Dapagliflozin — a key pawn on the new guidelines chessboard

ABSTRACT

Treatment of patients with heart failure and reduced left ventricular ejection fraction (HFrEF) aims to reduce mortality, prevent rehospitalizations due to heart failure (HF) exacerbation, and improve the clinical status, functional capacity, and quality of life. All these goals were achieved in the DAPA-HF trial. In this trial, the reduction in the primary outcome, defined as a composite of worsening of HF or cardiovascular death, was achieved in patients receiving dapagliflozin [hazard ratio (HR) 0.74; 95% confidence interval (CI) 0.65–0.85; p < 0.001] as compared with placebo. In addition, the beneficial effect of dapagliflozin on the primary outcome was generally consistent across prespecified subgroups regardless of baseline treatment, diagnosis of diabetes, or left ventricular ejection fraction (LVEF).

Data from multiple countries was obtained in the CVD-REAL study. The use of different sodium-glucose co-transporter 2 (SGLT2) inhibitors, versus other glucose-lowering drugs, was associated with lower rates of hospitalization for HF (HR 0.61; 95% CI 0.51–0.73; p < 0.001) and death (HR 0.49; 95% CI 0.41–0.57; p < 0.001). These findings were confirmed in the CVD-REAL-2 study.

The exceptional clinical benefits of SGLT2 inhibitors applied on top of the previously guideline-recommended treatment in patients with chronic HFrEF led to fundamental changes in the recommended treatment strategy proposed in the 2016 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic HF.

To conclude, the new treatment algorithm for HFrEF is based on the findings of many groundbreaking trials. However, it is the results of trials with SGLT2 inhibitors, applied in patients with HFrEF on top of the optimal treatment including an implantable cardioverter-defibrillator and/or cardiac resynchronization therapy, that have fundamentally changed the strategy of treatment.

Key words: heart failure, SGLT2i, dapagliflozin
Material and methods

The DAPA-HF trial

Treatment of patients with HF aims to reduce mortality, prevent rehospitalizations due to HF exacerbation, and improve the clinical status, functional capacity, and quality of life [7]. All these goals were achieved in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial (Fig. 2) [8].

In this trial, 4744 patients with HF (NYHA II–IV) with reduced ejection fraction (<40%) were randomized to receive dapagliflozin 10 mg/day or placebo, on top of optimal standard therapy for HF [9, 10]. Patients with (45%) or without diabetes (55%) were enrolled. A significant reduction in the primary outcome, defined as a composite of worsening of HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or cardiovascular death, was achieved in patients receiving dapagliflozin (HR 0.74; 95% CI 0.65–0.85; p < 0.001) (Fig. 3). Each of the components of the primary outcome was also reduced — by 30% [HR 0.70 (95% CI 0.59–0.83); p < 0.0001] and 18% [HR 0.82 (95% CI 0.69–0.98); p = 0.029], respectively. Moreover, the reduction of all-cause mortality was also observed [HR 0.83 (95% CI 0.71–0.97); p = 0.022] in subjects treated with dapagliflozin [9]. It should be highlighted that patients with or without diabetes appeared to benefit to the same extent. The benefit of dapagliflozin could be seen soon after treatment initiation, and the number needed to treat during the follow-up period of 18.2 months was only 21 [8, 11]. The beneficial effect of dapagliflozin on the primary outcome was generally consistent across prespecified subgroups regardless of baseline treatment, diagnosis of diabetes, and LVEF [12]. However, patients in NYHA functional class III or IV appeared to have reduced benefit than those in class II [8, 13]. The efficacy and safety of dapagliflozin were also similar irrespectively of the diuretic dosage [14], the use of glucose-lowering therapy, or its type, in patients with diabetes and HF and reduced ejection fraction (HFrEF) [15]. Moreover, the benefit of dapagliflozin was almost identical, regardless of baseline sacubitril/valsartan use, suggesting that these 2 therapies have complementary biological mechanisms of action [16]. Longer HF duration was associated with an increased rate of the primary outcome. The absolute benefit of dapagliflozin was greatest in longest-duration HF. However, the relative benefit of dapagliflozin was consistent across the whole spectrum of HF duration. The hazard ratio for the primary outcome of HF duration of ≥ 2 to ≤ 12 months was 0.86 (0.63–1.18), > 1 to 2 years 0.95 (0.64–1.42), > 2 to 5 years 0.74 (0.57–0.96), and > 5 years 0.64 (0.53–0.78); p for interaction = 0.26 [17].
The use of dapagliflozin also resulted in improvement of symptoms of HF, as measured on the Kansas City Cardiomyopathy Questionnaire (KCCQ) — a validated, self-administered instrument that quantifies HF-related symptoms, function, and quality of life [18]. Fewer patients on dapagliflozin had a deterioration in KCCQ total symptom score (odds ratio (OR) 0.84 (95% CI 0.78–0.90); p < 0.0001). More patients had at least small [OR 1.15 (95% CI 1.08–1.23); p < 0.0001], moderate [OR 1.15 (95% CI 1.08–1.22); p < 0.0001], and large improvements [OR 1.14 (95% CI 1.07–1.22); p < 0.0001] [18]. The high efficacy of dapagliflozin was accompanied by a favorable safety profile and very good drug tolerance. Serious adverse events related to volume depletion occurred in 29 patients (1.2%) in the dapagliflozin group and in 40 patients (1.7%) in the placebo group (p = 0.23). Serious renal adverse events occurred in 38 patients (1.6%) in the dapagliflozin group and in 65 patients (2.7%) in the placebo group (p = 0.009). Major hypoglycemia was very rare (0.2% in both arms), as was diabetic ketoacidosis (0.1%) in patients on dapagliflozin, and both of these adverse events occurred only in patients with diabetes [8]. The rate of study treatment discontinuation due to adverse events was similar in both arms. It occurred in 111 patients (4.7%) in the dapagliflozin group and 116 patients (4.9%) in the placebo group [8].

Scientific evidence supporting the clinical efficacy of SGLT2 inhibitors

The DEFINE-HF study (Dapagliflozin Effects on Biomarkers, Symptoms and Functional Status in Patients
with HF with Reduced Ejection Fraction) demonstrated a beneficial effect of dapagliflozin, with clinically significant improvements in disease-specific health status and natriuretic peptides levels in patients with HFrEF, with and without diabetes, receiving optimal medical therapy [19].

A meta-analysis of the two large-scale trials - DAPA-HF and EMPEROR-Reduced — was performed to assess the effects of SGLT2 inhibitors on cardiovascular outcomes in patients with HFrEF with or without diabetes. The estimated effect of SGLT2 inhibition was a 13% reduction in all-cause death (HR 0.87; 95% CI 0.77–0.98; p = 0.018) and 14% reduction in cardiovascular death (HR 0.86; 95% CI 0.76–0.98; p = 0.027) [20]. The scale of risk reduction of cardiovascular death was inconsistent in both trials, as the significant reduction was only achieved in the DAPA-HF trial. The relative reduction in cardiovascular death was 18% (HR 0.82; 95% CI 0.69–0.98) in the DAPA-HF trial (with dapagliflozin) and 8% (HR 0.92; 95% CI 0.75–1.12) in the EMPEROR-Reduced trial (with empagliflozin) [20]. A 26% reduction in the combined risk of cardiovascular death or first hospitalization for HF (HR 0.74; 95% CI 0.68–0.82; p < 0.0001) was seen in patients treated with dapagliflozin or empagliflozin versus placebo. Moreover, the composite renal end-point was also reduced (HR 0.62; 95% CI 0.43–0.90; p = 0.013) [20].

Data from multiple countries obtained in the CVD-REAL study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT2 Inhibitors) allowed comparison of the risk for HF hospitalization and death in patients with diabetes type 2 who were new users of SGLT2 inhibitors versus other glucose-lowering drugs in real-world practice [21]. The data were collected via medical claims, primary care/hospital records, and national registries from the United States, Norway, Denmark, Sweden, Germany, and the United Kingdom. After propensity matching for SGLT2 inhibitors initiation, the analysis was performed in 309,056 patients (154,528 patients in each treatment group). Patients on canagliflozin (53%), dapagliflozin (42%), and empagliflozin (5%) were included. The use of SGLT2 inhibitors, versus other glucose-lowering drugs, was associated with lower rates of hospitalization for HF (HR 0.61; 95% CI 0.51–0.73; p < 0.001) and death (HR 0.49; 95% CI 0.41–0.57; p < 0.001). The lower rates of death and hospitalization for HF associated with SGLT2 inhibitors are likely class-related, as there was no significant heterogeneity across countries, despite considerable
geographic variations in the use of specific SGLT2 inhibitors (≈76% canagliflozin in the United States and ≈92% dapagliflozin in Europe) [21].

The CVD-REAL-2 study was a continuation of the CVD-REAL project. It was conducted across 6 countries in the Asia Pacific, the Middle East, and North American regions [22]. After propensity-matching, there were 235,064 episodes of treatment initiation in each group (SGLT2 inhibitors versus other glucose-lowering drugs). Dapagliflozin, empagliflozin, ipragliflozin, canagliflozin, tofogliflozin, and luseogliflozin accounted for 75%, 9%, 8%, 4%, 3%, and 1% of exposure time in the SGLT2 inhibitors group, respectively. The use of SGLT2 inhibitors was associated with a lower risk of death (HR 0.51; 95% CI 0.37–0.70; p < 0.001), hospitalization for HF (HR 0.64; 95% CI 0.50–0.82; p = 0.001), and stroke (HR 0.68; 95% CI 0.55–0.84; p < 0.001). The results were directionally consistent across countries and patient subgroups, including those with and without cardiovascular disease [22].

The key role of SGLT2 inhibitors in the ESC guidelines

The 2016 ESC guidelines for the diagnosis and treatment of acute and chronic HF recommended a gradual introduction of key drugs into therapy, depending on their effect on clinical symptoms [23]. The exceptional clinical benefits of SGLT2 inhibitors applied on top of the previously guideline-recommended treatment [23] in patients with chronic HFrEF, regardless of coexistence of diabetes mellitus [8, 24], led to fundamental changes in the recommended strategy of treatment [25, 26].

A new simplified treatment algorithm for HFrEF (Fig. 4) and the addition of a phenotype-specific treatment algorithm for HFrEF (Fig. 5) are pivotal new concepts introduced in the new 2021 ESC guidelines for the diagnosis and treatment of acute and chronic HF [7]. According to the new algorithm, the first-line therapy should include four elements: angiotensin-converting enzyme inhibitors (ACE-I) or an angiotensin receptor-neprilysin inhibitor (ARNI), beta-blockers (BB), mineralocorticoid receptor antagonists (MRA), and SGLT2i (dapagliflozin or empagliflozin) unless the drugs are contraindicated or not tolerated. ACE-I should be replaced with ARNI in patients who remain symptomatic on ACE-I, beta-blocker, and MRA. However, instead of ACE-I, ARNI may also be applied as first-line therapy. Angiotensin-receptor blockers should be used in patients intolerant to ACE-I or ARNI [7]. The recommended 4-component (ACE-I/ARNI + BB + MRA + SGLT2i) first-line therapy proved to reduce the risk of HF hospitalization and death [8, 20, 24].

The new ESC guidelines emphasize the key role of multidisciplinary team management to implement HF management programs to prevent and treat chronic HF [7]. These programs, designed to improve clinical outcomes, should cover adequate preparation for hospital discharge and the further collaboration between members of the multidisciplinary team and patients. Furthermore, the organization of HF management programs should be adapted to the local healthcare system, available resources, administrative policies, and tailored to the patient’s needs [7]. Finally, implementing these recommendations implies the need to monitor the effectiveness of the actions taken using validated diagnostic tools to assess the readiness for discharge from the hospital, the implementation of the therapeutic plan, and functioning in chronic disease [27–36].
Figure 5. A phenotype-specific treatment algorithm for HFrEF – adapted from 2021 ESC guidelines [7]. ACE-I — angiotensin-converting enzyme inhibitors; ARB — angiotensin receptor blocker; ARNI — angiotensin receptor-neprilysin inhibitor; BB — beta-blockers; BTC — bridge to candidacy; BTT — bridge to transplantation; CABG — coronary artery bypass grafting; CRT-D — defibrillator with cardiac resynchronization therapy; CRT-P — pacemaker with cardiac resynchronization therapy; DT — destination therapy; ESC — the European Society of Cardiology; HF — heart failure; HFrEF — heart failure and reduced ejection fraction; ICD — implantable cardioverter-defibrillator; LBBB — left bundle branch block; LVEF — left ventricular ejection fraction; MCS — mechanical circulatory support; MRA — mineralocorticoid receptor antagonists; QoL — quality of life; SGLT2i — sodium-glucose co-transporter 2 inhibitors; SR — sinus rhythm; TEE — transoesophageal echocardiography
Figure 6. Selected groundbreaking trials in patients with HFrEF
Conclusion

In conclusion, the new treatment algorithm for HFrEF is based on the findings of many groundbreaking trials [8, 24, 37–44] (Fig. 6). However, it is the results of trials with SGLT2 inhibitors, applied in patients with HFrEF on top of the optimal treatment including an implantable cardioverter-defibrillator and/or cardiac resynchronization therapy, that have fundamentally changed the strategy of treatment.

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