When Should We Start Sodium–Glucose Co-transporter Inhibitors in Patients with Heart Failure? The Importance of Early Intervention

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Sodium–glucose co-transporter (SGLT2) inhibitors were primarily developed as anti-diabetic drugs to increase the excretion of glucose in the urine. However, SGLT2 inhibitors have been reported to have multifactorial effects, such as renal protection and improvement of myocardial energy metabolism and anaemia symptoms, which may exert protection against progression of heart failure beyond their mere diuretic action.

Based on the results of large-scale clinical trials (DAPA-HF, EMPEROR-Reduced), the 2021 European Society of Cardiology heart failure guideline has recommended SGLT2 inhibitors as one of the first-line drugs for treatment of heart failure with reduced ejection fraction (HFrEF) in diabetic and non-diabetic patients.[1–3] Furthermore, in heart failure with preserved ejection fraction (HFpEF; left ventricular ejection fraction [LVEF] >40%), empagliflozin and dapagliflozin were recently shown to significantly reduce the combined endpoint of cardiovascular death and hospitalisation for heart failure in the EMPEROR-Preserved and DELIVER trials, respectively.[4,5] The benefit of these drugs was mainly seen in reducing hospitalisation due to worsening heart failure. Although there were slight differences in the enrolment criteria for the EMPEROR-Preserved and DELIVER trials, the patients' backgrounds in both trials were similar.[4,5] However, the ratio of patients with New York Heart Association (NYHA) III/IV was higher in the DELIVER trial than in the EMPEROR-Preserved trial (NYHA III/IV: 25% in DELIVER versus 18% in EMPEROR-Preserved), and the ratio of patients with loop diuretics use was higher in the DELIVER trial (77%) than in the EMPEROR-Preserved trial (68%). Therefore, a possibility exists of slightly more serious cases being enrolled in the DELIVER trial.

The PARAGON-HF trial, which investigated the efficacy of angiotensin receptor-neprilysin inhibitor (ARNI) for HFpEF, showed no efficacy of ARNI in the group with LVEF above the median (ejection fraction >57%).[6,7] Unlike the PARAGON-HF trial, an integrated analysis of the EMPEROR-Preserved and DELIVER trials showed a significant reduction in cardiovascular death and hospitalisation for heart failure with SGLT2 inhibitors in the normal LVEF group (≥60%), as well as in the low LVEF group (<60%), and the efficacy of SGLT2 inhibitors was consistent regardless of LVEF.[8]

SGLT2 inhibitors have been shown to be effective in a broad spectrum of heart failure patients. The question arises, then: at what time point should we begin prescribing these drugs?

A secondary analysis of the DELIVER trial revealed a reduction in cardiovascular death and worsening heart failure soon after the initiation of the drug.[9] The results of an integrated analysis of four trials on SGLT2 inhibitors for treatment of HFrEF and HFpEF suggest that the efficacy of SGLT2 inhibitors may decrease in patients with heart failure with severe symptoms (NYHA III/IV) compared to those with NYHA II (interaction p=0.015).[5] Regarding the acute phase of heart failure, the early initiation of SGLT2 inhibitors was shown to have few side effects and interactions, and it was easy to find the correct dose.[10,11]

A randomised, double-blind, placebo-controlled, multicentre trial, which evaluates the efficacy and safety of initiating empagliflozin in the acute phase before clinical stabilisation in high-risk patients with acute heart failure, is currently ongoing.[12] Furthermore, a large-scale randomised controlled trial showed that SGLT2 inhibitors reduced new-onset heart failure in patients with pre-heart failure.[13]

Considering these results, SGLT2 inhibitors are beneficial across the entire spectrum of heart failure; from prevention of worsening chronic heart failure to improvement of acute heart failure. The benefits may be more significant if treatment with SGLT2 is started during the early stages of heart failure rather than in the more advanced stages. Therefore, these drugs should be administered as soon as heart failure symptoms have developed, even if patients are in a stable state. To prevent the progression and worsening of this condition, it is necessary to raise awareness about the need to introduce SGLT2 inhibitors in the early stages of heart failure. ❑

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