CHAPTER I

INTRODUCTION

1.1. Background

Heart Failure (HF) is determined to be a clinical syndrome with current or prior & Symptoms and or signs caused by a structural and/or functional cardiac abnormality (Bozkurt et al., 2021). Clinical syndrome in HF consisting of dyspnea, malaise, swelling and/or decreased exercise capacity due to the loss of compensation for cardiac pumping function due to structural and/or functional abnormalities of the heart (Tsutsui et al., 2017). HF is classified into three subtypes according to their ejection fraction, namely heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF) and heart failure mid-range ejection fraction (HFmrEF). It is generally believed that, of those with HF, about 50% have HFrEF and 50% have HFpEF/HFmrEF,mainly based on studies in hospitalized patients (McDonagh et al., 2021).

Currently, the incidence of HF in Europe is about 3/1000 person-years (all age-groups) or about 5/1000 person-years in adults. The prevalence of HF appears to be 1-2% of adults (McDonagh et al., 2021). In Southeast Asia 9 million people suffer from HF with a prevalence of 6.7% in Malaysia and 4.5% in Singapore (Savarese & Lund, 2017). In Indonesia alone, from a total of 853 patients with heart failure, the number of male patients was more (68.2%) than women (31.8%) (Mumpuni et al., 2021). A number of recent reports suggest that the overall number of people with heart failure is

increasing because of a substantial increase in predisposing or comorbid diseases (such as diabetes, obesity, and hypertension) and because the population is aging in general (Lueder & Stefan, 2018).

In the latest guideline, the first line pharmacotherapy for HFrEF has been revised, there are angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor-neprilysin inhibitors (ARNI), beta blockers, mineralocorticoid receptor antagonists (MRA), diuretics, and sodium-glucose cotransporter 2 inhibitors (SGLT2i) (McDonagh et al., 2021). SGLT2i is a class of drugs developed for the treatment of type 2 DM, which lower glucose concentrations by increasing urinary glucose excretion. Drugs in the SGLT-2 inhibitor class include canagliflozin, dapagliflozin, empagliflozin, sotagliflozin, and ertugliflozin (Nelinson et al., 2021). However, based on recent large trials such as DAPA-HF and EMPEROR-Reduced, it has been shown that SGLT2i has a significant effect in reducing the risk of cardiovascular death and hospitalization for heart failure in HFrEF patients with both DM and non-DM (McMurray et al., 2019; Packer et al., 2019).

It is now known that SGLT2i has a favorable effect on the prognosis of HFrEF patients. However, there are still no studies or trials that directly compare SGLT2i with other first-line HFrEF pharmacotherapy drugs. Yan et al., 2021 in their meta-analysis study tried to compare SGLT2i with ARNI in HFrEF patients using the indirect comparison method, where in their study the results showed that SGLT2i and ARNI had the same potential in reducing the risk of cardiovascular death and hospitalization for heart failure. The analysis also showed that the combination of SGLT2i and ARNI was better

than monotherapy with ARNI. (Yan et al., 2021). However, such comparisons between SGLT2i and other drugs have not been carried out, one of which is MRA. As is known, MRA is a drug that works by replacing aldosterone to bind to the mineralocorticoid receptor (McDonagh et al., 2021). Several previous large trials have suggested that MRA has a significant effect in preventing mortality and morbidity in HFrEF patients (Zannad et al., 2011; Pitt et al., 2003; Pitt et al., 1999).

There is no comparison between SGLT2i and MRA and the various results from existing studies regarding prognosis, especially cardiovascular and renal outcomes in these HFrEF patients, cause the clinician to be confused in making decisions in providing therapy. So, it is necessary to have a systematic review and meta-analysis that summarizes the results of the study. Therefore, the authors are interested in conducting a systematic review and meta-analysis regarding the Cardiovascular and Renal Outcome of SGLT2i versus MRA in HFrEF patients.

1.2. Research Question

The Research question of this study as follows:

- How does sodium-glucose cotransporter 2 inhibitors (SGLT2i) affect cardiovascular and renal outcome in heart failure with reduced ejection fraction (HFrEF) patients?
- How does mineralocorticoid receptor antagonists (MRA) affect cardiovascular and renal outcome in heart failure with reduced ejection fraction (HFrEF) patients?

- How is the comparison of sodium-glucose cotransporter 2 inhibitors (SGLT2i) against mineralocorticoid receptor antagonists (MRA) on composite cardiovascular death or hospitalization of heart failure by indirect treatment comparison (ITC) method in heart failure with reduced ejection fraction (HFrEF) patients?
- Is the combination of sodium-glucose cotransporter 2 inhibitors (SGLT2i) and mineralocorticoid receptor antagonists (MRA) better than monotherapy in heart failure with reduced ejection fraction (HFrEF) patients?

1.3. Research Objectives

1.3.1. General Objectives

To determine cardiovascular and renal outcomes of sodium-glucose cotransporter 2 inhibitors (SGLT2i) versus mineralocorticoid receptor antagonists (MRA) in heart failure with reduced ejection fraction (HFrEF) patients.

1.3.2. Specific Objectives

a. To determine effect of sodium-glucose cotransporter 2 inhibitors (SGLT2i) on cardiovascular and renal outcome in heart failure with reduced ejection fraction (HFrEF) patients

b. To determine effect of mineralocorticoid receptor antagonists (MRA) on cardiovascular and renal outcome in heart failure with reduced ejection fraction (HFrEF) patients

c. To determine comparison of sodium-glucose cotransporter 2 inhibitors (SGLT2i) against mineralocorticoid receptor antagonists (MRA) on composite cardiovascular death or hospitalization of heart failure by indirect treatment comparison (ITC) method in heart failure with reduced ejection fraction (HFrEF) patients

d. To know whether combination of sodium-glucose cotransporter 2 inhibitors (SGLT2i) and mineralocorticoid receptor antagonists (MRA) better than monotherapy in heart failure with reduced ejection fraction (HFrEF) patients

1.4. Significances of the Study

1.4.1. Theoretical Significances

a. Provides a summary of studies on cardiovascular and renal outcomes of sodium-glucose cotransporter 2 inhibitors (SGLT2i) versus mineralocorticoid receptor antagonists (MRA) in heart failure with reduced ejection fraction (HFrEF) patients.

b. Provide a better understanding of pharmacological therapy in heart failure patients with reduced ejection fraction (HFrEF).

1.4.2. Practical Significances

a. For Researchers

This study is expected to be additional information for the development of further studies related to pharmacological therapy in heart failure patients with decreased ejection fraction (HFrEF).

b. For Educational Institution

Can be additional information to expand knowledge related to pharmacological therapy in heart failure patients with decreased ejection fraction (HFrEF).

c. For Clinicians

This research is expected to be a reference and recommendation for staff health to make decisions regarding pharmacological therapy in patients with heart failure with decreased ejection fraction (HFrEF).

d. For Public

This study is expected to provide insight and information about pharmacological therapy in patients with heart failure with decreased ejection fraction (HFrEF).

1.5. Research Risk

This research has no risk because it was conducted by reviewing the literature without any direct intervention to the research subjects/humans.