

Surprising Results of the EMPA-REG OUTCOME study have brought a New Insight into Use of Sodium-Glucose Co-transporter 2 Inhibitors in Patients with Type 2 Diabetes

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Abstract

A surprising new study EMPA-REG OUTCOME has shown that empagliflozin, one of sodium-glucose co-transporter 2 (SGLT2) inhibitors, in addition to standard care had beneficial effects on cardiovascular morbidity and mortality in patients with type 2 diabetes at high risk for cardiovascular events. Subgroup analyses of the study revealed a better hazard ratio for the primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) in Asian than Caucasian and in patients with age ≥ 65 years, body-mass index < 30 , glycated hemoglobin $< 8.5\%$ or higher cardiovascular risk than with the respective counterparts. Patients on diuretics also had the hazard ratio favoring empagliflozin, similar to that of patients not on diuretics. I infer that in poorly-controlled diabetic patients, pre-existing osmotic diuresis is supposed to be augmented by the administration of SGLT2 inhibitors, possibly leading to an acceleration of their dehydration in spite of amelioration of hyperglycemia. Hypovolemia is inferred to be more likely to occur due to osmotic diuresis without an increase in blood glucose level to retain water. It may be recommended that use of SGLT2 inhibitors should be avoided in diabetic patients with glycated hemoglobin $\geq 8.5\%$ at high risk for cardiovascular events. Because empagliflozin seems to have had no significant effect on nonfatal myocardial infarction or stroke, its ability to reduce cardiovascular mortality may be mediated through osmotic diuresis. SGLT2 inhibitors could be used as a new oral osmotic diuretic to excrete water with a little sodium into urine for non-diabetic patients with heart failure as well. Such action of SGLT2 inhibitors seems to be rather close to that of tolvaptan to promote water diuresis. Thus, the EMPA-REG OUTCOME study has brought a new insight into use of SGLT2 inhibitors in patients with type 2 diabetes.

Keywords: EMPA-REG Outcome; Sodium-glucose co-transporter 2 inhibitor; Osmotic diuresis; Cardiovascular mortality; Type 2 diabetes

Commentary

Surprising results of the EMPA-REG OUTCOME study have been published in the New England Journal of Medicine on September 17, 2015, at NEJM.org [1]. The study (median observation time, 3.1 years) has shown that empagliflozin, one of sodium-glucose co-transporter 2 (SGLT2) inhibitors, in addition to standard care had beneficial effects on cardiovascular morbidity and mortality in a total of 7020 patients with type 2 diabetes (glycated hemoglobin level, 7.0 to 10.0%) at high risk for cardiovascular events. The empagliflozin group has demonstrated a significant reduction in the rates of death from cardiovascular causes (38% relative risk reduction), hospitalization for heart failure (35% relative risk reduction), and death from any cause (32% relative reduction). Recent similar trials with other glucose-lowering drugs have demonstrated non-inferiority for cardiovascular outcomes, including the TECOS trial with sitagliptin [2], a dipeptidyl peptide-4 inhibitor, and the ELIXA trial with lixisenatide [3], a glucagon-like peptide 1 receptor agonist.

In Japan, however, unexpected adverse effects of SGLT2 inhibitors were reported frequently soon after the first one was marketed in April 2014. Dehydration, which seemed to be occasionally linked to fatal adverse events, was added as a severe adverse effect to a package insert in January 2015. In a position statement of "Management of

hyperglycemia in type 2 diabetes, 2015" [4], it is noted that SGLT2 inhibitors with a diuretic effect should be used cautiously in the elderly, in any patient already on a diuretic, and in anyone with a tenuous intravascular volume status. It is surprising that subgroup analyses of the EMPA-REG OUTCOME study [1] revealed a better hazard ratio for the primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) in Asian than Caucasian and in patients with age ≥ 65 years, body mass index < 30 , or higher cardiovascular risk than with the respective counterparts. Patients on diuretics also had the hazard ratio favoring empagliflozin, similar to that of patients not on diuretics.

SGLT2 inhibitors decrease hyperglycemia independently of insulin by increasing urinary glucose excretion through the inhibition of glucose reabsorption in the proximal renal tubule. Familial renal glucosuria with normoglycemia is often referred to as a natural model for SGLT2 inhibition. Plasma volume depletion resulting from osmotic diuresis was indicated by activation of the renin-angiotensin-aldosterone system in cases of severe renal glucosuria (> 10 g/1.73 $m^2/24h$) with a favorable prognosis [5,6]. Such activation has been shown after the administration of empagliflozin in type 1 diabetic patients [7]. I infer that in poorly-controlled diabetic patients, pre-existing osmotic diuresis is supposed to be augmented by the administration of SGLT2 inhibitors, possibly leading to an acceleration of their dehydration in spite of amelioration of hyperglycemia. Hypovolemia is inferred to be more likely to occur due to osmotic diuresis without an increase in blood glucose level to retain water [8].

In subgroup analyses of the EMPA-REG OUTCOME study, it is of note that the primary cardiovascular outcomes were increased in patients with glycated hemoglobin $\geq 8.5\%$ who received empagliflozin [1]. It may be recommended that use of SGLT2 inhibitors should be avoided in diabetic patients with glycated hemoglobin $\geq 8.5\%$ at high risk for cardiovascular events. It seems to be a plausible option for such patients to decrease carbohydrate intake by 50 to 100 g of carbohydrate per day during hyperglycemia, instead of excreting a similar amount of glucose into urine with SGLT2 inhibitors [8], especially for Asian people who preferentially eat carbohydrate-rich foods.

Then, how was empagliflozin working for the secondary prevention of cardiovascular events in the EMPA-REG OUTCOME study? SGLT2 inhibitors have some advantages including modest weight loss, low risk of hypoglycemia and mild decrease of blood pressure [9]. However, in the study, all patients received standard care by optimal blood-pressure lowering and glucose-lowering therapy with agents other than SGLT2 inhibitors. Several mechanisms behind the cardiovascular benefits of empagliflozin were raised in the discussion of the original article [1], such as changes in arterial stiffness and cardiorenal function. Because empagliflozin did not seem to have any effect on nonfatal myocardial infarction and stroke, some clinical researchers think that its beneficial effect on cardiovascular mortality was mediated through osmotic diuresis probably as a class effect of all SGLT2 inhibitors [10]. I agree with this idea, and expect that SGLT2 inhibitors can be used as a new oral osmotic diuretic to excrete water with a little sodium into urine [11-13] for non-diabetic patients with heart failure as well. Such diuretic action of SGLT2 inhibitors, possibly hard to cause electrolyte imbalance, seems to be rather close to that of tolvaptan, a selective oral vasopressin V_2 -receptor antagonist to promote water diuresis or aquaresis (excretion of electrolyte-free water) [14]. Tolvaptan was effectively and safely added to sodium diuretics for a short period in patients with decompensated heart failure [15,16]. Thus, the EMPA-REG OUTCOME study has brought a new insight into use of SGLT2 inhibitors in patients with type 2 diabetes. Still caution and prudence should be required for its adverse effects such as genital infection increased in the study.

Conflict of Interest: The author declares that he has no conflict of interest.

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