BRIEF COMMUNICATION

Effect of Background Diuretic Therapy on the Clinical Efficacy of SGLT2 Inhibitors in Patients of Heart Failure with Reduced Ejection Fraction: Current Evidence

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ABSTRACT

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a fundamental therapy for heart failure with reduced ejection fraction (HFrEF). The clinical efficacy of SGLT2 inhibitors in the presence of background diuretic therapy has been questioned, mainly because of the overlapping diuretic mechanism of action. However, recently, data analysis from two landmark trials, DELIVER and EMPEROR-Reduced, has attempted to settle this question. Both analyses demonstrate a consistent benefit of SGLT2 inhibitors across a wide range of background diuretic therapy. This brief communication sheds light on the key findings from these scientific studies.

Keywords: SGLT2 inhibitors, heart failure, DELIVER, EMPEROR-Reduced

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have been given class 1 recommendation for managing patients of heart failure with reduced ejection fraction (HFrEF)[1,2]. SGLT2 inhibitor treatment can significantly reduce the rates of cardiovascular death and hospitalization due to heart failure (HF). The beneficial effect of SGLT2 inhibitors is regardless of the patient's glycemia levels and extends even in patients with an estimated glomerular filtration rate (eGFR) as low as 20 mL/min/1.72 m^2 [3,4]. Additionally, the clinical benefits of SGLT2 inhibitors are regardless of the dose or combination of other novel disease-modifying therapies used for HFrEF.

KEY QUESTION

Considering the osmotic diuretic effect of SGLT2 inhibitors, physicians worldwide have expressed concerns that the favorable clinical results demonstrated by SGLT2 inhibitors in patients with HFrEF might be attributed to the concomitant use of loop diuretic therapy. Therefore, there is a debate about how diuretic use affects the effectiveness of SGLT2 inhibitors in patients with HFrEF.

In the context of HFrEF, two scientific papers prespecified the analysis of the DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With Preserved Ejection Fraction Heart Failure) trial[5], and a post-hoc analysis of the EMPEROR-Reduced (EMPagliflozin outcomE tRial in Patients with chrOnic heaRt Failure With Reduced Ejection Fraction) trial[6] recently explored the effect of background diuretic therapy on the clinical efficacy of SGLT2 inhibitors.

The DELIVER trial[7] looked at patients with HF who had mildly reduced to preserved ejection fraction, whereas the EMPEROR-Reduced trial[4] examined patients with more advanced HF. Both analyses showed similar findings regarding the cardiac impact of background diuretic therapy on the clinical effectiveness of SGLT2 inhibitors.

KEY FINDINGS

Four critical findings are worth mentioning.

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Higher Baseline Diuretic Doses Indicate More Advanced HF

Individuals with high initial prescription of diuretics are likely to have more advanced HF, making them more susceptible to various negative clinical outcomes. Such individuals have elevated levels of N-terminal pro–B-type natriuretic peptide levels, higher rates of HF hospitalization, and poor baseline Kansas City Cardiomyopathy Questionnaire (KCCQ) scores. Additionally, these patients also have higher body mass index, higher rates of diabetes, and chronic kidney disease.

Attenuated Efficacy of SGLT2 Inhibitor in the Background of Higher Baseline Diuretic

A post-hoc analysis of the EMPEROR-Reduced trial revealed that empagliflozin was less effective in reducing the number of HF hospitalizations in patients taking high doses of diuretic agents. These patients are typically sicker and have a higher burden of comorbidities. The trial also found that such individuals had higher rates of discontinuing guideline-directed medical treatment. This partially explains why empagliflozin is less effective in individuals of HFrEF on higher baseline diuretics.

The Treatment Effect of SGLT2 Inhibitor Remains Consistent Irrespective of Baseline Diuretic Therapy

SGLT2 inhibitors demonstrated consistent beneficial effects irrespective of the baseline diuretic therapy. SGLT2 inhibitors lead to consistent improvement in cardiovascular death, time-to-first hospitalization for HF, and worsening HF events, including urgent hospital visits for need of intravenous HF therapies. Additionally, benefits did not significantly vary by baseline diuretic use/type or loop diuretic dose. SGLT2 inhibitors result in an improvement of the KCCQ total symptom score across all doses of diuretics.

SGLT2 Inhibitor Exhibited a Diuretic-Sparing Effect

SGLT2 inhibitor exhibits a diuretic-sparing effect. It delays the first diuretic dose increase (except for those taking the highest doses of diuretic agents) and diuretic initiation (in those not taking diuretic agents at baseline). Individuals on dapagliflozin, when compared to placebo, less frequently experience a loop diuretic initiation or dose increase (14.8% vs. 19.6%, $p < 0.001$) and more regularly experience a loop diuretic discontinuation or dose decrease (14.7% vs. 16.5%, $p < 0.001$). Additionally, treatment with dapagliflozin significantly attenuates the rate of rise in loop diuretic dose relative to placebo, resulting in a mean dose reduction over time of 2.5 mg/year (95% confidence interval [CI]: −1.5, −3.7, $p < 0.001$). Similarly, empagliflozin lengthens the time to first diuretic dose increase in all patients taking diuretic agents at baseline (hazard ratio [HR]: 0.68 [95% CI: 0.58-0.80]; $p < 0.001$) and time to diuretic initiation among patients taking no diuretic agents at baseline (HR: 0.62 [95% CI: 0.44-0.88]; $p < 0.01$).

CONCLUSION

To sum up, the results from these analyses confirm the scientific assertion that the positive impact of SGLT2 inhibitors on individuals with HFrEF is consistent across the various doses of background diuretic therapy. Moreover, these insightful analyses allay any apprehensions that certain clinical benefits observed in trials may be attributed to concurrent diuretic therapy.

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