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Sodium Glucose Co-Transporter-2 (SGLT 2) Inhibitor as A Therapy For Heart Failure with Low Ejection Fraction (HFrEF)

Muhammad Gilang Dwi Putra[1], Sidhi Laksono[2,3*]
[1]*Department of Emergency Medicine, RSUD Sumedang, West Java, Indonesia*
[2] *Department of cardiology and vascular medicine, RS Pusat Pertamina, Jakarta, Indonesia*
[3]*Faculty of medicine of Universitas Muhammadiyah Prof Dr Hamka, Tangerang, Indonesia*
**Corresponding author: sidhilaksono@uhamka.ac.id*

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ABSTRACT

Heart failure is a major cause of cardiovascular morbidity and mortality worldwide despite advances in prevention and management. Recent clinical trial findings have shown that sodium-glucose co-transporter 2 inhibitor (SGLT2i) produces effects other than lowering blood glucose levels, i.e., exhibits beneficial cardiovascular effects. The purpose of this paper is to determine the role of SGLT2i in heart failure patients with low ejection fraction (HFrEF) so that it can be used as a guide for future management. This study is a narrative review by searching on Google Scholar through several keywords. The period including articles obtained is articles from 2014 to 2022. The diuretic effect of SGLT2i can cause an increase in cardiac preload. The reduction in cardiac afterload likely occurs through a decrease in blood pressure and arterial stiffness resulting in increased endocardial blood flow. SGLT2i has a beneficial effect on the heart remodeling process. SGLT2i can prevent heart failure by increasing the production of ATP from the oxidation of ketone bodiesSGLT2i in heart failure patients can reduce blood pressure, maintain a decrease in eGFR and reduce the risk of acute kidney injury (AKI) in patients. SGLT2i is very effective in the treatment of HFrEF patients. Because of these advantages, further research is needed in Indonesia in order to determine the effectiveness and impact of giving SGLT2i to HFrEF patients in Indonesia.

Keywords: SGLT2 inhibitors; Heart Failure; Therapy

INTRODUCTION

Heart failure is a functional or structural disorder of the heart ventricles that results in symptomatic left ventricular dysfunction. Heart failure is a complex clinical syndrome. Symptoms that arise are the amount of cardiac output that is inadequate so that it fails to meet the body's metabolic needs. Heart failure is a major cause of cardiovascular morbidity and mortality worldwide despite advances in prevention and treatment (Laksono et al., 2022; Hajouli & Ludhwani, 2022).

The prevalence of heart failure is projected to increase by 46% from 2012 to 2030 affecting >8 million people over 18 years of age. The percentage of the total population with heart failure in the world is projected to increase from 2.4% in 2012 to 3.0% in 2030. In 2018 more than 6 million people in the United States in the age group over 20 years had heart failure. This situation has increased when compared to data from 2015 which was only 5.7 million. Heart failure contributes to life expectancy and disability in men in North America, sub-Saharan eastern Africa, East Asia, and Southeast Asia (Tsao et al., 2022). Data from the *Riset Kesehatan Dasar* (Riskesdas) of the Indonesian Ministry of Health in 2018, the prevalence of heart failure in Indonesia based on a doctor's diagnosis was

estimated at 1.5% or an estimated of 29,550 people (Indonesian Central Bureau of Statistics, 2020; Rukmini R et al., 2022).

Recent clinical trial findings have shown that SGLT2i produces effects other than lowering blood glucose levels i.e., exhibits beneficial cardiovascular effects. It has been studied in various patients with type 2 diabetes mellitus (DM2) with heart failure (Laksono et al., 2022; Verma, 2019). Clinical guidelines from the American Heart Association in 2022 show that currently, therapy for patients with HFrEF includes 4 treatment groups namely 1) inhibition of the renin-angiotensin system with angiotensin receptor-neprilysin blockers (ARNi) such as sacubitril, angiotensin-converting enzyme (ACEi) inhibitors such as ramipril, perindopril, or angiotensin receptor (II) receptor blockers alone such as valsartan, candesartan; 2) beta-blockers such as bisoprolol, metoprolol; 3) mineralocorticoid receptor antagonists (MRAs) such as spironolactone, eplerenone; and 4) a new group, SGLT2i such as dapagliflozin and empagliflozin (Heidenreich et al., 2022). Previously, in 2021 the European Society of Cardiology released guidelines for the management of heart failure and added SGLT2i as a treatment option (Tomasoni et al., 2022).

With these conditions, the authors need to conduct a review study related to the role of SGLT2i in HFrEF so that it can be used as a guide for future management, especially for practitioners in Indonesia as empagliflozin and dapagliflozin are available in our country.

METHODS

This study is a narrative review by searching for related research on Google Scholar. The keywords used for the literature search were "SGLT2 inhibitor in HFrEF", "Clinical Considerations SGLT2i Heart Failure", "Heart Failure in Indonesia" and "Heart Failure Guidelines". The period including articles obtained is articles from 2014 to 2022. Journals using the guidelines, meta-analysis, non-case reports, systematic reviews, and literature review methods are included in this literature study. The authors then summarized and synthesized the findings from the articles found.

RESULT AND DISCUSSION

Mechanism of Action and Effect of SGLT2i in Heart Failure Patients

Heart failure is often accompanied by symptoms of fluid accumulation in the lungs and edema. The diuretic effect of SGLT2i can cause an increase in cardiac preload. SGLT2i acts differently compared to thiazides and loop diuretics. The effects of SGLT2i are immediate in the proximal renal tubule. The processes of natriuresis and glucosuria cause continuous osmotic diuresis. SGLT2i reduces sodium reabsorption directly and water clearance occurs passively. SGLT2i do not produce reflex sympathetic activity, suggesting that the decrease in blood pressure is not accompanied by a compensatory change in heart rate. An increase in heart rate has been associated with a higher risk of cardiovascular complications and death (Lytvyn et al., 2017; Verma, 2019).

The reduction in cardiac afterload likely occurs through a decrease in blood pressure and arterial stiffness resulting in increased endocardial blood flow. SGLT2i has consistently shown a reduction in blood pressure in clinical trials, contribute to the cardioprotective benefits of SGLT2i. Reduced blood pressure lowers ventricular filling pressure and lowers cardiac afterload thereby improving arterio-ventricular composition and cardiac efficiency. In addition, blood pressure monitoring is important in assessing cardiovascular risk in patients with type 2 diabetes mellitus (T2DM) (Mazidi et al., 2017).

The left ventricular remodeling process characterized by hypertrophy, inflammation, increased extracellular matrix production, and cardiomyocyte cell death is the main cause of heart failure process. It is suspected that SGLT2i has a beneficial effect on this pathway process. Fibroblasts play an important role in cardiac structural remodeling in heart failure through the regulation of extracellular matrix

production. In vitro studies of human cardiac fibroblasts have shown that empagliflozin attenuates extracellular matrix remodeling and suppresses the expression of profibrotic markers, including type I collagen, smooth muscle actin, connective tissue growth factor, and matrix metalloproteinases, thereby inhibiting cardiac remodeling (Kang et al., 2017).

SGLT2i is known to increase the production of ketone bodies. SGLT2i can prevent heart failure by increasing the production of ATP from the oxidation of ketone bodies thereby providing a more energy-efficient source of ATP and increasing the efficiency of cardiac performance. In a study of diabetic rats, it was shown that empagliflozin increased ATP production in the heart. Increased cardiac energy production is a result of increased levels of glucose and fatty acid oxidation in the heart (Verma et al., 2018). The replacement of myocardial fuel use from glucose with ketone bodies, free fatty acids, and Branched-chain amino acids (BCAAs) was also demonstrated by empagliflozin in a study with the hearts of nondiabetic pigs. This shift is accompanied by an amelioration of the detrimental cardiac remodeling process (Santos-Gallego et al., 2019).

Sodium-hydrogen exchanger (NHE)1 inhibitor are another hypothesized pathway that contributes to the cardioprotective effects of SGLT2i. NHE1 activity was increased in experimental model heart failure studies. These conditions are associated with increased levels of sodium and calcium in the cytosol which can cause myocyte injury and then end up being cardiomyopathy (Packer et al., 2017; Santos-Gallego et al., 2019). The benefits of NHE1 inhibitors are minimizing injury conditions to cardiomyocytes, hypertrophy, fibrosis, and remodeling processes. This has been demonstrated in various studies in the form of an experimental model (Packer et al., 2017). In a study of isolated ventricular myocytes from rabbits and mice, an empagliflozin-induced NHE1 inhibitor resulted in a reduction of intracellular calcium. A similar effect was also shown with dapagliflozin and canagliflozin (Baartscheer et al., 2017).

Obesity, insulin resistance, and DM2 conditions cause adipokine production to be altered, resulting in pro-inflammatory conditions. Recent studies show increased levels of adipokine leptin in obese patients cause sodium retention and volume expansion, as well as inflammation and fibrosis in the heart and kidneys. The natriuretic action of SGLT2i may ameliorate leptin-induced sodium retention. In addition, SGLT2i is thought to reduce the accumulation and inflammation of perivisceral adipose tissue thereby limiting leptin secretion (Packer, 2018). Post hoc analysis of clinical studies showed that canagliflozin can improve adipose tissue function and induce changes in serum leptin, adiponectin, and IL-6 that favorably affect insulin sensitivity and risk of cardiovascular disease (Garvey et al., 2018).

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a recommended surrogate marker for the diagnosis and management of heart failure and potentially predicts coronary heart disease and stroke. In a study of patients with diabetes mellitus given canagliflozin, it was shown that treatment with canagliflozin delayed the rise in serum NT-proBNP for more than 2 years compared with a placebo. Thus, canagliflozin could prevent the rise of NT-proBNP in these patients (Januzzi et al., 2017).

Study of SGLT2i as A Treatment for Heart Failure with Low Ejection Fraction

SGLT2i was initially known as a blood glucose-lowering drug, but it turns out that SGLT2i has a good effect in patients with heart failure with T2DM. In 2019, the DAPA-HF study (Dapagliflozin and Prevention of Adverse Outcome in Heart Failure) was the first study to show a significant benefit of SGLT2i in patients with HFrEF regardless of history of diabetes, namely a reduction in cardiovascular risk with a yield of 26% (McMurray et al., 2019).

In 2020, the EMPEROR-reduced study (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction) confirmed the results of DAPA-HF in a population with slightly different eligibility criteria for patients with more severe HF compared to DAPA-HF. The inclusion criteria in this study were patients with a left ventricular ejection fraction (LVEF) of 31% – 40% at least one hospitalization in the last 12 months or a higher NT-proBNP. The combined risk of cardiovascular death or hospitalization was 25% lower among patients receiving empagliflozin compared with a placebo (Packer et al., 2021).

EMPULSE is a study to examine the effects of empagliflozin in hospitalized patients with acute heart failure. This trial tested the safety and effectiveness of initiating empagliflozin in the hospital immediately after initial stabilization in patients with acute decompensated heart failure. Empagliflozin reduced the primary end point of death, the number of HF events, time to first HF event, and improvement from the baseline Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) 90 days after treatment. The clinical benefit rate was quite high at 53.9% in the empagliflozin group compared to only 39.7% in the placebo group ($p = 0.0054$). There was also a significantly greater weight loss effect in the group receiving empagliflozin compared to the placebo group. Patients treated with empagliflozin had a lower rate of acute renal failure of 7.7% compared with a placebo of 12.1% (Tromp et al., 2021).

Recommendations for SGLT2i as a Treatment for Heart Failure with Low Ejection Fraction

EMPEROR-reduced and DAPA-HF recommend initiation of SGLT2i treatment based on the condition of patients with symptomatic HFrEF regardless of previous therapy, systolic blood pressure 100mmHg for empagliflozin and 95mmHg for dapagliflozin, eGFR ≥20mL/min/1.73 for empagliflozin and eGFR ≥25mL/min/1.73 for dapagliflozin (McMurray et al., 2019; Packer et al., 2021). EMPULSE recommends initiation of SGLT2i treatment if there has been no increase in diuretic dose in the past 6 hours, no intravenous vasodilator or inotropic treatment for the past 24 hours, systolic blood pressure 100mmHg, and eGFR 20mL/min/1.73 m2 (Tromp et al., 2021).

A meta-analysis reported that treatment with SGLT2i inhibitors did not appear to be associated with an increased risk of hypotension and volume depletion. However, SGLT2i provided a 32% relative risk reduction for AKI in HFrEF patients (Vukadinović et al., 2022). There is evidence that SGLT2i inhibitors can lower blood pressure in patients with DM2, hypertension, or cardiovascular disease. This reduction in blood pressure appears to be a class effect of all SGLT2i. chronic kidney disease (CKD) is a very common comorbidity and is a major independent predictor of mortality in patients with heart failure (Damman et al., 2014). Therefore, it is very important to avoid the decline in renal function during the treatment of heart failure. While SGLT2i in heart failure patients can maintain a decrease in eGFR over time, SGLT2i also reduces the risk of AKI in patients.

SGLT2i has now become a leader in the treatment of heart failure and has been officially recommended by the European Society of Cardiology and the American College of Cardiology for the treatment of HFrEF (Heidenreich et al., 2022; McDonagh et al., 2021; Vaduganathan et al., 2020). Treatment with SGLT2i, along with other pillars of heart failure treatment, has been shown to reduce risk hospitalization for heart failure, cardiovascular death for more than 60%, and less than 50% all-cause mortality compared to ACEi, ARB, and beta-blockers (Bassi et al., 2020). In the heart failure population with low blood pressure or impaired renal function, caution should be done but the use of SGLT2i inhibitors is not associated with clinically relevant risks of hypotension and volume depletion. SGLT2i

can reduce the risk of AKI and maintain eGFR (Vukadinović et al., 2022).

In the United States, the addition of SGLT2i to the standard of care could prevent 34,000 deaths among heart failure patients each year, therefore, the international impact would be much greater. Administration of SGLT2i is also considered to be cost-effective and of high value in the management of patients with heart failure (Bassi et al., 2020; McEwan et al., 2020).

CONCLUSIONS

SGLT2i affects afterload, preload, cardiac remodeling, blood pressure, arterial stiffness, and the formation of ketone bodies that can prevent the process of heart failure. The use of SGLT2i in the management of patients shows the effect of lowering blood pressure and preventing the occurrence of AKI so that the condition is quite safe. SGLT2i is very effective and efficient in the treatment of heart failure patients. Because of its usefulness, further research is needed in Indonesia in order to determine the effectiveness and impact of giving SGLT2i to heart failure patients in Indonesia.

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