone Evaluation Study studied a much sicker group of subjects with heart failure and no diabetes.[9] Despite having a diuretic action that contributes to the rapid improvement of heart failure by mineralocorticoids, mineralocorticoid receptor antagonists have additional properties that contribute to reduction in myocardial and vascular fibrosis.[10] And in both these trials, mineralocorticoid receptor antagonists were added to optimized diuretic regimes. Hence, it would not be wise to compare them with SGLT-2 blockers. In a meta-analysis of trials of antihypertensive drugs in subjects with diabetes, using diuretics reduced the risk of heart failure, but not mortality, CV disease, stroke, or coronary artery disease in comparison with other antihypertensive agents.[15]

Thinking beyond "diuretic hypothesis"

Thus, the diuretic hypothesis may be supported by rapid time course of event reduction and by exclusion of other possible known pathophysiological mechanisms contributing to systolic heart failure. The essential difference of activation of RAAS by SGLT2 inhibition (vs. inhibition by mineralocorticoid receptor blockers and ACE inhibitors), lack of significant effect on sympathetic nervous system (vs. inhibition by beta blockers), enhanced favorable effect of the drug even in diabetic subjects without heart failure, and favorable benefits in endpoints other than those directly related to volume expansion (e.g., other CV deaths, sudden cardiac deaths, and all-cause mortality) favors an alternate hypothesis other than a diuretic effect. The role of SGLT1 in the cardiac myocardium and animal models of improvement in left ventricular mass with empagliflozin are research findings of interest.[16,17]

If it were predominantly a diuretic effect accounting for CV benefits of empagliflozin, then other SGLT2 blockers would also be expected to show a positive benefit in CV outcome trials: the more potent one producing potentially more benefits. The aim of this commentary is not to negate the "diuretic hypothesis" but to encourage scientific thinking to explore various other possibilities that may contribute to the CV benefits of this unique molecule.

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