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The Clinical Evidence of Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitor, Dapaglifozin, a New Pillar of Treatment for Heart Failure with Reduced Ejection Fraction

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ABSTRACT

Heart failure with reduced ejection fraction (HFrEF) remains burdensome because its morbidity and mortality is still relatively high. The current treatments implementing multiple drugs for controlling symptoms and reduced fatal event have been proposed, however the mortality rate remains constant. Sodium-glucose cotransporter-2 (SGLT2) inhibitor, a novel class of drugs, had been introduced as a new pillar for HFrEF treatment. The DAPA-HF trial showed the beneficial impression of dapagliflozin, an SGLT2 inhibitor, on reducing the risk of hospitalization and mortality in HFrEF patients with or without type 2 diabetes mellitus.

Introduction

The prevalence of heart failure remains high worldwide. As many as one in five people will develop heart failure during their lifetime.[1] Heart failure was estimated to affect more than 64 million people worldwide in 2016.[2] Patients with heart failure are at higher risk for morbidity and mortality. Heart failure morbidity and mortality rates are high despite advances in therapy.[3] In many developed countries, the 5-year heart failure mortality after diagnosis is around 50%.[4]

The improvement in mortality rate has been seen in major cardiovascular disease, including ischemic heart disease and stroke, but not for heart failure.[5] The data from the US National Health Interview Survey from 1988 to 2015 indicated that mortality rate for heart failure and arrhythmia remains constant despite the guideline-directed medical treatment implementation.5 Furthermore, the data from the cardiology practice registry showed that among heart failure with reduced ejection fraction (HFrEF), the guideline-directed medical treatments were not fully complied due to multiple factors.6 The use of angiotensin converting enzyme (ACE) inhibitors, angiotensin-receptor blocker (ARB), angiotensin-receptor neprilysin inhibitor (ARNI), beta blocker and mineralocorticoid receptor antagonist (MRA) as pillars for HFrEF treatments is inadequate. There were significant gaps in guideline-directed use and dosing of treatments.[6] Among these, MRA and ARNI were particularly underused.[6] The majority of patients were given sub target doses of ACE inhibitor/ARB/ARNI and beta-blocker with high proportions were prescribed <50% of target dose.[6]

The 2021 European Society of Cardiology (ESC) guidelines designate the trio of ACE inhibitor or ARNI, a beta-blocker, and MRA as the foundation treatment for all patients with HFrEF.[7] A considerable update was presented by this 2021 guideline for heart failure concerning the management of patients with HFrEF. One new recommendation was the approval the use of sodium-glucose cotransporter-2 (SGLT2) inhibitors, such as dapagliflozin and empagliflozin.[7] These drugs, in addition with the trio, were proven to lessen the risk of rehospitalization of worsening heart failure and mortality rate among HFrEF.[7] This brief review will discuss the clinical evidence of dapagliflozin, one of SGLT2 inhibitors, as a new pillar for treatment of HFrEF.

Discussion

The investigated effect of SGLT2 inhibition in improving heart failure outcomes was mediated by its hemodynamic fortification and myocardial protection. The inhibition of SGLT-2 implicates the reduction of both cardiac preload and afterload, by decreasing the plasma volume and diminishing vascular resistance.[8] The inhibition of SGLT-2 mediates the improvement of myocardial energetics by reducing the reliance on fatty acids metabolism, increasing the formation of ketone body and dropping the expression of cardiac sodium-hydrogen exchanger 1.[9,10] Cardiac remodeling was improved by the inhibition of SGLT2 by

weakening cardiac inflammation and fibrosis and reducing the cardiac wall stress.[9,10] All these beneficial effects are translated into clinical outcomes to protect against myocardial injury or heart failure (figure 1). Furthermore, the natriuresis and diuresis properties of SGLT2 inhibition reduce the necessity to intensify the use of diuretics to enhance decongestion in heart failure.[7]

The DAPA-HF (Dapagliflozin and Prevention of Adverse-outcomes in Heart Failure) trial is the first and largest clinical trial of SGLT2 inhibitor, dapagliflozin, in patients with HFrEF wich successfully improve the outcomes and recover the symptoms.[11] DAPA-HF recruited 4.744 subjects among who 45% were patients with type 2 diabetes mellitus and 55% without diabetes mellitus. This 1-1 allocation, randomized, double-blinded, placebo-controlled clinical trial enrolled 2373 subjects for being allocated into 10 mg oral dapagliflozin and 2371 in placebo arms. The inclusion criteria of this study were as follows: age ≥18 years with or without type 2 diabetes mellitus, left ventricle ejection fraction ≤40%, NYHA class functional II-IV, elevated level of NT-proBNP, estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2, and on stable standard of care for HFrEF treatment. The median follow-up period of DAPA-HF trial was 18.2 months. The primary endpoint was the time to first occurrence of any of the components of the composite of cardiovascular death or hospitalized heart failure or an urgent heart failure visit.[11]

The primary result of DAPA-HF trial showed the significant reduction in composite of cardiovascular death or worsening of heart failure. The 26% relative risk reduction (HR 0.74, 95%CI (0.65-0.85), p<0.001 was achieved in composite endpoints. The number-needed to treat for this end-point was 21, as shown in figure 2. For cardiovascular death, there was 18% relative risk reduction (p=0.029), while for worsening heart failure, including hospitalized or urgent heart failure visit, there was 30% relative risk reduction (p=0.00003) as compared to placebo, as shown in figure 3.[11]

The results of DAPA-HF trial were consistent across a broad and representative population of diabetes status, background of heart failure treatments, the use of diuretics and their doses, the baseline left ventricle ejection fraction, the level of NT-proBNP and the eGFR.[11] The risks of both first and recurrent heart failure events were reduced. The reduction of all-cause mortality was also significantly observed in DAPA-HF trial, with dapagliflozin associated with 17% relative risk reduction for all-cause mortality.[11] In subjects who received dapagliflozin, the improvement of symptoms of heart failure was more common and the deterioration was less common. The significantly reduced risk of cardiovascular death or worsening of heart failure was observed as early as 28 days of dapagliflozin administration.[11]

For safety evaluation, the DAPA-HF trial showed that 10 mg dapagliflozin was well tolerated in patients both with type 2 diabetes mellitus and without diabetes mellitus.[11] The adverse events rarely led to the discontinuation of treatment, namely volume depletion, renal adverse event, fracture, and amputation, which showed no significant difference as compared to placebo. There was no event of major hypoglycemia or diabetic ketoacidosis in patients without diabetes mellitus.[11]

The 2021 ESC guideline recommendation for HFrEF management endorses the use of dapagliflozin, among SGLT-2 inhibitors, for patients with HFrEF to reduce the risk of hospitalization and death due to heart failure.[7] The DAPA-HF trial result prompts class I and level A recommendation for the use of dapagliflozin, together with other I-A-list drugs (ACE inhibitors, beta blocker and MRA). Except contraindicated or not tolerated, dapagliflozin is recommended for patients with HFrEF already treated with ACE inhibitorARNI, beta-blocker, and MRA, regardless diabetes or not.[7]

The 2021 Update to the 2017 ACC expert consensus decision pathway for optimization of heart failure places SGLT-2 inhibitor as recommended treatment for stage C HFrEF along with ACE-inhibitor/ARNI/ARB, evidence-based beta blocker with diuretic agent as needed, if the eGFR value met.[12] For dapagliflozin, 10 mg daily is recommended if the eGFR ≥30 mL/min/1.73^2 for patients with HFrEF with or without diabetes mellitus, NYHA functional class II-IV and administered in conjunction with a background of optimal/guideline-directed medical treatment for heart failure.[7,12]

In the scientific statement by Working Group on Heart Failure and Cardiometabolic Indonesian Heart Association regarding the use of SGLT2 inhibitor for treatment of HFrEF, dapagliflozin can be recommended to heart failure NYHA functional class II-IV with LVEF ≤ 40% with or without type 2 diabetes mellitus to reduce mortality and risk of hospitalization due to worsening heart failure, attention to contraindication and tips of therapeutic approach is an important points to get the result according to the existing studies.[13]

Conclusion

There is still a huge burden on morbidity and mortality in heart failure. The DAPA-HF trial showed robust data on the risk reduction on heart failure and mortality by SGLT2 inhibitor, dapagliflozin, for heart failure with reduced ejection fraction in addition to recommended medical treatment. Both ESC and ACC/AHA in 2021 recommend the newest update and placement of dapagliflozin as one pillar of heart failure management.

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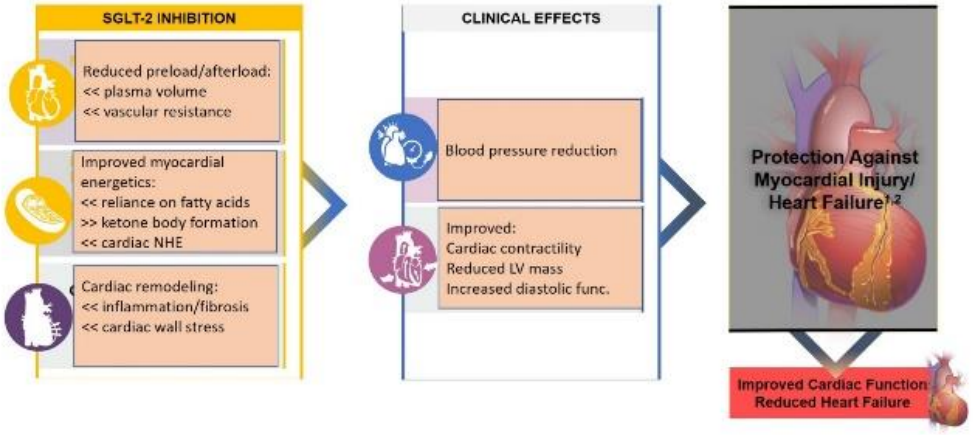

Figure 1. SGLT2 inhibition and its effect on clinical protection of heart failure (source: courtesy AstraZeneca Indonesia)

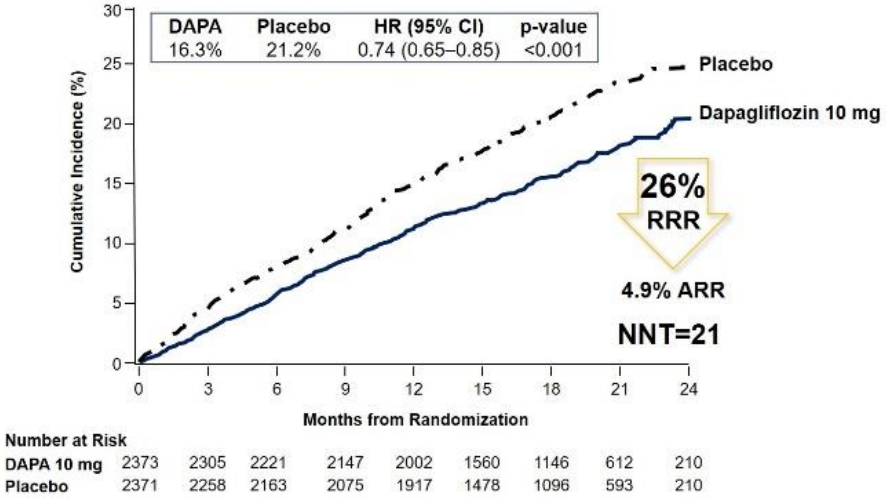

Figure 2. Dapagliflozin significantly reduced the relative risk of cardiovascular death or worsening heart failure on top of standard of care by 26% (source: DAPA-HF trial (courtesy AstraZeneca Indonesia)

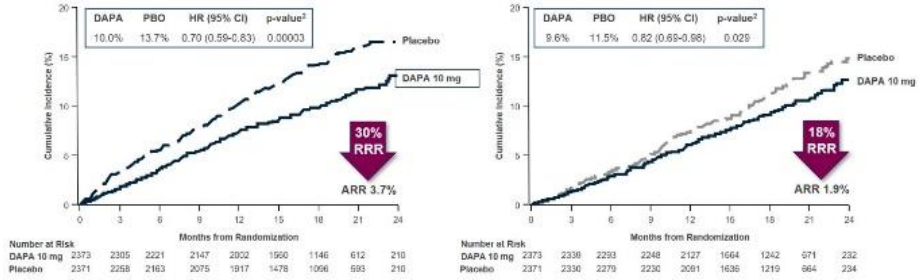

Figure 3. Individual components of the primary endpoint, worsening heart failure (left) and cardiovascular death (right), were significantly reduced with dapagliflozin (source: DAPA-HF trial (courtesy AstraZeneca Indonesia).

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