Clinical and Non-Clinical Markers of Prognosis in Heart Failure

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Summary

Heart failure (HF) is a major cause of morbidity and mortality, and the prevalence of HF is only increasing globally. The rise in prevalence is primarily attributed to a combination of increasing survival especially in patients in industrialized countries and increasing incidence in low- and middle-income countries (mostly in a younger population).

The clinical course of HF varies from patient to patient. For some, an initial diagnosis of HF is soon followed by multiple hospitalisations deeply impacting their quality of life, others have a fairly indolent course and some die soon after a diagnosis of HF is made. The treatment for many also depends on various factors including the phenotype of HF, the aetiology of HF and other co-existent chronic conditions to name a few. There are patients with HF who may not be candidates for intensive invasive procedures but would on the other hand benefit from supportive care and palliative care advice with treatment being directed towards preservation of quality of life.

Physicians are therefore often faced with the question of the prognosis their patients with HF face. Accurate assessment of prognosis is therefore important in shared decision making for patients with HF. However, assessment of prognosis is not straightforward. Reliance on a clinician's acumen or single prognostic markers such as left ventricular ejection fraction (LVEF) and New York heart association (NYHA) class can be inaccurate and is not advised.

Therefore, multivariable models were turned to in order to paint a more accurate picture of a patient's prognosis by incorporating different individual markers known to be associated with clinical outcomes in HF. Multiple prognostic models have consequently been developed for assessment of prognosis in HF. However, uptake of these in clinical practice remain low. Many factors contribute including issues with reproducibility of prognostic ability in different populations, unavailability of variables and complexity of statistical methodologies. The evolving risk of different outcomes due to pharmacological and non-pharmacological advances in HF is another influencing factor.

I consequently conducted a systemic analysis of the literature of prognostic models in HF – focusing primarily on a single phenotype of HF – HF with reduced ejection fraction (HFrEF). I identified several variables common to most models, with LVEF, sex, age, NYHA class being some of the most frequently featured. Inclusion of more contemporary prognostic markers such as NT-proBNP and non-clinical markers such as region, race/ethnicity and socioeconomic status was however very less frequent or absent altogether.

Given this background, the aim of this thesis was to explore a select set of clinical and non-clinical markers, some of which have featured in previous models to review their prognostic importance along with a few which have not been featured in risk models in the past.

The analyses presented were conducted in three contemporary clinical trial datasets in HFrEF – ATMOSPHERE, PARADIGM-HF and DAPA-HF. I used a variety of statistical measures to assess the association between 3 commonly used markers – LVEF, sex & chronic obstructive pulmonary disease (COPD) and 4 uncommonly/previously unused markers – geography & ethnicity, income inequality and frailty – and common clinical outcomes examined in HF. Different outcomes were tested – including cardiovascular, non-cardiovascular & all-cause death and first & recurrent HF, cardiovascular & all-cause hospitalisations. Cox regression was used to study the association between LVEF and COPD with various clinical outcomes. I used competing risk regression to study the other markers of prognosis and their association with clinical outcomes.

In the DAPA-HF cohort, each 5% decrease in LVEF was associated with a 20% higher risk of HF hospitalisation (95% CI 1.13 – 1.27) and a 20% higher risk of cardiovascular death (95% CI 1.13 – 1.28). The risks of the same outcomes in those with COPD was 78% (95% CI 1.44 – 2.20) and 28% (95% CI 1.00 – 1.63) respectively. The rest of the analyses were carried out in a pooled cohort of the ATMOSPHERE and PARADIGM-HF trials. Women had a 19% lower risk of HF hospitalisation (95% CI 0.74 – 0.90) and 26% lower risk of cardiovascular death (95% CI 0.67 – 0.81). Among the Asian countries, the highest and lowest risk of hospitalisation for HF was seen in patients belonging to Taiwan (1.88; 95% CI 1.46 – 2.42) and India (0.44; 95% CI 0.36 – 0.54) respectively. In the same

chapter patients living in the Philippines had the highest risk of cardiovascular death (sHR 1.87; 95% CI 1.36 – 2.57) and the lowest risk of the same outcome was seen in those living in Japan (subdistribution hazard ratio (sHR) 0.68; 95% CI 0.46 – 0.98). When levels of income inequality were examined, patients lining in countries with the greatest inequality had a 57% higher risk of hospitalisation for HF (95% CI 1.36 – 1.81) and the risk of cardiovascular death was 50% greater (95% CI 1.29 – 1.74) compared to patients living in countries with the lowest income inequality. Using an acceptable method, I found that 69% of the population in ATMOSPHERE and PARADIGM-HF were frail. In the same population, the frailest patients carried a 89% higher risk of HF hospitalisation (95% CI 1.69 – 2.11) and the sHR for cardiovascular death was 2.14 (95% CI 1.92 – 2.38). All the above listed associations were statistically significant.

In conclusion, I found that a select set of traditionally featured markers in prognostic models in HF remained strong predictors of hospitalisation and mortality in contemporary set of HF populations. In addition, several non-clinical and clinical markers that have infrequently featured in previous prognostic markers also carry significant value in measuring risk of clinical outcomes in HF. The inclusion of such markers may improve the predictive ability and clinical applicability of prognostic models in HF in the future.

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Table of Contents

List of Tables

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5

Chapter 6

Chapter 7

Chapter 8

List of Figures

Chapter 3

Chapter 4

Chapter 5

Chapter 6

Chapter 7

Chapter 8

Abbreviations

ACEI	-	Angiotensin-Converting Enzyme Inhibitor
AF	-	Atrial Fibrillation
AG	-	Anderson Gill
ALPHA	-	T-Wave Alternans in Patients With Heart Failure
ANOVA	-	Analysis Of Variance
ARB	-	Angiotensin Receptor Blocker
ARIC	-	Atherosclerosis Risk In Communities Study
ARNI	-	Angiotensin Receptor Neprilysin Inhibitor
ASIAN-HF	-	Asian Sudden Cardiac Death In Heart Failure
ATMOSPHERE	-	Aliskiren Trial To Minimize Outcomes In Patients With Heart Failure
BBB	-	Bundle Branch Block
BCN Bio-HF	-	Barcelona bio-heart failure
BNP	-	B-Type Natriuretic Peptide
BUN	-	Blood Urea Nitrogen
CAD	-	Coronary Artery Disease
CARE-HF	-	Cardiac Resynchronization — HF
CHARM	-	Candesartan Cilexetil In HF Assessment Of Reduction In Mortality
CHS	-	Cardiovascular Heart Study
CIBIS-II	-	Cardiac Insufficiency Bisoprolol Study II
CMR	-	Cardiac Magnetic Resonance
COMPANION	-	Comparison Of Medical Therapy, Pacing, And Defibrillation In HF
CONSENSUS	-	Cooperative North Scandinavian Enalapril Survival Study
COPD	-	Chronic Obstructive Pulmonary Disease
COPERNICUS	-	Carvedilol Prospective Randomised Cumulative Survival
CRT	-	Cardiac Resynchronization Therapy
CSS	-	Clinical Summary Score
DAPA-HF	-	Dapagliflozin And Prevention of Adverse-Outcomes In Heart Failure
DELIVER	-	Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure
ECG	-	Electrocardiogram
EchoCRT	-	Echocardiography Guided Cardiac Resynchronization Therapy
eGFR	-	Estimated Glomerular Filtration Rate
EMPEROR-Preserved	-	EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction
EMPEROR-Reduced	-	Empagliflozin Outcome Trial In Patients With Chronic Heart Failure And A Reduced Ejection Fraction
EMPHASIS-HF	-	Eplerenone In Mild Patients Hospitalisation And Survival Study In Heart Failure
ESC	-	European Society of Cardiology

FHS	-	Framingham Heart Study
FI	-	Frailty Index
FRS	-	Framingham Risk Score
GDF-15	-	Growth Differentiation Factor-15
GENIUS-HF	-	Genetic and ElectroNic medIcal records to predict oUtcomeS in Heart Failure
GISSI-HF	-	Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico-Heart Failure
HbA1C	-	Haemoglobin A1C
HF	-	Heart Failure
HFA-ESC	-	Heart Failure Association of the European Society of Cardiology
HF-ACTION	-	Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training
HFmrEF	-	Heart Failure with mildly reduced Ejection Fraction
HFpEF	-	Heart Failure with preserved Ejection Fraction
HFPSI	-	Heart Failure Patient Severity Index
HFrEF	-	Heart Failure with reduced Ejection Fraction
HFSA	-	Heart Failure Society of America
HFSS	-	Heart Failure Survival Score
HDI	-	Human Development Index
HR	-	Hazard Ratio
hsTropT	-	high sensitivity troponin T
ICD	-	Implantable cardioverter-defibrillator
INTER-CHF	-	International Congestive Heart Failure
I-Preserve	-	Irbesartan In HFpEF Study
IRR	-	Incidence Rate Ratio
JHFS	-	Japanese Heart Failure Society
KCCQ	-	Kansas City Cardiomyopathy Questionnaire
KIM-1	-	Kidney injury molecule 1
KM	-	Kaplan Meier
LBBB	-	Left Bundle Branch Block
LMIC	-	Low-And-Middle-Income Countries
LVEF	-	Left Ventricular Ejection Fraction
LVSD	-	Left Ventricular Systolic Dysfunction
LWYY	-	Lin, Wei, Ting and Yang
MADIT II	-	Multicentre Automatic Defibrillator Trial II
MAGGIC	-	Meta-Analysis Global Group In Chronic Heart Failure
MAR	-	Missing At Random
MCAR	-	Missing Completely At Random
MERIT-HF	-	Metoprolol Cr/Xl Randomised Intervention Trial In-Congestive Heart Failure
MI	-	Myocardial Infarction
MMP	-	Metalloproteinase
MNAR	-	Missing Not At Random
MRA	-	Mineralocorticoid Antagonist

MUSIC	-	MUerte Subita en Insuficiencia Cardiaca
NB	-	Negative Binomial
NCD	-	Non-communicable Disease
NHANES	-	National Health And Nutrition Examination Survey
NP	-	Natriuretic Peptide
NT-proBNP	-	N Terminal Pro B-Type Natriuretic Peptide
NYHA	-	New York Heart Association
OR	-	Odds Ratio
OSS	-	Overall Summary Score
PAD	-	Peripheral Artery Disease
PARADIGM-HF	-	The Prospective Comparison of ARNI With ACEI To Determine Impact On Global Mortality And Morbidity In Heart Failure
PARAGON-HF	-	Prospective Comparison Of ARNI With ARB Global Outcomes In HFpEF
PRAISE1	-	Prospective Randomised Amlodipine Survival Evaluation
RR	-	Relative Risk
QoL	-	Quality Of Life
RALES	-	Randomised Aldactone Evaluation Study
RCT	-	Randomised Controlled Trial
SBP	-	Systolic Blood Pressure
SCD-HeFT	-	Sudden Cardiac Death in Hf
SES	-	Socioeconomic Status
SGLT-2	-	Sodium-glucose cotransporter-2
SHFM	-	Seattle Heart Failure Model
SHIFT		Systolic Heart failure treatment with the I*f* inhibitor ivabradine Trial
sHR	-	Subdistribution Hazard Ratio
SOLVD	-	Studies Of Left Ventricular Dysfunction
SPRINT	-	Systolic Blood Pressure Intervention Trial
ST2	-	Soluble Toll-like receptor-2
STICH	-	Surgical Treatment for Ischemic Heart Failure Trial
SwedeHF	-	The Swedish Heart Failure Registry
T2DM	-	Type 2 Diabetes Mellitus
TIMP-1	-	Tissue Inhibitor Metalloproteinase-1
TOPCAT	-	Treatment Of Preserved Cardiac Function HF with An Aldosterone Antagonist
TSS	-	Total Symptom Score
UK-HEART	-	United Kingdom Heart Failure Evaluation and Assessment of Risk Trial
UNDP	-	United Nations Development Programme
VHD	-	Valvular Heart Disease
WLW	-	Wei, Lin and Weissfeld

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Declaration

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I declare that, except where explicit reference is made, all the work in this thesis has been done by me. This thesis has not been submitted for any other degree at the University of Glasgow or any other institution.

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Chapter 1. Introduction

Patients with heart failure (HF) do not all carry the same prognosis. Some have a prolonged course marred by multiple hospitalisations, some live longer with fewer decompensations, while others live only a short time after diagnosis and may die suddenly.[1–3] Other outcomes of importance such as quality of life (QoL) also vary widely among different patients with HF.[4–6]

Several factors can be associated – both clinical and non-clinical, either at the level of the individual or at the population level, with the risk of morbidity and mortality in patients with HF. In this thesis, I have assessed the relationship of some of them with different outcomes in heart failure with reduced ejection fraction (HFrEF).

Chapter 1 presents an overview of current practices in HF and includes a systematic review of prognostic models in HF. In Chapter 2, I have defined the populations analysed in this thesis and have described methods of analyses applied in the subsequent chapters. The influence of left ventricular ejection fraction (LVEF) on outcomes in HFrEF is discussed in Chapter 3. Chapter 4 describes sex-related differences in HFrEF and prognostic implications of the same. The impact of chronic obstructive pulmonary disease (COPD) on outcomes in HFrEF is discussed in Chapter 5.

Differences in characteristics and outcomes within Asia and with the rest of the world is described in Chapter 6. In Chapter 7, I talk about income inequality and how it influences the risk of hospitalisations and mortality in HFrEF. Frailty and its relationship with HF is reviewed in Chapter 8. Finally, I discuss the overall results and their implications in Chapter 9.

Definition of heart failure

The Heart Failure Society of America (HFSA), the Heart Failure Association of the European Society of Cardiology (HFA-ESC) and the Japanese Heart Failure Society (JHFS) have jointly defined HF as a “clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and

corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion".[7]

Epidemiology of heart failure

The epidemiology of HF varies with different factors including age, sex, region, and socioeconomic status of the population examined.

The prevalence of HF continues to rise with global estimates ranging from an estimated 26 million to an estimated 64.3 million.[8-10] This has largely been attributed to an ageing population and longer survival with the condition.

The proportion of patients living with HF increases with increasing age – with an estimated prevalence of 10% or more in those older than 70 years of age.[4,11] The risk of HF is different in men and women with men having a lifetime risk at 55 years of 33% and the same being 28% in women.[4,12] The standardised prevalence of HF in a UK primary care population was also seen to be lower in women (1.2% vs 1.8% in men).[13]

In developed countries, HF is thought to affect 1% to 2% of the general adult population although some studies have estimated a much higher prevalence (based on echocardiographic screening) of 4.2%.[14,15] The estimated prevalence of HF in the USA is 2.5% in the National Health and Nutrition Examination Survey (NHANES) though this was based on self-reported data while in routine primary care data in the UK was an estimated 1.5 - 1.6%.[13,16] Much less information exists regarding prevalence of HF in low-and-middle-incomes countries (LMICs) even though it is estimated that they carry 80% of the cardiovascular disease burden.[17] Different studies have estimated prevalence rates between 1% and 6.7% in different parts of East and South-East Asia (estimated 9 million people with HF living in South-east Asian alone).[18] The prevalence in India is estimated to range between 1.3 and 4.6 million which translates to a prevalence of 0.12–0.44 %, although this may be underestimated due to inadequate surveillance systems.[19] In South America, the anticipated prevalence is 1%.[20] Population estimates from Africa are largely absent.

While overall the prevalence of HF has increased, the incidence of HF varies more widely between different regions and populations studied. In most Western

populations, the incidence of HF is thought to have stabilised or been decreasing.[14] However, the opposite is true in most of the LMICs.[17,18,21] This is attributed to the epidemiological transition from the burden of communicable diseases to noncommunicable diseases in low-and-middle-income countries (LMICs) largely as a result of a shift towards a Western-type lifestyle.[22]

The incidence of HF in the USA and European countries is thought to range between 1 and 9 per 1000 person-years.[22-26] In a study based on UK primary care data, the incidence of HF decreased by 7% between 2002 and 2014.[13] Age-standardised incidence rates were higher in men compared to women (IRR 1.52, 95% CI 1.50 – 1.54). While the decline was consistent across most age groups, an increase in incidence was noted in the very elderly and those younger than 55 years of age.[13] Similarly, in a Danish study, while the incidence fell in the older age group, a 50% increase in HF cases was seen in those aged 50 years or less.[27] Investigators of the Olmsted County cohort reported a decrease in incidence from 3.2 per 1000 person-years in 2000 to 2.2 per 1000 person-years in 2010.[24] The decline was greater in women and also in those with HFrEF compared to HF with preserved ejection fraction (HFpEF). In the Framingham Heart Study (FHS) and Cardiovascular Health Study (CHS), HF incidence over a 20 year period was relatively unchanged overall but when examined separately, the incidence rate ratio of HFrEF declined whereas that of HFpEF increased.[28]

As stated earlier, the incidence of HF in LMICs is increasing. However, information regarding reliable incidence rates in these areas is very limited.[21,29] The incidence of HF in India is estimated to be between 0.5 and 1.7 cases per 1000 person-years, amounting to 492,000 – 1.8 million new cases per year.[21]. An earlier report estimated the incidence of HF in China at 0.9% with approximately 500,000 new HF cases diagnosed each year.[30] In a single population study in South America, the incidence of HF was 2 per 1000 person-years.[20]

The impact of socioeconomic deprivation on the prevalence and incidence of HF has been described. In a UK study by Conrad and colleagues, age and sex standardised IRR for incident HF was 1.61 (95% CI 1.58 – 1.64) in patients belonging to the most deprived socioeconomic quintile.[13] In the same study patients from the most deprived socioeconomic quintile were about 3.5 years

younger when diagnosed compared to the least deprived. In another British study, men aged 60 to 79 years belonging to the most deprived socioeconomic groups had a 9% higher adjusted risk of developing HF over a 10 year follow up period.[31] On comparing high against low household income, in the Copenhagen City Heart Study, the incidence of HF among women and men was 33% and 34% lower respectively.[32] In a prospective cohort study among persons of low SES from 12 states in the United States, a single interquartile increase in neighbourhood deprivation index was associated with a 12% increase in the risk if HF (95% CI 1.07-1.18).[33]

Aetiology of heart failure

HF represents the end of a continuum of a variety of cardiovascular and non-cardiovascular conditions that can result in compromise of cardiac structure or function. Considerable overlap exists between aetiological factors of the two predominant types of HF – HFrEF and HFpEF, even though the strength of association with such aetiological conditions differs.[34] While coronary artery disease (CAD) is the most common cause of HFrEF, especially in the developed countries, hypertension is more often an aetiological factor for the development of HF worldwide. Moreover, aetiology varies widely between men and women with hypertension being more often the culprit in women and predisposing them to the development of HFpEF.[35] Aetiology has also been seen to vary widely with other factors such as race, geography, and other socio-economic factors.

Other causes of HF include toxins – mainly alcohol, diabetes, genetic causes, and infections. About 20-30% of all cases of HF may not have an identifiable aetiology and these cases are labelled as idiopathic. Table 1-1 lists the common causes of HF.

Table 1-1 Aetiology of heart failure

Alcohol and drugs	
Arrythmias	Bradyarrhythmias: conduction disorders Tachyarrhythmias: atrial fibrillation
Cardiomyopathy	Dilated Hypertrophic/obstructive Obliterative Restrictive
Coronary artery disease	Myocardial infarction Myocardial ischaemia
High output states	Anaemia Thyrotoxicosis
Hypertension	
Infective	Chagas disease Lyme disease Rheumatic heart disease Viral myocarditis
Pericardial disease	Constrictive pericarditis
Primary right heart failure	Pulmonary hypertension Tricuspid regurgitation
Valvular heart disease	Atrial septal defect Aortic valve disease Mitral valve disease Ventricular septal defect

Classification of heart failure

By cardiac function

HF can be classified based on measurement of the left ventricular ejection fraction (LVEF). According to a recent consensus document, patients who have LVEF ≤40% are termed as having HFrEF. Those who have LVEF between 41-49% are termed as having HF with mildly reduced ejection fraction (HFmrEF) and HFpEF is described in those with HF and LVEF ≥50%.[7]

This method of definition of HF is important as treatment is different for patients with HFpEF and HFrEF. HFmrEF still represents a "grey area" and therapy for HFrEF may extend to select patients with this phenotype of HF. While patients with HFrEF benefit from therapy derived from positive clinical trials, the same is not the case for patients with HFpEF.[4,36–40] Contemporary clinical trials have so far been guided by the broader definitions of HFrEF (LVEF ≤40%) and HFpEF (LVEF ≥45%).[4,37,38]

By time course and presentation

Another method of classifying patients with HF is according to clinical state. Patients who have decompensated and are hospitalised as described as having acute whereas those who are in the community are said to have ambulatory or chronic heart failure.

Acute HF is said to have occurred in patients who have an acute presentation with the clinical features of HF. This may be a "de novo" presentation in patients who have a precipitating event such as myocarditis or a myocardial infraction or an episode of decompensation of chronic HF may also present as acutely decompensated HF.[4] Patients who have had HF over a period of time have chronic HF.[34] For the rest of this thesis, I will only be referring to chronic HF when HF is mentioned. Any reference to patients with HF who are acutely decompensated will be specified.

By clinical severity of heart failure

HF may also be classified according to the severity of symptoms. The New York Heart Association (NYHA) functional classification developed in 1928 does this. It has undergone several revisions since then and its current form is described in

Table 1-2. While symptom severity may have poor correlation with several measures of cardiac function and, it is still widely used for risk stratification and determines eligibility for clinical trials and drugs and devices.[41] "Advanced HF" is sometimes used to characterize patients with severe symptoms, recurrent decompensation and severe cardiac dysfunction. They comprise an estimated 1% - 10% of the overall HF population.[42]

Table 1-2 New York Heart Association functional classification

Class I	No limitation of physical activity No symptoms with ordinary exertion
Class II	Slight limitation of physical activity Ordinary activity causes symptoms
Class III	Marked limitation of physical activity. Less than ordinary activity causes symptoms Asymptomatic at rest
Class IV	Inability to carry out any physical activity without discomfort.

Diagnosis of heart failure

The signs and symptoms of HF are often non-specific often leading to misdiagnosis. Signs and symptoms may be difficult to discern from those due to obesity or chronic lung disease and can also vary with age.[43–46]

Diagnosis entails a proper history of the illness which can usually point towards the aetiology and the type of HF that the patient presented with. In a patient with a high clinical suspicion of HF, the work-up needs to be aided by objective investigative measures to arrive at a definitive diagnosis of HF.

Resting electrocardiogram

A resting electrocardiogram (ECG) is recommended in a patient with a suspected diagnosis of HF. A normal ECG while non-specific is highly unlikely in patients with HF. An ECG also provides information on heart rate and QRS duration which in turn can help to guide further management such as determining eligibility for device therapy.[47]

Natriuretic peptides

Measurement of natriuretic peptides (NPs) is useful in aiding the diagnosis and prognostication of HF.[48] The European Society of Cardiology (ESC) recommends that it may be used as an initial diagnostic test to further guide the management of a patient with suspected HF especially in the non-emergent setting.[4] Cut-off levels of both B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) can be applied similarly to HFrEF and HFpEF although patients with HFpEF may have lesser degrees of such elevations.[49,50] Measurement of NPs is also helpful in determining the prognosis and the severity of HF and in titrating pharmacological dosing in euvolemic patients. However, it is also important to recognise that various cardiovascular and non-cardiovascular conditions also cause derangements of levels of NPs, thus solely relying on this measurement to diagnose HF is not recommended.[51,52] NPs may be higher in the elderly, those with atrial fibrillation (AF) or with renal impairment. BNPs may also be higher in patients being treated with angiotensin receptor neprilysin inhibitor (ARNI).[51–53] Levels of NPs may also be falsely low in obese patients.[54]

Assessment of left ventricular function

Cardiac imaging to assess left ventricular function is crucial for the diagnosis, evaluation, and management of HF. Echocardiography (transthoracic echocardiography) is the most useful and widely available test used for this purpose. It provides an assessment of the ejection fraction, chamber volumes, regional wall abnormalities, valve function and pulmonary hypertension.

As mentioned previously, classification of HF by cardiac function is important since it helps to distinguish patients who may benefit from various forms of therapy. Therefore, echocardiography is also helpful in this regard. It is also the imaging method of choice since it has a high level of accuracy, is portable, safe, and economically viable.

Other imaging modalities may be employed to complement echocardiography depending on the clinical situation. Chest x-rays can aid in excluding other thoracic pathologies and is also helpful in follow-up of pulmonary congestion and oedema in the acute setting. Transoesophageal and stress echocardiography may be helpful for the assessment of aortic dissection, intracardiac tumours and inducible myocardial ischaemia. Cardiac magnetic resonance (CMR) is considered the gold standard for the assessment of cardiac volume, mass and function but is not easily accessible and can be economically inviable in most situations.[55] Where available it is useful for cardiac imaging in non-diagnostic echocardiographic cases. More recently, myocardial strain imaging has been shown to provide additional information to the standard measurement of cardiac function.[56]

Management of heart failure

As discussed earlier, HF can be classified in several ways. The main advantage of classification is to guide therapy. Since this thesis is based on outcomes in different populations with HFrEF, I will only discuss the management of HFrEF in this section in detail.

The management of HF revolves around alleviating the symptoms of HF, preserving, and improving quality of life, reducing hospital admissions and

overall mortality. It involves the management of underlying causes and risk factors and tailoring pharmacological and non-pharmacological interventions.

Pharmacotherapy

Pharmacotherapy for HFrEF is backed by evidence-based on several randomised clinical trials based on neurohormonal blockade which include an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB), a beta-blocker and a mineralocorticoid antagonist (MRA). More recently neprilysin inhibition added to an ARB and sodium-glucose cotransporter-2 (SGLT-2) inhibitors have been added to this list.[38,40] On the other hand, results from clinical trials in HFpEF have not had much success.[37,39,57]

The evidence-base for pharmacotherapy in HF has been built over the past several years. The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) was one of the first large scale trials studying the effects of enalapril, an ACEI, that was conducted on the heels of the discovery that captopril another ACE inhibitor could prove to be beneficial in the treatment of HF.[58] CONSENSUS, published in 1987, showed a 31% reduction in one-year mortality from HF.[58] The Studies of Left Ventricular Dysfunction (SOLVD) was a second trial published in 1991 that showed evidence of reduction in HF mortality with the use of an ACE inhibitor.[59] The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II), Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure study (MERIT-HF) and Carvedilol Prospective Randomised Cumulative Survival study (COPERNICUS) were trials conducted to show survival benefits in HF with the use of beta-blockers bisoprolol, metoprolol and carvedilol respectively.[60-62] Candesartan – an ARB significantly reduced mortality and HF hospitalisations in patients with LVEF ≤40% in the Candesartan Cilexetil in HF Assessment of Reduction in Mortality (CHARM) clinical trials.[63,64] The Randomised Aldactone Evaluation Study (RALES) and Eplerenone in Mild Patients Hospitalisation and Survival Study in Heart Failure (EMPHASIS-HF) also demonstrated that the MRAs, spironolactone and eplerenone, respectively, reduced the risks of both death and HF hospitalisation in patients with chronic HF.[65,66] The Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF) tested if the addition of a new class of drug, a neprilysin inhibitor when added to a renin-

angiotensin aldosterone system inhibitor (in this case the ARB valsartan) was superior to renin-angiotensin aldosterone system inhibition alone with an ACEI (enalapril). The combination of sacubitril with valsartan was superior to enalapril in reducing the risk of cardiovascular death or hospitalisation for HF in patients with HFrEF.[38]

More recently in the Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure trial (DAPA-HF) and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) trials, SGLT-2 inhibitors dapagliflozin and empagliflozin respectively, proved efficacious in reducing the risk of cardiovascular death or HF hospitalisation in patients with HF when compared to placebo.[40,67]

Current guidelines recommend that all patients with symptomatic HFrEF be prescribed an ACEI unless contraindicated.[4,36] Those who are intolerant to ACEIs may be prescribed an ARB instead. Following on the results of PARADIGM-HF, ARNIs are recommended in ambulatory patients with HFrEF who fit the PARADIGM-HF trial criteria and remain symptomatic despite being on optimal pharmacotherapy.[4,36] Clinically stable patients with HFrEF should also be prescribed a beta-blocker alongside an ACEI (or ARB).[4]

In patients who remain symptomatic despite optimum therapy with ACEI (or ARB) and beta-blockers, the use of an MRA is also recommended.[4,36,65,66] Patients who have impaired renal function and those with serum potassium >5.0 mmol/l may need additional monitoring.

While the neurohormonal antagonists form the mainstay of pharmacotherapy in patients with HFrEF, several other drugs also play a role in the management of these patients. Although evidence to show a reduction of mortality with the use of diuretics is lacking, these are still recommended in patients with HFrEF to reduce the symptoms and signs of fluid overload.

Patients who are in sinus rhythm with heart rate >70 beats per minute (bpm) and not responding to optimal therapy with ACEI (or ARB), beta-blocker and MRA may benefit from the use of ivabradine which has been shown to reduce the risk of HF hospitalisation and cardiovascular death, mainly through a reduction in HF hospitalisations.[68] The combination of isosorbide dinitrate and hydralazine added

to conventional pharmacotherapy for HFrEF has been shown to reduce the risk of HF hospitalisation and overall mortality in patients who identify as being of African descent.[69]

Non-pharmacological interventions

In addition to pharmacological therapy, the use of devices in select populations with HFrEF have also demonstrated improvement in symptoms of HF and overall survival. Among the earlier trials with a sizable population, the Comparison of Medical Therapy, Pacing, and Defibrillation in HF (COMPANION) trial showed that patients who received cardiac resynchronization therapy (CRT) with or without and implantable cardioverter-defibrillator (ICD) had an approximately 20% reduction in the risk of the primary outcome - which was a composite of all-cause death or all-cause hospitalisation, compared to optimal pharmacotherapy alone.[70] The Cardiac Resynchronization — HF (CARE-HF) trial was the first to demonstrate a reduction in risk of overall mortality with CRT and subsequent trials have shown additional lowering of risk of other adverse clinical outcomes with the use of CRT.[71-73] Significant reduction in the risk of sudden death in patients with HFrEF with the use of ICDs have most robustly been documented in the Multicentre Automatic Defibrillator Trial II (MADIT II) and the Sudden Cardiac Death in HF (SCD-HeFT) trial.[74,75]

Use of CRT is recommended in symptomatic patients with HFrEF (NYHA class III/IV) with LVEF ≤35% and QRS duration ≥120 msec with features of left bundle branch block (LBBB).[4] CRT may also be considered in those without features of LBBB but with QRS duration ≥50 msec and in those with NYHA class II if LVEF ≤30% and QRS duration ≥130 msec or presence of LBBB.

ICD implantation is recommended only in symptomatic (NYHA II/III) patients in whom LVEF has remained ≤35% despite being on optimal HFrEF pharmacotherapy for a period of at least 3 months. Further considerations such as the presence of serious comorbidities and life expectancy are also made before recommending ICD implantation.[76,77]

Results from clinical trials have not been as encouraging in HFpEF. CHARM - Preserved, Irbesartan in HFpEF Study (I-Preserve) and Treatment of Preserved Cardiac Function HF with an Aldosterone Antagonist (TOPCAT) (respectively to

study the efficacy of candesartan, irbesartan and spironolactone) are examples of the large trials that failed to demonstrate any clinical benefit in patients with HFpEF.[39,57,78] Most recently, the Prospective Comparison of ARNI With ARB Global Outcomes in HFpEF (PARAGON-HF) trial also failed to show any clinical benefit of ARNIs in HFpEF, but a subgroup analysis demonstrated benefit in women.[79] However, despite the final results of PARAGON-HF – sacubitril/valsartan was approved by the FDA to treat significant proportion of patients with HFpEF and LVEF at the lower end of the range included in the study (45% - 57%).[37,80] These results also apply to HFmrEF as the HFpEF trials to date have recruited patients with LVEF 40-45%.[37]

Prognosis in heart failure

Since CONSENSUS was first published 30 years ago, several advances in pharmacological and non-pharmacological therapies have helped to improve the prognostic outlook for patients with HF.[4,58] However, mortality and rates of hospitalisations in HF remains high and QoL is severely affected.[6,81] In a systematic analysis of 60 studies and 1.5 million people by Jones and colleagues, estimated survival at 1, 2 , 5 and 10 years was 87%, 73%, 57% and 35% respectively.[81] In 2762 patients with incident HF in Olmsted county, mortality was high (24% for those 60 year olds and 54.4% for 80 years olds at 5 years of follow up) and rates did not decline over time.[24] In the International Congestive Heart Failure (INTER-CHF) prospective cohort study in HF patients in Africa, China, India, the Middle-East, South-East Asia and South America, the overall one year mortality was 16.5% with the highest in Africa (34%) and lowest in China (7%).[82]

Estimating prognosis for morbidity, mortality and disability in HF is important as it helps patients, their families, and clinicians with planning regarding the appropriate type and timing of therapies especially when making clinical decisions for optimal patient care especially with respect to invasive procedures and implantation of devices.[4,83] Estimation of prognosis is also important as it helps in the planning of health and social services, referrals to palliative care services and other resources.[84,85] Knowledge of prognosis can also facilitate the exploration of relevant subgroup analysis and design of clinical trials.[86]

Reliance on individual prognostic measures is not advised as even though they may have strong independent associations with morbidity and mortality, they provide limited overall outlook and interactions between different predictors exist.[87] Building multivariable prognostic models by incorporating multiple independent predictors is therefore a more accurate way for risk stratification of patients for different morbidity and mortality outcomes.[88]

One of the earliest models developed in a HF population was described by Aaronson and colleagues developed in a cohort recruited between 1986-1991.[88] The Heart Failure Survival Score (HFSS) was developed using data on 80 clinical characteristics including age, race, comorbidities, clinical symptoms, and laboratory and cardiac catheterization measures in 268 ambulatory patients derived from a single centre with LVEF≤40%. The outcome defined was urgent transplant or death without heart transplantation. A systematic review published in 2013 reported that validation of the HFSS in 8 subsequent cohorts showed poor discrimination with more frequent use of beta-blockers and ICDs.[86] Model discrimination also grew worse in more recent studies. The Seattle Heart Failure Model (SHFM) was developed using the Prospective Randomised Amlodipine Survival Evaluation (PRAISE1) cohort to predict a composite outcome of death, urgent HF transplant and ventricular assist device in 1125 patients with HF. PRAISE recruited patients between 1992 and 1994. In the above systematic review by Alba and colleagues, SHFM showed poorer discrimination in the cohort with higher use of ICDs. No such association with discriminative ability was seen with beta-blocker use or date of recruitment in the validation cohorts.

The SHFM was also validated in 9428 patients from the European Society of Cardiology Long-Term Registry along with three other risk models – CHARM which recruited patients between 1999 and 2001, GISSI-HF which recruited patients between 2002 and 2005 and MAGGIC which was published in 2013.[83,89–91] There was an obvious trend of improving discrimination with the more recent risk models (although the derivation cohort for MAGGIC also included CHARM).

The above demonstrates one of the main reasons thought to be behind the limited uptake of HF risk models into clinical practice. HFSS and SHFM were derived from populations before beta-blockers became a standard of care in

HF.[92] Since the publication of MAGGIC, ARNIs and SGLT-2 inhibitors have proven efficacious in improving outcomes in HF and are approved for use in clinical practice.[4,38,40] Moreover, powerful predictors such as NT-proBNP were largely absent in earlier models. In a study, the addition of BNP to the SHFM significantly improved discrimination from 0.72 to 0.78.[93]

Clinicians are also concerned about the applicability of models built in specific cohorts to wider populations and at the individual level. In a report published in 2016 calculating the SHFM and MAGGIC risk scores in 10930 ambulatory patients with HF, only 8 and 52 of 1661 patients who died in one year had a >50% mortality predicted using SHFM and MAGGIC scores respectively.[94] Moreover, the majority of patients who died had >70% estimated probability of one-year survival.

It is widely known that disparities in socioeconomic status (SES) influences outcomes in cardiovascular diseases and is an independent risk factor. Fiscella and colleagues demonstrated that the Framingham Risk Score (FRS) underestimated the risk of coronary artery disease in patients with low SES in the Atherosclerosis Risk In Communities Study (ARIC) sample.[95] Furthermore, they demonstrated that adding a composite measure of SES to FRS reduced this bias.

Several models to predict morbidity and mortality in HF have been developed. However, their clinical application remains limited due to a variety of reasons including the development of models in specific cohorts, evolving prognosis in HF patients due to the introduction of new drugs and devices, limited collection of variables in derivation cohorts and concerns of applicability at the individual level.

In this section, I will present a systematic review of the models that have been developed to estimate the risk of HF hospitalisation, cardiovascular hospitalisation, cardiovascular death, all-cause death either singly or as composite outcomes, in patients with HF. I will then present a comprehensive list of the most common variables used for model construction.

I will in subsequent chapters, present results from my analysis of three contemporary clinical trial cohorts where I explore some of these clinical and

non-clinical variables, including some of which have not been used in HF prognostic models previously.

Although the studies included in this systematic review will primarily cover HFrEF, some overlap is expected with the other phenotypes of HF due to models built in populations with both HFrEF and HFpEF. The results in the subsequent chapters that I present however, will entirely be based on patients with HFrEF.

Methods

Search strategy and eligibility

A systematic and comprehensive search of the electronic databases MEDLINE and EMBASE was conducted for studies examining prognosis in heart failure. The search was limited to studies involving humans, limited to adults, published in the English language, and including full text. Studies were identified using combinations of key terms “heart failure”, “cardiac failure”, “scor*”, “risk*”, “predict*”, “model*”, “outpatient”, “out-patient”, “ambulatory”, “stable”. The detailed results of the search strategy are shown in Appendix table 1. The initial search was performed in July 2020 and updated in July 2021.

Studies relating exclusively to HFpEF were excluded but those including both HFrEF and HFpEF were included. Studies that added new variables to an existing model to test prognosis were also excluded. Only studies with ambulatory patients were included.

Data extraction and synthesis

Titles of manuscripts produced from the database search were screened and the abstracts of the resultant manuscripts were then read to produce a final list of studies to be reviewed for this systematic review. From the list of manuscripts produced, I read through the methods and results section to identify the final manuscripts to be included in this systematic review.

I only included those manuscripts which had a minimum of 100 patients in their cohort, had detailed their method of analysis in the statistical section and had enumerated the variables in their final model. Information related to the cohort, type of HF, LVEF, variables included in the model, duration of follow-up and outcome of interest were extracted from the manuscripts. Not all the

publications included had listed variables that had been considered for univariable analysis. Those that had have been further summarised in Table 1-4.

For titles that have more than one outcome of interest, I have taken the cumulative number of variables into consideration.

Results

3167 titles were identified from the MEDLINE and EMBASE search after removing duplicates. Screening of the titles results in 41 abstracts that needed to be reviewed. Review of the abstracts resulted in 15 papers that were deemed suitable for this purpose. A further 3 manuscripts were identified by other means bring a total of 18 papers that will be included in this analysis.

Of the models reviewed here, 10 (56%) were based on observational studies, 7 (39%) were based on RCTs and 1 (6%) was a combination of both. 5 (28%) studies were based entirely on patients with HFrEF, 2 (11%) included patients with HFrEF or a recent history of HF hospitalisation and the rest were a combination of both HFrEF and HFpEF (and HFmrEF). All-cause death was the most common outcomes studied (12 models). 9 studies reported composite outcomes and cardiovascular death alone was the outcome of interest in one study.

The number of variables in a single model ranged from a minimum of 4 to a maximum of 28.

The average age of patients in the included studies ranged from 52 years to 70 years and most patients in the studies were male. Average LVEF was between 21% and 42% and 11 (61%) of the 18 studies were based on patients from a single country. Single country analysis all came out of North America and Europe except for two which were in Brazilian cohorts. 7 (38%) studies had fewer than 1000 patients in their final cohort with one having a final study population of less than 500.

Data variables

Age, LVEF, NYHA class and sex were the most commonly appearing individual variables in the final predictive models. Comorbidities, other baseline characteristics and select laboratory variables were also frequently found to be predictive of the outcomes examined in the models included in this review.

All 18 studies included in this review included age in their univariable analysis and it was the most common predictive variable appearing in 12 (67%) of the final models. Sex was considered for univariable analysis in 14 (82%) studies and was a final predictor in 9 (50%). Race and/or region appeared in 5 univariable models and one final multivariable model.

11 (61%) papers featured additional baseline variables such as systolic blood pressure (SBP), body mass index (BMI), heart rate, oedema, dyspnoea, and other physical parameters in their final models. 13 (72%) titles had them included in their univariable models. As with age, LVEF was included in univariable analysis in all 18 studies and was a predictor in 11 (61%) final models. Other variables from echocardiography and ECG such as cardiac dimensions and ECG parameters were significant predictors in 6 (33%) final multivariable models.

14 (78%) studies had at least one laboratory parameter in their final predictive models making this the most common group of variables amid the studies. Creatinine was a predictor in 6 studies, BUN and estimated glomerular filtration rate (eGFR) were included in 3 final models. NPs were included in the final models in 6 (37%) studies. Other laboratory parameters of note were haemoglobin which featured in models in 7 studies and sodium which was included in 4 final models.

Comorbidities were included as potential predictors of outcomes in 14 (78%) studies and featured in 10 final models. Diabetes (7 - 39%) was the most common comorbidity in any of the final models followed by atrial fibrillation/flutter (3 – 17%) and COPD (2 – 11%). NYHA class and other measures of HF severity were common prognostic variables included in 12 (67%) studies, prior HF hospitalisation and HF duration were each included in 5 (28%) and 4 (17%) final models respectively and aetiology of HF was a prognostic variable in 1 final model. Smoking and KCCQ scores were predictive of risk in 2 (11%) final models.

Drug therapy was included in 6 different studies. ACEI/ARBs appeared in 2 models and beta-blockers were included in 3 studies. ARNI, ivabradine and MRAs were included in one model each. Only one model featured the use of devices.

Table 1-3 Predictors of clinical outcomes in heart failure - final models

Sl. No.	Publication	Derivation number	Cohort	Outcome(s)	HF type	Variables in final model
1.	MT Kearney et. al. (2002)[96]	553	Observational (UK-HEART)	1. All-cause death	Both	Age, creatinine, CT ratio, LVESD, LVH, SDNN, sodium.
2.	Pocock et. al. (2006)[89]	7599	RCT (CHARM)	1. CV death/HF hospitalisation 2. All-cause death	Both	Age, ARB, atrial fibrillation, BBB, BMI, cardiomegaly, DBP, dependent oedema, diabetes, dyspnoea at rest, heart rate, prior HF hospitalisation, HF duration, LVEF, mitral regurgitation, myocardial infarction, NYHA class, pulmonary crackles, pulmonary oedema, sex, smoking
3.	WC Levy et. al. (2006)[97]	1125	RCT (PRAISE1)	All-cause death	Both	ACEI/ARB, aetiology, allopurinol, age, beta-blocker, biventricular pacemaker, cholesterol, diuretic dose, haemoglobin, ICD, LVAD, LVEF, MRA, NYHA, percentage of lymphocytes, SBP, sex, sodium, statin, uric acid
4.	F Gustafsson et. al. (2009)[98]	4012	Observational	All-cause death or all-cause hospitalisation	Both	Age, creatinine, NYHA, prior HF hospitalisation, T2DM
5.	R Vazquez et. al (2009)[99]	992	Observational (MUSIC)	All-cause death	Both	AVE, eGFR, hyponatraemia, LA size, LVEF, NSVT & frequent VPBs, NT-proBNP, troponin
6.	M Anselmino et. al. (2009)[100]	446	Observational (ALPHA registry)	All-cause death CV hospitalisation	HFrEF with nonischaemic heart disease	Creatinine, haemoglobin, LVEDD, LVEF, NYHA, peak oxygen uptake, QRS duration, SBP
7.	M Volpe et. al. (2010)[101]	106	Observational	All-cause death	All	ANP , age, HF severity, LVEF
8.	S Barlera et. al. (2012)[90]	6975	RCT (GISSI-HF)	All-cause death	HFrEF or HF hospitalisation within 1 year	Age, aortic stenosis, BMI, COPD, eGFR, haemoglobin, LVEF, NYHA, sex, SBP, T2DM, uricemia
9.	E Frigola-Capell et. al. (2012)[102]	7196	Observational	CV hospitalisation, readmissions, length of stay, long length of stay	-	CKD, COPD, hypertension, IHD, T2DM, urban population

10.	CM O'Connor et. al. (2012)[103]	2331	RCT (HF-ACTION)	All-cause death or all-cause hospitalisation	HFrEF	BUN, exercise duration on CPX test, KCCQ symptom stability, sex
11.	SL Hummel et. al. (2013)[104]	1536	Observational (HFPSI)	All-cause death and medical hospitalisation	All	Atrial fibrillation/flutter, BUN, BNP, NYHA class, prior HF hospitalisation, T2DM
12.	TJ Collier et. al. (2013)[105]	2737	RCT (EMPHASIS-HF)	CV death/ HF hospitalisation	HFrEF	Age, BMI, eGFR, heart rate, haemoglobin, myocardial infarction/CABG, prior HF hospitalisation, SBP, sex, T2DM
13.	SJ Pocock et. al. (2013)[87]	39372	RCT, observational	All-cause death	All	Age, ARB/ACEI, beta-blocker, BMI, creatinine, COPD, HF duration, LVEF, NYHA, SBP, sex, smoking, T2DM
14.	J Lupón et. al. (2014)[106]	864	Observational (BCN Bio-HF calculator)	All-cause death	HFrEF or recent HF hospitalisation	ACEI/ARB, age, beta-blocker, diuretic dose, eGFR, haemoglobin, hs-troponin, LVEF, NYHA, NT-proBNP, sex, sodium, statin, ST2
15.	I Ford et. al. (2015)[107]	6505	RCT (SHIFT)	1. CV death/HF hospitalisation 2. All-cause death	HFrEF	1. Age, atrial fibrillation/flutter, cholesterol, creatinine, heart rate, HF duration, ivabradine, LBBB, LVEF, NYHA, SBP, 2. Age, BMI, creatinine, heart rate, HF duration, LBBB, LVEF, NYHA, SBP, sex
16.	L Giolo-Pereira et. al. (2019)[108]	695	Observational (GENIUS-HF)	1. All-cause death 2. Hospitalisation/All-cause death	All	1. BNP, BUN, haemoglobin, LVEF, SBP, troponin 2. Age, BNP, BUN, haemoglobin, LVEF, SBP, troponin
17.	J Simpson et. al. (2020)[109]	8399	RCT (PARADIGM-HF)	1. CV death/HF hospitalisation 2. CV death 3. All-cause death	HFrEF	1. Absolute lymphocytes, absolute neutrophils, albumin, ARNI, BBB, beta-blocker, bilirubin, haemoglobin, HF duration, prior HF hospitalisation, LDL, LVEF, NT-proBNP, NYHA class, peripheral arterial disease, potassium, race/ethnicity, region, sex, T2DM, urea, uric acid, valvular heart disease 2. Albumin, age, ARNI, beta-blocker, bilirubin, haemoglobin, HF duration, LVEF, myocardial infarction, NT-proBNP, NHYA class, race/ethnicity, PCI, peripheral arterial disease, potassium, region, SBP, sex, T2DM, total cholesterol, urea, uric acid 3. Absolute neutrophils, albumin, age, ARNI, AST, beta-blocker, bilirubin, BMI, chloride, haemoglobin, HF duration, LDL, LVEF, monocytes, myocardial infarction, NT-proBNP, NHYA class, race/ethnicity, PCI,

						peripheral arterial disease, potassium, region, SBP, sex, T2DM, triglycerides, urea, uric acid
18.	MA Nakazone et. al. (2020)[110]	677	Observational	All-cause death	All	Age, Chagas cardiomyopathy, DBP, left anterior fascicular block, LVEF, RBBB, SBP

RCT – randomised controlled trial, CT – cardiothoracic, LVESD - left ventricular end-systolic diameter, LVH – left ventricular hypertrophy, SDNN - standard deviation of all normal-to-normal RR intervals, LVEF - left ventricular ejection fraction, HF – heart failure, NYHA – New York heart association, DBP, diastolic blood pressure, BBB – bundle branch block, BMI – body mass index, SBP – systolic blood pressure, ACEI – angiotensin converting enzyme inhibitor, ARB – angiotensin receptor blocker, MRA – mineralocorticoid receptor antagonist, ICD – implantable cardioverter-defibrillator, LVAD – left ventricular assist device, AVE – atherosclerotic vascular event, LA – left atrium, NVST – non-sustained ventricular tachycardia, VPBs – ventricular premature beats, eGFR – estimated glomerular filtration rate, NT-proBNP – N terminal pro-natriuretic peptide, LVEDD - left ventricular end-diastolic diameter, ANP – atrial natriuretic peptide, COPD – chronic obstructive pulmonary disease, T2DM – type 2 diabetes mellitus, IHD – ischaemic heart disease, CKD – chronic kidney disease, CPX – cardiopulmonary exercise, KCCQ – Kansas city cardiomyopathy questionnaire, BUN - blood urea nitrogen, BNP – brain natriuretic peptide, CABG – cardiopulmonary bypass graft, LBBB – left bundle branch block, ARNI – angiotensin receptor blocker neprilysin inhibitor, LDL – low density lipoprotein, PCI – percutaneous coronary intervention

Table 1-4 Univariable analysis for construction of prognostic models in heart failure

Sl. No.	Publication	Country (no. of centres)	Outcome(s)	Univariable variables/ variables considered
1.	MT Kearney et. al. (2002)[96]	UK (8)	All-cause death	Age, creatinine, CT ratio, HFP, LFP, LVEDD, LVESD, LVH, LVEF, NSVT, potassium, SDNN, sex, sodium, TP, urea, VLFP
2.	Pocock et. al. (2006)[89]	International (618)	1. CV death/HF hospitalisation 2. All-cause death	Aetiology, age, angina pectoris, ARB, atrial fibrillation, atrial fibrillation/flutter (ECG), bilateral pleural effusions, BBB, BMI, cancer, cardiomegaly, DBP, dependent oedema, diabetes, duration of HF, dyspnoea, height, HTN, LVEF, LVH, myocardial infarction, NYHA, prior HF hospitalisation, S3 gallop, SBP, sex, smoking, stroke, paced rhythm, pathological Q wave, pulmonary crackles, pulmonary oedema, pulmonary wheezes, weight, venous congestion
3.	WC Levy et. al. (2006)[97]	International	All-cause death	ACEI/ARB, aetiology, age, allopurinol, beta-blocker, biventricular pacemaker, creatinine, cholesterol, diuretic dose, haemoglobin, ICD, NYHA, LVAD, LVEF, MRA, percentage lymphocytes, SBP, sex, sodium, statins, uric acid, WBC
4.	F Gustafsson et. al. (2009)[98]	Denmark (18)	All-cause death or all-cause hospitalisation	Aetiology, age, sex, creatinine, LVEF, HF duration, heart rate, NYHA, prior HF hospitalisation, SBP, T2DM
5.	R Vazquez et. al (2009)[99]	Spain	All-cause death	Age, atrial fibrillation, AVE, BMI, eGFR, GGT, haemoglobin, heart rate, hyponatremia, LA size, LVEDd, MR, LVEF, LBBB/IVCD, NSVY & frequent VPB, NT-proBNP, QRS duration, restrictive filling pattern, troponin, T2DM
6.	M Anselmino et. al. (2009)[100]	Italy (9)	All-cause death CV hospitalisation	Age, BMI, creatinine, haemoglobin, heart rate, NYHA, LVEDd, LVEF, peak oxygen uptake, QRS duration, SBP, sex, T2DM
7.	M Volpe et. al. (2010)[101]	Italy	All-cause death	Aetiology, age, ANP, EPO, diuretics, heart rate, LVEF, LVDd, PRA, severity, T2DM
8.	S Barlera et. al. (2012)[90]	Italy (357)	All-cause death	Aetiology, age, ascites, atrial fibrillation, aortic stenosis, bilirubin, BMI, bypass, cholesterol, COPD, DBP, eGFR, fibrinogen, glycemia, haemoglobin, heart rate, HTN, hepatomegaly, ICD, LVE, MR, NYHA, potassium, prior HF hospitalisation, pacemaker, peripheral oedema, PTCA, PVC, PVD, pulmonary congestion, SBP, sex, smoking, sodium, stroke, T2DM, THS, triglycerides, uricemia

9.	E Frigola-Capell et. al. (2012)[102]	Spain (43)	CV hospitalisation, readmissions, length of stay, long length of stay	Age, COPD, CKD, HTN, hypercholesterolemia, IHD, sex, T2DM, urban population
10.	CM O'Connor et. al. (2012)[103]	International (80)	All-cause death or all-cause hospitalisation	Aetiology, age, atrial fibrillation/flutter, Beck depression index II, biventricular pacemaker, BMI, BUN, Canadian angina class, COPD, creatinine, DBP, exercise duration on CPX test, previous revascularization, haemoglobin, HF hospitalisation, ICD, heart rate, heart rate reserve on CPX, heart rate at peak exercise on CPX test, heart rate at end of 2nd stage of CPX test, LVEF, KCCQ-TSS, KCCQ-SS, KCCQ-QOL, KCCQ-SE, KCCQ-PL, KCCQ-SL, MR grade (echo), myocardial infarction, NYHA, race, rest ECG rhythm on CPX test, peak oxygen pulse on CPX test, peak respiratory exchange ratio on CPX test, ventricular conduction prior to CPX test, pacemaker, peak VO2, PVD, SBP, sex, smoking, six-minute walk distance, sodium, T2DM, treatment group, VE/VCO2 slope, weber class
11.	SL Hummel et. al. (2013)[104]	USA	All-cause death and medical hospitalisation	Age, atrial fibrillation/flutter, BNP, BUN, CAD, LVEF, NYHA, prior HF hospitalisation, race, sex, sodium, T2DM
12.	TJ Collier et. al. (2013)[105]	International (308)	CV death/ HF hospitalisation	Aetiology, age, albumin, ALT, angina, AST, asthma, atrial fibrillation/flutter, bilirubin, BMI, creatinine, CABG, COPD, DBP, eGFR, ICD, heart rate, HTN, LVEF, haemoglobin, HF duration, prior HF hospitalisation, myocardial infarction, PCI, pacemaker, potassium, QRS interval, race, SBP, smoking, sodium, stroke, T2DM, waist circumference
13.	SJ Pocock et. al. (2013)[87]	International	All-cause death	ACEI, age, angina, ARB, atrial fibrillation, BBB, BMI, beta-blocker, CABG, creatinine, COPD, DBP, duration of HF, dyspnoea, LVEF, haemoglobin, HTN, IHD, myocardial infarction, NYHA, race, rales, oedema, PCI, SBP, sex, smoking, sodium, stroke, T2DM
14.	J Lupón et. al. (2013) [106]	Spain	All-cause death	-
15.	I Ford et. al. (2015)[107]	International	1. CVD & HF hospitalisation composite 2. All-cause death	ACEI, aetiology, age, ALT, anaemia, anti-arrhythmic, atrial fibrillation/flutter, beta-blocker, BMI, cholesterol, COPD, creatinine, CRT, DBP, diuretic, duration of HF, dyslipidaemia, eGFR, ICD, heart rate, HTN, ivabradine, lipid lowering therapy, LBBB, LVEF, NYHA, MRA, myocardial infarction, prior coronary surgery, potassium, SBP, sex, sodium, stroke, T2DM, vitamin K antagonist,
16.	L Giolo-Pereora et. al. (2019)[108]	Brazil	1. All-cause death 2. Hospitalisation/All-cause death	Age, BNP, BUN, haemoglobin, LVEF, SBP, sex, sodium, troponin

17.	J Simpson et. al. (2020)[109]	International	1. CV death/HF hospitalisation 2. CV death 3. All-cause death	ACEI, ARB, age, angina, anti-coagulant, ARNI, aspirin, asthma, atrial fibrillation, beta-blocker, BMI, BNP, CABG, cancer, COPD, CRT, creatinine, CVA/TIA, DBP, digoxin, dyspnoea at rest, dyspnoea on effort, eGFR, fatigue, haemoglobin, HF duration, HR, HTN, ICD, JVP, KCCQ score, lipid lowering therapy, LVEF, myocardial infarction, MRA, NT-proBNP, oedema, orthopnoea, PCI, PND, prior HF hospitalisation, race, rales, renal disease, region, SBP, sex, smoking status, T2DM, THR, valvular heart disease, weight
18.	MA Nakazone et. al. (2020)[110]	Brazil	All-cause death	Aetiology, age, atrial fibrillation, creatinine, DBP, haemoglobin, ICD, LBBB, LVEF, LVESD, LVSD, NYHA class, pacemaker, potassium, RBBB, renal function, RVD, QRS, SBP, sex, sodium, T2DM, VPC,

CT – cardiothoracic, HFP – high frequency power, LFP – low frequency power, LVEDD – left ventricular end-diastolic diameter, LVESD - left ventricular end-systolic diameter, LVH – left ventricular hypertrophy, NSVT – non-sustained ventricular tachycardia, SDNN - standard deviation of all normal-to-normal RR intervals, TP – total power, VLFP – very low-frequency power, LVEF - left ventricular ejection fraction, HF – heart failure, NYHA – New York heart association, DBP, diastolic blood pressure, BBB – bundle branch block, BMI – body mass index, SBP – systolic blood pressure, ACEI – angiotensin-converting enzyme inhibitor, ARB – angiotensin receptor blocker, MRA – mineralocorticoid receptor antagonist, ICD – implantable cardioverter-defibrillator, LVAD – left ventricular assist device, AVE – atherosclerotic vascular event, LA – left atrium, NVST – non-sustained ventricular tachycardia, VPBs – ventricular premature beats, eGFR – estimated glomerular filtration rate, NT-proBNP – N terminal pro-natriuretic peptide, ANP – atrial natriuretic peptide, COPD – chronic obstructive pulmonary disease, T2DM – type 2 diabetes mellitus, IHD – ischaemic heart disease, CKD – chronic kidney disease, CPX – cardiopulmonary exercise, KCCQ – Kansas city cardiomyopathy questionnaire, BUN - blood urea nitrogen, BNP – brain natriuretic peptide, CABG – cardiopulmonary bypass graft, LBBB – left bundle branch block, ARNI – angiotensin receptor blocker neprilysin inhibitor, LDL – low density lipoprotein, PCI – percutaneous coronary intervention

Discussion

In this review of 18 studies of ambulatory patients with HF (HFrEF only or HFrEF with HFpEF/HFmrEF) and examining risk of all-cause death, cardiovascular death, HF hospitalisation, cardiovascular hospitalisation, or a composite of the individual outcomes in any given combination, a summary of variables – both clinical and non-clinical, used to predict these outcomes is presented.

Certain variables namely age, LVEF, sex, NYHA class, laboratory values and comorbidities appeared consistently in models regardless of the cohort, sample size, type of HF, the time of recruitment and the study setting.

The prognosis for patients with HF has improved greatly thanks to the development of a range of pharmacotherapy and devices that have had a great impact on morbidity and mortality in patients with HF.[111] Such developments have come at different times and some of the earlier models were constructed before the routine use of such therapies. MERIT-HF was published in 1999, 5 years after the end of the PRAISE1 recruitment which was the cohort used to development of the SHFM (benefits with beta-blocker & ICD use in the model were estimated from RCTs or meta-analyses) and almost a decade behind recruitment for HFSS (not included in the systematic review due to composite outcome including cardiac transplant).[61,88,97] The MAGGIC risk score was developed in a cohort who were receiving beta-blocker and ACEI/ARBs but this was well before ARNI, and SGLT-2 inhibitors were shown to be efficacious in reducing the risk of morbidity and mortality in HFrEF.[4,38,40,87] In 2020, Simpson and colleagues developed a globally representative risk model derived in PARADIGM-HF and validated in Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure (ATMOSPHERE) and The Swedish Heart Failure Registry (SwedeHF) to predict cardiovascular death or HF hospitalisation, cardiovascular death alone and all-cause mortality.[109] The models included ARNI, NPs, race and region as predictors. Whether the discriminative ability of the model will be sustained in patients treated with an SGLT-2 inhibitor has not yet been tested.[40,67]

Age was included in all univariable analyses and 67% of final models which was not surprising as patient characteristics and outcomes are known to vary with

age. Moreover, in the MAGGIC risk score, age was observed to interact with LVEF and increasing age varied with a higher risk of mortality with increasing age in patients with LVEF ≥40%.[91] While not a significant predictor in multivariable analyses, it was forced into the final model in the SHFM.[97] More recently, frailty which is a condition while thought to be related to but different from ageing, has been a focus of interest among clinicians due to its relationship with cardiovascular disease.[112,113] Frailty however was not included in the studies in this systematic review, and I will be discussing its association with HF in a later chapter in this thesis. Sex is another demographic factor which was commonly featured in the studies in this systematic review. Male sex is known to carry a higher risk of mortality in HF. In the MAGGIC risk score, rate ratio for male sex was 1.115 (95 % CI 1.073 – 1.159) and was predictive of mortality in both patient groups with LVEF <40% and ≥40%.[91] In SHFM, while not significantly predictive of the primary outcome in multivariable or univariable analysis, like age, it was included in the final predictive model.[97] However, despite lower risk of mortality, concerns regarding poorer QoL and inferior therapy in women with HF remain.[35,92,114–125] I have discussed if these sex-based differences in treatment, QoL and mortality still hold true in a contemporary cohort of HF patients in Chapter 4 in this thesis.

Other demographic factors featured in fewer studies. Race/region appeared in the one final multivariable model in this systematic review and only five other studies had taken region/race into account. Variations in patient characteristics and outcomes in HF by race/ethnicity and region is well known.[82,126,127] While certain variables may be excluded from final models through statistical means, region/race had been a part of univariable analysis in only 5 studies likely because less than half of the studies were carried out in international cohorts. This drawback adds to the concerns regarding limited generalizability of such models. No other social determinants of health were featured in any of the models in this review. Given this background, in Chapters 6 & 7, I discuss the associations of specific socioeconomic factors with clinical outcomes in HF.

Comorbidities frequently accompany HF and contribute to increased morbidity, mortality, and quality of life. In this systematic review, comorbidities were often included in the 10 final models and in the 13 univariable analyses. While

increasing prevalence of HF due to an ageing population has been mentioned, increased longevity also means that patients accrue greater number of chronic conditions further complicating care. An individual's comorbidity profile can also influence the mode of death and further help make decisions about individualised therapeutic targets. A frequent criticism of existing models in HF is their inability to discriminate between different modes of death. It was only very recently that models to specifically predict sudden death and pump failure – the two major modes of death in HF were published.[128] SHFM and MAGGIC are the two most frequently used calculators in clinical practice. Comorbidities did not feature in the final SHFM model, but the model included haemoglobin and uric acid levels along with the use of allopurinol.[97] Type 2 diabetes mellitus (T2DM) and COPD were significant predictors in the MAGGIC risk model. The coexistence of COPD and HF is particularly important due to known diagnostic and therapeutic challenges which I will discuss in detail in later chapters.[129,130] Comorbidities have also been included in a recent set of models to predict the risk of cardiovascular death or HF hospitalisation, cardiovascular death or all-cause death.[87,109] T2DM, valvular heart disease (VHD), peripheral artery disease (PAD), bundle branch block (BBB) and prior MI were all predictive of the primary composite outcome in a study by Simpson and colleagues.[109] While diabetes and CAD are common predictors in most models, the others are less commonly seen in models despite carrying a strong risk of poorer outcomes especially PAD, although this is likely attributable to the incomplete collection of these variables in prior studies.[131]

Anaemia, iron deficiency and kidney disease are all linked with poor outcomes in HF. Using parameters such as haemoglobin and eGFR as proxies for such conditions in models, adds valuable predictive information, and allows for regular updates on change in prognosis. Haemoglobin was a final predictive variable in 7 studies (and 10 final models). Renal function was also routinely assessed either with the use of creatinine, estimated glomerular filtration rate (eGFR) or blood urea nitrogen (BUN). NPs were included in 6 studies and 9 final models including in the models derived using patients enrolled in PARADIGM-HF. They were not included in two of the most frequently used risk calculators –

SHFM and MAGGIC although studies have shown that the addition of NPs improved the discriminative ability of older models.[93]

Drug therapy was included in 6 different studies. ACEI/ARBs appeared in 2 models and beta-blockers were included in 3 studies. ARNI, ivabradine and MRAs were included in one model each. Only one model featured the use of devices. The number of studies/models including drugs/devices in univariable analysis was also the same. Other than SHFM, where patients were recruited before the use of beta-blockers, it was surprising to see that ACEI/ARBs, beta-blockers or MRAs were not considered for univariable analysis in more studies. Inclusion of HF drugs especially to ACEIs, MRAs or beta-blockers would be unexpected in contemporary studies as barring any specific adverse event, all those who have an indication to receive these drugs should be receiving them.[4,36] However, inclusion of drugs in multivariable models also raises concerns regarding bias due to confounding by indication.[132]

QoL was considered as a prognostic indicator in only one model.[103] With advancing life expectancy, the recognition of the importance of preserving QoL has increased in recent times.[133] As a result, QoL has increasingly been used as a measure of therapeutic benefit in clinical trials more recently.[38,40] Moreover, while poor quality of life itself has been seen to be associated with worse outcomes in HF, a few analyses have shown poor correlation with other predictors of worse outcomes in HF.[134] Therefore, consideration of QoL as an independent predictor of outcomes in HF also carries importance.

Conclusion

As stated earlier, prognosis in patients with HF has continued to improve calling for regular update of existing models or the development of newer prognostic scores to keep up with the changing prognosis that has been occurring over the past several decades. Recently, two drugs have been shown to significantly reduce morbidity and mortality in patients with HF and use of these in routine practice should further improve the prognosis in contemporary cohorts of HF patients. However, there are likely many variables which are either not recognised as prognostically important or even measured. Increasing awareness of newer biological pathways and the importance of socioeconomic determinants

of health mean that risk models will continue to be updated and evolve. The importance of QoL in addition to conventional cardiovascular outcomes has already been alluded to.

In this thesis, I will explore some conventional prognostic variables that have featured in existing models and some potentially novel predictive variables. I have analysed them in three contemporary global clinical trial data sets.

Chapter 2. Methods

Study population

The entirety of the analysis in this theses is based on data from three global clinical trials in HFrEF – ATMOSPHERE, PARADIGM-HF and DAPA-HF.[38,40,135] ATMOSPHERE was a randomised controlled trial comparing the effects of enalapril alone with aliskiren (a renin inhibitor) alone and the combination or aliskiren and enalapril in patients with HFrEF.[135-137] Patients in PARADIGM-HF were randomised to receive either sacubitril/valsartan – an ARNI or enalapril and those in DAPA-HF were randomised to either dapagliflozin – SGLT 2 inhibitor (10 mg once daily) or placebo.[38,40,138-141] The design of the three trials have been published and the eligibility criteria are detailed in Table 2-1.[136,138,140] The study population will not be described separately in any of the subsequent chapters. As ATMOSPHERE and PARADIGM-HF were similar in their eligibility criteria (thereby having similar populations) and efficacy outcomes examined, had a common control group treated with enalapril, and were conducted in time periods overlapping each other, the analyses presented in Chapters 4, 6, 7 & 8 are performed in a combined cohort of the two trials. The added advantage of combining ATMOSPHERE and PARADIGM-HF was an increase in the size of the cohort and the total number of events thereby improving the robustness of the results. Chapters 3 and 5 are based on analyses of the DAPA-HF cohort alone.

On trial entry, ongoing therapy with an ACE inhibitor or ARB was stopped and patients entered a sequential run-in, first receiving enalapril followed by the combination of enalapril plus aliskiren in ATMOSPHERE and enalapril followed by sacubitril/valsartan in PARADIGM-HF. Patients tolerating both run-in periods were randomly assigned to double blind therapy with enalapril, aliskiren or both drugs in a 1:1:1 ratio in ATMOSPHERE or sacubitril/valsartan or enalapril in a 1:1 ratio in PARADIGM-HF.

In DAPA-HF randomisation to dapagliflozin or placebo was stratified based in either a history of diabetes or on a glycated haemoglobin level of ≥6.5% at enrolment.

The median follow-up time in ATMOSPHERE was 36.7 months (minimum – 1 day and maximum – 74.4 months, PARADIGM-HF was 26.6 months (minimum – 1 day and maximum – 50.4 months and in DAPA-HF was 18.2 months (minimum – 5 days and maximum – 27.4 months).

All three trials were approved by ethics committees at all participating centres in each country and all participants gave written informed consent.[142]

Table 2-1 Eligibility criteria of the trial populations analysed in this thesis.

ATMOSPHERE	PARADIGM-HF	DAPA-HF
INCLUSION CRITERIA		
≥18 years, male or female	≥18 years, male or female	≥18 years, male or female
Patients with a diagnosis of CHF (NYHA class II-IV): LVEF ≤35% at screening (measurement done anytime within the past 6 months) BNP ≥150 pg/ml or ≥100 pg/ml and unplanned hospitalisation with HF with 12 months prior to visit 1	Patients with a diagnosis of CHF (NYHA class II-IV): LVEF ≤40% at screening (measurement done anytime within the past 6 months); changed to ≤35% by amendment. BNP ≥150 pg/ml (NT-proBNP ≥600 pg/ml) or ≥100 pg/ml (NT-proBNP ≥400 pg/ml) and unplanned hospitalisation with HF with 12 months prior to visit 1	Patients with a diagnosis of CHF (NYHA class II-IV): LVEF ≤40% at screening (most recent measurement done anytime within the past 12 months); patients undergoing coronary revascularization, valve repair/replacement or implantation of a cardiac resynchronization therapy (CRT) device or any other surgical, device or pharmacological intervention that could improve LVEF must have had a measurement of LVEF at least 3 months after the intervention NT-proBNP ≥600 pg/ml or ≥400 pg/ml and hospitalisation with HF with 12 months prior to visit 1; if concomitant atrial fibrillation or flutter at visit 1, NT-proBNP ≥900 pg/ml
ACEI – at a stable dose (Enalapril 10 any other ACEI at stable dose) for at least 4 weeks prior to screening	ACEI or ARB at a stable dose of at least enalapril 0 mg/day or equivalent for at least 4 weeks before screening.	ACEI or ARB or ARNI at an optimized level and stable for at least 4 weeks before screening.
Beta-blocker for at least 4 weeks prior to screening if not contraindicated	Beta-blockers for at least 4 weeks prior to screening if not contraindicated	Beta-blockers for at least 4 weeks prior to screening if not contraindicated MRA if considered appropriate by treating physician for at least 4 weeks before screening eGFR ≥30 ml/min/1.73m^2 at visit 1
EXCLUSION CRITERIA		
Hypersensitivity or allergy to any of the study drugs, drugs of similar chemical classes, ACEIs, ARBS or NEP inhibitors as well as known or suspected C/Is to the study drugs	Hypersensitivity or allergy to any of the study drugs, drugs of similar chemical classes, ACEIs, ARBS or NEP inhibitors as well as known or suspected C/Is to the study drugs	

Those treated concomitantly with both ARB and MRA in addition to study drug at screening		
	Previous history of intolerance to recommended target doses of ACEIs or ARBs	Those receiving therapy with an SGLT-2 inhibitor within 8 weeks prior to enrolment or previous history of intolerance to an SGLT-2 inhibitor
		Type 1 diabetes mellitus
Current decompensated HF	Current acute decompensated HF	Current acute decompensated HF or hospitalisation due to acute decompensated HF <4 weeks prior to enrolment
	Requirement of treatment with both ACEIs and ARBs.	
	Known h/o angioedema.	
Symptomatic hypotension and/or SBP <95 mmHg at screening and/or <90 mmHg at randomisation.	Symptomatic hypotension and/or SBP <100 mmHg at screening and/or <95 mmHg at visit 3 or randomisation (visit 5).	Symptomatic hypotension or SBP <95 mmHg at 2 of 3 measurements either at visit 1 or visit 2
Renal disease likely to be life threatening or eGFR<40 at screening or eGFR<35 at randomisation or decrease of eGFR of >25% from screening to randomisation.	eGFR<30 at screening, visit 3 or visit 5 (randomisation) or decrease of eGFR of >25% between screening and visit 3 or between visit 3 and randomisation.	Severe (eGFR <30 ml/min/1.73m^2), unstable or rapidly progressing renal disease at the randomisation
Screening potassium >=5 or randomisation potassium >=5.2.	Screening potassium >=5.2 or potassium >=5.4 at visit 3 or randomisation.	
ACS, stroke. TIA, cardiac, carotid or major vascular surgery, PCI or carotid angioplasty within past 3 months prior to screening	ACS, stroke. TIA, cardiac, carotid or major vascular surgery, PCI or carotid angioplasty within past 3 months prior to screening	ACS, stroke, or TIA within past 12 weeks prior to enrolment
Coronary or carotid artery disease likely to require surgical or PCI within the 6 months after screening	Coronary or carotid artery disease likely to require surgical or PCI within the 6 months after screening	Coronary revascularization or valvular replacement/repair within the 12 weeks prior to enrolment or planned to undergo any of these operations after randomisation
	History of severe pulmonary disease.	

Right heart failure due to severe pulmonary disease.		
Diagnosis of peripartum or chemotherapy induced cardiomyopathy within 12 months prior to screening	Diagnosis of peripartum or chemotherapy induced cardiomyopathy within 12 months prior to screening	
History of heart transplant or who are on transplant list with an LVAD	History of heart transplant or who are on transplant list with an LVAD	History of heart transplant or implantation of a LVAD or similar device, or implantation expected after randomisation
Documented ventricular arrhythmia with syncopal episodes within past 3 months prior to screening that is untreated	Documented ventricular arrhythmia with syncopal episodes within past 3 months prior to screening that is untreated	
Symptomatic bradycardia or second-degree heart block without pacemaker	Symptomatic bradycardia or second-degree heart block without pacemaker	Symptomatic bradycardia or second- or third-degree heart block without pacemaker
Implantation of a CRT device within the prior 3 months to screening or intent to implant a CRT device.	Implantation of a CRT device within the prior 3 months to screening or intent to implant a CRT device.	Implantation of a CRT device with the prior 12 weeks to enrolment or intent to implant a CRT device
Presence of hemodynamically significant mitral and or aortic valve disease except mitral regurgitation secondary to left ventricular dilatation	Presence of hemodynamically significant mitral and or aortic valve disease except mitral regurgitation secondary to left ventricular dilatation	
Presence of other hemodynamically significant obstructive lesions of left ventricular outflow tract including aortic stenosis	Presence of other hemodynamically significant obstructive lesions of left ventricular outflow tract including aortic stenosis	
		HF due to restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, hypertrophic (obstructive) cardiomyopathy or uncorrected primary valvular disease
Long term requirement for NSAIDs or COX2 inhibitors except for aspirin at doses used for cardiovascular prophylaxis (<=325 mg od)		

		Known specified blood-borne diseases Hepatic impairment (AST or ALT >3 times the upper limit of normal; or total bilirubin >2 times the upper limit of normal at enrolment). Not excluded if an isolated increase in bilirubin in patients with known Gilbert syndrome
Treatment with either a direct renin inhibitor or intravenous vasodilators and/or intravenous inotropic drugs within the 4 weeks prior to visit 1 Current treatment with cyclosporin at screening		
		Active malignancy requiring treatment at the time of visit 1 (except successfully treated basal cell or treated squamous cell carcinoma)
Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of study drugs including but not limited to any of the following: h/o pancreatic injury, pancreatitis, or evidence of impaired pancreatic function/injury primary liver disease considered to be life threatening active duodenal or gastric ulcers during the 3 months prior to screening Current treatment with cholestyramine or colestipol resins	Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of study drugs including but not limited to any of the following: h/o active IBD during 12 months before screening active duodenal or gastric ulcers during the 3 months prior to screening e/o hepatic disease or gastric ulcers. Current treatment with cholestyramine or colestipol resins	
Presence of any disease (including malignancies) with a life expectancy of <5 years	Presence of any disease (including malignancies) with a life expectancy of <5 years	Presence of any disease outside the cardiovascular and renal disease area, such as but not limited to malignancy, with a life expectancy of less than 2 years based on investigator’s clinical judgement

Women of childbearing potential not willing to maintain reliable contraception throughout the study and for 7 days after study drug discontinuation or women who are pregnant or breastfeeding	Women of childbearing potential not willing to use a medically accepted method of contraception that is considered reliable in the investigator's judgement, from the time of signing the informed consent throughout the study and 4 weeks thereafter. Or those who have a positive pregnancy test at enrolment or randomisation or those who are breastfeeding
	Involvement in the planning and/or conduct of the study
	Previous randomisation in the present study
Participation in any current HF clinical trial	Participation in another clinical study with a IP in the last month prior to enrolment
History of noncompliance to medical regimens and patients who are considered potentially unreliable	In the investigator's opinion, inability of the patient to understand and/or comply with study medications, procedures and/or follow-up Or any conditions that may render the patient unable to complete the study

Outcomes of interest

Efficacy outcomes

The primary outcome in ATMOSPHERE and PARADIGM-HF trials was a composite of cardiovascular death or a first hospitalisation for heart failure.[38,135] Secondary outcomes included all-cause death and change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) – clinical summary score (CSS) from baseline to 12 months in ATMOSPHERE and 8 months in PARADIGM-HF. The KCCQ is scored from 0 to 100 with higher scores indicating better quality of life.[143] Heart failure hospitalisation, cardiovascular and all-cause deaths were adjudicated by the same clinical endpoint committee in both trials according to prespecified criteria.

The primary outcome in DAPA-HF was a composite of cardiovascular death or worsening HF defined as a first hospitalisation for HF or an urgent visit for HF requiring intravenous therapy.[40] In DAPA-HF, quality of life was measured by comparing change in the KCCQ - total symptom score (TSS) between baseline and 8 months. A composite of total HF hospitalisations and cardiovascular death was also measured in DAPA-HF.

Additional prespecified efficacy outcomes are detailed in Table 2-2.

In this thesis, the efficacy outcomes examined in chapters 3 to 8 vary slightly from each other and I have described them individually in the respective chapters.

Table 2-2 Efficacy outcomes examined in each trial

ATMOSPHERE	PARADIGM-HF	DAPA-HF
Primary composite outcome		
Cardiovascular death First hospitalisation for worsening heart failure	Cardiovascular death First hospitalisation for worsening heart failure	Hospitalisation or an urgent visit for heart failure Hospitalisation for heart failure Urgent heart failure visit Cardiovascular death
Secondary and other prespecified exploratory outcomes		
Death from cardiovascular causes, hospitalisation for heart failure, nonfatal myocardial infarction, nonfatal stroke or resuscitated cardiac arrest.		Death from cardiovascular causes or hospitalisation for heart failure,
		Total no. of hospitalisations for heart failure and cardiovascular deaths
Fatal or nonfatal stroke		
Change in KCCQ clinical summary score at 12 months	Change in KCCQ clinical summary score at 8 months	Change in KCCQ total symptom score at 8 months
First resuscitated cardiac arrest	New-onset atrial fibrillation	
Decline in renal function: 1) end stage renal disease or 2) a doubling of baseline serum creatinine to a value greater than the upper limit of normal as determined by 2 central laboratory measurements separated by >30 days.	Decline in renal function: 1) end-stage renal disease or 2) a decrease in eGFR of at least 50% or a decrease of >30 ml/min/1.73m^2 from randomisation to less than 60 ml/min/1.73m^2	Decline in renal function: 1) a sustained decline in eGFR of 50% or greater 2) end stage renal disease (ESRD) - defined as a sustained (≥28 day) eGFR of <15 ml/min/1.73m^2, sustained dialysis or renal transplantation 3) renal death.
Death from any cause	Death from any cause	Death from any cause

Safety outcomes

The safety outcomes examined in each trial are detailed in Table 2-3.

In this thesis, the safety outcomes examined in chapters 3 to 8 vary slightly from each other and I have described them individually in the respective chapters

Table 2-3 Safety outcomes examined in each trial

ATMOSPHERE	PARADIGM-HF	DAPA-HF
		Discontinuation due to adverse event
Hypotension Symptomatic hypotension Symptomatic hypotension with SBP <90 mmHg	Hypotension Symptomatic hypotension Symptomatic hypotension with SBP <90 mmHg	Volume depletion
Renal impairment Investigator reported renal impairment Serum creatinine ≥2.5 mg/dl ≥3.0 mg/dl	Elevated serum creatinine ≥2.5 mg/dl ≥3.0 mg/dl	Renal adverse event
Hyperkalaemia Investigator reported hyperkalaemia Serum potassium >5.5 mmol/litre >6.0 mmol/litre	Elevated serum potassium >5.5 mmol/litre >6.0 mmol/litre	
Cough	Cough Angioedema No treatment or use of antihistamines only Use of catecholamines or glucocorticoids without hospitalisation Hospitalisation without airway compromise Airway compromise	
		Fracture Amputation Major hypoglycaemia Diabetic ketoacidosis Fournier's gangrene

Statistical analysis

Data were analysed in several different ways in keeping with the themes of each of the chapters in this thesis. All analyses were conducted using Stata (College station, TX, USA).

Summary statistics

Normally distributed continuous data have been presented as mean ± standard deviation, skewed continuous data as median (quartile 1, quartile 3) and categorical data as number (proportions). Different tests of hypothesis to test for differences and trends as appropriate were employed in each chapter. Students t-test was used to compare means between 2 subgroups and one-way analysis of variance (ANOVA) was used for more than 2 subgroups. Mann-Whitney U test was used to compare medians between 2 subgroups and Kruskal-Wallis test for comparison of means between 2 or more subgroups. Chi square test was used to compare proportions. In chapters 3, 7 & 8 where the groups analysed are ordinal in nature, a nonparametric Wilcoxon-type rank sum test was carried out for the continuous variables.[144]

Survival analysis

Survival analysis is a form of statistical analysis where the outcome of interest is the time till when an event occurs.[145] An event might be death, hospitalisation, recovery or any other event of interest. An important concept in survival analysis is censoring where, if during the period of observation, an individual does not have the event of interest, they are described as being censored. Among the different types of censoring methods, right censoring is the most used in research practices and this what I employed for analysis in this thesis and is the only one which will be discussed here. Right censoring (referred to as simply "censoring" from this point on) occurs when the event of interest, from the time the individual (considered as "patient" from this point forward) enters the period of observation (randomisation for the purposes of analysis in this thesis), does not occur till the end of the observation period. As mentioned earlier, this could be simply because there was no event during that time, or it also could be due to other reasons such as losing the patient to follow-up or the occurrence of a competing event (which is discussed in greater length

subsequently).[146] Therefore, one of the drawbacks of survival analysis is that, the relationship of predictors and risk of an outcome can only be assumed for the period of observation as the event can occur even after censoring has occurred.

Another thing to keep in mind about survival analysis is that time refers to the period of observation that the individual is under, and it does not refer to any specific calendar date. Therefore, for different individuals, it is very common for entry dates to differ.

Analysis of time to event data may be non-parametric, parametric or semi-parametric.[145,147] In this analysis I have only analysed the data according to the non-parametric and semi-parametric models which are discussed in greater detail below.

Survival function

The survival function *S(t)* is the probability of surviving beyond time *t* and this is represented by the following when no event times are censored:

$$S(t) = P(T > t) = 1 - F(t)$$

The Kaplan-Meier estimator is a commonly used non-parametric estimator of the survival function in studies. Several studies also choose to use the Kaplan Meier (KM) curves to represent the failure instead of the survival function.

This is also what I have used to estimate the failure function in the analysis in this thesis. However, competing risk regression has also been more extensively employed to estimate and compare risks of outcomes in this thesis and I will be discussing it in later sections and how cumulative incidence function is instead used to represent the failure function in such cases.

Cox proportional hazards model

Cox regression is a semi-parametric method to estimate the hazard function in survival data represented by the following:

$$h_i(t) = h_{0i}(t)\exp\left(\beta_1 x_1 + \cdots + \beta_k x_k\right)$$

where t is the survival time, h(t) is the hazard function determined by the set of covariates (x_1, …, x_k), the coefficients ($ß_1$, …., $ß_k$) measure the effect size of the covariates.

Cox regression is known as a semi-parametric model because the baseline hazard involves time but none of the explanatory variables allowing the subsequent hazard modelling to be more flexible than parametric models for survival analysis. While the survival function is only useful in assessing the survival of the factor under observation, the Cox proportional hazards model allows simultaneous assessment of the effect of several risk factors on survival time, and it also allows for hazard estimation of continuous variables. A key assumption that needs to be met in the Cox model is the proportional hazards assumption which states that the hazard for each of the groups of observations being analysed should be proportional and cannot cross each other at any point of time.

Cumulative incidence function

In the presence of competing risks, the survival function does not give an accurate picture of the survival probability of the event being analysed. In such cases, the cumulative incidence function gives the proportion of patients at a given time who have died from any cause accounting for the fact that the patients could have died from other causes.

Competing risks regression

As mentioned earlier, one of the reasons that a patient does not experience an event before censoring occurs may be due to the presence of competing risks. A competing risk is the occurrence of an event that either hampers the observation of an event of interest or, modifies the chance of that event from occurring.

In conventional survival analysis, the risk set decreases each time there is an event from another cause – censoring. In competing risks regression, the subdistribution hazard considers that subjects dying from another cause remain in the risk set and are therefore given a censoring time that is larger than all event times.[148]

This is especially a problem when the distribution of the competing risk is unequal between groups being compared.

This essentially means that in the event of an occurrence of one incident, the recording of another may fail. An example that is common in HF population studies is the failure to estimate the risk of a subsequent HF hospitalisation in a patient who has died before a hospitalisation occurred.

Conventional survival function estimation and cox regression fail to take such events into consideration. As a result, a few ways to do this have been formulated. I have analysed competing risks in this thesis (chapters 4, 6, 7 & 8) using the Fine Grey model.[149]

Recurrent event analysis

There is a general view more recently that the analysis of recurrent non-fatal along with fatal events may offer a better representation of the burden of chronic disease especially HF which is more often than not plagued with recurrent hospitalisations.[150,151] More recently, the analysis of composites of recurrent hospitalisations and mortality is becoming more common in HF clinical trials. Recurrent events are analysed using a variety of methods such as negative binomial regression which uses count data and other which use time to event data such as Wei, Lin and Weissfeld (WLW), Anderson Gill (AG), Lin, Wei, Ying and Yang (LWYY) and the joint frailty model. With respect to clinical trials, there is no universally accepted method which is thought to be ideal. Each of the methods carry their own bias, overall, the inference that has to be made from the results is similar. The LWYY method is based on a gap-time approach considering the time since a previous event to account for the dependency of within-subject events and has proved to be popular in comparing treatments and their effects on recurrent events in recent clinical trials.[152,153]

The LWYY method was used to compare recurrent events in DAPA-HF and I have used the same in chapters 3 and 5 to study the composite outcome of total HF hospitalisations and cardiovascular death. I have also analysed recurrent hospitalisations by calculation of the incidence and incidence rate ratio using negative binomial (NB) regression. NB regression is a modified form of Poisson regression. It is used because a Poisson model assumes that the variance of the

dependent variable will be the same as its mean. Often in recurrent event analysis data, this assumption does not hold. The NB distribution therefore allows for analysis of over-dispersed count data.[154,155]

In chapters 4 & 8, I have analysed recurrent HF, cardiovascular, non-cardiovascular and all-cause hospitalisations. Additionally, the rate of hospitalisation is calculated by dividing the total number of hospitalisations by the total number of follow-up time in each group.

Logistic regression

Binomial logistic regression is a specific type of a generalised linear model and used to analyse the probability of an outcome which is binary in nature. The output that we get from this regression is the Odds Ratio (OR). In logistic regression, the outcome of interest for this analysis was the 5-point increase or decrease in the KCCQ – CSS from baseline to follow-up which has been done in chapters 8. ORs are also reported in the analysis of adverse events in chapter 8.

Mixed models

Mixed models are an extension of simple linear models to allow for both fixed and random effects in the same model. Repeated measures mixed effects model allows for longitudinal analysis of measures recorded at different points of time. It is especially useful for longitudinal analyses. It reduces bias by avoiding model misspecification and by its unbiasedness for data completely or at random.

This method is employed in chapters 3 & 5 to study the difference of effect between dapagliflozin and placebo on change in SBP, serum creatinine and serum potassium during follow-up.

Missing data

In population studies it is not unusual for certain aspects of a patient to be missing either at baseline or during follow-up. While most of missing data might be due to problems during follow-up, a considerable proportion of missingness at baseline is also possible. Missingness of data can occur due to a variety of reasons and are commonly categorised as being any one of the following:[156]

1. Missing at Random (MAR): occurs in cases when any systematic difference between the missing values and observed values can be explained by differences in the observed data.

2. Missing Completely at Random (MCAR): occurs when there are no systematic differences between the missing values and the observed values.

3. Missing Not at Random (MNAR): Occurs even when after the observed data are considered, systematic differences remain between the missing values and the observed values.

Different sets of covariates have been used in different chapters which will be discussed in greater detail in each of the chapters but the details of the missingness have been provided in Table 2-4.

Table 2-4 Missingness of variables used for adjustment in chapters 3-8 in this thesis

	ATMOSPHERE & PARADIGM-HF		DAPA-HF	
Covariate	**Missing/Total**	**% missing**	**Missing/Total**	**% missing**
randomised treatment	-	-	-	-
region	-	-	-	-
sex	-	-	-	-
age	-	-	-	-
baseline heart rate	2/15415	0.01	n/a	n/a
baseline SBP	2/15415	0.01	-	-
baseline BMI	29/15415	0.19	n/a	n/a
baseline NT-proBNP	678/15415	4.40	2/4744	0.04
baseline NYHA	13/15415	0.08	-	-
previous HF hospitalisation	-	-	-	-
baseline eGFR	2/15415	0.01	2/4744	0.04
HF duration	4/15415	0.03	n/a	n/a
aetiology of HF	-	-	n/a	n/a
smoking status	n/a	n/a	-	-
beta-blocker	n/a	n/a	-	-
MRA	n/a	n/a	-	-
per capita income	-	-	n/a	n/a
hospital bed density	334/15216	2.20	n/a	n/a
education index	-	-	n/a	n/a
health worker density	119/15216	0.78	n/a	n/a

SBP – systolic blood pressure, BMI – body mass index, NT-proBNP – N terminal-pro B-type natriuretic peptide, NYHA – New York heart association, HF – heart failure, eGFR – estimated glomerular filtration rate, MRA – mineralocorticoid antagonist
"n/a" variable not in final adjustment model.

In chapters 3-6, 8, “complete-case” analysis was performed as missingness (especially NT-proBNP) was MCAR. Complete case analysis means that only those cases without any missing variables are analysed. This can be done when the data is MCAR which was the case especially for NT-proBNP and number of missing values is small. Complete case analysis in the case of MCAR data, although may be associated with the loss of some power, is not associated with significant bias and is a well-accepted method of dealing with missing data in such cases.

In the case of the additional covariates in chapter 7, I used the missing indicator method to deal with missing hospital bed density and health worker density values. Here the data was MNAR and the missing indicator method is a well-accepted method to deal with such types of missing data and to preserve data without introducing significant bias.[157]

Chapter 3. Heart failure and left ventricular ejection fraction: association with clinical outcomes and effect on drug therapy

This chapter has been published as:

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LVEF is the most used measure of cardiac function. It also helps to diagnose HF, helps to distinguish between patients with HFrEF, HFpEF and more recently HFmrEF.[4,7] In addition, it is a well-recognised predictor of outcomes in HFrEF and in my systemic review in Chapter 1, LVEF was a significant predictor of outcomes in 61% of the final models examined. [87,89,90,97,99–101,106–110]

In this chapter I have compared outcomes in patients with HFrEF according to different levels of LVEF, both as continuous and categorical variables in a contemporary clinical trial dataset. I have also discussed if LVEF at baseline modifies the effects of the most recent pharmacological breakthrough in HFrEF, the SGLT-2 inhibitor dapagliflozin, overall and in participants with and without diabetes separately.

Methods

The trial population has been described in detail in Chapter 2.

Population analysed

The entire population in DAPA-HF who had an LVEF measured at baseline were included in this analysis.[40,140]

In DAPA-HF, LVEF was required to have been measured within 12 months of enrolment, by echocardiography, radionuclide ventriculography, contrast angiography or cardiac magnetic resonance imaging. Patients without a LVEF measurement within the previous 12 months were required to have LVEF measured at the time of enrolment.[140]

Outcomes

For this population, as outlined in Chapter 2, I have analysed the primary composite outcome of a worsening HF event (an unplanned hospitalisation for HF or an urgent visit for HF requiring intravenous therapy) or cardiovascular death and its components. Additional secondary endpoints analysed are the composite of cardiovascular death or hospitalisation for HF, its components, a composite of the total number of hospitalisations for HF (first and repeats) and cardiovascular death, the change from baseline to 8 months in the TSS of the KCCQ and all-cause death.[143]

Safety outcomes examined include serious adverse events, adverse events leading to treatment discontinuation and other adverse events of special interest (adverse events related to volume depletion, renal adverse events, bone fractures, amputations, major hypoglycaemic episodes) and laboratory findings of note.

Statistical analysis

For this analysis, I divided the patients in DAPA-HF into 4 categories, similar to those used in prior analyses and reflective of clinical practice, namely: (I)<26%, (ii) 26% - 30%, (iii) 31% - 35% ad (iv) >35%.[4,158,159] Baseline characteristics are reported for each LVEF category as discussed in Chapter 2. A nonparametric Wilkinson type rank-sum test was used to report the p-value for trend for the continuous variables.[144]

I used Cox regression to report hazard ratio (HR) per 5-point decrease in baseline LVEF for the primary outcome and its components, the composite outcome of cardiovascular death, total hospitalisation for HF and all-cause death. The model was adjusted for randomised treatment and previous HF hospitalisation (except for all-cause death as per trial pre-specifications). The relationship between LVEF as a continuous variable and the risk of the primary composite outcomes,

its components and all-cause death were examined in restricted cubic spline analyses.

The effect of dapagliflozin compared to placebo, on each outcome across the different LVEF categories was also examined. Event rates per 100 person-years and HRs calculated using Cox regression and adjusted for previous HF hospitalisation (except for all-cause death) are also reported. The likelihood ratio test was used to test for treatment effects across the different LVEF categories. LVEF modelled as a fractional polynomial to assess its interaction as a continuous variable with treatment is displayed graphically using the *mfpi* function in Stata.[160] The interaction between LVEF and treatment on change in KCCQ-TSS at 8 months was tested in a linear regression model with interaction between LVEF and treatment tested for using the Wald method. All survival models were stratified by diabetes status as per DAPA-HF protocol.

Logistic regression was used to compare the occurrence of the safety outcomes by treatment per LVEF category and a likelihood ratio test was used to assess for treatment effects.

All efficacy and safety outcomes mentioned here were also analysed by LVEF category and with LVEF as a continuous variable according to diabetes status at baseline.

Results

LVEF ranged from 2% to 40% (although one patient had a LVEF of 45%). The mean and median LVEF were 31.1 (±6.8) % and 32 (26 – 37) %, respectively. There were 1143 patients with a LVEF <26%, 1018 patients with a LVEF between 26% and 30%, 1187 with a LVEF between 31% and 35% and 1396 patients had a LVEF >35%.

Baseline characteristics

As shown in Table 3-1, patients with a lower LVEF were younger (mean 64 years in the lowest versus 68 years in the highest LVEF category), more likely to be male, less likely to be from Europe or of white race, compared to patients with a higher LVEF. Fewer patients with a lower LVEF had hypertension, diabetes, a previous MI or AF. When patients with and without diabetes were examined separately, those with diabetes more often had a history of hypertension and MI.

Table 3-1 Baseline characteristics

	LVEF category 1 n=1143 (<26%)	**LVEF category 2** n=1018 (26% – 30%)	**LVEF category 3** n=1187 (31% – 35%)	**LVEF category 4** n=1396 (>35%)	**p-value for trend**
LVEF (%) - mean ± SD	22.4 ± 3.7	28.8 ± 1.4	33.7 ± 1.4	38.4 ± 1.4	<0.001
Age (years.)	64.2 ± 11.3	66.0 ± 10.8	66.8 ± 10.6	68.1 ± 10.5	<0.001
Females – no. (%)	230 (20.1)	215 (21.1)	277 (23.3)	387 (27.7)	<0.001
Region – no. (%)					<0.001
North America	241 (21.1)	140 (13.8)	171 (14.4)	125 (9.0)	
Latin America	213 (18.6)	218 (21.4)	202 (17.0)	184 (13.2)	
Europe	406 (35.5)	398 (39.1)	556 (46.8)	794 (56.9)	
Asia/Pacific	283 (24.8)	262 (25.7)	258 (21.7)	293 (21.0)	
Race – no. (%)					<0.001
White	728 (63.7)	695 (68.3)	857 (72.2)	1053 (75.4)	
Black	104 (9.1)	43 (4.2)	48 (4.0)	31 (2.2)	
Asian	288 (25.2)	266 (26.1)	263 (22.2)	299 (21.4)	
Other	23 (2.0)	14 (1.4)	19 (1.6)	13 (0.9)	
SBP (mmHg)	116.5 ± 15.1	120.0 ± 15.3	123.4 ± 16.7	126.1 ± 16.2	<0.001
DBP (mmHg)	71.9 ± 10.1	72.9 ± 10.7	74.0 ± 10.7	74.8 ± 10.2	<0.001
Heart rate (bpm)	72.6 ± 12.4	71.5 ± 11.6	70.9 ± 11.5	71.0 ± 11.3	0.001
BMI* (kg/m^2)	27.7 ± 6.4	27.8 ± 5.8	28.4 ± 5.9	28.6 ± 5.8	<0.001
Comorbidities – no. (%)					
Hypertension	720 (63.0)	743 (73.0)	907 (76.4)	1153 (82.6)	<0.001
Diabetes	453 (39.6)	432 (42.4)	485 (40.9)	613 (43.9)	0.062
Atrial fibrillation	384 (33.6)	352 (34.6)	462 (38.9)	620 (44.4)	<0.001
Myocardial infarction	455 (39.8)	485 (47.6)	538 (45.3)	614 (44.0)	0.123
Stroke	103 (9.0)	104 (10.2)	107 (9.0)	152 (10.9)	0.210
COPD	137 (12.0)	111 (10.9)	143 (12.1)	194 (13.9)	0.088

All values are reported as mean ± standard deviation except where indicated.
*Median (interquartile range)
SBP – systolic blood pressure; DBP – diastolic blood pressure; BMI – body mass index; COPD – chronic obstructive pulmonary disease

Heart failure characteristics

A higher proportion of patients in the lowest LVEF category had a non-ischaemic aetiology and more had a previous hospitalisation for HF [Table 3-2]. Conversely, there was no statistically significant difference in median KCCQ-TSS score, or in the proportion of patients in NYHA class II versus III/IV, across the LVEF categories. Patients with diabetes more often had an ischaemic aetiology for HF and a worse NYHA class.

Table 3-2 Heart failure characteristics

	LVEF category 1 n=1143 (<26%)	**LVEF category 2** n=1018 (26% – 30%)	**LVEF category 3** n=1187 (31% – 35%)	**LVEF category 4** n=1396 (>35%)	**p-value for trend**
HF aetiology					
Ischaemic	548 (47.9)	575 (56.5)	703 (59.2)	848 (60.7)	
Non-Ischaemic	493 (43.1)	373 (36.6)	393 (33.1)	428 (30.7)	
Other/Unknown	102 (8.9)	70 (6.9)	91 (7.7)	120 (8.6)	
NYHA class					0.995
II	754 (66.0)	712 (69.9)	805 (67.8)	932 (66.8)	
III/IV	389 (34.0)	306 (30.1)	382 (32.2)	464 (33.2)	
KCCQ total summary score*	77 (59, 92)	79 (58, 94)	79 (58, 92)	76 (57, 92)	0.265
Previous HF hospitalisation	577 (50.5)	486 (47.7)	548 (46.2)	640 (45.8)	0.016

All values are reported as number (percentage) except where indicated.
*Median (interquartile range)
HF – heart failure; NYHA – New York heart association; KCCQ – Kansas City cardiomyopathy questionnaire

Investigations

Patients with a lower LVEF had a higher NT-proBNP level (median 1827 pg/ml in the lowest versus 1275 pg/ml in the highest LVEF category) and higher creatinine concentration [Table 3-3]. Those with diabetes had a higher NT-proBNP and lower eGFR, compared to participants without diabetes across the range of LVEF.

Table 3-3 Investigations

	LVEF category 1 n=1143 (<26%)	**LVEF category 2** n=1018 (26% – 30%)	**LVEF category 3** n=1187 (31% – 35%)	**LVEF category 4** n=1396 (>35%)	**p-value for trend**
NT-proBNP(pg/ml)	1827 (1055, 3385)	1551 (886, 2806)	1317 (798, 2353)	1275 (790, 2232)	<0.001
eGFR (mL/min/1.73 m^2)- mean ± SD	67.3 ± 19.9	64.8 ± 19.2	65.9 ± 19.7	65.2 ± 18.9	0.062
Creatinine (umol/L) - mean ± SD	105.1 ± 30.5	106.6 ± 31.8	104.3 ± 30.4	102.5 ± 29.2	0.006
Haemoglobin (g/L) - mean ± SD	136.6 ± 15.9	135.7 ± 16.0	135.0 ± 16.2	135.0 ± 16.6	0.005

All values are reported as mean ± standard deviation except where indicated.
*Median (interquartile range)
NT-proBNP – N terminal pro B type natriuretic peptide; eGFR – estimated glomerular fraction.

Baseline therapy

As shown in Table 3-4, a greater proportion of patients with low LVEF were prescribed diuretics. Use of sacubitril/valsartan, an MRA, digoxin, CRT and an ICD increased with decreasing LVEF, whereas the opposite trend was observed with an ACEI or ARB. These patterns were similar in patients with and without diabetes.

Among patients with diabetes at baseline, there was no significant difference in the use of specific glucose-lowering medications and insulin across the LVEF categories.

Table 3-4 Therapy at baseline

	LVEF category 1 n=1143 (<26%)	**LVEF category 2** n=1018 (26% – 30%)	**LVEF category 3** n=1187 (31% – 35%)	**LVEF category 4** n=1396 (>35%)	**p-value for trend**
Diuretic	1100 (96.2)	960 (94.3)	1098 (92.5)	1275 (91.3)	<0.001
Digoxin	265 (23.2)	207 (20.3)	193 (16.3)	222 (15.9)	<0.001
ACEI	590 (51.6)	582 (57.2)	655 (55.2)	834 (59.7)	<0.001
ARB	283 (24.8)	269 (26.4)	329 (27.7)	426 (30.5)	0.001
ARNI	188 (16.4)	118 (11.6)	130 (11.0)	72 (5.2)	<0.001
Any RAS blocker*	1051 (92.0)	958 (94.1)	1109 (93.4)	1324 (94.8)	0.009
Beta-blocker	1100 (96.2)	979 (96.2)	1146 (96.5)	1333 (95.5)	0.403
MRA	855 (74.8)	755 (74.2)	841 (70.9)	919 (65.8)	<0.001
Ivabradine	66 (5.8)	51 (5.0)	61 (5.1)	50 (3.6)	0.014
PCI	346 (30.3)	374 (36.7)	404 (34.0)	500 (35.8)	0.020
CABG	178 (15.6)	177 (17.4)	197 (16.6)	247 (17.7)	0.231
ICD	358 (31.3)	250 (24.6)	216 (18.2)	129 (9.2)	<0.001
CRT	116 (10.1)	86 (8.4)	90 (7.6)	62 (4.4)	<0.001
Diabetes medications#					
Biguanide	230 (50.8)	221 (51.2)	261 (53.8)	304 (50.0)	0.828
DPP-4 inhibitor	68 (15.0)	67 (15.5)	76 (15.7)	99 (16.2)	0.614
GLP-1 analogues	7 (1.6)	5 (1.2)	4 (0.8)	5 (0.8)	0.225
Sulfonylurea	93 (20.5)	105 (24.3)	107 (22.1)	133 (21.7)	0.919
Insulin	112 (24.7)	122 (28.2)	144 (29.7)	162 (26.4)	0.554

All values are shown as number (%).
ACEI – angiotensin-converting enzyme inhibitor, ARB – angiotensin receptor blocker, ARNI – angiotensin receptor neprilysin inhibitor, RAS – renin angiotensin system, MRA – mineralocorticoid receptor antagonist, PCI – primary coronary intervention, CABG – coronary artery bypass graft, CRT – cardiac resynchronization therapy, ICD – implantable cardioverter-defibrillator, DPP - Dipeptidyl peptidase, GLP - glucagon-like peptide.
*Any patient on ACEI/ARB/ARNI.
#Only in patients with a medical history of diabetes (1983)

Clinical outcomes

Relationship between baseline LVEF and hospitalisation and mortality outcomes

As illustrated in Figure 3-1, the risk of the clinical outcomes of interest increased as LVEF decreased. Table 3-5 shows that each 5-point decrease in LVEF was associated with an 18% higher risk of the primary outcome (HR 1.18; 95% CI 1.13–1.24) in the overall cohort. The corresponding HR for a 5-point decrease in LVEF in participants with diabetes was 1.20 (95% CI 1.12–1.27) compared to 1.17 (1.10–1.26) in patients without diabetes.

Median time from measurement of LVEF to randomisation was 48 days (Q1, Q3- 14, 130). 3962 (84%) patients had their LVEF measured within the 6 months prior to randomisation. The incremental increase in risk of clinical outcomes with decreasing LVEF was also consistent in both those who had LVEF measured ≤6 months prior to randomisation and in those who had LVEF measured >6 months prior to randomisation [Table 3-5].

In the overall population, the increment in risk of cardiovascular death was 20% per 5-point decrease in LVEF (HR 1.20;95% CI 1.13–1.28) with a similar increment in risk for an episode of worsening HF (HR 1.20;1.14–1.27). The HR for all-cause death was 1.13 (1.07–1.20). The increase in HR per 5-point decrease in LVEF for each of the latter three outcomes was similar in participants with and without diabetes [Table 3-5].

The rate of the primary outcome in placebo-treated patients in the lowest LVEF category was 20.7 (95% CI 17.7-24.1) per 100 person-years, compared with 11.9(9.9-14.3) per 100 person-years in patients in the highest LVEF category [Table 3-6]. The corresponding rates of the primary outcome in patients with diabetes in the lowest and highest LVEF categories were 26.8(21.8–33.0) and 14.6(11.5–18.6) per 100 person-years, respectively. In participants without diabetes these rates were 16.1(12.8–20.3) and 9.5(7.1–12.6) per 100 person-years, respectively [Appendix table 3].

Relationship between baseline LVEF and change in KCCQ-TSS

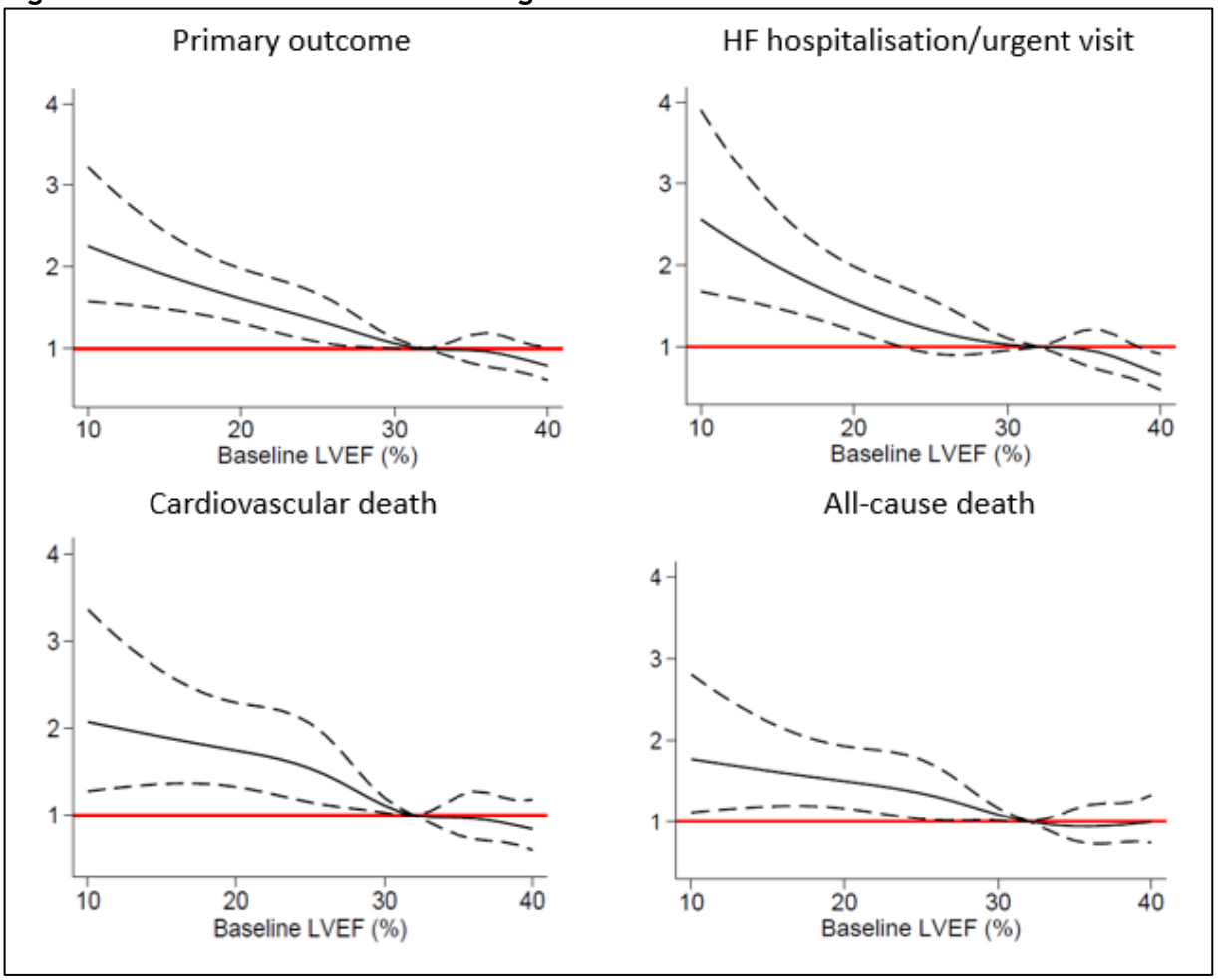
The mean increase (improvement) in KCCQ-TSS with dapagliflozin, compared with placebo, was similar in each of the LVEF categories (p-value for interaction: 0.607) [Table 3-6]. Compared with placebo, more patients treated with dapagliflozin showed a ≥5-point improvement, and fewer demonstrated a ≥5-point deterioration, in each of the LVEF categories analysed. These findings were similar in patients with and without diabetes.

Table 3-5 Change in risk of clinical outcomes per 5-point decrease in baseline left ventricular ejection fraction – overall, by diabetes status and according to the time of LVEF measurement

Overall	No diabetes	Diabetes	LVEF measured ≤6 months before randomisation	LVEF measured >6 months before randomisation
n=4744	n=2605	n=2139	n=3962*	n=779*
Primary outcome				
1.18 (1.13 – 1.24) <0.001	1.17 (1.10 – 1.26) <0.001	1.20 (1.12 – 1.27) <0.001	1.19 (1.13 – 1.25) <0.001	1.14 (1.02 – 1.27) 0.018
Cardiovascular death or HF hospitalisation				
1.18 (1.13 – 1.24) <0.001	1.19 (1.11 – 1.27) <0.001	1.18 (1.11 – 1.26) <0.001	1.18 (1.13 – 1.25) <0.001	1.15 (1.03 – 1.28) 0.015
HF hospitalisation/ urgent visit#				
1.20 (1.14 – 1.27) <.0.001	1.16 (1.06 – 1.26) 0.001	1.24 (1.15 – 1.34) <0.001	1.20 (1.12 – 1.27) <0.001	1.20 (1.05 – 1.37) 0.008
Cardiovascular death				
1.20 (1.13 – 1.28) <0.001	1.20 (1.10– 1.32) <0.001	1.20 (1.11 – 1.31) <0.001	1.22 (1.14 – 1.30) <0.001	1.09 (0.94 – 1.27) 0.234
HF hospitalisation				
1.20 (1.13 – 1.27) <0.001	1.17 (1.07 – 1.28) <0.001	1.22 (1.13 – 1.32) <0.001	1.19 (1.12 – 1.27) <0.001	1.21 (1.06 – 1.39) 0.006
Total HF hosp./cardiovascular death				
1.22 (1.16 – 1.28) <0.001	1.19 (1.10 – 1.28) <0.001	1.24 (1.15 – 1.33) <0.001	1.22 (1.15 – 1.29) <0.001	1.19 (1.05 – 1.35) 0.005
All-cause death				
1.13 (1.07 – 1.20) <0.001	1.15 (1.06 – 1.24) 0.001	1.12 (1.04 – 1.21) 0.004	1.15 (1.08 – 1.22) <0.001	1.03 (0.90 – 1.18) 0.663

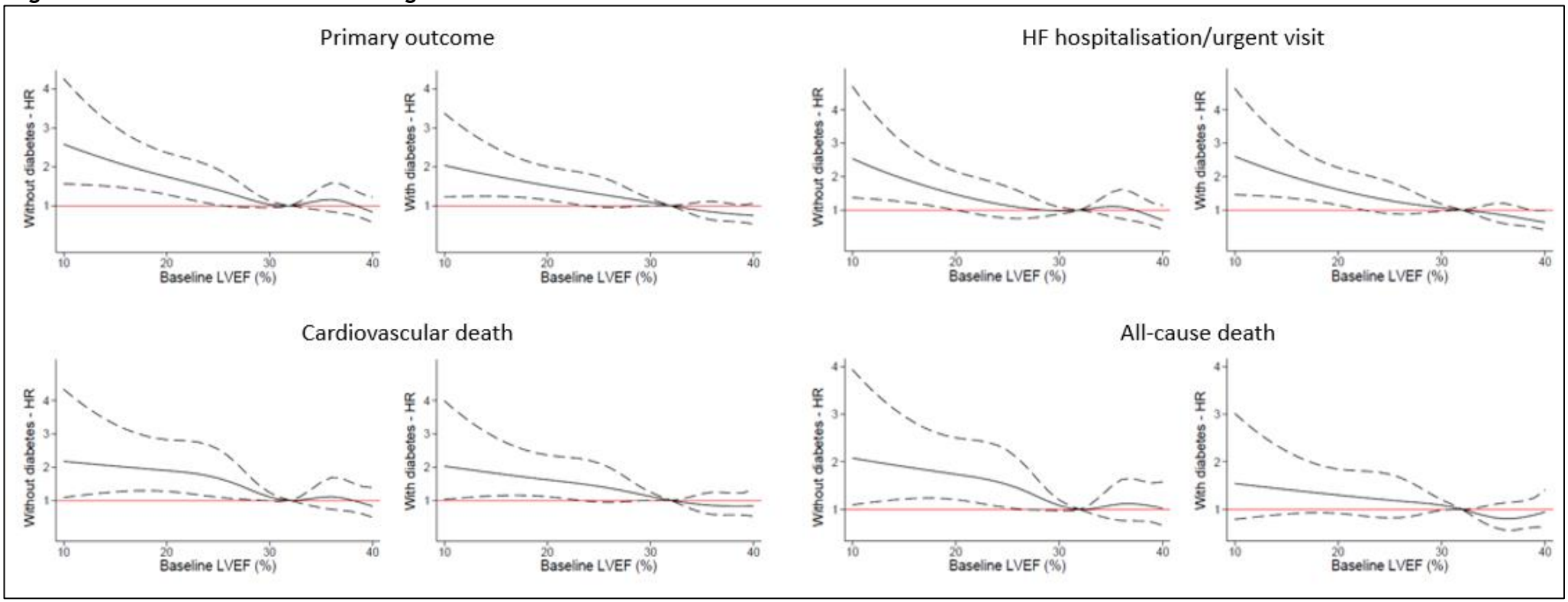
Numbers represent hazard ratio with 95% confidence interval in () for each 5-point increase in LVEF. Rate ratio for total HF hospitalisation/cardiovascular death.
Hazard ratios (and RR) adjusted for randomised treatment, previous heart failure hospitalisation at baseline (except all-cause death) and stratified by diabetes status.
*Date of LVEF measurement was set to missing for 3 patients.
Requiring intravenous therapy.

Figure 3-1 Clinical outcomes according to baseline LVEF



Figures have been restricted to 10-40% LVEF but the results are derived from models based on the entire spectrum of LVEF in DAPA-HF.

Figure 3-2 Clinical outcomes according to baseline LVEF and diabetes status



Figures have been restricted to 10-40% LVEF but the results are derived from models based on the entire spectrum of LVEF in DAPA-HF.

Effect of dapagliflozin, compared with placebo, on hospitalisation and mortality outcomes, according to baseline LVEF

For each of the hospitalisation and mortality outcomes examined, the event rate was lower in patients receiving dapagliflozin, than in those assigned to placebo, across all the LVEF categories [Table 3-6 and Figure 3-4].

The benefit of dapagliflozin over placebo for these outcomes was also consistent in patients with and without diabetes analysed separately, across the range of LVEF studied [Appendix table 3]. Similarly, the beneficial effects of dapagliflozin also remained constant across the range of LVEF regardless of the time of measurement of LVEF [Figure 3-5].

The favourable effect of dapagliflozin on the composite of HF hospitalisation (first and repeat) and cardiovascular death was also consistent across the spectrum of LVEF studied (in the overall cohort, and in participants with and without diabetes analysed separately).

Because the absolute risk of events was highest in patients in the lowest LVEF category, the absolute benefit of dapagliflozin was larger in patients with a lower LVEF. For example, applying the overall relative risk reduction of 26% to patients with a LVEF of <26% yielded an absolute risk reduction of 54 fewer patients with an event per 1000 person-years of follow-up, compared with 31 per 1000 person-years of follow-up in the LVEF >35% category.

Effect of dapagliflozin, compared with placebo, on change in KCCQ-TSS, according to baseline LVEF

The mean increase (improvement) in KCCQ-TSS with dapagliflozin, compared with placebo, was similar in each of the LVEF categories (p-value for interaction: 0.607) [Table 3-6; Figure 3-8]. Compared with placebo, more patients treated with dapagliflozin showed a ≥5-point improvement, and fewer a ≥5-point deterioration, in each of the LVEF categories analysed. These findings were similar in patients with and without diabetes.

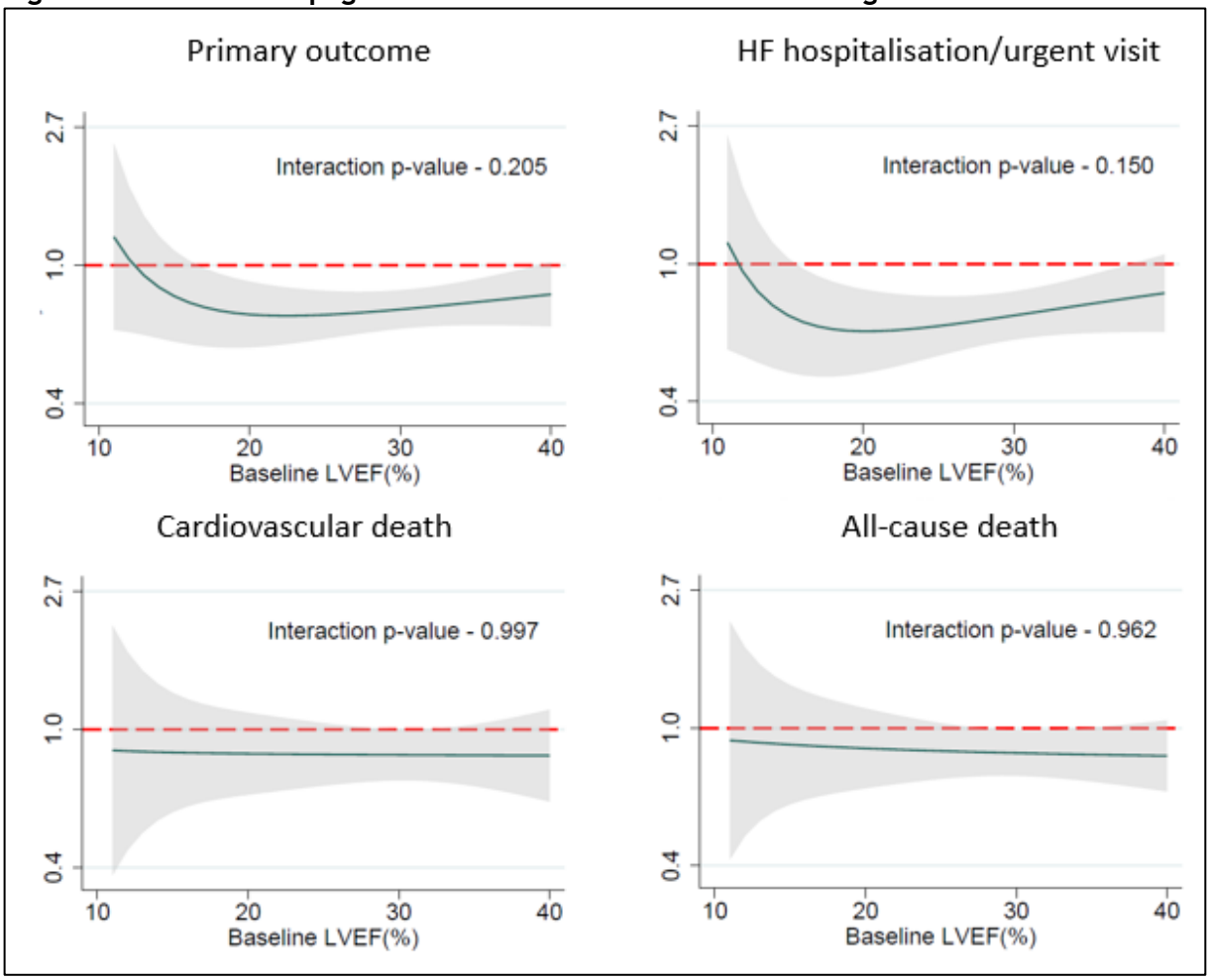
Table 3-6 Clinical outcomes by treatment according to LVEF

	Overall *n=4744*		LVEF category 1 n=1143 (<26%)		LVEF category 2 n=1018 (26% – 30%)		LVEF category 3 n=1187 (31% – 35%)		LVEF category 4 n=1396 (>35%)		p-value for interaction
	Placebo (n=2371)	*Dapagliflozin (n=2373)*	Placebo (n=601)	Dapagliflozin (n=542)	Placebo (n=498)	Dapagliflozin (n=520)	Placebo (n=581)	Dapagliflozin (n=606)	Placebo (n=691)	Dapagliflozin (n=705)	
Primary composite outcome											
Events (%)	*502 (21.2)*	*386 (16.3)*	161 (26.8)	110 (20.3)	114 (22.9)	94 (18.1)	113 (19.5)	84 (13.9)	114 (16.5)	98 (13.9)	
Event rate per 100 pt. yrs.	*15.8(14.5-17.2)*	*11.7(10.6-13.0)*	20.7(17.7-24.1)	15.2(12.7-18.4)	17.4(14.5-20.9)	13.2(10.8-16.2)	14.4(12.0-17.3)	9.9(8.0–12.3)	11.9(9.9-14.3)	9.7(8.0–11.8)	
Unadjusted hazard ratio	*0.74 (0.65 – 0.85) <0.001*		0.75 (0.59 - 0.95)		0.75 (0.57 - 0.98)		0.67 (0.51 – 0.89)		0.83 (0.63 - 1.09)		0.762
HF hospitalisation/ urgent visit*											
Events (%)	*326 (13.7)*	*237 (10.0)*	104 (17.3)	70 (12.9)	80 (16.1)	51 (9.8)	76 (13.1)	51 (8.4)	66 (9.6)	65 (9.2)	
Event rate per 100 pt. yrs.	*10.3(9.2-11.4)*	*7.2(6.3-8.2)*	13.3(11.0-16.2)	9.7(7.7–12.3)	12.2(9.8-15.2)	7.2(5.4–9.4)	9.7(7.7–12.1)	6.0(4.6–7.9)	6.9(5.4–8.8)	6.4(5.0–8.2)	
Unadjusted hazard ratio	*0.70 (0.59 – 0.83) <0.001*		0.74 (0.54 - 1.00)		0.57 (0.40 - 0.81)		0.61 (0.43 – 0.87)		0.95 (0.67 - 1.34)		0. 161
Cardiovascular death											
Events (%)	*273 (11.5)*	*227 (9.6)*	93 (15.5)	69 (12.7)	61 (12.3)	57 (11.0)	59 (10.2)	49 (8.1)	60 (8.7)	52 (7.4)	
Event rate per 100 pt. yrs.	*8.0(7.1-9.0)*	*6.6(5.8-7.5)*	11.0(9.0-13.5)	9.0(7.1–11.4)	8.7(6.7–11.1)	7.7(5.9–10.0)	7.0(5.4–9.1)	5.6(4.2–7.4)	5.9(4.6–7.6)	4.9(3.8–6.5)	
Unadjusted hazard ratio	*0.82 (0.69 – 0.98) 0.030*		0.84 (0.61 - 1.14)		0.88 (0.62 - 1.27)		0.77 (0.53 - 1.13)		0.85 (0.59 - 1.24)		0. 974
Total HF hospitalisation/ cardiovascular death											
Events	*742*	*567*	250	175	178	130	160	125	154	137	
Event rate per 100 pt. yrs.	*21.9(20.4-23.5)*	*16.5(15.2-18.0)*	29.8(26.4-33.8)	23.0(19.8-26.6)	25.3(21.8-29.3)	17.5(14.8-20.8)	19.1(16.4-22.3)	14.3(12.0-17.0)	15.3(13.0-17.9)	13.0(11.0-15.4)	
Unadjusted rate ratio	*0.75 (0.65 – 0.88) <0.001*		0.78 (0.59 - 1.03)		0.68 (0.51 – 0.92)		0.72 (0.53 – 1.00)		0.87 (0.64 – 1.18)		0.702
Mean change in KCCQ-TSS ± SD at 8 months											
Mean change ± SD at 8 months	*3.3 ± 19.2*	*6.1 ± 18.6*	3.2 ± 19.6	6.1 ± 19.8	2.0 ± 18.8	5.9 ± 19.0	3.3 ± 19.7	6.4 ± 17.4	4.3 ± 18.8	6.0 ± 18.6	0.607

Between treatment difference[#]	*2.8 (1.6 – 4.0)*		2.9 (0.4 – 5.5)		3.9 (1.3 – 6.5)		3.1 (0.8 – 5.5)		1.7 (-0.5 – 3.8)		
All-cause death											
Events (%)	*329 (13.9)*	*276 (11.6)*	100 (16.6)	77 (14.2)	72 (14.5)	68 (13.1)	75 (12.9)	59 (9.7)	82 (11.9)	72 (10.2)	
Event rate per 100 pt. yrs.	*9.7(8.7 – 10.8)*	*8.0 (7.1 – 9.0)*	11.8(9.7–14.4)	10.1(8.1–12.6)	10.2(8.1–12.9)	9.1(7.2–11.6)	8.9(7.1–11.2)	6.7(5.2–8.7)	8.1(6.5–10.0)	6.8(5.4–8.6)	
Unadjusted hazard ratio	*0.83 (0.71 – 0.97) 0.022*		0.87 (0.64 - 1.17)		0.89 (0.64 - 1.24)		0.73 (0.52 - 1.03)		0.86 (0.62 - 1.17)		0. 866

Hazard ratio represents comparison of dapagliflozin against placebo with 95% confidence interval in ().
Hazard ratios adjusted for previous heart failure hospitalisation at baseline (except all-cause death) and stratified by diabetes status.
* Requiring intravenous therapy.
#Expressed as difference with 95% confidence interval in () in dapagliflozin compared to placebo.
KCCQ-TSS – Kansas City Cardiomyopathy Questionnaire total symptom score.

Figure 3-3 Effect of dapagliflozin on clinical outcomes according to baseline LVEF



Figures have been restricted to 10-40% LVEF but the results are derived from models based on the entire spectrum of LVEF in DAPA-HF.

Figure 3-4 Effect of randomised treatment on clinical outcomes, according to LVEF

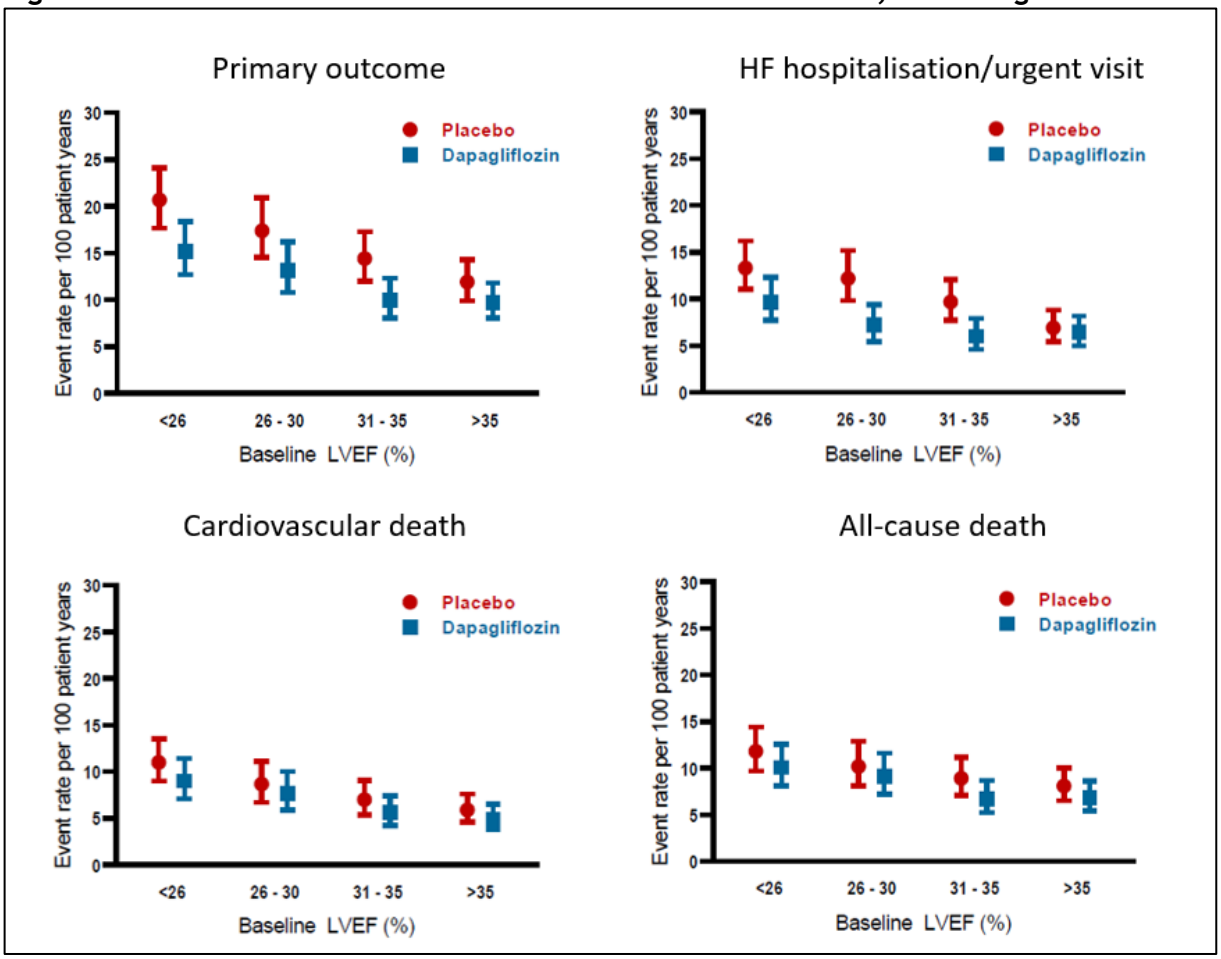
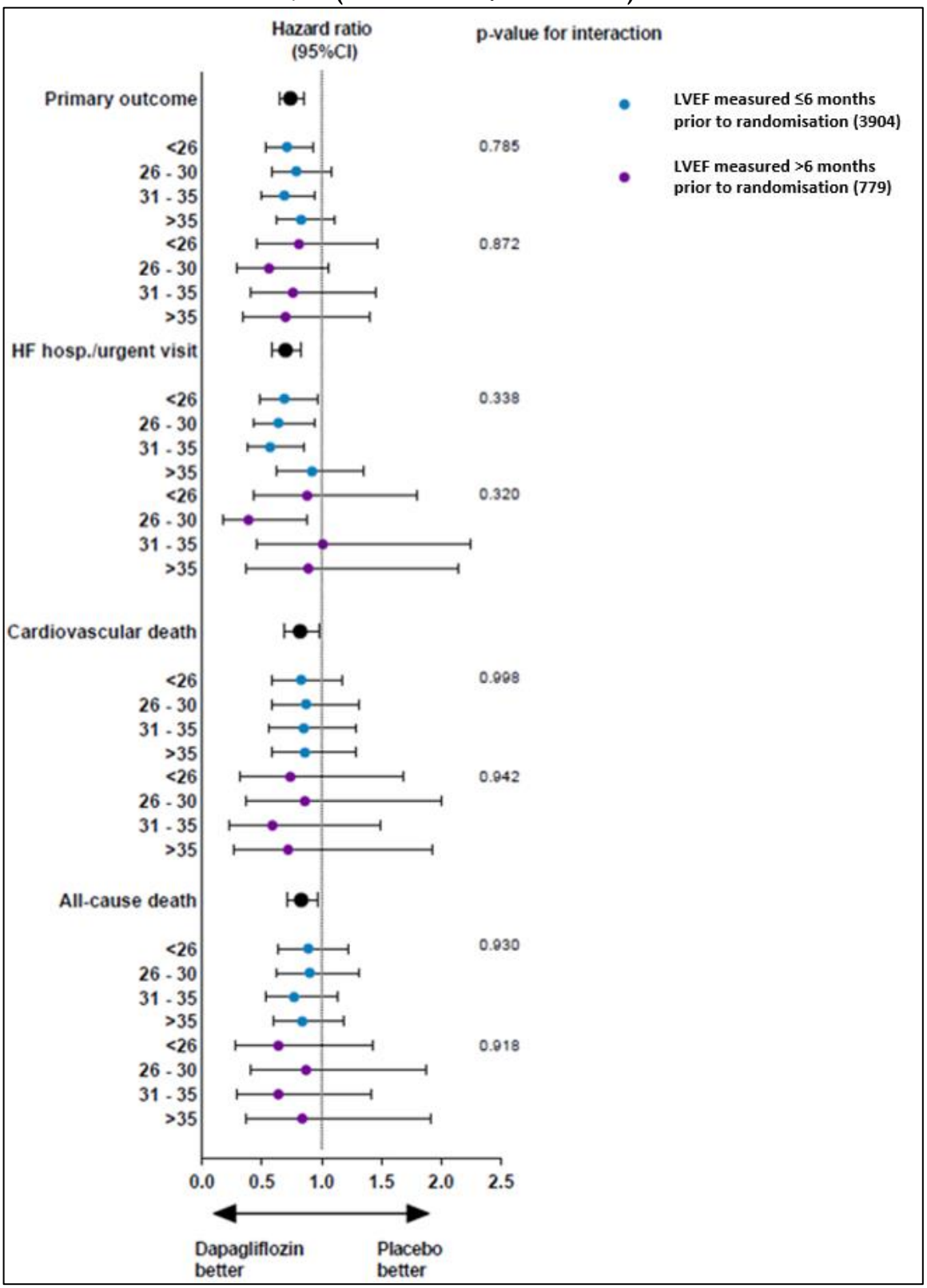
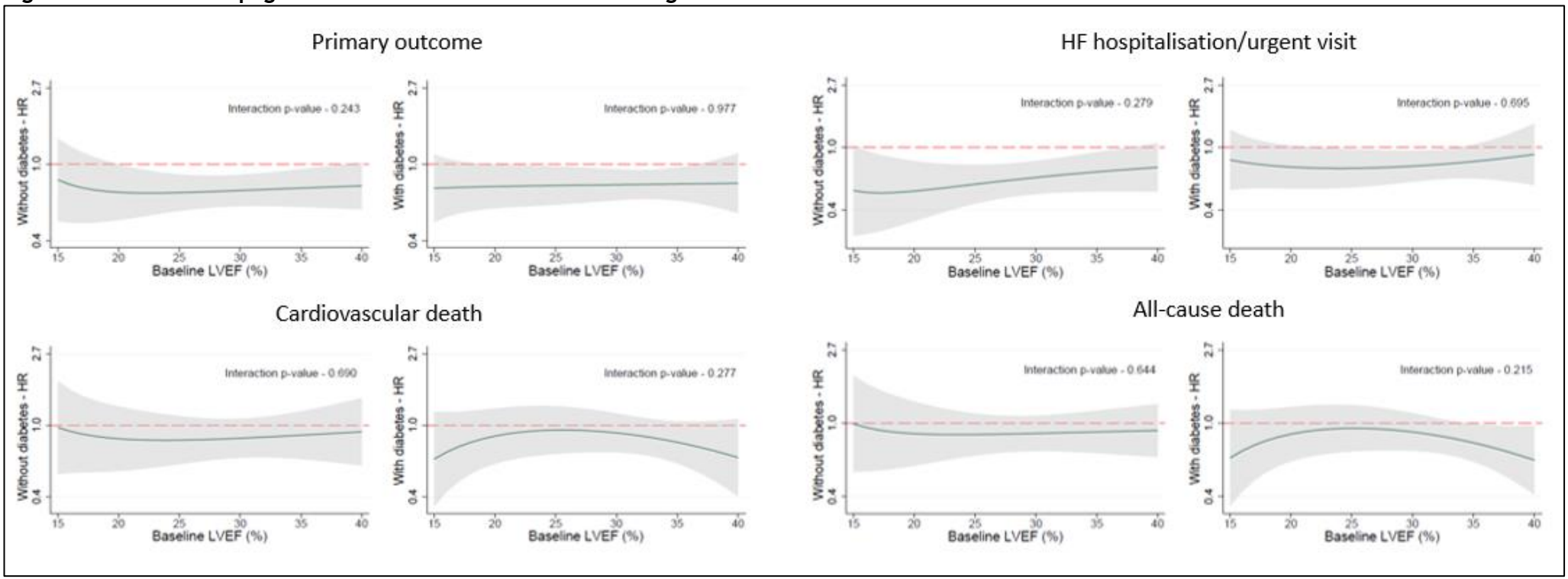


Figure 3-5 Forest plot showing the hazard ratios (95%CI) for the major clinical outcomes in DAPA-HF according to left ventricular ejection fraction (LVEF) and the time of measurement of LVEF (≤6 months vs. > 6 months)



Numbers in y-axis represent LVEF in %.
Data on date of LVEF measurement was missing in 61 patients.

Figure 3-6 Effect of dapagliflozin on clinical outcomes according to baseline LVEF and diabetes status



Figures have been restricted to 10-40% LVEF but the results are derived from models based on the entire spectrum of LVEF in DAPA-HF.

Figure 3-7 Effect of randomised treatment on clinical outcomes, according to LVEF and diabetes status

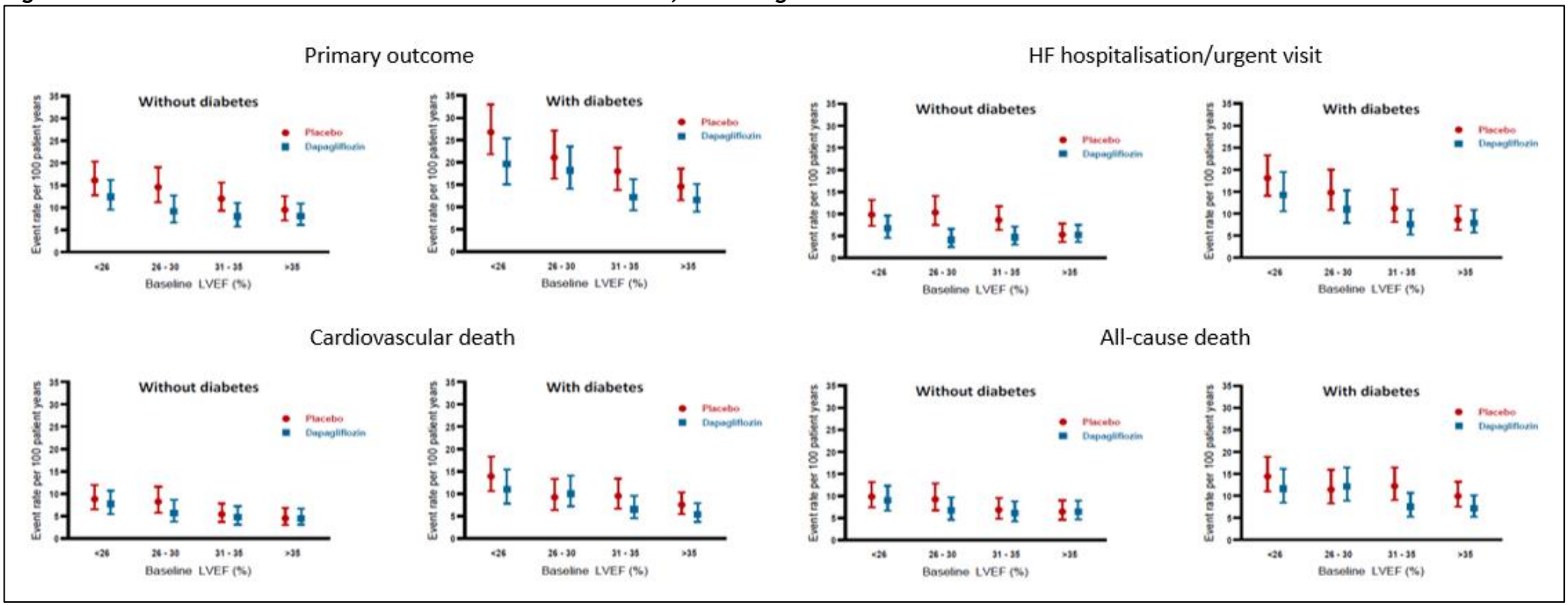
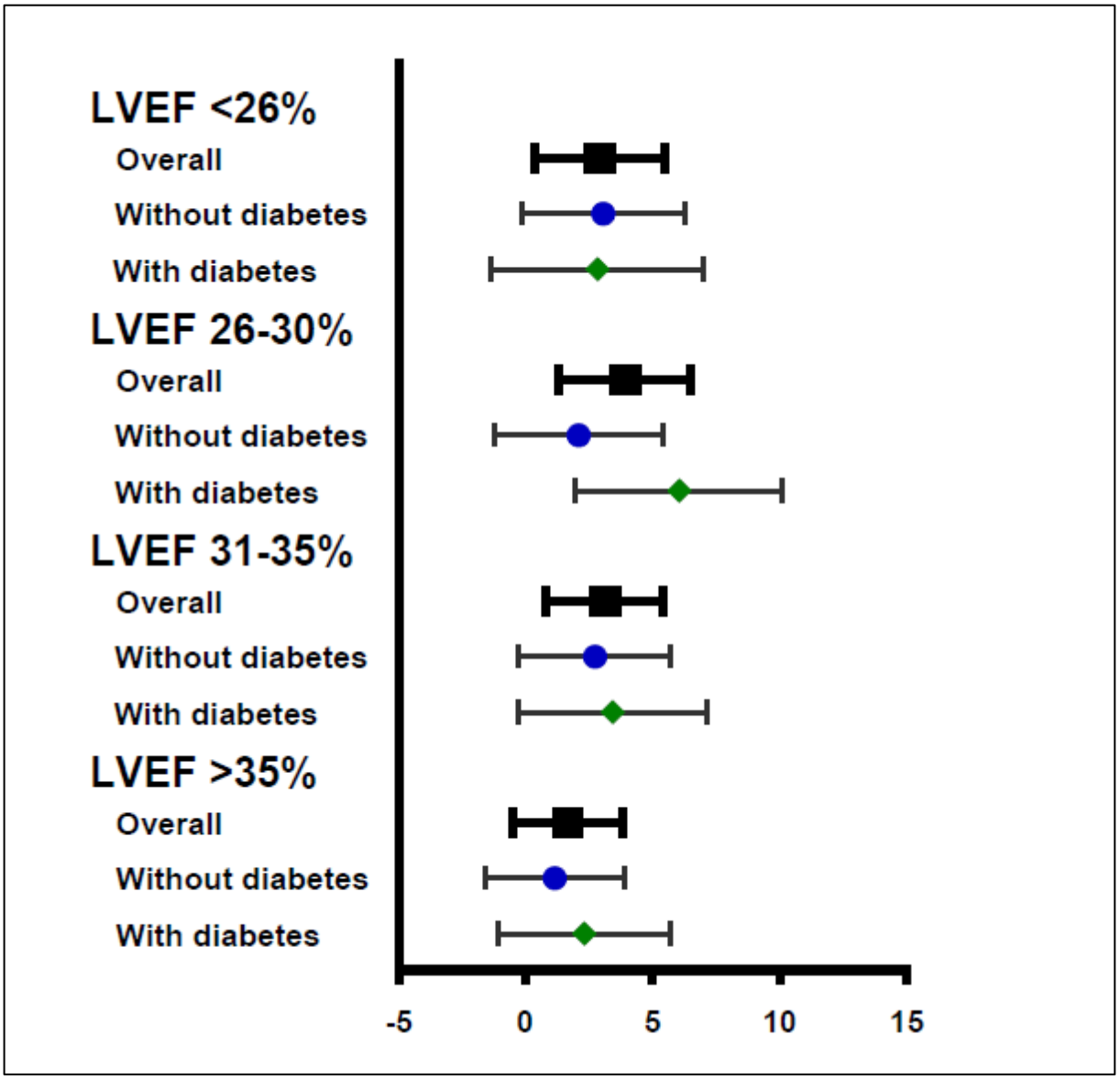


Figure 3-8 Placebo corrected mean change in KCCQ – Total summary score at 8 months according to left ventricular ejection fraction – overall and according to diabetic status



Relationship between baseline LVEF and prespecified safety outcomes

There was no significant difference in the proportion of those on placebo who discontinued study treatment due to any reason across the LVEF categories [Table 3-7]. Similarly, no difference was seen in the proportion of patients on placebo with adverse events due to renal causes, fractures, amputation, or major hypoglycaemic events. However, the proportion of patients with volume depletion was higher in the lower LVEF categories. Fall in systolic blood pressure (SBP) among those on placebo during follow-up was slightly higher in those with LVEF >35% but no such observation was made regarding change in creatinine [Table 3-7].

Effect of dapagliflozin, compared with placebo, on prespecified safety outcomes, according to baseline LVEF

There was no significant difference in the proportion of patient who discontinued for any reason or those who discontinued due to an adverse event between the treatment groups in any of the LVEF categories including due to volume depletion (p-value for interaction:0.548 & 0.544 respectively) [Table 3-7]. Similarly, no difference in the magnitude of change in SBP or creatinine during follow-up was seen between the treatment groups in each LVEF category (p-value for interaction:0.529 & 0.258 respectively) [Table 3-7].

Table 3-7 Adverse events

	Overall *n=4744*		**LVEF category 1** n=1143 (<26%)		**LVEF category 2** n=1018 (26% – 30%)		**LVEF category 3** n=1187 (31% – 35%)		**LVEF category 4** n=1396 (>35%)		**p-value for interaction**
	Placebo (n=2371)	*Dapagliflozin (n=2373)*	Placebo (n=601)	Dapagliflozin (n=542)	Placebo (n=498)	Dapagliflozin (n=520)	Placebo (n=581)	Dapagliflozin (n=606)	Placebo (n=691)	Dapagliflozin (n=705)	
Any discontinuation											
Events – no/total no. (%)	*258(10.9)*	*249 (10.5)*	65 (10.8)	66 (12.2)	57 (11.5)	62 (11.9)	71 (12.2)	60 (9.9)	65 (9.4)	61 (8.7)	
Odds ratio	*0.96 (0.80 – 1.15) 0.665*		1.15 (0.80 – 1.65)		1.05 (0.71 – 1.53)		0.79 (0.55 – 1.13)		0.90 (0.63 – 1.30)		0.548
Discontinuation due to AE*											
Events (%)	*116/2368 (4.9)*	*111/2368 (4.7)*	30/600 (5.0)	31/540 (5.7)	19/498 (3.8)	26/518 (5.0)	33/579 (5.7)	27/606 (4.5)	34/691 (4.9)	27/704 (3.8)	
Odds ratio	*0.95 (0.73 – 1.25) 0.734*		1.16 (0.69 – 1.95)		1.32 (0.72 – 2.43)		0.76 (0.45 – 1.28)		0.76 (0.45 – 1.28)		0.544
Volume depletion*											
Events (%)	*162/2368 (6.8)*	*178/2368 (7.5)*	49/600 (8.2)	54/540 (10.0)	42/498 (8.4)	37/518 (7.1)	29/579 (5.0)	39/606 (6.4)	42/691 (6.1)	48/704 (6.8)	
Odds ratio	*1.11 (0.89 – 1.38) 0.368*		1.26 (0.84 – 1.89)		0.83 (0.53 – 1.32)		1.29 (0.79 – 2.12)		1.14 (0.74 – 1.75)		0.400
Renal*											
Events (%)	*170/2368 (7.2)*	*153/2368 (6.5)*	47/600 (7.8)	39/540 (7.2)	37/498 (7.4)	33/518 (6.4)	45/579 (7.8)	37/606 (6.1)	41/691 (5.9)	44/704 (6.3)	
Odds ratio	*0.89 (0.71 – 1.12) 0.326*		0.94 (0.60 – 1.46)		0.84 (0.52 – 1.37)		0.75 (0.48 – 1.18)		1.07 (0.69 – 1.67)		0.899
Fracture*											
Events (%)	*50/2368 (2.1)*	*49/2368 (2.1)*	13/600 (2.2)	9/540 (1.7)	12/498 (2.4)	14/518 (2.7)	11/579 (1.9)	11/606 (1.8)	14/691 (2.0)	15/704 (2.1)	
Odds ratio	*0.98 (0.66 – 1.46) 0.919*		0.78 (0.33 – 1.85)		1.13 (0.52 – 2.47)		0.95 (0.41 – 2.21)		1.07 (0.51 – 2.23)		0. 857
Amputation*											
Events (%)	*12/2368 (0.5)*	*13/2368 (0.5)*	3/600 (0.5)	1/540 (0.2)	1/498 (0.2)	4/518 (0.8)	3/579 (0.5)	6/606 (1.0)	5/691 (0.7)	2/704 (0.3)	
Odds ratio	*1.08 (0.49 – 2.38)*		0.41 (0.04 – 3.97)		3.82 (0.43 – 34.35)		1.72 (0.43 – 6.95)		0.41 (0.08 – 2.12)		0.336

	0.842										
Major hypoglycaemic episode*											
Events (%)	*4/2368 (0.2)*	*4/2368 (0.2)*	0 (0.0)	0 (0.0)	0 (0.0)	1/518 (0.2)	0 (0.0)	0 (0.0)	4/691 (0.6)	3/704 (0.4)	
Systolic BP											
Change from baseline at 8 months	*-0.38* ± 15.3	*-1.92* ± 14.9	0.52 ± 15.6	-0.88 ± 15.2	-0.11 ± 14.8	-2.37 ± 13.8	-0.57 ± 15.9	-1.20 ± 14.9	-1.18 ± 14.7	-2.97 ± 15.4	0.529
Difference[#]	*-1.40 (-2.27 to -0.52) 0.002*		-1.13 (-2.87 to 0.61) 0.202		-2.09 (-3.96 to -0.22) 0.028		-0.63 (-2.40 to 1.14) 0.486		-1.69 (-3.32 to -0.05) 0.044		
Creatinine											
Change from baseline at 8 months	*0.04* ± 0.25	*0.07* ± 0.24	0.04 ± 0.2	0.08 ± 0.2	0.06 ± 0.3	0.07 ± 0.2	0.05 ± 0.2	0.05 ± 0.2	0.03 ± 0.2	0.06 ± 0.3	0.258
Difference[#]	*0.02 (0.01 to 0.04) 0.009*		0.04 (0.004 to 0.07) 0.029		0.01 (-0.02 to 0.05) 0.543		0.01 (-0.03 to 0.04) 0.675		-0.03 (0.001 to 0.06) 0.044		

*Only in safety analysis set.
dapagliflozin - placebo

Discussion

LVEF is the most used measure of left ventricular systolic function. Not only does it help diagnose HFrEF, and distinguish between patients with HFrEF and HFpEF, but it is also an important predictor of morbidity and mortality.[87,158] As demonstrated by previous studies, both the risk of HF hospitalisation and cardiovascular mortality were higher in patients with lower LVEF.[158]

In this analysis of 4744 patients with HFrEF in DAPA-HF, the baseline characteristics of patients varied across the spectrum of LVEF, as expected. Patients with and without diabetes also differed as expected, but these differences were consistent across the range of LVEF studied. LVEF was a powerful predictor of the risk of hospitalisation and death overall and in patients with and without diabetes separately. The benefit of dapagliflozin on mortality/morbidity outcomes was not modified by baseline LVEF, irrespective of diabetes status. By contrast, symptom severity at baseline did not vary according to LVEF. Symptoms improved to a similar extent with dapagliflozin across the range of LVEF studied. The benefit of dapagliflozin on symptoms, in relation to LVEF, was consistent in patients with and without diabetes.

As in previous studies, patients with lower LVEF were younger, more likely to be male, had fewer comorbidities and less likely to have an ischaemic aetiology. Although there was no difference in NYHA class across the LVEF categories, NT-proBNP was substantially higher in patients in the lowest, compared with the highest, LVEF category (despite a much higher prevalence of atrial fibrillation in the latter).

I found that each 5-point decrement in baseline LVEF was associated with a 20% higher risk of cardiovascular death, 20% higher risk of HF hospitalisation and 13% higher risk of all-cause death. These findings are very similar to what was reported in the PARADIGM-HF, where the corresponding increments in risk for each 5-point reduction in LVEF were 17%, 17% and 14%, respectively.[161] These findings are also consistent with earlier studies assessing the relationship between LVEF and outcomes in HFrEF.[158] The relative increase in the risk of death and hospitalisation for a 5-point decrement in baseline LVEF was similar in

participants with and without diabetes, although the absolute risk for a given LVEF was higher in individuals with diabetes.

While the benefit of effective therapies for HFrEF has generally been found to be similar across the LVEF spectrum, the range of LVEF in such analyses has been limited as few landmark trials included patients with a LVEF >35%.[38,59-61,64-66,68,70-73,162,163] Furthermore, several earlier studies suggested greater benefit of therapy at the lower end of the LVEF spectrum.[159] However, I found that, compared with placebo, the benefit of dapagliflozin on the primary and secondary mortality/morbidity outcomes was consistent across the range of LVEF studied. This benefit according to LVEF was also consistent in patients with and without diabetes. Consequently, patients with a low LVEF obtained a particularly large *absolute* benefit from dapagliflozin because individuals with a low LVEF, especially if diabetic, were at much greater absolute risk than patients with a higher LVEF.

Until very recently, retrospective subgroup analyses of prior trials with SGLT-2 inhibitors in individuals with T2DM and predominantly atherosclerotic cardiovascular disease (or cardiovascular risk factors) had suggested that these drugs may be beneficial in patients with HFpEF, but these findings were far from conclusive.[164,165] However, these findings have been confirmed, prospectively, in the EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved) trial, which enrolled 5988 patients with HF and LVEF >40%.[166] In EMPEROR-Preserved, patients randomised to receive empagliflozin – another SGLT-2 inhibitor - had a statistically significantly lower risk of cardiovascular death or HF hospitalisation. However, the risk of cardiovascular death was not significantly different between empagliflozin and placebo. Therefore, whether dapagliflozin will reduce cardiovascular mortality in patients with HFmrEF and HFpEF is a question of particular interested in the larger ongoing Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure (DELIVER; NCT03619213) trial which has a larger number of target primary events, deaths and, consequently, statistical power.[167]

Two novel aspects of this study were the analysis of symptoms and the analysis of recurrent events, in relation to baseline LVEF, and according to diabetes status, and the effect of treatment on these outcomes. The two large pharmacological therapy trials that have reported the effect of treatment on KCCQ in HFrEF have not described the relationship between KCCQ score and LVEF or the effect of therapy according to LVEF.[5,168] However, in the CHARM programme, there was no clear association between LVEF, and a different patient reported outcome, a finding that is consistent with the current observations in DAPA-HF.[134] In addition, KCCQ scores were similar in patients with HFrEF and HFpEF, which also suggests little correlation between this patient reported outcome and LVEF.[169] Interestingly, *change* in KCCQ-TSS from baseline was also independent of LVEF, and similar in patients with and without diabetes. The reason why symptoms and QoL correlate poorly with LVEF is uncertain but, importantly, dapagliflozin improved symptoms as well as other outcomes. This beneficial effect of dapagliflozin, whether assessed as mean change in KCCQ-TSS, or the proportion of patients with a clinically meaningful change (≥5points), was similar across LVEF categories, both overall, and in patients with and without diabetes.

Analysis of recurrent non-fatal, along with fatal, events may provide a better quantification of the full burden of HF, compared with conventional time-to-first event analysis.[152,153,170] Repeat admissions are distressing for patients, a marker of disease progression, represent an adverse prognostic change, and are expensive. Likewise, recurrent-events analysis is a rigorous test of the effect of treatment, as it measures persistence of pharmacologic effect and adherence (e.g. treatment discontinuation after a first event will reduce any effect of therapy on subsequent events).[150] That this type of analysis reflects disease burden is clearly shown by the very high event rates compared with time-to-first event analysis in this chapter e.g. reaching almost 40 per 1000 person-years of follow-up for HF hospitalisation and cardiovascular death in patients with diabetes in the lowest LVEF category. However, the benefit of dapagliflozin was almost identical in the recurrent events and time-to-first analyses, and the relative risk reduction with dapagliflozin was consistent across the range of LVEF examined overall, and in patients with and without diabetes.

Patients in DAPA-HF with lower LVEF were more likely to have adverse events related to volume depletion but no difference was seen between the treatment groups even in those with the lowest LVEF, allaying concerns of a potentially greater risk of volume depletion in HF patients in whom diuretic use is almost universal.[171,172] The only other significant observation among the safety outcomes was the larger fall in SBP in the highest LVEF category but this was most likely a function of their higher baseline SBP.

Strengths & Limitations

This study also has a few limitations. This was a post hoc analysis in which patients were divided into arbitrary, clinically relevant LVEF categories. Additionally, LVEF was measured using different methods at different sites and there was no core laboratory. Time of measurement of LVEF before randomisation also varied, but this variation did not affect outcomes. Information regarding the method used to measure LVEF was also unavailable. There was also digit preference in the reporting of LVEF measurements, as often found. SBP below 95 mmHg and eGFR below 30 ml/min/1.73m^2 were exclusion criteria in DAPA-HF and this may have skewed the characteristics of the patients in the lowest LVEF category, more of which might have been expected to have lower SBP and worse kidney function. Serial measurements of LVEF during follow-up were also not recorded.

Conclusions

In summary, LVEF at baseline was a significant predictor of hospitalisation and mortality (but not symptoms) in patients with HFrEF enrolled in DAPA-HF. LVEF did not modify the beneficial effect of dapagliflozin on mortality/morbidity outcomes, or symptoms, in patients with HFrEF overall, and separately in those with and without diabetes.

Chapter 4. Differential impact of heart failure with reduced ejection fraction in men and women

This chapter has been published as:

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Differences exist between women and men with HF as has been demonstrated by previous studies.[92,119–124,173] Most concerning was the suggestion that in common with other cardiovascular conditions, women were less well treated than men, Much has changed in the assessment and management of patients with HF since those trials were published which may give a new perspective on the management of, and outcomes in women with HFrEF.[4,36] Sex has also frequently been included as a marker of clinical outcomes in prognostic models in HF. In Chapter 1, sex was a predictor in 50% of the multivariable models in a systematic review. [87,89,90,97,103,105–107,109]

In this chapter, I will describe and compares the characteristics and clinical features of HFrEF in men and women. I will also compare the different morbidity and mortality outcomes between the two sexes using competing risks regression, Cox regression, and negative binomial regression.

Methods

The trial populations have been described in detail in Chapter 2. Briefly, I have analysed a population of ambulatory patients with HFrEF enrolled in two clinical trials – ATMOSPHERE and PARADIGM-HF.[38,135]

Population analysed

I have analysed the entire population of 15415 patients in the combined cohort for this chapter.

Outcomes

For this chapter, as outlined in Chapter 2, I have analysed the primary outcome of cardiovascular death or first HF hospitalisation, its components and non-cardiovascular and all-cause death.

Additional outcomes examined are sudden death, death due to worsening HF, fatal/non-fatal myocardial infarction, fatal/non-fatal stroke and recurrent HF, cardiovascular, non-cardiovascular and all-cause hospitalisations.

Statistical analysis

I have reported the incidence rates for the outcomes of interest as events per 100 person-years. Competing-risks regression, using the Fine-Gray method, was used to assess the outcomes.[149] The primary outcome and cardiovascular death were analysed accounting for the competing-risk of non-cardiovascular death. First HF hospitalisation was analysed accounting for the competing-risk of all-cause death. Sudden deaths were analysed accounting for the competing-risk of all non-sudden death and pump failure deaths were analysed accounting for the competing-risk of deaths not caused by pump failure. Non-cardiovascular deaths were analysed accounting for the competing-risk of all cardiovascular death. Fatal and non-fatal MI and strokes were analysed accounting for the competing-risk of all-cause death not due to MI or stroke. Along with the crude subdistribution hazard rations (sHRs), I have reported adjusted sHRs from models including age, heart rate, SBP, NT-proBNP, BMI, NYHA class, LVEF and eGFR. HF hospitalisation was additionally adjusted for previous HF hospitalisation. For multivariable adjustment, I chose clinically relevant variables known to be predictive of death and hospitalisation. All models were adjusted for randomised treatment and region at baseline.

I used Cox regression to assess risk of all-cause death, with adjustment for variables as listed in the previous paragraph. Recurrent hospitalisations (for HF, cardiovascular, non- cardiovascular and all causes) were analysed using a

negative binomial regression model. Both crude IRRs and incidence rate ratios (IRRs) adjusted for the variables mentioned above are reported.

All analyses are conducted using Stata ver.14 (Stata Corp. College Station, Texas, USA).

Results

In this population of 15415 patients with HFrEF, there were 12058 men and 3357 women accounting for 78.2% and 21.8% of the cohort respectively.

Baseline characteristics

Baseline characteristics for both sexes are listed in Table 4-1. Women were at an average 2 years older than men, had higher SBP and a higher heart rate. There was no significant difference in BMI, but women were more often obese (33.4% women vs. 29.2% men).

Apart from hypertension (70.6% women vs. 65.5% men) and clinically significant valvular heart disease (5.3% vs. 4.6%), women were less likely to have a history of major comorbid conditions such as atrial fibrillation (32.6% vs. 36.4%), previous MI (30.0% vs. 45.4%) and stroke (7.4% vs 8.0%). As well as having a lower prevalence of CAD, women had a much lower rate of prior coronary revascularization. Among non- cardiovascular comorbidities, women had a similar prevalence of diabetes (31.0% vs. 31.6%) but a lower prevalence of COPD (8.5% vs. 13.1%).

Women were also less likely to be current smokers (6.2% vs. 15.8%) and had lower intake of alcohol.

In the EQ-5D-3L State of Health Score, women were much more likely to report moderate to extreme anxiety/depression: 44.0% in women vs. 29.0% in men, p-value <0.001 (PARADIGM-HF only) [Table 4-2]. This was especially true of women with an ischaemic aetiology [Table 4-3].

Table 4-1 Baseline characteristics

	Women n=3357	Men n=12058	p-value
Age - (years.)	65.1 ± 11.9	63.1 ± 11.5	<0.001
Age Groups – no. (%)			<0.001
≤40 years	104 (3.1)	464 (3.8)	
41 – 55 years	584 (17.4)	2374 (19.7)	
56 – 70 years	1436 (42.8)	5832 (48.4)	
>70 years	1233 (36.7)	3388 (28.1)	
Region – no. (%)			<0.001
North America	132 (3.9)	647 (5.4)	
Latin America	698 (20.8)	1854 (15.4)	
Western Europe & other	733 (21.8)	3221 (26.7)	
Central Europe	1113 (33.2)	3657 (30.3)	
Asia - Pacific	681 (20.3)	2679 (22.2)	
Race – no. (%)			<0.001
White	2128 (63.4)	8008 (66.4)	
Black	166 (4.9)	371 (3.1)	
Asian	664 (19.8)	2609 (21.6)	
Other	399 (11.9)	1070 (8.9)	
SBP - (mmHg)	123.9 ± 17.0	122.0 ± 16.7	<0.001
Heart rate - (bpm)	72.8 ± 11.7	71.9 ± 12.4	<0.001
BMI* - (kg/m^2)	27 (24 - 32)	27 (24 - 31)	0.136
Obese	33.4%	29.2%	
Comorbidities – no. (%)			
Atrial fibrillation	1093 (32.6)	4388 (36.4)	<0.001
Hypertension	2369 (70.6)	7903 (65.5)	<0.001
CAD	1444 (43.0)	6755 (56.0)	<0.001
MI	1007 (30.0)	5474 (45.4)	<0.001
Unstable angina	307 (9.1)	1414 (11.7)	<0.001
Stable angina	698 (20.8)	2409 (20.0)	0.299
Prior PCI	445 (13.3)	2735 (22.7)	<0.001
Ischaemic – (%)	24.2	35.2	
Non-Ischaemic – (%)	2.3	3.5	
Prior CABG	226 (6.7)	2055 (17.0)	<0.0001
Ischaemic – (%)	12.9	27.6	
Non-Ischaemic – (%)	0.7	1.0	
VHD	178 (5.3)	553 (4.6)	0.084
Cerebrovascular disease	362 (10.8)	1574 (13.1)	0.004
Stroke	248 (7.4)	969 (8.0)	0.218
Known carotid artery disease	69 (2.1)	443 (3.7)	<0.001

PAD	93 (2.0)	719 (6.0)	<0.001
Prior lower limb revascularization	28 (0.8)	233 (1.9)	<0.001
Intermittent claudication	78 (2.3)	596 (4.9)	<0.001
Asthma	173 (5.2)	354 (2.9)	<0.001
COPD	285 (8.5)	1582 (13.1)	<0.001
Diabetes	1041 (31.0)	3810 (31.6)	0.517
Renal disease	392 (11.7)	1671 (13.9)	0.001
Cancer	153 (4.6)	505 (4.2)	0.349
Anaemia	700 (20.9)	2610 (21.7)	0.3221
Lifestyle Habits – n (%)			
Smoking Status			<0.001
Never Smoked	2694 (80.3)	5427 (45.0)	
Ex-Smoker	456 (13.6)	4729 (39.2)	
Current Smoker	207 (6.1)	1902 (15.8)	
Alcohol units/d			<0.001
<1	3269 (97.4)	10273 (85.2)	
1-2	79 (2.4)	1442 (12.0)	
>2	8 (0.2)	342 (2.8)	

All values are reported as mean ± standard deviation except where indicated.
*Median (interquartile range)
SBP – systolic blood pressure; BMI – body mass index; CAD – coronary artery disease; MI – myocardial infarction; PCI – primary coronary intervention; CABG – coronary artery bypass graft; VHD – valvular heart disease; PAD – peripheral artery disease; COPD – chronic obstructive pulmonary disease.

Table 4-2 EQ-5D-3L score (PARADIGM-HF only)

	Women n=3357	Men n=12058	p-value
Mobility			<0.001
I have no problems in walking about	864 (47.2)	3825 (58.3)	
I have some problems in walking about	919 (50.2)	2652 (40.4)	
I am confined to bed	8 (0.4)	11 (0.2)	
Self-care			<0.001
I have no problems with self-care	1377 (75.2)	5552 (84.5)	
I have some problems washing or dressing myself	403 (22.0)	914 (13.9)	
I am unable to wash or dress myself	11 (0.6)	21 (0.3)	
Usual activities			<0.001
I have no problems with performing my usual activities	858 (46.8)	3977 (60.6)	
I have some problems with performing my usual activities	873 (47.7)	2365 (36.0)	
I am unable to perform my usual activities	60 (3.3)	144 (2.2)	
Pain/ Discomfort			<0.001
I have no pain or discomfort	825 (45.3)	3820 (58.2)	
I have moderate pain or discomfort	912 (49.8)	2559 (39.0)	
I have extreme pain or discomfort	54 (3.0)	106 (1.6)	
Anxiety/ Depression			<0.001
I am not anxious or depressed	986 (53.8)	4605 (70.1)	
I am moderately anxious or depressed	741 (40.5)	1793 (27.3)	
I am extremely anxious or depressed	64 (3.5)	88 (1.3)	
Overall Score – mean ± SD	65.9 ± 20.2	68.0 ± 19.8	<0.001

Table 4-3 EQ-5D-3L score - Ischaemic and non-ischaemic aetiology (PARADIGM-HF only)

	Ischaemic			Non-ischaemic		
	Women	**Men**	**p-value**	**Women**	**Men**	**p-value**
	n=969	n=4067		n=796	n=2330	
Mobility			<0.0001			<0.0001
I have no problems in walking about	396 (40.9)	2205 (54.2)		433 (54.4)	1502 (64.5)	
I have some problems in walking about	541 (55.8)	1795 (44.1)		347 (43.6)	807 (34.6)	
I am confined to bed	6 (0.6)	9 (0.2)		2 (0.3)	2 (0.1)	
Self-care			<0.0001			<0.0001
I have no problems with self-care	681 (70.3)	3351 (82.4)		634 (79.7)	2055 (88.2)	
I have some problems washing or dressing myself	256 (26.4)	641 (15.8)		143 (18.0)	252 (10.8)	
I am unable to wash or dress myself	6 (0.6)	15 (0.4)		5 (0.6)	5 (0.2)	
Usual activities			<0.0001			<0.0001
I have no problems with performing my usual activities	407 (43.0)	2348 (57.7)		415 (52.1)	1515 (65.0)	
I have some problems with performing my usual activities	497 (51.3)	1552 (38.2)		348 (43.7)	761 (32.7)	
I am unable to perform my usual activities	39 (4.0)	106 (2.6)		19 (2.4)	36 (1.5)	
Pain/ Discomfort			<0.0001			<0.0001
I have no pain or discomfort	390 (40.3)	2282 (56.1)		397 (49.9)	1433 (61.5)	
I have moderate pain or discomfort	518 (53.5)	1649 (40.6)		366 (46.0)	849 (36.4)	
I have extreme pain or discomfort	35 (3.6)	75 (1.8)		19 (2.4)	29 (1.2)	
Anxiety/ Depression			<0.0001			<0.0001
I am not anxious or depressed	490 (50.6)	2794 (68.7)		457 (57.4)	1688 (71.6)	
I am moderately anxious or depressed	415 (42.8)	1158 (28.5)		300 (37.7)	591 (25.4)	
I am extremely anxious or depressed	38 (3.9)	55 (1.4)		25 (3.1)	32 (1.4)	

Overall Score – mean ± SD	64.4 ± 19.1	67.0 ± 19.5	0.0002	67.0 ± 21.5	69.3 ± 20.1	0.0062

Heart failure characteristics

As shown in Table 4-4, fewer women had been living with a diagnosis of HF for more than 5 years (27.5% vs. 31.4%). Women were also less likely to have an ischaemic aetiology for HF (50.0% vs. 60.5%).

Women were more symptomatic than men, with a higher prevalence of dyspnoea on effort (88.7% vs. 84.7%), paroxysmal nocturnal dyspnoea (7.1% vs. 4.3%) and more evidence of congestion (peripheral oedema, jugular venous congestion and rales).

Women were more likely to be in a higher NYHA class and had lower (worse) median KCCQ scores. Each of the individual KCCQ domain scores was also lower in women [Figure 4-1]. This observation also held when both sexes were compared according to the aetiology of HF [Figure 4-2 & Figure 4-3]. The State of Health Score (PARADIGM-HF only) showed large differences between women and men in their mobility, ability to undertake usual activities and to care for themselves (washing and dressing)–[Table 4-2]. This difference was even larger in those with an ischaemic aetiology for HF [Table 4-3].

Table 4-4 Heart failure characteristics and clinical features

	Women n=3357	Men n=12058	p-value
HF aetiology			<0.001
Ischaemic	1677 (50.0)	7289 (60.5)	
Non-ischaemic	1494 (44.5)	4277 (35.5)	
Other/Unknown	186 (5.5)	492 (4.1)	
HF duration			<0.001
<1 year	1168 (34.8)	3716 (30.8)	
1-5 years	1267 (37.7)	4558 (37.8)	
>5 years	922 (27.5)	3780 (31.4)	
Previous HF hospitalisation	1951 (58.1)	7511 (62.3)	<0.0001
NYHA Class			<0.001
I/II	2274 (67.7)	9047 (75.1)	
III	1046 (31.2)	2915 (24.2)	
IV	37 (1.1)	83 (0.7)	
KCCQ clinical summary score*	71.3 (53.4, 86.5)	81.3 (65.1, 92.7)	0.001
Clinical Features			
Dyspnoea at rest	204 (6.1)	408 (3.4)	<0.0001
Dyspnoea on exertion	2976 (88.7)	10191 (84.7)	<0.0001
Orthopnoea	290 (8.6)	681 (5.7)	<0.0001
PND	237 (7.1)	519 (4.3)	<0.0001
Peripheral oedema	787 (23.4)	2403 (19.9)	<0.0001
Third heart sound	341 (10.2)	1048 (8.7)	0.009
JVD	365 (10.9)	1112 (9.2)	0.004

All values are reported as number (percentage) except where indicated.
*Median (interquartile range)
HF – heart failure; NYHA – New York heart association; KCCQ – Kansas City cardiomyopathy questionnaire; PND – paroxysmal nocturnal dyspnoea; JVD – jugular venous distension.

Figure 4-1 Scores for KCCQ domains in women and men with HFrEF

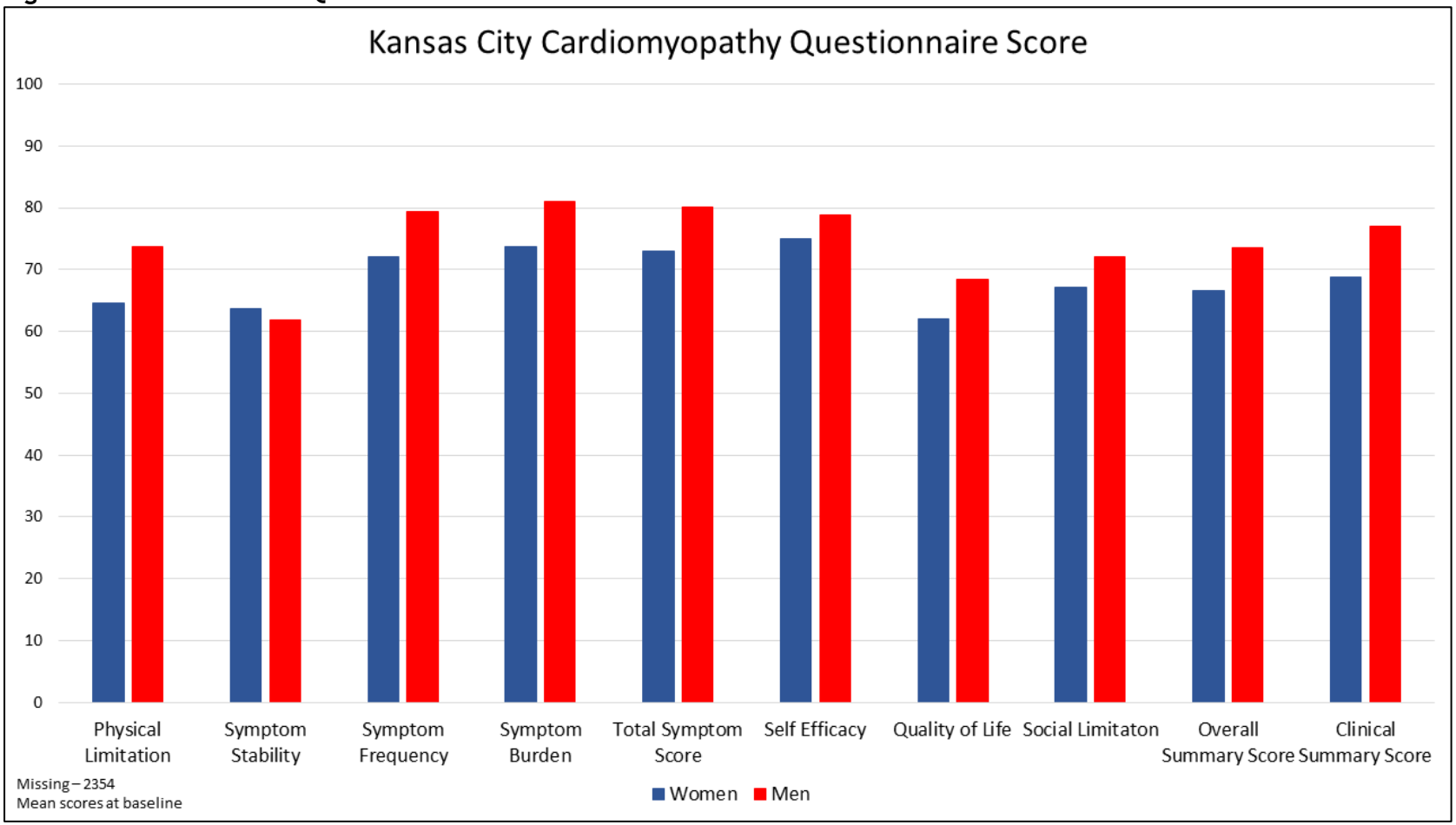


Figure 4-2 Scores for KCCQ domains in women and men with HFrEF - Ischaemic aetiology

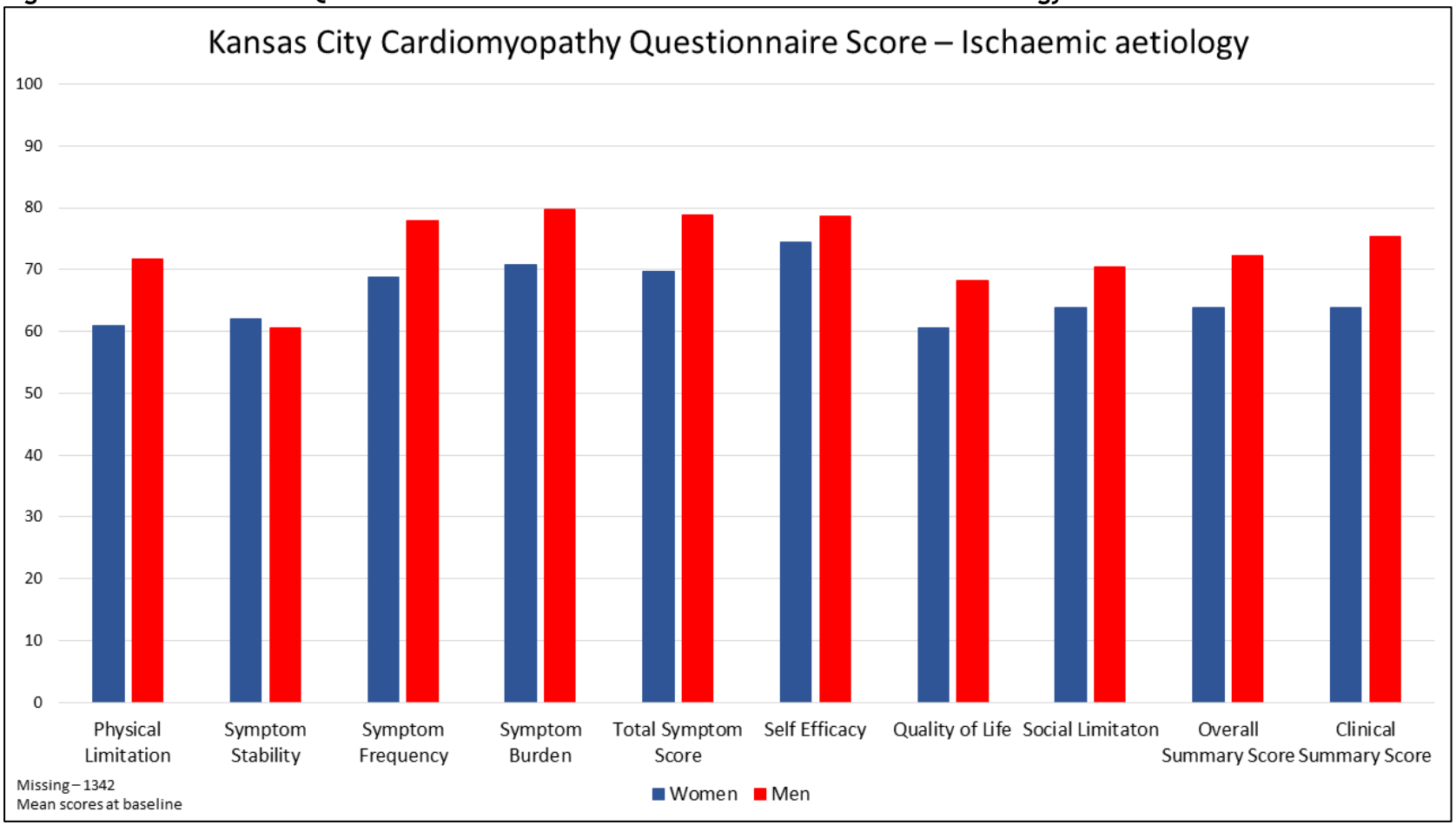
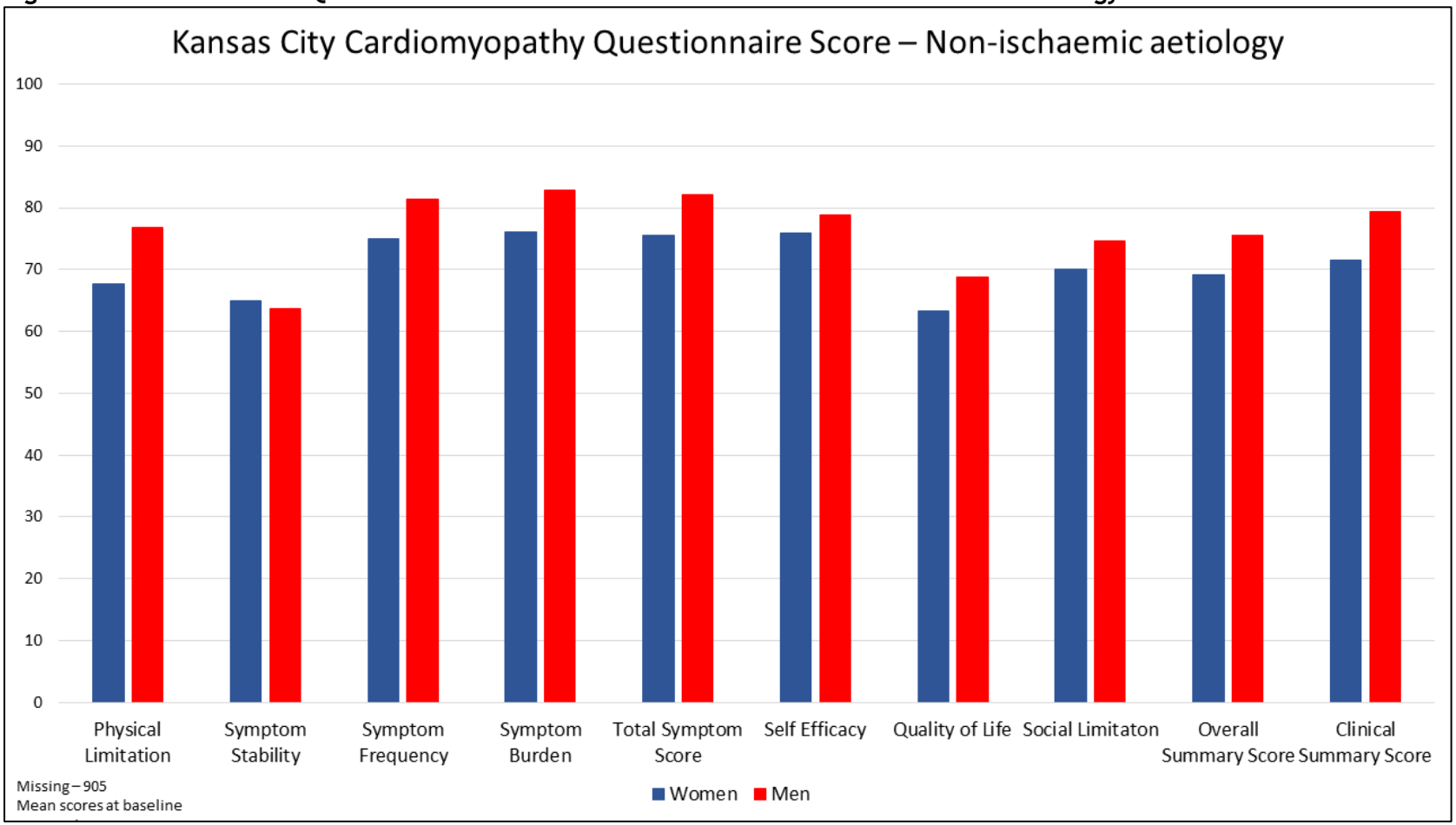


Figure 4-3 Scores for KCCQ domains in women and men with HFrEF - Non-ischaemic aetiology



Investigations and biomarkers

Women also had a slightly but significantly higher LVEF (29.6% vs. 28.8%) and LVEF was higher for both sexes with an ischaemic aetiology. Median NT-proBNP was not significantly different (women 1448 pg/ml vs. men 1406 pg/ml) overall but was significantly higher in women with an ischaemic aetiology of HF. BNP (PARADIGM-HF only) was lower in women than men: 234 (142, 430) pg/ml vs. 259 (157, 478) pg/ml, p-value <0.0001 [Table 4-5]. In PARADIGM-HF only, levels of high sensitivity troponin T (hsTropT), growth differentiation factor-15 (GDF-15) and soluble toll-like receptor-2 (ST2) were significantly lower in women.

Mean eGFR was lower in women and a higher proportion of women had an eGFR <60 ml/min/1.73m^2.

Table 4-5 Investigations

	Women n=3357	**Men** n=12058	**p-value**
Ejection fraction† – (%)	29.6 ± 5.9	28.8 ± 6.0	<0.0001
NT-proBNP* - (pg/ml)	1448 (801 - 2805)	1406 (761 - 2770)	0.158
Haemoglobin†- (gm/L)	129.9 ± 14.4	141.0 ± 15.7	<0.0001
Creatinine† - (umol/L)	81.0 ± 21.6	100.0 ± 25.5	<0.0001
eGFR† - (ml/min/1.73m^2)	68.2 ± 25.0	71.2 ± 21.3	<0.0001
eGFR <60 ml/min/1.73m^2	1267 (37.7)	3643 (30.2)	<0.001
Sodium† – (mmol/L)	140.6 ± 3.2	140.9 ± 3.2	<0.001
Potassium† – (mmol/L)	4.5 ± 0.5	4.5 ± 0.5	0.5294
PARADIGM-HF only			
HbA1C – no (%)			0.470
Prediabetes (6-6.4)	426 (23.3)	1479 (22.5)	
Undiagnosed Diabetes (>6.4)	193 (10.5)	645 (9.8)	
NT-proBNP (pg/ml)*	1585 (901 - 3148)	1624 (88 - 3237)	0.7177
BNP (pg/ml)*	234 (142 - 430)	259 (157 - 478)	<0.0001
Ejection fraction ≤30	257 (145 - 505)	292 (172 - 557)	
Ejection fraction >30	216 (140 - 371)	225 (144 - 399)	
MMP2 (ng/mL)*	133.6 (115.3 - 155.8)	134.8 (116.3 - 157.4)	0.9245
MMP9 (ng/mL)*	57.5 (39.8 - 124.6)	64.5 (38.4 - 127.4)	0.9431
hsTropT (ng/L)*	11.0 (8.0 - 17.0)	16.0 (11.0 - 25.0)	<0.0001
GDF 15 (ng/L)*	1482 (1014 - 2114)	1713 (1207 - 2468)	<0.0001
KIM-1 (pg/mL)*	134.0 (91.7 - 190.5)	128.0 (86.9 - 194.0)	0.4972

ST2[*] (ng/mL)	29.3 (22.9 - 36.7)	32.9 (26.2 - 42.2)	<0.0001
TIMP 1[*] (ng/mL)	122.4 (103.5 - 150.0)	124.2 (104.6 - 151.0)	0.4385
Galectin-3[*] (ng/mL)	17.7 (14.5 - 22.3)	16.8 (13.6 - 20.7)	0.0012
ECG			
LVH	*2118 (17.6)*	*637 (19.0)*	*0.059*
Atrial fibrillation	732 (21.8)	2905 (24.1)	0.006
LBBB	750 (22.3)	2332 (19.3)	0.0001
RBBB	182 (5.4)	956 (7.9)	<0.0001
QRS duration[†] – (msec)	104 (86 - 140)	110 (94 - 140)	<0.0001

All values are reported as number (percentage) except where indicated.
*Median (interquartile range)
†Mean ± standard deviation
Values in italics represent patients enrolled only in PARADIGM-HF.
HbA1c is randomisation.
BNP and NT-proBNP are screening values.
The remaining biomarkers are from visit 2 (after screening).
NT-proBNP – N-terminal pro Brain natriuretic peptide; eGFR – estimated glomerular filtration rate; HbA1C – Haemoglobin A1C; MMP – Metalloprotease; hsTropT – high sensitivity troponin T; GDF 15 – Growth differentiation factor 15; KIM-1 – Kidney injury molecule 1; ST2 – soluble toll-like receptor-2; TIMP 1 – Tissue inhibitor metalloproteinase 1; ECG – Electrocardiogram; LBBB – left bundle branch block; RBBB - Right bundle branch block.
PARADIGM-HF: women:men = 1832:6567

Table 4-6 Investigations - Ischaemic and Non-ischaemic aetiology

	Ischaemic			Non-ischaemic		
	Women	**Men**	**p-value**	**Women**	**Men**	**p-value**
	n=1677	N=7289		n=1494	n=4227	
Ejection fraction – (%)†	30.5 ± 5.6	29.3 ± 5.9	<0.001	28.6 ± 6.1	28.1 ± 6.1	0.006
NT-proBNP* - (pg/ml)	1448 (805 - 2716)	1352 (742 - 2622)	0.018	1450.0 (810 – 2885)	1504.0 (805 – 3028)	0.28
Haemoglobin† - (gm/L)	129.8 ± 14.1	140.2 ± 15.8	<0.001	130.2 ± 14.7	142.4 ± 15.7	<0.001
Creatinine† - (umol/L)	82.6 ± 21.6	101.9 ± 25.9	<0.001	79.5 ± 21.4	97.4 ± 24.7	<0.001
eGFR† - (ml/min/1.73m^2)	65.3 ± 19.9	68.8 ± 19.8	<0.001	70.7 ± 28.7	74.6 ± 22.0	<0.001
eGFR <60 ml/min/1.73m^2	701 (41.8)	2471 (33.9)	<0.001	503 (33.7)	1,067 (25.0)	<0.001
Sodium† – (mmol/L)	141.1 ± 3.3	140.7 ± 3.2	<0.001	140.7 ± 3.0	140.5 ± 3.0	0.019
Potassium† – (mmol/L)	4.5 ± 0.5	4.5 ± 0.5	0.76	4.5 ± 0.5	4.5 ± 0.5	0.48
PARADIGM-HF only						
HbA1C – no (%)			0.605			0.839
Prediabetes (6-6.4)	223 (23.0)	877 (21.6)		186 (23.4)	557 (23.9)	
Undiagnosed Diabetes (>6.4)	107 (11.0)	393 (9.7)		82 (10.3)	238 (10.2)	
NT-proBNP (pg/ml)*	1585.0 (88.50 – 2950.0)	1532.0 (838.5 – 2989.0)	0.2676	1566.0 (911.0 - 3403.0)	1796.0 (967.0 - 3699.0)	0.011
BNP (pg/ml)*	239.3 (150.6 – 432.5)	258.6 (160.7 – 463.8)	0.0081	224.3 (129.4 - 424.5)	259.4 (150.8 - 530.0)	<0.001
Ejection fraction ≤30	267.5 (154.1 - 499.2)	294.1 (177.9 - 524.8)	0.070	251.0 (131.9 - 505.1)	295.0 (164.5 - 617.4)	<0.001
Ejection fraction >30	222.1 (148.5 - 370.5)	226.8 (150.2 - 395.8)	0.37	196.4 (128.0 - 370.6)	221.6 (136.2 - 400.4)	0.09
MMP2 (ng/mL)*	133.6 (117.0 - 156.1)	135.7 (116.7 - 158.5)	0.72	133.1 (114.2 - 155.7)	132.7 (115.4 - 157.3)	0.79
MMP9 (ng/mL)*	55.3 (37.5 - 117.0)	60.4 (36.5 - 121.4)	0.85	67.9 (42.4 - 141.5)	73.8 (43.8 - 138.5)	0.64
hsTropT (ng/L)*	12.0 (8.0 - 18.0)	18.0 (12.0 - 27.0)	<0.001	11.5 (6.0 - 16.0)	18.0 (11.0 - 26.0)	<0.001
GDF 15 (ng/L)*	1549.4 (1108.7 - 2135.6)	1760.9 (1280.6 - 2516.5)	<0.001	1265.1 (942.2 - 1995.5)	1546.1 (1074.4 - 2392.8)	0.005
KIM-1 (pg/mL)*	129.0 (90.5 - 194.0)	129.0 (89.3 - 196.0)	0.64	135.0 (94.4 - 176.0)	124.0 (80.4 - 187.0)	0.38

ST2 (ng/mL)*	28.6 (22.5 - 34.8)	32.9 (26.0 - 42.2)	<0.001	30.8 (23.4 - 37.3)	33.4 (27.0 - 42.4)	0.004
TIMP 1 (ng/mL)*	124.9 (104.4 - 153.9)	122.1 (103.8 - 147.5)	0.51	119.8 (102.0 - 145.3)	127.3 (105.9 - 154.0)	0.044
Galectin-3 (ng/mL)*	18.1 (14.4 - 23.3)	16.9 (13.9 - 20.7)	0.025	17.4 (14.7 - 21.7)	16.4 (13.2 - 20.6)	0.014
ECG						
LVH	333 (19.9)	1,118 (15.3)	<0.001	288 (19.3)	925 (21.6)	0.055
Atrial fibrillation	351 (20.9)	1,467 (20.1)	0.46	336 (22.5)	1300 (30.4)	<0.001
LBBB	331 (19.7)	1,339 (18.4)	0.19	388 (26.0)	912 (21.3)	<0.001
RBBB	98 (5.8)	667 (9.2)	<0.001	63 (4.2)	234 (5.5)	0.059
QRS duration† – (msec)	100.0 (84.0 – 128.0)	110.0 (94.0 – 138.0)	<0.001	109.0 (90.0 – 142.0)	110.0 (96.0 – 140.0)	0.036

All values are reported as number (percentage) except where indicated.
*Median (interquartile range)
†Mean ± standard deviation
Values in italics represent patients enrolled only in PARADIGM-HF.
HbA1c is randomisation.
BNP and NT-proBNP are screening values.
Remaining biomarkers are from visit 2 (after screening).
NT-proBNP – N-terminal pro Brain natriuretic peptide; eGFR – estimated glomerular filtration rate; HbA1C – Haemoglobin A1C; MMP – Metalloprotease; hsTropT – high sensitivity troponin T; GDF 15 – Growth differentiation factor 15; KIM-1 – Kidney injury molecule 1; ST2 – soluble toll-like receptor 2; TIMP 1 – Tissue inhibitor metalloproteinase 1; ECG – Electrocardiogram; LBBB – left bundle branch block; RBBB - Right bundle branch block.
PARADIGM-HF: women:men = 1832:6567

Baseline therapy

The rates of use of a diuretic, beta-blocker and MRA were very similar in women and men [Table 4-7]. Women were slightly more likely to receive digitalis (32.4% vs. 30.6%) and ARBs (16.4% vs. 11.9%), compared with men, and less likely to receive an ACEI (84.7% vs. 88.7%). The difference in rates of use of statins, aspirin and anticoagulants were larger (47.6% vs. 56.3%; 46.4% vs. 53.0% and 26.7% vs. 32.4% in women and men, respectively).

Women were less likely to have received a device than men: ICD (8.6% vs. 16.6%) and CRT (4.1% vs. 6.9%).

In PARADIGM-HF only, women were also less likely to have received influenza vaccination in the 12 months before enrolment (19.2% vs. 21.6%, p-value: 0.024), to have been enrolled in a disease management program (13.3% vs. 15.8%, p-value: 0.008) or to have been prescribed an exercise regimen (15.0% vs. 18.1%, p-value: 0.002).

Table 4-7 Therapy at baseline

	Women n=3357	**Men** n=12058	**p-value**
Diuretics	2698 (80.4)	9638 (79.9)	0.574
Digoxin	1089 (32.4)	3692 (30.6)	0.048
ACEI	2842 (84.7)	10697 (88.7)	<0.0001
ARB	551 (16.4)	1434 (11.9)	<0.0001
Beta-blockers	3075 (91.6)	11168 (92.6)	0.049
MRAs	1555 (46.3)	5718 (47.4)	0.2599
CCBs	330 (9.8)	1035 (8.6)	0.0245
Statins	1598 (47.6)	6787 (56.3)	<0.0001
Aspirin	1557 (46.4)	6393 (53.0)	<0.0001
Anticoagulants	897 (26.7)	3906 (32.4)	<0.0001
In patients with atrial fibrillation on ECG - (%)	67.1	71.2	0.029
In patients with atrial fibrillation history - (%)	60.6	66.6	<0.001
CHA2DS2 VASc Score >=2 – (%)	67.1	71.5	0.019
Pacemaker	310 (9.2)	1490 (12.4)	<0.0001
ICD-any	290 (8.6)	2001 (16.6)	<0.0001

ICD-only	196 (5.8)	1371 (11.4)	<0.0001
CRT	137 (4.1)	830 (6.9)	<0.0001
PARADIGM-HF only			
Influenza vaccination in past 12 months	351 (19.2)	1418 (21.6)	0.0239
Pneumococcal Vaccination in past 12 months	87 (4.8)	390 (6.0)	0.0517
Patient been prescribed an exercise regimen	274 (15.0)	1190 (18.1)	0.0016
Patient enrolled in structured disease management program	244 (13.3)	1040 (15.8)	0.0081

All values are reported as number (percentage)
Values in italics represent patients enrolled only in PARADIGM-HF
ACEI – Angiotensin-converting enzyme inhibitor; ARB – Angiotensin receptor blocker; MRA – Mineralocorticoid receptor antagonist; CCB – Calcium channel blockers; PCI – Primary coronary intervention; CABG – Coronary artery bypass graft; ICD – Implantable cardioverter-defibrillator; CRT – Cardiac resynchronization therapy.
PARADIGM-HF: women:men = 1832:6567

Clinical outcomes

Women had a significantly lower rate of the primary composite outcome (9.88 vs. 12.52 events per 100 person-years), with an adjusted sHR of 0.75 (95% CI 0.69-0.81), as shown in Table 4-8 & Figure 4-4.

Looking at the components of this composite, the rate and risk of first hospitalisation for HF was also lower in women (adjusted sHR 0.80; 95% CI 0.72-0.89).

The risk of cardiovascular death was also lower, as were each of the two major modes of cardiovascular death i.e. sudden death and pump-failure death. The adjusted sHRs for these outcomes (0.65-0.70) were lower than for HF hospitalisation.

Interestingly, the risk of non-cardiovascular death was also lower in women and, as a result, so was the risk of all-cause death (adjusted HR 0.66; 95% CI 0.52-0.83 and 0.68; 95% CI 0.62-0.74, respectively).

When outcomes were examined according to investigator reported aetiology (non-ischaemic vs. ischaemic), men with both non-ischaemic and ischaemic aetiology did worse than women in the corresponding groups [Figure 4-5]. Among men, those with an ischemic aetiology had higher mortality rates than individuals with a non-ischemic aetiology. However, among women mortality did not vary by aetiology i.e. the "protection" conferred by a non-ischemic background in men (compared with an ischemic substrate) seemed to be absent in women [Figure 4-5].

While women were less likely to have a fatal/non-fatal MI than men (1.08 vs. 1.33 events per 100 person-years), the rate of stroke was higher in women (1.54 vs. 1.19 events per 100 person-years).

Recurrent events

During a median follow up of 908 days (1-2285), there was a total of 2988 hospitalisations for any cause in women and 13604 hospitalisations for any cause in men [Table 4-8]. Of these, 750 (25.1%) were due to HF in women and 3569 (26.2%)

were due to HF in men. Among women, 4.3% had more than one hospitalisation for HF and the same was true for 6.4% of men [Table 4-10].

The adjusted IRR for recurrent HF hospitalisation for women compared with men was 0.69 (95% CI 0.61-0.79). The IRRs for cardiovascular hospitalisation (adjusted IRR 0.74; 95% CI 0.68-0.80) (adjusted IRR 0.73; 95% CI 0.68-0.80), all-cause hospitalisation (0.75; 95% CI 0.71 0.70 -0.81) and non-cardiovascular hospitalisations (0.80; 95% CI 0.73-0.87) (0.81; 95% CI 0.74-0.88) were higher than for HF hospitalisation.

Table 4-8 Clinical outcomes

	Women n=3357		Men n=12058
Primary outcome			
Events – no (%)	808 (24.1)		3592 (29.8)
Event rate per 100 person-years	9.88 (9.22 - 10.59)		12.52 (12.12 - 12.94)
Unadjusted sHR		0.79 (0.73 - 0.85) <0.001	
Adjusted sHR		0.75 (0.69 - 0.81) <0.001	
First HF hospitalisation			
Events – no (%)	460 (13.7)		2059 (17.1)
Event rate per 100 person-years	5.63 (5.13 - 6.16)		7.18 (6.87 - 7.50)
Unadjusted sHR		0.81 (0.74 – 0.90) <0.001	
Adjusted sHR		0.80 (0.72 - 0.89) <0.001	
Cardiovascular death			
Events – no (%)	508 (15.1)		2364 (19.6)
Event rate per 100 person-years	5.74 (5.27 - 6.27)		7.56 (7.26 - 7.87)
Unadjusted sHR		0.74 (0.67 - 0.81) <0.001	
Adjusted sHR		0.70 (0.63 - 0.77) <0.001	
Sudden death			
Events – no (%)	196 (5.8)		1022 (8.5)
Event rate per 100 person-years	2.22 (1.93 - 2.55)		3.27 (3.07 - 3.47)
Unadjusted sHR		0.67 (0.57 - 0.78) <0.001	
Adjusted sHR		0.65 (0.56 - 0.76) <0.001	
Death due to worsening HF			
Events – no (%)	119 (3.5)		616 (5.1)
Event rate per 100 person-years	1.35 (1.12 - 1.61)		1.97 (1.82 - 2.13)
Unadjusted sHR		0.70 (0.57 - 0.85) <0.001	

Adjusted sHR		0.67 (0.55 - 0.82) <0.001	
Non-cardiovascular death			
Events – no (%)	93 (2.8)		476 (3.9)
Event rate per 100 person-years	1.05 (0.86 - 1.29)		1.52 (1.39 - 1.66)
Unadjusted sHR		0.71 (0.57 - 0.89) 0.003	
Adjusted sHR		0.66 (0.52 - 0.83) <0.001	
All-cause death			
Events – no (%)	601 (17.9)		2840 (23.6)
Event rate per 100 person-years	6.80 (6.27 - 7.36)		9.08 (8.75 - 9.42)
Unadjusted HR		0.73 (0.67 - 0.80) <0.001	
Adjusted HR		0.68 (0.62 - 0.74) <0.001	
Fatal/non-fatal MI			
Events – no (%)	94 (2.8)		412 (3.4)
Event rate per 100 person-years	1.08 (0.88 - 1.32)		1.33 (1.21 - 1.47)
Unadjusted sHR		0.86 (0.69 - 1.08) 0.186	
Adjusted sHR		0.79 (0.63 - 1.00) 0.048	
Fatal/Non-fatal stroke			
Events – no (%)	134 (4.0)		368 (3.1)
Event rate per 100 person-years	1.54 (1.30 - 1.82)		1.19 (1.08 - 1.32)
Unadjusted sHR		1.31 (1.07 - 1.59) 0.008	
Adjusted sHR		1.22 (0.99 - 1.50) 0.062	
Total HF hospitalisations			
Events – no	750		3569
Event rate per 100 person-years	8.48 (7.89 - 9.11)		11.40 (11.04 - 11.79)
Unadjusted IRR		0.70 (0.62 - 0.80) <0.001	
Adjusted IRR		0.69 (0.61 - 0.79) <0.001	
Total cardiovascular hospitalisations			
Events – no	1719		8017
Event rate per 100 person-years	19.44 (18.54 – 20.38)		25.62 (25.07 – 26.19)
Unadjusted IRR		0.74 (0.68 – 0.81) <0.001	
Adjusted sHR		0.73 (0.67 – 0.79) <0.001	
Total non- cardiovascular hospitalisations			
Events – no	1287		5624
Event rate per 100 person-years	14.55 (13.78 – 15.37)		17.98 (17.51 – 18.45)
Unadjusted IRR		0.87 (0.80 – 0.95) 0.001	
Adjusted IRR		0.82 (0.75 – 0.89) <0.001	

Total all-cause hospitalisations			
Events – no	3006		13641
Event rate per 100 person-years	33.99 (32.79 – 35.22)		43.60 (42.87 – 44.34)
Unadjusted IRR		0.79 (0.74 – 0.84) <0.001	
Adjusted IRR		0.75 (0.71 – 0.81) <0.001	

All risk/rate ratios shown compare women to men.
Sub-distribution hazard ratios reported as sHR (95% confidence interval) [hazard ratio for all-cause hospitalisation +/or death]
Event rates per 100 person-years with 95% confidence interval
All sHRs adjusted for region and randomised treatment at baseline.
Adjusted sHRs additionally adjusted for: age, heart rate, systolic blood pressure, body mass index, NT-proBNP, NYHA functional class, ejection fraction and estimated glomerular filtration rate.
Heart failure hospitalisation additionally adjusted for previous hospitalisation for heart failure.
Incidence rate ratios reported as IRRs (95% confidence interval)
All IRRs adjusted for region and randomised treatment at baseline.
Adjusted IRRs additionally adjusted for: age, heart rate, systolic blood pressure, body mass index, NT-proBNP, NYHA functional class, previous hospitalisation for heart failure, ejection fraction and estimated glomerular filtration rate.

Table 4-9 Clinical outcomes - Ischaemic and non-ischaemic aetiology

	Ischaemic		Non-ischaemic	
	Women	**Men**	**Women**	**Men**
	n=1677	n=7289	n=1494	n=4227
Primary outcome				
Events – no (%)	399 (23.8)	2222 (30.5)	355 (23.8)	1217 (28.5)
Event rate per 100 person-years	10.0 (9.0 - 11.0)	13.1 (12.5 - 13.6)	9.6 (8.6 - 10.6)	11.7 (11.0 - 12.4)
Adjusted sHR	0.72 (0.64 - 0.80) <0.001		0.80 (0.70 - 0.90) <0.001	
First HF hospitalisation				
Events – no (%)	223 (13.3)	1239 (17.0)	210 (14.1)	732 (17.1)
Event rate per 100 person-years	5.6 (4.9 - 6.4)	7.3 (6.9 - 7.7)	5.7 (5.0 - 6.5)	7.0 (6.5 - 7.6)
Adjusted sHR	0.79 (0.68 - 0.92) 0.002		0.83 (0.71 - 0.98) 0.027	
Cardiovascular death				
Events – no (%)	240 (14.3)	1459 (20.0)	240 (14.3)	803 (18.8)
Event rate per 100 person-years	5.5 (4.9 - 6.3)	7.9 (7.5 - 8.3)	5.8 (5.1 - 6.6)	7.1 (6.6 - 7.6)
Adjusted sHR	0.63 (0.55 - 0.73) <0.001		0.77 (0.66- 0.90) 0.001	
All-cause death				
Events – no (%)	286 (17.1)	1765 (24.2)	272 (18.2)	954 (22.3)
Event rate per 100 person-years	6.6 (5.9 - 7.4)	9.5 (9.1 - 10.0)	6.8 (6.1 - 7.7)	8.4 (7.9 - 8.9)
Adjusted HR	0.62 (0.54 - 0.71) <0.001		0.75 (0.65 - 0.86) 0.001	

All risk ratios shown compare women to men.
Sub-distribution hazard ratios reported as sHR (95% confidence interval) [hazard ratio for all-cause hospitalisation +/or death].
Event rates per 100 person-years with 95% confidence interval.
Adjusted sHRs additionally adjusted for: region, randomised treatment, age, heart rate, systolic blood pressure, body mass index, NT-proBNP, NYHA functional class, ejection fraction and estimated glomerular filtration rate.
Heart failure hospitalisation additionally adjusted for previous hospitalisation for heart failure.

Figure 4-4 Clinical outcomes

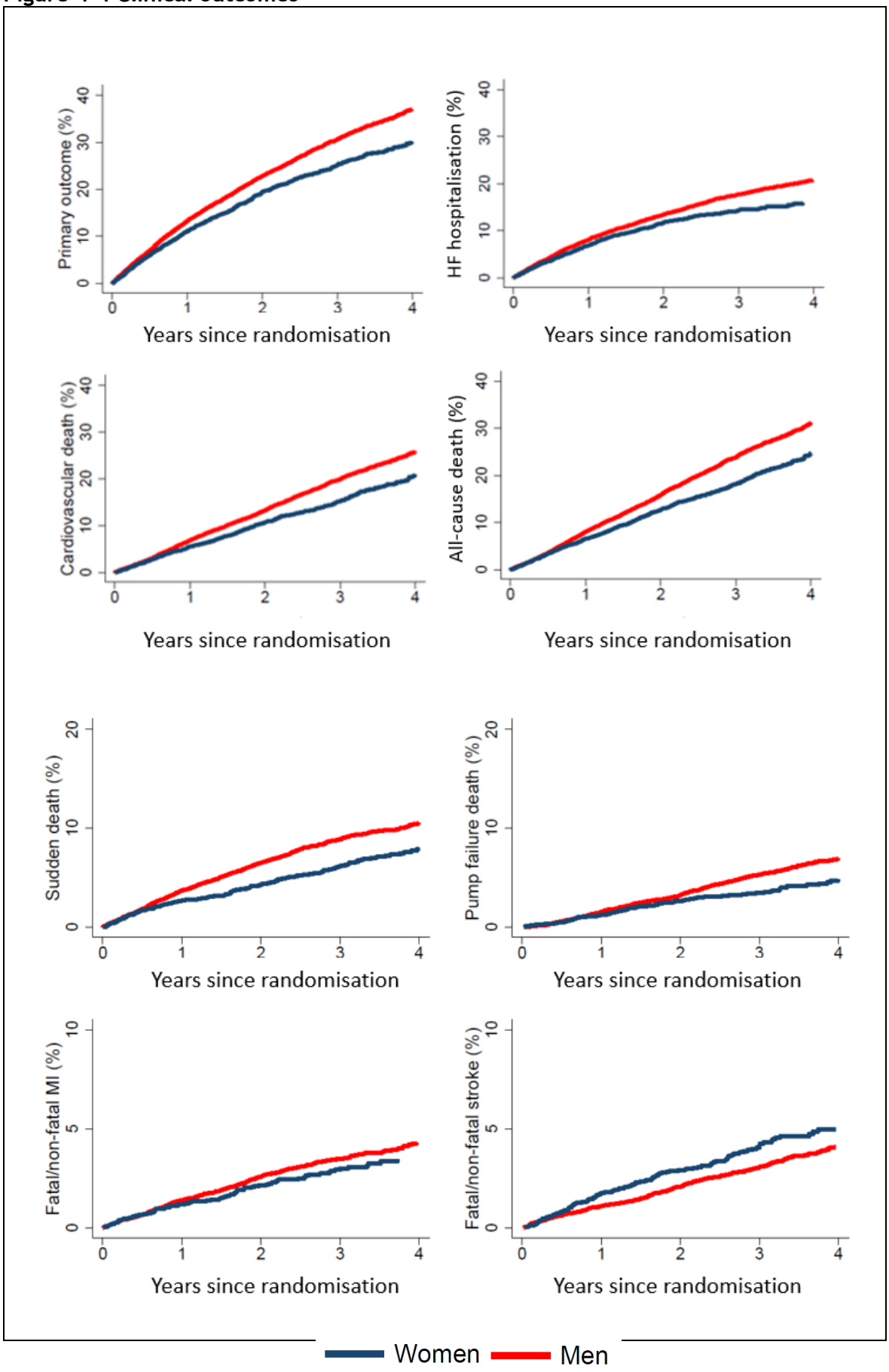


Figure 4-5 Clinical outcomes - Ischaemic and non-ischaemic aetiology

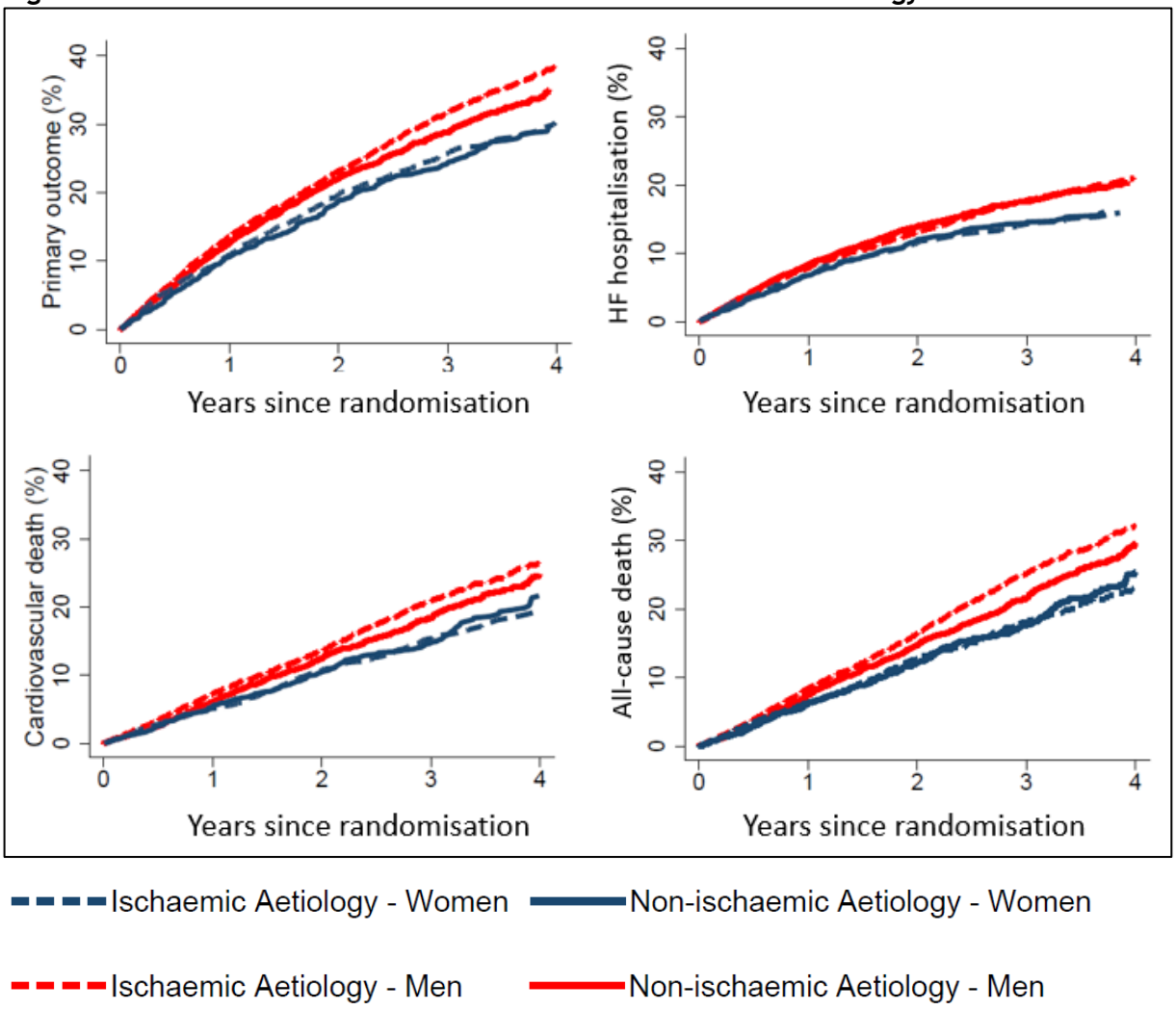


Table 4-10 Number of hospitalisations in women and men with HFrEF

	Women n=3357	Men n=12058
HF hospitalisation		
0	2897 (86.3)	9999 (82.9)
1	317 (9.4)	1287 (10.7)
≥2	143 (4.3)	772 (6.4)
Cardiovascular hospitalisation		
0	2445 (72.8)	7991 (66.3)
1	545 (16.2)	2234 (18.5)
≥2	367 (11.0)	1833 (15.2)
Non-cardiovascular hospitalisation		
0	2559 (76.2)	8833 (73.3)
1	527 (15.7)	2009 (16.7)
≥2	271 (8.1)	1216 (10.0)
All-cause hospitalisation		
0	1968 (58.6)	6312 (52.4)
1	749 (22.3)	2657 (22.0)
≥2	640 (19.1)	3089 (25.6)

Discussion

In an analysis of 15415 patients, including 3357 women from 55 countries, many known differences between men and women were confirmed.[92,119,120,123] In addition, I identified some new differences and, importantly, showed a narrowing of previously highlighted gaps, especially in pharmacological treatment (although anticoagulants were still underutilized in women). However, problems persist - women were undertreated with devices and less likely to receive influenza vaccination, to be enrolled in a disease-management program or to be prescribed an exercise regimen.

Women remain the minority of patients with HFrEF enrolled in trials, because HFrEF is more common in men. Women are older than men and less likely to have an ischaemic aetiology. Both physician-assessed (NYHA class) and patient-reported (KCCQ) severity of HF was greater in women than men. Women had more symptoms and signs of HF (and congestion), despite having more recently diagnosed HF, higher mean LVEF and similar NT-proBNP (and even lower BNP). Prior HF hospitalisation was less common in women than men. Looking at other markers of severity, more women had an eGFR<60ml/min/1.73m^2 and SBP was slightly higher than in men. The most striking difference was the large (10 point) difference in the median KCCQ score. This is notable given that older patients, generally report better QoL, compared with younger patients, and women were older than men.[134] To explore what lay behind this difference I examined different KCCQ domains. The largest difference was in “physical limitations”. This was supported by the State of Health Score (from the EQ-5D-3L) which showed striking differences between women and men in mobility, ability to undertake usual activities and self-care. The reasons for these differences in symptoms and HRQL between men and women are not clear as they do not seem to be explained by major differences in physiological markers of HF severity or by comorbidities. Clearly, however, HF appears to have a greater impact on the lives of women, compared with men, and women live with more symptoms and worse disease-specific and general quality-of-life than men.

The pattern of comorbidity differed strikingly between men and women. Given their less frequent ischemic aetiology, women had fewer manifestations of CAD

and athero-thrombotic disease more generally. Conversely, a history of hypertension was more common in women. Obesity was also more common although diabetes was not. AF was less common in women and COPD much less common, in keeping with the lower rate of previous or current smoking in women (although, this again highlights the greater dyspnoea experienced by women). While the prevalence of anaemia, was similar between men and women, mean haemoglobin in women was 12g/l, lower than in men. A remarkable proportion of women (45%) self-reported moderate-to-extreme anxiety/depression using the EQ-5D-3L score (especially if their aetiology was ischemic). This may suggest HF has a greater psychological impact on women than on men. These findings of worse symptoms and more physical and psychological disability related highlight the underutilization of disease-management programs and exercise regimens in women, the interventions likely to be particularly helpful for these problems.

HFrEF studies have shown that women may need lower doses of ACEIs or ARBs and beta-blockers than men.[174] In HFpEF, spironolactone and sacubitril/valsartan have been shown to lower the risk of different clinical outcomes in women while no such benefit was seen in men.[79,175] In this study, prior treatment with a renin-angiotensin system blocker was required in PARADIGM-HF and ATMOSPHERE and women were more often treated with an ARB (as opposed to ACEI), compared with men, probably reflecting the higher likelihood of cough with ACEI in women.[176,177] Beta-blocker use was also required, unless not tolerated or contraindicated, and was similar between sexes. MRA use was at the investigators' discretion and was similar, between sexes. Although women had more congestion than men, use of diuretics was similar between the sexes, as was the use of digoxin, even though women had less AF and despite digoxin use being associated with greater mortality in women.[118] Overall, therefore, and contrary to previous reports, I did not find evidence of significant undertreatment of women with most HF medications, except, perhaps diuretics which appeared relatively underused given the finding of more congestion in women.[123] This underuse of diuretics, overuse of digoxin and underutilization of disease-management programs and exercise prescription in women brings to focus potentially important questions about the role of sex differences in doctor-

patient communication, prescribing and medical practice more generally.[116,118,178–180] Do doctors fail to appreciate the impact of HF in women compared with men or are women less able to communicate the severity of the impact of their illness? I am not aware of any prior report of lower enrolment of women in disease management and exercise programs, but similar underutilization of cardiac rehabilitation has been reported and the explanation is likely multifactorial, and includes the older age of women, comorbidity, and socio-economic factors.[181] Women may also be more likely to withdraw from such programs even though trials such as Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) have shown potentially greater benefit from rehabilitation and exercise in women compared with men.[182,183]

In contrast to drugs for HF, device use, especially ICD use, was much lower in women than men. Further analysis according to aetiology, NYHA class, LVEF, rhythm and QRS duration/morphology did not account for the disparity in device use. The lower use of CRT in women is especially notable as that this intervention may be even more effective in women than men and given that LBBB is more common in women (as confirmed in the present study), often with a narrower QRS duration than in men.[184]

Anticoagulant use was significantly less common in women with a history of AF (and in those with AF on their baseline ECG), reflecting registry and "real-world" data showing underuse of these drugs in women.[185] Differences in other pharmacological therapies appeared to reflect differences in comorbidities e.g. the greater use of statins and aspirin in men likely reflected the higher prevalence of CAD in males.

As has been shown previously, women had better outcomes than men.[92,119,123] However, I did analyses additional to those carried out in previous clinical trial datasets. Because ATMOSPHERE and PARADIGM-HF were more contemporary than prior studies, measurement of NT-proBNP was available and I was able to adjust for this most powerful of all prognostic variables in HF. Given, the lower mortality rate in women than men, I also analysed hospitalisation for HF, taking

account of the competing risk of death (and examined the total burden of HF hospitalisations by examining repeat events).

Even after adjusting for NT-proBNP, and other prognostic variables, women remained less likely to die than men. Indeed, the differential increased somewhat so that the adjusted risk of death from any cause was 32% lower in women, greater than that identified in the largest prior gender-based analysis in HF from CHARM.[123] I also looked at the two major modes of cardiovascular death in HFrEF i.e. sudden death and death from pump failure/progressive HF. Both were less common in women (and the lower risk was proportionally similar for each, in women compared with men). The explanation for this is unknown although one possibility is the difference that has been described in cardiac remodelling between men and women, possibly aggravated by more unfavourable remodelling in response to ischemic injury in men (with a higher prevalence of CAD in males).[186,187]

In contrast to death, the lower risk of a first HF hospitalisation was less marked: women were 20% less likely to be hospitalised for HF than men. This more modest relative risk may be because I accounted for the substantial competing-risk of death. Interestingly, the lower risk of HF hospitalisation in women was apparent for second and subsequent (and not just first) admissions, and the gender-difference was larger when repeat admissions were examined. Moreover, the risk of hospitalisation for any cardiovascular reason and for any reason at all was lower in women (although the largest gender-difference was seen for HF and the smallest for all-cause hospitalisation). The absolute differences were substantial when repeat events were considered: 3, 6 and 10 fewer admissions per 100 person-years of follow-up in women, compared with men, for HF, any cardiovascular reason and all-causes, respectively.

Collectively, these differences in symptoms/QoL, mortality and hospitalisation highlight some interesting gender-related paradoxes. Intuitively, worse symptoms/QoL might have been expected to be associated with higher (rather than lower) rates of hospitalisation. Similarly, better survival might have led to a higher life-time burden of hospital admissions (especially if longevity was associated with greater symptoms and worse QoL). In both cases the converse

was observed, with women living longer than men but experiencing poorer QoL during their additional years of life. The explanation for the disconnect between symptoms/QoL and hospital admission rates is uncertain. Is it just about women's perception of the impact of their disease or are there gender-related confounders not measured in this study e.g. differences in access to health care, less caregiver support/living alone, socioeconomic, and educational factors, and less proactive seeking of help? This raises the possibility of emphasizing different aspects of management of HF in men and women with women needing relatively more attention paid to well-being than men.

As expected from the difference in background CAD, the risk of MI was lower in women than men. Conversely, the risk of stroke was greater and may, in part, be explained by the lower rate of anticoagulation in women, as mentioned above, as well as the higher prevalence of hypertension in women.

There have been a few other recent reports about sex-related differences in HFrEF trials. In DAPA-HF the risk of morbidity and mortality outcomes were lower in women but with a lower QoL in keeping with results in the present analysis.[188] The Surgical Treatment for Ischemic Heart Failure trial (STICH) enrolled 148 women between 2004 and 2007 and the Echocardiography Guided Cardiac Resynchronization Therapy trial (EchoCRT) enrolled 224 women between 2008 and 2013.[189,190] Apart from the small number of women in both these trials, it is difficult to draw any general conclusions because patients were also highly selected for specific interventions and EchoCRT was stopped early for harm, with only 64 primary events among women.

As alluded to earlier, HFpEF is the more prevalent HF phenotype in women. This is concerning since there are fewer treatment options available for patients with HFpEF. However, there exists the possibility that women with HF might benefit from treatment to a higher level of LVEF. I demonstrated this in a separated analysis of 7 clinical trials in HF.[191] Moreover, in the recent PARAGON-HF trial, a statistically significant reduction in risk of the primary outcome was only observed in women while there was no risk reduction observed in men. [79] In the same trial, while event rate for cardiovascular death was lower in women compared to men, similar to the findings in my analysis in HFrEF, no significant

difference in event rates for HF hospitalisation was seen. I also observed the same in a separate analysis I conducted comparing sex related differences in clinical outcomes in a pooled cohort of three clinical trials in HFpEF.[192] Here I found that women had worse symptoms, a lower quality of life but lower mortality similar to HFrEF but no difference in risk of HF hospitalisation was observed.

Strengths & Limitations

The patients enrolled were selected and are potentially better treated than those in the "real world". I focused on HFrEF whereas many women with HF have preserved LVEF. I did not have serial assessments of left ventricular structure and function. This study has strengths as well. It is the only large, contemporary, clinical trial dataset with as many women. In trials patients are well characterized, and outcomes are carefully collected and adjudicated. Because of the increasing globalization of trials, I was able to report most geographically representative analysis of women with HFrEF to date.

Conclusions

In summary, while women with HFrEF have fewer comorbidities, better survival and lower rates of hospitalisation, they have more symptoms and worse QoL than men. They also report much more anxiety/depression. Women appeared relatively undertreated with diuretics given their greater evidence of congestion and devices were underutilized more in women than in men. Women were less often referred to a disease management program or prescribed an exercise regimen. Although women with HFrEF live longer than men, their additional years of life are of poorer quality, with greater self-reported psychological and physical disability. This different sex-related experience of HFrEF is unexplained and it is uncertain whether physicians recognize it. Women continue to receive suboptimal treatment, compared to men.

Chapter 5. Heart failure and chronic obstructive pulmonary disease: association with clinical outcomes and effect on drug therapy

This chapter has been published as:

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COPD has a higher prevalence in patients with HF than in the general population.[43,44,129] Factors such as smoking, inflammation and oxidative stress have all been postulated to play a role in the pathogenesis of both conditions.[43,44,129] Additionally, clinical presentations of both conditions overlap, and coexistence of COPD in patients with HF poses diagnostic and therapeutic challenges for clinicians.[43,44,129,193–197] The presence of COPD in patients with HF is associated with worse prognosis.[43,44,129,198–200] COPD was a final predictor in 11% of the final models in the systematic review in Chapter 1. [87,90,102]

In this chapter I have compared the risk of various outcomes in patients with HFrEF with coexistent COPD and those without COPD enrolled in the DAPA-HF trial.[40] I have also analysed whether the effects of the SGLT-2 inhibitor dapagliflozin in DAPA-HF, were modified by the existence of COPD. In addition, the smaller proportion of patients who had asthma and compare and contrast their baseline characteristics and risk of outcomes with the rest of the population have also been studied.

Methods

The trial population has been described in detail in Chapter 2.

Population analysed

An investigator-reported history of COPD was identified from a check box on the case-report form for DAPA-HF. No specific instructions were given concerning the diagnosis of COPD. Investigators reported diagnosis of asthma similarly. There were no respiratory disease or respiratory treatment related exclusions, although investigators were asked to exclude patients with another condition likely to lead to life-expectancy of <2 years.

Outcomes

For this population, as outlined in chapter 2, I have analysed the primary composite outcome of a worsening HF event (an unplanned hospitalisation for HF or an urgent visit for HF requiring intravenous therapy) or cardiovascular death and its components. Additional secondary endpoints analysed are the composite of hospitalisation for HF or cardiovascular death, its components, a composite of the total number of hospitalisations for HF (first and repeats) and cardiovascular death, the change from baseline to 8 months in the total symptom score (TSS) of the KCCQ and all-cause death. In addition to the prespecified outcomes, I also analysed: i) KCCQ overall summary score (KCCQ-OSS) and KCCQ clinical summary score (KCCQ-CSS) and ii) non-cardiovascular deaths, because of the potential impact of COPD on QoL and deaths from respiratory causes and infection.

Safety outcomes examined include serious adverse events, adverse events leading to treatment discontinuation and other adverse events of special interest (adverse events related to volume depletion, renal adverse events, bone fractures, amputations, major hypoglycaemic episodes) and laboratory findings of note.

Statistical analysis

The primary analysis examined patients with an investigator-reported history of COPD, including a small number with concurrent asthma; patients with asthma alone were also examined.

Baseline characteristics are summarized as means (standard deviations), median (interquartile ranges), or percentages. Time-to-event data are evaluated using Kaplan-Meier estimates and Cox proportional-hazards models, stratified by diabetes status, and adjusted for history of HF hospitalisation (except for non-

cardiovascular and all-cause death) and treatment-group assignment. I used a semiparametric proportional-rates model to analyse total (including recurrent) events, as previously described. I also adjusted the effect of COPD status in two additional models: Model 1 included age, sex, region, SBP, history of atrial fibrillation, NYHA class III/IV, LVEF, log NT-proBNP, eGFR and smoking status. Model 2 had additional adjustments for baseline beta-blocker and MRA prescription. Mean change in KCCQ-TSS from baseline to 8 months was also analysed. Safety analyses are performed in randomised patients who had received at least one dose of dapagliflozin or placebo (8 of 4744 patients excluded). Interaction between COPD status and treatment effect on the occurrence of the pre-specified safety outcomes was tested in a logistic regression model with an interaction term between baseline COPD status and treatment.

All analyses were conducted using Stata version 16.1(College Station, TX, USA). p-value < 0.05 have been considered statistically significant.

Results

Overall, 585 (12.3%) of 4744 patients randomised had COPD, 299 (12.6%) in the dapagliflozin group and 286 (12.1%) in the placebo group.

Baseline characteristics

Table 5-1 shows baseline characteristics of those with and without COPD. Patients with COPD were more often male, older and current or ex-smokers, compared to those without COPD. A larger proportion of patients with COPD had additional comorbidities, differences in which were significant in the case of hypertension and atrial fibrillation. As shown in Table 5-1, of the 585 patients with COPD, investigators also reported a diagnosis of asthma in 56 and an additional 133 patients had an investigator-reported diagnosis of asthma only. Patients with asthma only compared to COPD were distinct in several respects e.g. slightly younger, more likely female and much less smoking history.

Table 5-1 Baseline characteristics

	Without COPD	With COPD	p-value	Without COPD/asthma	COPD only	Asthma only	COPD & asthma	p-value
	n=4159	n=585		n=4026	n=529	n=133	n=56	
Age (years.)	66.0±11.0	69.1±9.4	<0.001	65.9 ± 11.0	68.9 ± 9.5	66.6 ± 10.2	70.9 ± 8.9	<0.001
Females – no. (%)	1002 (24.1)	107 (18.3)	0.002	952 (23.6)	91 (17.2)	50 (37.6)	16 (28.6)	<0.001
Region – no. (%)			<0.001					<0.001
North America	541 (13.0)	136 (23.2)		515 (12.8)	114 (21.6)	26 (19.5)	22 (39.3)	
Latin America	750 (18.0)	67 (11.5)		734 (18.2)	62 (11.7)	16 (12.0)	5 (8.9)	
Europe	1858 (44.7)	296 (50.6)		1796 (44.6)	278 (52.6)	62 (46.6)	18 (32.1)	
Asia/Pacific	1010 (24.3)	86 (14.7)		981 (24.4)	75 (14.2)	29 (21.8)	11 (19.6)	
Race – no. (%)			<0.001					<0.001
White	2864 (68.9)	469 (80.2)		2777 (69.0)	430 (81.3)	87 (65.4)	39 (69.6)	
Black	202 (4.9)	24 (4.1)		191 (4.7)	18 (3.4)	11 (8.3)	6 (10.7)	
Asian	1028 (24.7)	88 (15.0)		999 (24.8)	77 (14.6)	29 (21.8)	11 (19.6)	
Other	65 (1.6)	4 (0.7)		59 (1.5)	4 (0.8)	6 (4.5)	0 (0.0)	
SBP (mmHg)	121.5 ± 16.3	123.8 ± 16.6	0.001	121.6 ± 16.3	124.0 ± 16.6	119.6 ± 15.4	122.1 ± 16.3	0.005
DBP (mmHg)	73.5 ± 10.5	73.2 ± 10.2	0.42	73.6 ± 10.5	73.5 ± 10.2	72.5 ± 9.5	69.9 ± 9.7	0.040
Heart rate (bpm)	71.4 ± 11.7	72.0 ± 11.4	0.24	71.4 ± 11.7	72.0 ± 11.4	73.5 ± 13.3	72.7 ± 11.3	0.11
BMI* (kg/m^2)	28.1 ± 5.9	28.3 ± 6.4	0.50	28.0 ± 5.8	28.3 ± 6.3	30.7 ± 7.7	28.4 ± 7.2	<0.001
Comorbidities – no. (%)								
Hypertension	3049 (73.3)	474 (81.0)	<0.001	2952 (73.3)	429 (81.1)	97 (72.9)	45 (80.4)	0.001
Diabetes	1861 (44.7)	278 (47.5)	0.21	1796 (44.6)	252 (47.6)	65 (48.9)	26 (46.4)	0.46
Atrial fibrillation	1557 (37.4)	261 (44.6)	<0.001	1501 (37.3)	238 (45.0)	56 (42.1)	23 (41.1)	0.005
Myocardial infarction	1825 (43.9)	267 (45.6)	0.42	1784 (44.3)	244 (46.1)	41 (30.8)	23 (41.1)	0.014

Stroke	405 (9.7)	61 (10.4)	0.60	392 (9.7)	57 (10.8)	13 (9.8)	4 (7.1)	0.79
Smoking status – no (%)			<0.001					<0.001
Never	1854 (44.6)	105 (18.0)		1782 (44.3)	88 (16.6)	72 (54.1)	17 (30.4)	
Former	1770 (42.6)	322 (55.0)		1726 (42.9)	290 (54.8)	44 (33.1)	32 (57.1)	
Current	535 (12.9)	158 (27.0)		518 (12.9)	151 (28.5)	17 (12.8)	7 (12.5)	

All values are reported as mean ± standard deviation except where indicated.
*Median (interquartile range)
SBP – systolic blood pressure; DBP – diastolic blood pressure; BMI – body mass index

Heart failure characteristics

As shown in Table 5-2, patients with COPD had lower (worse) median KCCQ-TSS, KCCQ-CSS and KCCQ-OSS scores and a worse NYHA functional class distribution than those without COPD. Those with only asthma were also similar to patients with COPD with worse KCCQ scores than the rest of the population.

Table 5-2 Heart failure characteristics

	Without COPD	With COPD	p-value	Without COPD/asthma	COPD only	Asthma only	COPD & asthma	p-value
	n=4159	n=585		**n=4026**	**n=529**	**n=133**	**n=56**	
HF aetiology			0.49					0.001
Ischaemic	2331 (56.0)	343 (58.6)		2275 (56.5)	321 (60.7)	56 (42.1)	22 (39.3)	
Non-ischaemic	1489 (35.8)	198 (33.8)		1425 (35.4)	171 (32.3)	64 (48.1)	27 (48.2)	
Unknown	339 (8.2)	44 (7.5)		326 (8.1)	37 (7.0)	13 (9.8)	7 (12.5)	
NYHA III/IV	1292 (31.1)	249 (42.6)	<0.001	1246 (30.9)	230 (43.5)	46 (34.6)	19 (33.9)	<0.001
KCCQ-TSS*	79 (60 - 93)	71 (53 - 85)	<0.001	79 (60 - 93)	71 (52 - 85)	73 (52 - 88)	72 (58 - 86)	<0.001
KCCQ-CSS*	75 (58 – 89)	67 (51 – 82)	<0.001	75 (58 - 89)	67 (51 - 82)	71 (47 - 85)	69 (53 - 82)	<0.001
KCCQ OSS*	72 (55 – 86)	65 (48 – 79)	<0.001	72 (55 - 86)	65 (48 - 79)	68 (49 - 85)	68 (50 - 81)	<0.001
Previous HF hospitalisation	1951 (46.9)	300 (51.3)	0.047	1891 (47.0)	273 (51.6)	60 (45.1)	27 (48.2)	0.23

All values are reported as number (percentage) except where indicated.
*Median (interquartile range)
HF – heart failure; NYHA – New York heart association; KCCQ – Kansas City cardiomyopathy questionnaire; TSS – total summary score; CSS – clinical summary score; OSS – overall summary score.

Investigations

LVEF and median NT-proBNP were higher and eGFR was lower in patients with COPD compared to those without and the same was true for those with asthma as well except for a lower LVEF.

Table 5-3 Investigations

	Without COPD	With COPD	p-value	Without COPD/asthma	COPD only	Asthma only	COPD & asthma	p-value
	n=4159	n=585		n=4026	n=529	n=133	n=56	
LVEF	31.0 ± 6.8	31.6 ± 6.8	0.036	31.0 ± 6.8	31.8 ± 6.8	30.1 ± 7.0	29.9 ± 6.1	0.017
NT-proBNP(pg/ml)	1418 (850 - 2616)	1574 (893 - 2807)	0.021	1417 (848 - 2614)	1572 (893 - 2793)	1456 (987 - 2874)	1669 (879 - 2932)	0.13
eGFR (mL/min/1.73 m^2)	66.1 ± 19.4	63.4 ± 19.4	0.001	66.3 ± 19.4	63.6 ± 19.3	61.4 ± 18.4	61.1 ± 20.3	<0.001
Creatinine (umol/L)	1652 (39.7)	274 (46.9)	<0.001	103.9 ± 30.0	107.4 ± 32.3	107.6 ± 30.4	109.6 ± 37.0	0.024
Haemoglobin (g/L)	104.0 ± 30.0	107.6 ± 32.8	0.007	135.5 ± 16.2	136.3 ± 16.4	134.9 ± 15.8	131.8 ± 15.8	0.23

All values are reported as number (percentage) except where indicated.
*Median (interquartile range)
HF – heart failure; NYHA – New York heart association; KCCQ – Kansas City cardiomyopathy questionnaire; TSS – total summary score; CSS – clinical summary score; OSS – overall summary score.

Baseline therapy

Patients with COPD were only slightly less likely to be treated with a beta-blocker and were also less likely to be prescribed a MRA. Patients who had COPD treated with beta-blocker were less likely to be taking a non-selective antagonist and more likely to have been prescribed a beta-1 adrenoceptor selective agent than those without COPD.

As shown in Table 5-4, among patients with COPD, 213 (36.4%) were treated with an inhaled beta-agonist, 138 (23.6%) with a muscarinic antagonist and 71 (12.1%) with a corticosteroid.

Although beta-blocker use was high (91.0%) in patients with asthma only, it was lower than in any group as shown in Table 5-4. Conversely the use of corticosteroids was highest in patients with asthma, compared with COPD only.

Table 5-4 Therapy at baseline

	Without COPD	With COPD	p-value	Without COPD/asthma	COPD only	Asthma only	COPD & asthma	p-value
	n=4159	n=585		n=4026	n=529	n=133	n=56	
Diuretics	3885(93.4)	548(93.7)	0.81	3757 (93.3)	495 (93.6)	128 (96.2)	53 (94.6)	0.58
Digoxin	786(18.9)	101(17.3)	0.34	754 (18.7)	91 (17.2)	32 (24.1)	10 (17.9)	0.34
ACEI	2340(56.3)	321(54.9)	0.53	2281 (56.7)	298 (56.3)	59 (44.4)	23 (41.1)	0.004
ARB	1161(27.9)	146(25.0)	0.13	1125 (27.9)	132 (25.0)	36 (27.1)	14 (25.0)	0.51
ARNI	437(10.5)	71(12.1)	0.23	411 (10.2)	58 (11.0)	26 (19.5)	13 (23.2)	<0.001
Beta-blocker	4018(96.6)	540(92.3)	<0.001	3897 (96.8)	487 (92.1)	121 (91.0)	53 (94.6)	<0.001
≥50% of target dose	2066(51.4)	283(52.4)	0.67	2002 (51.4)	258 (53.0)	64 (52.9)	25 (47.2)	0.82
Beta-1 selective*	2427(58.4)	352(60.2)	0.42	2351 (58.5)	315 (59.5)	76 (57.1)	37 (66.1)	0.65
Non-selective*	1587(38.2)	188(32.1)	0.005	1542 (38.3)	172 (32.5)	45 (33.8)	16 (28.6)	0.023
MRA	2987(71.8)	383(65.5)	0.002	2901 (72.1)	350 (66.2)	86 (64.7)	33 (58.9)	0.002
Ivabradine	203(4.9)	25(4.3)	0.52	192 (4.8)	21 (4.0)	11 (8.3)	4 (7.1)	0.17
PCI	1415(34.0)	209(35.7)	0.42	1378 (34.2)	189 (35.7)	37 (27.8)	20 (35.7)	0.39
CABG	687(16.5)	112(19.1)	0.11	672 (16.7)	104 (19.7)	15 (11.3)	8 (14.3)	0.099
ICD	830(20.0)	123(21.0)	0.55	288 (7.2)	42 (7.9)	17 (12.8)	7 (12.5)	0.041
CRT	305(7.3)	49(8.4)	0.37	797 (19.8)	108 (20.4)	33 (24.8)	15 (26.8)	0.30
Respiratory system drugs								
Adrenergic agonists †	73 (1.8)	145 (24.8)	<0.001	31 (0.8)	120 (22.7)	42 (31.6)	25 (44.6)	<0.001
Adrenergic agonists (in combinations) † ‡	55 (1.3)	119 (20.3)	<0.001	28 (0.7)	101 (19.1)	27 (20.3)	18 (32.1)	<0.001
Any inhaled adrenergic agonist †	116 (2.8)	213 (36.4)	<0.001	53 (1.3)	181 (34.2)	63 (47.4)	32 (57.1)	<0.001
Muscarinic antagonists †	34 (0.8)	138 (23.6)	<0.001	23 (0.6)	120 (22.7)	11 (8.3)	18 (32.1)	<0.001
Glucocorticoids†	45 (1.1)	71 (12.1)	<0.001	18 (0.4)	58 (11.0)	27 (20.3)	13 (23.2)	<0.001

Systemic adrenergic agonists	1 (0.01)	9 (1.5)	<0.001	1 (0.0)	9 (1.7)	0 (0.0)	0 (0.0)	<0.001
Other drugs	4 (0.1)	31 (5.3)	<0.001	4 (0.1)	28 (5.3)	0 (0.0)	3 (5.4)	<0.001
Diabetes medications#								
Biguanide	890 (51.2)	126 (51.2)	1.00	862 (51.5)	113 (50.7)	28 (45.2)	13 (56.5)	0.744
DPP-4 inhibitor	281 (16.2)	29 (11.8)	0.076	270 (16.1)	27 (12.1)	11 (17.7)	2 (8.7)	0.327
GLP-1 analogues	16 (0.9)	5 (2.0)	0.11	16 (1.0)	4 (1.8)	0 (0.0)	1 (4.4)	0.225
Sulfonylurea	380 (21.9)	58 (23.6)	0.55	370 (22.1)	51 (22.9)	10 (16.1)	7 (30.4)	0.515
Insulin	471 (27.1)	69 (28.0)	0.76	454 (27.1)	63 (28.3)	17 (27.4)	6 (26.1)	0.986

All values are shown as number (%).
ACEI – angiotensin-converting enzyme inhibitor, ARB – angiotensin receptor blocker, ARNI – angiotensin receptor neprilysin inhibitor, RAS – renin angiotensin system, MRA – mineralocorticoid receptor antagonist, PCI – primary coronary intervention, CABG – coronary artery bypass graft, CRT – cardiac resynchronization therapy, ICD – implantable cardioverter-defibrillator, DPP - Dipeptidyl peptidase, GLP - glucagon-like peptide.
*4 patients excluded
†Inhaled.
‡ In combination with corticosteroids /antimuscarinics/ other drugs.
§Only in patients with a medical history of diabetes (1983).

Clinical outcomes

Hospitalisation and mortality outcomes in patients with and without COPD

Primary outcome:
The incidence rate (per 100 person-years) of the primary composite outcome was higher in patients with COPD than in those without (18.9; 95% CI 16.0-22.2 versus 13.0; 95% CI 12.1-14.0) [Table 5-5 and Figure 5-1]. The elevated risk persisted after adjustment for other prognostic variables and use of a beta-blocker or MRA. The elevation of risk was somewhat higher when recurrent events were included [Table 5-5]. Figure 5-2 shows the excess risk associated with COPD was similar to the risk associated with CKD and diabetes, and greater than the other comorbidities examined.

Worsening HF event:
The adjusted risk of a worsening HF event was also significantly higher in patients with COPD, compared to those without.

Mortality:
By contrast, the crude incidence of cardiovascular death was only slightly higher in patients with COPD and the adjusted risk was not significantly elevated. However, unadjusted and adjusted risk of death from any cause was higher in patients with COPD, because of a substantially elevated (two-fold) risk of non-cardiovascular death [Table 5-5]. The excess of non-cardiovascular causes of death in patients with COPD were those attributed to infection and "other" [Figure 5-3].

Mortality and hospitalisation rates for patients with asthma only (compared with COPD only) are shown in Figure 5-4. Due to the small number of individuals in the latter group (n=133), formal statistical testing wasn't done although the rate of HF hospitalisation seemed to be almost as high in patients with COPD (but mortality was similar to patients without COPD or asthma).

Symptoms and quality of life assessed using KCCQ in patients with and without COPD

Figure 5-5 shows the impact of COPD on self-reported health status. All but one of the KCCQ domains were significantly worse in patients with COPD, compared to those without. Figure 5-6 shows health status in patients with COPD, compared with other common co-morbidities. Each of the KCCQ scores was lower (worse) in patients with COPD than in participants with other comorbidities.

Table 5-5 Clinical outcomes

	Without COPD n=4159	**With COPD** n=585
Primary outcome		
Events – no. (%)	744 (17.9)	144 (24.6)
Event rate/100 person-years	13.0 (12.1 – 14.0)	18.9 (16.0 – 22.2)
HR	1.00 (ref.)	1.44 (1.21 – 1.72) <0.001
HR-1	1.00 (ref.)	1.26 (1.05 – 1.52) 0.014
HR-2	1.00 (ref.)	1.24 (1.03 – 1.50) 0.023
HF hospitalisation/urgent visit		
Events – no. (%)	456 (11.0)	107 (18.3)
Event rate/100 person-years	8.0 (7.3 – 8.8)	14.0 (11.6 – 17.0)
HR	1.00 (ref.)	1.74 (1.41 – 2.15) <0.001
HR-1	1.00 (ref.)	1.53 (1.22 – 1.90) <0.001
HR-2	1.00 (ref.)	1.51 (1.21 – 1.89) <0.001
First HF hospitalisation		
Events–no. (%)	443 (10.7)	106 (18.1)
Event rate/100 person-years	7.7 (7.1 – 8.5)	13.9 (11.5 – 16.8)
HR	1.00(ref.)	1.78 (1.44 – 2.20) <0.001
HR-1	1.00(ref.)	1.58 (1.26 – 1.97) <0.001
HR-2	1.00(ref.)	1.57 (1.25 – 1.96) <0.001
Urgent visit for HF		
Events–no. (%)	30 (0.7)	3 (0.5)
Event rate/100 person-years	0.5 (0.4 – 0.7)	0.4 (0.1 – 1.1)
HR	1.00(ref.)	0.75 (0.23 – 2.45) 0.629
HR-1	1.00(ref.)	0.63 (0.19 – 2.12) 0.453

HR-2	1.00(ref.)		0.54 (0.16 – 1.86) 0.332
Cardiovascular death			
Events – no. (%)	424 (10.2)		76 (3.0)
Event rate/100 person-years	7.1 (6.4 – 7.8)		9.1 (7.2 – 11.4)
HR	1.00 (ref.)		1.28 (1.00 – 1.63) 0.049
HR-1	1.00 (ref.)		1.10 (0.85 – 1.42) 0.453
HR-2	1.00 (ref.)		1.08 (0.84 – 1.39) 0.553
Total HF hosp./cardiovascular death*			
Events – no.	1070		239
Event rate/100 person-years	17.9 (16.8 – 19.0)		28.8 (25.3 – 32.7)
RR	1.00 (ref.)		1.59 (1.31 – 1.93) <0.001
RR-1	1.00 (ref.)		1.40 (1.15 – 1.72) 0.001
RR-2	1.00 (ref.)		1.39 (1.14 – 1.70) 0.001
Non-cardiovascular death			
Events – no.	74 (1.8)		31 (5.3)
Event rate/100 person-years	1.2 (1.0 – 1.5)		3.7 (2.6 – 5.2)
HR	1.00 (ref.)		2.99 (1.97 – 4.56) <0.001
HR-1	1.00 (ref.)		2.18 (1.38 – 3.42) 0.001
HR-2	1.00 (ref.)		2.23 (1.42 – 3.51) 0.001
All-cause death			
Events – no.	498 (12.0)		107 (18.3)
Event rate/100 person-years	8.3 (7.6 – 9.1)		12.7 (10.5 – 15.4)
HR	1.00 (ref.)		1.53 (1.25 – 1.89) <0.001
HR-1	1.00 (ref.)		1.27 (1.02 – 1.58) 0.031
HR-2	1.00 (ref.)		1.26 (1.01 – 1.57) 0.041
KCCQ – Total symptom score			
Mean change ± SD at 8 months	4.8 ± 18.9		4.1 ± 19.8
Difference†		-0.67 (-2.52 – 1.18)	
Proportion with increase in score ≥5 at 8 months	55.4		49.0
Proportion with decrease in score ≥5 at 8 months	28.3		35.0

Risk and rate ratios adjusted for randomised treatment and previous heart failure hospitalisation at baseline (except non-cardiovascular and all-cause death) and stratified by diabetes status.
Model 1 adjusted for age, sex, region, systolic blood pressure, history of atrial fibrillation, NYHA class III/IV, left ventricular ejection fraction, log of NT-pro BNP, estimated glomerular filtration rate and smoking status.
Model 2 adjusted the same as model 1 with additional adjustment for beta-blocker and MRA prescription at baseline.
*Reported as a rate ratio
†Indicates difference in means between COPD and no COPD groups.

Figure 5-1 Clinical outcomes in HFrEF according to COPD status at baseline

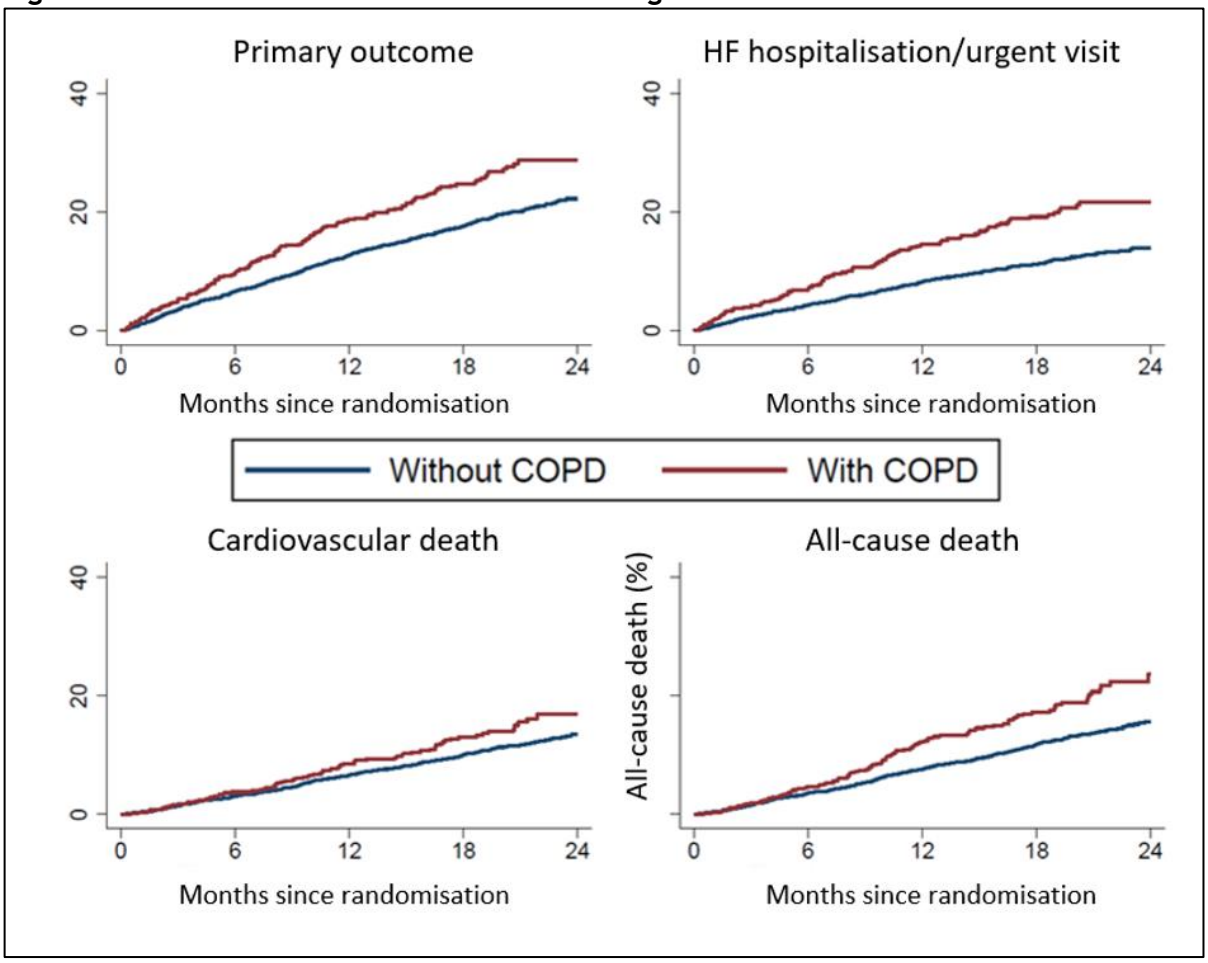
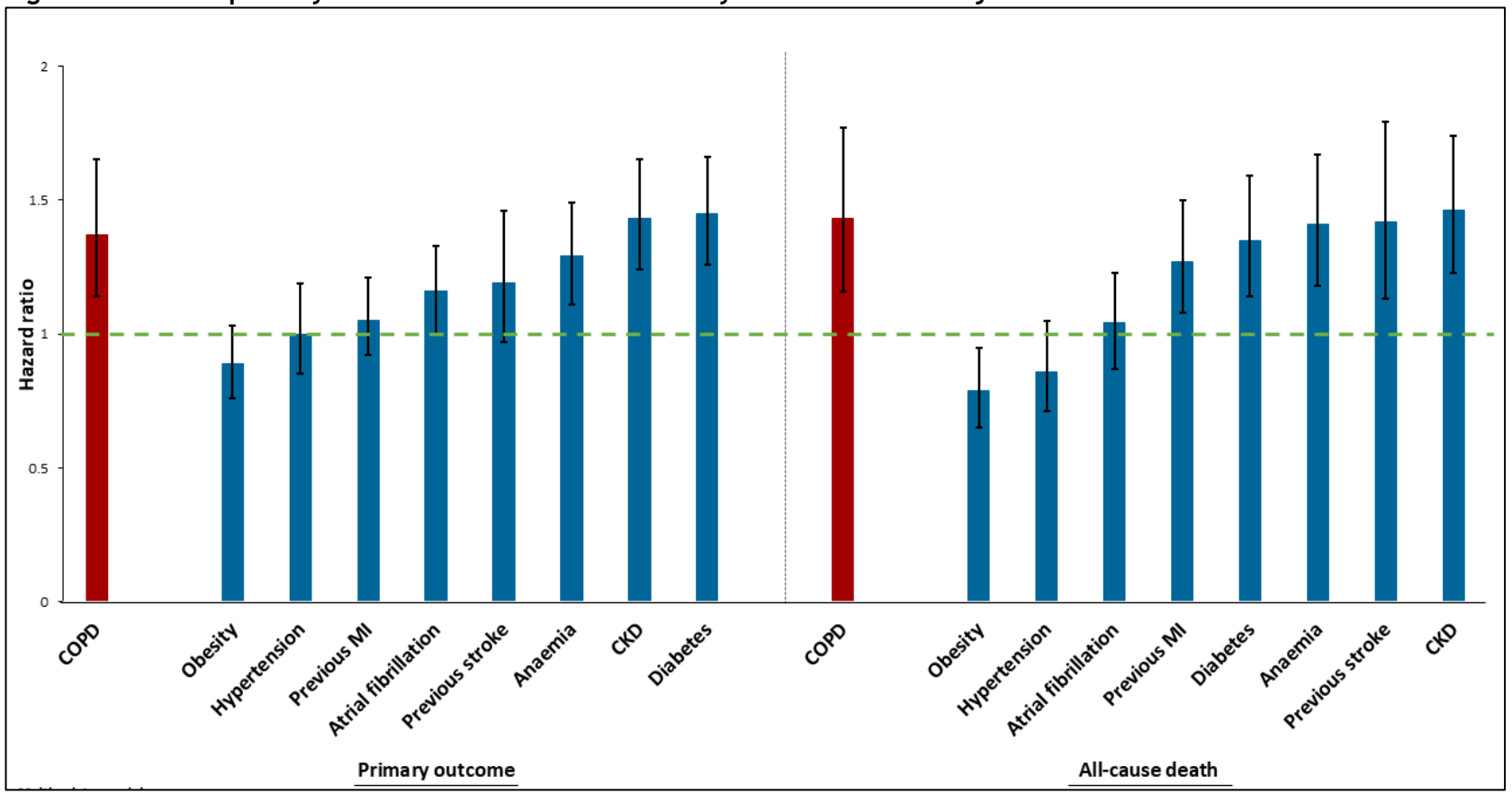
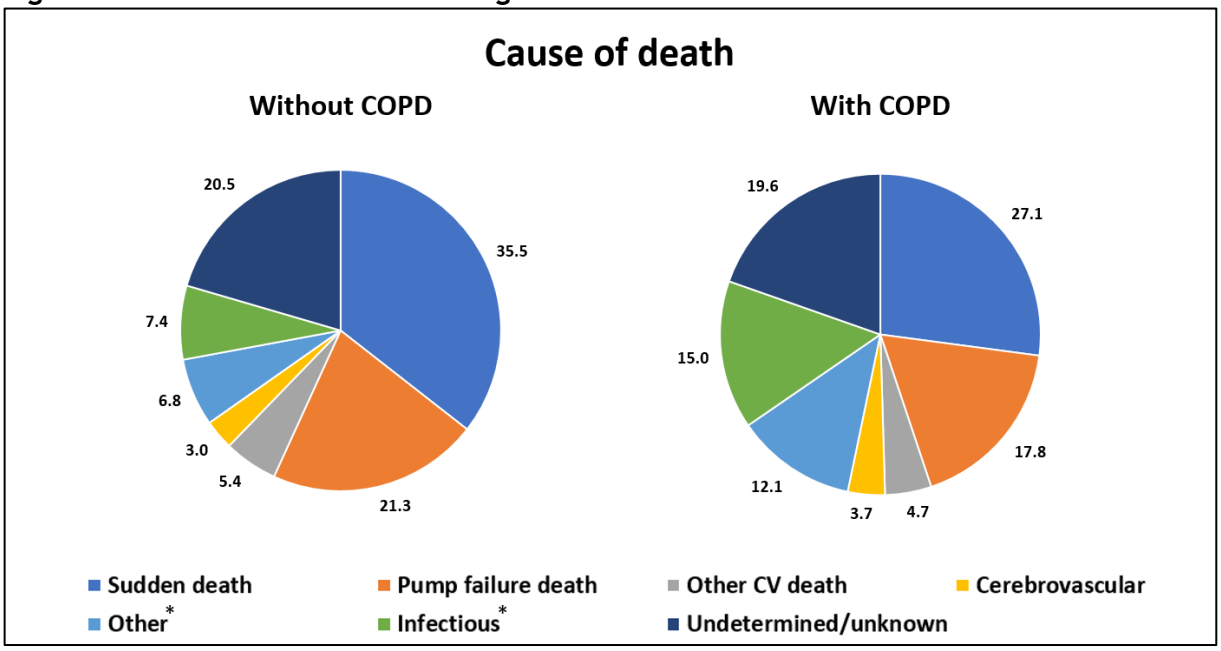


Figure 5-2 Risk of primary outcome and all-cause mortality associated with major comorbidities



Bars represent risk (hazard ratio) of the outcome examined for each comorbidity with 95% confidence interval.
All hazard ratios are adjusted for previous HF hospitalisation, randomised treatment, age, race and sex at baseline.

Figure 5-3 Causes of death according to COPD status



Other deaths: GI causes, Non-haemorrhagic/ stroke bleeding, hepatobiliary, malignancy, other, pancreatic, pulmonary failure, renal failure, suicide, trauma.
Numbers next to pie chart represent proportion of all deaths.
*represents significant difference patients with and without COPD

Figure 5-4 Clinical outcomes according to COPD and asthma status at baseline

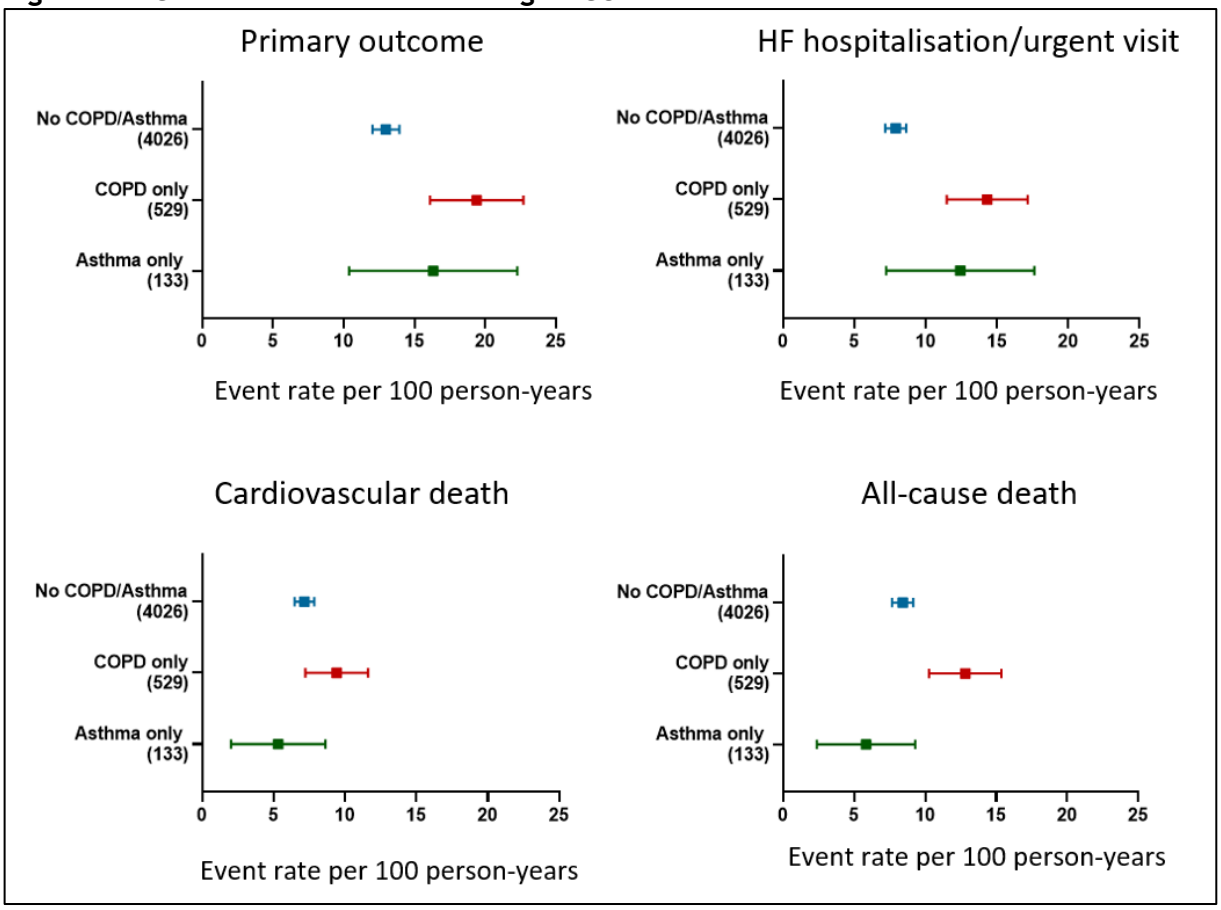
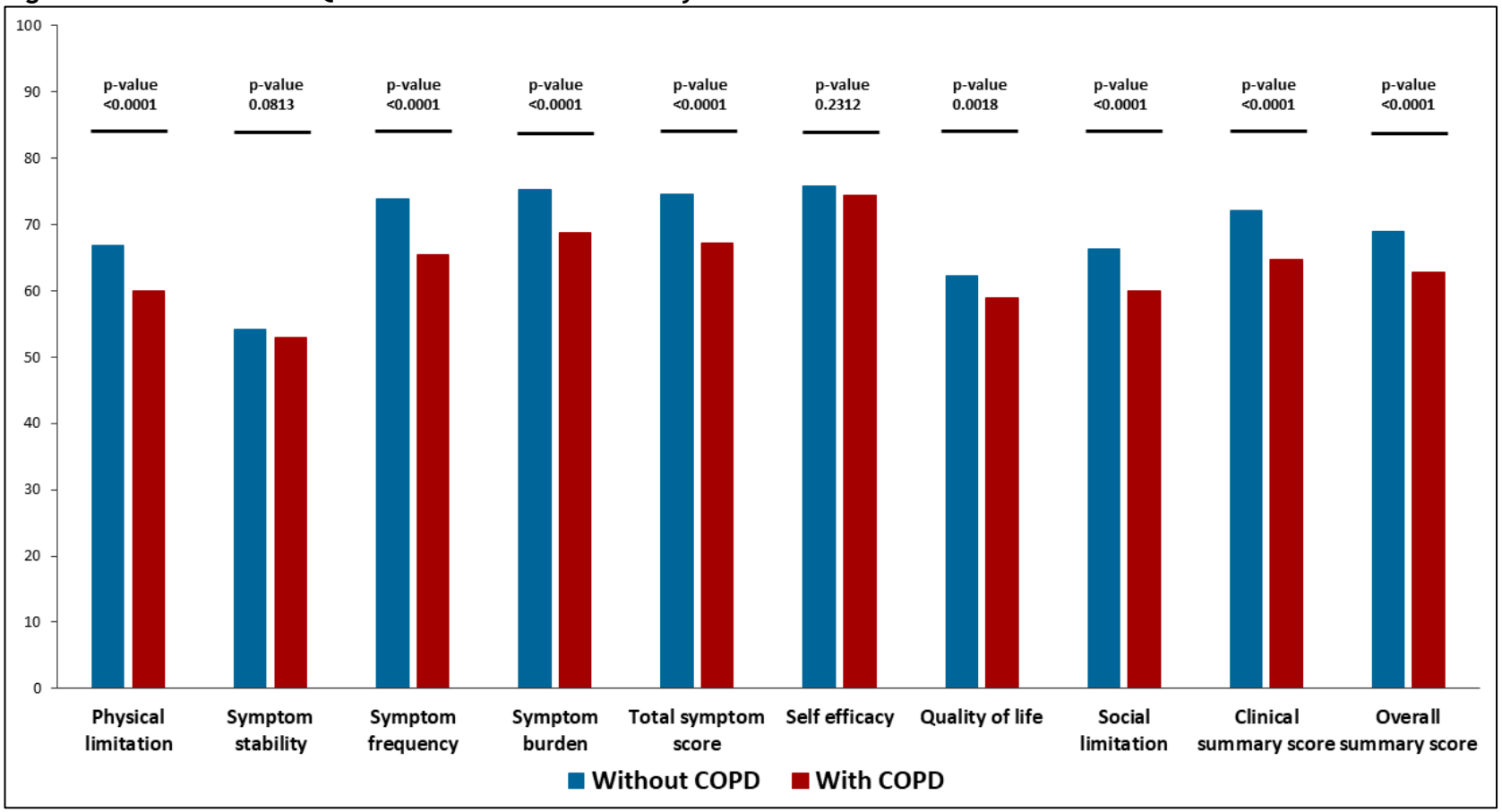
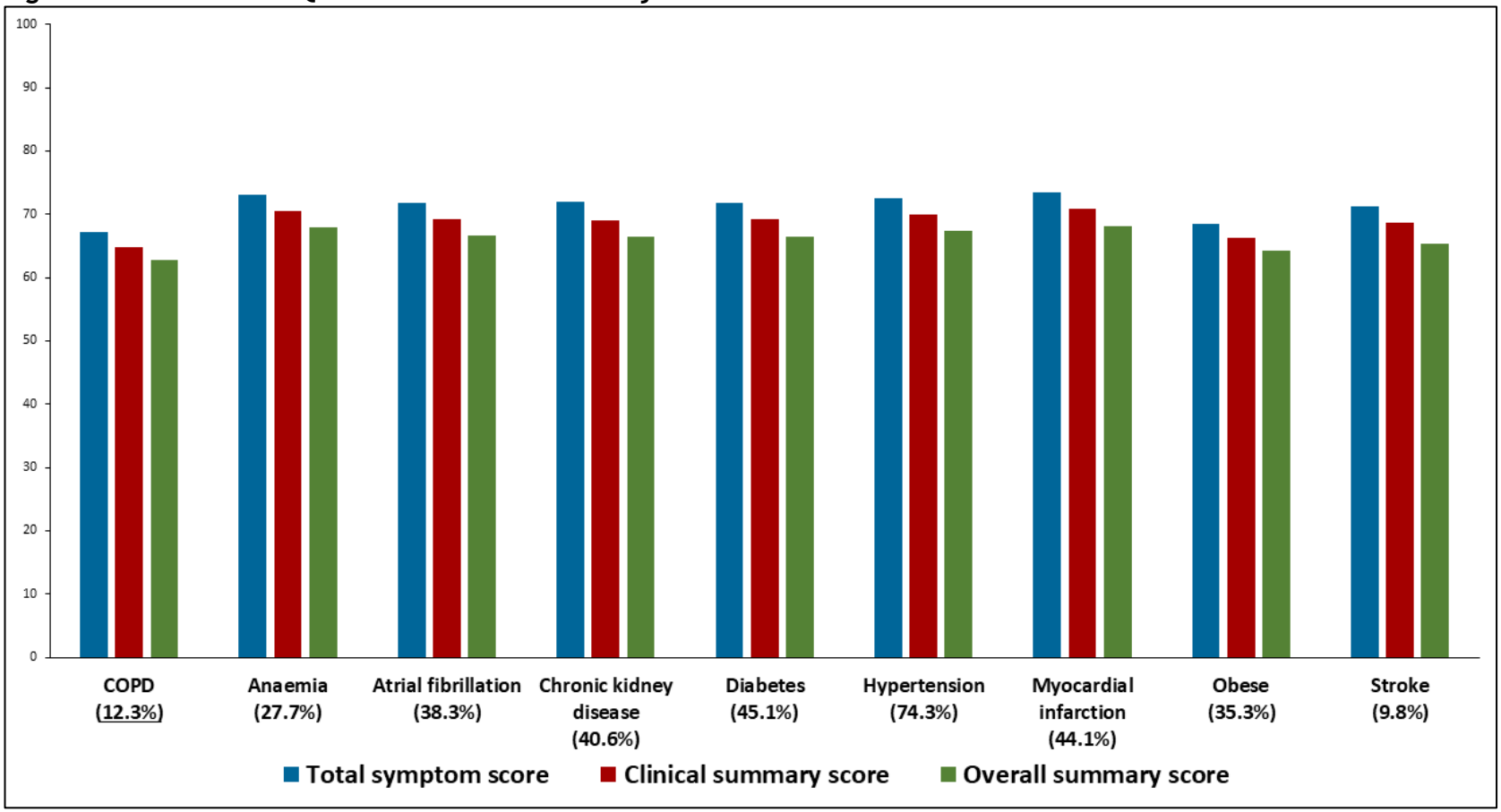


Figure 5-5 Individual KCCQ domain scores at baseline by COPD status



Bars represent mean values for each domain and KCCQ summary scores

Figure 5-6 Baseline KCCQ scores associated with major comorbidities



Bars represent mean values for KCCQ total summary score, KCCQ clinical summary score and KCCQ overall summary score at baseline for each comorbidity examined.

Effects of dapagliflozin on hospitalisation and mortality outcomes

Table 5-6 and Figure 5-7 show the effect of dapagliflozin versus placebo, on prespecified outcomes, according to COPD status.

Primary outcome:
The effect of dapagliflozin, compared with placebo, on the primary outcome was consistent in patients with COPD (HR 0.67; 95% CI 0.48-0.93) and without COPD (0.76, 0.65-0.87) [Table 5-6 and Figure 5-7]; p-value for interaction: 0.47.

Worsening HF events:
The benefit of dapagliflozin, compared with placebo, on worsening HF events was also consistent in patients with and without COPD [Table 5-6 and Figure 5-7].

Mortality:
The effects of dapagliflozin on cardiovascular (p-value for interaction:0.47) and all-cause mortality (p-value for interaction: 0.96) were also consistent in patients with and without COPD [Table 5-6 and Figure 5-7].

Effect of dapagliflozin on symptoms and quality of life assessed using KCCQ

In the pre-specified KCCQ analysis, the improvement in KCCQ-TSS with dapagliflozin, compared to placebo, was similar in patients with and without COPD (p-value for interaction: 0.71) and the same was true for the exploratory analyses of KCCQ-CSS and -OSS [Table 5-6 and Figure 5-8].

Absolute benefits of dapagliflozin in patients with and without COPD

Applying the overall relative risk reduction (26%) to the placebo group event rate in those with COPD gave an absolute risk reduction of 5.9 fewer patients experiencing a primary outcome per 100 person-years. The equivalent reduction in patients without COPD was 3.9 fewer patients per 100 person-years.

Applying the overall relative risk reduction (30%) to the placebo group event rate in participants with COPD, gave an absolute risk reduction of 5.3 fewer patients experiencing a worsening HF event, per 100 person-years of follow-up. The equivalent reduction in patients without COPD was 2.8 per 100 person-years

The equivalent figures for death from any cause were 2.3 fewer per 100 person-years patients with COPD and 1.5 fewer per 100 person-years in patients without COPD.

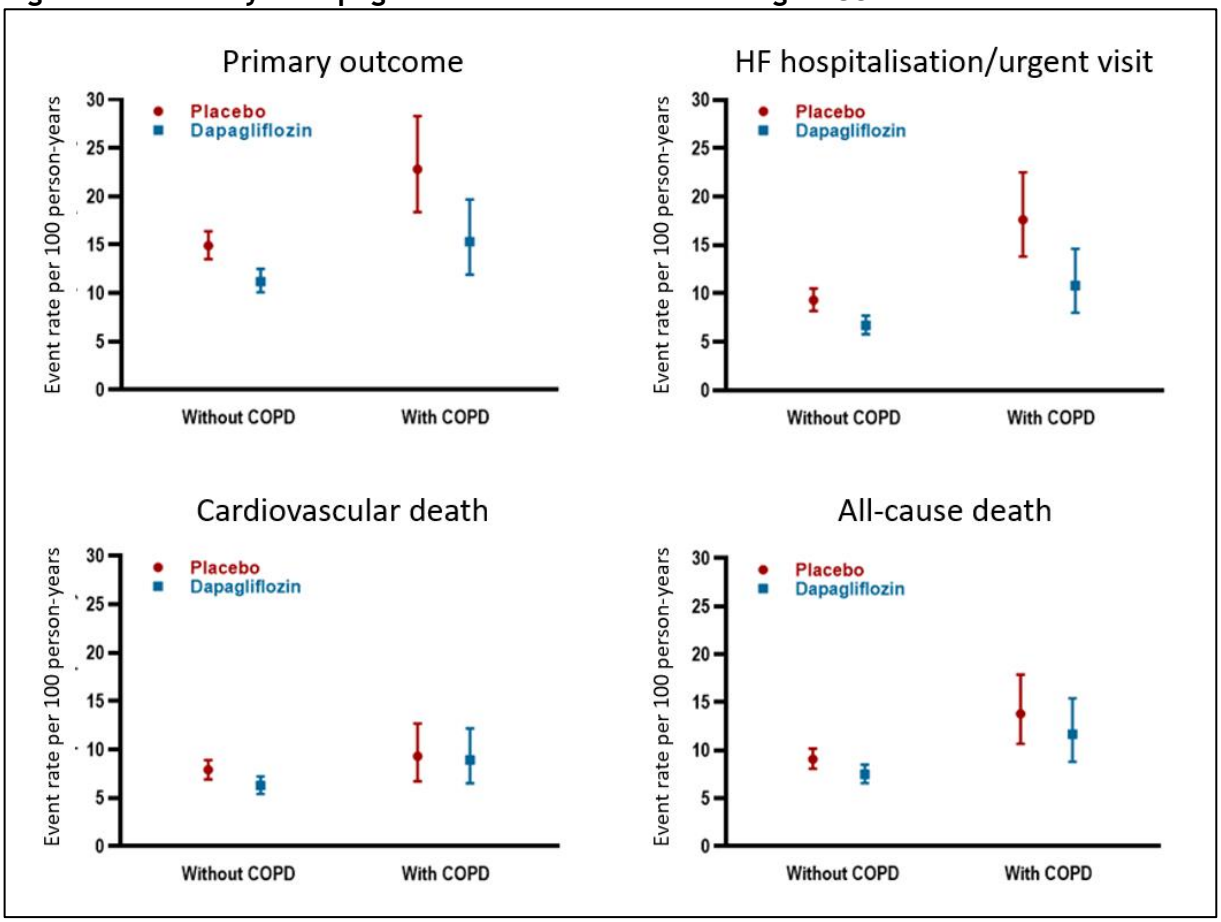
Table 5-6 Clinical outcomes according to COPD

	Without COPD		With COPD		p-value for interaction
	Placebo n=2085	Dapagliflozin n=2074	Placebo n=286	Dapagliflozin n=299	
Primary outcome					
Events (%)	419 (20.1)	325 (15.7)	83 (29.0)	61 (20.4)	
Event rate per 100 pt. yrs.	14.9 (13.5–16.4)	11.2 (10.1–12.5)	22.8 (18.4–28.3)	15.3 (11.9–19.7)	
Unadjusted HR	0.76 (0.65 – 0.87)		0.67 (0.48 – 0.93)		0.47
HF hospitalisation/urgent visit					
Events (%)	262 (12.6)	194 (9.4)	64 (22.4)	43 (14.4)	
Event rate per 100 pt. yrs.	9.3 (8.2–10.5)	6.7 (5.8–7.7)	17.6 (13.8–22.5)	10.8 (8.0–14.6)	
Unadjusted HR	0.72 (0.60 – 0.87)		0.61 (0.41 – 0.90)		0.42
First HF hospitalisation					
Events (%)	254 (12.2)	189 (9.1)	64 (22.4)	42 (14.1)	
Event rate/100 person-years	9.0 (8.0 – 10.2)	6.5 (5.7 – 7.5)	17.5 (13.7 – 22.4)	10.5 (7.8 – 14.3)	
Unadjusted HR	0.73 (0.60 – 0.88)		0.59 (0.40 – 0.88)		0.35
Cardiovascular death					
Events (%)	235 (11.3)	189 (9.1)	38 (13.3)	38 (12.7)	
Event rate per 100 pt. yrs.	7.9 (6.9 – 8.9)	6.3 (5.4 – 7.2)	9.3 (6.7 – 12.7)	8.9 (6.5 – 12.2)	
Unadjusted HR	0.80 (0.66 – 0.97)		0.96 (0.61 – 1.51)		0.47
Total HF hosp./cardiovascular death					
Events	605	465	137	102	
Event rate per 100 pt. yrs.	20.3 (18.2–22.7)	15.5 (13.7–17.5)	33.8 (27.0 - 42.9)	24.0 (18.2–32.1)	
Unadjusted RR	0.76 (0.65 – 0.90)		0.71 (0.50 – 1.03)		0.71
KCCQ – Total symptom score					
Mean change ± SD at 8 months	3.4 ± 19.2	6.2 ± 18.4	2.4 ± 19.2	5.8 ± 20.2	
Between treatment difference	2.73 (1.47 – 3.99)		3.42 (-0.19 – 7.04)		0.71
Proportion with increase in score ≥5 at 8 months	51.7	59.2	45.6	52.2	
	1.16 (1.08 – 1.24)		1.14 (0.96 - 1.36)		0.87
Proportion with decrease in score ≥5 at 8 months	31.9	24.6	39.9	30.3	

	0.84 (0.78 - 0.90)		0.81 (0.68 – 0.96)		0.69
All-cause death					
Events (%)	272 (13.1)	226 (10.9)	57 (19.9)	50 (16.7)	
Event rate per 100 pt. yrs.	9.1 (8.1-10.2)	7.5 (6.6-8.5)	13.8 (10.7-17.9)	11.7 (8.8-15.4)	
Unadjusted HR	0.83 (0.69 – 0.99)		0.83 (0.57 – 1.22)		0.96

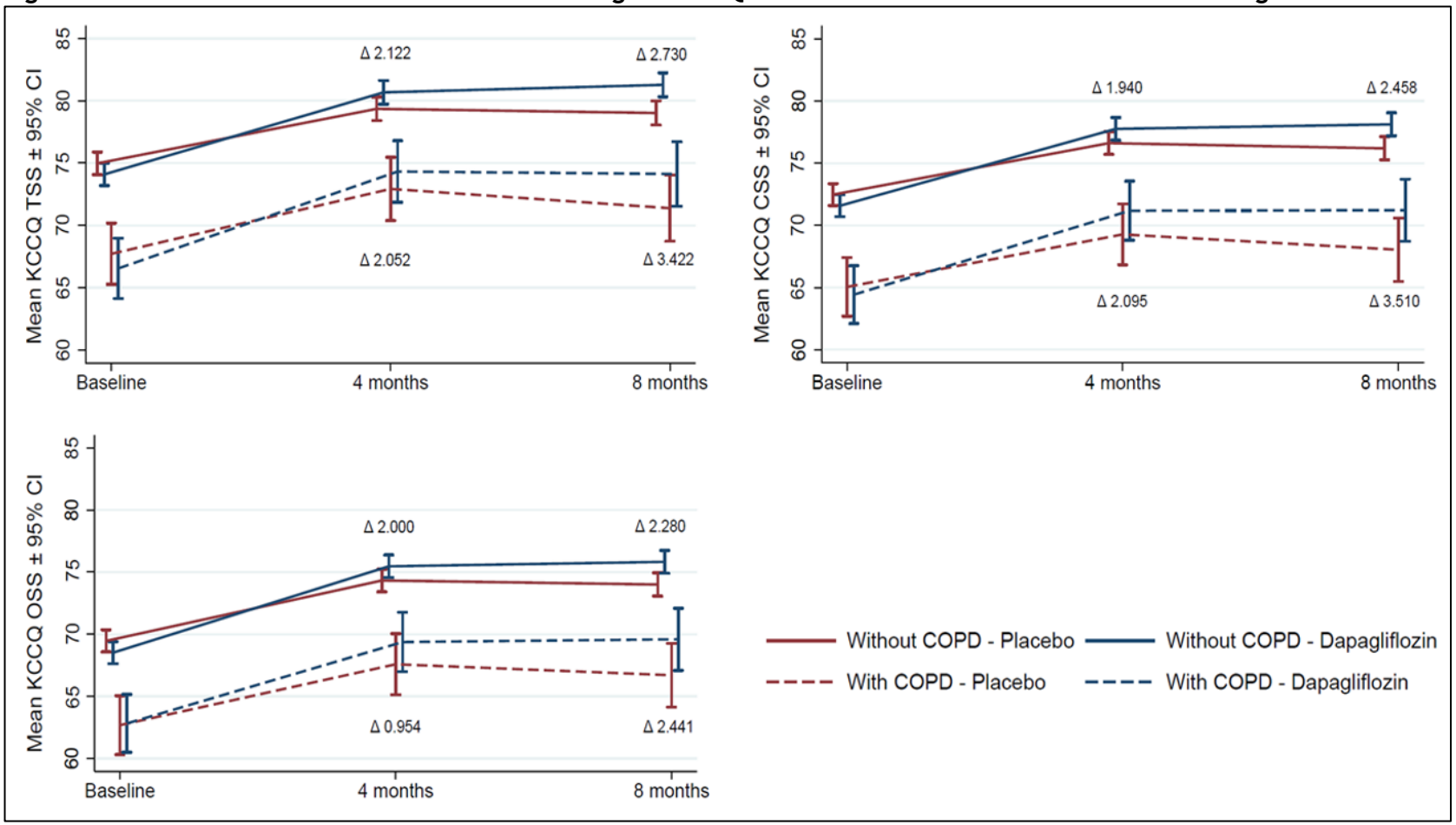
Risk ratios represents comparison of dapagliflozin against placebo.
Risk ratios adjusted for previous heart failure hospitalisation at baseline (except all-cause death) and stratified by diabetes status.
*Adjusted for baseline eGFR and stratified by diabetes status.

Figure 5-7 Efficacy of dapagliflozin in DAPA-HF according to COPD status at baseline



Panels show the point estimates (with 95% confidence interval) for the event rates per 100 person-years of follow up for the key hospitalisation and mortality outcomes of interest.

Figure 5-8 Effect of randomised treatment on change in KCCQ scores from baseline to 8 months according to COPD status



Panels show the KCCW total summary score, KCCQ clinical summary score and KCCQ overall summary score at baseline and during follow up.
Between treatment difference (dapagliflozin-placebo) in mean change from baseline for each KVVQ summary score examined is also shown.

Pre-specified safety assessments

The proportion of patients stopping study-drug for any reason in the *placebo group* was higher in patients with COPD, compared to those without COPD [Table 5-7]. However, the rate of discontinuation was similar between dapagliflozin and placebo in patients with and without COPD (p-value for interaction: 0.57).

Adverse events related to volume depletion were reported in 7.7% of the placebo group and in 8.4% of the dapagliflozin group in patients with COPD, compared to 6.7% and 7.4%, respectively, in patients without COPD. The rate of renal adverse events was numerically (but not significantly) lower in patients treated with dapagliflozin, compared with placebo, both in patients with and without COPD (p-value for interaction: 0.81).

Table 5-7 Prespecified safety outcomes & discontinuation according to randomised treatment and COPD status*

	Without COPD		With COPD		p-value for interaction
	Placebo n=2083	Dapagliflozin n=2071	Placebo n=285	Dapagliflozin n=297	
Any study drug discontinuation					
Events (%)	219/2085 (10.5)	214/2074 (10.3)	39/286 (13.6)	35/299 (11.7)	
OR	0.98 (0.80–1.20)		0.84 (0.51–1.38)		0.57
AE related study drug discontinuation					
Events (%)	95 (4.6)	93 (4.5)	21 (7.4)	18 (6.1)	
OR	0.98 (0.73–1.32)		0.80 (0.42–1.54)		0.59
Volume depletion					
Events (%)	140 (6.7)	153 (7.4)	22 (7.7)	25 (8.4)	
OR	1.11 (0.87–1.41)		1.08 (0.59–1.97)		0.96
Renal AE					
Events (%)	137 (6.6)	123 (5.9)	33 (11.6)	30 (10.1)	
OR	0.90 (0.70–1.16)		0.84 (0.50–1.42)		0.81

OR-odds ratio (95% confidence interval) adjusted for baseline diabetes status.
AE: adverse event.
*Only in safety set except for discontinuation due to any cause

Discussion

In DAPA-HF, patients with COPD were older and more commonly men with a history of smoking and atrial fibrillation and had worse renal function and a higher NT-proBNP level, than participants without COPD. Patients with COPD were slightly less likely to be treated with a beta-blocker or MRA and had more severe functional limitation and impairment of QoL than participants without COPD. During follow up, patients with COPD experienced higher rates of the primary composite endpoint and key secondary endpoints; fewer had a clinically meaningful improvement (and more deterioration) in symptoms and QoL, compared to those without COPD. The efficacy and tolerability of dapagliflozin were consistent in participants with and without COPD, with greater absolute risk reductions in hospitalisation and death in COPD patients due to their higher overall event rates. Mean improvements in symptoms and QoL were numerically larger in patients with COPD, compared to those without.

In DAPA-HF, 12.3% of patients had concomitant COPD, very similar to the frequency reported in most other trials, including PARADIGM-HF, where prevalence was 12.9%.[40,140,198–202] However, this is likely to be lower than the true prevalence of COPD in unselected patients with HFrEF for two reasons. First, the inclusion and exclusion criteria used in trials, including the requirement for patients to be treated with beta-blocker, unless contraindicated or not tolerated, likely led to the under-enrolment of patients with severe COPD. Second, the use of spirometry would likely have detected undiagnosed COPD. However, the prevalence of COPD in recent registry studies has not been much higher. In the European Society of Cardiology Long-Term Registry, the prevalence of COPD was 14.1%.[203] Moreover, 23% of patients in that registry had HFpEF and COPD is more common in HFpEF than HFrEF.[43,44,129] The proportion of HFrEF patients with COPD in a US registry was 16.5%.[204] In a large Asian registry, the prevalence of COPD was 8.3% (but varied across Asia from 4.7% to 11%).[205]

As expected, patients with COPD in DAPA-HF, had more adverse characteristics including older age and a more frequent history of hypertension and, notably, atrial fibrillation. The possibility that beta-agonists increase the risk of atrial

fibrillation has been raised previously.[129] Although prior and current smoking were, as expected, more common in patients with COPD, CHD was not more common. I also found patients with COPD had a higher mean NT-proBNP level, although only modestly so (and this was only the case in patients without atrial fibrillation). There was no clinically relevant difference in LVEF between patients with and without COPD. The latter findings contrasted strikingly with the substantially higher proportion of patients with COPD reported to be in NYHA class III/IV and the significantly lower (worse) KCCQ-TSS (and other KCCQ scores) in people with COPD compared to those without. Indeed, all but one of the domains of KCCQ was worse in patients with COPD compared to most other comorbidities. A similar overall mean decrement (-8 points) in KCCQ-OSS was reported in the HF-ACTION trial.[199] Likewise, I also confirmed a significantly greater fall in the KCCQ-CSS among patients with COPD a separate analysis of the PARADIGM-HF trial.[202]

Interestingly, and in contrast to most prior studies, I found beta-blocker use was high in patients with COPD (92.3%) although not as high as in patients without COPD (96.6%, P<0.001). This finding may indicate that the recommendation in HF guidelines that COPD is not a contraindication to the use of a beta-blocker may have been heeded in this selected clinical trial population.[199,206–209] More surprisingly, however was the finding that MRA use was also significantly less common in patients with COPD, despite their worse functional class. A likely explanation is the higher prevalence of renal dysfunction among patients with COPD, compared to those without COPD.[210]

Even after adjusting for differences in demographics, comorbidity, key disease-modifying therapy and NT-proBNP, COPD remained an independent predictor of the primary outcome, although the impact was greater on worsening HF events than on cardiovascular death. However, there was a clear association between COPD and death from any cause because of the higher risk of non-cardiovascular death in patients with COPD. The excess risk associated with COPD was striking when compared with other common comorbidities, with only CKD and diabetes showing a similar hazard; I am not aware of any comparative analysis of this type.

These data and the earlier observations on symptoms/QoL raise two questions about the interaction between COPD and HFrEF. The first is why is COPD associated with worse symptoms and functional status and a higher risk of HF hospitalisation? The explanation for the former could simply be that patients experience the extra impact of two cardiac and respiratory conditions causing dyspnoea and effort intolerance (and, potentially, the additional burden of atrial fibrillation). This doesn't readily explain higher natriuretic peptide levels in patients in sinus rhythm which I also observed in PARADIGM-HF.[202] COPD does have independent hemodynamic effects likely to be harmful in HFrEF, including hypoxia-induced pulmonary vasoconstriction with a consequent increase in right ventricular afterload, right ventricular enlargement, and potential right ventricular failure.[129,211] Right ventricular hypertrophy and dilatation can also cause leftward shift of the interventricular septum, reducing left ventricular cavity size, compliance, and contractility. Larger swings in intrapleural pressure can increase in left ventricular transmural pressure and afterload and high intrathoracic pressures can also compress the inferior vena cava and right atrium, decreasing venous return, right ventricle preload and cardiac output. It has also been suggested that a disproportionate fraction of cardiac output is diverted to overworked respiratory muscles in patients with COPD.[129,193]

The benefits of dapagliflozin were consistent in patients with and without COPD, both for worsening HF events and death. This finding is especially important because the risk was greater in patients with COPD and, therefore, the absolute risk reduction was larger in these individuals, than in participants without COPD and also because this risk reduction persisted despite the competing (nearly 2-fold) risk of non-cardiovascular death in the COPD group.

Similarly, dapagliflozin was as well tolerated, compared with placebo, in patients with and without COPD. Collectively, this preserved efficacy and tolerability is very important, given the risk faced by patients with COPD and the more limited alternative options for at least some of these patients.[130,211]

Strengths & Limitations

This study has a few limitations. Analysis was not prespecified and the proportion of patients with COPD was relatively small, compared to those without. COPD was investigator-reported, and likely, that the true prevalence of COPD would probably be higher if all patients had performed spirometry. Participants in this study were selected for a randomised controlled trial and were probably healthier, overall, than "real world" patients. Investigators were asked not to include patients with another condition likely to lead to a life-expectancy of <2 years, which may have led to exclusion of patients with severe COPD. The high rate of use of beta-blockers is also consistent with the trial participants representing healthier, better-treated, patients enrolled at sites practising evidence-based medicine.

Conclusions

In summary, in DAPA-HF, approximately one in eight patients with HFrEF had concomitant COPD. Participants with COPD had worse symptoms and functional limitation, compared to those without, and a higher risk of HF hospitalisation and death from any cause. The relative risk-reduction with dapagliflozin on all prespecified mortality/morbidity outcomes was the same in patients with and without COPD (and absolute risk reduction greater in those with COPD because of their higher baseline risk), as was the improvement in symptoms.

Chapter 6. Heart failure with reduced ejection fraction: comparison of patient characteristics and clinical outcomes within Asia and between Asia, Europe, and the Americas

This chapter has been published as:

Dewan P, Jhund PS, Shen L, Petrie MC, Abraham WT, Atif Ali M, Chen CH, Desai AS, Dickstein K, Huang J, Kiatchoosakun S, Kim KS, Køber L, Lai W Ter, Liao Y, Mogensen UM, Oh BH, Packer M, Rouleau JL, Shi V, Sibulo AS, Solomon SD, Sritara P, Swedberg K, Tsutsui H, Zile MR, McMurray JJV. Heart failure with reduced ejection fraction: comparison of patient characteristics and clinical outcomes within Asia and between Asia, Europe and the Americas. Eur J Heart Fail John Wiley & Sons, Ltd; 2019;21:577–587.

Nearly 60% of the global population lives in Asia with China and India alone constituting about 37% of the world's population. However, little is known about how the patients with HF living outside of Europe and North America regarding their characteristics, clinical outcomes, and response to therapy.[9] In the systematic review in Chapter 1, race/region was a significant predictor of outcomes in HF in only one 1 study.[109]

In this chapter, I have described and compared clinical characteristics and outcomes in patients with HFrEF within Asia and between Asia, Europe, and the Americas in a pooled cohort of two contemporary clinical trials in HFrEF.

Methods

Details of the eligibility criteria and recruitment of patients into ATMOSPHERE and PARADIGM-HF are given in chapter 2.

Population analysed

As stated in the methods section, patients from 52 countries were recruited in the ATMOSPHERE and PARADIGM-HF trials. In both trials, patients were asked to self-identify their race (as one of: Caucasian, Black, Asian, Native America,

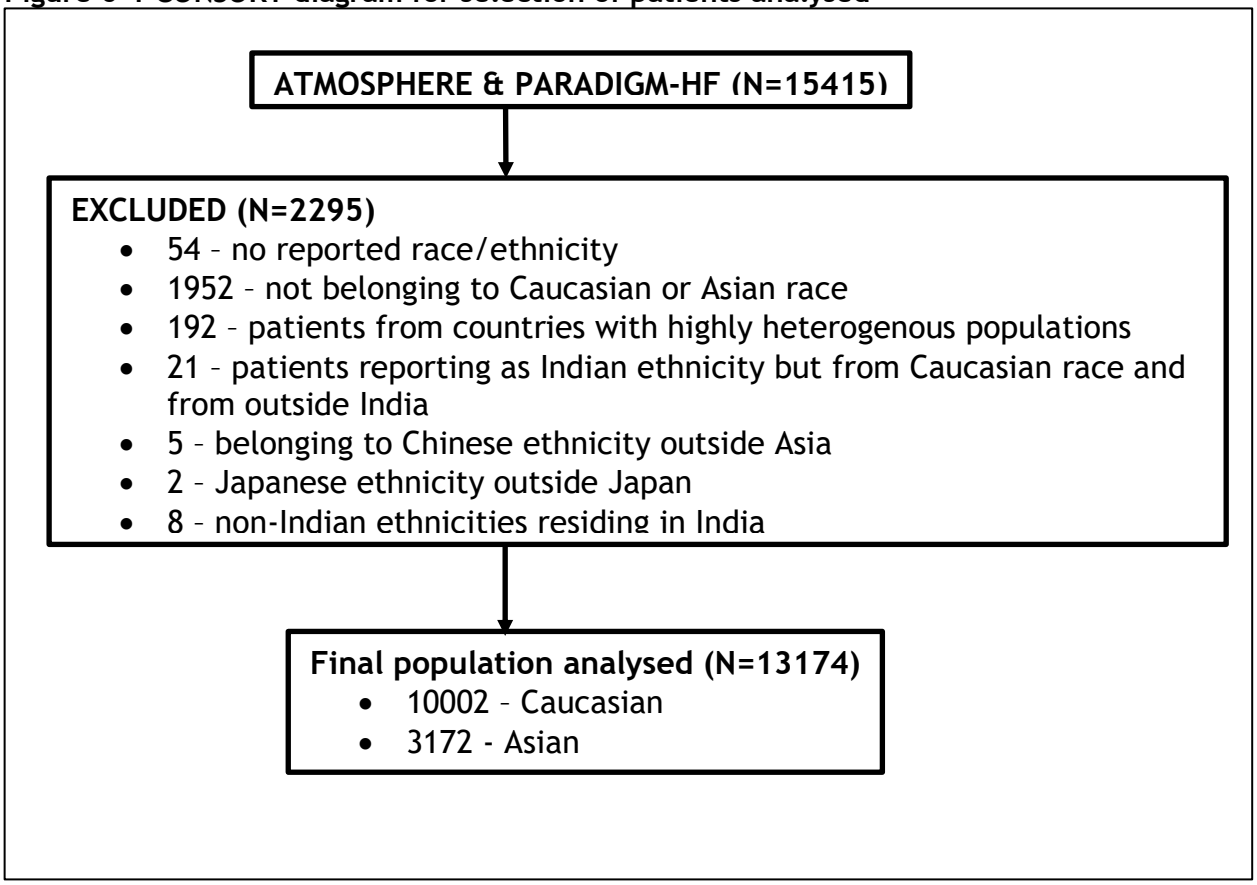
Pacific Islander or other) and ethnicity (as one of: Hispanic/Latino, Chinese, Indian, Japanese, mixed ethnicity, other or unknown) as shown in Table 6-1.

Out of the 15415 patients in the HFrEF dataset, 2295 patients were excluded as explained in Figure 6-1 Overall 13714 patients were therefore included in the analysis in this chapter.

Table 6-1 Self-reported race and ethnicity in ATMOSPHERE and PARADIGM-HF

	Hispanic/Latino	Chinese	Indian	Japanese	Mixed	Other
Caucasian	1405	0	14	0	195	8522
Black	207	1	2	0	10	317
Asian	2	1031	1419	211	64	546
Native American	207	0	3	0	2	2
Pacific Islander	0	0	0	0	1	1
Other	973	1	9	0	37	179

Figure 6-1 CONSORT diagram for selection of patients analysed



Patients thus included in this analysis were then categorised as Caucasians belonging to the regions of Western Europe (reference), Eastern Europe, North America and Latin America and Asians belonging to the different Asian countries. Asian countries which had at least 90 Asians enrolled were included in this analysis. These were: China (including Hong Kong), India, Japan, Korea, Philippines, Taiwan and Thailand.

Table 6-2 Ethnicity by region

	Hispanic/Latino	Chinese	Indian	Japanese	Mixed	Other
Western Europe	226	0	0	0	149	3146
Central/Eastern Europe/Russia	54	0	0	0	10	4694
North America	32	0	0	0	31	550
Latin America	1092	0	0	0	0	15
China	0	833		0	0	0
India	0	0	1390	0	0	0
Japan	0	0	0	209	0	0
South Korea	0	0	0	0	59	164
Philippines	0	0	0	0	2	221
Taiwan	0	167	0	0	0	32
Thailand	0	0	0	0	0	95

Outcomes

For this chapter, I have analysed the primary composite outcome of cardiovascular death or first HF hospitalisation, the individual components and all-cause death.

Statistical analysis

Baseline characteristics according to region and country by race and ethnicity have been reported as laid out in chapter 2.

I have reported the incidence rates for the outcomes of interest for each group as event rate per 100 person-years. Competing-risk regression using the Fine-Gray method, as outlined in chapter 2, was used to assess the risk of the outcomes examined. Primary outcome and cardiovascular death were analysed accounting for competing risk of non-cardiovascular death and HF hospitalisation

was analysed accounting for the competing risk of all-cause death. In this chapter, I have reported the crude sHRs and sHRs adjusted for age, sex, heart rate, systolic blood pressure, BMI, NT-proBNP, LVEF, eGFR and NYHA class. Both models have been adjusted for randomised treatment at baseline. Selection of covariates for multivariable adjustment were based on clinically relevant variables known to be predictive of death and hospitalisation in previous studies. Risk of all-cause death is analysed using Cox regression and reported as HR and has been reported in two models as described for the sHRs above.

All analyses were performed using Stata ver. 14 (Stata Corp. College Station, Texas, USA). Two-sided p-values <0.05 were considered significant.

Results

Of the 13174 patients that I included in this analysis, 833 (6.3%) were resident in China, 1390 (10.6%) in India, 209 (1.6%) in Japan, 223 (1.7%) in Korea, 223 (1.7%) in the Philippines, 199 (1.5%) in Taiwan and 95 (0.7%) Thailand; 3521 (27%) participants lived in Western Europe (reference region), 4758 (36.1%) in Eastern Europe, 613 (4.7%) in North America and 1110 (8.4%) in Latin America [Table 6-2]. All patients enrolled in China and Japan were of Chinese or Japanese ethnicity, respectively; those in the other Asian countries were of "other" or "mixed" Asian ethnicity except for Taiwan where 167 were of Chinese ethnicity and 32 of "other" ethnicity [Table 6-3].

Baseline characteristics

Asian patients were generally younger on average (55.0 to 61.2 years) when compared to patients from Western Europe (mean age 67.9 years) and North America (mean age 66.6 years). Among the Asians, only the Japanese were comparable in age (63.9 years compared to 63.3 years in Latin America).

Also as shown in Table 6-3, patients from Asia had a lower BMI (22.9 to 25.6 kg/m2) compared to other regions (e.g. 27.8 kg/m^2 in Western Europe and 29.8 27.8 kg/m^2 in North America). Patients from Asia also had a lower SBP than patients from Europe (but similar to patients from the Americas).

With the exceptions of India, Taiwan and the Philippines, Asian patients had a lower prevalence of diabetes than those in Europe and North America (although

not Latin America); the same pattern was seen for hypertension (although this was as common in Latin America as in Europe and North America. COPD was much less common in most Asian countries (Taiwan was the notable exception) than in Europe and North America (but not Latin America).

Table 6-3 Baseline characteristics

	Western Europe n=3521	Central/Eastern Europe/Russia n=4758	North America n=613	Latin America n=1110	China n=833	India n=1390	Japan n=209	South Korea n=223	Philippines n=223	Taiwan n=199	Thailand n=95
Age - (years.)	67.9 ± 9.9	64.9 ± 10.1	66.6 ± 10.7	63.3 ± 10.9	57.2 ± 11.9	56.4 ± 11.8	63.9 ± 11.5	59.1 ± 10.7	55.0 ± 12.1	61.2 ± 15.1	57.0 ± 13.6
Age Group - no (%)											
<=40 years	33 (0.9)	69 (1.5)	7 (1.1)	26 (2.3)	73 (8.8)	145 (10.4)	8 (3.8)	20 (9.0)	29 (13.0)	21 (10.6)	15 (15.8)
41-55 years	351 (10.0)	724 (15.2)	94 (15.3)	242 (21.8)	271 (32.5)	477 (34.3)	32 (15.3)	61 (27.4)	87 (39.0)	50 (25.1)	22 (23.2)
56-70 years	1594 (45.3)	2443 (51.3)	274 (44.7)	548 (49.4)	373 (44.8)	629 (45.3)	100 (47.8)	100 (44.8)	85 (38.1)	64 (32.2)	42 (44.2)
>70 years	1543 (43.8)	1522 (32.0)	238 (38.8)	294 (26.5)	116 (13.9)	139 (10.0)	69 (33.0)	42 (18.8)	22 (9.9)	64 (32.2)	16 (16.8)
Females – no. (%)	621 (17.6)	1113 (23.4)	87 (14.2)	283 (25.5)	143 (17.2)	328 (23.6)	30 (14.4)	50 (22.4)	46 (20.6)	30 (15.1)	22 (23.2)
SBP – (mmHg)	123.2 ± 18.3	127.4 ± 15.3	117.0 ± 15.0	119.9 ± 15.1	117.1 ± 16.6	117.6 ± 14.7	118.7 ± 19.1	112.9 ± 14.8	118.1 ± 17.6	120.6 ± 17.1	122.2 ± 18.0
Heart rate - (bpm)	68.7 ± 11.8	73.6 ± 12.6	69.0 ± 10.9	70.3 ± 11.5	72.8 ± 11.8	77.1 ± 9.9	71.5 ± 12.2	72.0 ± 14.7	75.0 ± 12.4	77.6 ± 13.0	73.3 ± 14.3
BMI* - (kg/m^2)	27.8 (25.1-31.2)	28.7 (25.7-32.5)	29.8 (26.4-34.2)	27.6 (24.8-30.9)	24.4 (22.0-27.1)	22.9 (20.4-25.5)	23.8 (21.5-26.2)	23.9 (22.3-26.6)	24.2 (21.3-26.6)	25.6 (23.0-28.1)	23.1 (20.4-26.3)
Comorbidities - no. (%)											
Hypertension	2132 (60.6)	3970 (83.4)	485 (79.1)	768 (69.2)	390 (46.8)	509 (36.6)	113 (54.1)	79 (35.4)	135 (60.5)	143 (71.9)	42 (44.2)
Diabetes	1167 (33.1)	1502 (31.6)	295 (48.1)	307 (27.7)	207 (24.8)	465 (33.5)	59 (28.2)	55 (24.7)	71 (31.8)	82 (41.2)	28 (29.5)
Atrial Fibrillation	1531 (43.5)	2356 (49.5)	246 (40.1)	300 (27.0)	186 (22.3)	58 (4.2)	59 (28.2)	83 (37.2)	44 (19.7)	70 (35.2)	22 (23.2)
Unstable angina	403 (11.4)	703 (14.8)	136 (22.2)	69 (6.2)	58 (7)	81 (5.8)	16 (7.7)	20 (9.0)	3 (1.3)	43 (21.6)	14 (14.7)
Myocardial Infarction	1640 (46.6)	2374 (49.9)	392 (63.9)	319 (28.7)	187 (22.4)	530 (38.1)	82 (39.2)	45 (20.2)	61 (27.4)	57 (28.6)	31 (32.6)
Stroke	305 (8.7)	449 (9.4)	56 (9.1)	78 (7.0)	54 (6.5)	30 (2.2)	21 (10.0)	14 (6.3)	22 (9.9)	16 (8.0)	10 (10.5)
COPD	567 (16.1)	738 (15.5)	153 (25.0)	71 (6.4)	31 (3.7)	58 (4.2)	7 (3.3)	8 (3.6)	19 (8.5)	36 (18.1)	4 (4.2)
Renal disease	538 (15.3)	919 (19.3)	164 (26.8)	65 (5.9)	19 (2.3)	22 (1.6)	20 (9.6)	9 (4.0)	23 (10.3)	55 (27.6)	5 (5.3)
Current Smoker	535 (15.2)	662 (13.9)	108 (17.6)	94 (8.5)	188 (22.6)	99 (7.1)	40 (19.1)	56 (25.1)	25 (11.2)	53 (26.6)	14 (14.7)

All values are reported as mean ± standard deviation except where indicated.
*Median (interquartile range)

SBP – systolic blood pressure; BMI – body mass index; VHD – valvular heart disease; PAD – peripheral arterial disease; COPD – chronic obstructive pulmonary disease.

Heart failure characteristics

As shown in Table 6-4, an ischaemic aetiology was less common in most Asian countries (e.g. 33.3% in China) than in other regions, although it was as common in India (69.7%) and the Philippines (66.4%) as in Europe (57.4% in Western and 70.9% in Eastern Europe) and North America (71.8%). Asian patients were generally less severely functionally limited, according to NYHA class, except those in China and India. Patients in Asian countries also had higher (better) KCCQ scores than in Europe and the Americas. History of pre-randomisation heart failure hospitalisation varied markedly across the world with the greatest variation within Asia, from 43.7 % in India to 76.9 % in Taiwan (the range in Europe and the Americas was 58.8% to 68.2%).

In terms of symptoms and signs, patients in Asia in general (except for Taiwan) had less evidence of congestion (oedema, raised JVP) than those in Europe and North America (with Latin America being more like Asia). Pre-trial use of an ARB (rather than ACEI) was higher in most Asian countries (ranging from 13.8% in China to 53.4% in the Philippines) than in Europe and the Americas (10.4% to 11.4%), with the exceptions of Japan (4.8%), Thailand (8.4%) and India (10.0%).

Table 6-4 Heart failure characteristics and clinical features

	Western Europe n=3521	Central/Eastern Europe/Russia n=4758	North America n=613	Latin America n=1110	China n=833	India n=1390	Japan n=209	South Korea n=223	Philippines n=223	Taiwan n=199	Thailand n=95
HF aetiology											
Ischaemic	2022 (57.4)	3373 (70.9)	440 (71.8)	449 (40.5)	277 (33.3)	969 (69.7)	89 (42.6)	85 (38.1)	148 (66.4)	87 (43.7)	36 (37.9)
Non-ischaemic	1383 (39.3)	1306 (27.5)	150 (24.5)	533 (48.0)	470 (56.4)	371 (26.7)	100 (47.9)	114 (51.1)	73 (32.7)	98 (49.3)	59 (62.1)
Other/Unknown	116 (3.3)	79 (1.7)	23 (3.8)	128 (11.5)	86 (10.3)	50 (3.6)	20 (9.6)	24 (10.8)	2 (0.9)	14 (7.0)	0 (0.0)
HF duration											
<1 year	851 (24.2)	1243 (26.1)	114 (18.6)	323 (29.1)	377 (45.3)	790 (56.9)	76 (36.4)	107 (48.0)	109 (48.9)	73 (36.7)	45 (47.4)
1-5 years	1174 (33.3)	2040 (42.9)	167 (27.2)	441 (39.7)	311 (37.3)	485 (34.9)	64 (30.6)	67 (30.0)	85 (38.1)	69 (34.7)	40 (42.1)
>5 years	1495 (42.5)	1474 (30.9)	332 (54.2)	346 (31.2)	145 (17.4)	113 (8.1)	69 (33.0)	49 (22.0)	29 (13.0)	57 (28.6)	10 (10.5)
Previous HF hospitalisation	2069 (58.8)	3245 (68.2)	365 (59.5)	622 (56.0)	636 (76.4)	607 (43.7)	151 (72.2)	143 (64.1)	127 (57.0)	153 (76.9)	60 (63.2)
NYHA class											
I + II	2,762 (78.5)	2,555 (53.7)	492 (80.5)	1,011 (91.2)	677 (81.4)	1,080 (77.7)	198 (94.7)	203 (91.0)	211 (94.6)	178 (89.5)	94 (99.0)
III	742 (21.1)	2,123 (44.7)	115 (18.8)	97 (8.8)	144 (17.3)	300 (21.6)	11 (5.3)	20 (9.0)	12 (5.4)	21 (10.6)	1 (1.1)
IV	13 (0.4)	77 (1.6)	4 (0.7)	1 (0.1)	11 (1.3)	10 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
KCCQ Clinical Summary Score*	80.2 (63.5-91.7)	70.8 (54.7-85.0)	78.1 (62.5-90.6)	86.5 (72.9-95.0)	91.7 (83.3-97.9)	83.3 (68.8-93.8)	93.8 (85.5-100.0)	-	80.2 (69.4-96.4)	-	-
Clinical Features											
Dyspnoea on effort	3067 (87.3)	4499 (94.6)	463 (75.9)	954 (86.0)	558 (67.1)	1270 (91.4)	62 (29.7)	151 (67.7)	104 (46.6)	141 (70.9)	52 (54.7)
Orthopnoea	208 (5.9)	244 (5.1)	87 (14.3)	45 (4.1)	2 (0.2)	68 (4.9)	0 (0.0)	7 (3.1)	22 (9.9)	4 (2.0)	3 (3.2)
PND	137 (3.9)	331 (7.0)	23 (3.8)	25 (2.3)	13 (1.6)	84 (6.0)	1 (0.5)	5 (2.2)	5 (2.2)	6 (3.0)	1 (1.1)
Peripheral oedema	599 (17.0)	1470 (30.9)	188 (30.8)	156 (14.0)	51 (6.1)	206 (14.8)	12 (5.7)	6 (2.6)	18 (8.1)	51 (25.6)	5 (5.3)
Third heart sound	116 (3.3)	473 (9.9)	59 (9.7)	68 (6.1)	8 (1.0)	416 (29.9)	13 (6.2)	4 (1.8)	26 (11.7)	32 (16.1)	3 (3.2)
JVD	177 (5.0)	623 (13.1)	49 (8.0)	136 (12.3)	19 (2.3)	123 (8.8)	8 (3.8)	6 (2.7)	2 (0.9)	8 (4)	4 (4.2)

All values are reported as number (percentage) except where indicated.
*Median (interquartile range)
HF – heart failure; NYHA – New York heart association; KCCQ – Kansas City cardiomyopathy questionnaire; PND – paroxysmal nocturnal dyspnoea; JVD – jugular venous distension.

Investigations

LVEF was generally lower in patients in Asian countries compared with Europe and, to a lesser extent, North America [Table 6-5]. NT proBNP levels were at least as high in China (1470 pg/ml) and the Philippines (2241pg/ml) (and nearly as high in India and Thailand) as in Europe (1381pg/ml Western Europe, 1454 pg/ml in Eastern Europe) and the Americas but markedly lower in other Asian countries (e.g. median 1263 pg/ml in Taiwan and 943 pg/ml in Korea).

Level of creatinine and haemoglobin varied considerably among countries/regions without a definite pattern. The lowest average haemoglobin was in India (127 g/l) and highest in the Philippines (141 g/l), compared with 139 to 141 g/l in Europe and the Americas.

The prevalence of atrial fibrillation (on an ECG) was lower in most Asian countries and strikingly lower in India (2.5 %) than in Europe or the Americas (14.8 to 36.7%). LBBB was less prevalent in most Asian countries than elsewhere. Consistent with this, the average QRS duration was shorter in Asia than in the other regions (although QRS duration was shorter in Eastern Europe than in the other non-Asian regions).

Table 6-5 Investigations

	Western Europe n=3521	Central/Eastern Europe/Russia n=4758	North America n=613	Latin America n=1110	China n=833	India n=1390	Japan n=209	South Korea n=223	Philippines n=223	Taiwan n=199	Thailand n=95
Ejection fraction – (%)†	28.9 ± 6.0	30.8 ± 5.4	26.7 ± 7.0	28.5 ± 5.8	29.5 ± 4.9	27.9 ± 5.6	28.5 ± 5.5	27.0 ± 6.6	28.1 ± 6.2	28.1 ± 6.0	26.2 ± 6.0
NT-proBNP* - (pg/ml)	1381(787-2580)	1454(780-2740)	1494(801-2885)	1302(712-2547)	1470(718-3109)	1260(669-2628)	921(550-1548)	943(545-1765)	2241(1126-4806)	1263(719-2647)	1288(724-2674)
Haemoglobin † - (gm/L)	139.3 ± 14.9	141.4 ± 15.1	138.5 ± 14.8	139.9 ± 15.1	141.6 ± 15.9	126.7 ± 16.7	136.8 ± 14.8	138.3 ± 17.6	141.3 ± 16.9	139.0 ± 18.5	130.7 ± 19.4
Creatinine† - (umol/L)	101.0 ± 27.2	94.3 ± 24.2	107.3 ± 25.8	93.8 ± 25.5	86.5 ± 20.5	90.1 ± 25.5	94.2 ± 20.4	88.3 ± 22.8	100.4 ± 25.6	101.1 ± 26.5	97.1 ± 21.9
eGFR – ml/min/1.73m^2	65.8 ± 19.1	70.0 ± 19.5	61.7 ± 17.7	71.7 ± 23.5	80.4 ± 21.0	77.5 ± 29.5	71.3 ± 18.0	77.7 ± 22.5	68.3 ± 19.2	68.0 ± 21.0	69.1 ± 18.4
eGFR<60ml/min/m^2 – no. (%)	1408 (40.0)	1449 (30.5)	316 (51.6)	354 (31.9)	134 (16.1)	320 (23.0)	58 (27.8)	49 (22.0)	78 (35.0)	74 (37.2)	33 (34.7.7)
Sodium† – (mmol/L)	140.6 ± 3.1	141.7 ± 2.9	139.7 ± 3.0	139.6 ± 3.1	140.8 ± 2.5	138.7 ± 3.9	140.0 ± 2.7	140.7 ± 2.7	142.3 ± 2.2	140.7 ± 3.1	140.7 ± 2.5
Potassium† – (mmol/L)	4.5 ± 0.4	4.5 ± 0.5	4.4 ± 0.5	4.5 ± 0.5	4.3 ± 0.4	4.4 ± 0.5	4.3 ± 0.4	4.5 ± 0.4	4.3 ± 0.4	4.2 ± 0.5	4.2 ± 0.4
ECG											
LVH	281 (8.0)	1190 (25.0)	52 (8.5)	208 (18.7)	132 (15.8)	183 (13.2)	48 (23.0)	63 (28.3)	48 (21.5)	39 (19.6)	34 (35.8)
Atrial fibrillation	881 (25.0)	1748 (36.7)	91 (14.8)	219 (19.7)	152 (18.2)	35 (2.5)	37 (17.7)	58 (26.0)	30 (13.5)	40 (20.1)	17 (17.9)
LBBB	784 (22.3)	990 (20.8)	106 (17.3)	278 (25.0)	115 (13.8)	223 (16.0)	14 (6.7)	23 (10.3)	22 (9.9)	25 (12.6)	12 (12.6)
RBBB	250 (7.1)	388 (8.2)	37 (6.0)	119 (10.7)	38 (4.6)	100 (7.2)	16 (7.7)	9 (4.0)	11 (4.9)	13 (6.5)	7 (7.4)
QRS duration† – (msec)†	127.2 ± 37.2	112.7 ± 31.6	133.7 ± 36.6	116.5 ± 41.0	117.0 ± 31.9	102.5 ± 33.9	118.5 ± 29.4	113.3 ± 25.9	93.6 ± 27.2	115.8 ± 28.4	116.0 ± 24.4

All values are reported as number (percentage) except where indicated.
*Median (interquartile range)
†Mean ± standard deviation
NT-proBNP – N-terminal pro Brain natriuretic peptide; eGFR – estimated glomerular filtration rate; ECG – Electrocardiogram; LBBB – left bundle branch block; RBBB - Right bundle branch block.

Baseline therapy

Table 6-6 shows that diuretics were less commonly taken by patients in most Asian countries, compared with elsewhere (with the exceptions of India and Japan). Conversely, the use of digoxin was much more common (except in Japan). While beta-blocker use was uniformly high globally (although lower in India, the Philippines and Taiwan), MRA prescription varied greatly, with the highest use in China (66.3%) the Philippines (64.1%) and Latin America (62.8%) compared with other countries and regions (range 32.8% to 49.6% in Europe and North America). The use of anticoagulants was lower in most Asian countries (as low as 5.1% in India and 7.8% in China). Device use was low overall but much less in all Asian countries than in Western Europe and North America (device use was also uncommon in Latin America and Eastern Europe).

Table 6-6 Therapy at baseline

	Western Europe	Central/Eastern Europe/Russia	North America	Latin America	China	India	Japan	South Korea	Philippines	Taiwan	Thailand
	n=3521	n=4758	n=613	n=1110	n=833	n=1390	n=209	n=223	n=223	n=199	n=95
Diuretics	2845 (80.8)	3887 (81.7)	486 (79.3)	877 (79.0)	573 (68.8)	1188 (85.5)	163 (78.0)	165 (74.0)	96 (43.0)	146 (73.4)	68 (71.6)
Digoxin	681 (19.3)	1417 (29.8)	161 (26.3)	300 (27.0)	425 (51.0)	658 (47.3)	32 (15.3)	83 (37.2)	100 (44.8)	57 (28.6)	38 (40.0)
ACEI	3175 (90.2)	4289 (90.1)	554 (90.4)	997 (89.8)	718 (86.2)	1260 (90.6)	209 (100.0)	186 (83.4)	105 (47.1)	142 (71.4)	86 (90.5)
ARB	386 (11.0)	494 (10.4)	70 (11.4)	116 (10.5)	115 (13.8)	139 (10.0)	10 (4.8)	38 (17.0)	119 (53.4)	57 (28.6)	8 (8.4)
Beta-blockers	3292 (93.5)	4485 (94.3)	594 (96.9)	1038 (93.5)	779 (93.5)	1181 (85.0)	194 (92.8)	202 (90.6)	181 (81.2)	168 (84.4)	88 (92.6)
MRAs	1436 (40.8)	2362 (49.6)	201 (32.8)	697 (62.8)	552 (66.3)	468 (33.7)	82 (39.2)	91 (40.8)	143 (64.1)	70 (35.2)	32 (33.7)
Statins	2350 (66.7)	2634 (55.4)	481 (78.5)	416 (37.5)	246 (29.5)	765 (55.0)	108 (51.7)	88 (39.5)	129 (57.8)	61 (30.7)	60 (63.2)
Aspirin	1746 (49.6)	2451 (51.5)	428 (69.8)	546 (49.2)	433 (52.0)	619 (44.5)	109 (52.2)	119 (53.4)	125 (56.1)	110 (55.3)	58 (61.1)
Anticoagulants	1609 (45.7)	1853 (38.9)	235 (38.3)	236 (21.3)	65 (7.8)	71 (5.1)	108 (51.7)	69 (30.9)	25 (11.2)	29 (14.6)	20 (21.1)
PCI	1068 (30.3)	936 (19.7)	258 (42.1)	161 (14.5)	122 (14.6)	162 (11.7)	62 (29.7)	48 (21.5)	3 (1.3)	54 (27.1)	19 (20.0)
CABG	767 (21.8)	723 (15.2)	240 (39.2)	80 (7.2)	34 (4.1)	165 (11.9)	21 (10.0)	12 (5.4)	7 (3.1)	19 (9.5)	4 (4.2)
Pacemaker	744 (21.1)	408 (8.6)	204 (33.3)	98 (8.8)	62 (7.4)	11 (0.8)	17 (8.1)	3 (1.3)	0 (0.0)	14 (7.0)	1 (1.1)
ICD-any	1199 (34.1)	412 (8.7)	328 (53.5)	30 (2.7)	29 (3.5)	1 (0.1)	24 (11.5)	1 (0.4)	0 (0.0)	9 (4.5)	6 (6.3)
CRT	460 (13.1)	172 (3.6)	138 (22.5)	16 (1.4)	49 (5.9)	5 (0.4)	12 (5.7)	0 (0.0)	0 (0.0)	7 (3.5)	1 (1.1)

All values are reported as number (percentage)
ACEI – Angiotensin-converting enzyme inhibitor; ARB – Angiotensin receptor blocker; MRA – Mineralocorticoid receptor antagonist; PCI – Primary coronary intervention; CABG – Coronary artery bypass graft; ICD – Implantable cardioverter-defibrillator; CRT – Cardiac resynchronization therapy.

Outcomes

As shown in Table 6-7, the event rates for the primary composite outcome were higher in patients in Taiwan (17.2 per 100 person-years), China (14.9), and Thailand (13.8) compared to those in Europe (10.4 in Western and 12.3 in Eastern Europe) and the Americas (12.8 in North and 12.6 in Latin America). The adjusted risk was significantly higher in these Asian countries than in Western Europe, the reference region. However, the picture was quite different when the components of the composite were examined separately. The adjusted risk of cardiovascular death was higher in India, China, the Philippines, Thailand, and Taiwan, than in Western Europe, whereas the risk of this outcome tended to be lower in patients in Japan [Table 6-7]. A broadly similar pattern was observed for all-cause mortality (with a significantly lower all-cause mortality in Japan than in Western Europe). Conversely, the risk of hospital admission was significantly lower in India and in the Philippines than in Western Europe, whereas this risk was significantly higher in China, Japan, and Taiwan [Table 6-7].

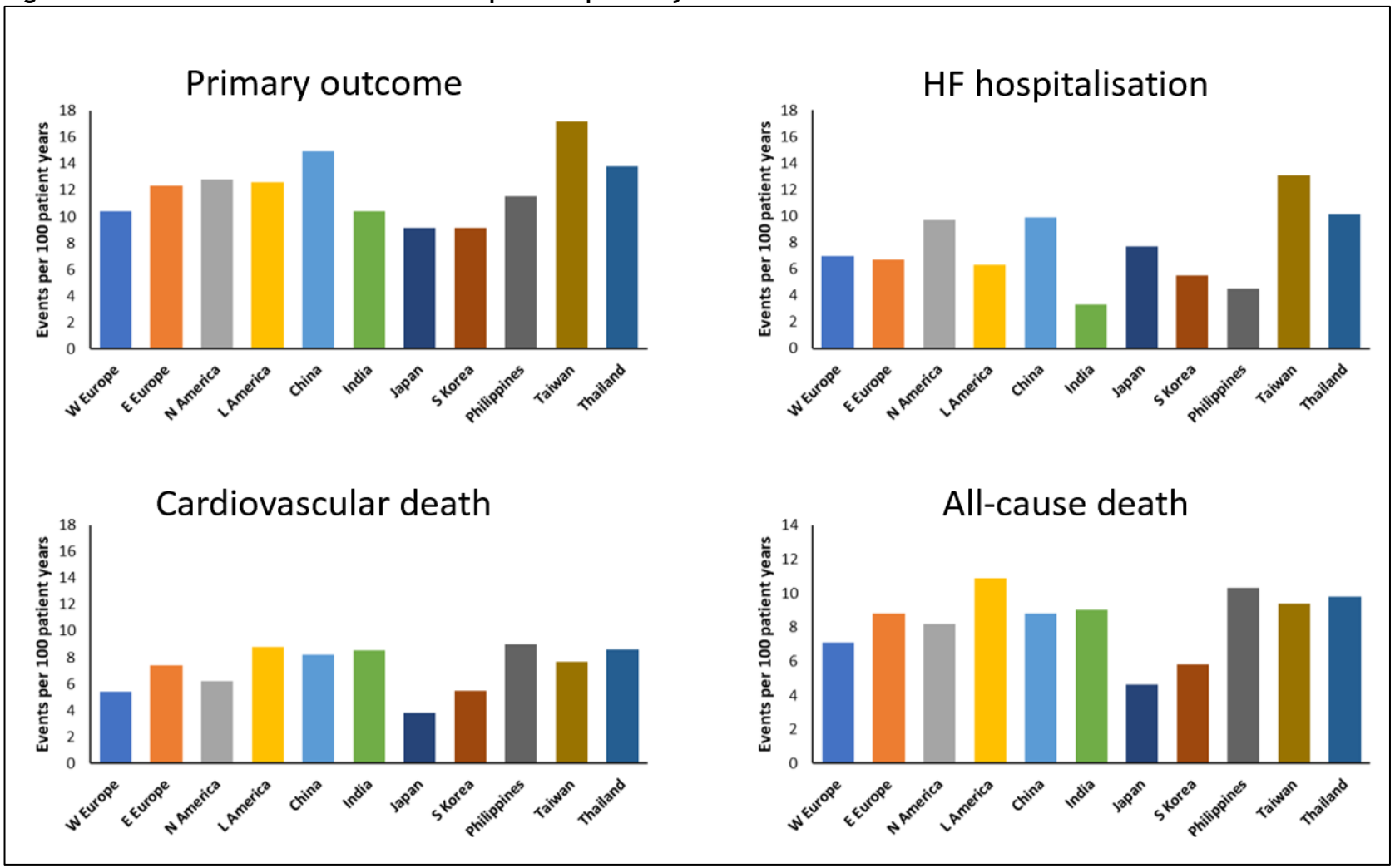
Table 6-7 Clinical outcomes

	Western Europe n=3521	Central/Eastern Europe/Russia n=4758	North America n=613	Latin America n=1110	China n=833	India n=1390	Japan n=209	South Korea n=223	Philippines n=223	Taiwan n=199	Thailand n=95
Primary outcome											
Events – no. (%)	949 (27.0)	1371 (28.8)	181 (29.5)	317 (28.6)	290 (34.8)	356 (25.6)	69 (33.0)	59 (26.5)	51 (22.9)	88 (44.2)	31 (32.6)
Events per 100 person-years	10.4 (9.7-11.0)	12.3 (11.7-13.0)	12.8 (11.0-14.8)	12.6 (11.3-14.0)	14.9 (13.3-16.8)	10.4 (9.4-11.6)	10.4 (8.2-13.2)	9.1 (7.0-11.7)	11.5 (8.8-15.2)	17.2 (14.0-21.2)	13.8 (9.7-19.6)
Unadjusted sHR	1.00 (ref.)	1.19 (1.09-1.29)	1.24 (1.06-1.46)	1.18 (1.04-1.34)	1.44 (1.26-1.64)	1.01 (0.89-1.14)	1.02 (0.79-1.30)	0.90 (0.69-1.17)	1.13 (0.85-1.50)	1.67 (1.34-2.08)	1.30 (0.91-1.85)
Adjusted sHR -1	1.00 (ref.)	1.20 (1.10-1.32)	1.09 (0.92-1.28)	1.38 (1.21-1.57)	1.76 (1.52-2.02)	1.13 (0.97-1.30)	1.24 (0.97-1.58)	1.12 (0.85-1.46)	1.28 (0.95-1.74)	1.86 (1.50-2.30)	1.51 (1.05-2.18)
Adjusted sHR -2	1.00 (ref.)	1.25 (1.14-1.36)	1.02 (0.87-1.21)	1.43 (1.26-1.64)	1.92 (1.66-2.22)	1.22 (1.06-1.42)	1.28 (1.00-1.64)	1.14 (0.87-1.51)	1.30 (0.96-1.77)	1.78 (1.44-2.20)	1.63 (1.13-2.35)
First HF hospitalisation											
Events – no. (%)	643 (18.3)	740 (15.6)	137 (22.3)	159 (14.3)	193 (23.2)	113 (8.1)	51 (24.4)	36 (16.1)	20 (9.0)	67 (33.7)	23 (24.2)
Events per 100 person-years	7.0 (6.5-7.6)	6.7 (6.2-7.1)	9.7 (8.2-11.4)	6.3 (5.4-7.4)	9.9 (8.6-11.5)	3.3 (2.8-4.0)	7.7 (5.9-10.2)	5.5 (4.0-7.7)	4.5 (2.9-7.0)	13.1 (10.3-16.7)	10.2 (6.8-15.4)
Unadjusted sHR	1.00 (ref)	0.90 (0.81-1.00)	1.36 (1.13-1.63)	0.82 (0.69-0.98)	1.35 (1.15-1.58)	0.44 (0.36-0.54)	1.16 (0.87-1.54)	0.82 (0.59-1.14)	0.58 (0.37-0.92)	1.88 (1.46-2.42)	1.40 (0.93-2.12)
Adjusted sHR -1	1.00 (ref.)	0.91 (0.81-1.02)	1.14 (0.94-1.38)	0.93 (0.78-1.11)	1.65 (1.38-1.96)	0.51 (0.41-0.66)	1.45 (1.09-1.94)	1.01 (0.71-1.42)	0.64 (0.40-1.03)	1.94 (1.47-2.56)	1.63 (1.06-2.49)
Adjusted sHR -2	1.00 (ref.)	0.95 (0.85-1.07)	1.05 (0.87-1.28)	0.97 (0.81-1.16)	1.83 (1.53-2.19)	0.57 (0.45-0.72)	1.53 (1.14-2.05)	1.10 (0.77-1.55)	0.67 (0.42-1.08)	1.83 (1.37-2.43)	1.83 (1.19-2.80)
Cardiovascular death											
Events – no. (%)	537 (15.3)	899 (18.9)	98 (16.0)	238 (21.4)	180 (21.6)	299 (21.5)	29 (13.9)	39 (17.5)	42 (18.8)	47 (23.6)	21 (22.1)
Events per 100 person-years	5.4 (4.9-5.8)	7.4 (7.0-7.9)	6.2 (5.1-7.5)	8.8 (7.7-10.0)	8.2 (7.1-9.5)	8.5 (7.5-9.5)	3.8 (2.6-5.4)	5.5 (4.0-7.5)	9.0 (6.7-12.2)	7.7 (5.8-10.3)	8.6 (5.6-13.1)
Unadjusted sHR	1.00 (ref)	1.42 (1.2-1.58)	1.20 (0.97-1.48)	1.62 (1.39-1.89)	1.56 (1.32-1.84)	1.61 (1.39-1.85)	0.68 (0.46-0.98)	1.03 (0.75-1.42)	1.87 (1.36-2.57)	1.42 (1.06-1.92)	1.60 (1.04-2.46)
Adjusted sHR -1	1.00 (ref.)	1.48 (1.32-1.66)	1.08 (0.87-1.34)	1.96 (1.68-2.29)	1.89 (1.58-2.27)	1.76 (1.49-2.09)	0.77 (0.53-1.12)	1.27 (0.92-1.78)	2.14 (1.52-3.00)	1.57 (1.17-2.10)	1.87 (1.18-2.96)
Adjusted sHR -2	1.00 (ref.)	1.53 (1.36-1.72)	1.03 (0.82-1.28)	2.04 (1.74-2.38)	2.02 (1.69-2.42)	1.91 (1.60-2.27)	0.79 (0.54-1.14)	1.29 (0.93-1.80)	2.14 (1.52-3.01)	1.51 (1.13-2.02)	1.99 (1.26-3.14)

All-cause death											
Events – no. (%)	717 (20.4)	1065 (22.4)	131 (21.4)	297 (26.8)	192 (23.0)	317 (22.8)	35 (16.7)	41 (18.4)	48 (21.5)	57 (28.6)	24 (25.3)
Events per 100 person-years	7.1 (6.6-7.7)	8.8 (8.3-9.4)	8.2 (6.9-9.8)	10.9 (9.8-12.3)	8.8 (7.6-10.1)	9.0 (8.0-10.0)	4.6 (3.3-6.3)	5.8 (4.2-7.8)	10.3 (7.8-13.7)	9.4 (7.2-12.2)	9.8 (6.6-14.6)
Unadjusted HR	1.00 (ref)	1.25 (1.14-1.38)	1.19 (0.99-1.44)	1.55 (1.35-1.77)	1.23 (1.05-1.44)	1.26 (1.10-1.44)	0.61 (0.43-0.85)	0.79 (0.58-1.08)	1.55 (1.16-2.08)	1.30 (0.99-1.70)	1.37 (0.92-2.06)
Adjusted HR -1	1.00 (ref.)	1.32 (1.19-1.46)	1.11 (0.92-1.35)	1.89 (1.64-2.18)	1.51 (1.27-1.79)	1.41 (1.21-1.64)	0.68 (0.48-0.96)	0.98 (0.71-1.36)	1.80 (1.33-2.44)	1.41 (1.07-1.85)	1.63 (1.07-2.48)
Adjusted HR -2	1.00 (ref.)	1.37 (1.23-1.52)	1.05 (0.87-1.28)	1.98 (1.72-2.28)	1.61 (1.36-1.91)	1.51 (1.29-1.77)	0.69 (0.49-0.98)	1.00 (0.72-1.37)	1.80 (1.32-2.44)	1.32 (1.00-1.73)	1.74 (1.14-2.65)

Sub-distribution hazard ratios reported as sHR (95% confidence interval) [hazard ratio for all-cause death]
Event rates per 100 person-years with 95% confidence interval
All sHRs adjusted for randomised treatment at baseline
Model 1 - Adjusted for age, sex, heart rate (HR), systolic blood pressure (SBP), body mass index (BMI), left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) classification, NT pro Brain natriuretic peptide (NT proBNP) and estimated glomerular filtration rate (eGFR).
Model 2 – Adjusted for NT proBNP and the variables found in the MAGGIC risk score (age, sex, HR, SBP, BMI, LVEF, NYHA classification, creatinine, current smoking, diabetes, chronic obstructive pulmonary disease, heart failure duration, beta-blocker use, ACEI/ARB, interaction between LVEF and age, interaction between LVEF and SBP)

Figure 6-2 Clinical outcomes - event rates per 100 person-years



Discussion

Together, the patients enrolled in ATMOSPHERE and PARADIGM-HF, comprise the largest, most contemporary and most geographically, racially and ethnically diverse cohort of patients with HFrEF enrolled in clinical trials, with participants from 55 countries. In the present analyses, I focussed on 3172 patients enrolled from 7 countries in Asia, including 1390 from India and 833 from China. I believe this to be the only report describing long-term non-fatal and fatal outcomes in HFrEF patients in Asia and comparing these with other regions of the world.

Although this analysis was by country, it should be noted that this geographical division of patients was largely synonymous with their categorization by race and ethnicity. For example, all patients in China, India and Japan were reported be of Asian race but to have Chinese, Indian or Japanese ethnicity, respectively. All patients in the remaining Asian countries were described as of Asian race and, in most cases, "other" ethnicity. The one exception was Taiwan where most patients described themselves as having Chinese ethnicity. Very small numbers of participants in the comparator regions were of Asian race.

I found substantial differences among patients within countries in Asia and between Asia and elsewhere. This was true for both clinical characteristics at baseline and for clinical outcomes. However, the differences within Asia were not consistent and varied for different characteristics. For example, patients in many Asian countries were considerably younger than in Europe and North America. However, patients in Japan and Taiwan were older than in other Asian countries. There are two other large studies of Asian patients with heart failure.[82,127] INTER-CHF included consecutive patients with a clinical diagnosis of HF from outpatient clinics and inpatient hospital wards at participating centres in India (n=858 patients), China (n=991) and South-East Asia (defined as Malaysia, and the Philippines, n=811), as well as patients in Africa (n=1294), Latin America (n=869) and the Middle East (n=1000).[82] The average age of patients in India, China, South-East Asia and Latin America, was 56, 66, 57 and 67 years, respectively. However, the proportion of patients with HFpEF in these countries/regions varied considerably (47%, 63%, 61% and 47%, respectively), which is important for the interpretation of age as patients with HFpEF are

generally older than patients with HFrEF (and I studied only patients with HFrEF).[212] Despite this, the age of patients in all these countries/regions were similar in the two studies, except for China (patients in INTER-CHF in China were older than in this study). The Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry enrolled symptomatic HFrEF in- or out-patients (with at least one episode of decompensated HF in the previous 6 months that resulted in hospital admission or was treated in an outpatient clinic) at 46 medical centres in 11 Asian countries/territories: China (n=477)/Hong Kong (n=50), India (n=1436), Indonesia (n=290), Japan (n=540), Korea (n=317), Malaysia (n=541), Philippines (n=91), Singapore (n=1066), Taiwan (n=274), and Thailand (n=194). The mean age in these countries was 57.0/67.7, 57.8, 55.8, 64.9, 63.3, 57.4, 54.3, 60.7, 63.3 and 60.0 years, respectively.[127] This age profile and ranking within Asian countries was very similar to what I found in this analysis. Genetic differences, stage of epidemiological transition, environmental factors, foetal programming, SES and other factors are thought to account for the increasing prevalence and early development of cardiovascular disease in low and middle-income countries. South Asians may be especially prone to the premature development of cardiovascular diseases because of their high frequency of insulin resistance, in part related to pattern of fat distribution (abdominal obesity).[213-215] Atrial fibrillation was generally less frequent in Asian countries, especially India, possibly because it is a particularly age-related condition, or potentially because of ethnic or genetic differences.[216,217] The particularly low prevalence of atrial fibrillation in India (2.5% in this study) doesn't reflect ascertainment bias (as it was based on ECG analysis) and was also found in the ASIAN-HF registry (4.2%; frequency of atrial fibrillation was not reported in INTER-CHF).[127] Conversely, India and the Philippines differed from other Asian countries in their high prevalence of diabetes (but not higher BMI) whereas the Philippines and Taiwan had a higher prevalence of hypertension (but not a higher blood pressure) than other Asian countries.

LVEF varied little among Asian countries or between Asia and elsewhere whereas NT proBNP varied much more, with several Asian counties (Japan and Korea and, to a lesser extent, India and Taiwan) having notably lower median concentrations than elsewhere which in some of these countries may be attributed to younger age, lower prevalence of atrial fibrillation and better

renal function.[215,218] This did not seem to be explained by differences in LVEF or NYHA class distribution and know of no other obvious explanation. Unfortunately, neither the ASIAN-HF registry nor INTER-CHF reported NT proBNP.[82,127]

Patients in Asian countries generally had a higher heart rate than in Western Europe and North America and this was not readily explicable by either prevalence of atrial fibrillation or rate of beta-blocker treatment, although beta-blocker dosing may be lower in Asian countries. Heart rate was not recorded in INTER-CHF and, although the ASIAN-HF registry doesn't provide a direct comparison with other regions, heart rate was generally higher than in similar studies from elsewhere.[82,127]

Interestingly, peripheral oedema was reported less frequently in Asian patients which was not obviously explained by differences in diuretic therapy but could relate to climatic conditions or MRA therapy, the use of which was higher in China and the Philippines than in any other Asian country and higher than in any other region, except Latin America (which also reported a low prevalence of oedema). The strikingly low use of diuretics found in the Philippines in the present study was supported by both the ASIAN-HF registry and INTER-CHF. In an analysis of diuretic therapy in DAPA-HF, patients from Asia who were taking diuretics were observed to be taking the lowest dose.[219] The high use of MRAs in China (and the Philippines in the ASIAN-HF registry) was also confirmed by each of these studies (and high use in Latin America too by INTER-CHF).[82,127] In China, this may be related to national programmes to promote the use of spironolactone.[220]

There were other notable differences in treatment patterns, with some Asian countries reporting much higher use of digoxin than others (and elsewhere), despite a low prevalence of atrial fibrillation. Digoxin use was not reported in the ASIAN-HF registry and was difficult to interpret in INTER-CHF given the mix of patients with HFrEF and HFpEF. However, low use of anticoagulants in India corroborated the low prevalence of atrial fibrillation in the two countries (neither ASIAN-HF nor INTER-CHF reported use of anticoagulants). Device use was uniformly low in Asia (as in Eastern Europe and Latin America), with only Japan reporting above 10% use, likely reflecting economic considerations as

much as clinical ones. Device use was not reported in INTER-CHF and was generally low in the ASIAN-HF registry, except for Japan.[82,127]

Appropriate versions of the KCCQ were available for 4 of the 7 Asian countries that have been studied here (India, China, Japan and Philippines). In one previous study, Indians had a higher mean OSS (64.8) compared with Chinese who lived in several Asian countries (mean score 60.1) and Japanese and Koreans (reported as a single group) had the highest score (67.3).[221] While I found the highest median KCCQ clinical summary score in patients enrolled in Japan, a reverse ranking existed in patients from India and China compared with this prior study. Clearly, there is a huge gap in this knowledge of patient reported outcomes in different parts of Asia and compared with the rest of the world.

A particular strength of the present study is the availability of information on long-term fatal and non-fatal outcomes. Here the differences within Asia and between Asia and elsewhere were stark. For example, the highest and lowest HF hospitalisation rates, globally, were found in Asian countries (Taiwan and India, respectively). I know of no previous comparison of HF hospitalisation rates in ambulatory HFrEF patients in Asia (and between Asia and elsewhere).

The low rate of hospitalisation in India was especially striking, being a third to half that in Europe and North America and about a quarter of the rate in Taiwan. This was not explained by a particularly high competing risk of death. Younger age, shorter duration of HF and a higher KCCQ score (better QoL) may be relevant, as well as differences in access to, or utilization of, hospital care in some countries (such as India).

Conversely, the high hospitalisation rates in other Asian countries were not explained by a lower risk of death. In fact, Asian countries generally had high mortality rates with two notable exceptions, namely Japan and Korea which had the lowest and second-lowest mortality rates globally. These low rates reflect the known long life-expectancy in these two countries, especially Japan.[222] It is of interest to compare these findings about mortality with other studies which included patients from Asia. The only study to do this that I know of was INTER-CHF which included consecutive patients with a clinical diagnosis of HF from outpatient clinics and inpatient hospital wards at participating centres in India

(n=858 patients), China (n=991) and (defined as Malaysia, and the Philippines, n=811).[82] The 1-year mortality was 23.3% in India, 7.3% in China and 15.0% in South-East Asia (non-fatal outcomes were not collected). However, the proportions of patients enrolled as an in-patient (i.e. at higher risk of death) differed considerably (45%, 35% and 23%, respectively) as did the proportion of patients with HFrEF (53%, 27% and 39%, respectively). Clearly, these differences make comparison with this dataset impossible but highlight the need for a better understanding of mortality and morbidity rates in Asia.

Such differences in hospitalisation and mortality also clearly have implications for clinical trials which are increasingly being conducted on a global, wider population. Accordingly, I addressed these concerns in a separate analysis to study the effect of sacubitril/valsartan on clinical outcomes by different Asian regions in PARADIGM-HF.[223]

Strengths & Limitations

This study has several strengths and weaknesses. Comparison of countries within Asia (and comparing countries in Asia with other regions) is extremely complex, reflecting many influences including geography, climate and other environmental factors, diet and lifestyle, type of health care system, race/ethnicity, cultural influences, genetics and economic considerations. Using information from clinical trials also has disadvantages and advantages. Patients in trials are selected and not necessarily representative of patients in the population in general, especially those living in non-urban areas with inadequate access to health facilities. Compared to epidemiological studies, however, the common inclusion and exclusion criteria used in trials result in a more homogenous study population, overall. This allows a more "like-with-like" comparison between countries. This difference from epidemiological studies is highlighted by the mix of in-patients and out-patients and patients with HFrEF and HFpEF in INTER-CHF.[82] Patients in trials are usually characterized in more detail than in epidemiological studies as illustrated here by measurement of NT proBNP, for example. Event ascertainment in trials is also vigorous and consistent across countries. However, this study has other limitations, including the absence of information on patients from other key regions, namely Africa and the Middle East.

Conclusions

In summary, although patient characteristics and outcomes vary markedly between Asia and other global regions there are equally striking variations among Asian countries (e.g. the highest and lowest HF hospitalisation rates, globally, were found in Asian countries). These findings highlight the need to better understand the explanations for the differences in mortality and morbidity rates across Asia to better inform health policy and also have implications for clinical trials in HF.

Chapter 7. Income inequality and outcomes in heart failure with reduced ejection fraction: a global between country analysis

This chapter has been published as:

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HF is a global public health problem not only in the Western world but also in LMICs.[224,225] Several studies have highlighted the differences that exist in HF outcomes between various regions and countries.[82,126] Some of these geographical variations are attributable to differences in well establishes prognostic factors such as age, severity of HF and comorbidities. Other factors such as income inequality may also be important. The income inequality hypothesis postulates that population health is influences by the degree to which income is unevenly distributed within a society.[226,227] Income inequality was not included in any of the studies included in the systematic review in Chapter 1.

In this chapter I will describe the effects of income inequality on outcomes in HFrEF.[226–229] I will apply the Gini coefficient for each country to classify the patients by tertiles of the Gini coefficient.

Methods

This study was conducted in a pooled cohort of two HFrEF clinical trials – ATMOSPHERE and PARADIGM-HF.[38,135] The trial populations have been described in detail in Chapter 2.

Study groups

The Gini coefficient (also known as Gini index or Gini ratio) is a measure of income inequality in a population and is derived from the Lorenz curve (Figure 7-1). The Lorenz curve is a graphical representation of the distribution of income

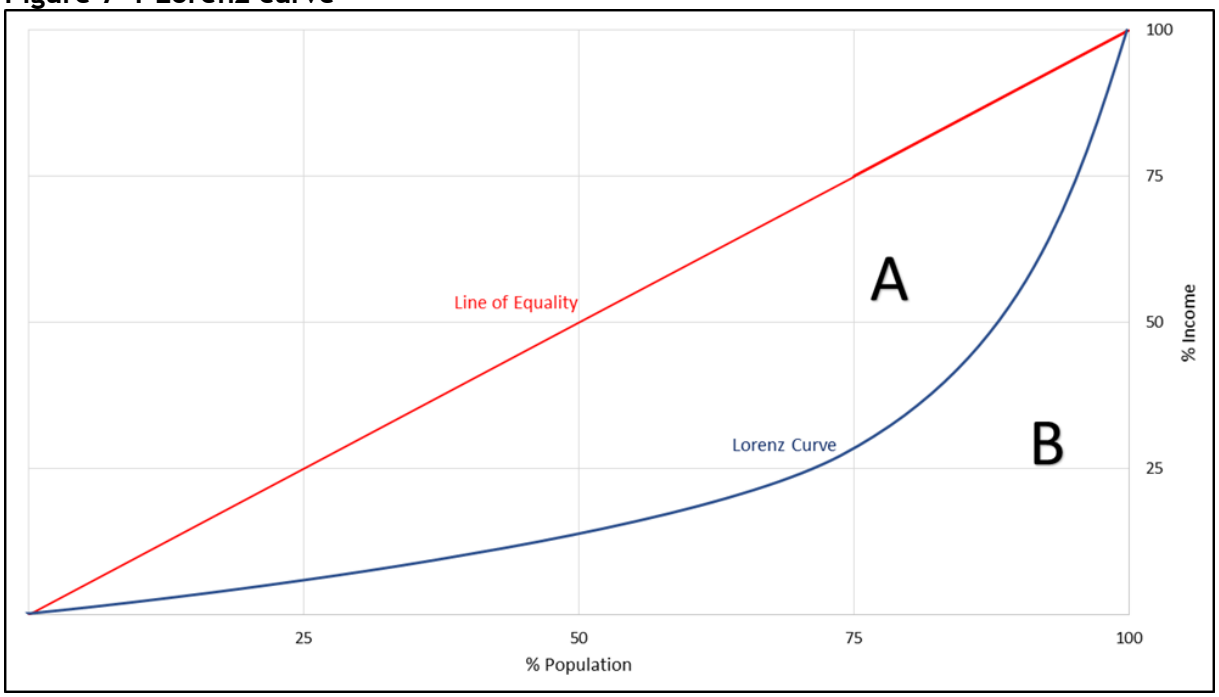
or of wealth. The curve is drawn on a graph with the percentage of the total population on the x-axis and the percentage of total income on the y-axis.

In a state of perfect equality, the bottom 25% of the population earns the bottom 25% of the total income, the bottom 75% of the population earns the bottom 75% of the total income and so on leading to a straight line known as the line of equality as is labelled in the figure below. However, this is very uncommon and more often than not, total income is not as equally divided in the population. This deviation from the line of equality is known as the Lorenz curve which is also labelled in Figure 7-1.

The Gini index is derived from this curve using the following formula:

Gini coefficient=A/(A+B); where A is the area between the line of equality and the Lorenz curve and B is the rest of the area under the Lorenz curve. In a state of perfect equality, A=0 and consequently according to the given formula, the Gini coefficient = 0. Perfect inequality is conversely indicated by a Gini coefficient=1 as B=0.

Figure 7-1 Lorenz curve



I applied the Gini coefficients obtained from the United Nations Development Programme (UNDP) for 50 of the 55 countries in the combined dataset.[230] Gini coefficients for Hong Kong, Japan, Korea and Singapore were derived from other sources. Taiwan was excluded from this analysis as social indicators could not be

derived from UNDP and reports from other sources were inconsistent and unreliable. Data from 2003 were used, to take account of a lag effect, whereby inequality up to 15 years previously may have a stronger association with health than current income-inequality.[231] For countries where a Gini coefficient for 2003 was unavailable, the value from the year closest to 2003 was used.

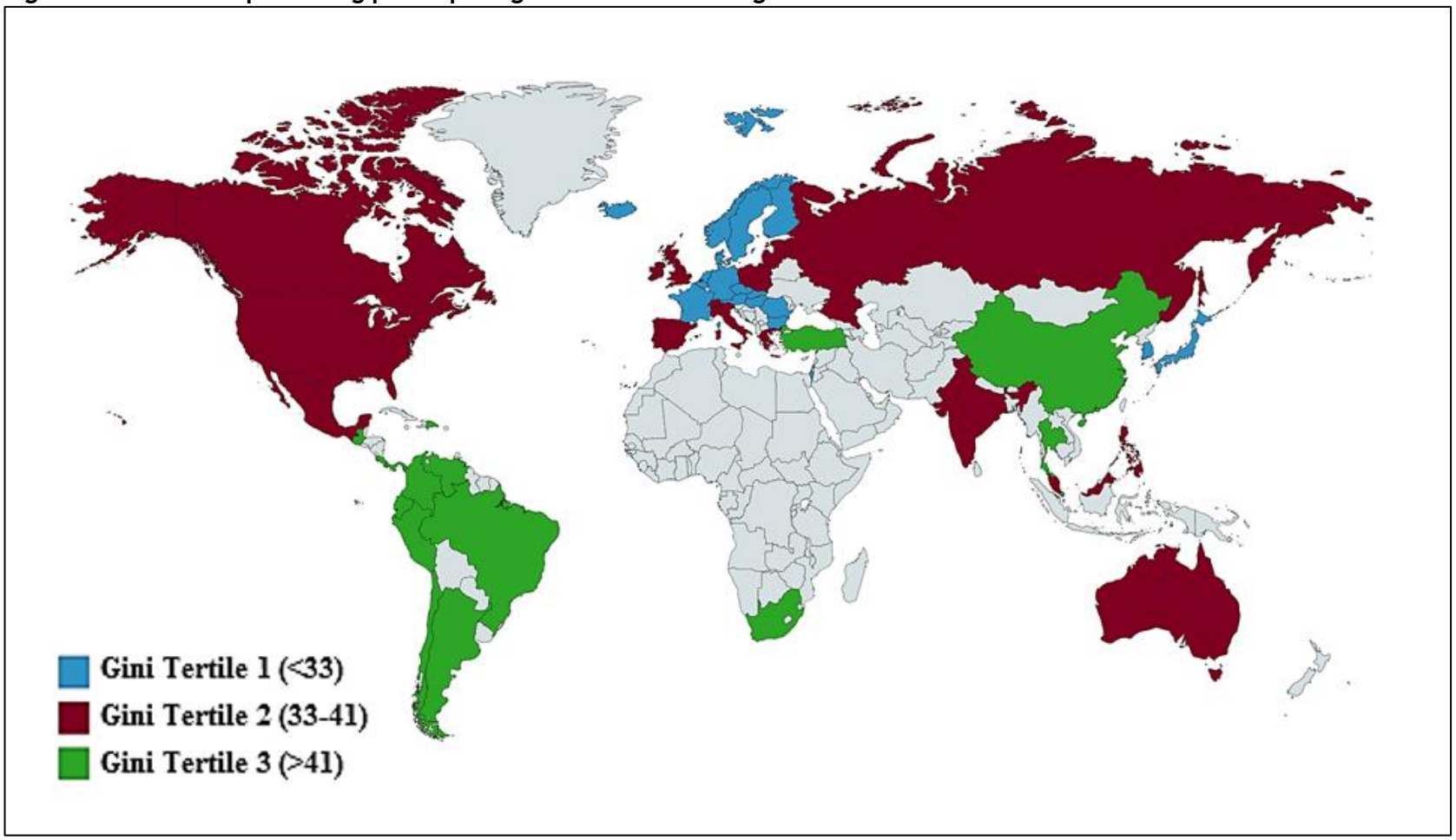
I categorized the patients into 3 groups by tertiles according to their distribution of Gini coefficient. Group 1(least inequality) had Gini coefficient<33, Group 2 comprised those countries with Gini coefficients between 33 and 41 and Group 3(greatest inequality) had Gini coefficient>41. I also tested the association between income-inequality and outcomes using the Gini coefficient as a continuous variable. The Gini coefficients for each country along with the number of patients from each country as per tertile of the Gini coefficient are shown in Table 7-1 and also illustrated in Figure 7-2.

Table 7-1 Gini coefficient and number of patients enrolled by country of origin

Country	Gini coefficient	Number of patients
Gini Tertile 1 (Least inequality)		
Austria	29.9	59
Belgium	30.6	144
Bulgaria	28.9	510
Czech Republic	27.5	517
Denmark	25.9	359
Finland	27.9	59
France	30.8	103
Germany	32.8	941
Hungary	30	444
Iceland	28.1	18
Israel	31.9	112
Japan	32.1	210
Korea	29.5	225
Netherlands	30.7	329
Norway	31.7	22
Romania	30	424
Slovakia	28.9	675
Sweden	26.4	169
Gini Tertile 2 (Intermediate inequality)		
Australia	34	41
Canada	33.9	229
Estonia	34	76

Greece	34	59
India	35.1	1417
Ireland	33.7	16
Italy	34.5	508
Lithuania	35.2	83
Latvia	36.8	84
Mexico	46	187
Malaysia	46	13
Philippines	44	223
Poland	35.4	494
Portugal	38.9	103
Russia	40.9	1399
Spain	33.4	337
Switzerland	34.5	15
United Kingdom	36.2	290
United States	40.6	550
Gini Tertile 3 (Greatest inequality)		
Argentina	50.2	838
Brazil	56.9	494
Chile	54.6	43
China	42.8	812
Columbia	56.1	309
Costa Rica	48.9	17
Dominican Republic	52	39
Ecuador	54.1	103
Guatemala	54.9	138
Hong Kong	53.9	23
Panama	55.1	30
Peru	51.2	258
Singapore	45.8	32
South Africa	64.8	311
Thailand	42.5	95
Turkey	41.3	134
Venezuela	49.8	96

Figure 7-2 World map showing participating countries according to tertiles of Gini coefficient



Other socio-economic indicators

To account for other socioeconomic variables, I also collected information on national per capita income (US dollars from the World Bank), hospital bed-density (The World Factbook) and health worker-density (World Health Organization) per 1000 population and education index (derived from the Human Development Index (HDI) – from the UNDP database) for further analysis of outcomes as will be discussed subsequently.[232–235] To derive health worker-density, I took the average of physician and nurse/midwife-density as figures for other types of health care workers were not uniformly available for all countries. All figures were ascertained for 2013 or the closest year to 2013.

Outcomes

For this chapter, as outlined in chapter 2, I have analysed the association between income-inequality, as reflected by the Gini coefficient, and the risk of the primary outcome of cardiovascular death or first HF hospitalisation, its components and non-cardiovascular and all-cause death.

Statistical analysis

I carried out competing risks regression using the Fine-Gray model to analyse the outcomes of interest using 3 models.[149] All-cause mortality was analysed by using Cox regression. Model 1 was used to calculate the crude sHR for each outcome. Model 2 fitted age, sex, heart rate, SBP, BMI, NYHA class, LVEF, eGFR and NT-proBNP. Model 3 fitted per capita income, education index, hospital bed density and health worker-density in addition to the variables used in Model 2 . I compared results of a multilevel cox regression model accounting for random effects (region) with another cox model which only adjusted for region and found very little variability in the results.[236] Consequently, all models were adjusted for region along with randomised treatment at baseline. Schoenfeld residuals were used to test the proportional hazards assumption. p-values <0.05 were considered significant. All analyses were conducted using Stata ver.14 (College Station, TX, USA).

Results

Overall, I included 15126 patients from 54 countries [Table 7-1 & Figure 7-2]. The median Gini coefficient was 35.1 (range 25.9–64.8; IQR 31.9 and 40.9). The mean Gini coefficient was 38.1± 9. The highest Gini coefficient tertile (tertile 3, coefficient>41, greatest inequality) included 3772 patients in 17 countries from 4 of the 5 global regions (North America was excluded; Figure 7-2). The middle tertile (33-41) included 6124 individuals in 19 countries from all 5 regions and the lowest tertile (tertile 1, coefficient<33, least inequality) included 5320 participants in 18 countries from 3 of the 5 regions (North America and Latin America were excluded; Figure 7-2). As Gini coefficient increased, HDI, per capita income, the proportion of GDP spent on healthcare and hospital-bed density decreased [Table 7-1].

Baseline characteristics

As shown in Table 7-2, a higher proportion of patients in Gini tertile 3 were women (24.8% vs. 21.0% in tertile 1 and 20.8% in tertile 2, respectively). Patients in Gini tertile 3 were younger (61 vs. 66 and 63 years, respectively) and were less obese (23.7% vs. 34.8% and 30.5%). Gini tertile 3 had the highest proportion of patients who had never smoked and low alcohol consumers whereas tertile 1 had the highest proportion of smokers and heavier consumers of alcohol.

Gini tertile 3 had the lowest prevalence of all recorded comorbid conditions, including hypertension, diabetes, atrial fibrillation, stroke, COPD and renal disease [Table 7-1]. Gini tertile 1 had the highest prevalence, with the single exception of unstable angina (but not MI), which was slightly more common in tertile 2 than in tertile 1.

Table 7-2 Baseline characteristics

	Gini Tertile 1 n=5320 (Least inequality)	**Gini Tertile 2** n=6124 (Intermediate inequality)	**Gini Tertile 3** n=3772 (Greatest inequality)	**p-value for trend**
Gini coefficient - %	(<33)	(33 - 41)	(>41)	
Number of countries	18	19	17	
Age - (years.)	66.3 ± 10.3	62.8 ± 11.6	61.0 ± 12.2	<0.0001
Age Group - years – no. (%)				<0.0001
≤40	78 (1.5)	254 (4.1)	215 (5.7)	
41 – 55	690 (13.0)	1255 (20.5)	963 (25.5)	
56 – 70	2556 (48.0)	2932 (47.9)	1716 (45.5)	
>70	1996 (37.5)	1683 (27.5)	878 (23.3)	
Females – no. (%)	1118 (21.0)	1273 (20.8)	936 (24.8)	0.0001
Region – no. (%)				<0.0001
North America	0 (0.0)	779 (12.7)	0 (0.0)	
Latin America	0 (0.0)	187 (3.1)	2365 (62.7)	
Western Europe & other	2315 (43.5)	1328 (21.7)	311 (8.2)	
Central Europe	2570 (48.3)	2136 (34.9)	64 (1.7)	
Asia - Pacific	435 (8.2)	1694 (27.7)	1032 (27.4)	
Per capita income – (US$)	31582 ± 18675	20714 ± 17704	9980 ± 5706	
Percentage of national GDP spent on healthcare	9.1 ± 1.9	7.8 ± 3.4	6.8 ± 1.5	
HDI*	0.890 (0.834 - 0.920)	0.803 (0.676 – 0.877)	0.737 (0.723 – 0.780)	
Education Index*	0.847 (0.822 - 0.898)	0.814 (0.635 – 0.852)	0.664 (0.616 – 0.709)	
Life Index*	0.924 (0.847 - 0.935)	0.817 (0.740 – 0.931)	0.855 (0.834 – 0.863)	
Income Index*	0.865 (0.816 - 0.917)	0.830 (0.657 – 0.879)	0.725 (0.719 – 0.785)	
Hospital Beds per 1000*	6.4 (6.0 – 8.2)	2.9 (1.0 – 6.5)	2.5 (1.6 – 3.8)	
Health workers per 1000 *	6.0 (4.7 – 8.7)	4.5 (1.4 – 6.1)	1.9 (1.8 – 4.1)	
SBP - (mmHg)	125 ± 16.9	122 ± 16.5	120 ± 16.3	<0.0001
Heart rate - (bpm)	71.5 ± 12.8	72.5 ± 11.8	71.8 ± 12.2	0.0340
BMI* - (kg/m^2)	28.6 ± 5.2	27.7 ± 5.8	26.9 ± 5.2	<0.0001
Comorbidities - no. (%)				
Hypertension	3733 (70.2)	4072 (66.5)	2324 (61.6)	<0.0001
Diabetes	1804 (33.9)	2011 (32.8)	954 (25.3)	<0.0001
Atrial fibrillation	2496 (46.9)	2030 (33.2)	885 (23.5)	<0.0001
Unstable angina	626 (11.8)	788 (12.9)	264 (7.0)	<0.0001
Myocardial infarction	2292 (43.1)	3021 (49.3)	1111 (29.5)	<0.0001
Stroke	490 (9.2)	466 (7.6)	245 (6.5)	<0.0001
COPD	789 (14.8)	820 (13.4)	222 (5.9)	<0.0001
Renal disease	846 (15.9)	929 (15.2)	233 (6.2)	<0.0001
Obese	1853 (34.8)	1869 (30.5)	894 (23.7)	<0.0001
Lifestyle Habits – n (%)				

Smoking Status				<0.0001
Never Smoked	2536 (47.7)	3401 (55.5)	2129 (56.4)	
Ex-Smoker	1970 (37.0)	1949 (31.8)	1175 (31.2)	
Current Smoker	814 (15.3)	774 (12.6)	468 (12.4)	
Alcohol units/d+				<0.0001
<1	4368 (82.1)	5496 (89.8)	3492 (92.6)	
1-2	788 (14.8)	521 (8.5)	204 (5.4)	
>2	164 (3.1)	105 (1.7)	76 (2.0)	

All values are reported as mean ± standard deviation except where indicated.
*Median (interquartile range)
United States dollars (US$), inter quartile range (IQR), gross domestic product (GDP), HDI – human development index; SBP – systolic blood pressure; BMI – body mass index; COPD – chronic obstructive pulmonary disease.
*Only taking into account physician and nurses/midwife density per 1000 population.
+One drink equals:
12 ounces of beer
8 ounces of malt liquor
5 ounces of wine
1.5 ounces or a shot of spirits or liquor

Heart failure characteristics

As shown in Table 7-3, patients belonging to Gini tertile 3 were least likely to have an ischaemic aetiology of HF. Gini tertile 3 patients had the highest proportion of patients with a more recent diagnosis of HF although all groups had a similar proportion of patients with a prior HF hospitalisation. Gini tertile 3 patients had the highest proportion of patients in NYHA classes I & II and the highest (best) KCCQ score.

Gini tertile 3 had the lowest prevalence of dyspnoea on effort, paroxysmal nocturnal dyspnoea, third heart sound and peripheral oedema. Patients in tertile 3 also had the lowest SBP (120 vs 125 in tertile 1 and 122 mmHg in tertile 2). Gini tertile 3 had the highest average eGFR and tertile 1 the lowest [Table 7-2].

Table 7-3 Heart failure characteristics and clinical features

Gini coefficient - %	Gini Tertile 1 n=5320 (Least inequality) (<33)	Gini Tertile 2 n=6124 (Intermediate inequality) (33 - 41)	Gini Tertile 3 n=3772 (Greatest inequality) (>41)	p-value for trend
HF aetiology				<0.0001
Ischaemic	3251 (61.1)	4107 (67.1)	1521 (40.3)	
Non-ischaemic	1573 (29.6)	1428 (23.3)	1726 (45.8)	
Other/Unknown	496 (9.3)	589 (9.6)	525 (1.4)	
HF duration				0.0459
<1 year	1526 (28.7)	1928 (31.5)	1357 (36.0)	
1-5 years	1964 (36.9)	2278 (37.2)	1514 (40.1)	
>5 years	1829 (34.4)	1915 (31.3)	901 (23.9)	
Previous HF hospitalisation	3331 (62.6)	3686 (60.2)	2292 (60.8)	<0.0001
NYHA Class				<0.0001
I/II	3748 (68.6)	4264 (69.7)	3231 (85.7)	
III	1627 (30.6)	1793 (29.3)	520 (13.8)	
IV	45 (0.9)	58 (1.0)	17 (0.5)	
KCCQ clinical summary score*	77.1 (60.4 – 90.0)	76.0 (58.9 - 89.6)	87.5 (75.0 - 95.8)	<0.0001
Clinical Features				
Dyspnoea on exertion	4642 (87.3)	5387 (88.2)	2997 (79.5)	<0.0001
Orthopnoea	267 (5.0)	428 (7.0)	272 (7.2)	<0.0001
PND	345 (6.5)	276 (4.5)	129 (3.4)	<0.0001
Peripheral oedema	1213 (22.8)	1437 (23.5)	489 (13.0)	<0.0001
Third heart sound	409 (7.7)	748 (12.2)	200 (5.3)	0.0086
JVD	590 (11.1)	457 (7.5)	422 (11.2)	0.5119

All values are reported as number (percentage) except where indicated.
*Median (interquartile range)
HF – heart failure; NYHA – New York heart association; KCCQ – Kansas City cardiomyopathy questionnaire; PND – paroxysmal nocturnal dyspnoea; JVD – jugular venous distension.

Investigations

LVEF differed little across Gini tertiles [Table 7-4]. However, median NT-proBNP concentration was highest in Gini tertile 3 (1500 pg/ml; IQR–803-3130) with the lowest level seen in tertile 1 (1358 pg/ml; IQR–766-2540).

Table 7-4 Investigations

Gini coefficient - %	**Gini Tertile 1** n=5320 (Least inequality) (<33)	**Gini Tertile 2** n=6124 (Intermediate inequality) (33 - 41)	**Gini Tertile 3** n=3772 (Greatest inequality) (>41)	**p-value for trend**
Ejection fraction† – (%)	29.9 ± 5.7	28.9 ± 6.1	28.0 ± 6.0	**<0.0001**
NT-proBNP* - (pg/ml)	1358 (766 - 2540)	1424 (755 - 2816)	1500 (803 - 3130)	**<0.0001**
Haemoglobin† - (gm/L)	140.6 ± 14.8	136.7 ± 17.0	138.8 ± 16.0	**<0.0001**
eGFR† - (ml/min/1.73m^2)	68.1 ± 19.8	70.3 ± 22.3	74.7 ± 24.6	**<0.0001**
LVH	852 (16.0)	1693 (27.6)	950 (25.2)	**<0.0001**

All values are reported as number (percentage) except where indicated.
*Median (interquartile range)
†Mean ± standard deviation
NT-proBNP – N-terminal pro Brain natriuretic peptide; eGFR – estimated glomerular filtration rate, LVH – left ventricular hypertrophy.

Baseline therapy

Patients in Gini tertile 3 were least often treated with a diuretic and most often treated with MRA and digoxin [Table 7-5]. Pre-trial use of an ARB (instead of an ACEI) was most common in tertile 3. Use of devices was lowest in tertile 3 patients: CRT-pacemaker/defibrillator (CRT-P/D) 2.7% and ICD/CRT-D 4.4%, respectively; intermediate in tertile 2 (6.8%; 16.1%) and highest in the individuals in tertile 1 (8.3%; 21.3%). Prior coronary revascularization (and statin use) showed a similar pattern.

Table 7-5 Therapy at baseline

Gini coefficient - %	**Gini Tertile 1** n=5320 (Least inequality) (<33)	**Gini Tertile 2** n=6124 (Intermediate inequality) (33 - 41)	**Gini Tertile 3** n=3772 (Greatest inequality) (>41)	**p-value for trend**
Diuretics	4342 (81.6)	4903 (80.1)	2945 (78.1)	<0.0001
Digoxin	1374 (25.8)	1955 (31.9)	1395 (37.0)	<0.0001
ACEI	4772 (89.7)	5434 (88.7)	3191 (84.6)	<0.0001
ARB	621 (11.7)	717 (11.7)	590 (15.6)	<0.0001
Beta-blockers	4995 (93.9)	5591 (91.3)	3489 (92.5)	0.0029
MRAs	2381 (44.8)	2660 (43.4)	2162 (57.3)	<0.0001
Statins	3146 (59.1)	3741 (61.1)	1437 (38.1)	<0.0001
Aspirin	2469 (46.4)	3393 (55.4)	1978 (52.4)	<0.0001
Anticoagulants	2426 (45.6)	1717 (28.0)	631 (16.7)	<0.0001
PCI	1384 (26.0)	1232 (20.1)	510 (13.5)	<0.0001
CABG	969 (18.2)	1015 (16.6)	278 (7.4)	<0.0001
Pacemaker	780 (14.7)	709 (11.6)	297 (7.9)	<0.0001

ICD-any	1131 (21.3)	986 (16.1)	165 (4.4)	<0.0001
CRT	442 (8.3)	417 (6.8)	101 (2.7)	<0.0001

All values are reported as number (percentage)
ACEI – Angiotensin-converting enzyme inhibitor; ARB – Angiotensin receptor blocker; MRA – Mineralocorticoid receptor antagonist; PCI – Primary coronary intervention; CABG – Coronary artery bypass graft; ICD – Implantable cardioverter-defibrillator; CRT – Cardiac resynchronization therapy.

Clinical outcomes

Patients in Gini tertile 3 had the highest rate of the primary composite outcome (13.7 per 100 person-years) and the rate was intermediate in tertile 2 (11.7) and lowest in tertile 1 (10.9) [Table 7-6 and Figure 7-3]. This trend was also observed for both cardiovascular and all-cause death which were highest in tertile 3 (8.9 and 10.4, respectively) and lowest in tertile 1 (5.9 and 7.4, respectively) [Table 7-6 and Figure 7-3].

In the model adjusting for conventional prognostic variables, including NT-proBNP, patients in Gini tertile 3 remained at significantly higher risk of the primary composite outcome (57% higher risk) and of cardiovascular and all-cause death (55% and 48% higher, respectively) [Table 7-6].

When country per capita income, education index, hospital bed density and health worker-density were added to the multivariable models, the elevated risk in Gini tertile 3 was attenuated but remained significant (46%, 35% and 30% higher for the primary composite outcome, cardiovascular death and all-cause mortality, respectively) [Table 7-6]. When considered as a continuous, rather than categorical variable, Gini coefficient remained an independent predictor of outcomes. Each 10-point increase in Gini coefficient was associated with a higher risk of cardiovascular death (sHR 1.16, 95% CI 1.04-1.29; p-value: 0.005) and death from any cause (sHR 1.15, 95% CI 1.04-1.26; p-value: 0.006) [Appendix Table 8; Figure 7-4]. As can be seen from Figure 7-4, the impact on cardiovascular death of a 10-point increase in Gini coefficient was greater than that of most other predictive variables, including advancing age and previous myocardial infarction.

Hospital admission for heart failure

The unadjusted rate of HF hospitalisation was highest in Gini tertile 3 but intermediate in tertile 1 rather than tertile 2, as for the other outcomes. In the adjusted model accounting for country per capita income, hospital bed-density

and the competing risk of death, risk of hospital admission for HF was 99% higher in Gini tertile 3, compared with tertile 1 (sHR 1.92, 95% CI 1.58-2.33) [Table 7-6].

Table 7-6 Clinical outcomes

Gini coefficient - %	**Gini Tertile 1** n=5320 (Least inequality) (<33)	**Gini Tertile 2** n=6124 (Intermediate inequality) (33 - 41)	**Gini Tertile 3** n=3772 (Greatest inequality) (>41)
Primary outcome			
Events – no (%)	1480 (27.8)	1694 (27.7)	1138 (33.7)
Event rate per 100 person-years	10.9 (10.4 – 11.5)	11.7 (11.2 – 12.3)	13.7 (12.9 – 14.5)
Unadjusted sHR	1.00 (ref)	1.06 (0.99 – 1.15)	1.56 (1.39 – 1.76)
Adjusted sHR – 1	1.00 (ref)	1.03 (0.95 – 1.11)	1.57 (1.38 – 1.79)
Adjusted sHR – 2	1.00 (ref.)	0.99 (0.91 – 1.08)	1.46 (1.25 – 1.70)
First HF hospitalisation			
Events – no (%)	941 (17.7)	900 (14.7)	611 (16.2)
Event rate per 100 person-years	6.9 (6.5 - 7.4)	6.2 (5.8 - 6.6)	7.4 (6.8 – 8.0)
Unadjusted sHR	1.00 (ref)	0.83 (0.75 – 0.92)	1.57 (1.36 – 1.81)
Adjusted sHR – 1	1.00 (ref)	0.81 (0.72 – 0.90)	1.52 (1.30 – 1.77)
Adjusted sHR – 2	1.00 (ref.)	0.85 (0.76 – 0.96)	1.92 (1.58 – 2.33)
Cardiovascular death			
Events – no (%)	881 (16.6)	1143 (18.7)	801 (21.2)
Event rate per 100 person-years	5.9 (5.6 – 6.3)	7.3 (6.9 – 7.7)	8.9 (8.3 – 9.5)
Unadjusted sHR	1.00 (ref)	1.24 (1.13 – 1.37)	1.50 (1.29 – 1.74)
Adjusted sHR – 1	1.00 (ref)	1.21 (1.10 – 1.33)	1.55 (1.32 – 1.82)
Adjusted sHR – 2	1.00 (ref.)	1.12 (1.01 – 1.25)	1.35 (1.12 – 1.62)
All-cause death			
Events – no (%)	1097 (20.6)	1349 (22.0)	938 (24.9)
Event rate per 100 person-years	7.4 (7.0 – 7.8)	8.6 (8.2 – 9.1)	10.4 (9.8 – 11.1)
Unadjusted HR	1.00 (ref)	1.20 (1.10 – 1.30)	1.44 (1.25 – 1.65)
Adjusted HR – 1	1.00 (ref)	1.18 (1.08 – 1.28)	1.48 (1.29 – 1.71)
Adjusted HR - 2	1.00 (ref.)	1.13 (1.02 – 1.24)	1.30 (1.10 – 1.53)

Sub-distribution hazard ratios reported as sHR (95% confidence interval) [hazard ratio for all-cause death]
Event rates per 100 person-years with 95% confidence interval
All sHRs adjusted for region and randomised treatment at baseline
Adjusted sHRs - 1 additionally adjusted for: sex, age, heart rate, systolic blood pressure, body mass index, NT-proBNP, NYHA functional class, ejection fraction and estimated glomerular filtration rate.
Adjusted sHRs – 1 adjusted for all covariates as in model 1 along with: per capita income, education index, hospital bed density and health worker density.

Figure 7-3 Clinical outcomes

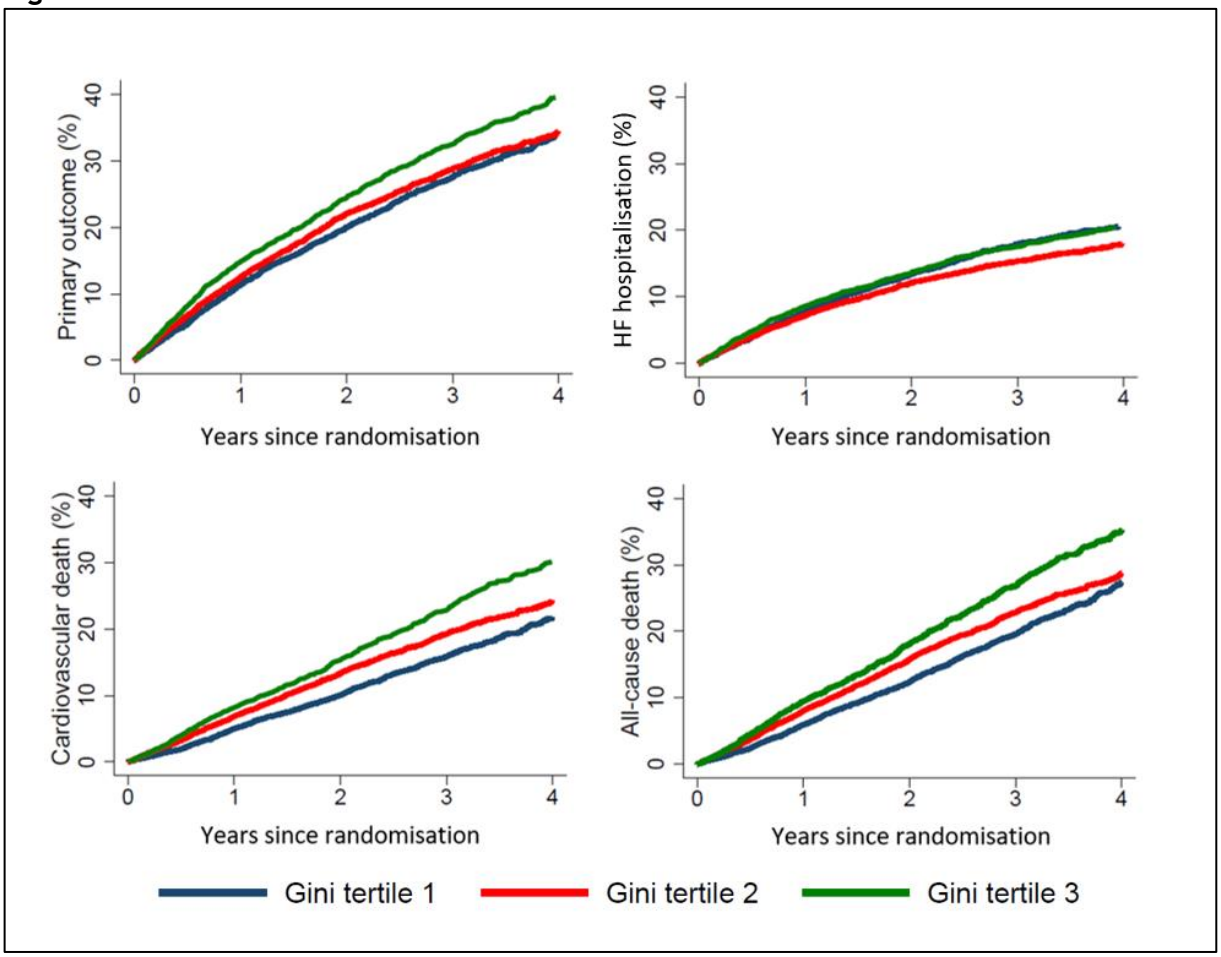
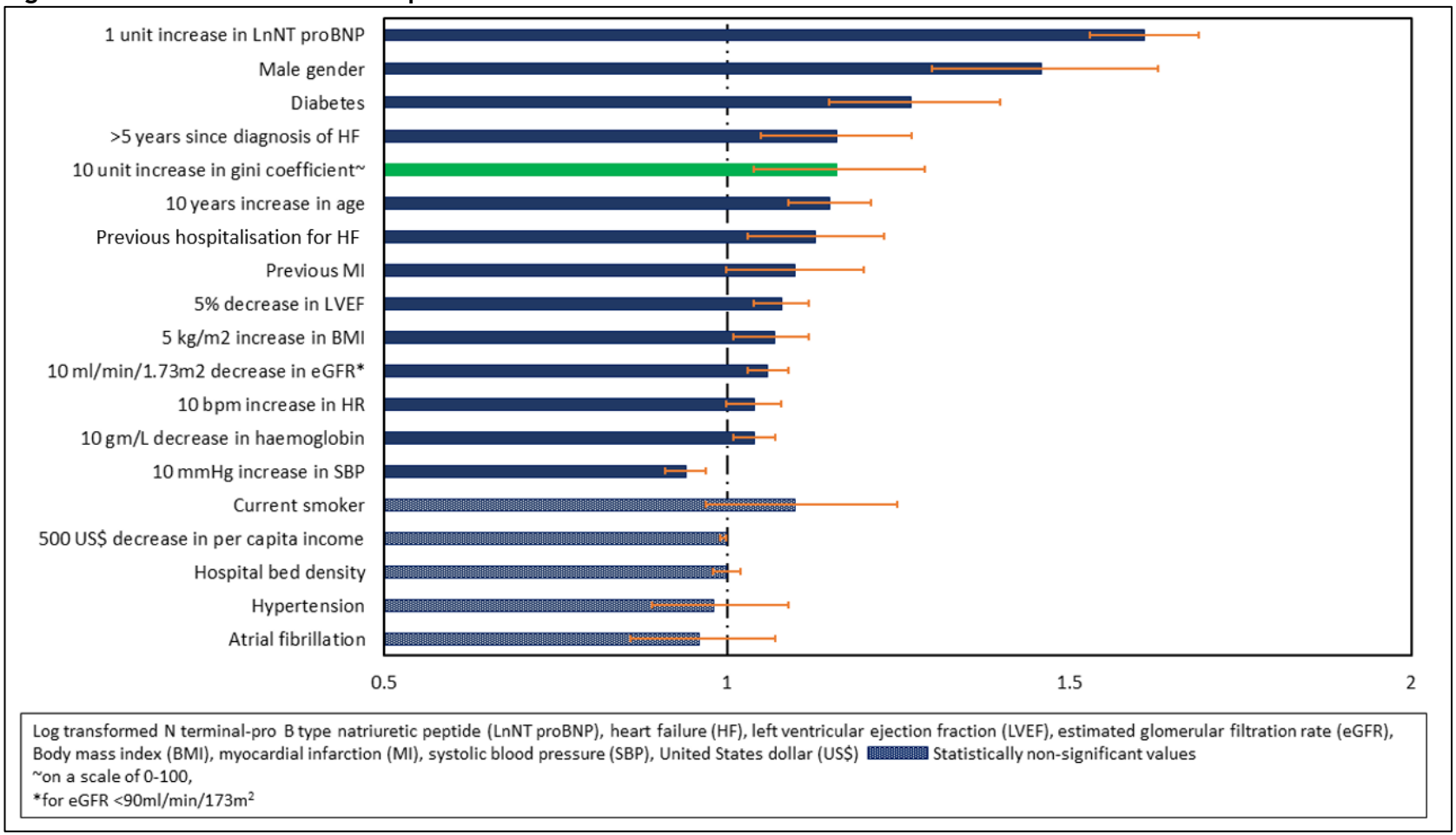


Figure 7-4 Multivariable model of predictors of cardiovascular death in heart failure



Discussion

In this study of 15,126 HFrEF patients from 54 countries, I found statistically significant and clinically substantial associations between income-inequality, patient characteristics and disease outcomes. These differences persisted after adjustment for recognized, patient-level prognostic variables, as well as country per capita income.

Over the past 20 years, a substantial body of evidence has accrued in support of an association between income-inequality and a variety of measures of population health. The income-inequality hypothesis states that an individual's health is not only affected by his or her own income but also by the distribution of income in that person's society, especially in high-income countries. Consistent with this, countries sharing the same gross domestic product (GDP) may have quite different health outcomes, reflecting the distribution of income within those societies i.e. it appears that it is not only the wealth of a society but the distribution of wealth within that society that influences health. Although these relationships are well established for broad health outcomes such as childhood and overall mortality, there are few studies of specific diseases, especially cardiovascular disease. However, in one analysis involving 78 countries, income-inequality was independently and positively associated with disability-adjusted life years and mortality related to coronary artery disease, as well as coronary risk factors.[237] In another investigation confined to the United States of America, a state-level analysis of the National Longitudinal Mortality Study showed that a 0.1 unit higher Gini coefficient predicted a one per cent higher probability of dying from coronary artery disease.[238] I have extended this examination of the relationship between income-disparity and cardiovascular health to HF.

The baseline characteristics, medical history and background treatment of patients differed markedly according to income-inequality but perhaps not predictably or intuitively given the association between higher Gini coefficient and worse outcomes. For example, patients in countries with the highest Gini coefficient (tertile 3, greatest income-inequality) were an average of 5 years younger than those in the lowest tertile, were more often women, had less

comorbidity, less often had an ischemic aetiology, had more recently diagnosed HF, had a better NYHA class profile and KCCQ score, and had the highest mean eGFR – all features expected to track with better rather than worse outcomes which could be attributable to patients Gini tertile 3 being younger.[143] Indeed, only a few variables associated with a poor prognosis were more unfavourable in the Gini coefficient tertile 3 patients: average LVEF was lower (-1.9%) in tertile 3 patients, compared with tertile 1 patients, as was SBP (-5.2 mmHg), whereas median NT-proBNP was somewhat higher (+142 pg/ml). There were also some treatment differences between the groups that were more expected: digoxin (inexpensive) was used most often in tertile 3 patients whereas devices (more expensive) were used much less often.

Even after correcting for patient-level biological characteristics known to predict outcomes, including the most powerful of these, NT-proBNP, patients in Gini tertile 3 had considerably higher mortality than those in tertile 1 – indeed the adjusted sHR was 1.48 (95% CI 1.29-1.71) for all-cause death and 1.55 (1.32–1.82) for death from cardiovascular causes. Because population health and life-expectancy are also associated with overall country affluence, I also adjusted for per capita income which attenuated but did not eliminate the relationship between income disparity and mortality (with a remaining 20-30% excess risk). This disconnect between mortality and clinical presentation in Gini tertile 3 is difficult to explain but most likely is a function of the unfavourable effects of income-inequality

Additional adjustment for education index, hospital bed-density and physician-density also did not attenuate the greater risk of this composite outcome among patients in Gini tertile 3 with a fully adjusted sHR of 1.46 (1.25 – 1.70). When the risk of HF hospitalisation was examined alone (but accounting for the competing risk of death), it was also found to be highest in countries with the greatest income disparity. These countries also had the lowest bed-density, suggesting that admission rates are not just a function of bed availability.

The large size of the “effect” of income-inequality on HF outcomes is worthy of comment. The adjusted risks of the fatal outcomes examined were approximately 20-30% higher in individuals living in the tertile of countries with the widest income distribution. This magnitude of the difference was similar to

or greater than that attributable to other major co-morbidities such as diabetes or previous myocardial infarction. I also looked at the risk associated with each 10 unit increase in Gini coefficient, noting the difference between the median coefficient in tertiles 1 and 3 was 20 units. The excess risk for cardiovascular mortality per 10 unit increase in Gini coefficient was 16%, similar to the risk associated with a 10% decrease in LVEF, a 27 mmHg decrease in SBP or a 27 ml/min/1.73 m^2 decrease in eGFR.

I divided the countries in this analysis according to thirds of Gini coefficient giving tertiles of <33%, 33-41% and >41%. There is no generally agreed categorization of nations according to Gini coefficient although in the study described above, which examined CHD and stroke, countries were divided into "low"(<0.38), "medium"(0.38-0.55) and "high"(>0.55) Gini coefficient groups (using a scale of 0-1.0). In a meta-analysis of nine multilevel longitudinal studies including nearly 60 million participants, Kondo and colleagues reported a relative risk of 1.08 (95% CI 1.06-1.10) for all-cause mortality per 0.05 unit increase in Gini coefficient (using a scale of 0-1.0).[239] In this analysis, the equivalent increase in Gini coefficient (5 points on a scale of 0-100) was associated with a HR of 1.07(95% CI 1.02–1.12; p-value: 0.006) i.e. an excess risk of similar magnitude.

Of course, the key question about my findings, and those about the income-inequality health hypothesis more generally, is why should greater income-disparity be associated with worse health outcomes? Many theories have been expounded. One way to consider these is under the broad headings of "societal-structural" and "psycho-social" explanations.

The "societal-structural" explanations posited are numerous and complex and not all necessarily relevant to outcomes in patients with an established clinical condition (as opposed to the future development of disease).[240,241] Many of these explanations focus on the corrosive effects of income-inequality on society, leading to loss of social cohesion, and divergence of the interests of the rich from those of the poor. It is argued that income-inequality leads to a decreased willingness of societies to invest in social services/welfare programmes, broad access to healthcare services, and safety nets.[242,243] These effects may lead to distortion of health care priorities and spending and can be exacerbated by the

geographical concentration of hospitals and physicians in more affluent areas, with the provision of medically unnecessary services and performance of discretionary procedures in these areas. Conversely, there may be underinvestment of health care infrastructure and resources in areas of greater need, with reduced access to and affordability of health care for the neediest.[243] Potentially, each of these factors could lead to higher disease prevalence, delayed care, more advanced disease at presentation, more preventable hospital admissions and, ultimately, more premature deaths. It is also easy to see how a syndrome as complicated as HF with the need for integration of primary and secondary health-care services, multidisciplinary management programmes, appropriate exercise prescription, complex polypharmacy and attendant electrolyte monitoring, tailored treatment of physical and psychological comorbidity, appropriate selection of devices, and, ultimately, provision of palliative-care might be particularly affected by gaps in services and aggravated by the failure of social and family networks related to loss of social cohesion.[244]

Some of these societal issues may also be greater in LMICs undergoing an epidemiological transition from infectious diseases to non-communicable diseases (NCDs).[245] Here, health strategies and policies need to change but these countries often display a high level of income-disparity, despite (or because of) accelerated economic growth in many cases.[246]

Among the "psycho-social" explanations, the one of most interest in HF is the belief that chronic stress as a consequence of income-inequality described above has detrimental psycho-neuroendocrine effects.[237] There is long-standing evidence that stress may be involved in at least some types of cardiovascular diseases. For example, in the INTERHEART study, Rosengren and colleagues found that psychosocial stressors are associated with a higher risk of acute myocardial infarction.[247] Chronic stress is associated with memory impairment, anxiety and depression, all of which are common in HF and potentially harmful because of adverse effects on adherence and self-management.[248,249] Moreover, recent evidence has suggested even more widespread biological consequences of stress including reduced immune responses and impaired endothelial function.[250]

Strengths and limitations

To the best of my knowledge, this is the first study to look at the association between income-inequality and outcomes in HF (or any chronic disease) transnationally. However, this study is based on a highly selected clinical trial population recruited from specific centres and may not necessarily be representative of the general population

Not all the countries in this analysis were from similar income categories and I did not have information on individual SES, but I adjusted for per capita income representing population-level income for each country. Accordingly, I also did not adjust for differences in health care systems as a majority of the countries did not follow any particular health care system.[251] I tried to make up for these shortcomings to a certain degree by including information on hospital bed density and health worker-density per 1000 population. Patients were mandated by protocol to have been on ACEI (or ARB) and beta-blocker therapy at the time of screening. There was poor representation from Africa in this analysis (only patients from South Africa were included). I did not have measures that might have supported or refuted a "psycho-social" explanation for the association between greater income-disparity and poor outcomes.

Conclusions

HF poses an enormous economic burden on society. It is the leading cause of hospitalisation in western countries and is steadily increasing in prevalence (especially worryingly in younger people) in developing countries. In countries with prominent levels of income-inequality, unfavourable social factors coupled with inadequate and inefficient public spending on healthcare may present considerable barriers not only to the prevention of cardiovascular disease (the focus of most studies to date) but also improving outcomes in patients with established and chronic diseases like HF.

Chapter 8. The prevalence and importance of frailty in HFrEF

This chapter has been published as:

Dewan P, Jackson A, Jhund PS, Shen L, Ferreira JP, Petrie MC, Abraham WT, Desai AS, Dickstein K, Køber L, Packer M, Rouleau JL, Solomon SD, Swedberg K, Zile MR, McMurray JJV. The prevalence and importance of frailty in heart failure with reduced ejection fraction – an analysis of PARADIGM-HF and ATMOSPHERE. Eur J Heart Fail John Wiley & Sons, Ltd; 2020;22:2123–2133.

Frailty is a health state in which multiple body systems gradually lose their in-built reserves and while it is related to ageing, it is its own distinct entity.[252] The recognition of frailty in cardiovascular diseases is important for several reasons. First, cardiovascular disease may accelerate development of frailty and frailty may worsen outcomes related to cardiovascular disease.[113] Both cardiovascular disease and frailty may share common pathophysiological mechanisms, like inflammation, and have common consequences, such as exercise intolerance, leading to a vicious cycle of decline. Moreover, frailty may be an 'effect modifier', adversely affecting the risk–benefit profile of both pharmacological and non-pharmacological interventions, for example surgery and device implantation.[253,254] Frailty was not a prognostic measure included in any of the studies in the systematic revie in Chapter 1.

In this chapter I have described the development of a frailty index (FI) according to the Rockwood criteria in patients with HFrEF. I have also categorized the patients into different levels of frailty and compared risks of various morbidity and mortality outcomes across the different groups. Competing risks regression using the Fine and Grey approach were used to assess the risks in each group.

Methods

The trial populations have been described in detail in Chapter 2.

Frailty Index (FI)

I have the cumulative deficits approach to construct a 42-item FI in patients with HFrEF. The frailty index (FI) was developed by Rockwood and colleagues as a means to assess an individual's biological ageing as opposed to individual ageing.[255,256] Rockwood and authors proposed that the likelihood of an individual being frail increased as the number of things wrong with them increased. The FI has since been validated in several other cohorts and is now a well-accepted method for the assessment of frailty. Following are the considerations to be made during the construction of a FI:

- Ideally the index should be made up of at least 30 items.
- The included variables must be associated with health and not be variables with are the normal processes of and saturate with ageing such as greying of hair, presbycusis or presbyopia.
- Deficits should increase with age therefore items such as smoking, etc should not be considered.
- The items included while constructing an index should cover a range of body systems and not be isolated to one system.
- The items used must be applied similarly throughout the sample.

I have used 15 questions (of 23) from the KCCQ as proxy measures of disability and social parameters that are known to be associated with frailty to form the basis of the index. The remaining 27 items are derived from the medical history, other patient characteristics and laboratory results, covering a range of body systems as is shown in Table 8-1. I excluded 8 questions from the KCCQ used to construct the symptom severity, symptom frequency and symptom burden domains to minimise defining the FI by symptoms of HF.

Binary variables are scored 0/1 (absent/present), ordinal variables are scored from 0 to 1 with 1 indicating greatest severity and 0 the least severity. Continuous variables are dichotomised and scores as 0/1 (normal/non-normal). Patients with ≥20% missing variables are excluded from the analysis. FI score is calculated by dividing the sum of the deficits by the total number of non-missing deficits being assessed.

Previous studies have used the cut off of FI >0.210 to define frailty. On analysing the relationship of the FI that I constructed for this cohort, I also found that there was a definite point of inflection for risk of all-cause death at an FI of 0.210 as shown in Figure 8-1. Thus, for this analysis, I have classified all patients with FI ≤0.210 as non-frail and those with higher scores are further divided into two categories using increments in score of 0.100.

Table 8-1 Components of the Frailty Index (42 items)

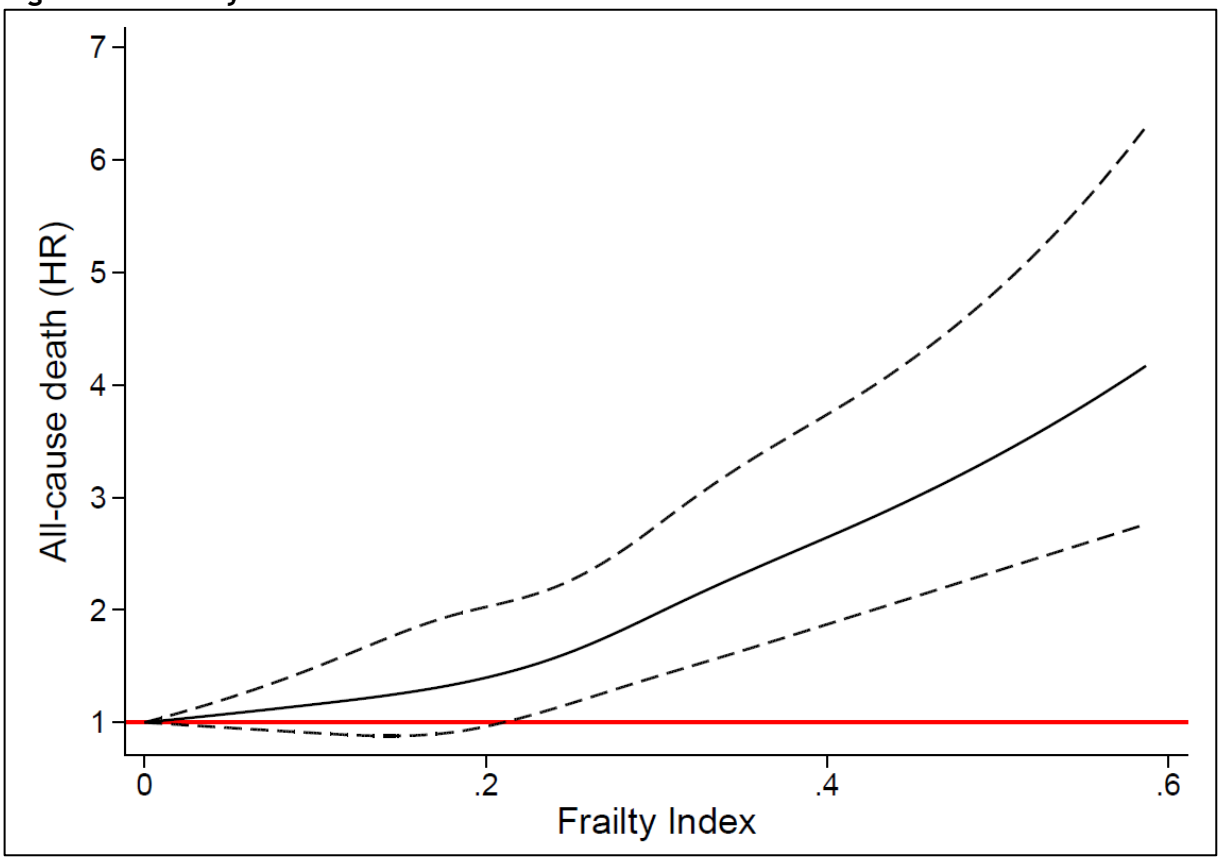
Sl. No.	Component	Cut off / Sub-component	Score
1.	Diastolic blood pressure – mmHg	>90	1
2.	Pulse pressure – mmHg	>55	1
3.	Systolic blood pressure - mmHg	<90/>140	1
4.	Body Mass Index – kg/m^2	≥25/<30	0.5
		<18.8/≥30	1
Laboratory measures			
5.	Albumin- gm/L	<35/>55	1
6.	BUN – mmol/L	<3/>7.5	1
7.	Calcium – mmol/L	<2.2/>2.7	1
8.	Creatinine – umol/L	<40/>150	1
9.	HDL Cholesterol – mmol/L	<0.4/>1.5	1
10.	Potassium – mmol/L	<3.5/>6	1
11.	RBC count – X10^9/L	<3.5/>5.5	1
12.	Sodium – mmol/L	<135/>145	1
13.	Total Cholesterol – mmol/L	<3.5/>7	1
14.	Uric acid – umol/L	Males - <200/>430	1
		Females - <140/ >360	1
15.	Haemoglobin – gm/L	Males - <130/>175	1
		Females - <120/>155	1
16.	Platelet count - X10^9/L	<150/>400	1
17.	WBC count – X10^9/L	<4/>12	1
Comorbidities			
18.	Atrial Fibrillation		1
19.	Hypertension		1
20.	Myocardial Infarction		1
21.	PCI or CABG		1
22.	Unstable angina		1
23.	Peripheral arterial disease		1
24.	Stroke		1
25.	Diabetes		1
26.	Cancer		1
27.	COPD		1
Quality of life measures – Kansas City Cardiomyopathy Questionnaire (all responses with respect to the two weeks prior to questioning)			
Mobility			
28.	Limited activities due to heart failure	Dressing yourself:	
		Not at all limited	0
		Limited for other reasons or did not do the activity	0.2
		Slightly limited	0.4
		Moderately limited	0.6
		Quite a bit limited	0.8
		Extremely limited	1
29.		Showering/bathing:	
		Not at all limited	0

		Limited for other reasons or did not do the activity	0.2
		Slightly limited	0.4
		Moderately limited	0.6
		Quite a bit limited	0.8
		Extremely limited	1
30.		Walking 1 block on level ground:	
		Not at all limited	0
		Limited for other reasons or did not do the activity	0.2
		Slightly limited	0.4
		Moderately limited	0.6
		Quite a bit limited	0.8
		Extremely limited	1
31.		Doing yard work, housework, or carrying groceries:	
		Not at all limited	0
		Limited for other reasons or did not do the activity	0.2
		Slightly limited	0.4
		Moderately limited	0.6
		Quite a bit limited	0.8
		Extremely limited	1
32.		Climbing a flight of stairs without stopping:	
		Not at all limited	0
		Limited for other reasons or did not do the activity	0.2
		Slightly limited	0.4
		Moderately limited	0.6
		Quite a bit limited	0.8
		Extremely limited	1
33.		Hurrying or jogging:	
		Not at all limited	0
		Limited for other reasons or did not do the activity	0.2
		Slightly limited	0.4
		Moderately limited	0.6
		Quite a bit limited	0.8
		Extremely limited	1
Memory and cognitive abilities			
34.		Completely sure	0
	Are you sure you know what to do or whom to call if your heart failure gets worse	Mostly sure	0.25
		somewhat sure	0.5
		Not very sure	0.75
		Not at all sure	1
35.		Completely understand	0
	How well do you understand what things you can do to keep your heart failure symptoms from getting worse	Mostly understand	0.25
		Somewhat understand	0.5
		Do not understand very well	0.75
		Do not understand at all	1
Mood vulnerabilities			
36.		Completely satisfied	0
	How would you feel if you had to spend rest of life with heart failure the way it is right now	Mostly satisfied	0.25
		Somewhat satisfied	0.5
		Mostly dissatisfied	0.75
		Completely dissatisfied	1
37.		I never felt that way	0
	How often have you felt discouraged or down in dumps because of your heart failure	I have rarely felt that way	0.25
		I have occasionally felt that way	0.5
		I have felt that way most of the time	0.75
		I have felt that way all the time	1
Functional abilities			

38.	How much has heart failure limited enjoyment of life	It has not limited my enjoyment of life at all	0
		It has slightly limited my enjoyment of life	0.25
		It has moderately limited my enjoyment of life	0.5
		It has limited my enjoyment of life quite a bit	0.75
		It has extremely limited my enjoyment of life	1
39.	How does heart failure affect lifestyle	Hobbies, recreational activities:	
		Did not limit at all	0
		Does not apply or did not do for other reasons	0.2
		Slightly limited	0.4
		Moderately limited	0.6
		Quite a bit limited	0.8
		Extremely limited	1
40.		Working or doing household chores:	
		Did not limit at all	0
		Does not apply or did not do for other reasons	0.2
		Slightly limited	0.4
		Moderately limited	0.6
		Quite a bit limited	0.8
		Extremely limited	1
41.		Visiting family or friends out of your home:	
		Did not limit at all	0
		Does not apply or did not do for other reasons	0.2
		Slightly limited	0.4
		Moderately limited	0.6
		Quite a bit limited	0.8
		Extremely limited	1
42.		Intimate relationships with loved ones:	
		Did not limit at all	0
		Does not apply or did not do for other reasons	0.2
		Slightly limited	0.4
		Moderately limited	0.6
		Quite a bit limited	0.8
		Extremely limited	1

BUN – Blood urea nitrogen, HDL – High density lipoprotein, WBC – White blood cell, PCI – Primary coronary intervention, CABG – Coronary artery bypass graft, COPD – Chronic obstructive pulmonary disease, BMI – Body mass index.

Figure 8-1 Frailty index and the risk of all-cause death



Population analysed

Out of the total 15415 patients in the combined dataset taken into consideration for this chapter, FI was calculable in 13265 patients.

Outcomes

For this chapter, as outlined in chapter 2, I have analysed the primary composite outcome of cardiovascular death or first HF hospitalisation, its components and non-cardiovascular and all-cause death. I have also analysed the composite of first all-cause hospitalisation or all-cause death. first cardiovascular, non-cardiovascular and all-cause hospitalisation. Additional outcomes examined are recurrent HF, cardiovascular, non-cardiovascular and all-cause hospitalisations. Fall in KCCQ summary score by ≥5 at 12 months is also examined.

Statistical analysis

Restricted cubic splines analysis was used to assess the relationship between FI and all-cause death taking the lowest FI as the reference point. I have reported the incidence rates for the outcomes of interest as events per 100 person-years. Competing-risk regression using the Fine-Gray method, as outlined in chapter 2, was used to assess the risk of the outcomes examined.[149] The primary outcome and cardiovascular death were analysed accounting for competing risk of non-cardiovascular death. First HF, cardiovascular, non-cardiovascular and all-cause hospitalisations were analysed accounting for competing risk of all-cause death. Non-cardiovascular deaths were analysed accounting for competing risk of cardiovascular death. Along with crude sHRs, I have reported adjusted sHRs from models including age, sex, heart rate, NT-proBNP, NYHA class, LVEF, duration of HF and additionally previous HF hospitalisation for HF hospitalisation. For multivariable adjustment, I chose clinically relevant variables known to be predictive of death and hospitalisation, but which were not part of the FI (e.g. LVEF and NT-proBNP).

I used Cox regression to assess the risk of the composite outcome of all-cause hospitalisation or all-cause death and all-cause death, with adjustment for variables as listed in the previous paragraph. I also used Cox regression to analyse the primary composite outcome and all-cause death for 12 subgroups to

report the effects of sacubitril/valsartan versus enalapril according to FI in patients enrolled in PARADIGM-HF only (as was done in the clinical trial).[38]

A decrease in KCCQ-CSS from baseline to 12 months of ≥5 points was analysed using logistic regression and is reported as OR adjusted for two models- model 1 for KCCQ-CSS at baseline and model 2 additionally adjusted for variables listed above.

Recurrent hospitalisations (HF, cardiovascular, non-cardiovascular and all-cause) were analysed using a negative binomial regression model. Both crude IRR and IRR adjusted for the variables listed above, as well as previous HF hospitalisation, are reported.

I also carried out a sensitivity analysis for all the time to first event outcomes by different age groups - ≤60 years, 61-70 years and >70 years.

All models were adjusted for randomised treatment and region at baseline. p-values <0.05 were considered significant. All analyses were conducted using Stata ver.15 (College Station, TX, USA).

Results

In this HFrEF population, FI was calculable for 13265 (86.0%) patients. The mean (±SD) and median (IQR) FI was 0.250 (0.10) and 0.244 (0.176-0.318), respectively. The range was 0.0-0.686 and the 10th and 90th percentiles were 0.126 and 0.382, respectively.

Overall, 4882 patients were in FI Class 1 (≤0.210 – non-frail), 4770 in FI Class 2 (0.211-0.310 - frail) and 3613 in FI Class 3 (≥0.311 – most frail).

Baseline characteristics

As shown in Table 8-2, age and proportion of women increased with increase in FI. Figure 8-2 shows a rightward shift of the density distribution of FI in women compared to men. Mean and median FI in men was 0.247 (0.098) and 0.240 (0.173-0.315), respectively and 0.261 (0.098) and 0.259 (0.189-0.330), respectively in women (p-value <0.001 for each, men vs. women). Mean FI for age increased at a similar rate in men and women as is shown in Figure 8-3.

Table 8-2 Baseline characteristics

	FI class 1 n=4882 (≤0.210)	FI class 2 n=4770 (0.211 – 0.310)	FI class 3 n=3613 (≥0.311)	p-value for trend
Age (years.)	61.0 ± 11.7	64.9 ± 10.8	67.1 ± 10.3	<0.001
Females – no. (%)	893 (18.3)	1059 (22.2)	882 (24.4)	<0.001
Region – no. (%)				0.853
North America	199 (4.1)	265 (5.6)	295 (8.2)	
Latin America	1165 (23.9)	671 (14.1)	265 (7.3)	
Western Europe & other	1225 (25.1)	1385 (29.0)	1094 (30.3)	
Central Europe	1086 (22.2)	1789 (37.5)	1739 (48.1)	
Asia - Pacific	1207 (24.7)	660 (13.8)	220 (6.1)	
Race – no. (%)				<0.001
White	2963 (60.7)	3644 (76.4)	3127 (86.6)	
Black	207 (4.2)	168 (3.5)	109 (3.0)	
Asian	1176 (24.1)	625 (13.1)	209 (5.8)	
Other	535 (11.0)	332 (7.0)	167 (4.6)	
SBP (mmHg)	119.0 ± 14.8	123.5 ± 16.6	127.2 ± 17.9	<0.001
Heart rate (bpm)	71.1 ± 11.7	72.0 ± 12.5	72.6 ± 12.5	<0.001
BMI* (kg/m^2)	26.4 (23.7 - 29.6)	27.7 (24.6 - 31.3)	29.1 (25.7 - 33.0)	<0.001
Comorbidities – no. (%)				
Hypertension	2599 (53.2)	3460 (72.5)	3040 (84.1)	<0.001
Diabetes	982 (20.1)	1619 (33.9)	1635 (45.3)	<0.001
Atrial fibrillation	1242 (25.4)	1811 (38.0)	1910 (52.9)	<0.001
VHD	202 (4.1)	257 (5.4)	200 (5.5)	0.002
Unstable angina	224 (4.6)	573 (12.0)	754 (20.9)	<0.001
Myocardial infarction	1409 (28.9)	2219 (46.5)	2105 (58.3)	<0.001
Stroke	183 (3.7)	385 (8.1)	495 (13.7)	<0.001
PAD	86 (1.8)	249 (5.2)	436 (12.1)	<0.001
COPD	319 (6.5)	588 (12.3)	801 (22.2)	<0.001
Renal disease	351 (7.2)	664 (13.9)	874 (24.2)	<0.001
Current smoker	709 (14.5)	660 (13.8)	469 (13.0)	0.246

All values are reported as mean ± standard deviation except where indicated.
*Median (interquartile range)
SBP – systolic blood pressure; BMI – body mass index; VHD – valvular heart disease; PAD – peripheral arterial disease; COPD – chronic obstructive pulmonary disease.

Figure 8-2 Density distribution of FI in men and women

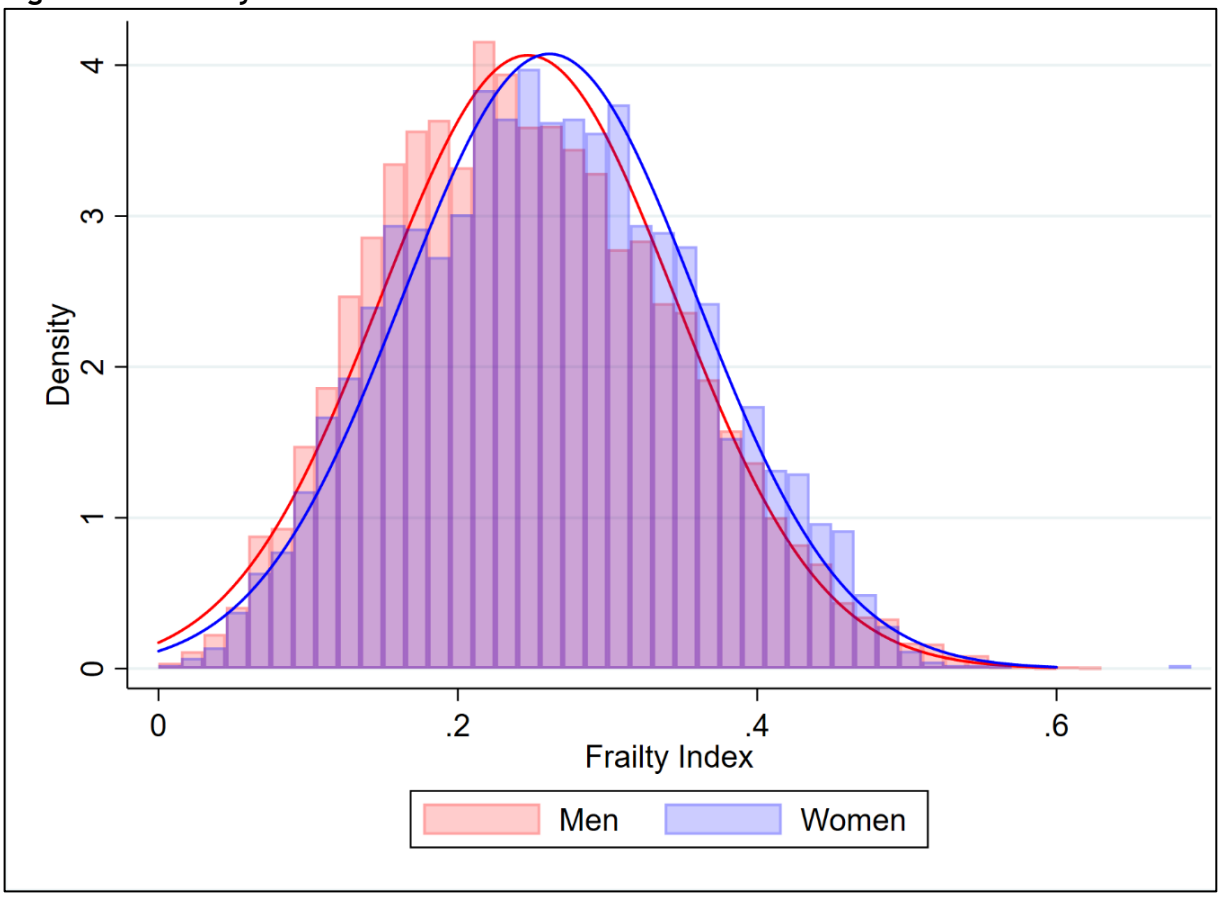


Figure 8-3 Mean FI by age in men and women

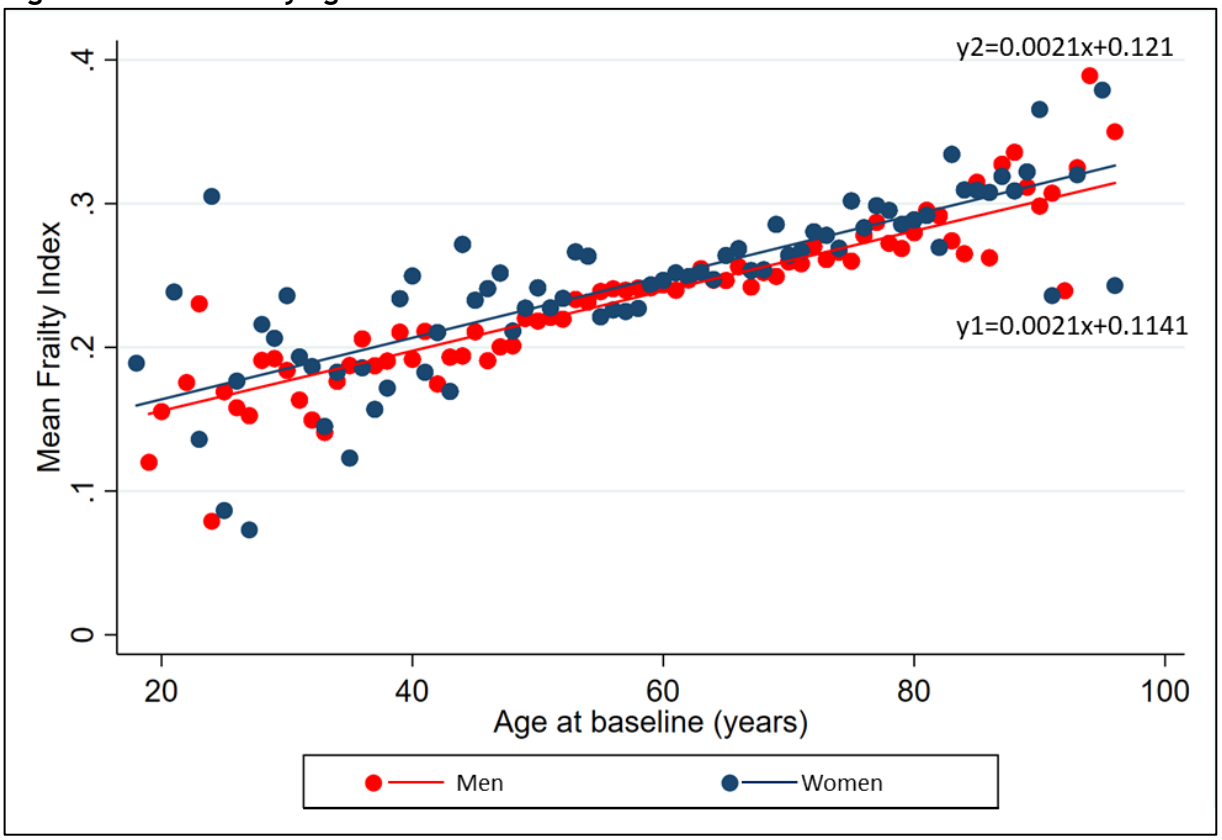
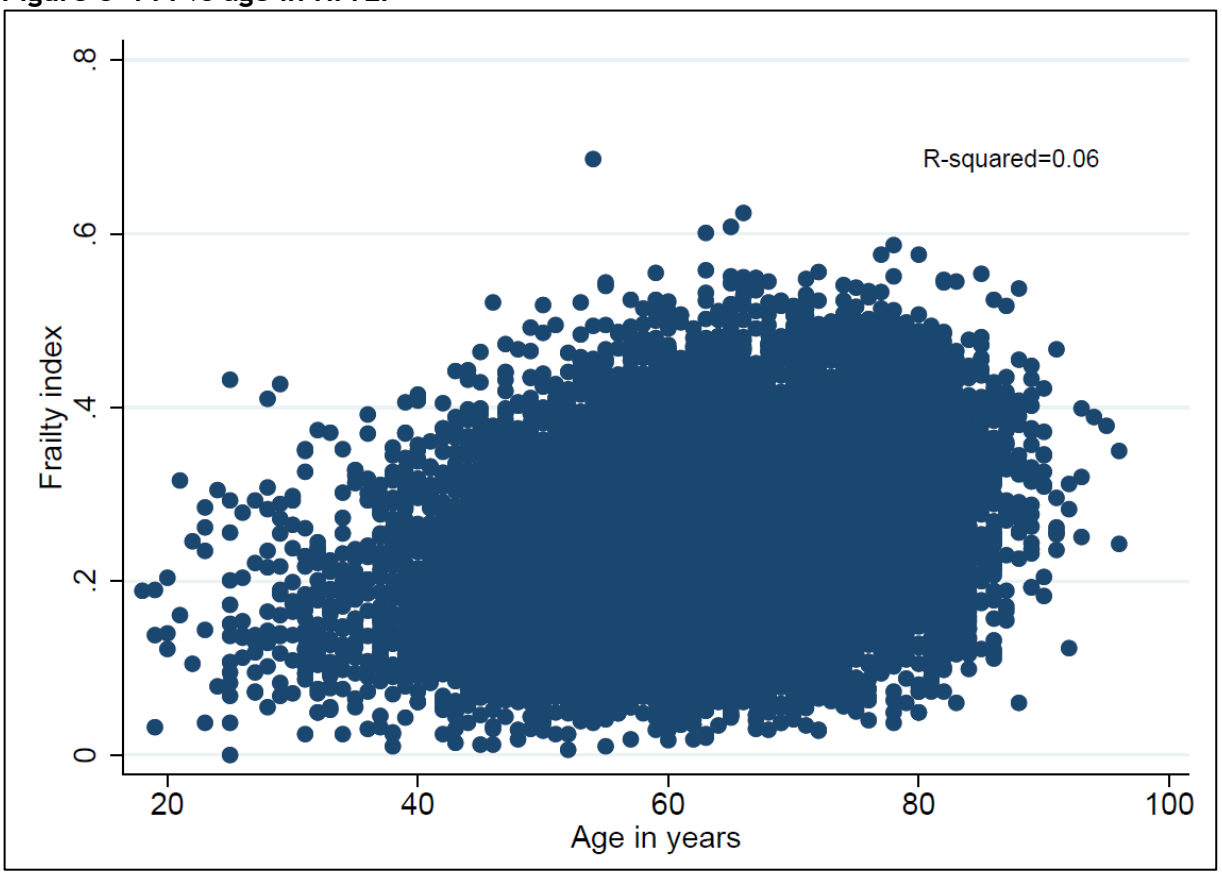


Figure 8-4 FI vs age in HFrEF



Heart failure characteristics

As shown in Table 8-3, the frailest patients had the highest prevalence of an ischemic aetiology, longer duration of HF and a higher rate of previous hospitalisation for HF. The frailest patients also had the worst NYHA class distribution and the highest mean MAGGIC risk score.

Features of congestion were most prominent in patients with the highest FI scores.

As outlined in Table 8-4, in patients in PARADIGM-HF only, 81.4% of the non-frail patients reported no problems in walking compared to 22.9% of those who were in the frailest category. Some problems with self-care were reported by 39.5% of the frailest among whom >70% reported problems with performing day-to-day activities. Moderate/extreme levels of anxiety/depression were more common in the frailest patients (53% in frailest compared to 19% in the non-frail).

Table 8-3 Heart failure characteristics and clinical features

	FI Class 1 n=4882 (≤0.210)	**FI Class 2** n=4770 (0.211 – 0.310)	**FI Class 3** n=3613 (≥0.311)	**p-value for trend**
HF aetiology				<0.001
Ischaemic	2122 (43.5)	2961 (62.1)	2675 (74.0)	
Non-ischaemic	2422 (49.6)	1643 (34.4)	857 (23.7)	
Other/Unknown	338 (6.9)	166 (3.5)	81 (2.2)	
HF duration				<0.001
<1 year	1856 (38.0)	1336 (28.0)	763 (21.1)	
1-5 years	1756 (36.0)	1878 (39.4)	1434 (39.7)	
>5 years	1268 (26.0)	1555 (32.6)	1416 (39.2)	
Previous HF hospitalisation	2835 (58.1)	2994 (62.8)	2412 (66.8)	<0.001
NYHA Class				<0.001
I/II	4323 (88.6)	3422 (71.8)	1832 (50.8)	
III	540 (11.1)	1320 (27.7)	1702 (47.2)	
IV	16 (0.3)	24 (0.5)	73 (2.0)	
KCCQ clinical summary score*	92.7 (85.4 - 97.9)	77.1 (65.6 - 85.9)	55.2 (43.3 - 67.7)	<0.001
KCCQ overall summary score*	89.6 (82.3 – 95.1)	73.2 (63.0 – 82.3)	51.3 (40.6 – 63.5)	<0.001
MAGGIC risk score	19.5 ± 5.0	21.3± 5.4	23.1 ± 5.5	<0.001
Clinical Features				

Dyspnoea on exertion	3901 (80.0)	4203 (88.2)	3383 (93.8)	<0.001
Orthopnoea	141 (2.9)	270 (5.7)	409 (11.3)	<0.001
PND	85 (1.7)	219 (4.6)	374 (10.4)	<0.001
Fatigue	1826 (37.4)	2574 (54.0)	2496 (69.2)	<0.001
Peripheral oedema	501 (10.3)	1010 (21.2)	1343 (37.2)	<0.001
Third heart sound	369 (7.6)	401 (8.4)	334 (9.3)	0.005
JVD	302 (6.2)	430 (9.0)	516 (14.3)	<0.001

All values are reported as number (percentage) except where indicated.
*Median (interquartile range)
HF – heart failure; NYHA – New York heart association; KCCQ – Kansas City cardiomyopathy questionnaire; MAGGIC -Meta-Analysis Global Group in Chronic Heart Failure; PND – paroxysmal nocturnal dyspnoea; JVD – jugular venous distension.

Table 8-4 EQ-5D-3L score (PARADIGM-HF only)

	FI Class 1 n=2836 (≤0.210)	**FI Class 2** n=2663 (0.211 – 0.310)	**FI Class 3** n=1972 (≥0.311)	**p-value for trend**
Mobility				<0.001
I have no problems in walking about	2305 (81.4)	1374 (51.7)	451 (22.9)	
I have some problems in walking about	524 (18.5)	1280 (48.1)	1506 (76.6)	
I am confined to bed	1 (0.1)	5 (0.2)	10 (0.5)	
Self-care				<0.001
I have no problems with self-care	2745 (97.0)	2280 (85.7)	1172 (59.6)	
I have some problems washing or dressing myself	84 (3.0)	370 (13.9)	776 (39.5)	
I am unable to wash or dress myself	1 (0.0)	9 (0.3)	19 (1.0)	
Usual activities				<0.001
I have no problems with performing my usual activities	2371 (83.8)	1409 (53.0)	481 (24.5)	
I have some problems with performing my usual activities	450 (15.9)	1216 (45.7)	1344 (68.3)	
I am unable to perform my usual activities	9 (0.3)	33 (1.2)	142 (7.2)	
Pain/ Discomfort				<0.001
I have no pain or discomfort	2095 (74.0)	1433 (53.9)	617 (31.4)	
I have moderate pain or discomfort	716 (25.3)	1188 (44.7)	1255 (63.8)	
I have extreme pain or discomfort	19 (0.7)	37 (1.4)	95 (4.8)	
Anxiety/ Depression				<0.001
I am not anxious or depressed	2300 (81.3)	1750 (65.8)	912 (46.4)	
I am moderately anxious or depressed	505 (17.8)	882 (33.2)	970 (49.3)	
I am extremely anxious or depressed	25 (0.9)	27 (1.0)	85 (4.3)	
Overall Score – mean ± SD	75.1 ± 18.9	66.1 ± 18.0	56.0 ± 17.9	<<0.001

Investigations and biomarkers

NT-proBNP was significantly higher in the frailest patients [Table 8-5]. Levels of most biomarkers that were measured in PARADIGM-HF also increased with increasing frailty except for matrix metalloprotease-9.

Table 8-5 Investigations

	FI Class 1 n=4882 (≤0.210)	**FI Class 2** n=4770 (0.211 – 0.310)	**FI Class 3** n=3613 (≥0.311)	**p-value for trend**
Ejection fraction† – (%)	28.5 ± 6.1	29.4 ± 5.9	29.8 ± 5.8	<0.001
NT-proBNP* - (pg/ml)	1230 (713 -2353)	1435 (787 – 2708)	1706 (894 -3336)	<0.001
Haemoglobin† - (gm/L)	141.1 ± 14.1	139.1 ± 15.7	136.6 ± 17.6	<0.001
Creatinine† - (umol/L)	90.7 ± 21.6	96.9 ± 25.0	103.3 ± 30.5	<0.001
eGFR† - (ml/min/1.73m^2)	75.7 ± 22.5	69.0 ± 20.9	64.1 ± 20.5	<0.001
Sodium† – (mmol/L)	140.6 ± 2.8	140.7 ± 3.1	141.0 ± 3.5	<0.001
Potassium† – (mmol/L)	4.5 ± 0.4	4.5 ± 0.5	4.5 ± 0.5	0.063
PARADIGM-HF only				
HbA1C – no (%)				<0.001
Prediabetes (6-6.4)	700 (32.4)	612 (36.6)	402 (40.9)	
Undiagnosed Diabetes (>6.4)	299 (13.8)	282 (16.8)	158 (16.1)	
NT-proBNP* (pg/ml)	1364 (817 – 2736)	1653 (906 – 3204)	1885 (1037 – 3961)	<0.001
BNP* (pg/ml)	66 (41 – 121)	73 (45 – 132)	82 (49 – 149)	<0.001
MMP2* (ng/mL)	128 (113 - 148)	136 (116 - 159)	138 (120 - 162)	<0.001
MMP9* (ng/mL)	62 (39 - 132)	64 (41 - 124)	63 (37 - 126)	0.562
hsTropT* (ng/L)	14 (9 - 20)	16 (11 - 24)	21 (13 - 31)	<0.001
GDF 15* (ng/L)	1387 (1020 - 1914)	1645 (1148 - 2287)	2035 (1440 - 3038)	<0.001
KIM-1* (pg/mL)	108 (74 - 159)	133 (91 - 189)	154 (101 - 233)	<0.001
ST2* (ng/mL)	31 (25 - 39)	32 (26 - 41)	34 (27 - 45)	<0.001
TIMP 1* (ng/mL)	116 (99 - 141)	124 (105 - 147)	136 (114 - 165)	<0.001
Galectin-3* (ng/mL)	16 (13 - 19)	17 (14 - 21)	19 (15 - 23)	<0.001
ECG				
LVH	774 (15.9)	791 (16.6)	693 (19.2)	<0.001
Atrial fibrillation	861 (17.6)	1220 (25.6)	1218 (33.7)	<0.001
LBBB	1042 (21.3)	944 (19.8)	715 (19.8)	0.063
RBBB	325 (6.7)	348 (7.3)	337 (9.3)	<0.001
QRS duration† – (msec)	118.1 ± 36.2	117.5 ± 34.9	118.1 ± 36.0	0.998

All values are reported as number (percentage) except where indicated.
*Median (interquartile range)
†Mean ± standard deviation
Values in italics represent patients enrolled only in PARADIGM-HF.
HbA1c is randomisation.
BNP and NT-proBNP are screening values.
The remaining biomarkers are from visit 2 (after screening).

NT-proBNP – N-terminal pro Brain natriuretic peptide; eGFR – estimated glomerular filtration rate; HbA1C – Haemoglobin A1C; MMP – Metalloprotease; hsTropT – high sensitivity troponin T; GDF 15 – Growth differentiation factor 15; KIM-1 – Kidney injury molecule 1; ST2 – soluble toll-like receptor-2; TIMP 1 – Tissue inhibitor metalloproteinase 1; ECG – Electrocardiogram; LBBB – left bundle branch block; RBBB - Right bundle branch block.

Baseline therapy

Table 8-6 shows that frailer patients were prescribed more drugs (44.5% of the frailest group were prescribed >4 drugs compared to 30% in the non-frail) and had higher rates of implantation of a pacemaker, ICD and CRT therapy. Vaccination and enrolment in disease management programmed increased with increasing frailty in patients enrolled in PARADIGM-HF.

Table 8-6 Therapy at baseline

	FI Class 1 n=4882 (≤0.210)	**FI Class 2** n=4770 (0.211 – 0.310)	**FI Class 3** n=3613 (≥0.311)	**p-value for trend**
Diuretics	3677 (75.3)	3885 (81.4)	3104 (85.9)	<0.001
Digoxin	1495 (30.6)	1362 (28.6)	1060 (29.3)	0.149
ACEI	4352 (89.1)	4191 (87.9)	3188 (88.2)	0.154
ARB	551 (11.3)	612 (12.8)	460 (12.7)	0.032
MRAs	2522 (51.7)	2288 (48.0)	1669 (46.2)	<0.001
CCBs	283 (5.8)	472 (9.9)	473 (13.1)	<0.001
Statins	2301 (47.1)	2738 (57.4)	2287 (63.3)	<0.001
Aspirin	2418 (49.5)	2485 (52.1)	1920 (53.1)	0.001
Anticoagulants	1277 (26.2)	1610 (33.8)	1484 (41.1)	<0.001
≥5 drugs+	1468 (30.1)	1826 (38.3)	1606 (44.5)	<0.001
PCI	675 (13.8)	675 (13.8)	1064 (29.4)	<0.001
CABG	435 (8.9)	818 (17.1)	842 (23.3)	<0.001
Pacemaker	473 (9.7)	616 (12.9)	587 (16.2)	<0.001
ICD-any	656 (13.4)	814 (17.1)	687 (19.0)	<0.001
ICD-only	460 (9.4)	554 (11.6)	458 (12.7)	<0.001
CRT	266 (5.4)	339 (7.1)	298 (8.2)	<0.001
PARADIGM-HF only				
Influenza vaccination in past 12 months	*557 (19.6)*	*603 (22.6)*	*526 (26.7)*	*<0.001*
Pneumococcal Vaccination in past 12 months	*155 (5.5)*	*161 (6.0)*	*144 (7.3)*	*0.010*
Patient been prescribed an exercise regimen	*532 (18.8)*	*456 (17.1)*	*385 (19.5)*	*0.658*
Patient enrolled in structured disease management program	*418 (14.7)*	*461 (17.3)*	*352 (17.8)*	*0.003*

All values are reported as number (percentage)
Values in italics represent patients enrolled only in PARADIGM-HF
ACEI – Angiotensin-converting enzyme inhibitor; ARB – Angiotensin receptor blocker; MRA – Mineralocorticoid receptor antagonist; CCB – Calcium channel blockers; PCI – Primary coronary intervention; CABG – Coronary artery bypass graft; ICD – Implantable cardioverter-defibrillator; CRT – Cardiac resynchronization therapy.
+Only cardiovascular drugs listed in the table taken into account.

Clinical outcomes

Heart failure specific outcomes

The risk of the primary composite outcome and its components was highest in the frailest, with unadjusted sHRs between 1.89 and 2.14 and adjusted sHRs of 1.69 and 1.75 [Table 8-7]. A similar increase in the risk of the primary composite outcome and its components with increasing frailty was seen in patients aged ≤60 years, those age 61 – 70 years and those >70 years of age [Table 8-8].

All-cause death and all-cause hospitalisation

The rates of hospitalisation for all cardiovascular causes and for any reason were also significantly higher in the frailest patients, with sHRs of 1.69 (1.55-1.84, p<0.001) and 1.60 (1.49-1.71, p-value <0.001), respectively [Table 8-7] The risk of death from any cause was approximately twice as high in the frailest patients, compared to those who were not frail, although the proportions of deaths that were cardiovascular and non-cardiovascular were similar across the FI categories [Table 8-7]. Similar differences in risk of death and hospitalisation were observed when frailty was examined across the different age groups as shown in Table 8-8.

Recurrent events

The frailest patients had the highest risk of all repeat events analysed [Table 8-7]. The adjusted IRR for HF hospitalisation in those who were the frailest was 1.90 (1.64-2.20); 1.76 (1.60-1.95) for cardiovascular hospitalisation, 1.75 (1.58-1.94) for non-cardiovascular hospitalisation and 1.76 (1.62-1.90) for all-cause hospitalisation.

Subgroup analysis

No differences in the risk of the primary composite outcome or all-cause death were seen in any of the 12 subgroups examined except for race as shown in Figure 8-6 & Figure 8-7.

Effect of treatment with sacubitril/valsartan according to FI in PARADIGM-HF

In PARADIGM-HF only, there was no evidence of any interaction between treatment and frailty for any of the four events examined as shown in Figure 8-8.

Table 8-7 Clinical outcomes

	FI Class 1 n=4882 (≤0.210)	FI Class 2 n=4770 (0.211 – 0.310)	FI Class 3 n=3613 (≥0.311)
Primary outcome			
Events – no (%)	1104 (22.6)	1328 (27.8)	1314 (36.4)
Event rate per 100 person-years	8.8 (8.3 - 9.3)	11.6 (11.0 - 12.3)	17.1 (16.2 - 18.0)
Unadjusted sHR	1.00 (ref)	1.35 (1.25 – 1.47) <0.001	1.99 (1.83 – 2.16) <0.001
Adjusted sHR	1.00 (ref)	1.24 (1.14 – 1.35) <0.001	1.71 (1.56 – 1.88) <0.001
First HF hospitalisation			
Events – no (%)	625 (12.8)	759 (15.9)	787 (21.8)
Event rate per 100 person-years	5.0 (4.6 - 5.4)	6.6 (6.2 - 7.1)	10.2 (9.5- 11.0)
Unadjusted sHR	1.00 (ref)	1.29 (1.16 – 1.44) <0.001	1.89 (1.69 – 2.11) <0.001
Adjusted sHR	1.00 (ref)	1.20 (1.07 – 1.34) 0.001	1.69 (1.50 – 1.90) <0.001
Cardiovascular death			
Events – no (%)	701 (14.4)	842 (17.7)	875 (24.2)
Event rate per 100 person-years	5.3 (4.9 - 5.7)	6.8 (6.3 - 7.3)	10.0 (9.4 - 10.7)
Unadjusted sHR	1.00 (ref)	1.38 (1.25 - 1.53) <0.001	2.14 (1.92 - 2.38) <0.001
Adjusted sHR	1.00 (ref)	1.25 (1.12 - 1.39) <0.001	1.75 (1.56 - 1.96) <0.001
First cardiovascular hospitalisation			
Events – no (%)	1306 (26.8)	1605 (33.6)	1477 (40.9)
Event rate per 100 person-years	12.8 (12.1 - 13.5)	18.2 (17.4 - 19.2)	26.5 (25.2 - 27.9)
Unadjusted sHR	1.00 (ref)	1.33 (1.24 - 1.43) <0.001	1.79 (1.65 - 1.93) <0.001
Adjusted sHR	1.00 (ref)	1.29 (1.19 - 1.39) <0.001	1.69 (1.55 – 1.84) <0.001
Non-cardiovascular death			
Events – no (%)	137 (2.8)	176 (3.7)	188 (5.2)
Event rate per 100 person-years	1.0 (0.9 - 1.2)	1.4 (1.2 - 1.6)	2.2 (1.9 - 2.5)
Unadjusted sHR	1.00 (ref)	1.34 (1.07 – 1.68) 0.012	1.94 (1.53 – 2.45) <0.001
Adjusted sHR	1.00 (ref)	1.26 (1.00 – 1.60) 0.053	1.75 (1.35 – 2.25) <0.001
First non-cardiovascular hospitalisation			
Events – no (%)	1088 (22.3)	1261 (26.4)	1158 (32.1)
Event rate per 100 person-years	10.7 (10.0 - 11.3)	14.3 (13.6 - 15.1)	20.8 (19.6 - 22.0)
Unadjusted sHR	1.00 (ref)	1.22 (1.13 – 1.33) <0.001	1.62 (1.48 - 1.77) <0.001
Adjusted sHR	1.00 (ref)	1.17 (1.08 - 1.28)	1.52 (1.38 - 1.67)

		<0.001	<0.001
All-cause hospitalisation/ all-cause death			
Events – no (%)	2251 (46.1)	2569 (53.9)	2271 (62.9)
Event rate per 100 person-years	22.1 (21.2 – 23.0)	29.2 (28.1 - 30.3)	40.7 (39.1 - 42.4)
Unadjusted sHR	1.00 (ref)	1.29 (1.22 - 1.37) <0.001	1.77 (1.67 - 1.89) <0.001
Adjusted sHR	1.00 (ref)	1.23 (1.16 - 1.31) <0.001	1.63 (1.53 - 1.75) <0.001
First all-cause hospitalisation			
Events – no (%)	1969 (40.3)	2268 (47.5)	2024 (56.0)
Event rate per 100 person-years	19.3 (18.5 - 20.2)	25.8 (24.7 - 26.9)	36.3 (34.7 – 37.9)
Unadjusted sHR	1.00 (ref)	1.27 (1.19 - 1.34) <0.001	1.71 (1.60 - 1.82) <0.001
Adjusted sHR	1.00 (ref)	1.21 (1.14 - 1.29) <0.001	1.60 (1.49 - 1.71) <0.001
All-cause death			
Events – no (%)	838	1018	1063
Event rate per 100 person-years	6.3 (5.9 - 6.7)	8.2 (7.7 - 8.7)	12.2 (11.5 - 13.0)
Unadjusted HR	1.00 (ref)	1.39 (1.27 - 1.53) <0.001	2.19 (1.99 - 2.41) <0.001
Adjusted HR	1.00 (ref)	1.26 (1.14 - 1.39) <0.001	1.80 (1.62 – 2.00) <0.001
Total HF hospitalisations			
Total Events	1021	1280	1426
Events per 100 person-years	7.7 (7.2 - 8.2)	10.3 (9.6 - 10.9)	16.4 (15.5 - 17.2)
Unadjusted IRR	1.00 (ref.)	1.41 (1.24 - 1.61) <0.00	2.40 (2.09 - 2.76) <0.001
Adjusted IRR	1.00 (ref.)	1.25 (1.09 - 1.42) <0.001	1.90 (1.64 - 2.20) <0.001
Total cardiovascular hospitalisations			
Total Events	2441	3050	3118
Events per 100 person-years	18.3 (17.6 - 19.1)	24.6 (23.7 - 25.4)	35.8 (34.6 - 37.1)
Unadjusted IRR	1.00 (ref.)	1.36 (1.25 - 1.49) <0.001	2.03 (1.85 - 2.22) <0.001
Adjusted IRR	1.00 (ref.)	1.26 (1.16 - 1.38) <0.001	1.76 (1.60 - 1.95) <0.001
Total non-cardiovascular hospitalisations			
Total Events	1713	2132	2235
Events per 100 person-years	12.9 (12.3 - 13.5)	17.2 (16.5 - 17.9)	25.7 (24.6 - 26.8)
Unadjusted IRR	1.00 (ref.)	1.30 (1.19 - 1.42) <0.001	1.93 (1.76 - 2.12) <0.001
Adjusted IRR	1.00 (ref.)	1.21 (1.11 - 1.33) <0.001	1.75 (1.58 - 1.94) <0.001
Total all-cause hospitalisations			
Total Events	4154	5182	5353
Events per 100 person-years	31.2 (30.3 - 32.2)	41.7 (40.6 - 42.9)	61.5 (59.8 - 63.1)
Unadjusted IRR	1.00 (ref.)	1.35 (1.26 - 1.44) <0.001	2.00 (1.86 - 2.16) <0.001
Adjusted IRR	1.00 (ref.)	1.24 (1.16 - 1.33) <0.001	1.76 (1.62 - 1.90) <0.001
Fall in KCCQ clinical summary score ≥5 at 12 months			
No. (%)	1598 (33.8)	1628 (35.6)	1230 (36.3)
Adjusted OR1	1.00 (ref.)	1.32 (1.20 - 1.45) <0.001	1.83 (1.60 - 2.10) <0.001

Adjusted OR2	1.00 (ref.)	1.22 (1.10 - 1.35) <0.001	1.62 (1.40 - 1.87) <0.001

Sub-distribution hazard ratios reported as sHR (95% confidence interval) [hazard ratio for all-cause hospitalisation +/or death]
Event rates per 100 person-years with 95% confidence interval
All sHRs adjusted for region and randomised treatment at baseline
Adjusted sHRs additionally adjusted for: sex, age, heart rate, NT-proBNP, NYHA class I/II vs. II/IV, duration of heart failure and ejection fraction.
Heart failure hospitalisation additionally adjusted for previous hospitalisation for heart failure.
Incidence rate ratios reported as IRRs (95% confidence interval)
All IRRs adjusted for region and randomised treatment at baseline
Adjusted IRRs additionally adjusted for: sex, age, heart rate, NT-proBNP, NYHA class I/II vs. II/IV, duration of heart failure, hospitalisation for heart failure and ejection fraction
Odds ratio reported as OR (95% confidence interval)
ORs adjusted for region and randomised treatment at baseline
Adjusted OR1 additionally adjusted for: KCCQ clinical summary score at baseline
Adjusted OR2 additionally adjusted for: sex, age, heart rate, NT-proBNP, NYHA class and ejection fraction

Figure 8-5 Clinical outcomes

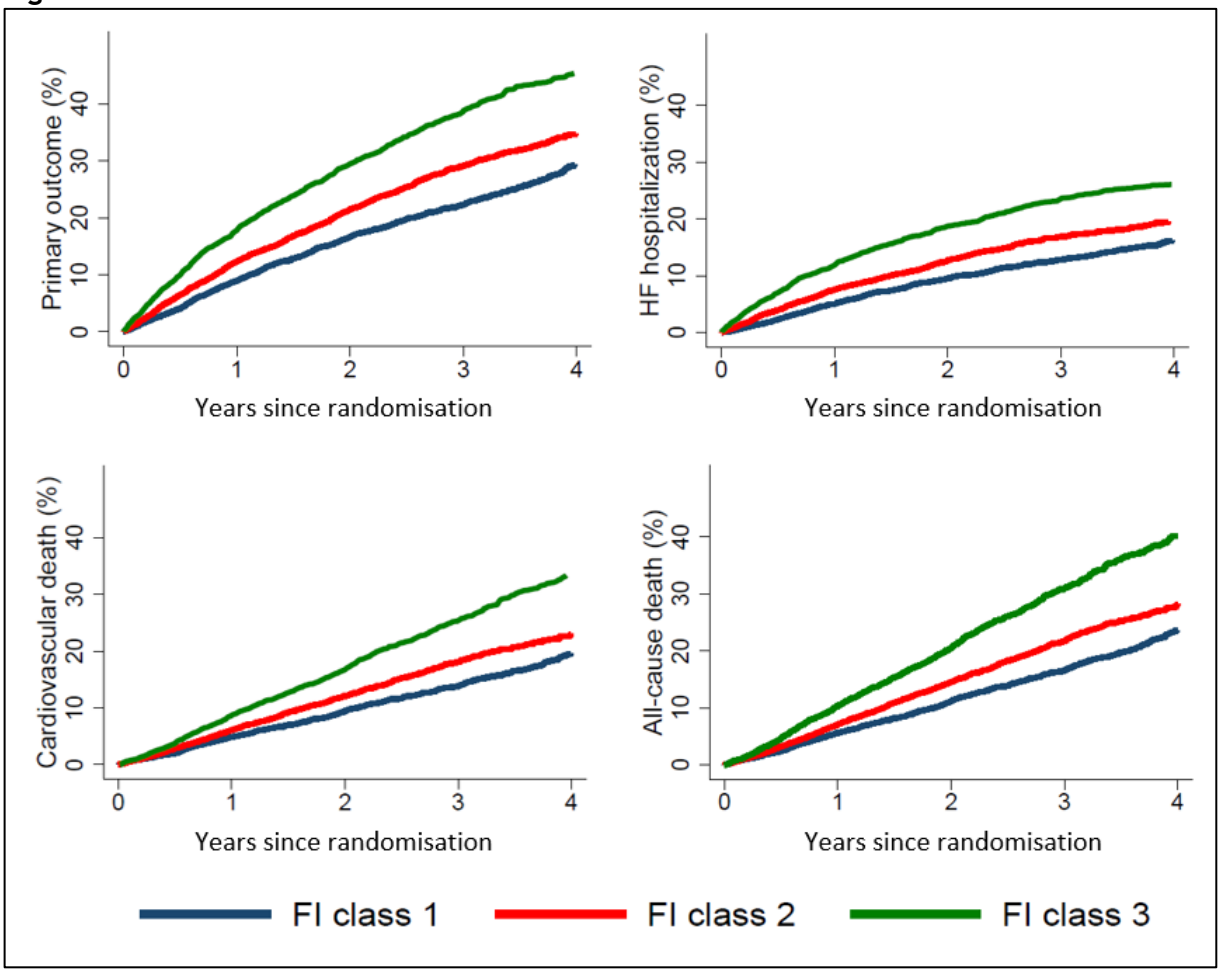


Table 8-8 Clinical outcomes according to frailty in patients in different age groups.

	FI Class 1 n=4882 (≤0.210)	FI Class 2 n=4770 (0.211 – 0.310)	FI Class 3 n=3613 (≥0.311)
18 – 60 years			
Primary outcome – event rate per 100 person-years	8.9 (8.2 – 9.7)	11.6 (10.6 – 12.8)	15.1 (13.6 – 16.9)
– sHR	1.00 (ref.)	1.33 (1.17 – 1.52) <0.001	1.76 (1.51 – 2.05) <0.001
HF hospitalisation – event rate per 100 person-years	5.0 (5.9 – 7.5)	6.6 (5.9 – 7.5)	9.4 (8.2 – 10.8)
– sHR	1.00 (ref.)	1.24 (1.04 – 1.47) 0.014	1.64 (1.36 – 1.99) <0.001
Cardiovascular death – event rate per 100 person-years	5.3 (4.8 – 5.9)	6.4 (5.7 – 7.3)	8.3 (7.2 – 9.5)
– sHR	1.00 (ref.)	1.33 (1.12 – 1.57) 0.001	1.84 (1.52 – 2.23) <0.001
All-cause death – event rate per 100 person-years	6.0 (5.4 – 6.7)	7.2 (6.4 – 8.0)	9.6 (8.4 – 10.9)
- HR	1.00 (ref.)	1.29 (1.10 – 1.51) 0.002	1.85 (1.55 – 2.21) <0.001
61 – 70 years			
Primary outcome – event rate per 100 person-years	8.2 (7.3 – 9.1)	11.9 (10.8 – 13.0)	16.1 (14.6 – 17.7)
– sHR	1.00 (ref.)	1.48 (1.28 – 1.71) <0.001	2.04 (1.75 – 2.37) <0.001
HF hospitalisation – event rate per 100 person-years	4.8 (4.2 – 5.5)	7.1 (6.3 – 8.0)	9.7 (8.5 – 11.0)
– sHR	1.00 (ref.)	1.42 (1.18 – 1.70) <0.001	1.87 (1.54 – 2.28) <0.001
Cardiovascular death – event rate per 100 person-years	4.6 (4.0 – 5.3)	6.6 (5.9 – 7.4)	9.3 (8.3 – 10.5)
– sHR	1.00 (ref.)	1.48 (1.23 – 1.78) <0.001	2.20 (1.81 – 2.67) <0.001
All-cause death – event rate per 100 person-years	5.8 (5.1 – 6.5)	8.1 (7.3 – 9.0)	11.3 (10.1 – 12.6)
- HR	1.00 (ref.)	1.47 (1.25 – 1.74) <0.001	2.15 (1.81 – 2.56) <0.001
71 – 96 years			
Primary outcome – event rate per 100 person-years	9.6 (8.5 – 10.8)	11.4 (10.4 – 12.5)	19.2 (17.7 – 20.8)
– sHR	1.00 (ref.)	1.20 (1.03 – 1.40) 0.018	1.99 (1.71 – 2.31) <0.001
HF hospitalisation – event rate per 100 person-years	5.2 (4.4 – 6.2)	6.2 (5.5 – 7.1)	11.3 (10.1 – 12.5)
– sHR	1.00 (ref.)	1.13 (0.92 – 1.40) 0.233	1.87 (1.53 – 2.29) <0.001
Cardiovascular death – event rate per 100 person-years	6.1 (5.2 – 7.0)	7.3 (6.5 – 8.2)	11.8 (10.7 – 13.0)
– sHR	1.00 (ref.)	1.26 (1.05 – 1.52) 0.014	2.07 (1.73 – 2.49) <0.001
All-cause death – event rate per 100 person-years	7.6 (6.7 – 8.7)	9.3 (8.4 – 10.3)	14.8 (13.5 – 16.1)
- HR	1.00 (ref.)	1.30 (1.10 – 1.53) 0.002	2.17 (1.84 – 2.55) <0.001

Table 8-9 Number of hospitalisations according to frailty class

	FI Class 1 n=4882 (≤0.210)	FI Class 2 n=4770 (0.211 – 0.310)	FI Class 3 n=3613 (≥0.311)	p-value for trend
HF hospitalisation				<0.001
0	4257 (87.2)	4011 (84.1)	2826 (78.2)	
1	429 (8.8)	484 (10.1)	476 (13.2)	
≥2	196 (4.0)	275 (5.8)	311 (8.6)	
Cardiovascular hospitalisation				<0.001
0	3576 (73.2)	3165 (66.4)	2136 (59.1)	
1	780 (16.0)	905 (19.0)	775 (21.5)	
≥2	526 (10.8)	700 (14.7)	702 (19.4)	
Non-cardiovascular hospitalisation				<0.001
0	3794 (77.7)	3509 (73.6)	2455 (67.9)	
1	730 (15.0)	800 (16.8)	660 (18.3)	
≥2	358 (7.3)	461 (9.7)	498 (13.8)	
All-cause hospitalisation				<0.001
0	2913 (59.7)	2502 (52.5)	1589 (44.0)	
1	1054 (21.6)	1069 (22.4)	861 (23.8)	
≥2	915 (18.7)	1199 (25.1)	1163 (32.2)	

Figure 8-6 Subgroup analysis by FI class - Primary outcome

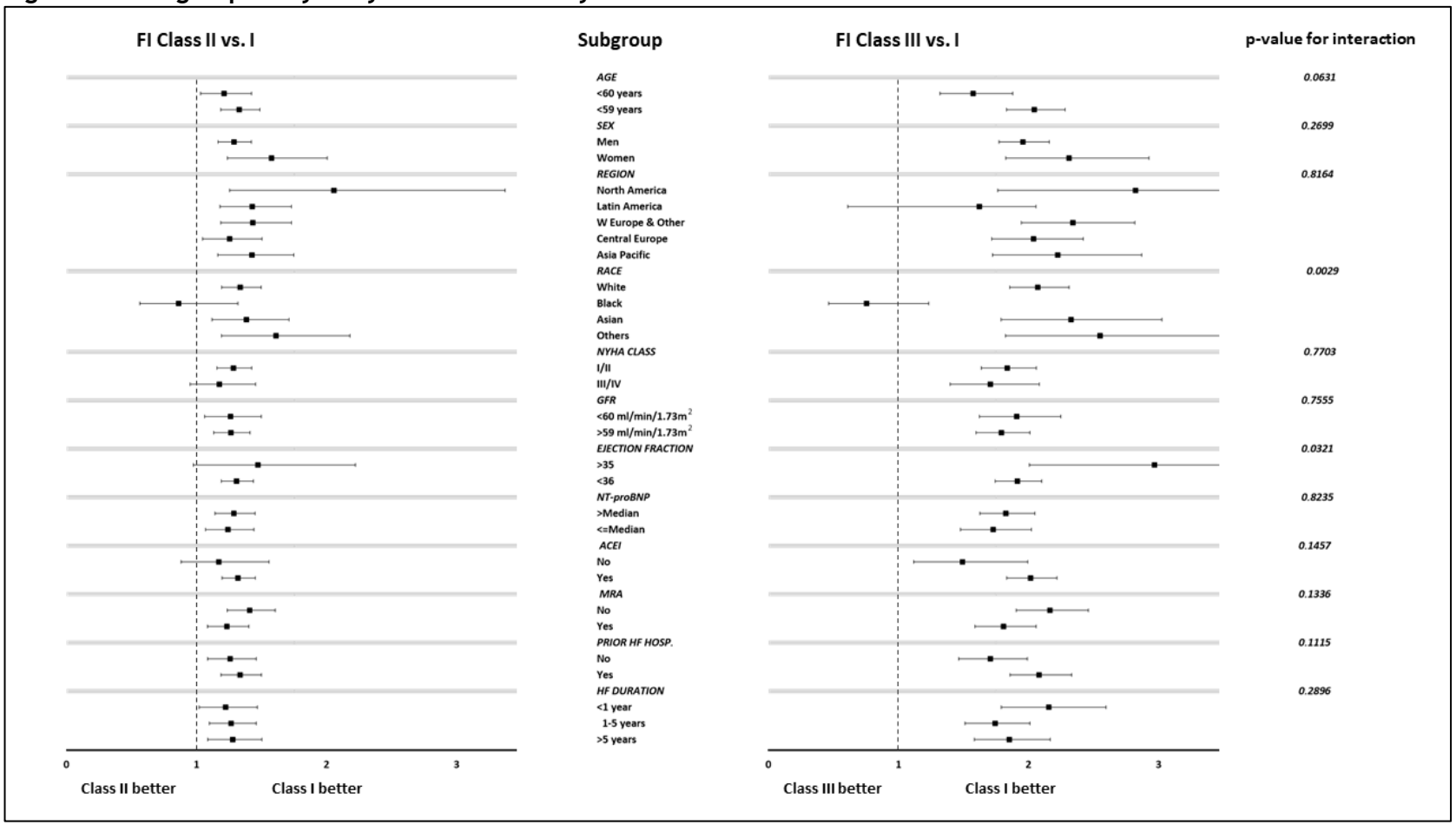


Figure 8-7 Subgroup analysis by FI class - All-cause death

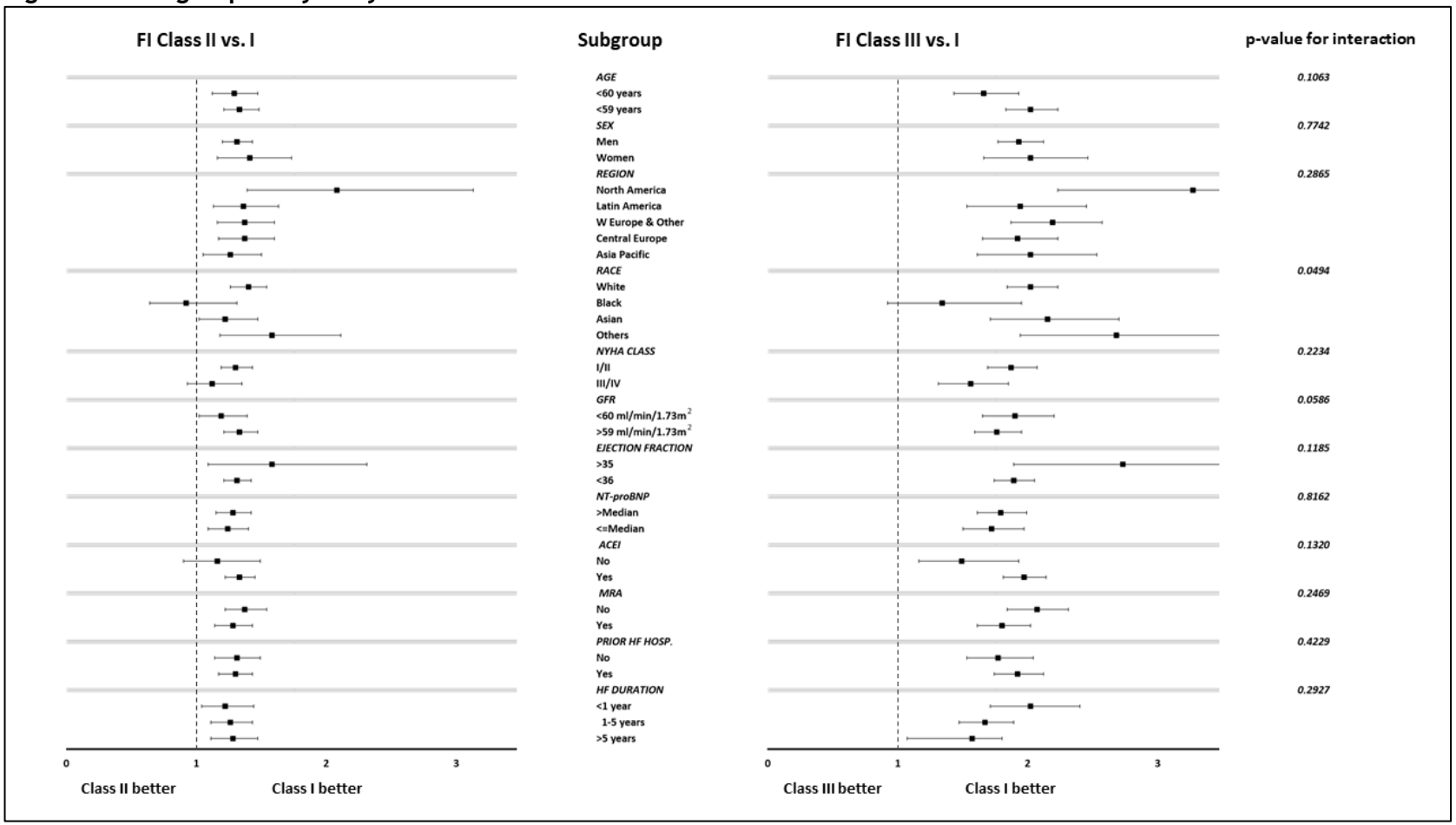
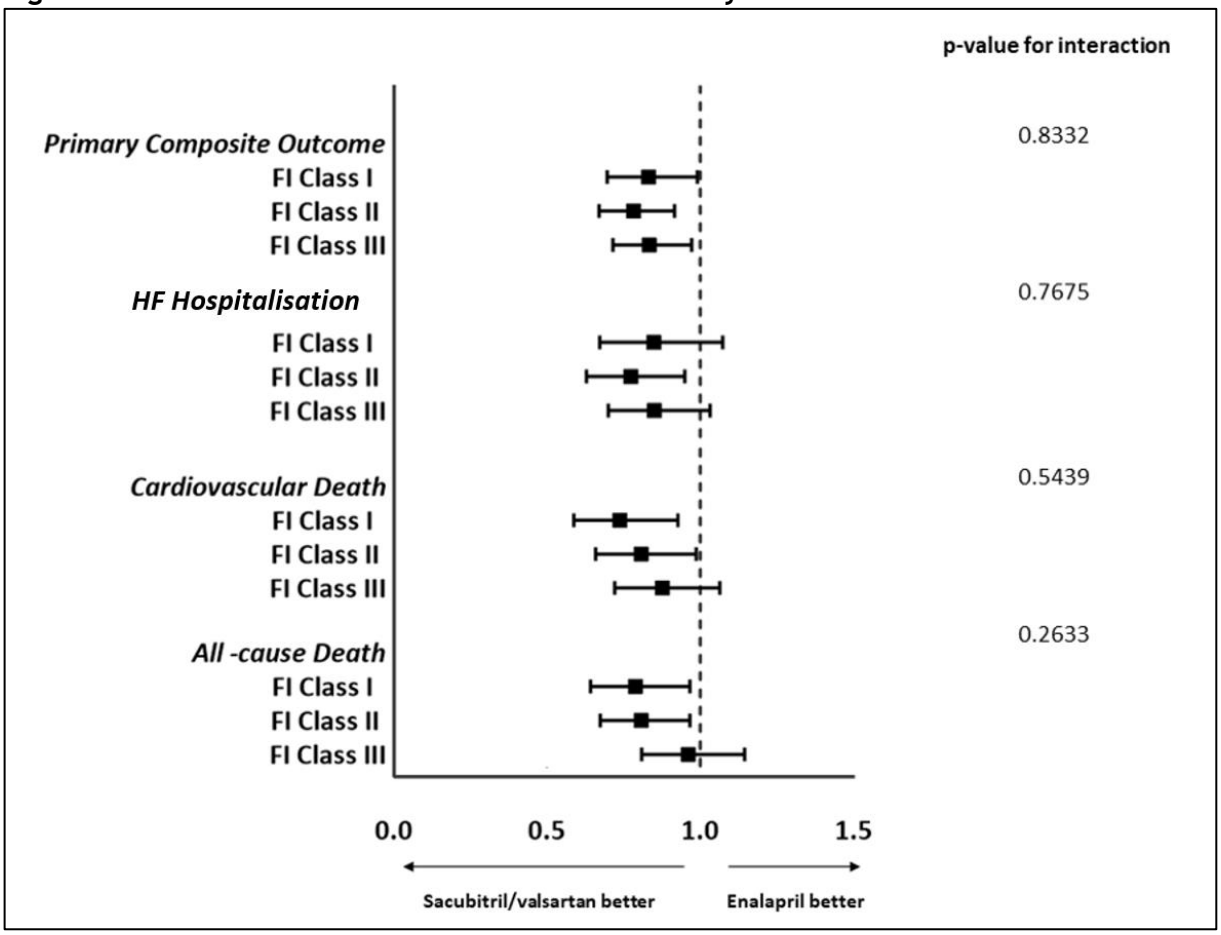


Figure 8-8 Treatment effect of sacubitril/valsartan by FI class.



Adverse events

Although the number of events was small the risk of falls and fractures increased with increasing frailty [Table 8-10.]. the risks of hypotension, hyperkalaemia, and study drug discontinuation due to any adverse event were also higher in the frailest patients.

Table 8-10 Adverse events

	FI Class 1	FI Class 2	FI Class 3
	n=4882	n=4770	n=3613
	(≤0.210)	(0.211 – 0.310)	(≥0.311)
Falls			
Events – no. (%)	52 (1.1)	95 (2.0)	92 (2.5)
Odds ratio	1.00 (ref.)	1.89 (1.34 – 2.65)) <0.001	2.43 (1.72 – 3.42) <0.001
Fractures			
Events – no. (%)	116 (2.4)	158 (3.4)	157 (4.3)
Odds ratio	1.00 (ref.)	1.41 (1.10 – 1.79) 0.006	1.87 (1.46 – 2.38) <0.001
Cough			
Events – no. (%)	573 (11.7)	482 (10.1)	391 (10.8)
Odds ratio*	1.00 (ref.)	0.84 (0.74 – 0.96) 0.008	0.91 (0.79 – 1.04) 0.177
Hypotension			
Events – no. (%)	520 (10.7)	578 (12.1)	510 (14.1)
Odds ratio*	1.00 (ref.)	1.17 (1.03 – 1.33) 0.016	1.39 (1.22 – 1.59) <0.001
Hyperkalaemia			
Events – no. (%)	400 (8.2)	596 (12.5)	458 (12.7)
Odds ratio*	1.00 (ref.)	1.59 (1.39 – 1.82) <0.001	1.62 (1.41 – 1.87) <0.001
Angioedema			
Events – no. (%)	11 (0.2)	12 (0.3)	9 (0.2)
Odds ratio*	1.00 (ref.)	1.16 (0.51 – 2.63) 0.728	1.14 (0.47 – 2.77) 0.765
Any adverse event leading to treatment withdrawal			
Events – no. (%)	662 (13.6)	784 (16.4)	728 (20.1)
Odds ratio*	1.00 (ref.)	1.22 (1.09 – 1.38) 0.001	1.62 (1.43 – 1.83) <0.001

All unadjusted odds ratios are reported with 95% confidence interval.
*Adjusted for randomised treatment.

Discussion

Among 13265 patients with HFrEF in whom an FI could be calculated, 63% (69% in patients >60 years old) were frail even though they were relatively young and had been selected for inclusion in clinical trials.[257] Frail patients were more likely to experience a decline in QoL, be hospitalised for any cause and were twice as likely to die due to any reason during follow-up. These increased risks of adverse outcomes during follow-up persisted even after adjustment for powerful clinically prognostic variables such as NT-proBNP.

As the concept of frailty can be considered to result from an aggregation of insults across multiple organ systems, one approach to quantify frailty, therefore, is counting the number of "health deficits", assessed by symptoms, signs, diseases, and disabilities, as well as laboratory, radiographic ad electrocardiographic abnormalities, across a wide range of domains.[256,257] The more deficits accumulated, the more likely a patient will be frail. This "deficit accumulation" approach allows calculation of a FI which has proved to be predictive of mortality, hospitalisation, and institutionalization in the general population, as well as in specific diseases.[256] This FI appeared valid as higher scores were associated with poorer self-reported and physician-assessed functional status and traditional frailty outcomes such as falls. Moreover, in a restricted cubic spline analysis, the significant point of inflexion in risk of death related to FI was consistent with the conventional threshold defining frailty (FI ≥0.210).[257]

To give some context to the findings in this chapter, the mean FI in a general population (UK Biobank, n=5000,336), was 0.129 in those aged 60-65 and 0.139 in ≥65 years (compared with a mean of 0.250 in this HFrEF population, a higher score reflecting greater frailty).[258] In 2.69 million American Medicare beneficiaries >65 years without cancer, FI at age 66 was 0.198 and at age 70 was 0.197.[259] In two hypertension trials, the median FI in patients over 80 years was 0.17 and 0.18, respectively. In the Systolic Blood Pressure Intervention Trial (SPRINT), 27% of patients were classified as frail. In general population studies, 20-30% of individuals are identified as frail, rising to 43% at the age of 85 years in a large Canadian study.[260,261] In the patients in this study with a mean age of

64 years, 63% were frail. These striking differences between patients with HFrEF and those with hypertension, and the general population, are an important reminder that frailty is not confined to the very elderly. The high prevalence of frailty in this relatively young HFrEF population is also consistent with the hypothesis that frailty partly reflects accelerated ageing – essentially the patients in this study have a prevalence of frailty usually only found in extreme old age. Moreover, frailty seems to be particularly prevalent in HF compared with other diseases; for example, lower frailty indices, and a lower proportion of patients classified as frail, have been reported in chronic kidney disease, chronic obstructive pulmonary disease, and acute coronary syndrome.[262–271] Only in myeloma patients, with a mean age of 76 years, were similar levels of frailty observed: median FI 0.24, with 52% categorized as frail.[259]

Chronic inflammation, sarcopenia and a general reduction in physiological reserves are implicated in the pathogenesis of the frailty syndrome.[262–271] Interestingly, I found that increasing frailty was associated with higher levels of inflammation and tissue turnover related biomarkers, especially, GDF-15, one of a core panel of frailty biomarkers, thought to reflect mitochondrial dysfunction and cellular senescence, increased with increasing frailty.[272–277]

Consistent with previous studies, a higher proportion of women in this study were frail (68% vs. 62%), which has been attributed to their lower muscle mass. Quality-of-life, overall, was lower in women and whether this is a marker of frailty or a contributor to frailty is unknown.

Several studies have examined frailty in HF, although most were small and many used different methods to define frailty; additionally, some focused on hospitalised patients or HFpEF patients or included patients without LVEF measurement. Only three prior studies in ambulatory patients were large (>1000 participants) and reported clinical outcomes. In a Spanish study, 44% of 1314 HF outpatients (76% HFrEF and 24% HFpEF, mean age-67 years) were categorized as frail using an approach based on 4 geriatric scales.[278] Frailty was independently predictive of all-cause mortality, although the multivariable model did not include natriuretic peptides. No other outcomes were reported. Recently, an electronic FI (eFI), calculated for 6,360 patients with a diagnosis of HF (but without LVEF or natriuretic peptides) in a large UK primary care dataset, was

predictive of any hospitalisation at one year but not of HF hospitalisation.[279] Mortality was not reported. Of these patients (mean age not reported but 83% ≥65 years), only 15% were categorized as frail using an eFI cut-off point of 0.24 compared to 51% using this threshold in the present analysis. Patients in the UK study had been diagnosed with HF within the past 3 years whereas 36% of the patients in this study were diagnosed with HF more than 5 years previously. In the patients in this cohort diagnosed with HF less than 2 years before enrolment, only 19% of the patients had an FI ≥0.24 whereas, of those diagnosed less than 5 years before enrolment, 33% had an FI ≥0.24. It is important to note here that duration of HF is unlikely to be an effect modifier in HF therapy as my colleagues and I demonstrated separately in the PARADIGM-HF and DAPA-HF populations.[1,3] Using an approach similar to the one I have used here, the TOPCAT investigators reported a mean FI of 0.37±0.11(median 0.36; IQR 0.29–0.44) in 1767 patients with HFpEF from North and South America (mean age 71.5 years, 49% female).[280] A remarkable 94% had a FI >0.21. As in the present study, a higher FI was associated with higher rates of HF hospitalisation, cardiovascular death and all-cause death, although these outcomes were not adjusted for other predictive variables. A greater proportion of the patients in TOPCAT had diabetes and hypertension, along with a much lower mean KCCQ-OSS (58.1±23.4 vs.72.3±19.5 in the patients in this study), which could have contributed to a higher proportion of their patients being described as frail.[280] Patients with HFrEF were also less likely to be frail than HFpEF patients in a smaller recent study assessing different frailty tools in HF.[281]

The high prevalence of frailty in HFrEF is highly clinically relevant, as reflected in the worse outcomes seen in frail patients. Frail patients have reduced ability to cope with stressors that may precipitate worsening of HF, meaning that exacerbations become more frequent and increasingly difficult to recover from. I certainly found a marked difference in the rate of HF hospitalisation when comparing frail to non-frail patients. But rates of admission and deaths from other reasons were also higher in frail individuals, although the proportion of deaths that was attributed to non-cardiovascular causes (around 19%) was similar across FI categories. Importantly, the absolute risks in the frailest patients were remarkably high - for example, 4 in 10 of the frailest individuals were admitted to hospital at least once or died during each year of follow-up. In addition, when

repeat admissions were accounted for, the rate of hospitalisation was 62 episodes per 100 person-years. Two recent studies using the same FI (the Hospital Frailty Risk Score) in patients hospitalised with HF have shown that frailty is also associated with higher rates of short and long-term mortality after discharge; a third confirmed the distinction between frailty and comorbidity by demonstrating a poor correlation between the Hospital Frailty Risk Score and the Charlson Comorbidity Index.[282,283]

Frailty may also reduce a patient's ability to self-care and impair adherence because of several factors most prominently cognitive impairment that can be associated with poor health status and to a certain degree due to normal ageing.[275–277] Most recently dapagliflozin proved to be efficacious in improving clinical outcomes in HF only 5 years after the positive results of the PARADIGM-HF trial adding to the evidence-base for therapy of HF. Polypharmacy has become increasingly relevant in patients with HF with concerns of increased risk of drug interactions and adverse effects. To address these concerns, in recent study I demonstrated that there was no increase in the risk of adverse events in those receiving concurrent dapagliflozin and ARNI in a population optimally treated for HF.[284] However, the analysis was done in the overall DAPA-HF population and the elderly and frail were not separately studied. In this study, polypharmacy increased with increasing frailty, not only causing concerns about adherence but also about drug-related adverse effects and interactions. Consistent with this, study drug discontinuation was significantly more common in frailer patients. This is especially important to consider as health and social care systems globally vary widely, and care of this vulnerable age group also varies widely.

The obvious question is what, if anything, can be done to prevent or treat frailty? Frailty is believed to evolve over time, with initially fit individuals progressing through a pre-frail stage to overt frailty and ultimately terminal disability and death.[112,255,256,285–287] Often, early frailty may be undetected as limitations in daily activities (and associated symptoms such as fatigue) are often attributed to the normal consequences of ageing by patients and their care-givers. It is easy to see how this could be especially so in HF. Identifying frailty early may be important as some of the limitations caused by it may be

amenable to nutritional and lifestyle interventions and, if employed at the pre-frail stage, these may delay progression to frailty.[112,255,256,285–289] In this respect, cardiac rehabilitation and exercise training programmes may be particularly relevant, yet the latter was prescribed in only around 1 in 10 patients in this study.[290] However, as frailty seems to reflect several insults to multiple systems, a multifaceted approach to its prevention and treatment may be required.

Concerns regarding the inclusion of the elderly and the frail in clinical trials, either due to the perceived burden to the frail patients or due to doubts regarding the benefit of such therapies to the elderly and frail exist.[291] I did not see any evidence of an interaction between treatment and frailty in the PARADIGM-HF patients in this analysis. Similarly, other studies have also shown that frailty does not alter the effect of therapy.[260] I and my colleagues in the PARADIGM-HF and DAPA-HF datasets also demonstrated separately that no difference in treatment effects according to duration of HF which is likely to be longer in frail patients with HF.

The FI lends itself to incorporation into routine datasets, including patient electronic heath records (EHR). It is possible to conceive of how a hospital admission record or outpatient/primary care EHR might automatically calculate a FI and alert the physician/nurse to individuals with a high score, although, as alluded to above, it cannot be said for sure, yet, whether the identification of frailty should trigger any monitoring or therapeutic intervention. Likewise, in nationwide audits and comparison of outcomes, FI might be an important determinant of differences in outcome, that could be adjusted for when conducting between-institution and other comparisons.

Strengths and limitations

There are several strengths and limitations in this analysis. The patients were those selected for inclusion in clinical trials and not fully representative of the general population. Frailty is likely even more prevalent in an unselected cohort of patients with HFrEF. The FI constructed here is not an independently validated prediction model and may not apply to other cohorts. Also, I could not test other types of frailty scores which include tests of muscle strength and functional capacity, and I recognize that in the absence of these factors, the current frailty index may be viewed as a surrogate measure of frailty. On the

other hand, I had access to a detailed and near-complete collection of baseline variables enabling me to create the 42-item FI. I also had careful collection of long-term adjudicated outcomes.

Conclusion

In this study of 13265 ambulatory patients with HFrEF and mainly mild symptoms, frailty showed a high prevalence. Frailty was associated with greater deterioration in QoL and higher risk of hospitalisation and death. Frailty, did not, however, modify the effect of sacubitril/valsartan. Strategies to prevent and treat frailty are needed in HFrEF.

Chapter 9. Final Discussion

Prognosis in HFrEF

Heart failure is a complex syndrome that affects from 26 million to an estimated 64.3 million people globally. [4,9,36] It has a profound impact on mortality, hospital admissions and quality of life. Moreover, with ageing populations, an increasing incidence of cardiovascular disease globally, improving survival in cardiovascular and other conditions increasing the risk of HF and better survival of patients who have developed HF, the prevalence of HF is only set to rise.[14,21,29]

Accurately measuring prognosis in patients with HF is important as it helps clinicians inform their patients about their condition and facilitates decision-making about advanced therapies (such as cardiac transplantation) and end-of-life care.[4] Use of single prognostic markers for this purpose is poorly discriminative and not recommended. Consequently, multivariable risk models have been developed but their application in routine clinical care is still limited.[83,86] There are several explanations for this including concerns about reproducibility in different populations, poor reliability at the individual patient level, inclusion of variables not routinely collected, and the complexity of statistical methodologies employed. Also relevant is the ever-improving prognosis of patients with HF, in part due to rapid development of pharmacotherapies in HF which have reduced mortality (and morbidity) in HF.[38,40,61,62,64–66,111,292]

In a review of the models developed to estimate prognosis in patients with HF, I presented a comprehensive list of the most commonly reported predictive variables – both clinical and non-clinical in Chapter 1. I found that over the past 30 years, while a few variables were common to most models, there was a great deal of heterogeneity in the other variables included in the models. Age, sex, LVEF, and NYHA class were frequently included. Some other variables such as comorbidities, physiological biomarkers (such as blood pressure and heart rate) and routine laboratory measurements were also commonly included. However, newer circulating biomarkers, especially natriuretic peptides, and certain demographic characteristics such as race/ethnicity and geographical region were

less frequently utilised. This was especially true of older models, emphasising the limitations of previous models in terms of contemporary diagnostic strategies and therapy and, importantly, their applicability to diverse HF populations.[83,86]

Taking these factors into account, the purpose of this thesis was to study a select set of variables – both clinical and non-clinical and, both conventional which have featured consistently in previous models and a few less frequently considered factors which may potentially improve the prognostic ability of such models.[109] In keeping with the theme of analysing the prognostic relevance of such variables, the analysis presented in this thesis were carried out in three contemporary global clinical trial datasets in HFrEF – ATMOSPHERE, PARADIGM-HF and DAPA-HF.[38,40,135]

While numerous measures of cardiac function have been included in models, LVEF remains the most widely used measure of cardiac function in everyday clinical practice.[87,158] It guides most pharmacotherapy in HF and determines eligibility for ICD and CRT.[4,36] Indeed, in my systematic review, LVEF featured as a predictor of outcomes in the earliest model, was included in all the univariate analyses, and was shown to be a predictor in 71% of the final multivariable models.[87,89,90,97,99–101,106–110] At the time of the writing of the first draft of this thesis, DAPA-HF was the most recent of the global clinical trials in patients with HFrEF. In DAPA-HF, I found that the association between baseline LVEF and outcomes (primarily HF hospitalisation, cardiovascular and all-cause death) was consistent with previous analyses, despite the many changes in therapy that have been implemented in patients with HFrEF in recent years. In a series of HF trials from over 20 years ago, the CHARM program, every 5% reduction (below 45%) in LVEF was associated with an approximately 13% increase in the adjusted risk of cardiovascular death or HF hospitalisation.[158] The corresponding increment in risk of the same outcome for each 5% reduction in LVEF was 15% in PARADIGM-HF and 18% in the DAPA-HF trial.[161]

While an important predictor of outcomes in HFrEF, LVEF alone cannot be relied upon to influence decision making regarding long term prognosis. LVEF, like any other individual prognostic variable, can vary with other patient-level factors.[4,293] Sex is one such factor where it is well known that the distribution of

LVEF is different in women and men, with women on average having higher LVEF both in the general and the HF population.[191,294]

In my review of the literature in chapter 1, sex was retained as a final prognostic variable in 50% of studies.[87,89,90,97,103,105–107,109] The importance of including sex in prognostic models cannot be overemphasised. Biological variation based on sex is common knowledge. Not only is overall life expectancy known to vary with sex, but previous studies have also shown that women with HF are very different than men. Of concern, at least in previous studies, women may not receive the same level of care as men.[92,114–125] Moreover, variation in drug response across the LVEF spectrum has been proposed to exist between men and women.[79,118,191,295]

In chapter 4 in a contemporary clinical trial cohort, women were older, reported greater psychological and physical disability but on a more positive note, a narrowing of previously highlighted gaps between the sexes was observed, especially concerning pharmacological therapy. Interestingly, despite more reported signs/symptoms of HF and a significantly lower QoL, women had a lower risk of HF hospitalisation and mortality even after accounting for NT-proBNP level when compared to men. Reasons to explain this paradox were difficult to elucidate from the information that was available in the dataset.

It is well known that HFpEF is the more common phenotype of HF in women.[35] While different theories have been advanced to explain these differences, predisposition to microvascular /endothelial dysfunction in women compared to predisposition to macrovascular CAD in males has been a central hypothesis to explain these differences.[35,186,187] Accordingly a lower prevalence of CAD among women was seen. In addition, stark differences in the comorbidity in keeping with the literature was observed – women had a higher prevalence of hypertension and asthma, and COPD and diabetes (along with coronary artery disease) were more common in men.[202,296,297] These likely had implications on the differences in the risk of mortality observed.[186,187]

As in the general population, prognosis in HF is strongly driven by an individual's comorbidity profile. Prognosis is related to both the number of and the type of comorbidities in an individual.[87,89,298,299] Diabetes, anaemia and advanced kidney

disease are each well known to be associated with the worst prognosis and often cluster within an individual. Less well recognised is the impact of other comorbidities that are both relatively common and associated with substantial risk, for example, COPD.[4,299,300] As demonstrated in my review of the literature, COPD as a comorbidity was behind only diabetes and atrial fibrillation/flutter in frequency of inclusion in risk models.[87,90,102] Both COPD and HF have several common risk factors, overlapping clinical presentations, increase in prevalence with advancing age, are more common in men and are common causes of frequent hospitalisations.[129,130] However, there is very little in common other than modification of lifestyle factors and supportive care in the management of these two conditions.

Patients with coexisting COPD in DAPA-HF as presented in this thesis had worse outcomes in keeping with previous studies. Indeed, the point estimate for the risk of the primary outcome of cardiovascular death or HF hospitalization/urgent visit for HF, associated with COPD was equal to that of CKD and higher than that associated with diabetes. QoL at baseline, as measured by the KCCQ score, was the worse in patients with COPD than in patients with any other comorbidity.

The incidence and prevalence of the chronic conditions that constitute the growing problem of multimorbidity in ageing populations in general, and HF, is determined by genetic makeup, social and lifestyle factors as well as senescence.

Regional differences in HF outcomes have also been highlighted by prior studies, although often within one country (e.g. the USA) or limited geographical areas (e.g. Europe); very few have included Asia, despite more than half of the World's population living in that region.[82,126,127] In Chapter 6, I demonstrated differences in baseline demography, clinical presentation, drug and device use and overall clinical outcomes, both within Asia and between Asia and the rest of the world. Only Caucasians were included in the non-Asian regions and within the Asian region, those self-reporting ethnicity generally reported an ethnicity corresponding to their specific Asian country e.g. Japanese in Japan) except Taiwan. The analysis in Chapter 6 was, therefore, representative of ethnic/racial differences as much as it was representative of differences in geography.

Patients from Asia were generally younger (except Japan), had lower BMI, had more CAD, were diagnosed with HF relatively recently, had a lower symptom burden and had much lower percapita income compared to North America and Western Europe. Differences existed in patient characteristics within Asia as well. Indians were the youngest but had a relatively higher burden of CAD and diabetes. The use of digoxin was high despite fewer patients suffering from atrial fibrillation. Within Asia, Japan had the highest percapita income as well as the greatest spending in healthcare and the opposite was the case in India which had the lower percapita income and among the lowest expenditure on healthcare. The use of ICDs/CRTs was also higher in regions with higher percapita income. While event rates for HF hospitalisation and mortality were highest in Taiwan, there was a striking disparity between hospitalisation and mortality rates in India and the Philippines, both of which were countries with the lowest percapita incomes.

Racial/ethnic differences in the profile of disease and comorbidities are known to exist.[301–303] Consequently, the aetiology of HF also varies considerably between different geographic areas. [82,126,127] In some, comorbidities behave differently. Asians are at a greater risk of development of CAD and related chronic conditions compared to Whites with the same or even lower BMI.[304] I however did not observe this in Chapter 6 where, even though Asians overall had lower median BMI, they had lower prevalence of unstable angina and myocardial infarction. For interactions to occur between markers of prognosis and different racial/ethnic groups would not be entirely unexpected. Although not analysed separately in Chapter 6, people of Black heritage have a higher prevalence of hypertension. The response to different cardiovascular drugs may also differ between races and this has even led to race-based treatment recommendations e.g. first-line therapy for hypertension is different in Black patients and white patients (with renin-angiotensin system blockers relatively less effective in Black patients). These race-based differences may also be important in HF e.g. the combination of hydralazine and isosorbide dinitrate has a specific indication in African Americans and Asians are more likely to suffer cough with ACEIs.

Taking socio-economic considerations into account is also important while discerning the basis for regional differences in characteristics and outcomes in

HF. As mentioned earlier, this was illustrated by the high mortality rate in India and the Philippines, yet these countries had the lowest rate of HF hospitalisation. Although modes of death were not examined in Chapter 6 due to smaller numbers, it could also be that sudden death was more common in these countries where very few patients had had an ICD implanted –0.1% and 0% of the patients in India and Philippines, respectively. The low rates of hospitalisation are likely attributable to bed availability and lack of affordability/access to in-patient care. However, patient-level data on these factors was not available in either ATMOSPHERE or PARADIGM-HF (and have never, to my knowledge, been reported in any trial). The explanation for these findings is probably even more complex than just low healthcare spending as although health insurance in the Indian population is very low, the Philippines has a universal health coverage system.[305,306]

As discussed in Chapter 1, only 38.9% of the prognostic models examined were built in international cohorts.[89,91,97,103,105,107,109] Moreover, race/region was included in univariable analysis in only 4 studies and featured in one final model.[87,103–105,109] Concerns regarding the applicability of current HF models to a diverse population is an important reason behind their limited use by health professionals. Consideration of different regional and ethnic/racial backgrounds could improve the applicability and acceptance of future prognostic models in HF.

To focus more specifically on socioeconomic status and its importance in predicting outcomes in HF, I took the analysis of countries as done in Chapter 6 one step forward and analysed differences according to levels of income inequality using the Gini coefficient in the pooled ATMOSPHERE and PARADIGM-HF cohort.[230] Better socioeconomic status should afford better care but not all countries with a high percapita income fare the same when their quality of healthcare is compared. Some of the richest countries still have high overall levels of morbidity and mortality especially when it comes to chronic diseases, including HF.[240,307] A series of seminal studies by Wilkinson and colleagues proposed that this was ultimately explained by the extent of income inequality - the gap in income between a country/society's wealthy and its poor.[226,227,240]

The contrast between patient characteristics and outcomes in Chapter 7 were stark. Baseline characteristics – younger age, lower SBP and BMI, fewer comorbidities, better NYHA class and better QoL, all indicated healthier patients in the group with the greatest income inequality. However, the same patients had the highest risk of hospitalisation and death even after adjusting for standard predictors in HF, NT-proBNP, percapita income and other relevant socioeconomic and health care indicators. Even when examined as a continuous variable in a multivariable model, the Gini coefficient was a strong and significant predictor of cardiovascular death, only behind NT-proBNP, sex and diabetes in predicting death due to cardiovascular causes. In the same model, percapita income was not a significant predictor of cardiovascular death.

Socioeconomic indicators did not feature in any of the models featured in my review of the literature in Chapter 1 despite socioeconomic status being a powerful independent predictor of outcomes in HF.[308] A recent study showed that the risk of mortality in the first year after heart transplant was high in young Black recipients – 53% percent higher in those aged 31-40 years, and 20% higher in those aged 41-60 years, respectively - when compared to non-Black recipients.[309] Adjustment for comorbidities and transplant indications did not explain this elevated risk. One explanation put forth in the study was while Medicare is available to those 65 years or older in the United States, financial constraints in the young with varying insurance cover could have influenced the ability to remain adherent to follow-up visits and medications in the post-transplant period.[309]

While the above study was conducted in a wealthy country with high inequality, the impact of income inequality may be even more extreme in countries with low income and high inequality. In Chapter 7, countries with the greatest inequality also had the lowest percapita income. In another analysis in a separate population, my colleagues and I demonstrated that patients who lived in countries with the lowest percapita income and the greatest inequality had the worst cardiovascular outcomes.[310]

One of the reasons put forth for poorer HF outcomes with increasing inequality is the lack of social cohesion in such societies, with a large disparity in healthcare delivery to those at the opposite ends of the income spectrum and reduced

access to and affordability of health care for the neediest. In the Western world, to a large extent, formal systems are in place to take care of the vulnerable and elderly, either in their own homes or established nursing/care homes. The vulnerable in poorer countries on the other hand have benefited from largely informal social care in the form of familial support. However, with urbanisation, such systems are becoming compromised with potential caregivers moving away from family homes, In these societies, in the absence of structured formal support systems, the vulnerable may be at an increased risk of compromised self-care and adverse outcome.[311]

The increase in prevalence of HF is largely attributable to the ever-ageing, more vulnerable, global population mainly to advances in research and healthcare delivery.[9] By 2025, it is estimated that about 1.2 billion people will be over the age of 60 and by 2050, more than 2 billion people will be over the age of 80. Old age is an important determinant of health.[312] However, there can be a significant disparity in the pace of ageing among individuals, attributable to a variety of factors - economic, behavioural, personal, and social determinants, environmental and availability of health and social services, some of which have been touched upon in this discussion already.

Frailty is increasingly being recognised as a syndrome that affects outcomes in patients with chronic conditions. It is defined as a multisystem disorder characterised by loss of homeostatic reserves, rendering affected individuals vulnerable to physiological decompensation, and placing them at increased risk of adverse outcomes when exposed to a stressor.[256] While the focus of addressing frailty largely remains on the elderly, it is distinct from ageing.[255,285] And while thought, to be related to aggregations of insults across multiple organ systems, it is separate from multimorbidity.[285]

In Chapter 8, I used the cumulative deficits approach to construct a 42-item Frailty Index in patients in PARADIGM-HF and ATMOSPHERE. A large proportion of the patients in in the pooled cohort were frail. Overall, 63% of the population was frail and the prevalence was even higher in those aged ≥60 years (69%) in keeping with previous studies which have shown higher frailty in those with HF compared to the general population.[313] The risk of mortality and hospitalisation was the highest in the frailest patients.

Frailty did not feature in any of the models in my systematic review in Chapter 1. Even in the general literature, predictive models have been built to estimate the risk of frailty but models including frailty as predictive variables are largely absent. The purpose of estimating prognosis is not only to identify those who need specific devices or for cardiac transplantation. Estimating prognosis is also helpful in avoiding unnecessary interventions in those who may not gain any worthwhile benefit. Moreover, it helps in identifying those who could benefit from assessment for social care or palliative care referral. Frailty may therefore add substantial value to prognostic models in heart failure.

Limitations

Overall, as with all studies, this thesis has limitations. The results of all my studies were based on three clinical trial populations where patients had to meet specific criteria to be eligible, were younger than average, were more likely to be receiving guideline directed medical therapy and therefore may not be fully representative of the general population. However, the datasets examined had detailed and near-complete collection of baseline variables and all outcomes were carefully collected and adjudicated.

I only studied patients with HFrEF in this thesis even though patients with HFpEF account for half of all patients with HF. However, focusing on a single phenotype of HF is also a strength of these studies as patients with HFrEF and HFpEF have very different clinical characteristic, event rates for mortality and hospitalisation vary and modes of death are also different between the two phenotypes.

I did not carry out a formal assessment of the variables examined here in a single multivariable model using methods that are commonly used to build models, assess their discriminative abilities, and validate them subsequently.

QoL as a prognostic variable which has not frequently been included in previous models but could be a powerful prognostic marker was not studied in this thesis. However, its importance in being assessed as a clinical outcome was covered extensively in Chapters 4,5 and 8.

Granular information regarding socioeconomic indicators were not collected in the trials and I used data available from various sources available online to present the analysis in Chapters 6 and 7.

Implications for future research

Estimating prognosis in HF is clinically valuable. Several multivariable models have been developed to predict morbidity and mortality in HF.

In this thesis, I have proposed that while conventional markers of prognosis are still important in contemporary HF populations, other non-conventional variables are also associated with clinical outcomes in HF. The addition of these might even improve the performance of future prognostic models in HF. However, I unfortunately, did not have the time to build a new prognostic model incorporating the novel variables I have studied. The development of such models requires the use of relatively sophisticated statistical methods, is time-consuming and really is a different project from the one I have undertaken. However, this would be a logical progression of my work. This next step would also involve finding a validation dataset. Simpson and colleagues have recently demonstrated how prognostic models can be updated and improved with the development of the PREDICT-HF model.[109] Importantly, these investigators showed that a model developed in a clinical trial cohort retained its predictive and discriminative ability when validated in a real-world registry.

I found that socioeconomic status, at a country level, was a powerful independent predictor of outcome and it would be of great interest to obtain this information at an individual patient level, within the boundaries of anonymity. This may be even more powerful than aggregated data. I hope my findings will inform the collection of such data in future HF clinical trials.

The same is true of frailty. Using a “cumulative deficits approach”, I showed the importance of frailty but alternative approaches using assessments of muscle strength and functional capacity may be even more informative and could also be collected in future trials.

Conclusion

Heart failure is a complex syndrome. The clinical course varies greatly from patient to patient depending on age, sex, age at diagnosis, aetiology to name a few factors. Other factors such as race, geography and socioeconomic background also influence the risk of death and various other outcomes associated with morbidity and disability. For such a complex condition, a formal assessment of risk prediction can help clinicians inform their patients better about treatment decisions and help in planning of palliative and social services. While the clinical uptake of models to predict prognosis in HF has been limited to date, expanding the pool of variables previously used to build such models may help in improving their clinical applicability in different populations.

Appendix

List of Tables - appendix

Appendix table 1

Sl. No.	Search terms	Number of items
1	Heart failure or cardiac failure [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	679980
2	Scor* or risk* or predict* or model* [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	18858984
3	Outpatient* or out-patient* or stable* or ambulatory* [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	2124504
4	Death or mortality or survival or hospitali* or admission [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	7781925
5	1 & 2 & 3 & 4	16711
6	Limited to – adults, English language, and humans	3872
7	Duplicates removed & only full text articles retained	3167

Appendix table 2 Baseline characteristics according to left ventricular ejection fraction and diabetes status at baseline.

	LVEF category 1 n=1143 (<26%)		LVEF category 2 n=1018 (26% – 30%)		LVEF category 3 n=1187 (31% – 35%)		LVEF category 4 n=1396 (>35%)	
	Without diabetes (n=655)	With diabetes (n=488)	Without diabetes (n=550)	With diabetes (n=468)	Without diabetes (n=660)	With diabetes (n=527)	Without diabetes (n=740)	With diabetes (n=656)
LVEF (%) - mean ± SD	21.3 ± 3.7	21.4 ± 3.6	28.9 ± 1.4	28.7 ± 1.5	33.7 ± 1.4	33.7 ± 1.5	38.4 ± 1.4	38.3 ± 1.4
Placebo	335 (51.1)	266 (54.5)	272 (49.5)	226 (48.3)	341 (51.7)	240 (45.5)	359 (48.5)	332 (50.6)
Dapagliflozin	320 (48.9)	222 (45.5)	278 (50.5)	242 (51.7)	319 (48.3)	287 (54.5)	381 (51.5)	324 (49.4)
Age (years) - mean ± SD	64.0 ± 12.2	64.4 ± 10.0	65.8 ± 11.8	66.2 ± 9.5	66.9 ± 11.3	66.6 ± 9.7	67.9 ± 11.0	68.2 ± 9.9
Women	140 (21.4)	90 (18.4)	130 (23.6)	85 (18.2)	169 (25.6)	108 (20.5)	193 (26.1)	194 (29.6)
Region								
Europe	232 (35.4)	174 (35.7)	224 (40.7)	174 (37.2)	317 (48.0)	239 (45.4)	430 (58.1)	364 (55.5)
Asia/Pacific	178 (27.2)	105 (21.5)	136 (24.7)	126 (26.9)	151 (22.9)	107 (20.3)	152 (20.5)	141 (21.5)
North America	120 (18.3)	121 (24.8)	74 (13.5)	66 (14.1)	83 (12.6)	88 (16.7)	65 (8.8)	60 (9.1)
Latin America	125 (19.1)	88 (18.0)	116 (21.1)	102 (21.8)	109 (16.5)	93 (17.6)	93 (12.6)	91 (13.9)
Race								
White	409 (62.4)	319 (65.4)	383 (69.6)	312 (66.7)	484 (73.3)	373 (70.8)	568 (76.8)	485 (73.9)
Black	52 (7.9)	52 (10.7)	20 (3.6)	23 (4.9)	14 (2.1)	34 (6.5)	12 (1.6)	19 (2.9)
Asian	180 (27.5)	108 (22.1)	139 (25.3)	127 (27.1)	152 (23.0)	111 (21.1)	154 (20.8)	145 (22.1)
Other	14 (2.1)	9 (1.8)	8 (1.5)	6 (1.3)	10 (1.5)	9 (1.7)	6 (0.8)	7 (1.1)
Heart rate (bpm) - mean ± SD	72.0 ± 12.4	73.5 ± 12.4	70.6 ± 11.5	72.6 ± 11.5	70.6 ± 12.3	71.4 ± 10.5	70.3 ± 11.4	71.9 ± 11.0
SBP (mmHg) - mean ± SD	116.0 ± 14.8	117.2 ± 15.5	118.6 ± 15.2	121.6 ± 15.4	121.7 ± 16.4	125.7 ± 16.9	125.2 ± 16.2	127.1 ± 16.3
DBP (mmHg) - mean ± SD	72.0 ± 9.9	71.7 ± 10.4	72.6 ± 10.8	73.4 ± 10.7	73.8 ± 11.1	74.2 ± 10.3	74.7 ± 10.3	75.0 ± 10.0
BMI (kg/m^2) - mean ± SD	26.8 ± 6.1	28.9 ± 6.5	27.2 ± 5.9	28.6 ± 5.5	27.3 ± 5.6	29.7 ± 5.9	27.5 ± 5.3	29.8 ± 6.1

Medical history								
Hypertension	363 (55.4)	357 (73.2)	363 (66.0)	380 (81.2)	472 (71.5)	435 (82.5)	574 (77.6)	579 (88.3)
Myocardial infarction	231 (35.3)	224 (45.9)	242 (44.0)	243 (51.9)	273 (41.4)	265 (50.3)	308 (41.6)	306 (46.6)
Atrial fibrillation	220 (33.6)	164 (33.6)	193 (35.1)	159 (34.0)	274 (41.5)	188 (35.7)	335 (45.3)	285 (43.4)
Stroke	55 (8.4)	48 (9.8)	54 (9.8)	50 (10.7)	52 (7.9)	55 (10.4)	71 (9.6)	81 (12.3)
COPD	73 (11.1)	64 (13.1)	46 (8.4)	65 (13.9)	79 (12.0)	64 (12.1)	109 (14.7)	85 (13.0)
Features of HF								
HF aetiology								
Ischaemic	277 (42.3)	271 (55.5)	283 (51.5)	292 (62.4)	355 (53.8)	348 (66.0)	426 (57.6)	422 (64.3)
Non-Ischaemic	321 (49.0)	172 (35.2)	223 (40.5)	150 (32.1)	248 (37.6)	145 (27.5)	241 (32.6)	187 (28.5)
Unknown	57 (8.7)	45 (9.2)	44 (8.0)	26 (5.6)	57 (8.6)	34 (6.5)	73 (9.9)	47 (7.2)
Prior HF hospitalisation	324 (49.5)	242 (49.6)	297 (54.0)	235 (50.2)	362 (54.8)	277 (52.6)	420 (56.8)	336 (51.2)
KCCQ-TSS - median (IQR)	79 (60-92)	75 (58-93)	79 (61-94)	77 (56-92)	79 (63-94)	76 (56-91)	77 (60-92)	75 (53-92)
NYHA class								
II	449 (68.5)	305 (62.5)	403 (73.3)	309 (66.0)	472 (71.5)	333 (63.2)	517 (69.9)	415 (63.3)
III/IV	206 (31.5)	183 (37.5)	147 (26.7)	159 (34.0)	188 (28.5)	194 (36.8)	223 (30.1)	241 (36.7)
NT-proBNP (pg/ml) - median (IQR)	1744 (987-3229)	1884 (1135-3626)	1525 (869-2636)	1568 (908-3028)	1288 (792-2293)	1355 (807-2468)	1267 (772-2154)	1291 (816-2347)
eGFR (mL/min/1.73 m^2)- mean ± SD	69.2 ± 19.7	64.6 ± 19.8	66.8 ± 19.6	62.4 ± 18.4	67.2 ± 19.3	64.2 ± 19.9	67.6 ± 18.3	62.4 ± 19.2
Creatinine (umol/L) - mean ± SD	101.8 ± 29.6	109.4 ± 31.1	102.3 ± 28.8	111.7 ± 34.2	100.5 ± 26.7	109.1 ± 33.9	98.8 ± 26.9	106.7 ± 31.1
Haemoglobin (g/L) - mean ± SD	137.8 ± 15.5	134.9 ± 16.1	136.9 ± 15.2	134.4 ± 16.9	136.1 ± 15.7	133.5 ± 16.6	136.1 ± 16.3	133.6 ± 16.8
Haemoglobin A1C (%) – mean ± SD	5.8 ± 0.4	7.4 ± 1.5	5.7 ± 0.4	7.4 ± 1.6	5.8 ± 0.4	7.5 ± 1.5	5.8 ± 0.4	7.3 ± 1.6
Treatment								
Diuretic	627 (95.7)	473 (96.9)	514 (93.5)	446 (95.3)	606 (91.8)	492 (93.4)	658 (88.9)	617 (94.1)

ACEI	349 (53.3)	241 (49.4)	315 (57.3)	267 (57.1)	367 (55.6)	288 (54.6)	458 (61.9)	376 (57.3)
ARB	166 (25.3)	117 (24.0)	139 (25.3)	130 (27.8)	176 (26.7)	153 (29.0)	211 (28.5)	215 (32.8)
ARNI	95 (14.5)	93 (19.1)	69 (12.5)	49 (10.5)	77 (11.7)	53 (10.1)	38 (5.1)	34 (5.2)
Beta-blocker	632 (96.5)	468 (95.9)	528 (96.0)	451 (96.4)	633 (95.9)	513 (97.3)	698 (94.3)	635 (96.8)
MRA	490 (74.8)	365 (74.8)	411 (74.7)	344 (73.5)	460 (69.7)	381 (72.3)	480 (64.9)	439 (66.9)
Digoxin	135 (20.6)	130 (26.6)	109 (19.8)	98 (20.9)	97 (14.7)	96 (18.2)	117 (15.8)	105 (16.0)
Ivabradine	26 (4.0)	40 (8.2)	18 (3.3)	33 (7.1)	34 (5.2)	27 (5.1)	31 (4.2)	19 (2.9)
PCI	166 (25.3)	180 (36.9)	174 (31.6)	200 (42.7)	201 (30.5)	203 (38.5)	243 (32.8)	257 (39.2)
CABG	73 (11.1)	105 (21.5)	79 (14.4)	98 (20.9)	91 (13.8)	106 (20.1)	130 (17.6)	117 (17.8)
CRT	67 (10.2)	49 (10.0)	50 (9.1)	36 (7.7)	51 (7.7)	39 (7.4)	35 (4.7)	27 (4.1)
ICD	187 (28.5)	171 (35.0)	134 (24.4)	116 (24.8)	117 (17.7)	99 (18.8)	65 (8.8)	64 (9.8)
Diabetes medications*								
Biguanide	2 (0.3)	230 (47.1)	1 (0.2)	222 (47.4)	3 (0.5)	262 (49.7)	4 (0.5)	306 (46.6)
DPP-4 inhibitor	-	68 (13.9)	-	67 (14.3)	-	76 (14.4)	-	99 (15.1)
GLP-1 analogues	-	7 (1.4)	-	5 (1.1)	-	4 (0.8)	-	5 (0.8)
Sulfonylurea	-	93 (19.1)	-	106 (22.6)	-	108 (20.5)	-	133 (20.3)
Insulin	-	112 (23.0)	-	122 (26.1)	-	144 (27.3)	-	162 (24.7)

All values are shown as number (%) unless otherwise indicated. SD – standard deviation, SBP systolic blood pressure, DBP – diastolic blood pressure, BMI – body mass index, COPD – chronic obstructive pulmonary disease, HF – heart failure, KCCQ-TSS – Kansas City Cardiomyopathy Questionnaire total symptom score, NYHA – New York heart association, LVEF – left ventricular ejection fraction, NT-proBNP – N terminal pro brain natriuretic peptide, IQR – interquartile range, eGFR – estimated glomerular filtration rate, ACEI – angiotensin converting enzyme inhibitor, ARB – angiotensin-receptor blocker, ARNI – angiotensin receptor neprilysin inhibitor, MRA – mineralocorticoid receptor antagonist, PCI – primary coronary intervention, CABG – coronary artery bypass graft, CRT – cardiac resynchronization therapy, ICD – implantable cardioverter-defibrillator, DPP - Dipeptidyl peptidase, GLP - glucagon-like peptide.

Appendix table 3 Clinical outcomes according to left ventricular ejection fraction and diabetes status at baseline.

	Overall *n=4744*		**LVEF category 1** n=1143 (<26%)		**LVEF category 2** n=1018 (26% – 30%)		**LVEF category 3** n=1187 (31% – 35%)		**LVEF category 4** n=1396 (>35%)	
	Placebo (n=2371)	*Dapagliflozin (n=2373)*	Placebo (n=601)	Dapagliflozin (n=542)	Placebo (n=498)	Dapagliflozin (n=520)	Placebo (n=581)	Dapagliflozin (n=606)	Placebo (n=691)	Dapagliflozin (n=705)
Primary composite outcome										
Without diabetes										
Events/Total pts.	*231/1307*	*171/1298*	72/335	54/320	54/272	36/278	57/341	36/319	48/359	45/381
Event rates	*12.8 (11.3-14.6)*	*9.3 (8.0 – 10.8)*	16.1 (12.8-20.3)	12.4 (9.5 – 16.2)	14.6 (11.2-19.0)	9.1 (6.6 – 12.7)	12.0 (9.3 – 15.6)	8.0 (5.8 – 11.1)	9.5 (7.1 – 12.6)	8.1 (6.1 – 10.9)
Hazard ratios	*0.73 (0.60 – 0.88)*		0.78 (0.54 – 1.10)		0.62 (0.41 – 0.95)		0.66 (0.44 – 1.01)		0.86 (0.57 – 1.29)	
With diabetes										
Events/Total pts.	*271/1064*	*215/1075*	89/266	56/222	60/226	58/242	56/240	48/287	66/332	53/324
Event rates	*19.6 (17.4-22.1)*	*14.8 (12.9-16.9)*	26.8 (21.8-33.0)	19.6 (15.1-25.4)	21.1 (16.4-27.2)	18.2(14.1-23.6)	18.0(13.8-23.3)	12.2 (9.2 – 16.2)	14.6 (11.5-18.6)	11.6 (8.9 – 15.2)
Hazard ratios	*0.75 (0.63 – 0.90)*		0.72 (0.51 – 1.01)		0.86 (0.60 – 1.23)		0.68 (0.46 – 1.00)		0.80 (0.56 – 1.14)	
Cardiovascular death										
Without diabetes										
Events/Total pts.	*125/1307*	*106/1298*	42/335	35/320	32/272	23/278	27/341	22/319	24/359	26/381
Event rates	*6.6 (5.5 – 7.8)*	*5.6 (4.6 – 6.8)*	8.8 (6.5 – 11.9)	7.7 (5.5 – 10.7)	8.2 (5.8 – 11.6)	5.7 (3.8 – 8.6)	5.4 (3.7 – 7.8)	4.8 (3.1 – 7.2)	4.5 (3.0 – 6.8)	4.5 (3.1 – 6.7)
Hazard ratios	*0.85 (0.66 – 1.10)*		0.88 (0.56 – 1.38)		0.70 (0.41 – 1.19)		0.89 (0.50 – 1.55)		1.01 (0.58 – 1.75)	
With diabetes										
Events/Total pts.	*148/1064*	*121/1075*	51/266	34/222	29/226	34/242	32/240	27/287	36/332	26/324
Event rates	*9.9 (8.4 – 11.6)*	*7.8 (6.6 – 9.4)*	13.9 (10.6-18.3)	11.0 (7.8 – 15.4)	9.2 (6.4 – 13.3)	10.0 (7.2 – 14.1)	9.5 (6.7 – 13.4)	6.5 (4.5 – 9.5)	7.5 (5.4 – 10.3)	5.4 (3.7 – 7.9)

Hazard ratios	*0.79 (0.63 – 1.01)*		0.79 (0.51 – 1.22)		1.09 (0.66 – 1.78)		0.69 (0.41 – 1.15)		0.73 (0.44 – 1.21)	
HF hospitalisation/ urgent visit										
Without diabetes										
Events/Total pts.	*150/1307*	*95/1298*	44/335	29/320	38/272	16/278	41/341	21/319	27/359	29/381
Event rates	*8.3 (7.1 – 9.8)*	*5.2 (4.2 – 6.3)*	9.8 (7.3 – 13.2)	6.7 (4.6 – 9.6)	10.3 (7.5 – 14.1)	4.1 (2.5 – 6.6)	8.6 (6.4 – 11.7)	4.7 (3.0 – 7.1)	5.3 (3.7 – 7.8)	5.2 (3.6 – 7.5)
Hazard ratios	*0.62 (0.48 – 0.80)*		0.67 (0.42 – 1.08)		0.39 (0.22 – 0.70)		0.54 (0.32 – 0.91)		0.99 (0.58 – 1.67)	
With diabetes										
Events/Total pts.	*176/1064*	*142/1075*	60/266	41/222	42/226	35/242	35/240	30/287	39/332	36/324
Event rates	*12.8 (11.0-14.8)*	*9.8 (8.3 – 11.5)*	18.1 (14.1-23.3)	14.3 (10.6-19.5)	14.8 (10.9-20.0)	11.0 (7.9 - 15.3)	11.2 (8.1 - 15.6)	7.6 (5.3 – 10.9)	8.6 (6.3 – 11.8)	7.9 (5.7 – 10.9)
Hazard ratios	*0.77 (0.61 – 0.95)*		0.78 (0.52 – 1.16)		0.74 (0.47 – 1.15)		0.68 (0.42 – 1.11)		0.91 (0.58 – 1.44)	
Total HF hospitalisation/cardiovascular death										
Without diabetes										
Events/Total pts.	*327*	*239*	105	80	83	44	77	51	62	64
Event rates	*17.3 (15.5-19.3)*	*12.7 (11.2-14.4)*	22.2 (18.3-26.8)	17.7 (14.2-22.0)	21.3 (17.2-26.4)	10.9 (8.1 - 14.6)	15.4(12.3-19.2)	11.1 (8.4 - 14.6)	11.7 (9.2-15.1)	11.2 (8.8-14.3)
Hazard ratios	*0.73 (0.59 – 0.91)*		0.80 (0.54 – 1.19)		0.51 (0.32 – 0.81)		0.72 (0.45 – 1.15)		0.95 (0.61 – 1.48)	
With diabetes										
Events/Total pts.	*415*	*328*	145	95	95	86	83	74	92	73
Event rates	*27.7 (25.2-30.5)*	*21.3 (19.1-23.7)*	39.8 (33.8-46.8)	30.7 (25.1-37.5)	30.2 (24.7-36.9)	25.5(20.6-31.5)	24.6(19.9-30.5)	17.9(14.3-22.5)	19.1 (15.6-23.5)	15.2 (12.1-19.1)
Hazard ratios	*0.77 (0.63 – 0.94)*		0.77 (0.53 – 1.12)		0.83 (0.57 – 1.22)		0.73 (0.47 – 1.12)		0.80 (0.53 – 1.20)	
Mean change in KCCQ-TSS ± SD at 8 months										
Without diabetes	*3.1 ± 17.9*	*5.4 ± 17.7*	2.4 ± 18.2	5.4 ± 19.2	3.2 ± 17.1	5.3 ± 18.5	3.0 ± 19.1	5.7 ± 15.8	3.9 ± 17.0	5.1 ± 17.4

Between treatment difference*	2.2 (0.7 – 3.7)		3.1 (-0.1 – 6.3)		2.1 (-1.2 – 5.4)		2.7 (-0.2 – 5.7)		1.2 (-1.6 – 3.9)	
With diabetes	*3.5 ± 20.8*	*7.0 ± 19.7*	4.2 ± 21.3	7.1 ± 20.6	0.6 ± 20.5	6.7 ± 19.6	3.7 ± 20.5	7.1 ± 19.0	4.8 ± 20.6	7.1 ± 19.9
Between treatment difference*	3.5 (1.6 – 5.4)		2.8 (-1.3 – 7.0)		6.1 (2.0 – 10.1)		3.4 (-0.3 – 7.1)		2.3 (-1.1 – 5.7)	
Proportion with increase in KCCQ-TSS ≥5 at 8 months										
Without diabetes	*51.7*	*57.7*	46.7	57.3	56.6	60.5	51.4	59.2	53.1	54.8
With diabetes	*49.9*	*58.9*	49.9	58.0	45.8	56.9	51.1	61.2	51.9	59.2
Proportion with decrease in KCCQ-TSS ≥5 at 8 months										
Without diabetes	*31.3*	*26.0*	36.7	30.3	28.8	24.6	32.2	20.9	27.4	27.7
With diabetes	*34.8*	*24.5*	33.6	27.3	41.4	25.2	33.8	23.6	32.0	22.9
All-cause death										
Without diabetes										
Events/Total pts.	*151/1307*	*133/1298*	47/335	41/320	36/272	27/278	34/341	28/319	34/359	37/381
Event rates	*7.9 (6.8 – 9.3)*	*7.0 (5.9 – 8.3)*	9.8 (7.4 – 13.1)	9.0 (6.6 – 12.3)	9.2 (6.7 – 12.8)	6.7 (4.6 – 9.7)	6.8 (4.8 – 9.5)	6.1 (4.2 – 8.8)	6.4 (4.6 – 9.0)	6.4 (4.7 – 8.9)
Hazard ratios	*0.88 (0.70 – 1.12)*		0.92 (0.61 – 1.40)		0.72 (0.44 – 1.19)		0.89 (0.54 – 1.47)		1.01 (0.63 – 1.61)	
With diabetes										
Events/Total pts.	*178/1064*	*143/1075*	53/266	36/222	36/226	41/242	41/240	31/287	48/332	35/324
Event rates	*11.8 (10.2-13.7)*	*9.2 (7.8 – 10.9)*	14.4 (11.0-18.9)	11.6 (8.4 - 16.1)	11.4 (8.3 - 15.9)	12.1 (8.9 - 16.4)	12.2 (9.0 - 16.5)	7.5 (5.3 – 10.6)	9.9 (7.5 – 13.2)	7.2 (5.2 – 10.1)
Hazard ratios	*0.78 (0.63 – 0.97)*		0.80 (0.53 – 1.23)		1.06 (0.68 – 1.66)		0.61 (0.39 – 0.98)		0.73 (0.47 – 1.13)	

Hazard ratio represents comparison of dapagliflozin against placebo with 95% confidence interval in ().
Hazard ratios adjusted for previous heart failure hospitalisation at baseline (except all-cause death) and stratified by diabetes status.
*Expressed as difference with 95% confidence interval in () in dapagliflozin compared to placebo.
KCCQ-TSS – Kansas City Cardiomyopathy Questionnaire total symptom score.

Appendix table 4 Safety outcomes according to left ventricular ejection fraction and diabetes status at baseline.*

	Overall n=4744		LVEF category 1 n=1143 (<26%)		LVEF category 2 n=1018 (26% - 30%)		LVEF category 3 n=1187 (31% - 35%)		LVEF category 4 n=1396 (>35%)	
	Placebo	*Dapagliflozin*	Placebo	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Dapagliflozin
Any discontinuation										
Without diabetes	*141 (10.8)*	*144 (11.1)*	30 (9.0)	39 (12.2)	32 (11.8)	35 (12.6)	40 (11.7)	32 (10.0)	39 (10.9)	38 (10.0)
With diabetes	*117 (11.0)*	*105 (9.8)*	35 (13.2)	27 (12.2)	25 (11.1)	27 (11.2)	31 (12.9)	28 (9.8)	26 (7.8)	23 (7.1)
Discontinuation due to AE										
Without diabetes	*59 (4.5)*	*68 (5.3)*	13 (3.9)	20 (6.3)	7 (2.6)	17 (6.1)	17 (5.0)	15 (4.7)	22 (6.1)	16 (4.2)
With diabetes	*57 (5.4)*	*43 (4.0)*	17 (6.4)	11 (5.0)	12 (5.3)	9 (3.7)	16 (6.7)	12 (4.2)	12 (3.6)	11 (3.4)
Volume depletion										
Without diabetes	*79 (6.1)*	*94 (7.3)*	21 (6.3)	34 (10.7)	23 (8.5)	17 (6.1)	16 (4.7)	18 (5.6)	19 (5.3)	25 (6.6)
With diabetes	*83 (7.8)*	*84 (7.8)*	28 (10.5)	20 (9.0)	19 (8.4)	20 (8.3)	13 (5.4)	21 (7.3)	23 (6.9)	23 (7.1)
Renal										
Without diabetes	*78 (6.0)*	*62 (4.8)*	21 (6.3)	18 (5.6)	17 (6.3)	11 (4.0)	22 (6.5)	15 (4.7)	18 (5.0)	18 (4.7)
With diabetes	*92 (8.7)*	*91 (8.5)*	26 (9.8)	21 (9.5)	20 (8.8)	22 (9.1)	23 (9.6)	22 (7.7)	23 (6.9)	26 (8.0)
Fracture										
Without diabetes	*25 (1.9)*	*27 (2.1)*	7 (2.1)	3 (0.9)	5 (1.8)	12 (4.3)	6 (1.8)	7 (2.2)	7 (1.9)	5 (1.3)
With diabetes	*25 (2.4)*	*22 (2.1)*	6 (2.3)	6 (2.7)	7 (3.1)	2 (0.8)	5 (2.1)	4 (1.4)	7 (2.1)	10 (3.1)
Amputation										

Without diabetes	*3 (0.2)*	*1 (0.1)*	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
With diabetes	*9 (0.8)*	*12 (1.1)*	3 (1.1)	1 (0.5)	0 (0.0)	3 (1.2)	2 (0.8)	6 (2.1)	4 (1.2)	2 (0.6)
Major hypoglycaemic episode										
Without diabetes	*0 (0.0)*	*0 (0.0)*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
With diabetes	*4 (0.4)*	*4 (0.4)*	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	4 (1.2)	3 (0.9)

*Only in safety analysis set except any discontinuation (4744 patients).

Appendix table 5 Baseline characteristics according to left ventricular ejection fraction and randomisation arm

	LVEF category 1 n=1143 (<26%)		LVEF category 2 n=1018 (26% - 30%)		LVEF category 3 n=1187 (31% - 35%)		LVEF category 4 n=1396 (>35%)	
	Placebo (n=601)	Dapagliflozin (n=542)	Placebo (n=498)	Dapagliflozin (n=520)	Placebo (n=581)	Dapagliflozin (n=606)	Placebo (n=691)	Dapagliflozin (n=705)
LVEF (%) - mean ± SD	21.4 ± 3.8	21.4 ± 3.6	28.8 ± 1.4	28.8 ± 1.4	33.8 ± 1.4	33.6 ± 1.5	38.4 ± 1.4	38.4 ± 1.4
Age (years) - mean ± SD	64.1 ± 11.5	64.2 ± 11.1	66.3 ± 10.3	65.7 ± 11.2	67.5 ± 10.6	66.1 ± 10.6	68.0 ± 10.3	68.1 ± 10.7
Women	124 (20.6)	106 (19.6)	103 (20.7)	112 (21.5)	144 (24.8)	133 (21.9)	174 (25.2)	213 (30.2)
Region								
Europe	214 (35.6)	192 (35.4)	192 (38.6)	206 (39.6)	265 (45.6)	291 (48.0)	389 (56.3)	405 (57.4)
Asia/Pacific	152 (25.3)	131 (24.2)	127 (25.5)	135 (26.0)	124 (21.3)	134 (22.1)	150 (21.7)	143 (20.3)
North America	119 (19.8)	122 (22.5)	74 (14.9)	66 (12.7)	90 (15.5)	81 (13.4)	59 (8.5)	66 (9.4)
Latin America	116 (19.3)	97 (17.9)	105 (21.1)	113 (21.7)	102 (17.6)	100 (16.5)	93 (13.5)	91 (12.9)
Race								
White	391 (65.1)	337 (62.2)	343 (68.9)	352 (67.7)	419 (72.1)	438 (72.3)	518 (75.0)	535 (75.9)
Black	49 (8.2)	55 (10.1)	18 (3.6)	25 (4.8)	24 (4.1)	24 (4.0)	13 (1.9)	18 (2.6)
Asian	152 (25.3)	136 (25.1)	130 (26.1)	136 (26.2)	127 (21.9)	136 (22.4)	155 (22.4)	144 (20.4)
Other	9 (1.5)	14 (2.6)	7 (1.4)	7 (1.3)	11 (1.9)	8 (1.3)	5 (0.7)	8 (1.1)
Heart rate (bpm) - mean ± SD	72.9 ± 12.3	72.4 ± 12.6	71.7 ± 11.8	71.4 ± 11.4	70.5 ± 11.6	71.3 ± 11.4	71.1 ± 11.3	71.0 ± 11.3
SBP (mmHg) - mean ± SD	116.3 ± 15.2	116.8 ± 15.0	119.9 ± 15.9	120.1 ± 14.8	123.6 ± 16.5	123.3 ± 17.0	125.7 ± 16.1	126.4 ± 16.4
DBP (mmHg) - mean ± SD	71.8 ± 10.1	71.9 ± 10.1	72.9 ± 11.2	73.0 ± 10.2	73.4 ± 10.5	74.6 ± 10.9	74.9 ± 10.1	74.8 ± 10.2
BMI (kg/m^2) - mean ± SD	27.8 ± 6.4	27.5 ± 6.4	27.8 ± 5.7	27.9 ± 5.9	28.3 ± 5.9	28.4 ± 5.9	28.5 ± 5.8	28.7 ± 5.7
Medical history								

Hypertension	377 (62.7)	343 (63.3)	375 (75.3)	368 (70.8)	446 (76.8)	461 (76.1)	563 (81.5)	590 (83.7)
Diabetes	253 (42.1)	200 (36.9)	206 (41.4)	226 (43.5)	218 (37.5)	267 (44.1)	313 (45.3)	300 (42.6)
MI	241 (40.1)	214 (39.5)	245 (49.2)	240 (46.2)	272 (46.8)	266 (43.9)	307 (44.4)	307 (43.6)
Atrial Fibrillation	188 (31.3)	196 (36.2)	182 (36.5)	170 (32.7)	227 (39.1)	235 (38.8)	305 (44.1)	315 (44.7)
Stroke	66 (11.0)	37 (6.8)	44 (8.8)	60 (11.5)	58 (10.0)	49 (8.1)	72 (10.4)	80 (11.4)
COPD	66 (11.0)	71 (13.1)	59 (11.9)	52 (10.0)	66 (11.4)	77 (12.7)	95 (13.8)	99 (14.0)
Features of HF								
HF aetiology								
Ischaemic	300 (49.9)	248 (45.8%)	286 (57.4%)	289 (55.6%)	356 (61.3%)	347 (57.3%)	416 (60.2%)	432 (61.3%)
Non-Ischaemic	254 (42.3)	239 (44.1%)	179 (35.9%)	194 (37.3%)	189 (32.5%)	204 (33.7%)	208 (30.1%)	220 (31.2%)
Unknown	47 (7.8)	55 (10.1%)	33 (6.6%)	37 (7.1%)	36 (6.2%)	55 (9.1%)	67 (9.7%)	53 (7.5%)
Prior HF hospitalisation	300 (49.9)	277 (51.1%)	236 (47.4%)	250 (48.1%)	270 (46.5%)	278 (45.9%)	321 (46.5%)	319 (45.2%)
NYHA class								
II	394 (65.6)	360 (66.4%)	342 (68.7%)	370 (71.2%)	383 (65.9%)	422 (69.6%)	478 (69.2%)	454 (64.4%)
III/IV	207 (34.4)	182 (33.6%)	156 (31.3%)	150 (28.8%)	198 (34.1%)	184 (30.4%)	213 (30.8%)	251 (35.6%)
KCCQ-TSS - median (IQR)	77 (59, 92)	78 (59, 94)	80 (61, 94)	78 (56, 92)	79 (60, 94)	79 (58, 92)	76 (58, 92)	75 (57, 92)
NT-proBNP (pg/ml) - median (IQR)	1722 (1028, 3229)	1919 (1095, 3512)	1681 (890, 2913)	1435 (878, 2746)	1311 (795, 2320)	1318 (799, 2379)	1304 (791, 2267)	1263 (790, 2186)
eGFR (mL/min/1.73 m^2)- mean ± SD	67.1 ± 20.5	67.5 ± 19.1	63.9 ± 18.2	65.7 ± 20.0	65.4 ± 18.9	66.4 ± 20.4	65.6 ± 19.1	64.8 ± 18.8
Creatinine (umol/L) - mean ± SD	106.1 ± 32.1	103.9 ± 28.6	108.1 ± 32.4	105.2 ± 31.0	103.8 ± 29.3	104.8 ± 31.4	102.5 ± 30.4	102.5 ± 28.1
Haemoglobin (g/L) - mean ± SD	136.9 ± 16.0	136.3 ± 15.7	135.9 ± 15.3	135.5 ± 16.7	135.1 ± 15.7	134.8 ± 16.6	135.1 ± 16.3	134.8 ± 16.8
Treatment								

Diuretics	578 (96.2)	522 (96.3)	468 (94.0)	492 (94.6)	536 (92.3)	562 (92.7)	635 (91.9)	640 (90.8)
ACEI	312 (51.9)	278 (51.3)	273 (54.8)	309 (59.4)	320 (55.1)	335 (55.3)	424 (61.4)	410 (58.2)
ARB	140 (23.3)	143 (26.4)	134 (26.9)	135 (26.0)	160 (27.5)	169 (27.9)	198 (28.7)	228 (32.3)
ARNI	95 (15.8)	93 (17.2)	63 (12.7)	55 (10.6)	67 (11.5)	63 (10.4)	33 (4.8)	39 (5.5)
Beta-blockers	575 (95.7)	525 (96.9)	482 (96.8)	497 (95.6)	560 (96.4)	586 (96.7)	663 (95.9)	670 (95.0)
MRAs	441 (73.4)	414 (76.4)	379 (76.1)	376 (72.3)	398 (68.5)	443 (73.1)	456 (66.0)	463 (65.7)
Digoxin	136 (22.6)	129 (23.8)	105 (21.1)	102 (19.6)	87 (15.0)	106 (17.5)	114 (16.5)	108 (15.3)
Ivabradine	32 (5.3)	34 (6.3)	29 (5.8)	22 (4.2)	27 (4.6)	34 (5.6)	21 (3.0)	29 (4.1)
PCI	181 (30.1)	165 (30.4)	187 (37.6)	187 (36.0)	200 (34.4)	204 (33.7)	254 (36.8)	246 (34.9)
CABG	101 (16.8)	77 (14.2)	83 (16.7)	94 (18.1)	105 (18.1)	92 (15.2)	126 (18.2)	121 (17.2)
CRT	55 (9.2)	61 (11.3)	45 (9.0)	41 (7.9)	34 (5.9)	56 (9.2)	30 (4.3)	32 (4.5)
ICD	187 (31.1)	171 (31.5)	128 (25.7)	122 (23.5)	110 (18.9)	106 (17.5)	61 (8.8)	68 (9.6)
Diabetes medications*								
Biguanides	133 (52.6)	97 (48.5)	107 (51.9)	114 (50.4)	118 (54.1)	143 (53.6)	154 (49.2)	150 (50.0)
DPP-4 inhibitors	36 (14.2)	32 (16.0)	34 (16.5)	33 (14.6)	32 (14.7)	44 (16.5)	47 (15.0)	52 (17.3)
GLP-1 analogues	3 (1.2)	4 (2.0)	2 (1.0)	3 (1.3)	2 (0.9)	2 (0.8)	3 (1.0)	2 (0.7)
Sulfonylurea	49 (19.4)	44 (22.0)	50 (24.3)	55 (24.3)	43 (19.7)	64 (24.0)	68 (21.7)	65 (21.7)
Insulin	65 (25.7)	47 (23.5)	60 (29.1)	62 (27.4)	57 (26.2)	87 (32.6)	84 (26.8)	78 (26.0)

All values are shown as number (%) unless otherwise indicated.
SD – standard deviation, SBP systolic blood pressure, DBP – diastolic blood pressure, BMI – body mass index, MI – myocardial infarction, COPD – chronic obstructive pulmonary disease, HF – heart failure, KCCQ-TSS – Kansas City Cardiomyopathy Questionnaire total symptom score, NYHA – New York heart association, LVEF – left ventricular ejection fraction, NT-proBNP – N terminal pro brain natriuretic peptide, IQR – interquartile range, eGFR – estimated glomerular filtration rate, ACEI – angiotensin-converting enzyme inhibitor, ARB – angiotensin receptor blocker, ARNI – angiotensin receptor neprilysin inhibitor, MRA – mineralocorticoid receptor antagonist, PCI – primary coronary intervention, CABG – coronary artery bypass graft, CRT – cardiac resynchronization therapy, ICD – implantable cardioverter-defibrillator, DPP - Dipeptidyl peptidase, GLP - glucagon-like peptide.
*Only in patients with a medical history of diabetes (1983)

Appendix table 6 Baseline characteristics by treatment and chronic obstructive pulmonary disease (COPD) status

	Without COPD		With COPD	
	Placebo (N=2085)	Dapagliflozin (N=2074)	Placebo (N=286)	Dapagliflozin (N=299)
Age (years)	66.1 ± 10.9	65.8 ± 11.1	69.2 ± 9.5	69.0 ± 9.4
Female sex	492 (23.6)	510 (24.6)	53 (18.5)	54 (18.1)
Region				
Asia/Pacific	511 (24.5)	499 (24.1)	42 (14.7)	44 (14.7)
Europe	916 (43.9)	942 (45.4)	144 (50.3)	152 (50.8)
North America	275 (13.2)	266 (12.8)	67 (23.4)	69 (23.1)
South America	383 (18.4)	367 (17.7)	33 (11.5)	34 (11.4)
Race				
White	1442 (69.2)	1422 (68.6)	229 (80.1)	240 (80.3)
Black	92 (4.4)	110 (5.3)	12 (4.2)	12 (4.0)
Asian	521 (25.0)	507 (24.4)	43 (15.0)	45 (15.1)
Other	30 (1.4)	35 (1.7)	2 (0.7)	2 (0.7)
HR (bpm)	71.4 ± 11.8	71.4 ± 11.7	72.1 ± 11.6	72.0 ± 11.2
SBP (mmHg)	121.3 ± 16.2	121.8 ± 16.4	124.0 ± 17.4	123.7 ± 15.8
DBP (mmHg)	73.4 ± 10.5	73.7 ± 10.5	73.0 ± 10.2	73.3 ± 10.2
BMI (kg/m2)	28.1 ± 5.9	28.1 ± 5.9	28.2 ± 6.6	28.4 ± 6.3
Hypertension	1532 (73.5)	1517 (73.1)	229 (80.1)	245 (81.9)
Diabetes	934 (44.8)	927 (44.7)	130 (45.5)	148 (49.5)
Myocardial infarction	933 (44.7)	892 (43.0)	132 (46.2)	135 (45.2)
Atrial fibrillation	779 (37.4)	778 (37.5)	123 (43.0)	138 (46.2)
Stroke	212 (10.2)	193 (9.3)	28 (9.8)	33 (11.0)
HF aetiology				
Ischaemic	1185 (56.8)	1146 (55.3)	173 (60.5)	170 (56.9)
Non-Ischaemic	742 (35.6)	747 (36.0)	88 (30.8)	110 (36.8)
Unknown	158 (7.6)	181 (8.7)	25 (8.7)	19 (6.4)
Previous HF hospitalisation	975 (46.8)	976 (47.1)	152 (53.1)	148 (49.5)
KCCQ-TSS	79 (61 - 94)	79 (59 - 93)	70 (54 - 84)	71 (51 - 88)
NYHA III/IV	651 (31.2)	641 (30.9)	123 (43.0)	126 (42.1)
LVEF (%)	30.8 ± 6.9	31.2 ± 6.7	31.7 ± 6.5	31.5 ± 7.0
NT-proBNP (pg/ml)	1430 (846 - 2615)	1409 (859 - 2616)	1579 (931 - 2765)	1562 (850 - 2841)
No AFib	1241 (737 - 2257)	1229 (742 - 2311)	1423 (857 - 2776)	1526 (768 - 2885)
With AFib	1809 (1114 - 3229)	1784 (1113 - 2984)	1837 (1136 - 2765)	1587 (1006 - 2787)
eGFR (ml/min/1.73m^2)	65.9 ± 19.2	66.3 ± 19.5	62.7 ± 19.2	64.0 ± 19.6
eGFR<60	829 (39.8)	823 (39.7)	135 (47.2)	139 (46.6)

Creatinine (µmol/l)	104.3 ± 30.4	103.7 ± 29.7	109.2 ± 35.3	106.1 ± 30.2
Haemoglobin (g/l)	135.6 ± 15.9	135.3 ± 16.4	136.6 ± 15.8	135.1 ± 16.9
Potassium(nmol/l)	4.5 ± 0.5	4.5 ± 0.5	4.6 ± 0.6	4.5 ± 0.5
Diuretics	1950 (93.5)	1935 (93.3)	267 (93.4)	281 (94.0)
ACEI	1170 (56.1)	1170 (56.4)	159 (55.6)	162 (54.2)
ARB	563 (27.0)	598 (28.8)	69 (24.1)	77 (25.8)
ARNI	225 (10.8)	212 (10.2)	33 (11.5)	38 (12.7)
Beta-blocker	2016 (96.7)	2002 (96.5)	264 (92.3)	276 (92.3)
≥50 % of target dose	1030 (51.1)	1036 (51.7)	140 (53.0)	143 (51.8)
Beta-1 selective*	1203 (57.8)	1215 (58.6)	177 (61.9)	174 (58.2)
Non-selective*	806 (38.7)	781 (37.7)	86 (30.1)	102 (34.1)
MRAs	1494 (71.7)	1493 (72.0)	180 (62.9)	203 (67.9)
Digoxin	394 (18.9)	392 (18.9)	48 (16.8)	53 (17.7)
Ivabradine	96 (4.6)	107 (5.2)	13 (4.5)	12 (4.0)
PCI	713 (34.2)	702 (33.8)	109 (38.1)	100 (33.4)
CABG	352 (16.9)	335 (16.2)	63 (22.0)	49 (16.4)
CRT	141 (6.8)	164 (7.9)	23 (8.0)	26 (8.7)
ICD	425 (20.4)	405 (19.5)	61 (21.3)	62 (20.7)
Respiratory system drugs				
Adrenergic agonists †	30 (1.4)	43 (2.1)	77 (26.9)	68 (22.7)
Adrenergic agonists (in combinations) † ‡	26 (1.2)	29 (1.4)	67 (23.4)	52 (17.4)
Any inhaled adrenergic agonist †	50 (2.4)	66 (3.2)	118 (41.3)	95 (31.8)
Muscarinic antagonists †	14 (0.7)	20 (1.0)	78 (27.3)	60 (20.1)
Glucocorticoids†	17 (0.8)	28 (1.4)	37 (12.9)	34 (11.4)
Systemic adrenergic agonists	1 (0.0)	0 (0.0)	5 (1.7)	4 (1.3)
Other drugs	3 (0.1)	1 (0.1)	21 (7.3)	10 (3.3)
Diabetes medications§				
Biguanides	454 (51.7)	436 (50.8)	58 (51.8)	68 (50.7)
DPP-4 inhibitors	135 (15.4)	146 (17.0)	14 (12.5)	15 (11.2)
GLP-1 analogues	9 (1.0)	7 (0.8)	1 (0.9)	4 (3.0)
Sulfonylureas	186 (21.2)	194 (22.6)	24 (21.4)	34 (25.4)
Insulin	229 (26.1)	242 (28.2)	37 (33.0)	32 (23.9)

Data are presented as mean ± SD or median (IQR) for continuous measures and n (%) for categorical measures.
HR – heart rate bpm – beats per minute SBP – systolic blood pressure BMI – body mass index HF – heart failure KCCQ-TSS – Kansas City Cardiomyopathy Questionnaire total symptom score NYHA – New York heart association classification NT-proBNP – N terminal pro B-type natriuretic peptide eGFR – estimated glomerular filtration rate ACEI – angiotensin-converting enzyme inhibitor ARB – angiotensin receptor blocker ARNI – angiotensin receptor blocker-neprilysin inhibitor PCI – primary coronary intervention CABG – coronary bypass surgery CRT – cardiac resynchronization therapy ICD – implantable cardioverter-defibrillator.
*4 patients excluded
†Inhaled.
‡ In combination with corticosteroids /antimuscarinics/ other drugs.
§Only in patients with a medical history of diabetes (1983)

Appendix table 7 Baseline characteristics by asthma status

	Total (N=4744)	Without asthma (N=4555)	With asthma (N=189)	p-value
Age (years)	66.3 ± 10.9	66.3 ± 10.9	67.9 ± 10.0	0.046
Female sex	1109 (23.4)	1043 (22.9)	66 (34.9)	<0.001
Region				<0.001
Asia/Pacific	1096 (23.1)	1056 (23.2)	40 (21.2)	
Europe	2154 (45.4)	2074 (45.5)	80 (42.3)	
North America	677 (14.3)	629 (13.8)	48 (25.4)	
South America	817 (17.2)	796 (17.5)	21 (11.1)	
Race				0.007
White	3333 (70.3)	3207 (70.4)	126 (66.7)	
Black	226 (4.8)	209 (4.6)	17 (9.0)	
Asian	1116 (23.5)	1076 (23.6)	40 (21.2)	
Other	69 (1.5)	63 (1.4)	6 (3.2)	
HR (bpm)	71.5 ± 11.7	71.4 ± 11.6	73.3 ± 12.7	0.033
SBP (mmHg)	121.8 ± 16.3	121.9 ± 16.3	120.3 ± 15.7	0.20
DBP (mmHg)	73.5 ± 10.5	73.6 ± 10.5	71.7 ± 9.6	0.016
BMI (kg/m^2)	28.2 ± 6.0	28.1 ± 5.9	30.0 ± 7.6	<0.001
Hypertension	3523 (74.3)	3381 (74.2)	142 (75.1)	0.78
Diabetes	2139 (45.1)	2048 (45.0)	91 (48.1)	0.39
Myocardial infarction	2092 (44.1)	2028 (44.5)	64 (33.9)	0.004
Atrial fibrillation	1818 (38.3)	1739 (38.2)	79 (41.8)	0.32
Stroke	466 (9.8)	449 (9.9)	17 (9.0)	0.70
HF aetiology				<0.001
Ischaemic	2674 (56.4)	2596 (57.0)	78 (41.3)	
Non-Ischaemic	1687 (35.6)	1596 (35.0)	91 (48.1)	
Unknown	383 (8.1)	363 (8.0)	20 (10.6)	
Previous HF hospitalisation	2251 (47.4)	2164 (47.5)	87 (46.0)	0.69
Smoking Status				0.25
Never	1959 (41.3)	1870 (41.1)	89 (47.1)	
Former	2092 (44.1)	2016 (44.3)	76 (40.2)	
Current	693 (14.6)	669 (14.7)	24 (12.7)	
KCCQ-TSS	77 (58 - 92)	78 (58 - 92)	73 (54 - 88)	0.029
NYHA III/IV	1541 (32.5)	1476 (32.4)	65 (34.4)	0.57
LVEF (%)	31.1 ± 6.8	31.1 ± 6.8	30.1 ± 6.8	0.044
NT-proBNP (pg/ml)	1437.4 (856.8 - 2649.6)	1434.0 (854.0 - 2641.1)	1504.3 (981.0 - 2900.1)	0.42

eGFR (ml/min/1.73m2)	65.8 ± 19.4	66.0 ± 19.4	61.3 ± 18.9	0.001
Creatinine (µmol/l)	104.4 ± 30.4	104.3 ± 30.3	108.2 ± 32.4	0.080
Baseline Potassium (nmol/L)	4.5 ± 0.5	4.5 ± 0.5	4.4 ± 0.5	0.001
Haemoglobin (g/l)	135.5 ± 16.2	135.6 ± 16.2	133.9 ± 15.9	0.17
Diuretics	4433 (93.4)	4252 (93.3)	181 (95.8)	0.19
ACEI	2661 (56.1)	2579 (56.6)	82 (43.4)	<0.001
ARB	1307 (27.6)	1257 (27.6)	50 (26.5)	0.73
ARNI	508 (10.7)	469 (10.3)	39 (20.6)	<0.001
Beta-blocker	4558 (96.1)	4384 (96.2)	174 (92.1)	0.004
≥50 % of target dose	2349 (51.5)	2260 (51.6)	119 (63.0)	0.013
Beta-1 selective*	2779 (58.6)	2666 (58.6)	113 (59.8)	0.74
Non-selective*	1775 (37.4)	1714 (37.7)	61 (32.3)	0.13
MRAs	3370 (71.0)	3251 (71.4)	119 (63.0)	0.013
Digoxin	887 (18.7)	845 (18.6)	42 (22.2)	0.20
Ivabradine	228 (4.8)	213 (4.7)	15 (7.9)	0.040
PCI	1624 (34.2)	1567 (34.4)	57 (30.2)	0.23
CABG	799 (16.8)	776 (17.0)	23 (12.2)	0.080
CRT	354 (7.5)	330 (7.2)	24 (12.7)	0.005
ICD	953 (20.1)	905 (19.9)	48 (25.4)	0.063
Respiratory system drugs				
Adrenergic agonists†	218 (4.6)	151 (3.3)	67 (35.4)	<0.001
Adrenergic agonists (in combinations) †‡	174 (3.7)	129 (2.8)	45 (23.8)	<0.001
Any inhaled adrenergic agonist†	329 (6.9)	234 (5.1)	95 (50.3)	<0.001
Muscarinic antagonists†	172 (3.6)	143 (3.1)	29 (15.3)	<0.001
Glucocorticoids†	116 (2.4)	76 (1.7)	40 (21.2)	<0.001
Systemic adrenergic agonists	10 (0.2)	10 (0.2)	0 (0.0)	0.52
Other drugs	35 (0.7)	32 (0.7)	3 (1.6)	0.16
Diabetes medications§				
Biguanides	1016 (51.2)	975 (51.4)	41 (48.2)	0.572
DPP-4 inhibitors	310 (15.6)	297 (15.7)	13 (15.3)	0.930
GLP-1 analogues	21 (1.1)	20 (1.1)	1 (1.2)	0.914
Sulfonylureas	438 (22.1)	421 (22.2)	17 (20.0)	0.635
Insulin	540 (27.2)	517 (27.2)	85 (27.1)	0.971

Data are presented as mean ± SD or median (IQR) for continuous measures and n (%) for categorical measures.

HR – heart rate; bpm – beats per minute; SBP – systolic blood pressure; BMI – body mass index; HF – heart failure; KCCQ-TSS – Kansas city cardiomyopathy questionnaire; total symptom score; CSS – clinical summary score; OSS – overall summary score; NYHA – New York heart association classification; NT-proBNP – N terminal pro B-type natriuretic peptide; eGFR – estimated glomerular filtration rate; ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin receptor blocker; ARNI – angiotensin receptor blocker-

neprilysin inhibitor; PCI – primary coronary intervention; CABG – coronary bypass surgery; CRT – cardiac resynchronization therapy; ICD – implantable cardioverter-defibrillator.
*4 patients excluded
†Inhaled.
‡ In combination with corticosteroids /antimuscarinics/ other drugs.
§Only in patients with a medical history of diabetes (1983).

Appendix table 8 Multivariable models for different clinical outcomes in HFrEF

A) Cardiovascular Death

	Hazard Ratio	Standard Error	p-value	95% CI
5 unit increase in Gini coefficient	1.08	0.03	0.005	1.02 – 1.13
10 unit increase in Gini coefficient	1.16	0.06	0.005	1.04 – 1.29
1 unit increase in Ln NT proBNP	1.61	0.04	<0.001	1.53 – 1.69
Male gender	1.46	0.09	<0.001	1.30 – 1.63
Diabetes	1.27	0.06	<0.001	1.15 – 1.40
>5 years HF duration	1.16	0.05	0.002	1.05 - 1.27
10 years increase in age	1.15	0.03	<0.001	1.09 – 1.21
Previous HF hospitalisation	1.13	0.05	0.009	1.03 – 1.23
Current smoker	1.10	0.07	0.144	0.97 – 1.25
Previous MI	1.10	0.05	0.043	1.00 – 1.20
5% decrease in LVEF	1.08	0.02	<0.001	1.04 – 1.12
5 kg/m^2 increase in BMI	1.07	0.03	0.012	1.01 – 1.12
10 ml/min/1.73m^2 decrease in eGFR*	1.06	0.02	<0.001	1.03 – 1.09
10 bpm increase in HR	1.04	0.02	0.036	1.00 – 1.08
10 gm/L decrease - Haemoglobin	1.04	0.02	0.009	1.01 – 1.07
1 unit increase in hospital bed density	1.00	0.01	0.882	0.98 – 1.02
500 US$ decrease in per capita income	1.00	0.00	0.069	0.99 – 1.00
Hypertension	0.98	0.05	0.713	0.89 – 1.09
Atrial fibrillation	0.96	0.05	0.434	0.86 – 1.07
10 mmHg increase in SBP	0.94	0.01	<0.001	0.91 – 0.97

B) All-cause Death

	Hazard Ratio	Standard Error	p-value	95% CI
5 unit increase in Gini coefficient	1.07	0.03	0.006	1.02 – 1.12
10 unit increase in Gini coefficient	1.15	0.06	0.006	1.04 - 1.26
1 unit increase in Ln NT proBNP	1.54	0.03	<0.001	1.48 - 1.61
Male gender	1.50	0.08	<0.001	1.35 - 1.67
Diabetes	1.31	0.06	<0.001	1.20 - 1.44
10 years increase in age	1.21	0.03	<0.001	1.16 - 1.26
Current smoker	1.16	0.07	0.013	1.03 - 1.31
>5 years HF duration	1.14	0.05	0.003	1.05 - 1.23
Previous HF hospitalisation	1.13	0.05	0.004	1.04 - 1.22
5% decrease in LVEF	1.07	0.02	<0.001	1.03 - 1.10
Previous MI	1.07	0.04	0.26	0.98 - 1.16
10 ml/min/1.73m^2 decrease in eGFR*	1.06	0.02	<0.001	1.03 - 1.10
10 bpm increase in HR	1.06	0.04	<0.001	1.03 - 1.10
10 gm/L decrease – Haemoglobin	1.05	0.01	<0.001	1.02 - 1.08
5 kg/m^2 increase in BMI	1.04	0.02	0.101	0.99 - 1.09
1 unit increase in hospital bed density	1.00	0.01	0.97	0.98 – 1.02
500 US$ decrease in per capita income	1.00	0.00	0.128	-
Hypertension	1.00	0.05	0.957	0.91 - 1.09
Atrial fibrillation	0.95	0.05	0.86	0.86 – 1.04
10 mmHg increase in SBP	0.94	0.01	<0.001	0.92 - 0.97

C)Hospitalisation for Heart Failure

	Hazard Ratio	Standard Error	p-value	95% CI
5 unit increase in Gini coefficient	0.99	0.03	0.804	0.94 – 1.05
10 unit increase in Gini coefficient	0.99	0.06	0.804	0.88 – 1.10
Previous HF hospitalisation	1.64	0.08	<0.001	1.48 – 1.81

1 unit increase in Ln NT proBNP	1.51	0.04	<0.001	1.43 – 1.59
Diabetes	1.38	0.07	<0.001	1.25 – 1.53
>5 years HF duration	1.33	0.06	<0.001	1.21 – 1.46
Male gender	1.26	0.08	<0.001	1.12 – 1.42
5 kg/m^2 increase in BMI	1.17	0.03	<0.001	1.12 – 1.23
Current smoker	1.10	0.08	0.15	0.96 – 1.26
Previous MI	1.08	0.05	0.109	0.98 – 1.19
5% decrease in LVEF	1.09	0.02	<0.001	1.05 – 1.13
10 bpm increase in HR	1.07	0.02	0.001	1.03 – 1.11
Hypertension	1.06	0.06	0.291	0.95 – 1.18
10 ml/min/1.73m^2 decrease in eGFR*	1.04	0.02	0.032	1.00 – 1.07
10 years increase in age	1.03	0.03	0.208	0.98 – 1.09
1 unit increase in hospital bed density	1.02	0.01	0.137	0.99 – 1.04
10 gm/L decrease - Haemoglobin	1.01	0.02	0.536	0.98 – 1.04
500 US$ decrease in per capita income	1.00	0.00	0.520	-
10 mmHg increase in SBP	0.95	0.01	0.004	0.93 – 0.99
Atrial fibrillation	0.89	0.05	0.047	0.79 – 1.00

Confidence interval (CI), heart rate (HR), systolic blood pressure (SBP), body mass index (BMI), myocardial infarction (MI), heart failure (HF), left ventricular ejection fraction (LVEF), log transformed N terminal pro Brain natriuretic peptide (Ln NT proBNP), estimated glomerular filtration rate (eGFR), United States dollars (US$).

*for eGFR <90 ml/min/173m2

Cardiovascular death was tested for competing risk of all non-cardiovascular death. Heart failure hospitalisation was tested for competing risk of all cause death

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