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Review Article

Sglt-2 Inhibitors: A Useful Addition for Treatment of Heart Failure with Mildly Preserved and Preserved Ejection Fraction

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Abstract:

Background: The use of sodium-glucose cotransporters type 2 (SGLT2) inhibitors is associated with reduction in cardiorenal outcomes in patients with heart failure and reduced left ventricular ejection fraction (HFrEF).

Objective: To clarify the therapeutic role of SGLT2 inhibitors in patients with heart failure and mildly preserved ejection fraction (HFmpEF) and heart failure with preserved ejection fraction (HFpEF).

Methods: Pubmed search until October 13, 2022. Search terms included: heart failure, SGLT2 inhibitors, hospitalization, mortality, safety. Randomized clinical trials and guidelines of major societies were reviewed.

Results: 2 well-designed trials, the EMPEROR-Preserved and DELIVER trials, have shown that use of SGLT2 inhibitors was associated with decrease cardiac events in patients with HFmpEF and HFpEF. In the EMPEROR-Preserved, empagliflozin 10 mg/d decreased a composite primary outcome of cardiovascular (CV) death or hospitalization for heart failure (HHF) compared with placebo, hazard ratio (HR) 0.79 (95% CI, 0.69-0.90, P<0.001). In the DELIVER Trial, dapagliflozin 10 mg/d decreased the primary outcome of CV death or worsening HF, HR 0.82 (95% CI 0.73-0.92, P<0.001). The effects of empagliflozin and dapagliflozin on the primary outcome were evident and statistically significant versus placebo after 13-18 days post randomization. In both EMPEROR-Preserved and DELIVER trials, no significant effects on CV death were demonstrated. By pooling data from the 2 trials, the effects of empagliflozin and dapagliflozin on CV death was close but did not reach statistical significance, HR 0.88 (95% CI 0.77-1.00, P=0.052). Meanwhile, after pooling 2 dapagliflozin trials to include patients with HFrEF (DAPA-HF trial) and HFmpEF + HFpEF (DELIVER trial), dapagliflozin significantly decreased CV death, HR 0.86 (95% CI, 0.75-0.98, P=0.02) and all-cause mortality, HR 0.90 (95% CI, 0.82-0.99, P=0.03). The CV effects of empagliflozin and dapagliflozin were consistent regardless of age, gender, presence or absence of diabetes or atrial fibrillation. Yet, the effect of empagliflozin on decreasing HHF was attenuated in patients with baseline left ventricular ejection fraction (LVEF) of ≥60% and disappeared at LVEF ≥65%. On the other hand, dapagliflozin effects on cardiac outcomes remained consistent regardless of baseline LVEF. Both empagliflozin and dapagliflozin were generally well tolerated, with rates of drug discontinuation due to adverse effects similar to those with placebo.

Conclusions: SGLT2 inhibitors should be the standard of care in patients with HFmpEF and HF pEF similar to their established indication in patients with HFrEF. Until direct comparison between empagliflozin and dapagliflozin becomes available, dapagliflozin should be the SGLT2 inhibitor of choice, particularly in patients with HFmpEF and HFpEF.

Keywords: SGLT2 inhibitors; heart failure; mortality; ejection fraction; safety

Introduction

Accumulating evidence have shown that use of SGLT-2 inhibitors was associated with decrease in HHF and CV death in patients with HFrEF (defined as LVEF ≤40%) with and without diabetes [1,2]. Accordingly, current guidelines recommend SGLT2 inhibitors in patients with HFrEF to reduce HHF and CV mortality irrespective of presence of type 2 diabetes (class IA recommendation, i.e., strong recommendation, high-quality evidence) [3]. In patients with HFmpEF (LVEF 41-49%) and HFpEF (LVEF ≥50%), treatment options of are limited [3]. The first study that suggested a role of SGLT2 inhibitors in treatment of HFpEF was the SOLOIST-WHF trial that evaluated sotagliflozin versus placebo in patients with diabetes and recent HF (n=1,222) [4]. In the latter study, sotagliflozin decreased HHF, urgent visits for HF, or

CV death by an impressive 52% (HR 0.48, 95% 0.27-0.86) in the subgroup of patients with LVEF ≥50%. This subgroup constituted 21% of the study population) [4]. Unfortunately, the SOLIST-WHF was terminated prematurely after a median follow-up of 9 months due loss of funding [4].

More recently, 2 landmark trials, the EMPEROR-Preserved and DELIVER, were published [5,6]. Both trials were specifically designed to examine the effects of empagliflozin and dapagliflozin, respectively on CV clinical outcomes in patients with HFmpEF and HFpEF [5,6]. The main purpose of this review is to provide a critical appraisal on the therapeutic role of the 2 SGLT2 inhibitors empagliflozin and dapagliflozin in patients with HFmpEF and HFpEF based on the findings of the EMPEROR-Preserved and DELIVER trials.

Overview of the EMPEROR-Preserved and the DELIVER trials

The EMPEROR-Preserved and the DELIVER trials are 2 large multinational randomized trials that examined the effects of empagliflozin and dapagliflozin, respectively on CV events in patients with symptomatic HFpEF [5,6]. Overview and main results of the 2 studies are summarized in table 1. Participants had New York Heart Association (NYHA) class II-IV and an LVEF of >40%, with evidence of structural heart disease (left ventricular hypertrophy or left atrial enlargement) associated with N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels of > 300 pg/ml and > 900 pg/ml in patients with atrial fibrillation. In general, inclusion and exclusion criteria of the 2 trials are similar with 2 differences. First, the DELIVER included patients with improved LVEF, i.e., those who had had a previous LVEF of < 40% but improved to > 40% at the time of enrollment [6]. Second, the cutoff of estimated glomerular filtration rate (eGFR) required for enrollment was different. Thus, patients were excluded from EMPEROR-preserved and DELIVER trials if their eGFR was < 20 ml/min/1.73 m^2 and < 25 ml/min/1.73 m^2, respectively [5,6]. Patients were randomized into 2 equal groups to receive empagliflozin 10 mg/d and dapagliflozin 10 mg/d versus placebo in addition to standard care of HF [5,6]. The primary outcome in the EMPEROR-Preserved trial was a composite of CV death or HHF. In the DELIVER trial, the primary outcome was a composite of CV death or worsening heart failure. The latter included HHF in addition to urgent visit for heart failure (i.e., a non-scheduled visit to an office or emergency department for a main diagnosis of HF requiring intravenous diuretic therapy) [6]. Thus, the DELIVER trial added urgent visits for HF to the composite primary outcome. Secondary outcomes differ between the 2 trials and are outlined in table 1.

Main results of EMPEROR-Preserved and the DELIVER trials

In the EMPEROR-Preserved trial, over a median of 26.2 months, a primary outcome event occurred in 13.8% and 17.1% of patients randomized to empagliflozin and placebo, respectively; HR 0.79 (95% 0.69-0.90; P< 0.001) [5]. In the DELIVER trial, over a median of 2.3 years, the primary outcome occurred in 16.4% and 19.5% of patients randomized to dapagliflozin and placebo respectively, HR 0.82 (95% CI, 0.73-0.92; P< 0.001) [6]. Interestingly, in both trials, the decrease in the primary outcome events was mainly driven by the significant reduction in incidence of HHF. Thus, HR for the decrease in HHF were 0.73 (95% CI 0.61-0.88) and 0.77 (0.67-0.89), with empagliflozin and dapagliflozin, respectively [5,6]. The difference in occurrence of CV death, HHF, or an urgent visit for heart failure between empagliflozin and placebo was recorded early becoming statistically significant at 18 days after randomization [7]. In case of dapagliflozin, this difference occurred at 13 days post-randomization and was sustained to the end of follow-up [8].

Effect on empagliflozin and dapagliflozin on cardiovascular and all-cause mortality

In EMPEROR-Preserved and DELIVER trials, the decreased risk of the second component of primary outcome, CV death, did not reach statistical significance (table 1) [5,6]. Similarly, neither empagliflozin nor dapagliflozin significantly decreased all-cause mortality (table 1) [5,6]. After pooling the results of both trials (n=12,251), the effect of empagliflozin and dapagliflozin on all-cause mortality remained non-significant, HR 0.97 (95% CI, 0.88-1.06), and reduction in CV death was close to statistically significant, HR 0.88 (95% 0.77-1.00; P =0.052) [9]. Meanwhile, in a meta-analysis of the 2 trials of dapagliflozin including patients (n=11,007) with HFrEF (DAPA-HF trial) and HFmpEF + HFrEF (DELIVER trial), dapagliflozin significantly decreased CV mortality (HR 0.86, 95% CI 0.75-0.98, P=0.02) as well as all-cause mortality (HR 0.90, 95% CI 0.82-0.99), P=0.03) [10]. Taken together, the above observations suggest that dapagliflozin, but not empagliflozin, may decrease CV death and all-cause mortality in patients with HF across the whole spectrum of EF i.e HFrEF, HFmpEF and HFpEF.

Subgroup analysis

The CV effects of empagliflozin and dapagliflozin on cardiac outcomes did not vary in subgroups classified by age, gender, body mass index, presence or absence of diabetes or atrial fibrillation, degree of frailty, or background use of CV medications [5,6,11-16]. However, a remarkable difference between empagliflozin and dapagliflozin emerged in terms of baseline LVEF. Thus, in case of dapagliflozin, its effects on CV outcomes did not differ across different values of LVEF ranging from ≤30% up to ≥ 60% [17]. However, in case of empagliflozin, the risk reduction in CV death and HHF was attenuated with LVEF ≥60% and is totally lost with LVEF≥65% [5, 18].

Patients with improved LVEF

Improved LVEF refers to those patients with a previous LVEF < 40% that improved to > LVEF > 40% [3]. Patients with improved EF deserves particular attention due to the following causes. First, despite their growing prevalence, they are usually excluded from trials of HFpEF [19]. Second, even when LVEF return to normal range, these subjects may have worse clinical outcomes than patients with no history of HF [19]. Third, preliminary data suggest that withdrawal of pharmacological HF drugs was associated with relapse in 36% of patients within 6 months of withdrawal [20]. Accordingly, current guidelines recommend that patients with improved EF should continue HF treatment [3]. Patients with improved LVEF were excluded from the EMPEROR-Preserved trial but were allowed to participate in DELIVER trial forming 18.3% of the study population [6,21]. Importantly, results from the DELIVER trial showed that the CV benefit of dapagliflozin was consistent in the subgroup of patients with improved EF [6].

Effects on symptoms of heart failure

Dapagliflozin and empagliflozin improved health-related quality of life symptoms of HF as evaluated by the Kansas City Cardiomyopathy Questionnaire (KCCQ) scored from 0 to 100, with higher scores indicating fewer symptoms and physical limitation. The amelioration in the KCCQ score was modest (mean improvement < 5 points) but statistically significant. Thus, mean placebo-corrected difference between baseline and month 8 in KCCQ total symptom score was in favor of dapagliflozin group, 2.4 points (95% CI, 1.5-3.4) [6]. With empagliflozin, corresponding difference was 1.53 (95% CI 0.85-2.40) at 32 weeks and 2.07 (95% 1.15-2.99) at 52 weeks [22].

Effects of empagliflozin on renal function

Effect of empagliflozin on renal function was among the prespecified secondary outcomes of the EMPEROR-Preserved trial but was not reported in the DELIVER trial [5,6]. The EMPEROR-preserved showed that the rate of decline in the eGFR was slower in the empagliflozin group than in the placebo group (-1.25 versus -2.62 ml/min/1.73 m^2 per year; P<0.001) [5]. In addition, Feirrera et al [23] performed post-hoc analysis of pooled data from the EMPEROR-REDUCED that evaluated patients with HFrEF and the EMPEROR-Reduced trials (total patient number 9,673). They found that empagliflozin, as compared with placebo, reduced the incidence of macroalbumimuria, defined as spot urine albumin-to-creatinine ratio (UACR) >300 mg/g, by 19% (HR 0.81; 95% CI 0.70-0.94; P=0.005) [23]. The latter effect was consistent in patients with baseline LVEF ≤40% and >40%, with eGFR ≤ 60 and > 60 ml/min/1.72 m^2, and those with and without diabetes [23].

Safety of empagliflozin and dapagliflozin

Both empagliflozin and dapagliflozin were well tolerated. Proportions of patients with serious adverse effects and those who discontinued treatment due to adverse effects were similar to those randomized to placebo (table 1) [5,6]. In EMPEREOR-Preserved, some adverse effects were reported more commonly with empagliflozin compared with placebo including hypotension (10.4% vs 8.6%), urinary tract infections (UTI) (9.9% vs 8.1%), and genital

infections (2.2% vs 0.7%) [5]. These adverse effects were not mentioned in DELIVER trial, except for "serious" UTI, which occurred equally in 1% of dapagliflozin and placebo groups [6]. It was reassuring that frequency of acute renal injury and hypoglycemia was not increased with empagliflozin or dapagliflozin [5,6].

Differences between empagliflozin and dapagliflozin

In terms of treatment of HF, dapagliflozin seems to be superior

to empagliflozin in 3 aspects. First, as mentioned above, when data from DELIVER trial and DAPA-HF trial were pooled to encompass the whole range of LVEF, dapagliflozin was associated with significant 14% reduction in CV death and 10% in all-cause death [10]. On the contrary, no mortality benefit was shown with empagliflozin [5]. Second, the cardiac benefits of dapagliflozin extends to patients with LVEF >60%, whereas in case of empagliflozin, this benefit was attenuated with LVEF >60%, and is totally lost with LVEF > 65% [5,18]. Third, in terms of safety, hypotension, UTI, and genital infections were reported more frequently with empagliflozin compared with placebo, whereas these adverse effects were not mentioned with dapagliflozin. The reasons for this discrepancy between empagliflozin and dapagliflozin are unclear but might be related to differences in patients' characteristics and presence of some dissimilarities in drug properties. Therefore, until head-to-head trials for direct comparison of empagliflozin and dapagliflozin become available, dapagliflozin should be the agent of choice in patients with HF in general, and those with HFpEF in particular.

Limitations

Although the EMPEROR-Preserved and DELIVER trials are well-designed, they suffer from several limitations [5,6]. First, owing to the multiple exclusion criteria, included patients are relatively healthier than patients in real-life. For instance, patients with eGFR <20 ml/min/1.73 m^2 have yet to studied. Second, while Asians were fairly represented in the 2 trials (13-20%), other ethnic groups are underrepresented. In fact, less than 5% of subjects were Blacks, and proportions of Hispanics were not reported. Therefore, it is still unknown whether SGLT2 inhibitors have similar or different effects in various ethnic groups and minorities. Third, some types of cardiomyopathies were excluded such as infiltrative cardiomyopathy (e.g., amyloidosis, sarcoid), genetic or obstructive hypertrophic cardiomyopathy.

Conclusions and current directions

Empagliflozin-Preserved and DELIVER trials provide strong evidence that the use of SGLT2 inhibitors in patients with HFmpEF and HFpEF may be associated with significant reduction in HHF [5,6]. These 2 categories of HF are of utmost need for new medications that convincingly reduce CV morbidity and mortality. Most recent guidelines published before the release of DELIVER Trial recommend SGLT2 inhibitors as class 2aB recommendation, i.e moderate-strength recommendation, moderate quality evidence, in patients with HFmpEF and HFpEF [3]. After release of results of the DELIVER Trial, it is likely that this recommendation will be upgraded to class 1A, similar to that in HFrEF. While neither empagliflozin nor dapagliflozin individually demonstrated decreased CV death and all-cause mortality in patients with HFmpEF and HFpEF over a median follow-up of up to 2.3 years, longer follow-up (e.g. 5 years) is needed to clarify the effects of SGLT2 inhibitors on these 2 outcomes. Nevertheless, pooling data of the 2 dapagliflozin trials, DAPA-HF and DELIVER, suggest that dapagliflozin may be associated with significant 14% reduction in CV death and 10% in all-cause death [10]. In addition, contrary to empagliflozin, dapagliflozin cardiac benefits persist at LVEF > 60%. Moreover, safety profile might be more favorable with dapagliflozin (table 1) [5,6]. Therefore, until head-to-head trials become available, dapagliflozin may be the SGLT2 inhibitor of choice for use in patients with HF. Advantages and limitations of SGLT2 inhibitors for treatment of HFmpEF and HFpEF are summarized in table 2.

	EMPEROR-Preserved [5]	**DELIVER Trial [6]**
Design	Randomized, double-blind, placebo controlled, 622 sites, 23 countries	Randomized, double-blind, placebo controlled, 350 sites in 20 countries
Patients' characteristics		
Number	5,988	6,263
Age (mean ±SD)	71.9 ± 9.5	71.7±9.5
Percentage women	44.6%	44.0%
Race	76% Whites, 4.3% Blacks, Asians 13.7%	Whites 70.8%, Blacks 2.5% Asians 20.4%
Main inclusion criteria	LVEF > 40% and NT-proBNP > 300 pg/ml	LVEF > 40% and NT-proBNP > 300 pg/ml. Patients with improved EF were allowed to participate.
Percentage with diabetes	49%	44.8%
LVEF (mean ±SD)	54.3±8.8%	54.1 ± 8.8%
Intervention	Empagliflozin 10 mg qday vs placebo	Dapagliflozin 10 mg qday vs placebo
Primary outcome	Composite of CV death or HHF	Composite of CV death or worsening heart failure
Secondary outcomes	First + recurrent HHF, rate of decline in the eGFR	Worsening HF + CV death, change from baseline in the total symptom score on the (KCCQ) at month 8, CV death, all-cause death
Median follow-up	2.18 years (26.2 months)	2.3 years
Effect SGLT2 inhibitor on primary outcome vs placebo	HR 0.79 (95% CI 0.69-0.90; P< 0.001)	HR 0.82 (95% CI 0.73-0.92; P<0.001)
Effect on HHF vs placebo	HR 0.73 (95% CI 0.61-0.88; P<0.001)	HR 0.77 (95% CI 0.67-0.89)
Effect on CV death vs placebo	HR 0.91 (95% CI 0.76-1.09)	HR 0.88 (95% CI 0.74-1.05)
Effect on death from any cause vs placebo	HR 1.00 (0.87-1.15)	HR 0.94 (95% 0.83-1.07)
Adverse effects		
Hypotension	Empagliflozin 10.4% vs placebo 8.6%	Not reported
Genital infections	Empagliflozin 2.2% vs placebo 0.7%	Not reported
Drug discontinuation due to adverse effects	Empagliflozin 19.1% vs placebo 18.4%	Dapagliflozin 5.8% vs placebo 5.8%

Table 1: Trials of empagliflozin and dapagliflozin on heart failure with preserved ejection fraction

Conflict of interest

The author has no conflict of interest to declare.

Abbreviations:

NT-proBNP: N-terminal pro-B type natriuretic peptide, LVEF: left ventricular ejection fraction, CV: cardiovascular, HHF, hospitalization for heart failure, eGFR: estimated glomerular filtration rate, KCCQ: Kansas City Cardiomyopathy Questionnaire, SGLT2: sodium-glucose cotransporter 2, HR: hazard ratio

Advantages

1. Rapid effect (after 13-18 days) on reduction of the composite outcome of CV death and HHF
2. Decrease in HHF is consistent with EF up to ≥ 60% with dapagliflozin, but disappears with EF ≥65% with empagliflozin
3. Significant amelioration of quality of life
4. Slow progression of CKD and decrease incidence of macroalbuminuria (UACR > 300 mg/g) demonstrated with empagliflozin
5. Similar benefits in patients with and without type 2 diabetes

Limitations

1. No evidence for decrease in CV death or all-cause death but significant reduction in those outcomes with dapagliflozin after pooling data across all spectrum of LVEF
2. Not studied in patients with eGFR < 20 ml/min/1.73 m^2
3. Not sufficiently evaluated in different ethnic groups.
4. High cost

Abbreviations:

CV: cardiovascular, HHF: hospitalization for heart failure, UACR; urine albumin-creatinine ratio, LVEF: left ventricular ejection fraction, CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate.

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