Sodium-glucose cotransporter 2 inhibitors (SGLT2i), a newly emerging class of oral therapeutic agent for diabetes mellitus (DM), inhibit sugar reabsorption in the proximal renal tubule and reduce blood glucose levels by excreting sugar into the urine. In recent years, 2 large clinical trials (EMPA-REG OUTCOME and CANVAS) have revealed that SGLT2i can improve the prognosis of type 2 DM patients with high cardiovascular risk. In particular, an improvement in the hospitalization rate for heart failure (HF) has been presented from the early phases of these trials, with the spotlight on the diuretic effect of SGLT2i as a hypothesized mechanism for improved prognosis.

One hypothesized mechanism underlying the cardiovascular benefit of SGLT2i is a diuretic effect (Figure). SGLT2i reduce renal glucose reabsorption, leading to glucose excretion into the urine, transient natriuresis, and mild but persistent osmotic diuresis. SGLT2i primarily act on the proximal tubule to induce osmotic diuresis, but this effect is minimal and the principal mechanism for the improvement of prognosis is focused on the loop diuretic effect attributed to resorption in Henle’s loop. Thus, SGLT2i reduce body fluid volume, resulting in an antihypertensive effect equivalent to that of low-dose thiazide diuretics. In a subanalysis of the EMPA-REG trial, myocardial protective agents such as renin-angiotensin-aldosterone inhibitors and β-blockers were shown to contribute to the prognosis of HF, independent of SGLT2i. Furthermore, the diuretic effect of SGLT2i has been
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suggested to improve HF prognosis, as the prognostic effect of SGLT2i was not significant under treatment with diuretics. Regarding body composition, the total fat and extracellular water content has been reported to decrease at 3 months after administration of SGLT2i. In a subanalysis of the EMPA-REG OUTCOME trial, a risk reduction of HF hospitalization in the empagliflozin group was observed within 1 month of commencing treatment with SGLT2i, and this effect persisted throughout the study period. However, detailed data on cardiac function have been lacking in both of these large clinical trials to date, and the efficacy and safety of SGLT2i in DM patients with advanced HF therefore remain unknown.

In this issue of the Journal, Seo et al11 investigate the efficacy and safety of SGLT2i in 12 DM patients with advanced HF. In this preliminary study, a reduction in B-type natriuretic peptide level and improvement in New York Heart Association functional class 6 months after treatment are reported. In addition, no cardiac events or adverse effects were observed. These important results represent a key step towards the future management of HF using SGLT2i. However, some concerns remain unresolved in this study. First, regarding cardiac function, left ventricular end-diastolic volume was statistically decreased but ejection fraction and grade of mitral regurgitation were unchanged. However, the left ventricular velocity-time integral (LVOT-VTI) reflecting stroke volume was statistically increased. Second, weight loss and blood pressure reduction, which were reported in the previous trials, were not observed. However, in the previous trials, these findings may have been the result of the aforementioned diuretic effect or other multifaceted effects. Finally, changes in cardiac output were unknown in this study. LVOT-VTI was increased but heart rate was decreased. It is essential to ensure adequate cardiac output and maintain systemic organ perfusion in the management of advanced HF. Decrease in pre/afterload caused by rapid natriuresis may result in decomposition of hemodynamics in some cases. No studies to date have examined in detail the acute hemodynamic changes in HF patients during SGLT2i administration. Although it is unclear whether these inconsistencies arise from the small patient number or biased etiology, further studies in larger numbers of patients are needed before the findings can be applied more generally in advanced HF.

Several clinical trials of SGLT2i, with a focus on the management of HF, are ongoing at present, including an evaluation of the effect of dapagliflozin on the incidence of worsening HF or cardiovascular death in patients with chronic HF (Dapa-HF),12 a randomized, non-inferiority trial to examine the safety of canagliflozin in diabetic patients with chronic HF (CANDLE),13 and an empagliflozin outcome trial in patients with chronic HF (EMPEROR HF Program).14 Of particular interest, the CANDLE trial will investigate the safety and non-inferiority of canagliflozin compared with glimepiride in Japanese patients with type 2 DM and chronic HF. This trial has the potential to determine the clinical safety and efficacy of SGLT2i against HF. Of additional interest, the EMPEROR HF Program is unique because HF patients both with and without type 2 DM are being enrolled, meaning that the efficacy and safety of empagliflozin will be evaluated both with and without DM as a comorbidity.

Little evidence has been reported to date on how to exploit the diuretic effect of SGLT2i in the management of HF. However, it is first necessary to establish the efficacy and safety of SGLT2i in HF patients in large-scale clinical trials. Furthermore, investigation of acute hemodynamic change or diuretic response with the use of SGLT2i will be required for patient stratification in HF.

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