A RETROSPECTIVE STUDY ON THE EFFECTS OF SGLT2 INHIBITORS ON LEFT VENTRICULAR FUNCTION AND HEART FAILURE HOSPITALIZATION AMONG HEART FAILURE WITH REDUCED EJECTION FRACTION IN HUSM PATIENTS.

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LIST OF SYMBOLS

= Equal to

> More than

< Less than

/ Or

% Percentage

1-b Statistical power

N number of subjects

P_0 Probability of exposure in controls

P_1 Probability of exposure in cases

P stat p-value

E/e` E to early diastolic mitral annular tissue velocity (E/e') to estimate LV filling pressures.

Vs. Versus

LIST OF ABBREVIATION

ACEI:	Angiotensin converting enzyme inhibitor
ARB:	Angiotensin receptor blocker
ARNI:	Angiotensin receptor/ neprilysin inhibitor
AF:	Atrial fibrillation
BB:	Beta blocker
CKD:	Chronic kidney disease
CVA:	Cereberovascular accident
DM:	Diabetes mellitus
EF	Ejection fraction
GLS	Global longitudinal strain
HfrEF:	Heart failure with reduced ejection fraction
HfpEF	Heart failure with preserved ejection fraction
HfmrEF	Heart failure with mildly reduced ejection fraction
LV:	Left ventricular

MRA:	Mineralcorticoid receptor antagonist
NYHA	New York Heart Association classification
SGLT2i:	Sodium Glucose Transporter 2 inhibitor
ADHF:	Acute Decompensated Heart Failure

ABSTRAK

Latar belakang: Kegagalan jantung adalah kebimbangan di seluruh dunia dan pelbagai langkah diambil untuk merawat kegagalan jantung. Penggunaan penghalang ko-transporter-2 natrium glukosa seperti (SGLT2i) telah menunjukkan manfaat klinikal dalam mengurangkan risiko kemasukan ke hospital dan risiko kematian. Walau bagaimanapun, kesan SGLT2i terhadap fungsi ventrikel kiri dan kemasukan ke hospital di negara ini adalah masih belum jelas.

Objektif: Untuk menentukan kesan SGLT2i (empaglifozin dan dapaglifozin) pada fungsi ventrikel kiri dan kemasukan ke hospital untuk kegagalan jantung dalam pesakit gagal jantung

Metodologi : Kajian kohort retrospektif ini telah dijalankan dari Oktober 2022 hingga Februari 2023 di Hospital USM. Data pesakit gagal jantung yang menghadiri klinik kardiologi dari tahun 2018 hingga 2022, dengan pecahan ejeksi ventrikel kiri (LVEF) $\leq$ 40%, telah diambil. Pesakit dibahagikan kepada dua kumpulan berdasarkan rawatan yang diterima: SGLT2i dan tanpa SGLT2i. Ekokardiografi dilakukan pada peringkat awal dan selepas enam bulan sehingga 24 bulan selepas dapagliflozin atau empaglifozin. Penelitian ini mengkaji perubahan dalam fungsi ventrikel kiri dan kemasukan ke hospital untuk kegagalan jantung. Selain itu, faktor yang dikaitkan dengan perubahan fungsi ventrikel kiri dan kemasukan ke hospital juga diteliti.

Keputusan: Sebanyak 110 HFrEF pesakit gagal jantung telah dimasukkan dalam kajian ini. Selepas median 14.5 (SGLT2i) dan 13.3 bulan (bukan SGLT2i), terdapat

peningkatan fungsi ventrikel kiri dalam kedua-dua kumpulan. Peningkatan 5.6% fungsi ventrikel kiri diperhatikan dalam kumpulan SGLT2i manakala peningkatan 4.6% diperhatikan dalam kumpulan bukan SGLT2i. Pesakit kegagalan jantung (HF) yang menerima SGLT2i mempunyai risiko yang lebih rendah untuk dimasukkan ke hospital untuk kegagalan jantung. Di antara 55 pesakit yang menerima SGLT2i, 20% (11 pesakit) mempunya kemasukan ke hospital untuk kegagalan jantung, manakala 38.2% (21 pesakit) tidak menerima SGLT2i mempunyai kemasukan ke hospital dengan nilai p- value 0.036. Risiko kemasukan ke hospital adalah 2.7 untuk pesakit yang tidak menerima DGLT2i. Kajian ini juga mendapati bahawa pesakit gagal jantung yang menerima oral furosemide mempunyai kemungkinan untuk kemasukan ke hospital 3.512 lebih tinggi berbanding mereka yang tidak menerima oral furosemide.

Kesimpulan: SGLT2i (dapaglifozin dan empaglifozin) menurunkan risiko kemasukan ke hospital apabila digunakan dengan ubat kegagalan jantung yang lain. Pesakit yang menjalani terapi kegagalan jantung standard menunjukkan peningkatan yang ketara dalam fungsi jantung kiri (LVEF) selepas lebih daripada 13.3 bulan. Selepas analisis multivariate, kajian ini juga mendapati bahawa furosemide oral dikaitkan dengan peningkatan risiko kemasukan ke hospital.

Kata kunci: *SGLT2i. empaglifozin, dapaglifozin, kemasukan hospital, fungsi jantung*

ABSTRACT

Background: Heart failure is a worldwide concern, and multiple measures are taken to treat heart failure. Using sodium glucose like co-transporter 2 inhibitor (SGLT2i) has shown clinical benefit in reducing the risk of heart failure hospitalization and mortality. However, the effect of SGLT2i on the left ventricular function and heart failure hospitalization in heart failure patients with reduced ejection fraction (HFrEF) in this country is unclear.

Objective: To determine the effect of SGLT2i (empaglifozin and dapaglifozin) on left ventricular function and heart failure hospitalization in HFrEF patients.

Materials and Methods: This retrospective cohort study was conducted from December 2022 until February 2023 in Hospital USM. The data of patients who attended the cardiology and heart failure clinic from 2018 to 2022, with left ventricular ejection fraction (LVEF) $\leq 40\%$, were retrieved. The patients were divided into two groups based on the received treatment: with SGLT2i and without SGLT2i. The echocardiography data at baseline and after six months up to 24 months also obtained from medical records. The primary endpoint was the changes in LVEF and hospitalization for heart failure. Additionally, factors associated with LVEF changes and admission to the hospital were also determined.

Results: A total of 110 HFrEF were included in the study. After a median of 14.5 (SGLT2i) and 13.3 months (non-SGLT2i) of follow-up, there was an improvement of left ventricular function in both groups. A 5.6 % improvement of LV function was observed in SGLT2i groups while 4.6% improvement was observed in non-SGLT2i group. Heart failure (HF) patients receiving SGLT2i have a lower risk of hospitalization for heart failure. Among 55 patients on SGLT2i, 20% (11 patients) had been admitted for heart failure, while 38.2% (21 patients) were not on SGLT2i admitted for heart failure with a significant p-value 0.036. The odds of being admitted in patient who did not receive SGLT2i was 2.7. This study also found out that HF patients who received oral furosemide had the odds of being admitted for heart failure at 3.512 compared to those who did not.

Conclusions: SGLT2i (empaglifozin and dapagliflozin) reduces heart failure hospitalization when added into ~~prescribed~~ standard heart failure therapy. Patients who were on standard heart failure therapy shows significant improvement in LVEF after more than 13.3 months. ~~however,~~ After multivariate analysis, this study also found that oral furosemide was associated with an increased risk of hospitalization.

Keywords: SGLT2i, left ventricular function, heart failure hospitalization

CHAPTER 1

BACKGROUND

1. INTRODUCTION

Heart failure is a clinical syndrome due to any structural or physiological abnormality of the heart resulting in its inability to meet the body's metabolic demands. (CPG Heart Failure 2019', 2019)

It is a primary concern worldwide. It was estimated that about 64.3 million people live with heart failure. According to an analysis of primary care data in the United Kingdom, the found out that people living with heart failure increased by 23% between 2002 and 2014 number kept on increase from 750 125 to 920 616 (1.4% of the population). It is supported by our country's Ministry of Health data about 6%-10% of all acute medical admissions are due to heart failure. The total cost for heart failure management is 1.8% of total health expenditure. (Ministry of Health Malaysia, 2019; Groenewegen et al., 2020a)

Ischemic heart disease remains a significant contributor to heart failure incidence. The high prevalence of heart failure is contributed by increased myocardial infarction survival. Patients have swifter access to emergency percutaneous coronary interventions (PCI), which make them survive myocardial infarction but succumb to heart failure as a complication of the myocardial infarction. (Clare J. Taylor et al., 2019; Groenewegen et al., 2020b). People with heart failure admitted to the hospital around the time of diagnosis had significantly worse survival compared to those not requiring hospital

admission (with a median difference of 2.4 years) (5.3 v 2.9 years, log-rank test, P<0.001). One-year survival was 81.2% vs. 68.8%, five-year survival was 51.8% vs. 36.7%, ten-year survival was 28.8% vs. 17.8%, and 15-year survival was 15.5% versus 8.1% for patients not admitted to hospital and admitted to hospital, respectively. (Clare J. Taylor et al., 2019)

Medications that are associated with reduced mortality in heart failure are ACEI/ ARB/ARNI, beta-blocker (BB), mineralocorticoid receptor antagonist (MRA), and sodium glucose co-transporter-2 inhibitor (SGLT2i). The challenge in managing patients with heart failure is not only to initiate these four medications but to titrate the dose to specific doses that are used in the specific trial. (Ministry of Health Malaysia, 2019). For example:

ACEI/ ARB/ ARNI (Angiotensin Receptor Neprilysin Inhibitor)

The use of ARNI in the treatment of heart failure is based on the PARADIGM-HF study, which showed a reduction in the risk of mortality in patients with HfrEF compared to ACEI (enalapril). In fact, this study was stopped early because of its overwhelming benefits. The dose for salcubitril/valsartan (ARNI) used in the study was 200 mg daily. (Pablo A. Olavegogeascoechea, 2017). Acute Infarction Ramipril Efficacy (AIRE) study incorporated ramipril (target dose 10 mg/day) following AMI complicated by clinical evidence of heart failure. Ramipril improved survival benefit and is associated with increased survival up to 14.5 months for, on average, 13 months of treatment duration. (Wu, Hall, and Gale, 2021). A Randomized Trial of the Angiotensin-Receptor Blocker Valsartan in Chronic Heart Failure (ValHeft) 2005 incorporated valsartan 160 mg twice

daily and valsartan significantly reduces the combined endpoint of mortality and morbidity and also improves clinical signs and symptoms in patients with heart failure (Ripley, 2005)

Beta Blocker

The use of beta-blockers also improves survival. One of the earliest control trials involving beta-blockers is MERIT-HF, in which the starting dose is metoprolol 5 mg and titrated up every two weeks to 200 mg/ daily. In CIBIS I trial, they used Bisoprolol at 10 mg, and the study was stopped early due to its benefits in reducing mortality. CIBIS II trial has no run-in period; therefore, this study may represent beta-blocker use in clinical practice. According to the CIBIS II trial, treating 23 patients with bisoprolol would reduce one mortality.(Niriayo *et al.*, 2020)

Mineralocorticoid Receptor Antagonists (MRA)

Spironolactone is a widely used MRA in heart failure. Eplerenone is another example of MRA that is used in HF. Eplerenone is a selective aldosterone receptor antagonist with a lower affinity for the progesterone and androgen receptors, so it lacks sex-related adverse side effects. Randomized Aldactone Evaluation Study (RALES) 1999 trial used spironolactone 25–50 mg daily (with a mean daily study dose of 26 mg). (Vizzardi *et al.*, 2014) Eplerenone Post-myocardial infarction Heart failure Efficacy and Survival Study (EPHESUS) 2003 demonstrated the benefit of aldosterone receptor antagonists in patients with LVEF ≤40% after MI. Eplerenone was started at 25 mg/d, then increase to

a maximum of 50 mg/day. The use of eplerenone in heart failure significantly reduce morbidity and mortality. (Vizzardi *et al.*, 2014)

Sodium glucose cotransporter-2 inhibitor (SGLT2i)

The latest and newest drug added to the list is the SGLT2 inhibitor which is assessed in this study. Initially, this drug is used for T2DM patients who are at risk of cardiovascular events as a primary prevention for cardiovascular events. However, a recent trial proved that its benefits are beyond primary prevention. (Williams and Evans, 2020) Recent landmark trials such as DAPA-HF and EMPEROR-REDUCE prove that SGLT2i benefits heart failure patients despite their diabetic status. (McMurray, DeMets, Inzucchi, Køber, Kosiborod, Langkilde, et al., 2019; Packer et al., 2021)

RESEARCH OBJECTIVE

1.1.1. General:

To determine the effect of SGLT2 inhibitors (empaglifozin and dapaglifozin) in heart failure with reduced ejection fraction (HfrEF) patients.

1.1.2. Specific:

1. To compare the mean changes of left ventricular ejection fraction between the SGLT2 inhibitor group and non-SGLT2i group after six months up to 24 months of usage.

2. To compare the proportion of heart failure hospitalization between SGLT2i and non-SGLT2i groups after six months up to 24 months of usage.
3. To identify factors associated with the improvement of left ventricular function.
4. To identify factors associated with ~~the improvement of~~ heart failure hospitalization. ~~associated with improvement of heart failure hospitalization~~

RESEARCH HYPOTHESIS

There is an improvement in left ventricular function and the proportion of heart failure hospitalization in HFrEF patients after starting SGLT2i (dapaglifozin and empaglifozin)

RESEARCH QUESTION

In a patient with heart failure with reduced ejection fraction, does SGLT2 inhibitor improve left ventricular function and reduce the proportion of heart failure hospitalization in HUSM?

CHAPTER 2

LITERATURE REVIEW

2.1. LITERATURE REVIEW

There is a new paradigm for treating heart failure with SGLT2i after multiple large trials targeting heart failure with reduced ejection fraction (HFrEF) with or without diabetes.

SGLT2i in heart failure hospitalization and mortality

SGLT2i was known as a glucose-lowering drug in the earlier days of its emergence in the market, and was used in treating diabetes only. Then it started to be used on diabetic patient who had established atherosclerotic cardiovascular disease (ASCVD) as secondary prevention for coronary artery disease. Empagliflozin Cardiovascular Outcomes Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME) trial in 2015 randomized 7020 diabetic patients who had established atherosclerotic cardiovascular disease (ASCVD) as secondary and 4687 received 10 or 25 mg of empagliflozin with a median observation time of 3.1 years. The primary outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The secondary composite outcome was the primary outcome plus hospitalization for unstable angina. The primary outcome occurred in 10.5% (490 of 4687 patients) in the empaglifozin group and 12.1% (282 of 2333 patients) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95% confidence interval,

0.74 to 0.99; P = 0.04 for superiority) with lower rates of death from cardiovascular causes (3.7% in empagliflozin group vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7% vs. 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% vs. 8.3%, respectively; 32% relative risk reduction). But, there was an increased rate of genital infection among patients receiving empaglifozin, but no increased risk in other adverse events.(Ingelheim Pharma, 2015; Fitchett *et al.*, 2019)

The use of SGLT2i expands from the prevention of cardiovascular disease in diabetic patients to a recommended therapy in heart failure with reduced ejection fraction (HFrEF) despite their diabetic status. However, only two types of SGLT2i are proven to benefit these groups, empaglifozin and dapaglifozin. Based on two trials which are EMPEROR-REDUCE (Empagliflozin in Patients With Heart Failure, Reduced Ejection Fraction, and Volume Overload) and DAPA-HF (The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure) (McMurray et al., 2019; Packer et al., 2021)

DAPA-HF (2019), evaluating the effect of dapagliflozin 10mg in addition to standard care of heart failure treatment on 4,744 patients, demonstrated a marked reduction in worsening heart failure, cardiovascular death, and time to first event. (McMurray et al., 2019)

More recently, the EMPEROR-reduced trial published in 2020 recruited 3,730 patients with an ejection fraction of 40% or less, NYHA class II to IV with or without diabetes. In addition to recommended therapy, they were randomly assigned to receive either empagliflozin 10 mg once daily or a placebo. In a median of 16 months, empaglifozin

reduced cardiovascular death and hospitalization for worsening heart failure in 361 of 1863 patients (19.4%) in the empagliflozin group and 462 of 1867 patients (24.7%) in the placebo group (hazard ratio for cardiovascular death or hospitalization for heart failure, 0.75; 95% confidence interval [CI], 0.65 to 0.86; P<0.001). The benefit of empagliflozin in reducing cardiovascular death or hospitalization for worsening heart is consistent regardless of diabetes or non-diabetes. This trial supported a similar outcome as per an earlier study of dapaglifozin in heart failure (DAPA-HF). (Packer *et al.*, 2020a)

This two landmark trial (EMPEROR-Reduce and DAPA-HF) evaluated the effects of SGLT2i on heart failure hospitalization and mortality. There was only one study that evaluated the effect of SGLT2i on left ventricular function. A study on diabetic patient by Hwang *et al.*, 2020, where they retrospectively identified 76 HFrEF patients without SGLT2i and 74 patients that were on SGLT2i. They all underwent echocardiography before, and 6 to 24 months after therapy. And after median 13 months of follow‐up, HF patients with SGLT2i showed an improvement in LV‐EF (from 36.1% [25.6–47.5] to 45.0% [34.8–56.3]; p < 0.001).

So far the use of SGLT2i in HUSM is still limited due to cost. These drugs are only available to patient with support such as HUSM staff and pensioner. For those who are not eligible to these drugs they need to self-purchased.

1.2 CONCEPTUAL FRAMEWORK

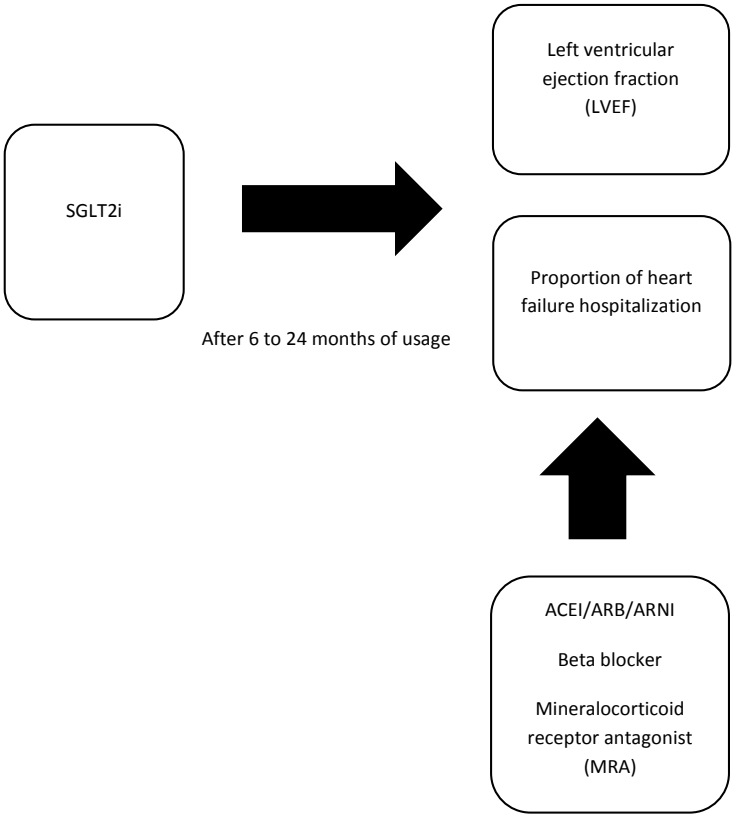

Figure 1: Conceptual framework

2.3 PROBLEM STATEMENT & STUDY RATIONALE

Heart failure has a high mortality rate, and heart failure hospitalization is used to predict mortality in HF patients. A recent meta-analysis including over 1.5 million all-type heart failure patients estimated the 1,2,5, and 10-year survival to be 87%, 73%, 57%, and 35%, respectively. Moreover, according to Groenwegan et al.2020, patients with newly diagnosed heart failure in primary care with no prior hospital admission had a 5-year mortality rate of 56%, compared to 78% in patients hospitalized for heart failure who did not have primary care records. (Groenewegen *et al.*, 2020)

Another study by Clare J Taylor et al.2019 reported that patients with established heart failure admitted for acute decompensated heart failure have high mortality rates; up to one in six patients (1:6) die during admission or within 30 days after discharge. The survival rate for heart failure patients identified during screening is better, with around half of all study participants alive at five years.(Taylor *et al.*, 2019)

Despite established guidelines on managing heart failure, managing HF is still challenging in term of optimizing and combining medication that will benefit HF patients. Teng et al. 2018 reported that the medication used to treat heart failure was monotherapy instead of combined therapy. The recommended target doses achieved only 17% of those given ACEI or ARBs, 13% of beta-blockers, and 29% of those given MRAs. Other challenges are in term of lengthy periods of up-titrate medication to a maximum tolerated dose, patients not adhering to lengthy treatment processes, and

adverse events of the medication started (such as hypotension, hyperkalemia, and acute kidney injury) (Teng *et al.*, 2018; Lam *et al.*, 2019)

However, among four different class of drugs that are use in treating HF, SGLT2i are generally well tolerated, do not require dose titration, and can regress the progression of chronic kidney disease. Packer et al., 2020 stated that the estimated glomerular filtration rate (eGFR) decline rate was slower in the empagliflozin group than in the placebo group. The reduction rate was –0.93 ml per minute per 1.73 m^2 (95% CI, –1.97 to 0.11) in the empagliflozin group and by –4.21 ml per minute per 1.73 m^2 (95% CI, –5.26 to –3.17) in the placebo group. (Packer *et al.*, 2020b)

This study was conducted to evaluate the effectiveness of SGLT2i with other standard heart failure treatments to reduce heart failure hospitalization and improve left ventricular function in heart failure patients in the local population.

We hope that with this study, more clinicians will use SGLT2i not only for diabetes mellitus but in all HFrEF. And institute/ hospital/ government will give more financial support to patients who did not afford to purchase but benefits from SGLT2i.

CHAPTER 3

METHODOLOGY

3.1. RESEARCH DESIGN

This study was approved by the Human Research Ethics Committee of HUSM (USM/JEPeM/ 22090594). This retrospective cohort study incorporated secondary data from 2018 to 2022. HFrEF were screened from heart failure and cardiology clinic registry book. Then medical record was traced. Out of 421 patients that were screened, only 55 patients that fulfilled criteria in each group were included in the study.

From medical record, the echocardiography done (one at baseline and the second at least after six months of SGLT2i initiation up to 24 months) were recorded. The first to the second echocardiography duration cannot be fixed at six months as this was a retrospective study. Instead, within the range after six months up to 24 months from SGLT2i initiation wal allowed in the study.

The data for heart failure hospitalizations were traced from discharge summaries or medical records and were analyzed categorically: with or without hospitalization. The heart failure hospitalization was counted after 30 days of initiation of the SGLT2i group and 30 days after diagnosis for the non-SGLT2i group.

Clinical data such as blood pressure, heart rate, age, and comorbidities were taken from the medical record. Laboratory data, such as HbA1c, renal profile, and haemoglobin,