

Acute Effects of Preventing Heart Failure by Sodium-Glucose Cotransporter 2 Inhibitors

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To the Editor

EMPA-REG OUTCOME showed a significantly lower rate of hospitalization for heart failure by 35% than placebo [1]. In the CANVAS program [2], there was a significantly lower rate of hospitalization for heart failure in the canagliflozin group (33% relative risk reduction) than placebo. In DECLARE-TIMI 58, dapagliflozin resulted in a lower rate of hospitalization for heart failure (hazard ratio: 0.73; 95% confidence interval (CI): 0.61 - 0.88) [3].

A significant difference in hospitalization for heart failure between sodium-glucose cotransporter 2 inhibitors (SGLT2i) and placebo immediately after the start of the trial [1-3] made us think of acute and chronic effects of reducing heart failure by SGLT2i [4]. An early decline of estimated glomerular filtration rate (eGFR) from the start of SGLT2i and a subsequent gradual increase in eGFR were observed in EMPA-REG OUTCOME trial and our previous study [5, 6]. The phase showing a decline of eGFR may indicate acute effects of SGLT2i. Osmotic diuresis and increased urinary sodium excretion may induce body fluid depletion, which may result in reducing blood pressure and preventing the development of heart failure by acting like diuretics (Fig. 1) [4].

In our previous study, an increase of hematocrit levels in the B-type natriuretic peptide (BNP)-increased group was significantly smaller than the BNP-decreased group [7]. The change in plasma BNP levels was negatively and significantly correlated with change in hematocrit levels. The eGFR decreased in the BNP-decreased group, and eGFR increased in the BNP-increased group. The change in plasma BNP levels was positively and significantly correlated with change in eGFR. Serum blood urea nitrogen (BUN) increased in the BNP-decreased group, and BUN decreased in the BNP-increased group. These results support a significant contribution of SGLT2i-induced body fluid depletion to prevention of heart failure in the early phase [7]. Chronic effects of SGLT2i for prevention of heart failure include improvement of myocardial energetics, reduction of al-

buminuria, suppression of eGFR decline, reduced sympathetic overactivity and anti-atherosclerotic effects (Fig. 1) [4, 8, 9].

Recent randomized controlled trials (RCTs), DAPA-HF and EMPEROR-Reduced showed that reduced hospitalization for heart failure with administration of SGLT2i to non-diabetic patients with heart failure can better explain the acute effects of SGLT2i on improving heart failure [10, 11]. I calculated the risk reduction of hospitalization for heart failure at 6 months after the start of SGLT2i (regarded as acute phase) by using the cumulative incidence of hospitalization for heart failure in the pooled SGLT2i group and the placebo group (Fig. 2). All patients studied in EMPA-REG and CANVAS Program had type 2 diabetes. In both studies, SGLT2i significantly reduced the risk of hospitalization for heart failure during an early phase. DAPA-HF and EMPEROR-Reduced included over 50% of non-diabetic patients. Risk reduction of the hospitalization for heart failure in DAPA-HF and EMPEROR-Reduced was smaller than that in EMPA-REG and CANVAS Program (Fig. 2).

SGLT2 is the major cotransporter involved in reabsorption of filtered glucose in the proximal tubule of the kidney. In type 2 diabetes, an increased amount of glucose is filtered by the kidneys and SGLT2 is upregulated, leading to increased glucose absorption and worsening hyperglycemia [12]. SGLT2i cause osmotic diuresis and calorie leakage into the urine; therefore, the benefits of SGLT2i could include blood pressure lowering and weight control [12]. Therefore, acute effects of SGLT2i such as osmotic diuresis, increased sodium excretion and reduced blood pressure may be greater in diabetic patients than in non-diabetic patients, which can explain the smaller risk reduction of the hospitalization for heart failure in DAPA-HF and EMPEROR-Reduced as compared with that in EMPA-REG and CANVAS Program. Smaller reduction of systolic blood pressure in DAPA-HF (-1.27 mm Hg) and EMPEROR-Reduced (-0.7 mm Hg) as compared with that in EMPA-REG (-3 to -4 mm Hg) and CANVAS Program (-3.93 mm Hg) supports my hypothesis.

In conclusion, osmotic diuresis and increased urinary sodium excretion may induce body fluid depletion and reduction of blood pressure, which may be acute effects of preventing heart failure by SGLT2i.

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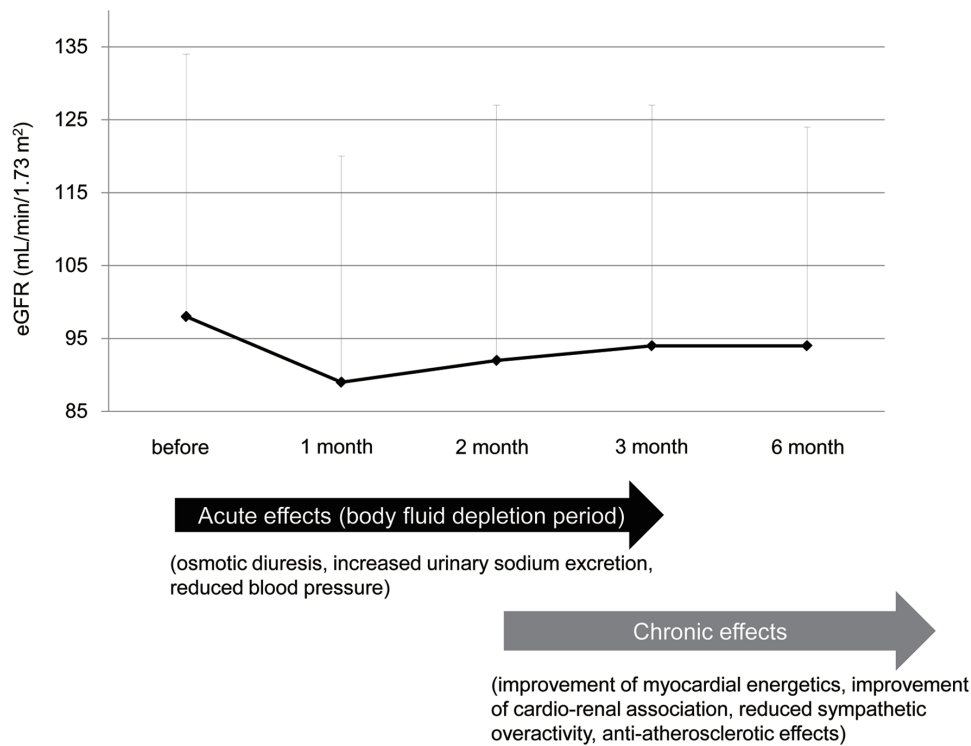


Figure 1. Acute and chronic effects of preventing heart failure by sodium-glucose cotransporter 2 inhibitors (SGLT2i). The change of estimated glomerular filtration rate (eGFR) was made by modification of our previous study [6].

Trials	EMPA-REG	CANVAS Program	DAPA-HF	EMPEROR-Reduced
Patients with type 2 diabetes (%)	100%	100%	41.8%	49.8%
Patients with heart failure (% SGLT2i and placebo)	9.5% and 10.5%	13.9% and 15.1%	100%	100%



Figure 2. Risk reduction of the hospitalization for heart failure at 6 months after the start of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in randomized controlled trials (RCTs) which included non-diabetic patients or not.

Financial Disclosure

Author has no financial disclosures to report.

Conflict of Interest

The author declares that he has no conflict of interest concerning this article.

Informed Consent

Not applicable.

Author Contributions

HY designed the research, and collected and analyzed data. HY wrote and approved the final paper.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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