COST EVALUATION OF HEART FAILURE TREATMENT, COST-EFFECTIVENESS ANALYSIS AND BUDGET IMPACT OF ADDING EMPAGLIFLOZIN TO STANDARD TREATMENT FOR HEART FAILURE WITH REDUCED EJECTION FRACTION

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LIST OF SYMBOLS

Ai (ti)	The cumulative cost until the time, t for a patient, i
cv	Ratio of standard deviation to mean
n	Total sample size, including censored and uncensored patients
Sc (ti)	The probability of being uncensored beyond time, t
ti	Time to fix endpoint, death, or loss to follow up for each patient (in months)
V	Width of 95% confidence interval, expressed as a percentage of mean

LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACEi	Angiotensin-converting enzyme inhibitor
ADVANCE	Action in Diabetes and Vascular Disease study
AF	Atrial fibrillation
ANOVA	Analysis of variance
ARB	Angiotensin receptor blocker
ARNi	Angiotensin receptor-neprilysin inhibitor
ASIAN-HF	Asian Sudden Cardiac Death in Heart Failure
BIA	Budget impact analysis
CAD	Coronary artery disease
CEA	Cost-effectiveness analysis
CET	Cost-effectiveness threshold
CI	Confidence interval
CKD	Chronic kidney disease
CPI	Consumer price index
CRD	Centre for Reviews and Dissemination
CSS	Clinical summary score
CUA	Cost-utility analysis
CV	Cardiovascular
DRG	Disease-Related Group
DSA	Deterministic sensitivity analysis
eGFR	Estimated glomerular filtration rate
EMPA-REG	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose
EMPEROR-Reduced	Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction trial
EQ-5D	EuroQoL Five-Dimension scale

ESC	European Society of Cardiology
GDP	Gross domestic product
HF	Heart failure
HF*mr*EF	Heart failure with mildly reduced ejection fraction
HF*p*EF	Heart failure with preserved ejection fraction
HF*r*EF	Heart failure with reduced ejection fraction
hHF	Hospitalisation due to heart failure
HQE2	Hospital Queen Elizabeth II
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
INTER-HF	International Congestive Heart Failure study
IPW	Inverse probability weighting
IQR	Interquartile range
ISPOR	The Professional Society for Health Economics and Outcome Research
ITT	Intention-to-treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
LOS	Length of stay
LVEF	Left ventricular ejection fraction
LYG	Life-years gained
M	Mean
MD	Mean difference
MeSH	Medical Subject Headings
MoH	Ministry of Health
MRA	Mineralocorticoid receptor antagonist
MyHF	Malaysia Heart Failure Registry
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

NT-pro BNP	Amino-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
PGH	Penang General Hospital
PPPY	Per patient per year
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life-year
RAAS	Renin-angiotensin-aldosterone system
SD	Standard deviation
SE	Standard error
SGLT2i	Sodium-glucose co-transporter 2 inhibitor
SH	Serdang Hospital
SoC	Standard of care
T2DM	Type 2 diabetes mellitus
vs	Versus

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PENILAIAN KOS RAWATAN KEGAGALAN JANTUNG, ANALISIS KEBERKESANAN KOS DAN IMPAK BELANJAWAN TERHADAP PENAMBAHAN EMPAGLIFLOZIN KEPADA RAWATAN STANDARD UNTUK KEGAGALAN JANTUNG DENGAN PECAHAN EJEKSI TERKURANG

ABSTRAK

Kegagalan jantung (HF) ialah diagnosis klinikal yang disebabkan oleh keabnormalan struktur atau fungsi jantung. Peningkatan prevalens HF dan kemasukan ke hospital yang kerap akibat kegagalan jantung (hHF) memberi kesan ketara kepada perbelanjaan penjagaan kesihatan. Tambahan pula, terdapat data yang terhad berkaitan beban ekonomi bagi HF merentasi fraksi ejeksi (EF) yang berbeza. Empagliflozin ialah ubat antidiabetik baharu yang meningkatkan hasil klinikal HF dengan pesakit pecahan ejeksi terkurang (HF*r*EF). Oleh itu, kajian ini bertujuan untuk menentukan kos rawatan HF, keberkesanan kos dan kesan belanjawan untuk menambah empagliflozin kepada standard penjagaan (SoC) berbanding monoterapi SoC daripada perspektif Kementerian Kesihatan Malaysia. Kajian analisis kos bawah-atas berasaskan prevalens telah dijalankan di tiga buah hospital tertier di Malaysia untuk menganggarkan kos langsung dan penggunaan sumber sepanjang satu tahun susulan. Jumlah kos terdiri daripada pesakit luar, kemasukan ke hospital, pengubatan, ujian makmal dan prosedur, yang dikategorikan mengikut fraksi ejeksi. Keberkesanan kos bagi empaglifozin telah ditentukan dengan menggunakan model peralihan keadaan berasaskan kohort dengan keadaan kesihatan yang ditakrifkan sebagai sukuan Soal Selidik Kardiomiopati Kota Kansas-Skor Ringkasan Klinikal dan kematian. Kos perubatan langsung semasa hayat dan tahun hayat kualiti pelarasan (QALYs) untuk

kedua-dua kumpulan rawatan telah dibandingkan dan insiden kematian dan hHF dimodelkan untuk setiap kitaran bulanan. Insiden kematian dan hHF dimodelkan untuk setiap kitaran bulanan. Input dan utiliti klinikal dianggarkan daripada percubaan klinikal EMPEROR-Reduced, ditambah dengan data penentuan kos tempatan. Peningkatan keberkesanan kos tambahan (ICER) dinilai berdasarkan ambang keberkesanan kos yang ditakrifkan oleh keluaran dalam negara kasar per kapita (RM 47,439/QALY). Kesan kewangan bagi penambahan empagliflozin kepada SoC telah dinilai menggunakan analisis kesan belanjawan. Purata kos penjagaan kesihatan tahunan HF bagi setiap pesakit ialah RM8,146. Kos penjagaan kesihatan didorong oleh kos pesakit dalam (74.7% daripada jumlah keseluruhan), terutamanya oleh kos prosedur dan ujian diagnostik. Setiap episod hHF ialah RM5,247. Purata kos tahunan bagi setiap pesakit untuk HF*r*EF, HF dengan EF berkurang sedikit (HF*mr*EF) dan HF dengan EF terpelihara (HF*p*EF) masing-masing ialah RM7,892, RM10,218 dan RM9,961. Berbanding dengan SoC sahaja, empagliflozin + SoC menghasilkan tambahan 0.18 QALY dengan kos yang lebih tinggi (RM3,658), dan menghasilkan ICER sebanyak RM20,400/QALY, yang mengesahkan keberkesanan kos. Kesan belanjawan bersih terkumpul 5 tahun untuk menambah empagliflozin pada SoC ialah RM27.62 juta, meningkat sebanyak 0.5% daripada belanjawan HF semasa. Walaupun pencegahan hHF secara sebahagiannya mengimbangi kos tambahan untuk memperoleh empaglifozin, keputusan untuk memasukkan empagliflozin dalam formulari memerlukan pemeriksaan teliti terhadap keberkesanan klinikal dan beban kewangan.

COST EVALUATION OF HEART FAILURE TREATMENT, COST-EFFECTIVENESS ANALYSIS AND BUDGET IMPACT OF ADDING EMPAGLIFLOZIN TO STANDARD TREATMENT FOR HEART FAILURE WITH REDUCED EJECTION FRACTION

ABSTRACT

Heart failure (HF) is a clinical condition caused by structural or functional heart abnormalities. The increasing prevalence of HF and frequent hospitalisation due to HF (hHF) significantly impact healthcare expenditure. Moreover, there is limited data on the economic burden of HF across different ejection fractions (EF). Empagliflozin is a novel antidiabetic medication that improves clinical outcomes of HF with reduced ejection fraction (HF*r*EF) patients. Therefore, this study was designed to determine the cost of HF treatment, cost-effectiveness, and budget impact of adding empagliflozin to the standard of care (SoC) compared to SoC monotherapy from the Ministry of Health Malaysia perspective. A prevalence-based, bottom-up cost analysis study was conducted in three tertiary hospitals in Malaysia to estimate the direct cost and resource utilisation throughout a one-year follow-up. The total costs consisted of outpatient, hospitalisation, medications, laboratory tests, and procedure costs, categorised according to ejection fraction. The cost-effectiveness of empagliflozin was determined using a cohort-based transition states model with health states defined as Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score quartiles and death. The lifetime direct medical costs and quality-adjusted life-years (QALYs) were compared, and the incidence of death and hHF were modelled for each monthly cycle. The clinical inputs and utilities were estimated from the EMPEROR-Reduced trial and supplemented by local costing data. The incremental cost-effectiveness ratio (ICER)

was assessed against cost-effectiveness thresholds defined by the country's gross domestic product per capita (RM 47,439/QALY). The financial consequence of adding empagliflozin to SoC was evaluated using a budget impact analysis. The mean annual healthcare cost of HF per patient was RM 8,146. The healthcare cost of HF was driven by the inpatient cost (74.7% of the total), particularly by the cost of procedures and diagnostic tests. Each hHF episode costed RM 5,247. The mean annual costs per patient for HF*r*EF, HF with mildly reduced EF (HF*mr*EF), and HF with preserved EF (HF*p*EF) were RM 7,892, RM 10,218, and RM 9,961, respectively. Compared to SoC alone, empagliflozin + SoC yielded an additional 0.18 QALYs at a higher cost (RM 3,658) and generated an ICER of RM 20,400/QALY, thus confirming cost-effectiveness. The 5-year cumulative net budget impact of adding empagliflozin to SoC was RM 27.62 million, increasing by 0.5% to the current HF budget. While the prevention of hHF partially offsets the additional cost of acquiring empagliflozin, the decision to include empagliflozin in the formulary requires a careful examination of clinical efficacies and financial burden.

CHAPTER 1

INTRODUCTION

1.1 Definition of heart failure

Heart failure (HF) is the terminal form of various cardiovascular (CV) diseases. Its aetiology varies within and across countries or populations (Ponikowski et al., 2016). The aetiology of HF can range from diseased myocardium (e.g., coronary artery disease [CAD]), abnormal loading of the heart (e.g., hypertension), to cardio-arrhythmias (McDonagh et al., 2021).

Although some patients with HF remain clinically asymptomatic, they have functional and structural abnormalities known as HF precursors (Ponikowski et al., 2016). Identifying these precursors is crucial to establishing an effective and individualised treatment regimen that can improve clinical outcomes in asymptomatic patients. In HF patients, clinical symptoms and physical activity tolerance are classified according to the New York Heart Association (NYHA) functional classification (Dolgin M et al., 1994) (Table 1.1).

Table 1.1 New York Heart Association functional classification

Class	The severity of symptoms and physical activity
I	No limitations in performing physical activities
II	Slight limitations in performing physical activities. Ordinary activities lead to mild symptoms.
III	Marked limitation in performing physical activities, whereby less-than-ordinary activities cause symptoms.
IV	Inability to perform any physical activities without discomfort. Symptoms persist even at rest.

Dolgin M, Fox AC, Gorlin R, Levin RI, & New York Heart Association (1994). Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. In (9th ed., pp. 253-256). Lippincott Williams and Wilkins.

Besides that, patients with HF can be categorised based on left ventricular ejection fraction (LVEF). The European Society of Cardiology (ESC) classifies HF

into three phenotypes based on the functionality of the left ventricle: HF with reduced ejection fraction (HF*r*EF) with LVEF ≤40%; HF with mildly-reduced ejection fraction (HF*mr*EF) with LVEF of 41 – 49%; and HF with preserved ejection fraction (HF*p*EF) with LVEF ≥ 50% (McDonagh et al., 2021). Although patients can have HF*r*EF, they can remain relatively asymptomatic and have only slight limitations on physical activity (NYHA class I-II).

HF*r*EF patients are associated with a higher risk of readmission and CV death than HF*mr*EF and HF*p*EF patients (Lam et al., 2018; MacDonald et al., 2020). The higher level of baseline NT-pro-brain type natriuretic peptide (NT-proBNP) among HF*r*EF patients explains the elevated risks of readmission and CV death. Frequent hospitalisation would likely increase the healthcare cost of managing HF*r*EF patients compared to other phenotypes. Cost analysis can break down the healthcare cost of managing HF patients into individual components. The detailed cost breakdown enables the stakeholders to identify the cost drivers associated with managing HF*r*EF patients, such as inpatient costs. Together with evidence from cost-effective analysis, the stakeholders can make informed decisions to adopt cost-effective interventions to reduce the risk of admission among HF*r*EF patients. Preventing hospitalisation among HF*r*EF patients provides a cost-saving opportunity for the healthcare system.

1.2 Epidemiology of heart failure

The Institute of Health Metrics performed a Global Burden of Diseases, Injuries, and Risk Factors Study and Evaluation on HF from 1990 to 2017 to determine the disease burden, injuries, and risk factors at different regions and national levels (Bragazzi et al., 2021). The study found that the age-adjusted prevalence rate of HF per 100,000 persons was 831, with a higher prevalence of males living with HF than

females (845 vs. 818) in 2017. Furthermore, the global number of people living with HF doubled from 33.5 million to 64.3 million between 1990 and 2017 (Bragazzi et al., 2021). Advancements in medical treatment for HF and the increasing proportion of older adults contribute to the future increment in the disease burden of HF (Braunschweig et al., 2011; Braunwald, 2015).

Countries in the Middle East, North Africa, and Central Europe were found to have the highest age-standardised prevalence rate of HF, ranging from 972 to 1,058 cases per 100,000 persons. The lowest prevalence rate was found in Eastern European and Southeast Asian countries, ranging from 655 – 704 cases per 100,000 persons (Bragazzi et al., 2021) (Figure 1.1). However, the prevalence rate of HF in Malaysia was one of the highest in the Southeast Asia region, with a prevalence rate of 721 cases per 100,000 persons in 2017, an increase of 7.7% from 669 cases per 100,000 persons in 1990 (Bragazzi et al., 2021) (Figure 1.2). The rise in the prevalence of HF in Malaysia could be explained by the marked increase in the risk factors for HF, such as sedentary lifestyles, hypertension, diabetes mellitus, obesity, and smoking (Agbor et al., 2020; Lam, 2015).

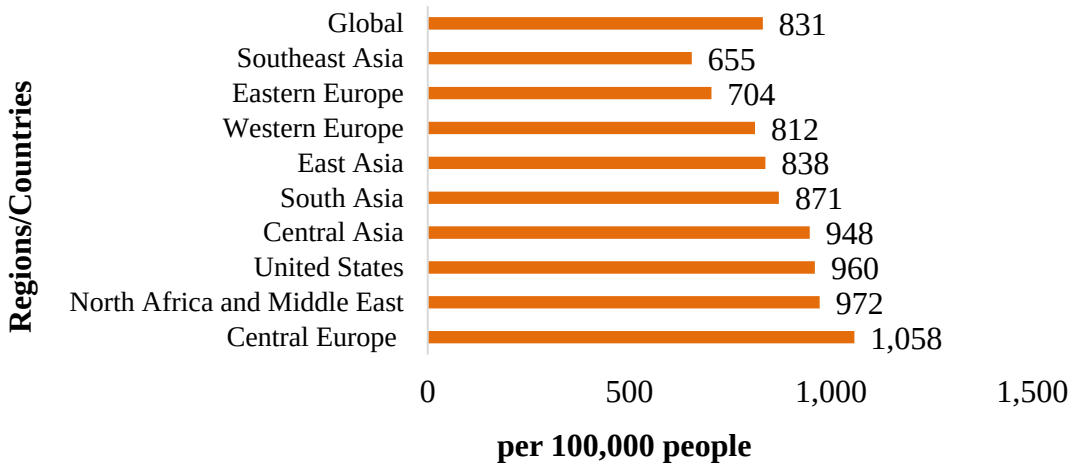

Figure 1.1 Age-Standardised Prevalence Rate of Heart Failure by Regions in 2017

Adapted from Bragazzi et al., 2021 (Supplemental materials)

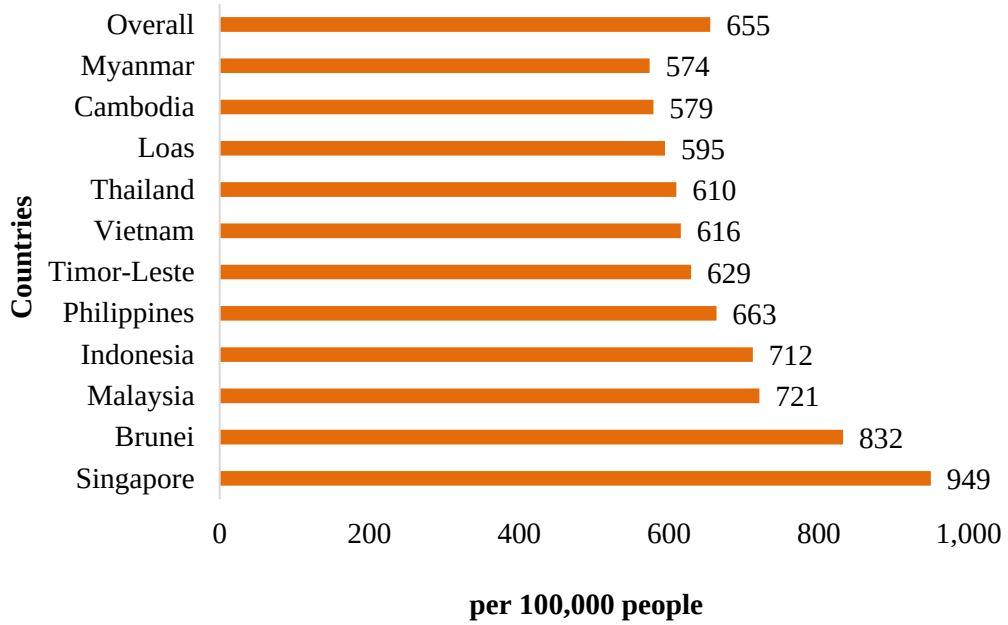

Figure 1.2 Age-Standardised Prevalence Rate of Heart Failure of Southeast Asia Countries in 2017
Adapted from Bragazzi et al., 2021 (Supplemental materials)

The aetiology spectrum of HF varies geographically due to the broad range of risk factors (Stanaway et al., 2018). Accounting for almost 75% of HF prevalence rates, the top three causes of HF worldwide are CAD (26.5%), hypertensive heart disease (23.4%), and chronic obstructive pulmonary disease (23.4%) (Bragazzi et al., 2021). CAD accounted for approximately 22% of the prevalence rates of HF in Southeast Asian countries (Bragazzi et al., 2021). However, observational studies in Malaysia found that 40-60% of HF cases were caused by CAD (Chong et al., 2003; Ling et al., 2020; Raja Shariff et al., 2021).

1.3 Outcomes of heart failure

1.3.1 Mortality associated with heart failure

In 2018, HF-related mortality accounted for about 13% of all deaths in the United States (Virani et al., 2020). A European survey found HF-associated mortality in one year to be 8.8% (Crespo-Leiro et al., 2016). The International Congestive Heart

Failure study (INTER-HF) and Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry, whereby Malaysia participated in both studies, reported that the one-year mortality rate for HF in Southeast Asia was between 13% – 15% (Dokainish et al., 2017; MacDonald et al., 2020). The ASIAN-HF registry also found that the all-cause mortality rate in Southeast Asia (13.0%) was significantly higher than in Northeast Asia (7.4%) and South Asia (7.5%). One possible explanation for the high mortality rate in Southeast Asia was the high rate of comorbidities among HF patients (MacDonald et al., 2020). Furthermore, the mean age of death of HF patients in Southeast Asia was 57 years, one of the lowest in the study (Dokainish et al., 2017). However, the 1-year mortality rate following HF readmission generated from the national discharge database of the Ministry of Health (MoH) Malaysia was 33.1%, which was higher than the mortality rate estimated by the registries (Lim et al., 2022). Patients who enrolled in the registries were found to have better clinical outcomes (Lund et al., 2017). The differences in the mortality rates were attributed to demographic selection bias, whereby patients who had better access to tertiary medical care were recruited into the registries for analysis. For example, the institutions participating in the INTER-HF and ASIAN-HF registries were tertiary hospitals.

In the ASIAN-HF registry, HF*r*EF patients had a higher all-cause mortality rate than HF*p*EF patients (10.6% vs. 5.4%) (MacDonald et al., 2020). A prospective longitudinal trial involving Singapore and New Zealand reported that the all-cause mortality for HF*p*EF, HF*mr*EF, and HF*r*EF were 75, 63, and 109 per 1,000 patient-years, respectively (Lam et al., 2018). One strong prognostic marker for CV mortality in HF patients is a cardiac biomarker known as NT-pro BNP (Oremus et al., 2014). Cardiomyocytes secrete NT-pro BNP when ventricular filling pressure is elevated (Rørth et al., 2020), thus indicating ventricular wall distress. The high baseline NT-

pro BNP level in HF*r*EF patients explained the exceptionally higher mortality than other HF phenotypes (Lam et al., 2018). However, the mortality difference between the three HF phenotypes diminished after adjusting for NT-pro BNP level (Lam et al., 2018). The mortality rates among the three phenotypes at a given level of NT-pro BNP were the same.

CV deaths contributed to about half of the total deaths in patients with HF*r*EF, with sudden death and HF-related death as the main types of CV deaths (MacDonald et al., 2020). A small observational study conducted in Malaysia found that 1-month all-cause mortality among patients with acute decompensated HF was 20.5% (Ling et al., 2020).

Risk factors significantly associated with all-cause mortality were advanced age, hospitalisation, NYHA class III/IV, atrial fibrillation (AF), and chronic kidney disease (CKD) (MacDonald et al., 2020). However, AF was not a risk factor for mortality in Southeast Asia (MacDonald et al., 2020). In addition, hospitalisation was associated with a poor prognosis in Northeast and South Asia but not in Southeast Asia because of disproportionately higher hospitalisation rates in Malaysia and Singapore, where there is good medical care (MacDonald et al., 2020).

1.3.2 Readmission associated with heart failure

HF is a severe medical condition requiring frequent hospitalisation and significantly reduced life expectancy and health-related quality of life (HRQoL). HF accounted for about one million admissions yearly in America (Jackson et al., 2018). During the first 30 days following hospital discharge, the readmission risk of HF patients ranged between 6.3 – 56% (Butler et al., 2019; Ku et al., 2017). All-cause readmission at six months ranged between 23 – 50% (Liao et al., 2008; Setoguchi et

al., 2009; Swindle et al., 2016). The 30-day all-cause readmission among HF patients in Malaysia ranged from 13 – 18.1% (Lim et al., 2022; National Heart Association Malaysia, 2021). Furthermore, the readmission rate of HF patients in Malaysia increased steadily from 16.6% in 2007 to 19.6% in 2015 (Lim et al., 2022). The reduced hospitalisation threshold for HF contributed to the increase in the readmission rate in Malaysia. Compared to stable patients, patients who had experienced a worsening HF event were more likely to have another episode of readmission within 30 days after discharge (Butler et al., 2020; Dharmarajan et al., 2013). This is because HF patients suffered from substantial sub-clinical haemodynamic abnormalities at discharge, even though their decompensated symptoms markedly improved during hospitalisation (Greene et al., 2015). In addition, each subsequent readmission following a decompensated event was associated with higher mortality and lower HRQoL (Lin et al., 2017; Nieminen et al., 2015)

Other risk factors associated with all-cause readmission in HF patients were underlying CV-related comorbidities (Allen et al., 2012), discontinued renin-angiotensin-aldosterone system (RAAS) inhibitor treatment, and failure to restart RAAS inhibitor treatment at the time of discharge (Gilstrap et al., 2017). A decrease in cardiac output causes the sympathetic nervous system and RAAS to over-activate (neurohormonal axis). The overactivation of the neurohormonal axis to compensate for the reduced cardiac output can further deteriorate the failing heart. RAAS inhibitors reduce the neurohormonal axis overactivity, preventing disease progression and adverse clinical outcomes in HF patients (Mann et al., 2021).

1.4 Quality of life in heart failure patients

HRQoL consists of a broad spectrum of determinants, including physical and social functioning, psychological and general health, energy or vitality, and cognitive function (Wilson et al., 1995). HF is known to negatively impact the HRQoL of patients (Sepehrvand et al., 2020). Persistent and recurrent symptoms associated with HF, such as dyspnoea, lethargy, and emotional distress, can severely impact patients' HRQoL, resulting in poorer HRQoL in HF patients compared to patients with other comorbidities (Dokainish et al., 2017; Salyer et al., 2019). Apart from the symptoms, HF also reduces patients' independence and ability to perform daily basic activities, further worsening their HRQoL (Comín-Colet et al., 2016; Fry et al., 2016). Thus, the treatment goals of managing patients with HF are not limited to alleviating their clinical symptoms, preventing hospital admission, and reducing mortality but also include improving HRQoL (McDonagh et al., 2021; Yancy et al., 2013).

The NYHA functional classification has been traditionally used in the clinical setting to evaluate clinical symptoms and functional status among HF patients, with NYHA class IV being the worst. In addition, the NYHA functional classification is widely employed as a proxy for disease severity and health states in HF-related economic evaluation (Di Tanna et al., 2019). However, evaluating the clinical status of HF patients using the NYHA functional status poses a few limitations: 1) it is highly subjective; 2) it has poor reproducibility among trained cardiologists; 3) the NYHA functional classification is not-patient centric (Papadimitriou et al., 2019). Furthermore, the wide variability in the reported HRQoL among each NYHA class suggests that the NYHA classification does not capture all the elements of HRQoL among HF patients (Gallagher et al., 2019). Hence, patient-reported outcome

instruments should be used in place of NYHA to quantify the health status of HF patients.

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a disease-specific patient self-reported instrument that measures the health status of HF patients. It was found to have a good correlation with clinical outcomes (Butler et al., 2021). The KCCQ scores are associated with risks of CV mortality, hospitalisation for HF (hHF), and a composite of either event in HF patients (Spertus et al., 2020). The questionnaire consists of 23 questions across four domains: physical limitations, symptoms, quality of life, and social limitations (Green et al., 2000). The score from each domain is aggregated and transformed into an overall score of 0-100, with higher scores indicating a better health status. KCCQ provides a complete overview and is sensitive to changes in the clinical condition of HF patients (Green et al., 2000). The overall summary score is the average of all the domains, while the clinical summary score (CSS) is the mean score from the physical limitations and symptoms domains. The most important element of the KCCQ questionnaire is that it is self-reported and, therefore, not biased by the clinician's interpretation of patients' clinical status. Furthermore, it is a more accurate measure of changes in the patient's clinical condition than the NYHA classification (Butler et al., 2021). It also has well-established thresholds to alert clinicians of significant changes (≥5 points changes) in health status (Luo et al., 2019; Pokharel et al., 2017). Every 5-point decrease in the KCCQ scores was associated with a significantly increased risk of CV mortality and hHF (Luo et al., 2019; Pokharel et al., 2017). In general, HF has a detrimental impact on the clinical outcomes and HRQoL of patients. Thus, treatment options that can mitigate these impacts should be adopted to improve clinical outcomes and HRQoL among HF patients.

1.5 Economic burden of heart failure

The management of HF is associated with increased healthcare resource utilisation and related costs, leading to an increase in economic and clinical burden during both the acute decompensated state and for a prolonged period after discharge (Butler et al., 2020). In developed countries such as Europe and the United States, HF consumes about 1 – 2% of their total annual healthcare budget (Liao et al., 2008). In 2012, the global economic burden of HF was estimated at more than USD 100 billion per year, with about 60% of the cost being attributed to the direct cost of managing HF (Cook et al., 2014). Conversely, the total cost associated with HF in Malaysia was about USD 194 million in 2012, which accounted for 1.8% of the total health expenditure and less than 1% of the country's gross domestic product (GDP) (Cook et al., 2014). Figure 1.3 illustrates the annual cost of HF in different countries. In general, the estimated healthcare costs of HF in Malaysia were markedly lower than those derived from European countries and the USA. The wide variation in HF-related healthcare costs between high-income countries (from Europe and the USA) and low-middle-income countries (from Asia and Africa) was partly due to the discrepancy in resource allocation by each country for their healthcare system in managing HF. Furthermore, the direct cost of HF increased with the country's GDP (Cook et al., 2014).

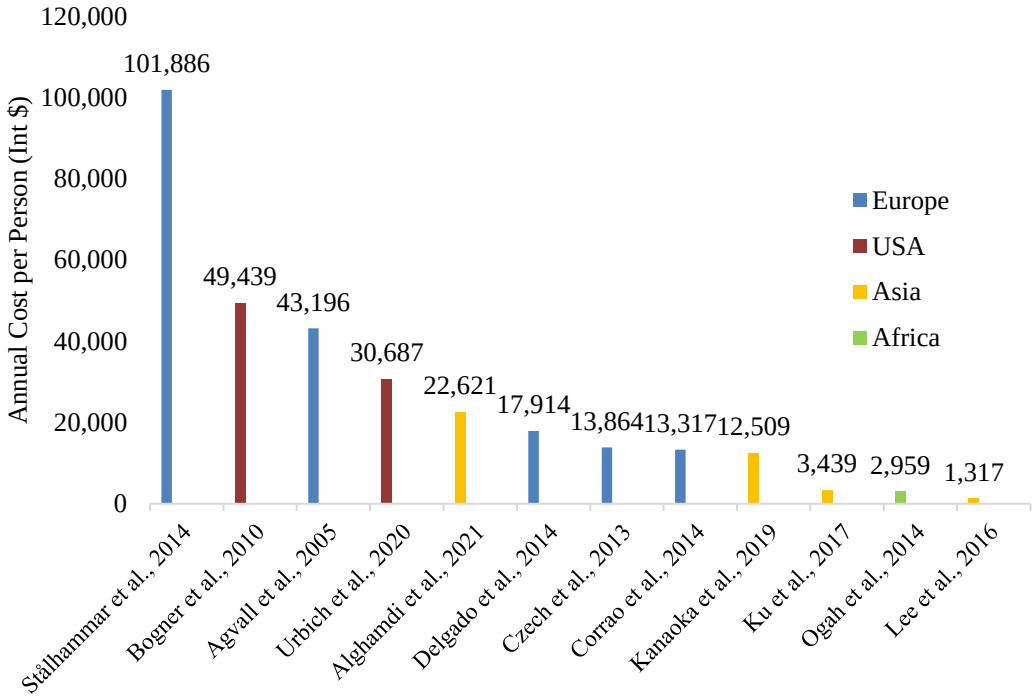

Figure 1.3 Annual cost of heart failure per person by regions

The differences were also attributed to the relative costs of delivering the treatment for HF, treatment protocols, and most notably, the methodology used in calculating the costs. For example, the annual cost of HF per person derived from the ASIAN-HF registry was RM 24,844 (Shafie et al., 2019), which was higher than in observational studies (Shafie et al., 2020; Yingchoncharoen et al., 2021) (Table 1.2). The ASIAN-HF and SwedeHF registries employed the same inclusion criteria (MacDonald et al., 2020). Patients in the registries experienced better quality of care, such as greater use of guideline-directed medical therapy (Lund et al., 2017), which eventually affected the healthcare cost of HF. Besides, a cost analysis study which employed expert opinions in estimating the resources utilised for the treatment of HF (Shafie et al., 2020) could have underestimated the actual healthcare cost of HF because the treatment of HF is individualised. Patients with severe disease would utilise more resources than patients with milder conditions. As a result, the distribution of cost data is often right-skewed with a ‘heavy tail’ (Drummond et al., 2015) because

patients with severe conditions contribute to higher healthcare costs. The cost of hHF per event calculated from the casemix database (Malaysia Disease-Related Group [DRG]®) (Ministry of Health Malaysia, 2021a) was lower than the cost calculated from the ASIAN-HF registry (Shafie et al., 2019) because the ASIAN-HF registry data was obtained from tertiary hospitals while the casemix database was obtained from all hospital categories. More sophisticated and expensive interventions such as percutaneous coronary intervention (PCI) and device implantation are performed only in the tertiary centres. Thus, the average costs calculated from all hospital categories were lower than costs calculated from the tertiary hospitals.

Table 1.2 Healthcare cost of heart failure in Malaysia

	RM*	Int $	Remarks
Annual cost of heart failure per person			
Yingchoncharoen et al. (2021)	6,701	4,214	
Shafie et al. (2019)	24,844	15,625	
Shafie et al. (2020)	5,160	3,245	Event year
Shafie et al. (2020)	1,448	2,303	Subsequent year
Cost per hospitalisation			
Ministry of Health Malaysia (2021a)	4,027	2,533	
Shafie et al. (2019)	14,075	9,657	

*Cost was inflated to the year 2021. International dollar (Int$) 1 = RM 1.59

Although a few studies have estimated the healthcare cost of HF in Malaysia (Shafie et al., 2019; Yingchoncharoen et al., 2021), none of these studies segregated the cost based on HF phenotypes. In addition, the sample size of these studies was insufficient to accurately quantify the healthcare cost of HF. Different HF phenotypes have been found to incur a substantial difference in healthcare system costs (Shafie et al., 2018). Thus, a cost analysis of HF to fill this knowledge gap is urgently needed. The increasing prevalence of HF in Malaysia necessitates a better utilisation of the scarce healthcare resources to adopt innovations and curb a potential ‘HF pandemic’.

1.6 Pharmacological treatment of heart failure with reduced ejection fraction

HF is a disease that involves multiple systemic mechanisms such as neurohormonal systems, RAAS, autonomic nervous system, inflammatory pathways, natriuretic systems, and the vasopressin system. Dysfunctions in these mechanisms ultimately lead to increased heart rate, arrhythmia, impairment in the ventricular-vascular coupling, and cardio-renal syndrome (Zannad et al., 2018). Among the three phenotypes of HF, patients with HF*r*EF have been associated with significant morbidity and reduced overall survival even after being adjusted for their comorbidities (Drozd et al., 2021; Lam et al., 2018). Thus, effective pharmacological treatments that target different pathophysiologies of HF remain the cornerstone for managing HF*r*EF patients preceding device therapy and non-pharmacological treatment (McDonagh et al., 2021).

The primary treatment outcomes in patients with HF*r*EF are to improve survivability, prevent recurrent hHF, and improve functional status and HRQoL (McDonagh et al., 2021; National Heart Association of Malaysia, 2019). Medications that inhibit RAAS (e.g., angiotensin-converting enzyme inhibitor [ACEi], angiotensin receptor blocker [ARB], angiotensin-receptor-neprilysin inhibitor [ARNi]), beta-blocker, and mineralocorticoid antagonist (MRA) are proven to reduce mortality and morbidities in HF*r*EF patients (Bonatto et al., 2022; McDonagh et al., 2021). In the recently updated clinical practice guideline, a novel pharmacological treatment known as sodium-glucose co-transporter type 2 inhibitors (SGLT2i) was added to the triad of ACEi/ARB/ARNi, a beta-blocker, and an MRA to form the foundational quadruple therapy in the treatment of HF*r*EF (Maddox et al., 2021; McDonagh et al., 2021).

SGLT2i blocks the reabsorption of sodium and glucose from the proximal convoluted tubule in the kidney (Joshi et al., 2021), resulting in glycosuria, natriuresis, and reduced plasma glucose levels (Kalra, 2014). The conventional mechanisms involved in the CV actions of SGLT2i are an increase in erythrocyte mass and haematocrit, improved glycaemic control, increased diuresis alongside a reduction in blood pressure, and weight loss (Joshi et al., 2021). Additionally, SGLT2i enhances myocardial energy production, increases cardiac contraction by improving ionic homeostasis, decreases inflammation and oxidative stress, and reduces epicardial fat (Joshi et al., 2021). The clinical efficacies of empagliflozin and dapagliflozin are summarised in Table 1.3.

Table 1.3 Major clinical trials of SGLT2i in patients with HF*r*EF

Trial	Drug	Major inclusion criteria	Primary outcomes	Other important results
DAPA-HF (McMurray et al., 2019)	Dapagliflozin (n = 2373) vs. placebo (n = 2371)	LVEF <40%, NYHA II-IV, presence or absence of T2DM	Reduction of composite outcomes of CV mortality or worsening HF by 26% (16.3% vs 21.2%, p<0.001).	Reduction in all-cause mortality, CV mortality, and worsening of HF by 17%, 18%, and 30%, respectively.
EMPEROR-Reduced (Packer et al., 2020)	Empagliflozin (n = 1863) vs. placebo (n = 1867)	LVEF <40%, NYHA II-IV, presence or absence of T2DM	Reduction of composite outcomes of CV mortality or hHF by 25% (19.4% vs 24.7%, p<0.001).	Reduction in the number of hHF by 29.8%.

DAPA-HF: Dapagliflozin and Prevention of Adverse outcomes in Heart Failure (trial); EMPEROR-Reduced: Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (trial); CV: cardiovascular; HF*r*EF: heart failure with reduced ejection fraction; hHF: hospitalisation due to heart failure; LVEF: left ventricular ejection fraction; n: number of patients; NYHA: New York Heart Association; SGLT2i: sodium-glucose co-transporter 2 inhibitors; T2DM: type 2 diabetes mellitus; vs: versus.

The standard of care (SoC) suggested by the Malaysia clinical practice guideline for the management of HF*r*EF consists of triple therapy comprising a RAAS inhibitor, a beta-blocker, and an MRA (National Heart Association of Malaysia, 2019). SGLT2i can only be added to triple therapy for HF patients with diabetes (National Heart Association of Malaysia, 2019). When the Malaysian guideline for managing HF 4th was published in 2019, the evidence supporting the use of SGLT2i, such as dapagliflozin and empagliflozin, in the treatment of HF patients was only available in diabetes patients (Wiviott et al., 2019; Zinman et al., 2015). Recently, two landmark trials showed that compared to triple therapy alone, incorporating SGLT2i into triple therapy reduced the risk of composite outcomes of CV mortality and hHF in HF*r*EF patients (McMurray et al., 2019; Packer et al., 2020). Thus, there is an unmet medical need in managing HF*r*EF patients. Adding SGLT2i to SoC can reduce the high CV mortality risk and hHF rate among HF*r*EF patients, eventually creating a cost-saving opportunity for the healthcare system. Nevertheless, the additional benefits of SGLT2i relative to the additional upfront cost require a complete economic evaluation of this medication before it is adopted in our clinical setting.

1.7 Cost-effectiveness of empagliflozin in HF*r*EF patients

Since 2017, the MoH Malaysia Medicine Formulary has indicated empagliflozin for the treatment of only diabetic patients with established CV disease (Ministry of Health Malaysia, 2017). The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) study reported that the clinical benefit of empagliflozin in reducing the risk of the composite outcomes CV death or hHF was consistent in HF*r*EF patients with diabetes and without diabetes (Packer et al., 2020). Since then, cardiologists have advocated

for the addition of empagliflozin into the SoC for treating HF*r*EF patients because empagliflozin is the sole SGLT2i listed in the national formulary. However, clinicians are only allowed to prescribe medications listed in the MoH formulary in the healthcare facilities under the jurisdiction of MoH. Applying for a new indication for empagliflozin for treating HF*r*EF patients allows quicker access to the medication than including a new SGLT2i in the formulary. Thus, an evaluation that assesses the economic effectiveness of empagliflozin in treating HF*r*EF patients is needed to justify the addition of a new indication for empagliflozin in the MoH formulary.

Economic evaluation plays a vital role in supporting the optimal allocation of limited resources available to the healthcare system (Turner et al., 2021). The demand for healthcare continues to increase, whereas the resources are constrained. As a result, governments worldwide have made it a priority to ensure the most efficient expenditure of funds on healthcare. Economic factors are also playing an increasingly important role in the planning, monitoring, and assessment of the performance of health systems (Drummond et al., 2015). Economic evaluation is a type of health economic analysis that compares the costs (resources used) and outcomes (effects) of the health intervention(s) of interest to an alternative course of action (comparator) (Drummond et al., 2015). The cost components of an economic evaluation are always valued as the monetary unit. The types of costs included in the analysis depend on the perspective from which the economic evaluation is performed. The Malaysian MoH recommends that economic evaluations on the cost-effectiveness of a health intervention in Malaysia should be conducted from the healthcare provider's perspective (Pharmaceutical Services Programme, 2019). The healthcare provider's perspective considers the costs borne by the healthcare system, also known as direct medical expenses, and includes costs associated with the diagnosis, treatment, and

rehabilitation (Jo, 2014). Conversely, the societal perspective adopts a broader approach consisting of both direct and indirect costs. Indirect costs are those incurred by the patient, family, society, or employer due to productivity losses attributed to mortality and morbidity (Jo, 2014).

The outcomes of an economic evaluation can be measured in various ways and are influenced by the type of evaluation conducted. There are three main types of economic evaluation, and they mainly differ in how the outcomes are evaluated. Cost-effectiveness analysis (CEA) assesses the health consequences as natural units (cases prevented or life-years gained), whereas cost-utility analysis (CUA) measures the health outcomes using a generic tool that evaluates the effects on both morbidity and mortality. In contrast, cost-benefit analysis (CBA) evaluates the outcomes of the health interventions in monetary terms (Table 1.4). Recent guidelines and health technology assessment (HTA) agencies advise using CUA for decision-making because it allows for comparisons across different diseases and fields (Drummond et al., 2015; Turner et al., 2021). The outcomes of an economic evaluation, known as the incremental cost-effectiveness ratio (ICER), are then compared to a cost-effectiveness threshold (CET) to determine the cost-effectiveness of an intervention (Turner et al., 2021).

Table 1.4 Characteristics of different types of economic evaluation analysis

Types of study	Valuation of costs in all alternatives	Valuation of consequences
Cost-effectiveness analysis	Monetary	Natural units (cases prevented or life-years gained)
Cost-utility analysis	Monetary	Healthy years (measured as quality-adjusted life-years)
Cost-benefit analysis	Monetary	Monetary

Although empagliflozin is a cost-effective treatment in HF*r*EF patients in the UK (National Institute for Health and Care Excellence, 2022), Asia Pacific countries (Liao et al., 2021) China (Jiang et al., 2021; Lin et al., 2022; Tang et al., 2022), and Thailand (Krittayaphong et al., 2022), its cost-effectiveness in Malaysia is yet to be determined. Country-specific GDP per capita was used as the CET to examine the cost-effectiveness of the intervention being evaluated (Jiang et al., 2021; Krittayaphong et al., 2022; Liao et al., 2021; Lin et al., 2022; Tang et al., 2022). However, Malaysia's GDP per capita in 2021 was markedly lower than that of countries in the Asia Pacific region (Liao et al., 2021; The World Bank, 2022a). In addition, scenario analysis using local costs from Thailand, which has a similar economic status to Malaysia, found that no iteration was cost-effective in the probabilistic sensitivity analysis (PSA) with one-time GDP per capita (Liao et al., 2021). From the Thailand healthcare system perspective, the addition of empagliflozin to SoC decreased the overall benefits (QALY) in their setting under all circumstances, regardless of the disease severity of HF*r*EF, medication cost, hospitalisation cost, utility value and incidence rate of hHF and CV mortality. Furthermore, the direct medical cost of HF increased with the country's GDP (Cook et al., 2014). Essentially, it is inappropriate to extrapolate the findings from published literature to assess the cost-effectiveness of empagliflozin in Malaysia; not only are there discrepancies between countries in resource allocation to manage HF, but the CET was also determined by the countries' income (Woods et al., 2016). The higher the countries' GDP, the higher the CET. This is because CET positively correlates with GDP (Woods et al., 2016). A higher CET permits more interventions to be deemed cost-effective and thus adapted in the clinical setting, assuming sufficient funding is available. Therefore, an economic evaluation must be conducted from the perspective of the

Malaysian healthcare provider before using empagliflozin in the treatment of HF*r*EF patients.

1.8 Budget impact analysis

Value for money and affordability are key factors that decision-makers take into account when evaluating new medications for reimbursement and general use (Hofmeister et al., 2022). A CEA provides insight into value for money by comparing various interventions and strategies in terms of costs and outcomes. Adopting a cost-effective health intervention increases the overall population health benefits and represents an efficient use of resources (Drummond et al., 2015). However, it is insufficient to depend solely on cost-effectiveness when deciding whether to implement a health intervention. The inputs of the cost-effectiveness model (CEM) can be manipulated; for example, a comparator and target population that does not represent actual clinical practice may be chosen, and the price of intervention may be modified to ensure that the final ICER is just below the CET for it to be listed in the formulary (Bertram et al., 2016). Consequently, the findings from the CEA do not reflect the actual context in which the decision has to be made. In addition, the affordability of adopting a new intervention remains unclear because it is not informed by the findings of the CEM. Furthermore, the intervention might require a massive budget allocation to be adopted and maintained. Hence, CEA by itself is not adequate for budget planning and decision-making.

Budget impact analysis (BIA) has been used in addition to CEA to determine the magnitude of budget change after implementing new interventions. BIA is frequently used (including in Malaysia) to help decision-makers determine the financial implications of adopting and disseminating a new healthcare intervention and

its impact on the organization's budget (Sullivan et al., 2014). A BIA cannot provide a single estimate relevant to all stakeholders due to the highly local nature of the systems and the varying perspectives of the stakeholders. Instead, a BIA aims to provide a useful computing framework that allows stakeholders to enter input values and view financial estimates that are relevant to their situation (Sullivan et al., 2014). As a result, rather than a normative 'base' case intended to be generally applicable, the outcomes of the BIA should reflect circumstances comprising various assumptions and data inputs of interest to the policymaker (Sullivan et al., 2014).

1.9 Problem statement

One of the key challenges highlighted in the Strategic Framework of the Medical Programme Ministry of Health 2021 – 2025 is the increasing economic burden of disease, especially non-communicable diseases, amidst the limited funding allocated to the healthcare system (Ministry of Health Malaysia, 2020b). The total expenditure for health was RM 8.55 billion in 1997 and increased to RM 64.31 billion in 2019 (Ministry of Health Malaysia, 2021b). Public sources funded more than half (52.5%) of the total health expenditure (Ministry of Health Malaysia, 2021b). The core strategy to address this challenge is to optimise resource management using health HTA as a decision tool towards value-based medicine.

According to global HF trends, the number of patients living with HF is estimated to continue increasing in the coming years (Bragazzi et al., 2021; Lippi et al., 2020) due to advancements in medical therapy prolonging the life expectancy of HF patients (Braunschweig et al., 2011; Braunwald, 2015) and the high burden of risk factors for HF (Agbor et al., 2020; Lam, 2015). Risk factors such as diabetes and hypertension have increased steadily in the Malaysian population since 2011 (Ministry

of Health Malaysia, 2020a). Eventually, the high prevalence of HF in the Malaysian population will be a significant economic burden on the healthcare system. Thus, systematic quantification of resources utilised in treating HF patients and their associated costs is necessary to inform policy decision-making by the stakeholders.

Cost analysis is an essential economic analysis tool used in healthcare resource allocation. By quantifying and comparing the different cost components of the disease, the study provides vital information for developing pragmatic measures to address the disease. The previous cost-analysis studies on HF in Malaysia have several limitations. For instance, they did not segregate the healthcare costs by HF phenotypes (Shafie et al., 2020; Shafie et al., 2019; Yingchoncharoen et al., 2021). The costs to the healthcare system are known to vary depending on the HF phenotype. Detailing the cost of HF based on phenotypes would enable the stakeholders to formulate a better intervention programme that targets specific causative and progressive risk factors of HF to flatten the HF prevalence curve in Malaysia. Besides, previous studies did not calculate the sample size before estimating the healthcare costs of HF (Shafie et al., 2020; Shafie et al., 2019; Yingchoncharoen et al., 2021). The included sample size could be insufficient to estimate the costs accurately and therefore introduce more uncertainties when the costs are used in the economic evaluation. Next, a study that estimated the healthcare cost of HF among diabetic patients using the standard treatment algorithm did not account for more severe cases. Severe cases usually incur higher costs because of prolonged hospitalisation, and more resources are needed to treat the patients. The costs could be underestimated without taking such cases into account.

One of the treatment outcomes associated with HF management is the reduction of hHF. However, the readmission rate among HF patients in Malaysia

increased steadily from 2007 to 2015 (Lim et al., 2022). Repeated hospitalisations for HF are not just associated with poor outcomes, such as higher mortality rates (Lin et al., 2017; Nieminen et al., 2015), but also incur higher healthcare costs (Lesyuk et al., 2018; Shafie et al., 2019). Accordingly, inpatient costs accounted for at least half of the direct costs associated with HF (Lesyuk et al., 2018). An intervention that can prevent hHF shifts the inpatient cost to the outpatient cost, thus creating cost-saving opportunities. In addition, HF*r*EF patients are associated with a higher risk of hHF and CV death than HF*mr*EF and HF*p*EF patients (Lam et al., 2018; MacDonald et al., 2020). Thus, reducing the rate of hHF among HF*r*EF provides greater cost-saving and prevents death. Evidence generated from the EMPEROR-Reduced trial reported that compared to SoC alone, empagliflozin + SoC reduced the risk of hHF by 31% (Packer et al., 2020), thus filling an unmet medical need in managing HF*r*EF patients. Prior to adding empagliflozin to our formulary for the treatment of HF*r*EF patients, we need to examine its cost-effectiveness carefully. Additionally, projected changes to the MoH budget must be evaluated before using limited healthcare resources to reimburse this medication. Until now, no available study has determined the cost-effectiveness and budget impact of empagliflozin from the perspective of MoH Malaysia. A CEA evaluates the cost-effectiveness of empagliflozin by comparing the costs and outcomes between empagliflozin + SoC and SoC monotherapy. In addition, a BIA determines the financial consequences of introducing empagliflozin into the MoH formulary.

1.10 Study significance

The findings of this study will redound to MoH Malaysia in allocating resources for the management of HF, given the increasing prevalence of HF and its substantial financial impact on the healthcare system. The healthcare costs of HF were

estimated from real-world data using the standard micro-costing approach after taking into account an appropriate sample size. In addition, the costs were categorised using HF phenotypes, thus allowing specific interventions to be adapted to target a particular HF phenotype. Furthermore, multiple underlying comorbidities in HF patients increase the complexity of HF management. Knowing the cost of HF with comorbidities assists healthcare providers in making informed decisions about treatment plans. Managing this group of high-risk HF patients requires more intensive and complicated interventions such as PCI and implanted devices. Early detection and targeted interventions can help to avoid costly complications and hospitalisations, lowering the healthcare costs of HF. The findings provide insight into the current economic burden of HF in Malaysia and help optimise the allocated budget for the treatment of HF, especially for newly launched medications and interventions. The resources and their associated costs estimated in the cost analysis were included in the CEA and BIA to determine the cost-effectiveness and affordability of empagliflozin + SoC compared to SoC monotherapy from the perspective of MoH Malaysia. The findings can help stakeholders make an informed decision on whether to add a new indication of empagliflozin in the national formulary for treating HF*r*EF in addition to its use as an anti-diabetic agent.

1.11 Research question

Previous studies on the healthcare cost of HF in Malaysia did not segregate the cost based on HF phenotypes (classification based on LVEF) and did not properly calculate the sample size. A cost analysis involving four Asian countries identified HF patients using the ICD-10 classification and did not specify the sample size used to estimate the healthcare cost of HF in Malaysia (Yingchoncharoen et al., 2021). In

addition, Shafie et al. derived the healthcare cost of HF from patients recruited in the ASIAN-HF registry, and the method of calculating the sample size did not include in the study (Shafie et al., 2019). Besides, another study estimated the healthcare cost of HF from treatment algorithms and expert opinion rather than the actual resource utilisation (Shafie et al., 2020). Hence, the estimated cost could be biased because all these studies did account for proper sample size. Although other countries have found empagliflozin + SoC to be cost-effective compared to SoC, its cost-effectiveness and affordability are yet to be established in Malaysia. The EMPEROR-Reduced trial was used as the primary source of evidence for the CEM because it is the pivotal phase III trial that has sufficient statistical power to confirm the effectiveness of adding empagliflozin to SoC against SoC monotherapy to reduce the risk of composite outcomes of CV death and hHF. The detailed justification for using the EMPEROR-Reduced trial was provided in Section 2.3.2(d). Thus, this study aims to answer the following questions:

i. What is the direct medical cost of HF per patient per year (PPPY) from the Malaysia MoH's perspective, categorised according to LVEF and underlying comorbidities?
ii. Is adding empagliflozin to SoC more cost-effective than SoC alone for treating HF*r*EF from the Malaysia MoH's perspective?
iii. What is the budget impact of adding empagliflozin to SoC for treating HF*r*EF over five years from the Malaysia MoH's perspective?

1.12 Research aims and objectives

This study aims to determine whether the addition of empagliflozin to SoC compared to SoC monotherapy for treating HF*r*EF is cost-effective and affordable