NEWEST RECOMMENDATION AND MECHANISM OF SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS IN HEART FAILURE PRESERVED EJECTION FRACTION : A LITERATURE REVIEW

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ABSTRACT

About 10 million people in Indonesia have been impacted by heart failure (HF), which is a complex clinical syndrome caused by insufficient cardiac output that is unable to meet the body's metabolic needs. The most frequent kind of HF, heart failure with preserved ejection fraction (HFpEF), has the fewest available treatments. Diuretics and SGLT-2 Inhibitors are the first-line treatments for HFpEF. This paper aim to determine the mechanism of sodium-glucose cotransporter-2 (SGLT-2) Inhibitors in HFpEF and the newest recommendation for it, so that it might be utilized as a reference for management in the future. This is a literature review study which conducting by gathering numerous books and journal articles which relevant with the topic. The mechanisms of SGLT-2 Inhibitors in HFpEF are not well understood, but some theories suggest that these medications affect preload, afterload, cardiac remodeling, blood pressure, arterial stiffness, and ketone body formation. They can also stimulate erythropoiesis, inhibit the myocardial Na+/H+ exchanger (NHE), and have anti-oxidant and anti-inflammatory effects, so they are no longer just seen as anti-diabetic medications. Recently, Perhimpunan Dokter Spesialis Kardiovaskular Indonesia (PERKI) published a Heart Failure guidelines and classify SGLT-2 Inhibitors as a class IB treatment for HFpEF.

Keywords *: SGLT-2 Inhibitors; HFpEF; EMPEROR-Preserved; DELIVER; PERKI*

ABSTRAK

Sekitar 10 juta orang di Indonesia telah terpengaruhi oleh gagal jantung (HF), yang merupakan sindrom klinis yang kompleks yang disebabkan oleh output jantung yang tidak mencukupi sehingga tidak mampu memenuhi kebutuhan metabolisme tubuh. Jenis HF yang paling sering, gagal jantung dengan fraksi ejeksi terpelihara (HFpEF), memiliki pilihan terapi yang paling sedikit tersedia. Diuretik dan penghambat sodium-glucose cotransporter-2 (SGLT-2) adalah terapi lini pertama untuk HFpEF. Tinjauan pustaka ini bertujuan untuk menentukan mekanisme penghambat SGLT-2 pada HFpEF dan rekomendasi terbaru dalam penggunaannya, sehingga dapat digunakan sebagai referensi untuk manajemen penyakit ini di masa depan. Ini adalah studi tinjauan pustaka yang dilakukan dengan mengumpulkan banyak buku dan artikel jurnal

yang relevan dengan topik tersebut. Mekanisme penghambat SGLT-2 dalam HFpEF belum dipahami dengan baik, tetapi beberapa teori menunjukkan bahwa obat-obatan ini mempengaruhi preload, afterload, remodeling jantung, tekanan darah, kekakuan arteri, dan pembentukan badan keton. Penghambat SGLT-2 juga dapat merangsang eritropoiesis, menghambat pertukaran Na + / H + miokard (NHE), dan memiliki efek antioksidan dan anti-inflamasi, sehingga mereka tidak lagi dilihat hanya sebagai obat anti-diabetes. Baru-baru ini, Perhimpunan Dokter Spesialis Kardiovaskular Indonesia (PERKI) menerbitkan pedoman gagal jantung dan mengklasifikasikan penghambat SGLT-2 sebagai pengobatan kelas IB untuk HFpEF.

Kata Kunci : Penghambat SGLT-2; HFpEF; EMPEROR-Preserved; DELIVER; PERKI

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INTRODUCTION

A structural and/or functional cardiac abnormality, which is supported by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion, can result in heart failure (HF), a complex clinical syndrome that has symptoms such as insufficient cardiac output that fails to meet the body's metabolic needs. HF is linked to a lower quality of life (QoL) as well as higher mortality and morbidity rates.(1,2) Around 50 million people worldwide and 10 million in Indonesia are affected by HF, which has a significant economic impact estimated at US$108 billion.(3–5)

HF is divided into four categories according to the measured left ventricular ejection fraction (EF): (1) HF with decreased EF (HFrEF; EF ≤40%), (2) HF with preserved EF (HFpEF; EF ≥50%), (3) HF with mid-range EF (HFmrEF; EF 41-49%), and (4) HF with improved EF (HFimpEF; baseline EF ≤40% and a second EF >40%).(2)

The most prevalent form of HF is HFpEF, formerly known as diastolic HF, and it affects about half of all HF patients in the general population.(3,6,7) In addition to having concurrent cardio-renal-metabolic comorbidities, patients with HFpEF are frequently older, and their main chronic symptom is extreme exercise intolerance.(8,9) According to a research from the Sardjito Heart Failure Registry, 43% of Indonesians have HFpEF. However, the diagnosis and treatment of HFpEF are challenging in underdeveloped nations like Indonesia because of nonspecific signs and symptoms (such as fatigue, shortness of

breath, and ankle swelling, etc.), diagnostic uncertainty, preexisting comorbidities, and a lack of resources to carry out more tests.(3)

HFpEF has fewer available treatments than HFrEF.(9,10) Up until now, Sodium-glucose cotransporter-2 (SGLT-2) Inhibitors and diuretics (in congestion) have been the first-line treatments for HFpEF. SGLT-2 Inhibitors are classified as class IB for HFpEF in the 2023 PERKI Heart Failure recommendations.(11)

A novel class of oral medications known as SGLT-2 Inhibitors was initially developed as a treatment for type II diabetes mellitus (T2DM). More recent research indicates that SGLT-2 Inhibitors are no longer only thought of as anti-diabetic medications because they now have the go-ahead to be administered to patients with HF and chronic kidney disease, regardless of the presence of diabetes mellitus.(12)

Due to the mounting evidence that SGLT-2 Inhibitors can significantly improve cardiovascular outcomes, including lowering the incidence of cardiovascular (CV) death and hospitalization for heart failure (HHF), in addition to increasing glucosuria excretion in T2DM patients.(13–15) SGLT-2 Inhibitors have thus become one of the four pillars of HFrEF treatment, along with renin-angiotensin blockers, mineralocorticoid antagonists, and beta blockers.(6,16) Empagliflozin and dapagliflozin have recently been shown to reduce the combined CV risk in patients with HFpEF, with the benefit of reduced HHF was attenuated even in higher left ventricular ejection fractions (LVEF>65%), according to the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved) trial, released in 2021, and the Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) trial, released in 2022.(17–19) This shows that regardless of the left ventricular ejection fraction, SGLT-2 Inhibitors may be beneficial for all individuals with HF.

Given these circumstances, the author should do a review study on the latest recommendation, mechanism and function of SGLT-2 Inhibitors in HFpEF so that it may serve as a manual for management in the future, particularly for practitioners in Indonesia since dapagliflozin and empagliflozin are available here.

METHODS

The literature review approach is the research design that was used. The process of conducting a literature review involves gathering numerous books and journal articles that are pertinent to the issue at hand and the study's goals, summarizing the key

points, and compiling them into a single paper. To gain a brief but thorough overview of the role of SGLT-2 Inhibitors in HFpEF, we searched journal papers about the relationship between SGLT2 Inhibitors and HFpEF, specially about their mechanism and latest recommendation.

RESULT AND DISCUSSION

Mechanism of action of SGLT-2 Inhibitors

It is now widely accepted that HFpEF develops over time as a result of a number of risk factors, including obesity, hypertension, and diabetes mellitus, as well as complex physiological and molecular processes, such as systemic inflammation, abnormal hemodynamics, and LV structural remodeling.(20,21) In the gut and renal glomerulus, sodium-glucose cotransporters (SGLT) are transmembrane proteins that typically encourage glucose absorption.(22) SGLT-1s are mostly expressed in the small intestine, whereas SGLT-2s are primarily found in the proximal renal tubule, more especially in the S1 and S2 segments, where they make sure that 90% of the glucose filtered into the renal glomerulus is reabsorption. The renal tubule's S3 segment is where SGLT-1 reabsorbs the remaining 10% of the filtered glucose because there is less of it readily available in the lumen there. Gliflozins, also known as SGLT-2 Inhibitors, are a novel class of anti-diabetic medications with a distinct mechanism of action. They work by encouraging glycosuria in an insulin-independent manner, which lowers blood sugar levels. They also cause natriuresis, which lowers blood pressure concurrently.(23,24) Numerous studies have shown that SGLT-2 Inhibitors have cardioprotective and nephroprotective effects on processes affecting the heart, kidney, vasculature, endocrine system, and potentially the entire body, in addition to their impact on glycemic management.(12,25) SGLT-2 Inhibitors are the first metabolic medicines due to their extensive impact on numerous organ systems. Additional CV outcome studies confirmed this evidence of a decrease in HHF and CV deaths, suggesting that SGLT-2 Inhibitors may have a direct effect on HF independent of their anti-hyperglycemic capabilities.(9) Through theorized processes that are not just the drug's diuretic or natriuretic actions, SGLT-2 Inhibitors are the only medication efficacious across the entire LVEF spectrum of HF. The molecular processes by which SGLT-2 Inhibitors affect HF are still largely unclear.(4) The use of SGLT-2 Inhibitors in HF models revealed several plausible pathways for the cardioprotective benefits, which may provide insight into how they operate.

Decrease preload

Unique natriuretic and diuretic effects without neurohormonal stimulation or electrolyte alteration are seen with SGLT-2 Inhibitors.(26,27) Due to the frequent presence of symptoms of pulmonary congestion and systemic edema in patients with HF, this has advantages in the management of volume status.(28) Continuous osmotic diuresis is brought on by the processes of natriuresis and glucosuria. Through passive water clearance and direct sodium reabsorption reduction, SGLT-2 Inhibitors lowers plasma and interstitial fluid volumes, which in turn lowers cardiac preload and supports cardiac remodeling by reducing strain on the cardiac wall.(29) Given that SGLT-2 Inhibitors do not result in reflex sympathetic activity, it is possible that the drop in blood pressure is not accompanied by a corresponding rise in heart rate. Heart rate increases have been linked to greater mortality and CV problem risks.(30) Furthermore, since proximal tubule action of diuretics is not only dependent on SGLT-2, the usage of SGLT-2 Inhibitors may improve the action of other diuretics in individuals with HF.(12)

Reduce afterload

The decrease in arterial stiffness and blood pressure brought on by SGLT-2 Inhibitors, which leads to an increase in endocardial blood flow, is most likely how the cardiac afterload is reduced. Lower blood pressure improves arterio-ventricular composition and cardiac efficiency through lowering ventricular filling pressure and cardiac afterload.(31)

Reduce cardiac remodeling

HF is primarily caused by the left ventricular remodeling process, which is characterized by hypertrophy, inflammation, increased extracellular matrix synthesis, and cardiomyocyte cell death. It is believed that SGLT-2 Inhibitors has a positive impact on this pathway's operation. Through the control of the synthesis of extracellular matrix, fibroblasts contribute significantly to the structural remodeling of the heart in HF. Empagliflozin inhibits extracellular matrix remodeling in human cardiac fibroblasts in vitro and suppresses the expression of profibrotic markers like type I collagen, smooth muscle actin, connective tissue growth factor, and matrix metalloproteinases, which prevents cardiac remodeling.(32,33)

Shift to ketone metabolism

SGLT-2 Inhibitors cause changes in body metabolism by increasing usage of ketone bodies, a more energy-efficient substrate, and fatty acids but it decreases cardiac glucose oxidation.(34,35) By enhancing ATP synthesis from the oxidation of ketone bodies by about 30%, SGLT-2

Inhibitors can prevent HF by providing a more energy-efficient source of ATP, improving cardiac activity, and reducing the buildup of toxic substances. It was demonstrated that empagliflozin boosted ATP generation in the heart in a study of diabetic rats.(36) In a study with the hearts of nondiabetic pigs, empagliflozin also shown that ketone bodies, free fatty acids, and branched-chain amino acids (BCAAs) substitute the myocardial fuel usage of glucose. This change is followed by a reduction in the harmful remodeling of the heart.(34)

Decreased pulmonary artery diastolic pressure

According to the EMBRACE-HF study, SGLT-2 Inhibitors reduced the patients' pulmonary artery diastolic pressure, a surrogate for left atrial pressure.(37) A rise in left atrial pressure may be the most significant hemodynamic factor influencing an individual's ability to exercise in HFpEF patients, according to a number of lines of research. Thus, SGLT-2 Inhibitors may lessen pulmonary congestion, which can lead to reductions in HF severity and HF hospitalization risk in these individuals.(38)

Stimulation of erythropoiesis

An indirect consequence of SGLT-2 Inhibitors that has been discovered as a potential advantageous mechanism is the stimulation of erythropoiesis. This is hypothesized to be generated by renal medullary hypoxia as a result of increased sodium active reabsorption in the distal convoluted tubule, which in turn produces hypoxia-inducible factors that release erythropoietin. Increased red cell mass, as seen by a rise in hematocrit, has the desired consequence of improving oxygen delivery to the heart and decreasing left ventricular mass.(39)

Inhibition of myocardial Na+/H+ exchanger (NHE)

Another potential mechanism for the cardioprotective effects of SGLT-2 Inhibitors is sodium-hydrogen exchanger (NHE)1 inhibitor. The SGLT-2 Inhibitors empagliflozin inhibits the cardiac Na-H exchanger, which is related with increased activity in HF in rabbits and rats.(40) These condition are linked to elevated cytosolic sodium and calcium levels, which can lead to myocyte damage and ultimately cardiomyopathy.(1) Increased resistance to natriuresis caused by an upregulated Na-H exchanger also lessens the effects of diuretic therapy.(12) NHE1 inhibitors have the advantages of reducing cardiomyocyte damage conditions, fibrosis, hypertrophy, remodeling processes, which considerably improve LV diastolic function, and they may also increase sensitivity to diuretics and endogenous natriuretic peptides.(1,41)

This has been shown in a number of studies using an experimental model, but these results have not yet been confirmed in humans. An empagliflozin-induced NHE1 inhibitor led to a decrease in intracellular calcium in a study of isolated ventricular myocytes from rabbits and mice. Canagliflozin and dapagliflozin both had effects that were comparable.(40)

Anti-oxidant and Anti-inflammation effect

Systemic inflammation and oxidative stress are major contributors to cardiac dysfunction.(42) Empagliflozin appears to work primarily by inhibiting NHE1, which reduces mitochondrial swelling by blocking intracellular calcium entry and the production of reactive oxygen species (ROS) from cardiac cells. Inducible NOS2 synthesis cannot be stimulated because the signaling pathway that activates AKT1/AKT2/Unit AKT318 is blocked concurrently. Oxidative stress is decreased as a result of these modifications.(12)

The use of SGLT-2 Inhibitors may also improve autophagic flux, a process by which cells eliminate damaged cells or organelles (such as mitochondria), signals caused by nutrient shortage, and reducing reactive oxygen species, which has a strong anti-oxidant effect.(9) In HF, the protective mechanism of autophagy is disrupted in a way that makes its stimulation appear beneficial in the development of the illness. A cell can provide a more metabolically advantageous environment by eliminating waste and possibly harmful byproducts of cellular stress through autophagy. Although the exact method by which SGLT-2 Inhibitors accelerate autophagy is unclear, it appears likely that they generate a state of "fasting mimicry" and then activating adenosine monophosphate-activated protein kinase (AMPK), sirtuin-1 (SIRT1) and hypoxia-inducible factor (HIF-1α and HIF-2α). A favorable metabolic balance for the myocardial cell is produced by the activation of these enzymes, which also has anti-inflammatory and anti-oxidant properties. At the same time, it is connected to the transcription of genes that guarantee the myocyte's access to oxygen.(12,41)

Recent research revealed that gliflozins have anti-inflammatory effects and may be used therapeutically to treat disorders like obesity, atherosclerosis, and non-alcoholic steatohepatitis. Among T2DM patients, inflammation appears to be a component that speeds up atherosclerosis. Macrophages are immune cells that are crucial to the inflammatory process; they are divided into two groups: the M1 subgroup (classically activated macrophages), which are triggered by Th1 cytokines or LPS bacterial lipopolysaccharides and cause the production of proinflammatory cytokines, and the M2 subgroup (alternatively

activated macrophages), which have an anti-inflammatory effect after being triggered by Th2 cytokines. The ability of gliflozins to encourage the transformation of M1 macrophages into M2—a feature that is maintained even in hyperglycemic conditions—is the primary mechanism by which they interfere with macrophages. Their aforementioned actions result in the reduction of the clinical effects of inflammation, such as atherosclerosis and fibrosis, in the CV system as well as in the liver and kidneys. By preventing macrophage growth in the plaque, empagliflozin, in particular, lessens the infiltration of atheromatous plaque by macrophages, aiding in the plaque's remission.(12)

Additionally, the use of SGLT-2 Inhibitors reduces cardiac inflammatory response and the resulting cardiac fibrosis that is seen. This property is primarily explained by the reduction of free radical formation in the cardiomyocyte, which leads to the induction of an anti-oxidative and anti-inflammatory environment that supports coronary endothelial function. It's also crucial to emphasize how SGLT-2 Inhibitors reduce the amount of fat called epicardial fat that surrounds the heart and is known for producing more pro-inflammatory cytokines. Pro-inflammatory cytokines drop as a result of this reduction, which also improves the environment.(43)

In addition, pro-inflammatory conditions are brought on by altered adipokine production, which is a result of obesity, insulin resistance, and T2DM disorders. The sodium retention caused by leptin may be lessened by the natriuretic effects of SGLT-2 Inhibitors. Additionally, it is believed that SGLT-2 Inhibitors inhibits leptin secretion by reducing the buildup and inflammation of perivisceral adipose tissue. Clinical investigations that underwent post hoc analysis revealed that canagliflozin can increase adipose tissue function and cause adjustments in serum leptin, adiponectin, and IL-6 that have a positive impact on insulin sensitivity and CV disease risk.(1)

Effect of SGLT-2 Inhibitors in HFpEF

According to multiple trials, SGLT-2 Inhibitors have the following benefits on HFpEF: 1) they lower the risk of HHF and CV death; 2) they lower NT-proBNP levels; and 3) they improve exercise capacity and QoL. According to these findings, SGLT-2 Inhibitors may be helpful for HFpEF patients throughout the entire range of ejection fraction.(44–47)

In the EMPEROR-Preserved trial, empagliflozin significantly reduced the risk of HF hospitalizations by 27%, resulting in a 19% decrease in the primary composite outcome of CV death and HHF (13.8% vs. 17.1%; HR, 0.79; 95% CI, 0.69-0.90).(17)

Whereas, according to the DELIVER trial, Dapagliflozin significantly reduced the primary composite endpoint by 18% when compared to placebo (16.4% vs. 19.5%; HR, 0.82; 95% CI, 0.73-0.92), largely due to a 21% decrease in HHF and urgent HF visits (11.8 vs 14.5%; HR, 0.79; 95% CI, 0.69-0.91).(19) The effects on the incidence of primary endpoint events were generally consistent across all predefined subgroups, including individuals with or without diabetes, in the two trials that have been described.(17) Additionally, a study that was presented at American Heart Association (AHA) 2020 and included pooled data from 739 patients with HFpEF from the SCORED and SOLOIST-WHF discovered that sotagliflozin in T2DM significantly reduced the composite risk of CV death or HHF by 37% (HR 0.63; 95% CI, 0.45-0.89; p = 0.009).(48)

Urinary tract infections and hypoglycemia were first feared to be more common, but several trials have not shown a substantial rise in either of these 2 side effects.(49,50) Although SGLT-2 Inhibitors does raise the chance of genital mycotic infections, this danger is minimal given the benefits of these medications and how quickly it can be treated. The unusual adverse impact known as Fournier's gangrene, which is described as necrotizing fasciitis of the perineal soft tissues, has also been documented and is now a safety warning.(51,52) Furthermore, a recent meta-analysis found that SGLT-2 Inhibitors were associated with a more than 2-fold elevated risk of diabetic ketoacidosis (DKA), which has been linked to the drugs' ability to promote ketogenesis and decrease insulin production.(53) Due to their natriuretic and diuretic actions, SGLT-2 Inhibitors can cause volume depletion. Non-selective SGLT inhibitors can also cause gastrointestinal side effects, and other diuretic drugs may need to be dosed differently.(54)

Recommendation of SGLT2i in HFpEF

Unless SGLT-2 Inhibitors are contraindicated or poorly tolerated, SGLT-2 Inhibitors has now emerged as a leader in the treatment of HF and has been formally recommended by both the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) to lower the risk of CV death and worsening HF in patients with HFrEF.(55,56)

SGLT-2 Inhibitors were classified as a class IIA, level B, medication for the treatment of HF with a mildly reduced or preserved left ventricular ejection fraction in the most recent guidelines issued by the AHA, ACC, and Heart Failure Society of America (HFSA) in 2022.(56) Given that these guidelines were released prior to the publication of the DELIVER trial, it is possible that SGLT-2 Inhibitors will be

given a stronger recommendation in subsequent guidelines. The 2021 ESC guidelines, meantime, did not address the use of SGLT-1 Inhibitors in HFmrEF and HFpEF because they were released before to the publication of the EMPEROR-Preserved and DELIVER studies.(55) In addition, the 2023 PERKI Heart Failure guidelines for Indonesia classify SGLT-2 Inhibitors as a class IB treatment for HFpEF.(11)

CONCLUSION

The most recent addition to pharmacological regimens that enhance QoL and lower morbidity and mortality in HF is the SGLT-2 Inhibitor, which is efficient across the full range of LVEF without an excess of adverse effects. Until now, the mechanisms of these benefits are not well-established. SGLT2i can affects preload, afterload, cardiac remodeling, blood pressure, arterial stiffness, and the formation of ketone bodies, also have ability to stimulate erythropoiesis, inhibit myocardial Na+/H+ exchanger (NHE), and have anti-oxidant and anti-inflammation effect that can slow the progression of heart failure. The 2022 AHA/ACC/HFSA HF Guidelines give a Class IIA indication for SGLT-2 Inhibitors to be use in HFpEF, but the benefit, which has now been verified in the dapagliflozin, DELIVER trial, and empagliflozin, EMPEROR-Preserved study, raises the possibility that SGLT-2 Inhibitors may be given a stronger class of recommendation in the future. With regard to HFpEF, SGLT-2 Inhibitors has been given a class IB indication in June 2023 PERKI Heart Failure recommendations.

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