MEASURING HEALTH-RELATED QUALITY OF LIFE AMONG PATIENTS WITH CHRONIC HEART FAILURE AND THE COST-EFFECTIVENESS AND AFFORDABILITY OF EMPAGLIFLOZIN FOR HEART FAILURE TREATMENT: THE MALAYSIAN PERSPECTIVE

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LIST OF SYMBOLS

B	Regression coefficient
β	Adjusted regression coefficient
n	Sample size

LIST OF ABBREVIATIONS

ACC/AHA	American Cardiology Society/American Heart Association
ACEi	Angiotensin-converting enzyme inhibitor
ACS	Acute coronary syndrome
ADHF	Acute decompensated heart failure
AE	Adverse event
AF	Atrial fibrillation
aOR	Adjusted odds ratio
ARB	Angiotensin receptor blocker
ARNi	Angiotensin receptor-neprilysin inhibitor
ASIAN-HF	Asian Sudden Cardiac Death in Heart Failure registry
BIA	Budget impact analysis
BIM	Budget impact model
BMI	Body mass index
CCI	Charlson comorbidity index
CEA	Cost-effectiveness analysis
CET	Cost-effectiveness threshold
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence interval
CKD	Chronic kidney disease
CPG	Clinical practice guidelines
CPI	Consumer Price Index
CSS	Clinical Summary Score
CV	Cardiovascular
DM	Diabetes mellitus
DSA	Deterministic sensitivity analyses
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
G-CHF	Global Congestive Heart Failure study
GBD	Global Burden of Disease study
GDMT	Guideline-directed medical treatment
HERO	Heart Failure Registry of Patient Outcomes study

HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HF-ACTION	Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training
hHF	Hospitalisation for heart failure
HICs	High-income countries
HR	Hazard ratio
HRQoL	Health-related quality of life
HRU	Healthcare resource utilisation
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IJN	National Heart Institute
IQR	Interquartile range
ITT	Intent-to-treat
KCCQ	Kansas City Cardiomyopathy Questionnaire (12- or 23-item)
LMICs	Low- to middle-income countries
LVEF	Left ventricular ejection fraction
LY	Life year
MCID	Minimal clinically important difference
MCS	Mental Component Summary
MICs	Middle-income countries
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MLR	Multivariable linear regression
MOH	Ministry of Health (Malaysia)
MOHMF	Ministry of Health (National) Medicines Formulary
MRA	Mineralocorticoid receptor antagonist
MY-DRG	Malaysian Diagnosis-Related Group
MYHF	Malaysian Heart Failure registry
NBS	Norm-based scoring
NICE	UK National Institute for Health and Care Excellence
NYHA	New York Heart Association
OR	Odds ratio
OSS	Overall Summary Score

PBM	Preference-based measure
pcGDP	Per-capita gross domestic product
PCS	Physical Component Summary
PSA	Probabilistic sensivitiy analysis
QALY	Quality-adjusted life year
SD	Standard deviation
SE	Standard error
SF-36	36-item Short Form Health Survey
SGLT2i	Sodium-glucose cotranspoter-2 inhibitor
SHOP	Singapore Heart Failure Outcomes and Phenotypes study
SoC	Standard of care
SRM	Standard response mean
T2D	Type 2 diabetes
TIA	Transient ischaemic attack
TSS	Total Symptom Score
UMICs	Upper-middle income countries
USD	United States Dollars
VIDA-IC	Calidad de VIDA e Insuficiencia Cardiaca en España: situación actual (*Quality of Life and Heart Failure in Spain: Current Situation*) study

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MENGUKUR KUALITI HIDUP BERKAITAN DENGAN KESIHATAN DALAM KALANGAN PESAKIT KEGAGALAN JANTUNG KRONIK SERTA KEBERKESANAN KOS DAN KEMAMPUAN MILIK EMPAGLIFLOZIN BAGI RAWATAN KEGAGALAN JANTUNG DARI PERSPEKTIF MALAYSIA

ABSTRAK

Kegagalan jantung (HF) menyebabkan gejala-gejala yang melesukan, kapasiti fungsian yang berkurangan, serta peningkatan risiko kemasukan ke hospital dan kematian. Hal ini menjadi beban kepada Kementerian Kesihatan Malaysia (KKM) dan memberi kesan buruk kepada kualiti hidup berkaitan dengan kesihatan (HRQoL) dalam kalangan penghidap HF. Meskipun dengan nilai prognostik, maklumat HRQoL daripada penghidap HF tempatan masih belum diterokai. HF sering dikategorikan berdasarkan pecahan ejeksi ventrikel kiri (LVEF), di mana titik potongan yang digunakan ialah 40% untuk membezakan antara subkumpulan LVEF≤40% dan LVEF>40% yang berbeza dari segi patofisiologi, komorbiditi, dan respons terhadap rawatan sedia ada. Walaupun ujian-ujian klinikal telah membuktikan keberkesanan dan keselamatan ubat Empagliflozin dalam perawatan kedua-dua subkumpulan HF, penilaian keberkesanan kos dan kemampuan milik empagliflozin adalah penting bagi membantu KKM membuat keputusan mengenai penggunaannya. Analisis ekonomi tempatan sebelum ini telah membuktikan keberkesanan kos dan kemampuan milik empagliflozin dalam perawatan subkumpulan LVEF≤40%, tetapi sama ada perkara ini juga betul bagi subkumpulan LVEF>40% adalah belum dikaji. Selain itu, analisis keberkesanan kos (CEA) sebelum ini tidak menggunakan data utiliti tempatan, bakal mengehadkan keterterapan hasil analisis tersebut. Penyelidikan ini bertujuan untuk

menyelesaikan kekurangan dalam data HRQoL dan utiliti tempatan bagi HF serta menjalankan CEA dan analisis impak bajet (BIA) terhadap empagliflozin dalam perawatan HF merentasi keseluruhan spektrum LVEF. Tinjauan kebangsaan HRQoL keratan lintang dijalankan untuk memperoleh data EQ-5D-5L, sosiodemografi, dan klinikal. Bagi CEA, sebuah model Markov yang telah disahkan digunakan untuk membandingkan kos dan kesan pada kesihatan sepanjang hayat antara empagliflozin bersama rawatan standard dengan rawatan standard sahaja bagi subkumpulan LVEF>40%. Hasil analisis bagi kedua-dua subkumpulan HF kemudian digabungkan. Sebuah model impak-bajet dibangunkan untuk membandingkan senario dengan/tanpa empagliflozin dalam kedua-dua subkumpulan HF selama 5 tahun. Data keberkesanan dan keselamatan empagliflozin diperolehi daripada hasil ujian klinikal. Data kos tempatan digunakan manakala input utiliti bagi CEA adalah diperolehi daripada data EQ-5D-5L. Hasil primer analisis ekonomi termasuk kos dan jangka-hayat-berlaras-kualiti (QALY) tambahan, nisbah keberkesanan-kos tambahan (ICER), serta impak-bajet kumulatif selama 5 tahun. Tinjauan HRQoL menunjukkan bahawa penghidap HF di Malaysia, walaupun lebih muda dan bergejala ringan, melaporkan HRQoL yang rendah, seperti penghidap HF di negara-negara maju. Analisis regresi multivariat mengenalpasti faktor etnik ($p<0.05$), hidup bersendirian ($p<0.05$), tahap pendidikan ($p<0.05$), pemberhentian pekerjaan atas sebab kesihatan ($p<0.01$), kelas fungsian berdasarkan *New York Heart Association* ($p<0.01$), serta pelaporan oleh wakil ($p<0.001$) sebagai peramal bebas terhadap HRQoL. Rawatan empagliflozin bagi subkumpulan LVEF>40% dan populasi HF keseluruhan menunjukkan keberkesanan-kos (ICER purata masing-masing ialah RM 16,279 dan RM 9,221 per QALY yang diperolehi), di bawah ambang yang dipersetujui. Penggunaan empagliflozin dianggar bakal menjimatkan kos sebanyak RM8.63 juta dalam tempoh 5 tahun lanjutan daripada

pengurangan perbelanjaan untuk merawat kes-kes yang membabitkan kemasukan ke hospital. Justeru itu, empagliflozin bakal membantu KKM dalam usaha meringankan beban humanistik dan ekonomi yang berikan oleh HF di negara ini.

MEASURING HEALTH-RELATED QUALITY OF LIFE AMONG PATIENTS WITH CHRONIC HEART FAILURE AND THE COST-EFFECTIVENESS AND AFFORDABILITY OF EMPAGLIFLOZIN FOR HEART FAILURE TREATMENT: THE MALAYSIAN PERSPECTIVE

ABSTRACT

Heart failure (HF) causes debilitating symptoms, reduced functional capacity, and an increased risk of hospitalisation and mortality, placing a significant strain on the Malaysian Ministry of Health (MOH), and adversely impacting patients' health-related quality of life (HRQoL). Despite its prognostic value, HRQoL among local HF patients remains unexplored. HF is often categorised using a left ventricular ejection fraction (LVEF) cut-off of 40% to distinguish between the LVEF≤40% and LVEF>40% subgroups, which differ in pathophysiology, comorbidities, and responses to available treatments. Although trials have demonstrated empagliflozin's efficacy and safety in both HF subgroups, evaluating its cost-effectiveness and affordability is crucial for decision-making about its adoption within the MOH. While local economic analyses suggest empagliflozin's cost-effectiveness and affordability for treating the LVEF≤40% subgroup, these factors remain to be confirmed for the LVEF>40% subgroup. Moreover, previous cost-effectiveness analysis (CEA) did not incorporate local utility data, limiting the generalisability of the findings to the local context. This research aimed to address gaps in local HRQoL and utility data for HF, and to perform a CEA and budget impact analysis (BIA) of empagliflozin treatment across the full LVEF spectrum. A nationwide cross-sectional HRQoL survey was conducted to collect EQ-5D-5L, sociodemographic, and clinical data. For the CEA, a pre-validated Markov model was used to compare lifetime costs and effects between empagliflozin

plus standard-of-care (SoC) versus SoC alone in the LVEF>40% subgroup, with results then combined for both HF subgroups. A budget impact model was developed to compare scenarios with or without empagliflozin in both HF subgroups over 5 years. Efficacy and safety data were derived from trials. Local cost data were used while and utility inputs for the CEA were derived from the HRQoL data. Primary outcomes of the economic analyses included incremental costs, quality-adjusted life-years (QALY), incremental cost-effectiveness ratio (ICER), and the 5-year cumulative budget impact. The HRQoL survey revealed that Malaysians with HF, although younger and mildly symptomatic, experienced poor HRQoL, consistent with findings in developed countries. Multivariable regression analyses identified ethnicity ($p<0.05$), solitary living ($p<0.05$), education status ($p<0.05$), health-related employment cessation ($p<0.01$), New York Heart Association functional class ($p<0.01$), and proxy-reporting ($p<0.001$) as independent predictors of HRQoL. Empagliflozin treatment was found to be cost-effective in the LVEF >40% subgroup and the overall HF population (mean ICERs of RM16,279 and RM9,221/QALY gained, respectively, below the locally accepted threshold). The adoption of empagliflozin was projected to save the MOH RM8.63 million over 5 years due to reduced hospitalisation costs. Thus, empagliflozin represents an opportunity for the MOH to mitigate the humanistic and economic burden of HF locally.

CHAPTER 1

INTRODUCTION

1.1 Heart Failure – definition, epidemiology, and prognosis

Heart failure (HF) has a standardised definition according to existing clinical practice guidelines (CPG), with the most widely followed guidelines being those provided by the American Cardiology Society/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC). Essentially, HF is a chronic condition caused by abnormalities in either the structure or the function of the heart, or both, resulting in elevated intracardiac pressures, impaired ventricular filling, and/or reduced cardiac output (reduced ejection of blood from the heart). These abnormalities lead to hallmark symptoms, including shortness of breath, oedema, and fatigue. (Bozkurt *et al.*, 2021; McDonagh *et al.*, 2021; Heidenreich *et al.*, 2022).

HF is classified in several ways based on the time frame of symptom occurrence, aetiology, ACC/AHA stages of HF, left ventricular ejection fraction (LVEF) measurement, and severity of symptoms and functional impairment using the New York Heart Association (NYHA) classification. These various classifications of HF are used simultaneously and are necessary as they can influence treatment decisions. **Table 1.1** gives an overview of the different descriptions of HF.

Table 1.1 Different classifications of HF by current guidelines

Classification	**Description**	**Focus in this thesis**
Acute versus chronic HF	Chronic HF presents through a gradual onset of symptoms in individuals already diagnosed with the condition. Conversely, acute HF means a sudden and often unexpected emergence of symptoms, necessitating immediate medical intervention. This acute presentation may either mark the first manifestation of HF (*de novo* HF) or happen secondary to a rapid deterioration of pre-existing chronic HF.	Chronic HF
Aetiology	HF is categorised based on the underlying cause, often into ischaemic or non-ischaemic HF. Ischaemic HF is attributed to the presence of coronary artery disease, whereas non-ischaemic HF includes subtypes such as hypertensive HF, HF due to valve disease, cardiomyopathies, congenital heart disease, infective, drug-induced, infiltrative, and other aetiologies.	Ischaemic and non-ischaemic HF
ACC/AHA stages of HF	The ACC/AHA classification categorises individuals into four stages of HF, delineating the progression from risk (stage A) to pre-HF (stage B), symptomatic HF (stage C) and advanced HF (stage D). Both stage C and stage D fulfil the definition of HF.	Stage C and D HF, with the former being far more common
LVEF measurement	HF is currently divided into three subtypes based on the following LVEF cut-offs: HF with reduced LVEF (HFrEF) with a LVEF ≤40%; HF with mildly reduced LVEF (HFmrEF) with a LVEF 41-49%; and HF with preserved LVEF (HFpEF) with LVEF ≥50%. Of note, the latter two subgroups are also collectively referred to as LVEF >40%, distinguishing them from the HFrEF or LVEF ≤40% subgroup.	All LVEF subtypes
NYHA functional classification	HF is characterised based on the severity of symptoms and physical limitations, which range from no limitation of physical activity (class I), through slight limitation (class II) and marked limitation (class III), to the inability to carry out any physical activity comfortably and experiencing symptoms at rest (class IV).	All NYHA classes, with NYHA class I-II being far more common

ACC/AHA = American Cardiology Society/American Heart Association; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association

The Global Burden of Disease (GBD) study estimated that in 2019, there were approximately 56.2 million cases of HF worldwide, with an age-standardised prevalence rate of 711.9 per 100,000 individuals. In Malaysia, the estimated age-standardised prevalence rate was higher at 809.5 per 100,000 individuals, equivalent to 192,456 people living with HF. Crude prevalence rates of HF have risen globally and in Malaysia. Between 2010 and 2019, there was a 29.4% increase in the number of HF cases worldwide, while Malaysia experienced a 42.0% increase during the same period. The age-standardised prevalence rate has declined worldwide, signifying that the observed increase in crude prevalence is partly due to the ageing population, however in Malaysia, the age-standardised prevalence rate remained relatively constant (Figure 1.1) (Global Burden of Disease Collaborative Network, 2020; Institute for Health Metrics and Evaluation (IHME), 2024). There is far less evidence available regarding the incidence of HF both globally and locally. However, it is generally accepted that the incidence rate of HF ranges approximately 1-20 cases per 1,000 patient-years (Savarese, Becher, *et al.*, 2022).

Prevalence studies in Europe, the USA, and Japan suggest that 50% of all HF cases belong to the HFrEF subtype, with HFmrEF and HFpEF accounting for the remaining 50% (Savarese, Becher, *et al.*, 2022; Desai *et al.*, 2024). Furthermore, there is a trend showing that the LVEF >40% subtype is becoming more common, potentially surpassing HFrEF as the dominant subtype. Nevertheless, local studies present a different scenario. In the local context, HFrEF remains the predominant HF subtype, constituting about two-thirds of cases, while the LVEF >40% subgroup makes up the remaining one-third (Ling *et al.*, 2020; Raja Shariff *et al.*, 2021; Mohd Ghazi, Teoh and Abdul Rahim, 2022; Wan Ahmad *et al.*, 2023).

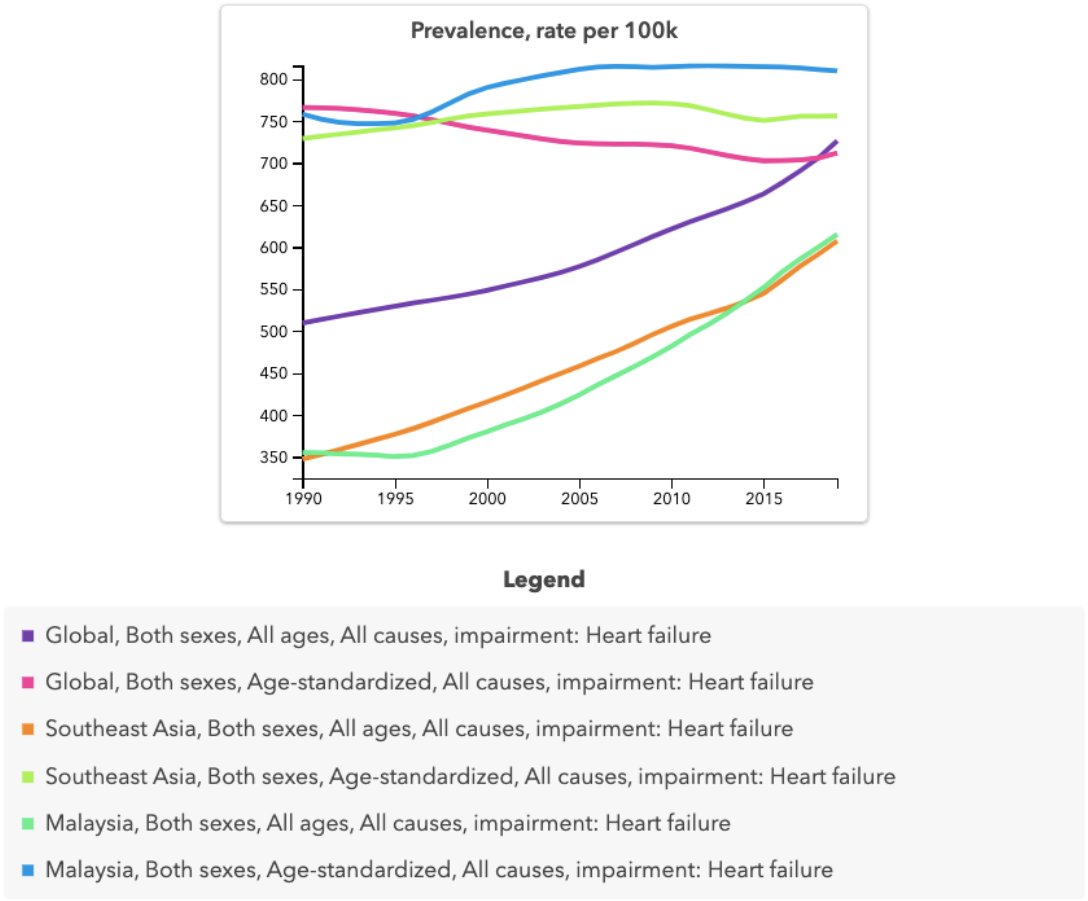

Figure 1.1 Crude and age-standardised prevalence rates of HF from 1990 to 2019 for the world, Southeast Asian region, and Malaysia.
The image was generated using GBD Results, an Interactive Data Visualisation Tool maintained by the Institute for Health Metrics and Evaluation, University of Washington based on the GBD Study in 2019. The image is available freely for non-commercial use.

While medical advancements have led to improved survival rates for HF patients over time, the prognosis of HF remains grim. A meta-analysis, including survival data for 1.5 million ambulatory patients with chronic HF from sixty studies, reported mortality rates of 4.3%, 13.5%, 27.4%, 43.3%, and 65.1% at 1 month, 1, 2, 5, and 10 years, respectively (Jones *et al.*, 2019). The analysis also noted a 31% improvement in 5-year survival rates between 1970-1979 and 2000-2009. It is worth noting that the majority of these studies were conducted in Western countries, with none from Malaysia or the Southeast Asia region.

A local study, using national discharge data from public hospitals spanning 2006 to 2017, reported in-hospital, 30-day, and 1-year mortality rates post-index hospitalisation for HF (hHF) at 5.3%, 11.2%, and 33.1%, respectively (Y. M. F. Lim *et al.*, 2022). Other single-centre cohort studies enrolling patients before the year 2019 reported similar short-term outcomes, with in-hospital and 30-day mortality rates ranging between 2-8% and 13-16%, respectively and one centre reporting a 1-year mortality of 49.7% (Ling *et al.*, 2020; Raja Shariff *et al.*, 2021; Mohd Ghazi, Teoh and Abdul Rahim, 2022). Although information regarding longer-term outcomes for the local HF population remains scarce, the Malaysian Heart Failure (MYHF) registry holds promise in this regard. Following 2,717 patients for 3 years since their index hHF between 2019 and 2020, the registry provides an opportunity for further insights (Wan Ahmad, Kader, Ross, A. W. Ramli, *et al.*, 2021). The investigators have reported encouraging findings so far, observing lower in-hospital and 30-day mortality rates at 2.8% and 6.1%, respectively among the MYHF cohort, signalling significant improvement in short-term outcomes for the local HF population in the last decade (Wan Ahmad, Kader, Ross, A. Wazi Ramli, *et al.*, 2021; Wan Ahmad *et al.*, 2023).

The Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry is a multinational prospective cohort study that followed over 6,000 HF patients enrolled between 2012 and 2016 for 3 years in forty-two centres spanning eleven Asian regions, including four sites in Malaysia as well as other countries in the Southeast Asian region, Indonesia, the Philippines, Singapore, and Thailand (Lam *et al.*, 2013). ASIAN-HF investigators reported a 1-year all-cause mortality rate of 13.0% for the Southeast Asian subgroup (MacDonald *et al.*, 2020), considerably lower compared to the known estimates for local patients (33.1-49.7%) (Ling *et al.*, 2020; Raja Shariff *et al.*, 2021; Y. M. F. Lim *et al.*, 2022; Mohd Ghazi, Teoh and Abdul Rahim, 2022).

There are inconsistent findings regarding the relative risk of short- and long-term mortality across the three HF subtypes, with some studies suggesting higher risk of death in the HFrEF compared to the LVEF >40% subgroup, while others indicate comparable mortality rates (Savarese, Becher, *et al.*, 2022). Data from the ASIAN-HF registry reveal that patients with HFrEF have a higher all-cause mortality risk at 1 year as compared to those in the HFpEF subgroup, and this pattern was consistently observed across South, Northeast and Southeast Asian regions (MacDonald *et al.*, 2020). A retrospective study conducted at the local National Heart Institute, which examined the short-term outcomes of 4,739 patients from 2009-2018, observed that HFrEF was associated with higher in-hospital mortality when compared to the HFmrEF and HFpEF subtypes (Mohd Ghazi, Teoh and Abdul Rahim, 2022). Conversely, the MYHF investigators and a single-centre cohort study respectively reported comparable in-hospital and 3-month mortality rates across LVEF subtypes (Ling *et al.*, 2020; Wan Ahmad *et al.*, 2023). What appears to be more consistent is that HFrEF patients often succumb to cardiovascular causes, whereas HFpEF patients tend to die from non-cardiovascular causes, with HFmrEF serving as an intermediate between the two HF subtypes (Savarese, Stolfo, *et al.*, 2022).

Individuals living with HF typically experience sudden worsening of symptoms, necessitating emergency department visits and hospitalisations for acute decompensated HF (ADHF). Existing evidence suggests that most HF patients would have had at least one hospitalisation for any cause in the last year (median number of all-cause hospitalisation over the last year: 1, interquartile range: 0 to 2) (Tay *et al.*, 2021; Y. M. F. Lim *et al.*, 2022). Additionally, local studies indicate that 6.8-18.1% of local HF patients would be re-hospitalised within 30 days, and 24.7-40.4% within a year of the index hHF (Ling *et al.*, 2020; Raja Shariff *et al.*, 2021; Y. M. F. Lim *et*

al., 2022; Mohd Ghazi, Teoh and Abdul Rahim, 2022). While local data on readmission rates due to HF remain elusive, pending the reporting of the longer-term outcomes by the MYHF investigators, the ASIAN-HF investigators reported a 1-year HF readmission rate of 18.5% and an all-cause readmission rate of 33.6% for the Southeast Asian subgroup (Tay *et al.*, 2021). The readmission rates are comparable across LVEF subtypes (Savarese, Becher, *et al.*, 2022). Table 1.2 summarises the literature currently available for informing the prognosis of the local HF population.

Table 1.2 Existing evidence regarding the prognosis of local HF patients

Study, sample size, setting	Study design, sampling and follow-up period	Patient characteristics	All-cause mortality	Readmission
(Y. M. F. Lim *et al.*, 2022) n=105,339; Ministry of Health hospitals enrolled in Hospital Discharge Register Database	Retrospective cohort study; 1 Jan 2007 to 31 Dec 2016; follow-up at 30 days and 1-year	Mean age: 64 years; 56% male. Clinical data were not available.	□ In-hospital: 5.3% (2007-2008: 6.9%; 2015-2016: 3.7%) □ 30-day: 11.2% (2007-2008: 13.1%; 2015-2016: 9.7%) □ 1-year: 33.1% (2007-2008: 34.5%; 2015-2016: 32.9%)	□ 30-day all-cause readmission: 18.1% (2007-2018: 16.6%; 2016: 19.6%; a 17.8% increase) □ Median number of readmissions in a year: 1 (interquartile range [IQR] = 0-2)
(Mohd Ghazi, Teoh and Abdul Rahim, 2022) n=3,923, National Heart Institute (IJN)	Retrospective cohort study using hospital database, 1 Jan 2009 to 31 Dec 2018.	Mean age: 62 years; 72% male; 63% diabetes; 66% ischaemic cause; 63% HFrEF, 12% HFmrEF, 13% HFpEF	□ In-hospital mortality: 7.2%	□ 30-day all-cause readmission: 6.8% □ 1-year all-cause readmission: 24.7%
(Raja Shariff *et al.*, 2021) n=1,307, Hospital Sungai Buloh	Retrospective cohort study using medical records; 1 Jan 2012 to 31 Dec 2016; follow-up at 30 days, 3 months, 6 months, and 12 months	Mean age: 63 years; 46% male; 62% diabetes; 62% ischaemic cause; 41% HFrEF, 11% HFmrEF, 24% HFpEF	□ In-hospital: 1.7% □ 30-day: 15.7% □ 90-day: 22.4% □ 6-month: 37.7% □ 1-year: 49.7%	□ 30-day all-cause readmission: 1.7% □ 90-day all-cause readmission: 17.5% □ 6-month all-cause readmission: 21.5% □ 1-year all-cause readmission: 40.4%

Study, sample size, setting	Study design, sampling and follow-up period	Patient characteristics	All-cause mortality	Readmission
ASIAN-HF registry, n=6,480 in 11 Asian countries (2,470 in Southeast Asia: Indonesia, Malaysia, the Philippines, Singapore, and Thailand)	Prospective cohort study, 1 Oct 2012 – 31 Oct 2016; follow-up at 6 months, 1 year, 2 years and 3 years.	Southeast Asian subgroup: mean age: 61 years; 77% male; 51% diabetes; 62% ischaemic cause; HFrEF 81.5%, HFpEF 18.5%	Southeast Asian subgroup: 1-year mortality: 13.6%*	Southeast Asian subgroup: 1-year all-cause readmission: 33.6%** 1-year HF readmission for HF: 18.5%**
(Ling *et al.*, 2020) (SGH-HF cohort), n=117, Sarawak General Hospital	Prospective cohort study; Sep 2017 to Aug 2018; follow-up at 30 days and 90 days	Mean age: 59 years; 59% male; 50% diabetes; 41% ischaemic cause; 49% LVEF >40%	In-hospital: 7.5% 30-day: 13.1% 90-day: 16.8%	30-day all-cause readmission: 11.2% 90-day all-cause readmission: 14.0%
(Wan Ahmad *et al.*, 2023) (Malaysian Heart Failure [MYHF] registry) n=2,717; 18 Ministry of Health specialist hospitals nationwide	Prospective cohort study; Aug 2019 – Dec 2020; Follow-up at 1 month, 6 months, 1 year and every 6 months until 3 years	Mean age: 60 years; 67% male; 60% diabetes; 63% ischaemic cause; 65% HFrEF, 11% HFmrEF, 21% HFpEF	In-hospital: 2.8% 30-day: 6.1% 6-month, 1-, 2-, 3-year: pending	30-day all-cause readmission: 12.5%*** 1-year readmission: pending 3-year readmission: pending

Data from related publications: *(MacDonald *et al.*, 2020); **(Tay *et al.*, 2021); ***(Wan Ahmad, Kader, Ross, A. Wazi Ramli, *et al.*, 2021); HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; LVEF = left ventricular ejection fraction; NR = no recommendation.

1.2 Heart Failure – current pharmacotherapy goals and strategies

Managing HF involves three primary goals: reducing mortality, preventing recurrent hHF, and enhancing the patient's clinical status, functional capacity, and quality of life (McDonagh *et al.*, 2021). Pharmacotherapy serves as the mainstay treatment of HF, complemented by non-pharmacological interventions, and device therapy in selected patients. ACC/AHA and ESC guidelines offer clear guidance on the selection of drug treatments and target doses to achieve optimal therapeutic outcomes. Table 1.3 provides a list of drug treatments available for HF along with their respective class of recommendation by the ACC/AHA and ESC guidelines. In addition to diuretics for relieving fluid overload as needed, guideline-directed medical treatments (GDMT) for HF, specifically the HFrEF subtype, include: (1) an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) or angiotensin receptor-neprilysin inhibitor (ARNi), (2) a beta-blocker (BB), (3) a mineralocorticoid receptor antagonist (MRA), and (4) a sodium-glucose cotranspoter-2 inhibitor (SGLT2i). These four treatments are termed the "four pillars" of HFrEF treatment (Straw, McGinlay and Witte, 2021), receiving a Class I recommendation from both the ACC/AHA and ESC guidelines based on moderate to high-quality evidence (McDonagh *et al.*, 2021, 2023; Heidenreich *et al.*, 2022). Refer to the notes below Table 1.3 for the rating systems used by ACC/AHA and ESC for classifying recommendations and levels of evidence.

Early and rapid up-titration of GDMT after hospitalisation for ADHF is beneficial and currently advocated, with a class I recommendation from the ESC (McDonagh *et al.*, 2023). This recommendation follows the findings of the STRONG-HF trial, a randomised controlled trial demonstrating that such an approach can reduce

the risk of death or HF readmissions and improve quality of life among patients with HF, without causing more adverse events (Mebazaa *et al.*, 2022).

Before the availability of SGLT2i, management strategies for patients in the LVEF >40% subgroup (i.e., HFmrEF and HFpEF) primarily focused on alleviating fluid retention and optimising the treatment of comorbidities such as atrial fibrillation (AF), chronic kidney disease (CKD), diabetes mellitus (DM), and hypertension (McDonagh *et al.*, 2021). The GDMT for HFrEF have not demonstrated the same potential to improve the outcomes of this subgroup. Consequently, medications such as ACEi/ARB, BB, and MRA receive only a class IIb recommendation from CPGs for the treatment of HFmrEF and no specific recommendation for the HFpEF subtype. However, these treatments are frequently prescribed to patients with HFmrEF or HFpEF to manage their comorbidities.

The findings from high-quality randomised controlled trials including the EMPEROR-Preserved and DELIVER trials, which evaluated the efficacy and safety of empagliflozin and dapagliflozin, respectively, as adjuncts to the standard of care (SoC), have profoundly reshaped the management approach for the LVEF >40% subgroup (Anker *et al.*, 2021; Solomon *et al.*, 2022). Both agents have demonstrated promise in achieving the treatment goals, not only for HFrEF but also for the underserved LVEF >40% subgroup. Consequently, in the 2022 ACC/AHA CPG, SGLT2i receive a class IIa recommendation for the treatment of the LVEF >40% subgroup (Heidenreich *et al.*, 2022). Following suit, in the 2023 focused update for their CPG, ESC conferred an unprecedented class I recommendation for the use of SGLT2i in treating the LVEF >40% subgroup (McDonagh *et al.*, 2023).

Table 1.3 Heart failure pharmacotherapy and classes of recommendation and level of evidence according to ESC and ACC/AHA guidelines

Drug class	**Also indicated for**	**Class of recommendation (COR) and level of evidence (LOE) across the LVEF spectrum of symptomatic HF**		
		HFrEF	**HFmrEF**	**HFpEF**
Guideline-directed medical therapy (GDMT) – recommended for all/most patients				
Angiotensin-converting enzyme inhibitor (ACEi)	Hypertension, prophylaxis of cardiovascular events in at-risk patients; prophylaxis after myocardial infarction; proteinuric chronic kidney disease	ESC: COR I, LOE A	ESC: COR IIb, LOE C	ESC: NR.
		ACC/AHA: COR 1, LOE: A	ACC/AHA: COR 2b, LOE B-R	ACC/AHA: NR
Angiotensin receptor blocker (ARB)		ESC: COR I, LOE B	ESC: COR IIb, LOE C	ESC: NR
		ACC/AHA: COR 1, LOE: A	ACC/AHA: COR 2b, LOE B-R	ACC/AHA: COR 2b, LOE B-R
Angiotensin receptor-neprilysin inhibitor (ARNi): sacubitril/ valsartan	-	ESC: COR I, LOE B	ESC: COR IIb, LOE C	ESC: NR
		ACC/AHA: COR 1, LOE: A	ACC/AHA: COR 2b, LOE B-R	ACC/AHA: COR 2b, LOE B-R
Beta-blocker (BB)	Angina, atrial fibrillation, hypertension, supraventricular tachycardia, ventricular arrhythmias, secondary prophylaxis of myocardial infarction	ESC: COR I, LOE A	ESC: COR IIb, LOE C	ESC: NR
		ACC/AHA: COR 1, LOE: A	ACC/AHA: COR 2b, LOE B-R	ACC/AHA: NR
Diuretics (on an as-needed basis for fluid retention)	Ascites, oedema or volume overload due to other causes (e.g., chronic kidney disease)	ESC: COR I, LOE C	ESC: COR I, LOE C	ESC: COR I, LOE C
		ACC/AHA: COR 1, LOE: B-NR	AHA/ACC: COR 1, LOE: B-NR	AHA/ACC: COR 1, LOE: B-NR
Mineralocorticoid receptor antagonist (MRA)	Ascites, hypertension, primary aldosteronism	ESC: COR I, LOE A	ESC: COR IIb, LOE C	ESC: NR
		ACC/AHA: COR 1, LOE: A	ACC/AHA: COR 2b, LOE B-R	ACC/AHA: COR 2b, LOE B-R
Sodium-glucose cotransporter-2 inhibitor (SGLT2i): dapagliflozin and empagliflozin	Chronic kidney disease, diabetes mellitus, prophylaxis of cardiovascular events in at-risk patients,	ESC: COR I, LOE A	ESC: COR I, LOE A	ESC: COR I, LOE A
		ACC/AHA: COR 1, LOE A	ACC/AHA: COR 2a, LOE B-R	ACC/AHA: COR 2a, LOE B-R

Additional treatments for select patients despite GDMT		Class of recommendation (COR) and level of evidence (LOE) across the LVEF spectrum of symptomatic HF		
Drug class	Patient group	HFrEF	HFmrEF	HFpEF
Digoxin	For those with persistent symptoms despite GDMT	ESC: COR IIb, LOE B	ESC: COR IIb, LOE C	ESC: NR
		ACC/AHA: COR 2b, LOE B-R	ACC/AHA: NR	ACC/AHA: NR
Hydralazine and isosorbide dinitrate	For Black people or intolerance of ACEi/ARB/ARNi	ESC: COR IIa/IIb, LOE B	ESC: NR	ESC: NR
		ACC/AHA: COR 1/2b, LOE A/C-LD	ACC/AHA: NR	ACC/AHA: NR
If-channel inhibitor: ivabradine	For those with persistent symptoms, LVEF ≤35%, sinus rhythm and a resting heart rate ≥70 bpm despite GDMT	ESC: COR IIa/IIb, LOE B/C	ESC: NR	ESC: NR
		ACC/AHA: COR 2a, LOE B-R	ACC/AHA: NR	ACC/AHA: NR
Soluble guanylate cyclase (sGC) stimulator: vericiguat	For those with persistent symptoms despite GDMT	ESC: COR IIb, LOE B	ESC: NR	ESC: NR
		ACC/AHA: COR 2b, LOE B-R	ACC/AHA: NR	ACC/AHA: NR

ACC/AHA = American Cardiology Society/American Heart Association; bpm = beats per minute; ESC= European Society of Cardiology; GDMT = guideline-directed medical treatment; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; LVEF = left ventricular ejection fraction; NR = no recommendation.

Note on the rating systems used by ACC/AHA and ESC for classifying recommendations and the level of evidence supporting the recommendations.

Class of recommendations (COR):

- COR 1 or COR I: strong recommendation (treatment is recommended or indicated)
- COR 2a or COR IIa: moderate (treatment should be considered)
- COR 2b or COR IIb: weak (treatment may be considered)
- COR 3 or COR III: no benefit (treatment is not recommended or can cause harm). ACC/AHA further subdivides COR 3 into COR 3: no benefit and COR 3: harm.

Level of evidence (LOE):

- LOE A: high-quality evidence from multiple randomised clinical trials or meta-analyses;
- LOE B: moderate-quality evidence from a single randomised clinical trial or large non-randomised studies
- LOE C: consensus of opinion of the experts and/or small studies, retrospective studies, registries. ACC/AHA further subdivides LOE B into LOE B-R (moderate-quality evidence from one or more randomised clinical trials or a meta-analysis of such studies) and LOE B-NR (moderate-quality non-randomised studies or a meta-analysis of such studies); and LOE C into LOE C-LD (observational or registry studies with limitations or a meta-analysis of such studies) and LOE C-EO (for consensus of expert opinion).

1.3 Economic burden of heart failure

The economic implications of HF are extensively documented through cost-of-illness studies, with a majority conducted in high-income countries like Europe and the USA (Lesyuk, Kriza and Kolominsky-Rabas, 2018; Shafie, Tan and Ng, 2018; Urbich *et al.*, 2020). Cook and colleagues estimated that the global spending on HF reached USD 108 billion in 2012, with direct costs constituting roughly 60% and indirect costs making up the remaining 40% (Cook *et al.*, 2014; Savarese, Becher, *et al.*, 2022). For Malaysia, the study delineated direct costs at USD 12 million and indirect costs at USD 182 million, with HF care accounting for a mere 0.1% of total health expenditure (Cook *et al.*, 2014). However, a recent local study found that the healthcare expenditure on HF was much higher at USD 482 million, representing about 1% of the country's total healthcare expenditure in 2021 (Ong and Low, 2023).

The Malaysian Ministry of Health (MOH) serves as the primary healthcare provider for the country, covering most of the direct costs of HF for approximately 70% of the population (National Institutes of Health, Ministry of Health Malaysia, 2020). According to the most recent estimate by a local costing study, healthcare costs borne by the MOH averaged approximately RM 8,295 per HF patient per year in, with inpatient costs being the primary cost driver, constituting 75% of the total expenditure (Ong *et al.*, 2022), consistent with studies conducted in industrialised countries (Lesyuk, Kriza and Kolominsky-Rabas, 2018; Urbich *et al.*, 2020; Hessel, 2021a). Procedures, diagnostic tests, and hospital stays were the most important contributors to inpatient costs, while medication was the primary contributor to outpatient costs (Ong *et al.*, 2022) (refer to Figure 1.2). Although its share is much smaller compared to hHF, lifelong pharmacotherapy is a significant contributor to the direct costs of HF (Lesyuk, Kriza and Kolominsky-Rabas, 2018; Escobar *et al.*, 2020; Hessel, 2021a;

Escobar *et al.*, 2022). Multiple new treatments such as ARNi, SGLT2i, and vericiguat have become available in recent years and have been shown to improve patient outcomes. The adoption of these long-term treatments also add costs for the healthcare system and patients (Allen, Lowe and Matlock, 2023), although they are currently seen as potentially cost-effective investments that can lower the economic burden of HF by reducing costly events such hHF and mortality (Hessel, 2021b).

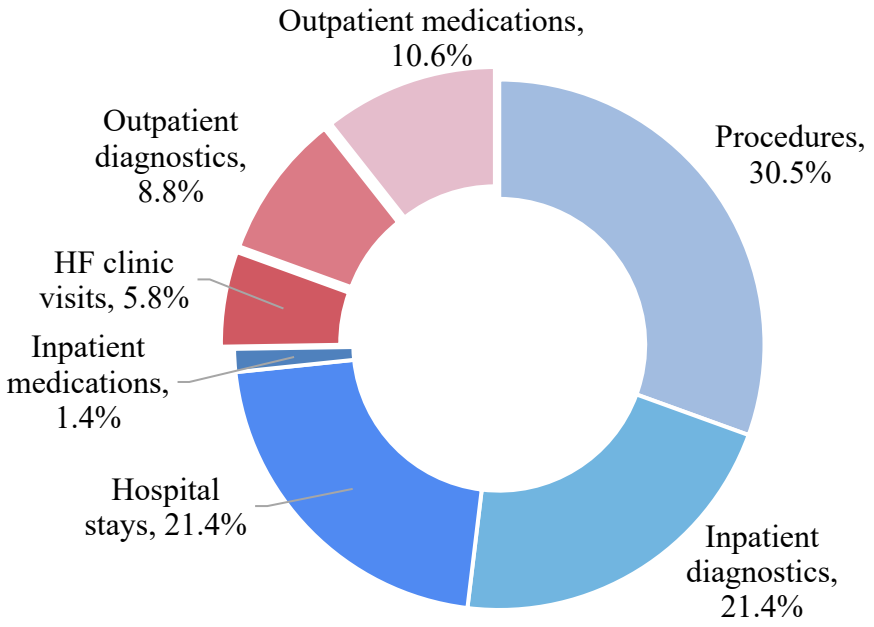

Figure 1.2 Share and breakdown of the Malaysian MOH's expenditure on HF based on a recent local study by (Ong *et al.*, 2022)
Outpatient costs (red segments) accounted for about 25% of the direct costs, primarily attributed to medications. Inpatient costs (blue segments) constituted 75% of the direct costs, driven mainly by procedures.

Factors linked to a higher annual healthcare cost include recent HF diagnosis, recent worsening HF event, history of procedures, presence of one or more comorbidities including CKD and DM, more severe symptoms (NYHA class III-IV), and use of novel drugs, with a majority of costs associated with hHF (Shafie, Tan and Ng, 2018; Butler *et al.*, 2020; Ong *et al.*, 2022; Savarese, Becher, *et al.*, 2022; Ferdinand *et al.*, 2023; Nichols *et al.*, 2023). The subtype of HF may also influence

healthcare resource utilisation (HRU) and incurred costs, although the specific subtype associated with higher costs may vary across healthcare settings. A French costing study revealed that patients with HFrEF, regardless of comorbidity burden, incurred greater costs related to hHF compared to those with HFpEF. This disparity was attributed to more frequent readmissions and longer hospital stays among HFrEF patients. However, it is important to note that in this study, only 30% of patients had a known LVEF measurement (Chemouni *et al.*, 2023). Escobar et al., 2022 also observed that HRU was higher among HFrEF compared to the LVEF >40% subgroup in the Spanish HF population. Conversely, a US-based study found that the annual cost was highest for HFpEF, followed by HFmrEF and HFrEF (Nichols *et al.*, 2023). The local study observed that the LVEF >40% subgroup incurred a higher mean annual cost compared to the HFrEF subgroup, although this difference did not reach statistical significance and the median costs were comparable (Ong *et al.*, 2022).

The indirect costs of HF, including premature mortality, productivity losses, and the burden on caregivers, are also profound given the morbidity and mortality associated with HF. However, even in developed countries, these costs are less frequently reported and have not been assessed locally. A Swedish study observed that individuals with HF were three times more likely to retire early compared to matched controls without HF (Steen Carlsson *et al.*, 2023). A consistent and concerning finding from local studies indicate that Malaysians are diagnosed at a younger age than their counterparts in developed countries, even before reaching retirement age at 60 years (Dokainish *et al.*, 2017; MacDonald *et al.*, 2020; Savarese, Becher, *et al.*, 2022; Wan Ahmad *et al.*, 2023). Hence, it is highly probable that indirect costs are substantial in the local context due to the early cessation from formal employment, social welfare, and caregiving needs.

1.4 Humanistic burden of heart failure

In addition to facing an increased risk of mortality and living with troublesome symptoms, patients with HF also experience bouts of acute decompensation, requiring immediate intervention. Moreover, they need to adhere to a strict and lifelong regimen, which includes engaging in physical activity, following dietary restrictions, monitoring weight daily, and taking prescribed medications. Consequently, HF has significant and wide-ranging effects on the functioning, wellbeing, and health-related quality of life (HRQoL) of individuals with HF, adversely affecting various aspects of their lives – physically, mentally, and socially (Savarese *et al.*, 2023).

Previous quantitative studies in developed countries consistently demonstrate that patients with HF report poorer HRQoL compared to the general population and even to those undergoing active anticancer treatment (Comín-Colet *et al.*, 2016; Giles *et al.*, 2020; Shah *et al.*, 2023). Sociodemographic and clinical characteristics, along with patient's self-efficacy and the adequacy of self-care behaviours can significantly influence how individuals with HF perceive their health status (Baert *et al.*, 2018; Giles *et al.*, 2020). For instance, the ASIAN-HF investigators identified ethnicity as an independent predictor, with patients with HF of Malay ethnicity reporting the lowest KCCQ scores compared to other ethnic groups (Luo *et al.*, 2017). Further exploration of HRQoL assessment in the HF population and the predictors of HRQoL will be provided in 2.1.

Due to the complexity of self-care behaviours, individuals with HF often require assistance from an informal caregiver, typically a family member, to support them. The availability of support from caregivers also has an indirect role in improving patient's HRQoL through the mediation of patient's self-care behaviours (Caggianelli *et al.*, 2024). However, the burden among informal caregivers of patients with HF is

significant and should not be overlooked, as caregiver burden has been shown to impact caregivers' quality of life and the quality of care they provide (Dionne-Odom *et al.*, 2017; Suksatan, Tankumpuan and Davidson, 2022).

1.4.1 Patient-reported outcomes

Patient-reported outcomes offer patients an opportunity to express their thoughts, needs and preferences about their wellbeing and treatment, allowing clinicians to understand patient's perception of their health status and identify any unmet needs. A study investigating the preferences of patients with HF regarding HRQoL or life expectancy found that most patients were willing to trade time for an improvement in HRQoL, particularly those experiencing more pronounced symptoms (Kraai *et al.*, 2013).

HRQoL is a key component of patient-reported outcomes that examines the impact of HF and its treatment on their physical, emotional, and social wellbeing (Savarese *et al.*, 2023). The routine collection of HRQoL data in clinic settings is gaining momentum in HF care (McDonagh *et al.*, 2021; Heidenreich *et al.*, 2022), supported by mounting evidence that confirms its prognostic value. HRQoL can independently identify patients at risk of adverse outcomes including hHF and death (Luo *et al.*, 2017; Johansson *et al.*, 2021; Seo *et al.*, 2023). There is also evidence indicating that clinician-assessed health status, typically evaluated using the NYHA functional class, may differ from self-reported health status (Greene *et al.*, 2021; Michelis *et al.*, 2021; Teramoto *et al.*, 2023). This suggests that clinician assessment often does not capture the full spectrum of health issues experienced by patients with HF.

1.5 Empagliflozin for the treatment of HF

1.5.1 Safety and efficacy

Empagliflozin, an SGLT2i originally introduced as an antidiabetic treatment for individuals with type 2 diabetes (T2D), was evaluated in the EMPA-REG OUTCOME trial (Zinman Bernard *et al.*, 2015). This randomised controlled trial was conducted to investigate the effects of empagliflozin on CV outcomes in patients with T2D at high risk for CV events. Empagliflozin resulted in a 14% reduction in the primary composite endpoint of CV death, non-fatal myocardial infarction, or nonfatal stroke (HR 0.86, 95% confidence interval [CI] 0.74, 0.99) when compared to placebo, primarily driven by a reduction in CV death (HR 0.62, 95% CI 0.49, 0.77). Moreover, the trial also demonstrated a decrease in the secondary outcome of hHF with empagliflozin (HR 0.65, 95% CI 0.50, 0.85). These findings prompted two subsequent trials, namely EMPEROR-Reduced and EMPEROR-Preserved trials, to confirm the benefits of empagliflozin in the HFrEF and LVEF >40% subgroups, respectively.

The EMPEROR-Reduced trial assessed the efficacy and safety of empagliflozin as an add-on therapy to the SoC in patients with symptomatic HFrEF, regardless of their T2D status (Packer *et al.*, 2020). Compared to placebo, empagliflozin significantly reduced the primary composite outcomes of CV death and first hHF (HR 0.75; 95% CI 0.65, 0.86), primarily driven by a reduction in hHF (HR 0.69; 95% 0.59, 0.81), with a non-significant reduction in CV death (HR 0.92; 95% CI 0.75, 1.12). In addition, the total number of hHF and all-cause hospitalisations was lower with empagliflozin (HR 0.70, 95% CI 0.58, 0.85; and HR 0.85; 95% CI 0.7, 0.95, respectively). Other benefits of empagliflozin included slower decline in kidney function as assessed by estimated glomerular filtration rate (eGFR), lower composite renal outcome (HR 0.50; 95% CI 0.32, 0.77), and a modest improvement in HRQoL

measured by KCCQ at 52 weeks (1.7 points; 95% CI 0.5, 3.0 points). Pre-specified subgroup analysis based on T2D status showed that empagliflozin lowered the primary composite outcomes in both T2D (HR 0.72; 95% CI 0.60, 0.87) and non-T2D patients (HR 0.78; 95% CI 0.64, 0.97). No major safety concerns were identified with empagliflozin treatment, except for a higher incidence of uncomplicated genital tract infection.

The EMPEROR-Preserved trial examined similar outcomes in patients with HFmrEF and HFpEF (Anker *et al.*, 2021). For the LVEF >40% subgroup, empagliflozin significantly reduced the primary composite outcome of CV death or hHF (HR 0.79; 95% CI 0.60, 0.90). Again, this was primarily driven by a reduction in hHF (HR 0.71; 95% CI 0.60, 0.83). The benefit was consistent regardless of T2D status, with both the T2D subgroup (HR 0.79; 95% CI 0.67, 0.94) and the non-T2D group (HR 0.78; 95% CI 0.64, 0.95) showing similar reductions. A non-significant decrease in CV death (HR 0.91; 95% CI 0.76, 1.09) was also noted. Similar to the HFrEF subgroup, empagliflozin reduced the total hHF counts (HR 0.73; 95% CI 0.6, 0.88) and led to modest improvement in KCCQ scores (+1.32 points; 95% CI 0.4, 2.19). However, the reduction in all-cause hospitalisation (HR 0.93; 95% CI 0.85, 1.01) was only borderline significant, and the decrease in composite renal outcome (HR 0.95; 95% CI 0.73, 1.24) did not reach statistical significance. No new safety signals were detected, although uncomplicated genitourinary infection and hypotension occurred more often in empagliflozin-treated subjects compared to those who received placebo.

1.5.2 Cost-effectiveness of empagliflozin for treatment of HF

The positive findings from these landmark trials have resulted in the approval of empagliflozin by regulatory agencies globally, including the local National Pharmaceutical Regulatory Agency, as an add-on treatment for HF, irrespective of LVEF and patient's T2D status. While empagliflozin shows promise in improving the health outcomes and prognosis of patients with HF, its widespread adoption may inadvertently increase the financial strain on the MOH. Cost-effectiveness analyses (CEAs) represent a valuable tool for decision-makers to evaluate whether the additional health benefits gained from empagliflozin use justify the additional costs compared to the scenarios where the intervention is not available or adopted. Such information is crucial for guiding funding decisions and resource allocation, allowing decision-makers to maximise the value of healthcare investments within the constraints of limited resources. Further details on the results of CEA evaluating empagliflozin therapy for both HFrEF and LVEF >40% subgroups across different jurisdictions, along with the models employed, will be discussed in 2.3.

1.6 Problem statements and study significance

1.6.1 The need for local HRQoL data

Although a substantial body of literature exists on HRQoL in the HF population, data from low- to middle-income countries (LMICs) remain scarce, as indicated by recent reviews (Di Tanna *et al.*, 2021; Savarese *et al.*, 2023; Hainsworth *et al.*, 2024). Neither the MYHF registry nor previous cohort studies conducted in Malaysia have included HRQoL as an outcome of interest alongside the hard endpoints. Moreover, routine HRQoL assessment has not been integrated into local HF clinic settings. Until then, our understanding of the HRQoL among the local HF population must rely on HRQoL surveys.

Although some information about the HRQoL of the local HF population was available from the ASIAN-HF study, which included 382 Malaysian patients (Luo *et al.*, 2017), HRQoL data for the local patients, separate from others in the Southeast region was not presented, and they were only limited to the HFrEF subgroup and certain ethnicities. Given the well-documented benefits of HRQoL data (Savarese *et al.*, 2023), there is a pressing need for more comprehensive, locally sourced HRQoL data. These data should encompass Malaysians living with HF from diverse demographic and socioeconomic backgrounds and across different LVEF subgroups. It is also of the interest of clinicians and healthcare policy makers to be cognizant of how various demographic, clinical, and social factors influence an individual's perception of their health status, thereby allowing for more personalised interventions.

HRQoL data in the form of health state utility values (hereinafter referred to as utility values) that reflect the preferences of local people are also required to support timely evaluation of cost-effectiveness of emerging treatments in the local context. These utility values, derived from generic, preference-based measures (PBMs) such as

EQ-5D, are needed for calculating quality-adjusted life years (QALYs) (Ministry of Health Malaysia, 2019).

The EQ-5D instrument is the most widely used generic PBM for HRQoL assessment in healthcare and clinical research involving individuals living with HF (Di Tanna *et al.*, 2021; Hainsworth *et al.*, 2024). The 5-level version (EQ-5D-5L) has been incorporated in recent HF trials such as the EMPEROR-Reduced and EMPEROR-Preserved trials alongside the HF-specific KCCQ instrument to support trial-based CEAs (Packer *et al.*, 2020; Anker *et al.*, 2021). Moreover, the EQ-5D-5L has been psychometrically validated across a broad range of populations (Feng *et al.*, 2021), including individuals with HF (Boczor *et al.*, 2019). Nonetheless, systematic reviews that compiled utilities associated with HF health states found that most values available are from the Western countries, which may not be generalisable to a multicultural society such as Malaysia (Di Tanna *et al.*, 2021; Hainsworth *et al.*, 2024). For local use, the EQ-5D-5L is suitable as it is available in local languages (EuroQol, 2024), validated among the local general adult population (Shafie, Vasan Thakumar, Lim and Luo, 2019), and comes with a Malaysian value set (Shafie, Vasan Thakumar, Lim, Luo, *et al.*, 2019), which enables the derivation of utility values from EQ-5D-5L responses.

1.6.2 Cost-effectiveness and affordability of empagliflozin for HF treatment

A local CEA has been conducted to assess the cost-effectiveness of treating the HFrEF subgroup with empagliflozin (Ong, Low and Linden, 2023). Utilising a validated cohort state-transition model and drawing on data from EMPEROR-Reduced trial, the economic analysis concluded that adding empagliflozin to the SoC of the HFrEF subgroup was cost-effective when compared to SoC alone from the MOH's perspective. However, as the HFrEF and LVEF >40% subgroups are inherently disparate, the generalisability of these findings to the latter may be limited, necessitating a separate CEA for the LVEF >40% subgroup.

Since the MOH is the primary healthcare provider in the country, most patients diagnosed with HF will be treated in MOH centres, where they have an opportunity to be treated with empagliflozin. Besides evaluating the value of empagliflozin, conducting a budget impact analysis (BIA) is essential to estimate the likely change in expenditure for the MOH, the budget holder in this case, associated with expanding empagliflozin coverage to include treatment of HF. This analysis will provide decision-makers at the MOH level with the information needed to examine whether the additional spending on empagliflozin is justifiable and could be offset by savings from the benefits of this new intervention, enabling them to make informed decisions about its listing in the National Medicines Formulary (MOHMF).