Addressing Unmet Needs in Chronic Heart Failure

Dr Sam Straw

BSc (hons), MBChB (hons), MRCP (London)

British Heart Foundation Clinical Research Fellow

Submitted in accordance with the requirements for the degree of

Doctor of Philosophy

The University of Leeds

Leeds Institute of Cardiovascular and Metabolic Medicine

School of Medicine

Submitted February 2023 for examination

Intellectual Property and Publication Statements:

The candidate confirms that the work submitted is their own, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. Where work is based upon publications prior to enrolment as a postdoctoral candidate in April 2021, this has been explicitly indicated and justified below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Chapter 1 contains work based on the following publication prior to April 2021, the contents of which have been substantially revised and expanded upon for this chapter:

> Straw S, Witte KK, Kearney MT. Heart Failure: A preventable and treatable complication of type 2 diabetes. *J Diabetes*. 2019 Jul;11(7):613-616.
>
> *Dr Sam Straw researched the topic and authored the literature review. Critical revision was provided by Professor Klaus K Witte and Professor Mark T Kearney.*

And the following publication prior to April 2021, the contents of which have been substantially revised and expanded upon for this chapter:

> Straw S, McGinlay M, Witte KK. Four Pillars of Heart Failure: Contemporary Pharmacological Therapy for Heart Failure with Reduced Ejection Fraction. *Open Heart.* 2021 Mar;8(1):e001585.
>
> *Dr Sam Straw researched the topic and authored the viewpoint. Critical revision was provided by Ms Melanie McGinlay and Professor Klaus K Witte.*

Chapter 2 contains work based on the following publication prior to April 2021, the contents of which have been substantially revised and expanded upon for this chapter:

Straw S, Klaus K Witte, Kearney MT. 94 End-stage congestive heart failure, in Bruera E (ed) *Textbook of Palliative Medicine and Supportive Care*. Third Edition. Taylor and Francis 2020.

Dr Sam Straw researched the topic and authored the literature review. Critical revision was provided by Professor Klaus K Witte and Professor Mark T Kearney.

Chapter 3 contains work based on the following publication published after April 2021:

Straw S, Gierula J, Witte KK. Designing clinical trials in heart failure with preserved ejection fraction: quality over quantity? *European Journal of Heart Failure*. 2022 May;24(5):851-854.

Dr Sam Straw researched the topic and authored the editorial. Critical revision was provided by Dr John Gierula and Professor Klaus K Witte.

And the following publication prior to April 2021, the contents of which have been substantially revised and expanded upon for this chapter:

Straw S, Schlosshan D, Witte KK. Secondary mitral regurgitation: reducing the leak, expanding the science. *European Society of Cardiology Heart Failure. 2020 7:3281-3284.*

Dr Sam Straw researched the topic and authored the editorial. Critical revision was provided by Dr Dominik Schlosshan and Professor Klaus K Witte.

Chapter 4 contains work based on the following publication prior to April 2021, the contents of which have been incorporated and revised to form this chapter:

Straw S, McGinlay M, Relton SD, Koshy AO, Gierula J, Paton MF, Drozd M, Lowry JE, Cole C, Cubbon RM, Witte KK, Kearney MT. Effect of disease modifying agents and their association with mortality in multi-morbid patients with heart failure with reduced ejection fraction. *European Society of Cardiology Heart Failure*. 2020 Sep 13;7(6):3859-3870.

Dr Sam Straw analysed the data and authored the manuscript. Critical revision provided by Professor Mark T Kearney, Professor Klaus K Witte. Other authors contributed to developing the protocol, recruiting participants, and data collection.

Chapter 5 contains work based on the following publication after April 2021:

Straw S, Cole CA, McGinlay M, Drozd M, Slater TA, Lowry JE, Paton MF, Levelt E, Cubbon R, Kearney MT, Witte KK, Gierula J. Guideline-directed medical therapy is similarly effective in heart failure with mildly reduced ejection fraction. 2022 Jul 4. Online ahead of print.

Dr Sam Straw analysed the data and authored the manuscript. Critical revision was provided by Professor Klaus K Witte and Dr John Gierula. Other authors contributed to developing the protocol, recruiting participants, and data collection.

Chapter 6 contains work which is unpublished and conducted after April 2021.

Chapter 7 contains work based published prior to April 2021, the contents of which have been revised and expanded upon for this chapter:

Straw S*, Byrom R, Gierula J, Paton MF, Koshy A, Cubbon RM, Drozd M, Kearney MT, Witte KK. Predicting one-year mortality in heart failure using the 'Surprise Question': a prospective pilot study. *Eur J Heart Fail* 2019 Feb;21(2):227-234. Editorial: Patel RB, Warraich HJ, Butler J, Vaduganathan M. Surprise, surprise: improving the referral pathway to palliative care intervention in advanced heart failure. *Eur J Heart Fail.* 2019 Feb;21(2):227-234.

Dr Sam Straw conceived the study, obtained ethical approval, collected, and analysed the data and authored the manuscript. Professor Klaus K Witte assisted with ethical approval and provided critical revision. Dr Richard M Cubbon provided guidance on statistical analysis Other authors provided critical revision of the manuscript.

Chapter 8 contains work based on the following publication prior to April 2021, the contents of which have been substantially revised and expanded upon:

Straw S, Witte KK. Observational data during the COVID-19 pandemic: opportunity with uncertainty. *Heart*. 2020 Oct;106(19):1461-1462.

Dr Sam Straw researched the topic and authored the editorial. Critical revision was provided by Professor Klaus K Witte.

And this publication prior to April 2021:

Straw S*, McGinlay M, Drozd M, Slater TA, Cowley A, Kamalathasan S, Maxwell N, Bird R, Koshy AO, Prica M, Patel PA, Relton SD, Gierula J, Cubbon

RM, Kearney MT, Witte KK. Advanced care planning during the COVID-19 pandemic: ceiling of care decisions and their implications for observational data. *BioMed Central Palliative Care.* 20, 10 (2021).

Dr Sam Straw conceived the study, obtained institutional governance approval, collected and analysed the data, and authored the manuscript. Professor Klaus K Witte provided critical revision. Dr Richard M Cubbon and Dr Samuel D Relton provided guidance on statistical analysis. Other authors contributed to data collection and critical revision.

Dedication

To my parents Sharon and Nigel, who have always supported my education, and to my wife Harriet for her love and support.

Acknowledgements

This thesis is the end result of an idea, which, not only was I encouraged to pursue but was proactively guided through every step, from conception to publication. Mentorship is crucial during the formative years of any career, and first and foremost I wish to thank Professor Klaus Witte for his unwavering support, encouragement, and enthusiasm for which I am immensely grateful. My doctoral fellowship has not been all plain sailing. First, a global pandemic curtailed our clinical studies for an entire year – but with setbacks come opportunities. A brief redeployment provided me with a crash course in the day-to-day running of clinical trials and the opportunity to be part of the RECOVERY collaborative which made some of the most crucial discoveries of the pandemic. The pandemic also offered the opportunity to analyse data, and to write - much of the work within this thesis began during this time. Second, a move abroad seemed like a major obstacle but was in fact only a minor setback thanks to your commitment and the new way of working we have become accustomed to.

I must also express my gratitude to the supervisors and mentors who have stepped up to support me, particularly Dr John Gierula and Dr Eylem Levelt, two of the kindest, most generous supervisors one could wish for. To Professor Mark Kearney for providing motivation and direction throughout my fellowship and to Dr Ric Cubbon and Dr Scott Bowen who were immensely helpful whilst I was finding my feet.

The studies contained within this thesis and published elsewhere are the result of a team effort. My own contributions were to collect and analyse data, and to author the first versions of these manuscripts. To that end I must extend my gratitude to others,

in particular the members of the Leeds Cardiovascular Research Facility – Dr Judith Lowry, Dr Maria Paton, Rowena Byrom-Goulthorpe, Charlotte Cole and Julie Corrigan. What a team.

The funding for this series of investigations was made available by the British Heart Foundation, initially through a generous Scholarship which supported me whilst working towards the award of a Clinical Research Training Fellowship. The latter came during an extremely challenging time for charities and speaks to the novelty and relevance of our group's work. Above all, I would like to thank the patients who provided their time, experience, and expertise. They are an essential part of our team and remain central to everything we do.

Abstract

Chronic heart failure (CHF) is the syndrome of breathlessness, fatigue and congestion resulting from reduced cardiac output at rest or during exercise. In recent decades, dramatic improvements in survival have been achieved largely due to the more widespread implementation of pharmacological and device therapies. Despite this, the impact of these therapies on symptoms and quality of life have been less consistent and whether the benefits of these agents extend to populations who were largely excluded from the relevant trials remains unknown.

This thesis comprises a series of prospective and retrospective observational studies which aim to address key unmet needs in CHF. I show that people with CHF often have co-morbidities, and these individuals are the least likely to receive therapies for CHF, although appear to derive the greatest benefits. I also show that for those with less severe CHF for whom there is little data to support their use, pharmacological therapies are associated with similar benefits compared to those with more severely impaired heart function. Additionally, I show that patients with CHF and normal heart function according to current definitions often have subtle systolic dysfunction which could be more easily identified by simple imaging techniques.

In a prospective, observational study I show the ‘Surprise Question’ is able identify those within the last year of life and be used by a diverse range of healthcare professionals. I also show that for people hospitalised with CHF, advanced care planning is seldom utilised. In a retrospective cohort study in a setting where advanced care planning became routine, I show that ceiling of care decisions were made broadly

in line with known predictors of a poor prognosis, with no suggestion these decisions were associated with worse outcomes.

Based on these novel findings, I can conclude that the benefits of pharmacological therapies extend to many more people with CHF than previously thought. However, advanced care planning and palliative care in this population remains underutilised, despite evidence of benefit and clear need.

“Some observational studies are correct – I just don’t know which ones.”

David J. Cohen

Table of Contents

List of Figures

List of tables

Abbreviations

ACCF/AHA	American College of Cardiology Foundation/American Heart Association
ACEi	Angiotensin converting enzyme inhibitor
ARB	Angiotensin II receptor blocker
ARNI	Angiotein receptor-neprilysin inhibitor
ATLAS	Assessment of Treatment with Lisinopril and Survival
BAME	Black, Asian and minority ethnic
BMI	Body mass index
CCI	Cardiac contractility index
CFS	Clinical Frailty Scale
CHARM	Candesartan in Heart failure – Assessment of moRtality and Morbidity
CHF	Chronic heart failure
CI	Confidence interval
CIBIS-II	Cardiac Insufficiency Bisoprolol Study II
CKD	Chronic kidney disease
CONSENSUS	Cooperative North Scandinavian Enalapril Survival Study
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CPAP	Continuous positive airway pressure
CPR	Cardiopulmonary resuscitation
CRT	Cardiac resynchronisation therapy
CRT-P	Cardiac resynchronisation therapy with pacemaker
CRT-D	Cardiac resynchronisation therapy with defibrillator

DANISH	Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality
DAPA-HF	Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure
EMPA-REG-OUTCOME	Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes
EMPEROR-Reduced	EMPagliflozin outcome tRial in Patients with chronic heart Failure with Reduced ejection fraction
EMPEROR-Preserved	EMPagliflozin outcome tRial in Patients with chronic heart Failure with Preserved ejection fraction
ESC	European Society of Cardiology
GWTG-HF	Get with the Guidelines Heart Failure
HFimpEF	Heart failure with improved ejection fraction
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
ICD	Implantable cardioverter defibrillator
ICU	Intensive care unit
IHD	Ischaemic heart disease
LTHT	Leeds Teaching Hospitals NHS Trust
LV	Left ventricular/left ventricle
LVAD	Left ventricular assist device
LVEDd	Left ventricular end-diastolic diameter
LVEF	Left ventricular ejection fraction

MADIT-II	Multicentre Automatic Defibrillator Implantation Trial II
MERIT-HF	The Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure
MRA	Mineralocorticoid receptor antagonist
NICE-CHF	2010 United Kingdom National Institute for Clinical Excellence Guidelines on Chronic Heart Failure
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
OR	Odds ratio
OVERTURE	Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events
PAL-HF	Palliative Care in Heart Failure
PARADIGM-HF	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 Heart Failure with Preserved Ejection Fraction
RAAS	Renin-angiotensin-aldosterone system
RALES	Randomized Aldactone Evaluation Study
ReSPECT	Recommended Summary Plan for Emergency Care and Treatment
RR	Relative risk
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SGLT2i	Sodium-glucose co-transporter 2 inhibitors
SOLVD	Studies of Left Ventricular Dysfunction

SOLOIST-WHF	Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure
TIA	Transient ischaemic attack
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist
TRED-HF	Therapy withdrawal in Recovered Dilated cardiomyopathy – Heart Failure
UK-HEART-2	United Kingdom Heart Failure Evaluation and Assessment of Risk Trial
V-HeFT	Vasodilator Heart Failure Trial
WHO	World Health Organisation

Chapter 1: Chronic heart failure: definitions, diagnosis, and disease modifying therapies

Chapter 1 will discuss the constellation of signs, symptoms, and objective markers of cardiac dysfunction, which together define the syndrome of chronic heart failure. The pathophysiology of chronic heart failure will be reviewed, as will how these maladaptations are targeted by disease modifying pharmacological and device therapies.

1.1 Introduction

Chronic heart failure (CHF) is the clinical syndrome which occurs when cardiac output is insufficient to meet the body's metabolic demands at rest or during exercise. CHF is the common endpoint of many disease processes which result in structural or functional abnormalities impairing the emptying or filling of the heart. Regardless of the underlying cause, the clinical syndrome is similar, and characterised by symptoms of breathlessness, fatigue, and congestion. These symptoms are often accompanied by clinical signs, such as elevated jugular venous pressure, rales, and oedema.

1.2 Epidemiology

CHF is a growing public health problem, estimated to affect 1-2% of the general adult population in developed countries (McDonagh, Metra et al. 2021). The prevalence of CHF increases with age, from <1% in those aged <55 years, to >10% in those aged >70 years (Benjamin, Virani et al. 2018). Although the age-adjusted incidence of CHF is falling, possibly due to improved management of cardiovascular diseases including ischaemic heart disease and hypertension, the background of an aging population

means the overall prevalence is increasing (Conrad, Judge et al. 2018). Furthermore, as observational studies only include individuals with a formal diagnosis, whilst the majority of patients with CHF present to primary care without comprehensive access to echocardiography, the prevalence is likely to be higher (van Riet, Hoes et al. 2014). Around half of individuals with CHF are female, although this varies across classifications of CHF (Conrad, Judge et al. 2018).

1.3 Definition and classification of chronic heart failure

The definition of CHF is broad, including many distinct pathologies resulting in reduced cardiac output. Traditionally, CHF has been classified according to the presence or absence of left ventricular (LV) systolic dysfunction, although exact definitions have varied. The Universal Definition and Classification of Heart Failure aims to standardise definitions and has been endorsed by the Heart Failure Association of the European Society of Cardiology, Heart Failure Society of America, and the Japanese Heart Failure Society (Bozkurt, Coats et al. 2021) (Table 1.1).

Table 1.1 Classification of chronic heart failure according to left ventricular ejection fraction

Classification	HFrEF	HFmrEF	HFpEF	HFimpEF
Clinical	Signs ± symptoms	Signs ± symptoms	Signs ± symptoms	Signs ± symptoms
LVEF	LVEF ≤40%	LVEF 41-49%	LVEF ≥50%	LVEF >40%
Natriuretic peptides	-	-	NT-proBNP ≥125pg/mL or BNP ≥35pg/mL	-
Additional criteria	-	-	LVH ± LA enlargement or LV diastolic dysfunction	Baseline LVEF ≤40% and ≥10% improvement.
Adopted from (McDonagh, Metra et al. 2021) and (Bozkurt, Coats et al. 2021).				
HFrEF; heart failure with reduced ejection fraction, HFmrEF; heat failure with mid-range ejection fraction, HFpEF; heart failure with preserved ejection fraction, HFimpEF; heart failure with improved ejection fraction, LVEF; left ventricular ejection fraction, LVH; left ventricular hypertrophy, LA; left atrial.				

1.3.1 Heart failure with reduced ejection fraction

Heart failure with reduced ejection fraction (HFrEF) describes the syndrome in which typical signs and symptoms of CHF occur as a result of significant LV systolic dysfunction. Central to this definition is the measurement of left ventricular ejection fraction (LVEF), the proportion of blood within the LV cavity ejected during each cardiac cycle, usually assessed non-invasively by echocardiogram. It is generally accepted that a value of <50% (or indeed <55%) is abnormal, however landmark trials assessing the effects of disease modifying pharmacological therapies have typically used cut-offs of <40% or ≤40% to define the syndrome of HFrEF. These criteria persist in clinical practice guidelines, in which there are clear recommendations for patients with significant LV systolic dysfunction, but less clear evidence to guide practice for those without (McDonagh, Metra et al. 2021).

1.3.2 Heart failure with mildly reduced ejection fraction

Heart failure with mildly reduced or ‘mid-range’ ejection fraction (HFmrEF) has been proposed as a classification applying to individuals who have typical signs and symptoms of CHF, and LVEF 41-49%. Recent guidelines for the first time recommend that pharmacological therapies may be considered for these patients. However, in the absence of clinical trials, the benefits of these therapies are largely unknown, with these recommendations derived from consensus opinion, observational studies, and *post hoc* analyses of randomised controlled trials (McDonagh, Metra et al. 2021).

1.3.3 Heart failure with preserved ejection fraction

Heart failure with preserved ejection fraction (HFpEF) is the term applied to individuals with signs and symptoms consistent with CHF in the absence of LV systolic dysfunction. The currently applied definition requires LVEF of ≥50%, alongside other objective markers of cardiac dysfunction (LV diastolic dysfunction or raised LV filling pressures evidenced by left atrial dilatation or LV hypertrophy) and elevated natriuretic peptides (N-terminal pro-brain type natriuretic peptide [NT-proBNP] ≥125pg/mL) (McDonagh, Metra et al. 2021). The syndrome of HFpEF is heterogenous, encompassing several cardiovascular conditions including atrial fibrillation.

1.3.4 Heart failure with improved ejection fraction

Observational studies have suggested that a large proportion of patients who have HFmrEF and HFpEF, previously had HFrEF. Heart failure with improved ejection fraction (HFimpEF) can be applied to individuals who previously had significant LV systolic dysfunction which has recovered, but who remain symptomatic. HFimpEF seems to be clinically distinct from both HFrEF and HFpEF, and more similar to HFrEF

in terms of its clinical characteristics, but associated with a favourable prognosis (Punnoose, Givertz et al. 2011).

1.4 Pathophysiology of chronic heart failure

The most common causes of CHF in developed countries are ischaemic heart disease, hypertension, valvular heart disease, and diabetes mellitus, which can often co-exist. Identification of the underlying cause is essential for diagnosis, to modify risk factors and to guide subsequent treatment. However, regardless of the underlying cause, common to all pathologies are abnormalities of multiple physiological systems, including the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system, natriuretic peptide system, and immune system. By attempting to compensate for impaired cardiac function, these adaptations are initially protective, but ultimately serve to contribute to the persistence and progression of the syndrome.

1.4.1 Renin-angiotensin-aldosterone system

The renin-angiotensin-aldosterone system (RAAS) is a neurohormonal mechanism involved in the long-term homeostasis of sodium and water (Figure 1.1). In CHF, reduced cardiac output is sensed by baroreceptors within the carotid sinus and juxtaglomerular cells within the macula densa of the kidney. Juxtaglomerular cells release renin which cleaves angiotensin I from angiotensinogen produced by the liver. Angiotensin I is then converted to angiotensin II by angiotensin converting enzyme contained within endothelial cells, particularly within the lungs. Angiotensin II is the major bioactive molecule within the RAAS, and results in arteriolar vasoconstriction and the release of aldosterone from the zona glomerulosa of the adrenal cortex, which in turn results in sodium and water reabsorption and upregulation of epithelial sodium

channels. The RAAS is a protective mechanism which maintains end-organ perfusion in response to volume depletion. In CHF activation of the RAAS is initially protective, maintaining end-organ perfusion in response to reduced cardiac output, but this comes at the expense of increased sodium and water reabsorption which augments preload resulting in congestion.

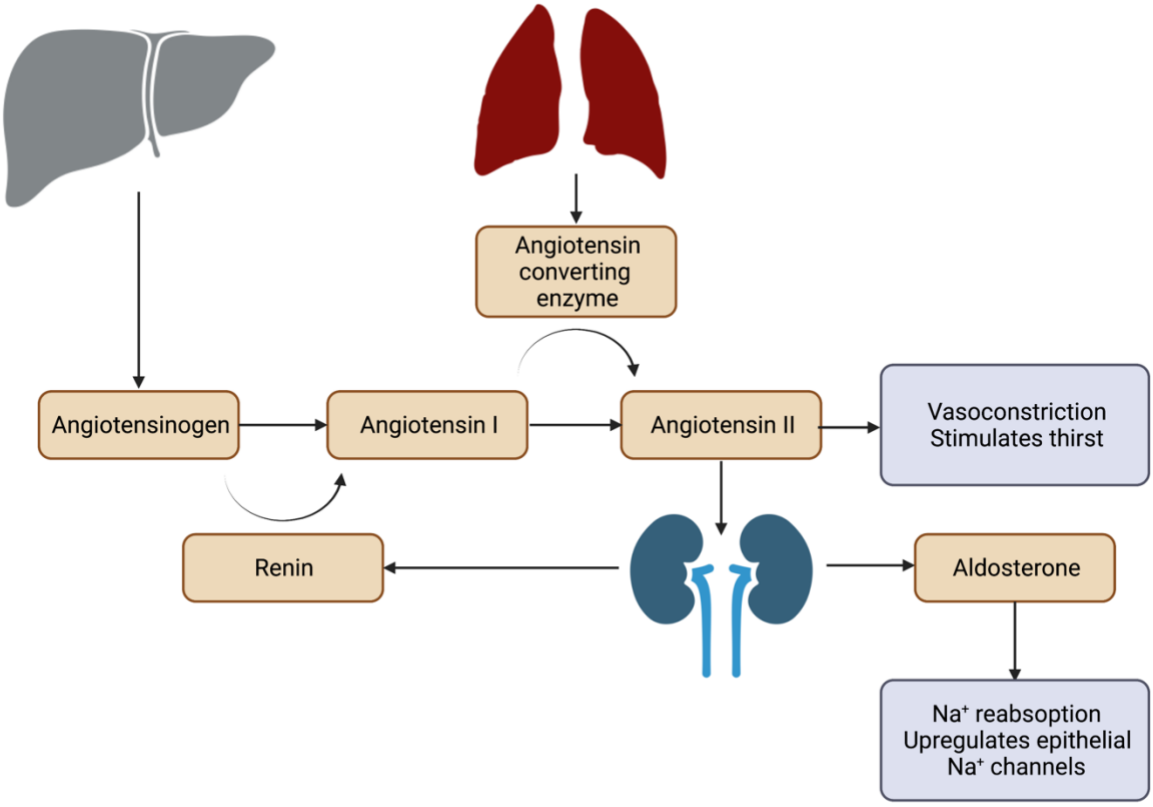


Figure 1.1 The renin-angiotensin-aldosterone system
Created with Biorender.com

1.4.2 Autonomic nervous system

In the short-term, augmentation of cardiac output is primarily regulated by the autonomic nervous system (Figure 1.2). In response to reduced cardiac output, activation of the sympathetic nervous system results in the release of adrenaline and noradrenaline, which agonise adrenoreceptors resulting in increased heart rate and

cardiac contractility. These adaptations improve cardiac output in the short-term, but ultimately the persistence of elevated sympathetic tone increases the heart's metabolic demands whilst also predisposing to ventricular tachyarrythmia and sudden cardiac death.

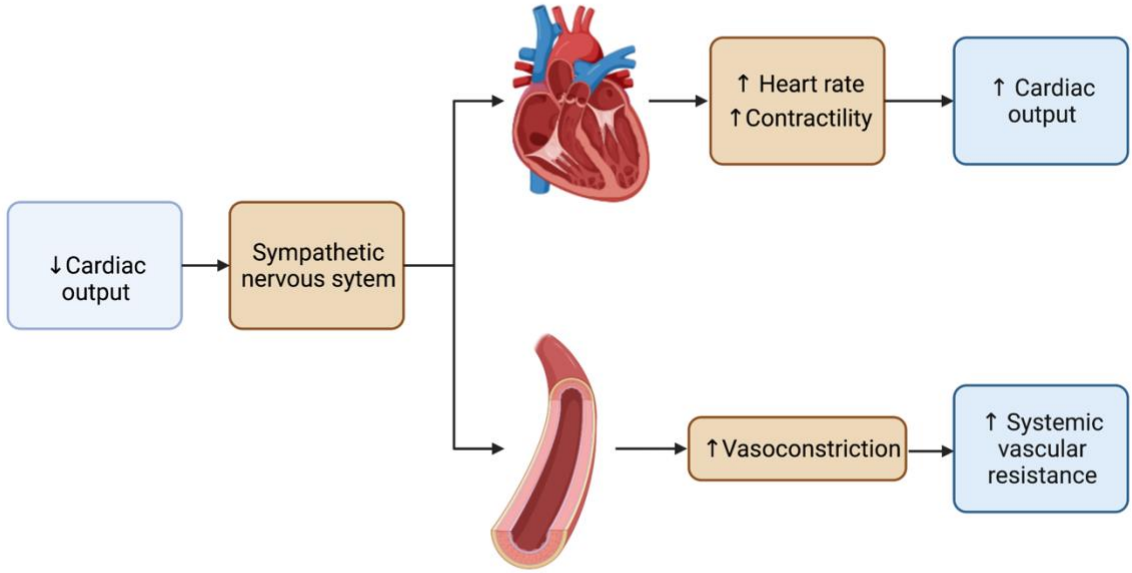


Figure 1.2 Autonomic nervous system in chronic heart failure
Created with Biorender.com

1.4.3 Natriuretic peptide system

The natriuretic peptide system is an endocrine system which maintains fluid homeostasis and is protective, counteracting the effects of the RAAS and sympathetic nervous system and is upregulated in CHF. Natriuretic peptides are released from the heart due to elevated wall stress because of raised intracardiac pressure. Natriuretic peptides include B-type natriuretic peptide (BNP), which is cleaved from metabolically inactive NT-proBNP and acts to promote vasodilation and natriuresis. Additionally,

atrial stretch leads to the release of A-type natriueretic peptide with similar actions to BNP (Daniels and Maisel 2007).

1.5 Pharmacological therapy for heart failure with reduced ejection fraction

Contemporary pharmacological therapy for HFrEF is supported by evidence from randomised controlled trials demonstrating reductions in cardiovascular mortality (Figure 1.3). These agents aim to limit the physiological maladaptations of the syndrome, resulting in improvements in symptoms and quality of life, LV reverse remodelling and improved survival.

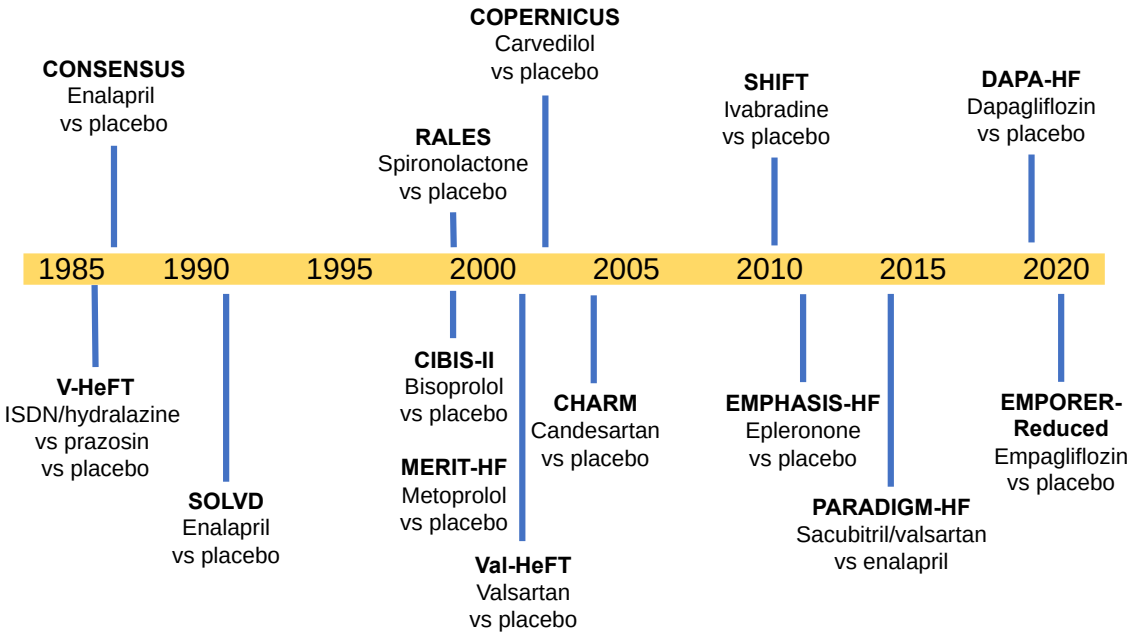


Figure 1.3 Landmark trials demonstrating mortality reductions with pharmacological therapies in heart failure with reduced ejection fraction
Adapted from (Tomasoni, Adamo et al. 2020).

Until recently, the approach recommended was built upon a foundation of inhibiting the two fundamental pathways which lead to the development of the syndrome of CHF (the RAAS and the sympathetic nervous system) using angiotensin converting

enzyme inhibitors (ACEi) and beta-adrenoceptor antagonists, the first pharmacological therapies proven to be of benefit in clinical trials (Ponikowski, Voors et al. 2016, Yancy, Jessup et al. 2017). Additional therapies such as mineralocorticoid receptor antagonists (MRA) or angiotensin receptor-neprilysin inhibitors (ARNI), were recommended for patients established on these agents, who remained symptomatic and had persistently impaired LV systolic function.

1.5.1 Angiotensin converting enzyme inhibitors

ACEi prevent the conversion of angiotensin I to angiotensin II and thereby inhibit several aspects of the RAAS, and are associated with haemodynamic and symptomatic improvements in HFrEF. The mortality benefit of ACEi was first demonstrated in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS 1987), which randomised 253 patients with New York Heart Association (NYHA) class IV symptoms and radiological evidence of cardiomegaly (LVEF was not an inclusion criteria) to either enalapril or placebo in addition to vasodilators, digoxin and diuretics – standard of care at the time. The trial was halted early on ground of efficacy, after a median follow-up of 188 days, due to reductions in all-cause mortality evident in participants receiving enalapril (relative risk (RR) 0.73, p=0.003). CONSENSUS established the benefits of ACEi for patients with advanced CHF, however the effects in less severe CHF were unknown. The Studies of Left Ventricular Dysfunction (SOLVD 1991) trial randomised patients with NYHA class II-IV symptoms and LVEF ≤35% to either enalapril or placebo, in addition to standard of care. In total, 2569 participants were enrolled and enalapril was associated with a 16% reduction in the primary endpoint of all-cause mortality (RR 0.84, 95% CI 0.74-0.95, p=0.0036), largely driven by a reduction in deaths due to progressive heart failure.

Cardiovascular hospitalisation was also noted to be lower in those receiving enalapril (RR 0.90, $p<0.001$).

1.5.2 Angiotensin receptor blockers

ACEi inhibit the conversion of angiotensin I to angiotensin II, however, this provides incomplete blockade of the RAAS. Logically, the addition of an ARB would provide more complete inhibition of the pathway and might yield further benefits over and above treatment with an ACEi. The Candesartan in Heart failure – Assessment of moRtality and Morbidity (CHARM) programme consisted of three trials which assessed the role of ARB for the treatment of CHF in addition to ACEi (McMurray, Ostergren et al. 2003), as an alternative in those who were unable to tolerate ACEi (Granger, McMurray et al. 2003) or in those with a preserved ejection fraction (CHARM-Preserved). CHARM-Added randomised 2548 patients with LVEF ≤40% and NYHA class II-IV symptoms who were receiving ACEi, to candesartan or placebo. The combined endpoint of cardiovascular mortality or hospitalisation for heart failure was lower in those receiving candesartan in addition to ACEi (hazard ratio (HR) 0.85, 95% CI 0.72-0.98, $p=0.029$), although there was no significant difference in all-cause mortality (HR 0.89, 95% CI 0.77-1.02, p=0.086), and combination therapy was associated with more renal dysfunction and hyperkalaemia. Additionally, in *post-hoc* analysis, these beneficial effects were not observed in the 17% of patients receiving mineralocorticoid receptor antagonists (MRA). Due to the adverse effects and questionable benefits in patients receiving MRA, the addition of ARB to patients already receiving ACEi is not recommended (McDonagh, Metra et al. 2021).

ACEi are not tolerated by many patients, the most common side effect being a persistent dry cough which results from the potentiation of bradykinin. ARB act by directly antagonising the angiotensin receptor, thereby resulting in RAAS inhibition without inhibiting the breakdown of bradykinin. In CHARM-Alternate, 2028 patients with LVEF ≤40% and NYHA class II-IV symptoms who were unable to tolerate ACEi were randomised to candesartan or placebo. Discontinuation rates were similar to placebo, and the combined primary endpoint of cardiovascular death or heart failure hospitalisation was observed to be 30% lower in those randomised to candesartan (HR 0.70, 95% CI 0.60-0.81, p<0.001) (McMurray, Ostergren et al. 2003), benefits which were comparable to ACEi (CONSENSUS 1987, SOLVD 1991). Based on these findings, ARB are considered an alternative to ACEi in those who are unable to tolerate these agents.

1.5.3 Beta-adrenoceptor antagonists

The hypothesis that inhibiting the sympathetic nervous system in HFrEF would improve outcomes had been suggested since the 1970s. However, it was not until the turn of the century when evidence that these agents reduce mortality was proven, with the near simultaneous publication of two sufficiently powered randomised trials (CIBIS-II 1999, MERIT-HF 1999), adding to observations from smaller studies of the beneficial effects on LV reverse remodelling (Doughty, MacMahon et al. 1994).

The Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure (MERIT-HF 1999) trial randomised patients with NYHA class II-IV symptoms and LVEF <40% to metoprolol CR/XL (mean dose 159mg) or placebo. Treatment with beta-adrenoceptor antagonist conferred a 34% reduction in all-cause mortality (RR

0.66, 95% CI 0.53-0.81). In the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II 1999) participants received either a maximally tolerated dose of bisoprolol (mean dose 6.2mg) or placebo, with a near identical reduction in the primary endpoint of all-cause mortality (HR 0.66, 95% CI 0.54-0.81, p<0.0001). Both trials demonstrated an association between beta-adrenoceptor antagonist use and a reduction in sudden progressive heart failure deaths, as well as dose-related improvements in LV function (Bristow, Gilbert et al. 1996).

1.5.4 Mineralocorticoid receptor antagonists

The final step in the RAAS is the release of aldosterone, which acts to promote sodium and water reabsorption and upregulates epithelial sodium channels. The Randomized Aldactone Evaluation Study (RALES) (Pitt, Zannad et al. 1999) trial allocated 1663 patients with LVEF ≤35%, NYHA Class IV symptoms (or Class III and having been IV within the past 6 months), and treated with an ACEi, to spironolactone or placebo. Receipt of spironolactone was associated with a 30% reduction in the primary endpoint of all-cause mortality (RR 0.70, 95% CI 0.59-0.82, p<0.001) and did not result in significantly higher rates of renal dysfunction or hyperkalaemia, although there were higher rates of gynaecomastia and mastalgia (10% vs 1%, p<0.001).

A limitation of RALES was the inclusion of only severely symptomatic patients, limiting the use of MRA in those with lower NYHA class symptoms. The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial randomised 2737 patients with LVEF ≤35% who had NYHA class II symptoms to either eplerenone or placebo. Despite the trial including less severe CHF, and most patients by this time being established on both ACEi (or ARB) and beta-adrenoceptor

antagonists at enrolment, there was a 37% reduction in cardiovascular death or heart failure hospitalisation (HR 0.63, 95% CI 0.54-0.74, $p<0.001$) in those receiving eplerenone. Eplerenone is a selective MRA, and so did not result in increased rates of gynaecomastia, although was associated with higher rates of hyperkalaemia (8.0% vs 3.7%, $p<0.001$). Until recently, MRA have been recommended for patients who remain symptomatic with persistently impaired LV systolic function who are receiving maximally tolerated doses of ACEi and beta-adrenoceptor antagonists (Ponikowski, Voors et al. 2016, Yancy, Jessup et al. 2017).

1.5.5 Neprilysin inhibitors

Neprilysin inhibitors have long been known to promote natriuresis (Gros, Souque et al. 1989) and reduce circulating natriuretic peptides (Northridge, Jardine et al. 1989, Kahn, Patey et al. 1990). However, neprilysin also breaks down angiotensin II, meaning the positive effects of neprilysin inhibition are greatly mitigated by the activation of the RAAS, potentially counteracting the beneficial actions of these peptides. Combining a neprilysin inhibitor with an ACEi would provide dual blockade of the RAAS and natriuretic peptide systems, and it would seem logical that this might improve outcomes in HFrEF. In the first large scale randomised trial of the combination of an ACEi and neprilysin inhibitor in the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE), receipt of the novel agent was not associated with a reduction in the primary endpoint of all-cause mortality or heart failure hospitalisation, but was associated with lower rate of cardiovascular death or hospitalisation ($p=0.024$). However, omapatrilat raised significant safety concerns due to high rates of angioedema, attributed to both agents potentiating bradykinin and the study of this agent was halted (Packer, Califf et al. 2002).

ARB antagonise the angiotensin receptor and so inhibit the RAAS without inhibiting the breakdown of bradykinin, therefore, combining a neprilysin inhibitor with an ARB was the next logical step. The Prospective comparison of angiotensin receptor-neprilysin inhibitor (ARNI) with ACEi to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial showed that the combination of sacubitril (a neprilysin inhibitor) with valsartan (an ARB) was associated with a reduction in cardiovascular deaths or hospitalisation for heart failure (HR 0.80, 95% CI, 0.73-0.87) and all-cause mortality (HR 0.84, 95% CI 0.76-0.93), compared to enalapril (McMurray, Packer et al. 2014). The trial was terminated early due to pre-specified criteria of efficacy, however there were several limitations of the trial design, and barriers to implementation of ARNI for people with HFrEF, which might in part explain the relatively slow uptake in clinical practice.

Firstly, and unusually, the licensing of ARNI for HFrEF was based upon a single trial, which was studied in an ‘A+B vs C’ fashion. Secondly, the comparator was a submaximal licensed dose of enalapril, which was compared to maximum licensed dose of valsartan combined with sacubitril. Those treated with sacubitril-valsartan had on average lower blood pressure, possibly suggesting undertreatment in the control arm, and the HR for the composite outcome in PARADIGM-HF was similar to that of the comparison of high versus low dosing of lisinopril in the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial (Packer, Poole-Wilson et al. 1999). On the other hand, the primary outcome in the ATLAS trial was not statistically significant, and the point estimates for low dose ARNI compared to low dose ACEi in PARADIGM-HF were identical to those of the overall trial (McMurray, Packer et al. 2014). A final

caveat is that the trial may have been additionally biased in favour of sacubitril-valsartan, as those randomised to ARNI had already received an ACEi and were therefore pre-selected, with around 20% of patients in the treatment arm having dropped out during the run-in period. Trial design aside, an additional limitation of employing ARNI across the board includes the wash-out period required following cessation of ACEi due to the aforementioned risks of angioedema. Scepticism, obstacles to implementation, and clinician inertia mean that the use of ARNI into the routine care of people with HFrEF has been lower than anticipated.

1.5.6 Sodium-glucose co-transporter 2 inhibitors

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are medications first developed to treat diabetes mellitus. SGLT2 receptors are expressed in the proximal convoluted tubule and are responsible for around 90% of glucose reabsorption (Hsia, Grove et al. 2017). In diabetes mellitus, a maladaptive process occurs in which the threshold for reabsorption of glucose increases alongside expression of SGLT2 receptors, resulting in worsening hyperglycaemia. SGLT2i have high affinity for these receptors, and by inhibiting these, reduce the threshold for glucose reabsorption, promote glucosuria and natriuresis.

Evidence to suggest benefits of SGLT2i for patients with CHF were first suggested by the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG-OUTCOME) trial, which randomised 7020 participants with established cardiovascular disease and diabetes mellitus to empagliflozin or placebo (Zinman, Wanner et al. 2015). The primary outcome (a composite of cardiovascular death, myocardial infarction, or stroke) occurred in 10.5% of participants receiving

Empagliflozin, compared to 12.1% receiving placebo (HR 0.86, 95% CI 0.74-0.99, *p*=0.04), primarily driven by reductions in cardiovascular deaths. A surprising finding was a 35% relative risk reduction for heart failure hospitalisation amongst those randomised to Empagliflozin.

These observations were then confirmed in two trials – the EMPagliflozin outcome tRial in Patients with chronic heart Failure with Reduced ejection fraction (EMPEROR-Reduced) and the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) designed to evaluate SGLT2i in the setting of HFrEF, with and without diabetes. These studies showed consistent and near identical 25% relative risk reductions of the primary endpoint of cardiovascular death or hospitalisation for heart failure for both dapagliflozin and empagliflozin (McMurray, Solomon et al. 2019, Packer, Anker et al. 2020). Both trials also demonstrated a slower decline in renal function, with a 50% relative risk reduction for the composite renal endpoints in EMPEROR-Reduced. Dapaglifozin has also been shown to prevent decline in renal function and progression to end-stage kidney disease in participants with chronic kidney disease (Heerspink, Stefansson et al. 2020). The beneficial effects on renal outcomes might be particularly attractive in a disease associated with progressive decline in kidney function which often prevents the initiation or intensification of RAAS inhibition.

SGLT2i are associated with a low rate of serious side effects (no patients without diabetes developed ketoacidosis in either DAPA-HF or EMPEROR-Reduced), and it is anticipated that more than four out of five patients with HFrEF will be eligible for SGLT2i based on the inclusion criteria of these trials (Sharma, Zhao et al. 2018). Given

the beneficial effects and the lack of dosing considerations, uptake is anticipated to be more enthusiastic than for ARNI.

1.5.7 Additional therapies

Additional therapies that might be considered for patients who remain symptomatic with persistently impaired LV systolic function include digoxin, ivabradine and hydralazine with isosorbide dinitrate. Digoxin is a cardiac glycoside which increases the force of myocardial contraction, promotes diuresis and has been used to treat CHF for more than two centuries. Digoxin is recommended for the treatment of HFrEF but reserved for those who remain symptomatic despite foundation therapies, and has a class IIb recommendation having been shown to reduce heart failure hospitalisations (albeit the relevant trial was conducted when most patients received only ACEi and diuretics), but not mortality (DIG 1997).

Ivabradine is licensed for patients who, despite maximally tolerated doses of beta-adrenoceptor antagonists, have a resting heart rate ≥ 70 bpm. The Systolic Heart Failure Treatment With the IF Inhibitor Ivabradine Trial (SHIFT) showed that the addition of the I*f* receptor inhibitor ivabradine resulted in a 5% absolute reduction in death or hospitalisation for heart failure (HR 0.82, 95% CI 0.75-0.90, p<0.0001), primarily driven by heart failure hospitalisations (Swedberg, Komajda et al. 2010).

The very first landmark trial in HFrEF, the Vasodilator Heart Failure Trial (V-HeFT), showed a trend towards mortality reductions in those receiving vasodilator therapies. However, hydralazine and isosorbide dinitrate is now reserved for self-identified Black-African patients who remain symptomatic with persistent LV impairment (LVEF ≤35%,

or ≤45% with LV dilatation and NYHA Class III-IV symptoms) despite treatment with ACEi, beta-adrenoceptor and MRA (or where ACEi or ARB are contraindicated or not tolerated). This recommendation is based upon a *post hoc* analysis of the V-HeFT trial showing a mortality benefit in this group, subsequently confirmed prospectively in the African-American Heart Failure (A-HeFT) trial, which enrolled only self-identified Black-African patients (RR 0.61, *p*=0.02) (Taylor, Ziesche et al. 2004). The A-HeFT trial included a large proportion of participants with hypertensive cardiomyopathy and a small proportion with ischaemic cardiomyopathy, meaning these data might not be generalisable to many patient populations. This, alongside the subsequent V-HeFT II trial showing ACEi were superior to vasodilator therapy (Cohn, Johnson et al. 1991), mean that these agents should not be used in preference to other more established therapies.

1.5.8 A simplified approach

It has been suggested that the linear approach recommended by guidelines (Ponikowski, Voors et al. 2016, Yancy, Jessup et al. 2017), on a background of an increasingly complex pharmacotherapy, has the potential to cause confusion and consequent delays initiating additional agents. The benefits from a comprehensive strategy are clear – the four drug classes of medications are complementary to each other and act on different pathways relevant to the pathophysiology of HFrEF. Cross-trial comparisons have shown significant aggregate benefits for those receiving comprehensive therapy beyond what most patients receive (an ACEi and beta-adrenoceptor antagonist) with ARNI, beta-adrenoceptor antagonists, MRA and SGLT2i. In a pooled analysis of the EMPHASIS-HF (Zannad, McMurray et al. 2011), PARADIGM-HF (McMurray, Packer et al. 2014) and DAPA-HF (McMurray, Solomon

et al. 2019) trials, the composite outcome of cardiovascular death or heart failure hospitalisation was reduced by 62% (HR 0.38, 95% CI 0.30-0.47) as well as their individual components (cardiovascular death HR 0.50, 95% CI 0.37,-0.67; heart failure hospitalisation HR 0.32, 95%CI 0.24-0.43; all-cause mortality HR 0.53, 95% CI 0.40-0.70). The estimated lifetime survival benefit for an average patient aged 55 and 80-years old were an additional 6.3 and 1.4 years, respectively (Vaduganathan, Claggett et al. 2020).

1.5.9 The ‘Four Pillars’ of Heart Failure

Recent guidelines recommend that for indicated patients, the four classes of medications proven to reduce morbidity and mortality – ARNI, beta-adrenoceptor antagonists, MRA and SGLT2i should be introduced in parallel, very early in the patient pathway, with subsequent optimisation of dosing where possible (Figure 1.2) (McDonagh, Metra et al. 2021). A linear approach, attempts to avoid ‘unnecessary’ treatments in patients who ‘respond’ and are therefore no longer strictly indicated, however has several important limitations. Firstly, whilst guidelines do not stipulate a time interval between intensification of therapy, the need for further clinical assessment and re-evaluation of LV function inevitably introduces delays. In routine clinical practice, it typically takes many months (or even years) before patients receive optimised dosing of these medications, and many never do, even where integrated hospital and community care is available (Greene, Fonarow et al. 2019).

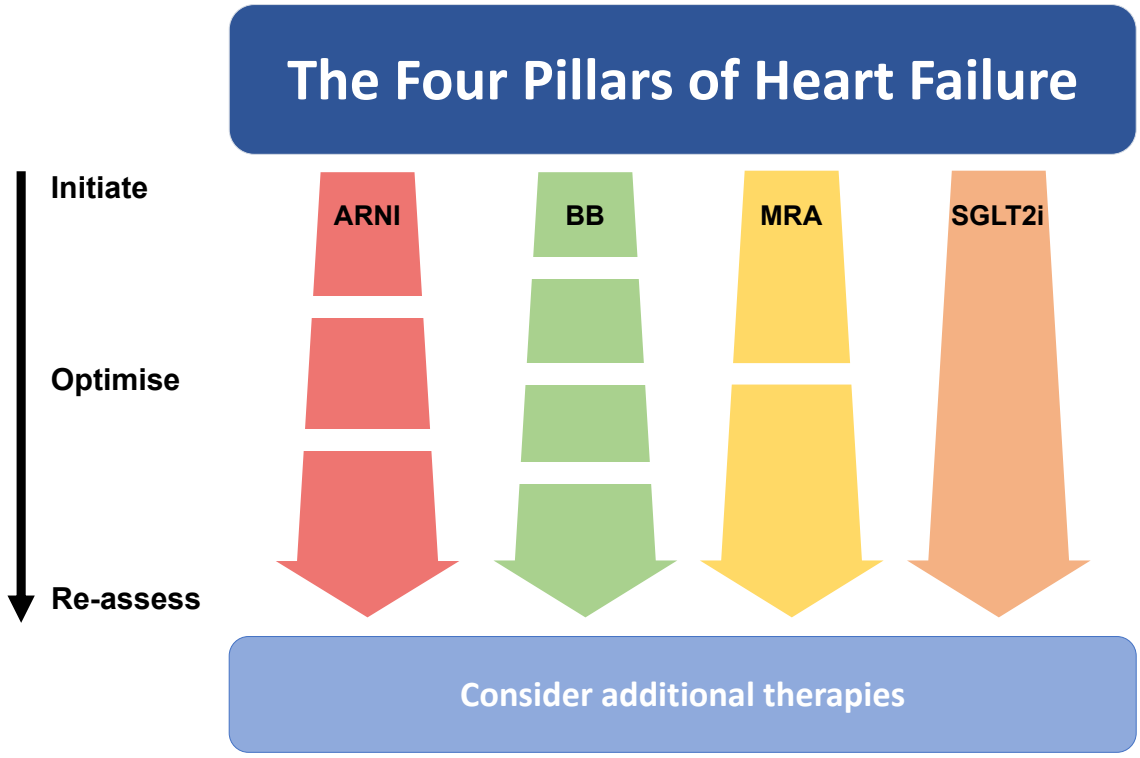


Figure 1.2 Novel conceptual framework for the administration of pharmacological therapy in heart failure with reduced ejection fraction
Reproduced from (Straw, McGinlay et al. 2021) under the terms of the Creative Commons Attribution Non-Commercial License.

Secondly, the barrier of 'response' is confusing and might be misplaced. It is unclear if response means asymptomatic or merely improved, and whether a subjective and poorly reproducible criteria such as symptomology based on the New York Heart Association (NYHA) classification is appropriate to select or deselect patients for the allocation of life-prolonging therapies, especially in view of recent data highlighting the substantial overlap between Class I and Class II symptoms (Blacher, Zimerman et al. 2020). Criteria requiring repeat assessment in clinical practice, act as a barrier to initiating MRA, ARNI or SGLT2i, which are regarded as second or third-line due to a hierarchical framework which places greater emphasis on therapies based upon the

chronical sequence in which the trials were performed (Figure 1.3). There is no logical basis to presume that the drugs trialled earliest would be the most beneficial, and yet this is what guidelines have implied.

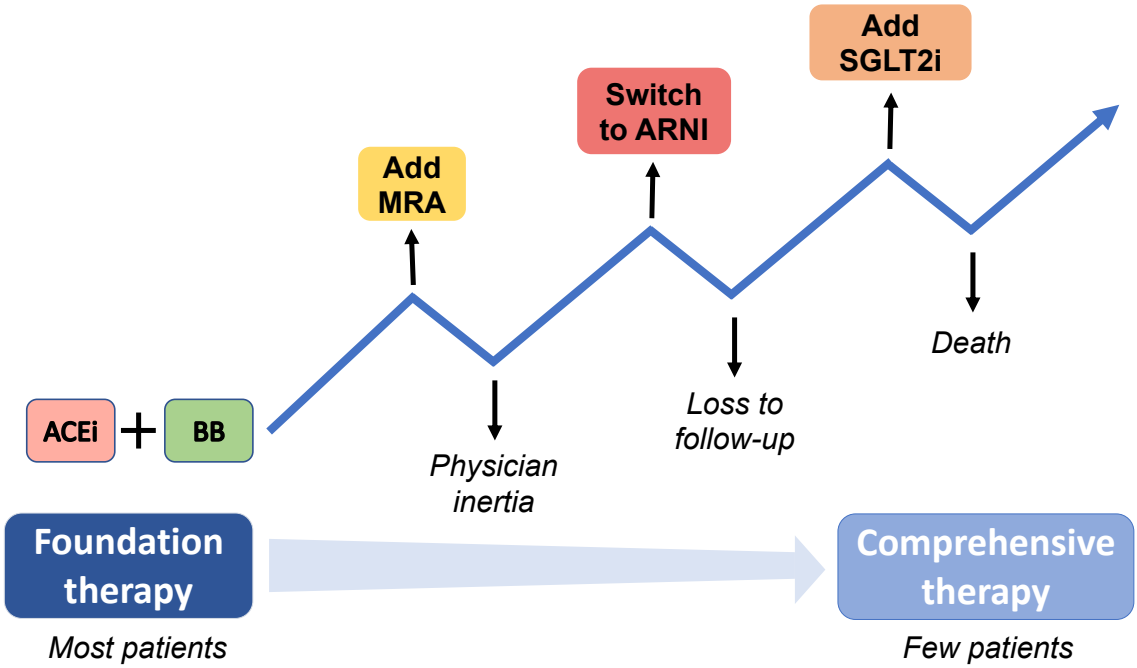


Figure 1.3 Potential drawbacks of a linear approach

A key obstacle to therapy initiation and intensification is physician inertia in patients who are stable or have 'responded' to treatment. For some patients with recent decompensation this might be appropriate (Wachter, Senni et al. 2019, Bhatt, Szarek et al. 2021), but the relevant trials were largely carried out in ambulatory patients receiving stable doses of previous generations of medical therapy, most of which had NYHA Class II symptoms (McMurray, Packer et al. 2014, McMurray, Solomon et al. 2019, Packer, Anker et al. 2020). This might be of particular relevance to SGLT2i, the effects of which were observed in the DAPA-HF trial within the first 28 days following randomisation (Berg, Jhund et al. 2021).

1.6 Pharmacological therapy for heart failure with mildly reduced or preserved ejection fraction

To date no cardiovascular outcomes trials have established mortality benefits by inhibiting neurohormonal pathways in patients with LVEF >40%. Furthermore, no trials have been conducted specifically in HFmrEF, although many trials assessing therapies in HFpEF have included participants who would be considered to have HFmrEF according to the proposed universal definition (Pitt, Pfeffer et al. 2014, Solomon, McMurray et al. 2019, Packer, Butler et al. 2021, Solomon, McMurray et al. 2022). For example, CHARM-Preserved showed that the addition of an ARB for patients with CHF and LVEF >40% had a moderate although non-significant effect of reducing rates of heart failure hospitalisations (HR 0.85, 95% CI 0.72-1.01, *p*=0.072), although did not prevent cardiovascular deaths (HR 0.99, 95% CI 0.80-1.22, *p*=0.92) (Yusuf, Pfeffer et al. 2003). This was despite including many patients with LVEF between 40 and 50% who would usually be regarded as having mildly impaired, or mildly reduced ejection fraction. The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial showed that MRA were not effective in reducing the composite endpoint of cardiovascular deaths, aborted cardiac arrest or hospitalisation for heart failure, enrolling participants with an LVEF or 45% or more (Pitt, Pfeffer et al. 2014). Similarly, neprilysin inhibition did not improve outcomes in participants with an LVEF of 45% or more in the Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction (PARAGON-HF) (Solomon, Rizkala et al. 2017).

More recently, the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) and Dapagliflozin

Evaluation to Improve the LIVEs of patients with pResevered ejection fraction heart failure (DELIVER) trials were the first positive trials in HFpEF (and HFmrEF). EMPEROR-Preserved was a double-blind trial, in which 5988 participants with NYHA Class II-IV symptoms and LVEF >40% were randomly assigned to receive empagliflozin or placebo. The novel therapy reduced the composite endpoint of cardiovascular death or hospitalisation for worsening heart failure (HR 0.79, 95% CI 0.69-0.90, p<0.001), mainly driven by a reduction in hospitalisation for heart failure (time to first event HR 0.73, 95% CI 0.61-0.88, p<0.001) (Anker, Butler et al. 2021, Solomon, McMurray et al. 2022). The total number of hospitalisations for heart failure was also lower in the empagliflozin group (HR 0.73, 95% CI 0.61-0.88, p<0.001). However, there were no significant differences in cardiovascular deaths (HR 0.91, 95% CI 0.76-1.09) or all-cause mortality (HR 1.00, 95% CI 0.87-1.15). DELIVER randomised 6263 patients with NYHA Class II-IV symptoms and LVEF >40% to dapagliflozin or placebo. Uniquely DELIVER included a population of patients who had been recently hospitalised, as well as a subgroup who had previously had HFrEF (HFimpEF). The composite primary outcome of cardiovascular mortality, hospitalisation for heart failure or urgent visit for heart failure was reduced in those randomised to dapagliflozin (time to first event HR 0.82, 95%CI 0.73-0.92; p<0.001), and consistent across subgroups. Again, these results were largely driven by first worsening heart failure events (HR 0.79, 95% CI 0.69-0.91) with cardiovascular death no different (HR 0.88, 95% CI 0.74-1.05).

EMPEROR-Preserved and DELIVER were conducted in ambulatory patients, who had mostly NYHA Class II symptoms, however are broadly in line with the Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure (SOLOIST-WHF) trial

(Bhatt, Szarek et al. 2021) which enrolled 1222 patients with diabetes mellitus who had experienced a recent heart failure decompensation. This study demonstrated a reduction in the primary composite endpoint of the rate of cardiovascular deaths or hospitalisations for heart failure (HR 0.67; 95% CI, 0.52 – 0.85, p<0.001) in participants randomised to sotagliflozin, with no interaction with LVEF with those with LVEF >50% appearing to derive similar benefit. In EMPEROR-Preserved the benefits of empagliflozin appeared to be attenuated for participants with LVEF ≥60% (HR 0.87 [95% CI 0.69-1.1) compared to LVEF <50% (HR 0.71 [95% CI 0.57-0.88]), however this was not the case in DELIVER where these groups appeared to derive similar benefit.

1.7 Pharmacological therapy for heart failure with improved ejection fraction

Many people with HFpEF and HFmrEF previously had HFrEF, and, possibly as a consequence of either favourable response to pharmacological or device therapies, or withdrawal of an initial insult, there is a growing population of patients with HFimpEF. The value of persistent pharmacological therapy for these patients was evaluated in the Therapy withdrawal in Recovered Dilated cardiomyopathy – Heart Failure (TRED-HF) trial, in which patients with idiopathic dilated cardiomyopathy, LVEF >50%, NT-proBNP <250ng/L and NYHA Class I symptoms, were randomised to open-label protocolised treatment withdrawal of pharmacological therapies, or usual care (Halliday, Wassall et al. 2019). Over a 6-month period, 44% of patients randomised to treatment withdrawal fulfilled criteria for relapse (either a reduction in LVEF, increase in LV volume or increase in NT-proBNP), compared to none randomised to usual care. At present, patients with HFimpEF might be regarded as having heart failure ‘in remission’ and likely have an indefinite indication for

pharmacological therapy, although there might be specific circumstances, for example following myocarditis, where supervised treatment withdrawal could be considered. Adding to this evidence, the DELIVER trial included a subgroup of patients who previously had LVEF <40%. In these patients there was no attenuation of benefit from the receipt of dapagliflozin for the primary endpoint (HR 0.74, 95% CI 0.56-0.97), suggesting these patients would also benefit from the introduction of an SGLT2i (Solomon, McMurray et al. 2022).

1.8 Device therapy for heart failure with reduced ejection fraction

1.8.1 Implantable cardioverter defibrillators

Sudden death is a major contributor to potentially reversible mortality in HFrEF (Packer 2020), with those who have ischaemic heart disease, severely impaired LV function, prior history of ventricular tachyarrhythmia, and diabetes mellitus, being at the highest risk (Myerburg, Mitrani et al. 1998, Walker and Cubbon 2015). A key mechanism of sudden death is ventricular tachyarrhythmia, which may occur as a consequence of coronary ischaemic events or catecholamine surges, electrolyte imbalances or without an acute precipitant. Implantable cardioverter defibrillators (ICD) are cardiac implantable electronic devices which provide protection against ventricular tachyarrhythmia. These devices consist of a generator, which sits in a pre-pectoral pocket, with a lead implanted into the right ventricular apex (with or without a lead in the right atrial appendage for patients in sinus rhythm).

Two trials investigated the role of ICD for primary prevention in people with HFrEF. The Multicentre Automatic Defibrillator Implantation Trial II (MADIT-II) randomised 1232 people with myocardial infarction and LVEF ≤30%, to ICD or standard of care,

demonstrating a reduction in all-cause mortality (HR 0.69, 95% CI 0.51-0.93, p=0.016) largely attributable to a reduction in sudden cardiac deaths (3.8% vs 10.0%, p<0.01) (Moss, Zareba et al. 2002). Subsequently, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) randomised 2521 people with NYHA Class II-III symptoms and LVEF <35%, to amiodarone, ICD or placebo demonstrating a 23% reduction in mortality compared to amiodarone or conventional therapy (HR 0.77, 97.5% CI 0.62-0.976, *p*=0.007), extending the indications to patients with non-ischaemic cardiomyopathy (Bardy, Lee et al. 2005).

Based on these trials, ICD implantation carries a Class I recommendation for patients with symptomatic CHF and LVEF ≤35%. However, all patients enrolled in MADIT-II, and the majority in SCD-HeFT, had ischaemic cardiomyopathy, and these trials were conducted in populations not receiving contemporary pharmacological therapies or cardiac resynchronisation therapy (CRT). The more recent Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality (DANISH) trial randomised 1116 people with non-ischaemic cardiomyopathy with LVEF ≤35%, to ICD or standard care (including CRT without defibrillator) (Kober, Thune et al. 2016). DANISH demonstrated a reduction in the rate of sudden cardiac death (HR 0.50, 95% CI 0.31-0.82, *p*=0.005), but did not meet its primary endpoint for all-cause mortality (HR 0.87, 95% CI 0.68-1.12, *p*=0.28). The trial was however powered to detect a 25% reduction in all-cause mortality in those allocated to ICD, and is likely to have been underpowered for a population with non-ischaemic cardiomyopathy receiving contemporary pharmacological therapies.

1.8.2 Cardiac resynchronisation therapy

Cardiac mechanical and electrical dysfunction can result in loss of synchronous contraction between the left and right ventricles (interventricular dyssynchrony), or between different parts of the LV myocardium (intraventricular dyssynchrony). Electromechanical dyssynchrony can occur as a consequence, or even as a primary cause of HFrEF, and has the effect of making an impaired LV even less effective. In patients with persistent LV systolic dysfunction despite optimised medical therapy and conduction delay, evidenced by broad QRS complex on electrocardiogram, the use of CRT, a specialised pacemaker which paces left and right ventricles simultaneously, has been shown to improve exercise capacity, reduce hospitalisation and extend longevity (Cazeau, Leclercq et al. 2001, Abraham, Fisher et al. 2002, Bristow, Saxon et al. 2004, Cleland, Daubert et al. 2005, Tang, Wells et al. 2010). Significant LV systolic dysfunction, particularly as a consequence of ischaemic cardiomyopathy, places patients at risk of sudden cardiac death due to ventricular tachyarrythmia. Many patients are therefore offered CRT in combination with defibrillator therapy in a single device.

1.9 Advanced heart failure therapies

Left ventricular assist devices (LVAD) are mechanical pumps which can either enhance cardiac output, or entirely replace the work of a failing LV, to maintain cardiac output and end-organ perfusion. In some patients, with an acute, reversible cause of heart failure, LVAD might be used as a bridge to recovery, however they are usually used as a bridge to heart transplantation (Ponikowski, Voors et al. 2016). Cardiac transplantation remains a limited therapeutic option for patients with advanced CHF

due to the scarcity of available organs, consequently LVAD are increasingly being utilised as ‘destination therapy’ (Table 1.2).

Table 1.2 Indications for left ventricular assist devices in advanced heart failure

Bridge to candidacy	LVAD to improve end-organ perfusion and achieve clinical stabilisation to make an ineligible patient eligible for heart transplantation.
Bridge to transplantation	LVAD in a patient at high risk of death awaiting a suitable organ.
Bridge to recovery	LVAD on a temporary basis to allow cardiac function to recover.
Destination therapy	LVAD as long-term therapy in a patient ineligible for heart transplantation.
Adapted from (McDonagh, Metra et al. 2021).	

1.10 Conclusions

CHF is a syndrome, characterised by breathlessness, exercise intolerance and congestion, which is classified according to the presence and degree of LV systolic dysfunction. Landmark trials have proven the efficacy of multiple pharmacological and device therapies in HFrEF, however there are more limited options for those with HFmrEF and HFpEF. An increasing number of pharmacological therapies for HFrEF have the potential to cause confusion and consequent delays in establishing patients on evidence-based therapies, but a more parallel approach might mitigate against this.

Chapter 2: Managing symptoms and caring for patients with chronic heart failure towards the end-of-life

In this chapter the focus shifts to managing symptoms and caring for people with chronic heart failure towards the end-of-life. The role of palliative care is introduced, how to identify patients who might benefit from such an approach, and how this might be better integrated into routine clinical care.

2.1 Introduction

Despite improvements in survival for people with established chronic heart failure (CHF) over the past two decades (Cubbon, Gale et al. 2011), largely as a result of the more widespread implementation of disease modifying therapies, the effect on symptoms has been more variable. It has been estimated that despite contemporary therapies, at least 5% of people living with CHF continue to have symptoms of breathlessness on minimal exertion or at rest (New York Heart Association [NYHA] class III/IV), whilst many more have persistent symptoms that limit their quality of life (Sobanski, Alt-Epping et al. 2020).

2.2 Improving access to palliative care

People with CHF are at risk of premature death, and even in ambulatory populations receiving contemporary therapies, a diagnosis of heart failure with reduced ejection fraction (HFrEF) is associated with an unpredictable and fluctuating disease trajectory, with 2.4-fold excess of life lost compared to matched healthy individuals (Drozd, Relton et al. 2021). Additionally, individuals with CHF report a burden of physical symptoms, psychological, and spiritual needs, comparable with many forms of cancer (O'Leary,

Murphy et al. 2009). Despite this, only a small proportion of patients with advanced CHF are ever referred for specialist palliative care services (Murray and Boyd 2011), or are enrolled in hospice care (Penrod, Deb et al. 2010). Even where this is done, it is likely to be within the last days of life (Cheung, Schaefer et al. 2013). As a result, palliative care teams may be less familiar with the complex care needs of CHF and may not feel confident caring for these patients (Goodlin, Trupp et al. 2007).

In response, palliative care teams and cardiologists have begun to appreciate the complex needs of this expanding patient group, with increasing integration of cardiology and specialist palliative care services. The evidence that palliative care is beneficial for patients with advanced CHF is well established. For instance, the Palliative Care in Heart Failure (PAL-HF) study investigated the effects of a multicomponent palliative care intervention in addition to standard care for patients with CHF, demonstrating improvements in anxiety, depression, and health-related quality of life (Rogers, Patel et al. 2017). Other studies have demonstrated that hospice care results in lower levels of hospitalisation after enrolment, even in highly symptomatic patients with advanced disease (Yim, Barron et al. 2017). However, despite palliative care *per se* having clear benefits in advanced CHF, there is less evidence to support specific interventions, and so in most circumstances standard palliative care techniques and practices should be followed.

2.3 Focussing on symptoms

2.3.1 Breathlessness and exercise intolerance

Breathlessness and exercise intolerance are the cardinal symptoms of CHF and are related to both prognosis and quality of life (Arena, Myers et al. 2008). Exercise

intolerance has traditionally been understood within the context of a haemodynamic model of CHF in which increased left ventricular (LV) filling pressures are required to maintain cardiac output, resulting in alveolar oedema. However, the degree of LV dysfunction correlates poorly to the severity of symptoms patients experience. Rather, both central and peripheral mechanisms contribute to the degree of exercise intolerance including skeletal muscle structure and function, anaemia, deconditioning, obesity and the central nervous system (Wolsk, Kaye et al. 2019, Koshy, Gallivan et al. 2020).

Breathlessness and fatigue often persist because standard pharmacological therapies have varying effects on symptoms, and for those with refractory symptoms there is little evidence to guide best practice. Opioids are commonly used to provide symptomatic relief for dyspnoea in advanced CHF not amenable to standard therapies, with randomised controlled trials demonstrating that opioids are effective in alleviating refractory dyspnoea and can be administered safely (Chua, Harrington et al. 1997, Johnson, McDonagh et al. 2002, Williams, Wright et al. 2003, Oxberry, Torgerson et al. 2011). This might be due to several mechanisms such as a reduction in respiratory drive, central perception of dyspnoea, and reduced anxiety. Studies have shown that opioids are not associated with adverse events in this population, with the precondition of starting at low doses and titrating to achieve adequate symptom control. Non-pharmacological interventions include breathing techniques, anxiety management, and the use of hand-held fans (McIlvennan and Allen 2016).

2.3.2 Oedema

Loop diuretics are the first line treatment for congestion, and those with advanced CHF often require high doses. Where significant right heart failure exists, the absorption of oral diuretics might be reduced due to enteral oedema and so intravenous diuretics may more efficacious, especially when given in combination with other agents (Oh and Han 2015, Mullens, Dauw et al. 2022). Episodes of decompensation become increasingly frequent in advanced CHF, and whilst this has traditionally required hospitalisation for intravenous diuretics, many patients do not wish to spend protracted periods in hospital, particularly towards the end-of-life. Heart failure specialist nurse led community administration of intravenous diuretics is a feasible alternative, which can safely avoid the requirement for hospitalisation (Austin, Hockey et al. 2013). A consideration is the difficulty of venous access in those towards the end-of-life, which can become increasingly troublesome. If fluid overload is a significant issue which is not managed by, or the patient is unable to take, oral therapy, then the subcutaneous route is an alternative (Beattie and Johnson 2012). Although off-license, subcutaneous diuretics have been used in clinical practice for decades and have the additional benefit that palliative care teams are familiar with infusions by this route.

2.3.3 Low mood and depression

Around a quarter of patients with CHF are at some point diagnosed with ‘clinically significant’ depression (Rutledge, Reis et al. 2006), with many reporting poor quality of life as well as social and spiritual distress (Bekelman, Havranek et al. 2007, Selman, Beynon et al. 2007). A diagnosis of depression is associated with increased risk of mortality and heart failure hospitalisation (Jiang, Alexander et al. 2001) and is more commonly observed in those with co-morbidities, rapid disease progression or those

who are diagnosed at a younger age (Jaarsma, Beattie et al. 2009). Depression is often overlooked, due to overlapping symptoms such as fatigue. Depression and cognitive function have been shown to worsen during episodes of decompensation and although recovery is typical following decompensation, it is often incomplete (Kindermann, Fischer et al. 2012).

Once recognised, treatment of depression is associated with improved quality of life and adherence to medical therapy (Connerney and Shapiro 2011). Selective serotonin reuptake inhibitors are often used as a first line pharmacological therapy due to their favourable side-effect profile, whereas tricyclic antidepressants and monoamine oxidase inhibitors should generally be avoided due to the increased risk of arrythmias or hypotension (Shapiro 2009). However, serotonin reuptake inhibitors have not consistently been shown to be more effective than placebo at reducing depression or improving cardiovascular status (O'Connor, Jiang et al. 2010). Non-pharmacological measures may also be effective and include exercise, psychotherapy, and cognitive behavioural therapy (McIlvennan and Allen 2016). In a randomised trial involving patients with CHF and depression, a combination of cognitive behaviour therapy which targeted depression and self-care was beneficial, reducing anxiety and fatigue, whilst improving social functioning and quality of life (Freedland, Carney et al. 2015).

2.3.4 Pain

Chronic pain is commonly reported by people with terminal illnesses and in that respect, CHF is no different. In an observational study, 84% of patients with advanced CHF reported some form of pain, and 70% believed it interfered with activities of daily living (Goodlin, Wingate et al. 2012). In CHF, chest pain is an important consideration,

particularly in those with ischaemic heart disease, being reported by around a third of patients (Blinderman, Homel et al. 2008). Refractory angina can become increasingly difficult to manage towards the end-of-life, especially where patients are deemed unsuitable for revascularisation and pharmacological therapies are poorly tolerated. Pain might occur elsewhere in the body, most commonly in the legs or back but can occur at multiple sites and be caused by a wide range of pathologies including neuropathy. Pain is likely to contribute to anxiety, poor sleep, and reduce performance status (Alemzadeh-Ansari, Ansari-Ramandi et al. 2017), as well as an autonomic response which can contribute to worsening of the CHF syndrome (Godfrey, Harrison et al. 2006). Cardiology teams are likely to be challenged by complex palliative care needs. Addressing pain by identification of the underlying cause and tailoring treatment appropriately, is best achieved by the close integration of cardiology and specialist palliative care teams.

2.3.5 Frailty

Frailty is a common clinical syndrome, characterised by increased vulnerability due to age-related decline in functional capacity and physiological reserve (Xue 2011). Frailty is more frequently observed in people with CHF than the general population, is an independent predictor of poor outcomes (Afilalo, Alexander et al. 2014), and can be ameliorated by more effective treatment of the underlying syndrome (Anker, Negassa et al. 2003). Substantial changes to the gastrointestinal tract in people with CHF result in altered permeability with the increased absorption of endotoxin with a resultant increase in proinflammatory cytokines (Romeiro, Okoshi et al. 2012). This proinflammatory response, coupled with decreased gastrointestinal nutrient absorption, contributes to the development of cardiac cachexia, a severe wasting

process, particularly affecting skeletal muscle, which reduces exercise tolerance, and increases dyspnoea and fatigue (Wood, Straw et al. 2021). The recognition of frailty provides valuable prognostic information in CHF, which might support an early adoption of a palliative approach.

2.4 Human factors

2.4.1 Understanding the condition

Patients with CHF are commonly poorly informed about the reality of their illness, their disease trajectory, and the purpose of disease modifying therapies. Often symptoms of the disease are misinterpreted for side effects of medications (Rogers, Addington-Hall et al. 2002), and a lack of education is often compounded by barriers to good communication including fatigue, confusion and cognitive dysfunction. Education is a key factor in the care of CHF, and this may go some way to ameliorate feelings of anxiety.

2.4.2 Support networks

The role of families and informal care givers in the care of patients with CHF often intensifies during decompensation or in the terminal phase of their illness. Patients with advanced CHF report having to rely heavily on family and others for help in performing activities of daily living, which might provoke feeling of being a burden upon others. Families are often asked to contribute to shared decision making towards the end-of-life. Poor mobility and inability to leave the house are not uncommon and may contribute to feelings of social isolation. Qualitative studies have shown that the majority of people with advanced CHF have thought about their death, although they

might find it difficult to communicate this with those close to them (Horne and Payne 2004).

2.5 Identifying those approaching the end-of-life

Clinical guidelines and consensus statements recommend the concurrent provision of palliative and supportive care, alongside contemporary evidence-based therapies (Hill, Prager Geller et al. 2020). The disease trajectory of CHF is highly variable and so identification of those nearing the end-of-life who may benefit from a palliative approach is difficult. As a result, many patients are not offered the psychological and medical support that they need as their condition deteriorates, for fear of providing this support 'too early' and increasing the workload of palliative care services, or adversely affecting prognosis by withdrawing life-sustaining therapies. There is no evidence of a nocebo effect of referral to palliative care, although it is conceivable that this might be a concern of cardiologists.

Regardless of how patients are identified, timely palliative care interventions which focus on quality of life for the individual patient, regardless of estimated prognosis are essential. Such a strategy does not require that a point in time be identified where the patient 'becomes palliative'. Rather, palliative care could become an early, integral part of the management of CHF alongside contemporary pharmacological and device therapies. This, together with a more integrated approach combining cardiology, community and palliative care services could support complex decision making.

2.5.1 New York Heart Association Classification

The NYHA classification is a simple clinical tool used to describe the severity of CHF symptoms, which grades symptoms into four categories from asymptomatic to symptomatic at rest. Worsening functional status is associated with a poor prognosis, for instance the one-year mortality for patients with NYHA class IV symptoms is 28%, compared to only 7% who are in class II (Muntwyler, Abetel et al. 2002). Focussing on symptoms seems likely to enable those caring for people with CHF to identify those who would benefit from a palliative approach, or referral to specialist palliative care services. Whether there is a poor prognosis or where patients have symptoms that are difficult to manage, or both, patients are best managed within a multidisciplinary palliative care team. However, it must be appreciated that for individual patients there is still a great amount of uncertainty, and NYHA class may either worsen, or improve over time. Furthermore, the NYHA class is inherently subjective and there is significant overlap between patients in different classes in terms of exercise tolerance and severity of the syndrome (Blacher, Zimerman et al. 2021).

2.5.2 The Surprise Question

The ‘Surprise Question’ has been proposed as a screening tool which could help identify patients with chronic illnesses who are within the last year of life, who might have the most to benefit from adopting an early palliative approach. The Surprise Question aims to facilitate discussions around advanced care planning and where appropriate, prompt earlier referral to specialist palliative care (Moss, Ganjoo et al. 2008, Murray and Boyd 2011, Weissman and Meier 2011, Rice, Hunter et al. 2018). Although clinician predicted prognosis is convenient, it may lack accuracy due to a tendency to overestimate prognosis and the effects of therapy, thereby leading to the

deferral of decisions around end-of-life care (Christakis and Lamont 2000, Selby, Chakraborty et al. 2011, Hui 2015). The Surprise Question aims to redress this tendency by asking not if is probable a patient might die, but merely if it is possible. It also aims to not provide an estimate of prognosis in time, rather to pose a reflection question: “Would you be surprised if this patient were to die within the next year?”.

The Surprise Question forms part of the Gold Standards Framework in the United Kingdom, recommended as a first step to aid recognition that patients are nearing the end-of-life, and is also included in the National Institute of Health and Care Excellence guidelines on end-of-life care (Muntwyler, Abetel et al. 2002). The Surprise Question has been validated in patients with cancer and in those with and without dialysis-dependent chronic kidney disease in whom it reliably and accurately predicts prognosis (Moss, Ganjoo et al. 2008, Cohen, Ruthazer et al. 2010, Moss, Lunney et al. 2010, Da Silva Gane, Braun et al. 2013, Pang, Kwan et al. 2013, Moroni, Zocchi et al. 2014, Hamano, Morita et al. 2015, Rhee and Clayton 2015, Amro, Ramasamy et al. 2016, Javier, Figueroa et al. 2017, Malhotra, Tao et al. 2017). Although decompensation of heart failure requiring hospitalisation is a poor prognostic sign, many patients have subsequent long periods of relative stability (Figure 2.1). It is this characteristic non-linear trajectory which casts doubt as to whether the Surprise Question is an appropriate tool in the setting of CHF. The ability of the Surprise Question to identify individuals hospitalised with CHF is explored in Chapter 7.

2.6 Deprescribing pharmacological therapy towards the end-of-life

Contemporary pharmacological therapies for HFrEF can draw from a broad evidence base, and most patients will be taking several agents proven to improve prognosis and

reduce adverse LV remodelling. The fundamental therapies in HFrEF inhibit the adverse neurohormonal maladaptations of the RAAS and sympathetic nervous systems (McDonagh, Metra et al. 2021). In advanced heart failure, RAAS inhibition may help alleviate symptoms up to the terminal stages of the disease, and so these agents should be not routinely discontinued, as long as patients are able to take and tolerate them. The major side effects of these agents are symptomatic hypotension (Turgeon, Kolber et al. 2019) and if patients experience this, then reduction in treatment dosages should be considered, accepting this may contribute to the progression of the syndrome. Where fluid overload is a predominate symptom, reduction in beta-adrenoceptor antagonists and ACEi should be considered to allow increases in diuretic doses, whereas in the absence of congestion, reductions in diuretics may be safely considered first.

2.7 Managing device therapy for heart failure towards the end-of-life

People who have HFrEF are at risk of sudden cardiac death, either due to severely impaired LV function, ischaemic aetiology of heart failure or prior ventricular arrhythmia or cardiac arrest and may be offered an implantable cardioverter defibrillator. This may be combined with a CRT device in those with electromechanical dyssynchrony. CRT should be treated in the same fashion as standard pacemakers for treatment of bradycardia when nearing the end-of-life. Deactivation of the device is not generally indicated and may result in an acute deterioration in symptoms and added distress to the patient. There may, of course, be patients who feel that their CRT device is prolonging their death, and request deactivation. In these circumstances, it is important to explain that deactivation will not necessarily hasten

death, and may increase discomfort in the final stages of life. As with all matters, a patient's right to choose must be respected.

On the other hand, ICD therapy has significant implications for patients nearing the end-of-life. By successfully treating arrhythmias, patients are more likely to suffer death from progressive heart failure or non-cardiovascular causes (Cubbon, Gale et al. 2011, Walker, Drozd et al. 2018). ICDs can be deactivated when the risk-benefit is no longer favourable. Often, patients do not understand that ICDs prevent sudden death thereby making a protracted death more likely. Patients and physicians rarely discuss deactivation of devices prior to implantation, and nor is this matter easily addressed as the clinical course progresses. Discussion about deactivation should ideally start prior to implantation, and guidelines encourage physicians to discuss deactivation should a terminal illness arise, and advocate the use of advanced directives to address these issues ahead of time (Tracy, Epstein et al. 2012). For many patients, quality of life is the priority over length (Goodlin, Hauptman et al. 2004). If patients receive repeated shocks towards the end-of-life from their device, this should certainly trigger discussions regarding deactivation of defibrillator function (MacIver, Rao et al. 2008). All institutions that implant ICDs should have procedures in place for the elective deactivation of devices. Likewise, all involved in the care of patients with CHF towards the end-of-life, should have pathways in place to access these facilities.

2.8 Left ventricular assist devices towards the end-of-life

As discussed in Chapter 1, left ventricular assist devices (LVAD) are mechanical pumps which provide the work of the LV to maintain cardiac output, and are increasingly offered to patients with advanced heart failure refractory to contemporary

pharmacological and device therapies. Heart transplantation remains a limited therapeutic option, in part due to the availability of suitable organs, but also because of co-morbidities in patients with advanced heart failure which preclude suitability for transplantation. The primary indication for LVAD is usually as a bridge to transplantation or bridge-to-candidacy in those who are either suitable for transplantation and are awaiting a suitable donor, or those who would be suitable following a period of stabilisation (Ponikowski, Voors et al. 2016). However, LVADs are increasingly being utilised as destination therapy, in those who are either unsuitable for transplantation or in whom a suitable organ never becomes available.

Assessment for suitability for LVAD therapy is an in-depth process, carried out in dedicated centres. Pre-assessment involves not only assessing the physical condition and the suitability for transplant, but also the patient's psychological ability to deal with this most invasive of treatments. LVAD have several inherent risks, such as need for repeated surgery, thrombosis, need for anticoagulation and the associated bleeding risk and infection. The majority of patients will not be suitable for LVAD, however due to the widespread use and expanding clinical indications, there are an increasing number of patients who deteriorate and approach the end-of-life with LVAD *in situ*. This brings about a number of complex considerations and the need to address decisions around end-of-life care and device deactivation. Decisions about patients' wishes in specific circumstances such as a terminal illness should ideally be held in advance, so that the family and multidisciplinary team are aware of these. Institutions that implant LVAD are encouraged to adopt an holistic approach, including palliative care support, to help with such decisions.

Parallels might be drawn between the use of LVADs and life-prolonging therapies in other medical co-morbidities. For instance, for patients with end-stage renal failure, the use of renal replacement therapy (dialysis) might be considered as destination therapy, or as a bridge to renal transplant in those who are suitable. Renal replacement therapy places considerable burden on a patient's quality of life, and so careful discussions about the role and limitations of these interventions must be had beforehand. For many, conservative management will be preferable, particularly in patients in whom quality of, rather than duration of life is their key priority.

2.9 Conclusions

Patients with CHF represent a highly symptomatic population with a poor prognosis. Despite clear need, and evidence that more would welcome this, only a small proportion are ever referred to specialist palliative care services. This may in part be due to an unpredictable disease trajectory, which complicates decision making for patients and carers. Those caring for patients with CHF should advocate an early adoption of a palliative approach, focussing of quality of life as a key priority alongside life-sustaining therapies. Palliative care can best be delivered by heart failure teams, with close integration with community and specialist palliative care services. A key priority for research will be to better identify those who may benefit from referral.

Chapter 3: Outcomes in chronic heart failure and assessing 'response'

In this chapter the concept of 'response' is introduced, and the inherent difficulties in measuring improvement or deterioration in studies of chronic heart failure. Additionally, the advantages and disadvantages of various outcome measures are discussed.

3.1 Introduction

Chronic heart failure (CHF) is the syndrome of breathlessness and exercise intolerance which occurs in the presence of objective cardiac dysfunction. The natural history of CHF is progression of the syndrome, invariably resulting in debilitating symptoms, hospitalisation, and death. Interventions for CHF could conceivably impact any of these aspects but should at the very least improve at least one without adversely affecting the other two (Packer 2016). Trials and observational studies have assessed various outcome measures including symptoms, exercise capacity, surrogate markers such as left ventricular (LV) function, hospitalisation, mortality, and composite endpoints.

3.2 Natural history of chronic heart failure

CHF is a progressive syndrome, but the clinical course for individual patients is highly variable compared with other chronic diseases. Patients typically have stable phases of variable duration, which are punctuated by episodes of decompensation of differing severities, which may require hospitalisation. As the syndrome progresses, these episodes of decompensation become more frequent, requiring longer periods of

treatment to re-achieve stabilisation. Figure 3.1 shows the clinical course of the syndrome in which death, represented by the vertical arrows can occur suddenly during any phase throughout the course of illness, including where patient's signs and symptoms are stable, or due to progressive heart failure. Although decompensation of heart failure requiring hospitalisation is a poor prognostic sign, and the function status is often less than it was previously, many patients subsequently have long periods of relative stability. It is this characteristically non-linear trajectory of heart failure which makes prognostication for individual patients inaccurate, and identifying those who respond or do not respond to treatments so difficult.

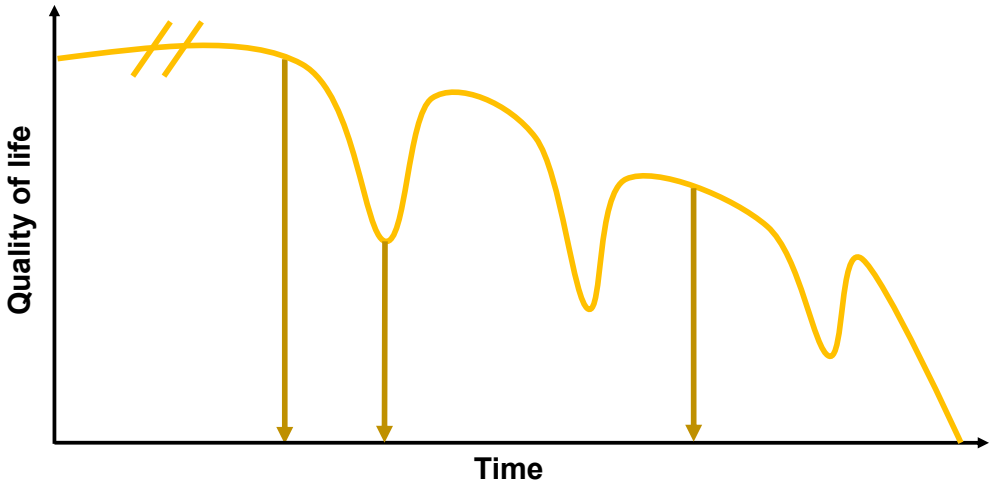


Figure 3.1 Typical clinical course of chronic heart failure
Adapted from (Straw, Witte et al. 2021)

3.3 'Response' – difficult to measure and hard to define

Measuring 'response' in CHF is difficult, due to the variable burden of symptoms, the unpredictable trajectory of the illness and deterioration anticipated, even in patients receiving optimal therapies. Figure 3.2 demonstrates how the concept of 'response' in CHF may cause confusion. For patients receiving a proven and effective therapy, the subsequent disease trajectory may be highly variable.

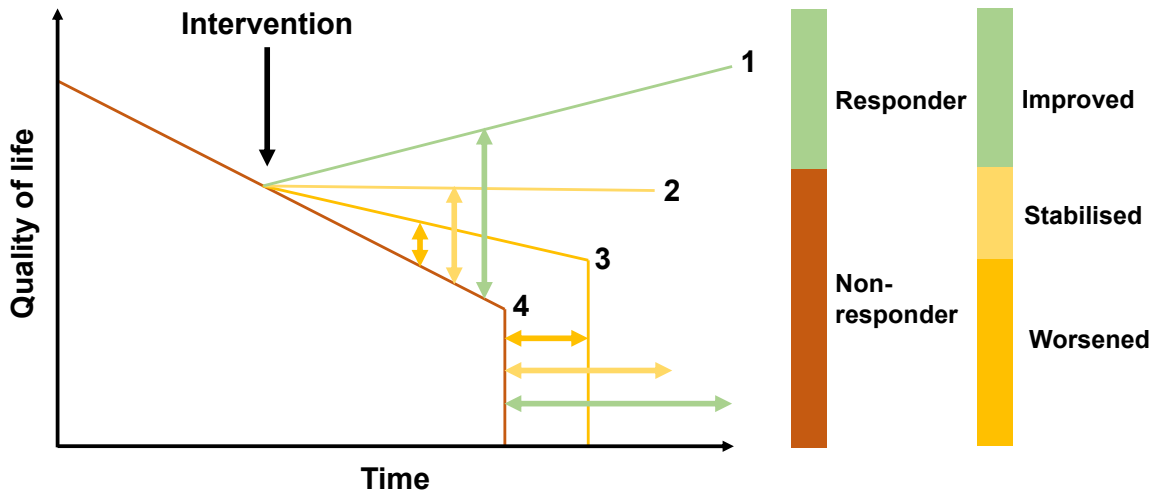


Figure 3.2 Measuring 'response' in chronic heart failure
Adapted from (Cubbon and Witte 2009) and (Mullens, Auricchio et al. 2020).

- Patient 1 receives the intervention and experiences an improvement in symptoms, quality of life or a surrogate marker.
- Patient 2 receives the intervention and remains stable.
- Patient 3 receives the intervention and continues to deteriorate, but less rapidly than they otherwise would have.
- Patient 4 does not receive the intervention and continues to deteriorate.

According to a binary definition of response, only patient 1 benefits from this intervention. However, at any point in the future, patients 1, 2 and 3 who receive the intervention, are more likely to have better quality of life, and be alive at any point than if they had not. This is true whether the symptomatic status or quality of life improves, stabilises, or continues to deteriorate (albeit less rapidly). For individual patients, staying the same or the syndrome progressing more slowly, are meaningful outcomes

associated with a favourable prognosis (Gold, Rickard et al. 2021). However, the benefits of an intervention which achieves stability are not possible to determine from longitudinal studies without appropriate comparisons to those not receiving the intervention (Cubbon and Witte 2009). Paradoxically, observational studies aiming to identify those with the best chance of meeting the criteria of response (and therefore deselect those with little chance of achieving this), may deny individuals treatments where there are prospective randomised data to support their use.

It is plausible that within the populations of participants enrolled in clinical trials, which often use broad inclusion criteria, there may be individuals for whom the benefits of an intervention are curtailed or do simply not exist. For example, the Sudden Cardiac Death in Heart Failure Trial enrolled participants with both ischaemic and non-ischaemic cardiomyopathies (Bardy, Lee et al. 2005), showing a reduction in all-cause mortality which resulted in the expansion of guideline indications for primary prevention implantation of ICDs. These findings were not replicated in the Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality trial, restricted to those with non-ischaemic cardiomyopathy (Kober, Thune et al. 2016). However, this approach comes with the risks of undertreatment of a population in which the benefits have been shown in prospective randomised studies.

3.4 The severity paradox

Clinical trials have often not enrolled participants who reflect the demographics of real-world populations, thereby limiting external validity. For example, the mean age of participants receiving device therapies in the relevant trials were at least a decade

younger than those encountered in routine clinical practice (Moss, Zareba et al. 2002, Bristow, Saxon et al. 2004). This may be one reason why older patients are less likely to be implanted with cardiac devices or receive contemporary pharmacological therapies. Another reason may be that patients who are older are perceived to have less to gain from life-extending therapies compared to younger patients. Whilst it is true that older patients die sooner, and in absolute terms the youngest attain the most additional life years, older patients may in fact experience the greatest *proportionate* medium-term gain. The same is true of disease severity, where those with advanced disease have the most proportionate gain from life sustaining therapies (CONSENSUS 1987), but this is vastly overwhelmed, in absolute terms, by populations with less severe disease (SOLVD 1991).

3.5 Which outcomes are relevant in chronic heart failure?

Outcomes of interest in CHF may include mortality, worsening heart failure events (including hospitalisation), symptoms, exercise tolerance, and quality of life. The discovery that pharmacological therapies could reduce mortality in patients with CHF, resulted in a moral imperative to conduct appropriately powered clinical trials to determine the effect on these outcomes, and to ensure therapies which improved symptoms or exercise tolerance did not do this at the expense of survival. All-cause mortality has become the primary outcome of interest of most clinical trials in CHF, the paradox being that patients present with symptoms of breathlessness and exercise intolerance, and the most commonly prescribed treatments have a variable impact on these (Bekelman, Rumsfeld et al. 2009).

3.6 Mortality

3.6.1 All-cause mortality

CHF remains a disease of shortened longevity, despite contemporary pharmacological and devices therapies. The earliest trials of angiotensin converting enzyme inhibitors (ACEi) and beta-adrenoceptor antagonists generally used all-cause mortality as their primary endpoint. *Post-hoc* analyses of these trials revealed that certain classes of medications differentially affected modes of death. For example, the ACEi enalapril reduces all-cause mortality (CONSENSUS 1987), primarily due to a reduction in deaths due to progressive heart failure (CONSENSUS 1987). In contrast, the beta-adrenoceptor antagonist bisoprolol reduces all-cause mortality (CIBIS-II 1999), primarily driven by reductions in sudden cardiac deaths.

3.6.2 Modes of death

The more widespread implementation of disease modifying pharmacological and device therapies for heart failure have resulted in reductions in mortality as well as the relative contribution of sudden cardiac deaths (Cubbon, Gale et al. 2011). Non-cardiovascular deaths are now the most frequent mode of death in people with HFrEF, and of these, deaths due to infections are the most common (Walker, Drozd et al. 2018, Drozd, Garland et al. 2020). Non-cardiovascular deaths are unlikely to be affected by pharmacological or device therapies which target the maladaptations of the heart failure syndrome, such that alternative solutions have been used to address the competing risks of non-cardiovascular deaths and increase the power of clinical trials. Contemporary cardiovascular outcomes trials typically incorporate cardiovascular deaths as primary outcome measures, often within a composite which includes worsening heart failure events (McMurray, Packer et al. 2014, McMurray,

Solomon et al. 2019). The disadvantages of such an approach are that, firstly, it is unlikely that the cause of death matters to patients, except where the mode of death is protracted, and may suggest a treatment is effective (in terms of extending longevity) despite all-cause mortality being similar due to other competing risks (Swedberg, Komajda et al. 2010).

3.7 Worsening heart failure events

Widespread implementation of pharmacological and device therapies over time has reduced event rates, and so to detect statistically significant and clinically meaningful reductions in mortality, randomised controlled trials would have to become considerably larger and prohibitively expensive. To improve statistical power, study designs now routinely adopts composite endpoints, most commonly comprising cardiovascular mortality and adjudicated heart failure hospitalisation (but could conceivably include seeking medical attention for heart failure decompensation or use of intravenous diuretics in the community) (Straw, Gierula et al. 2022). A limitation of such an approach is that hospitalisations are often complex and multi-factorial, meaning misclassification is possible. For example, in the Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) trial (Solomon, McMurray et al. 2019), sacubitril-valsartan did not reduce either hospitalisation for heart failure, or all-cause mortality compared to valsartan, both in terms of the individual components or as a composite outcome (rate ratio 0.87 [95% confidence interval 0.75-1.01], p=0.059). In PARAGON-HF, hospitalisations were adjudicated by a blinded committee according to standardised criteria in which for the primary diagnosis to be heart failure, the admission had to be unscheduled, lasting ≥24 hours, with documentation of at least one symptom, two clinical signs, objective

markers of congestions (chest radiograph, and elevated NT-proBNP), as well as the receipt of a treatment specifically designed to treat heart failure (significant augmentation of oral diuretics, intravenous diuretics or circulatory support) (Hicks, Mahaffey et al. 2018). Utilising this approach, the overall result of the trial was non-significant, however 28% (n=566) of investigator reported worsening heart failure events were negative adjudicated. In an unspecified *post hoc* analysis, investigator reported heart failure hospitalisations were categorised by the probability these related to heart failure, and then including mean probability for each event in multiple imputations suggested the novel agent was associated with a lower risk of heart failure hospitalisation (rate ratio 0.86, p=0.043). This approach is questionable and should be regarded as hypothesis generating but serves to highlight the difficulties in adjudicating modes of hospitalisation and how the endpoints of clinical trials are sensitive to the definitions applied.

3.8 Symptoms, exercise capacity and quality of life

From the perspective of the patient, the most clinically meaningful markers of disease severity are likely to be symptoms and exercise capacity. However, these are highly variable between patients and may change day-to-day without changes or intensification to background therapy. This variability creates challenges when assessing improvements in outcomes with novel therapies.

3.8.1 Exercise capacity

Time-to-event analyses of death and hospitalisation have not always been the principal focus of heart failure trials, with earlier work also recognising heart failure as a disease of physical limitation, commonly employing objective markers of exercise

capacity as trial endpoints (Packer 2016). Sadly, such an approach was greatly confounded by being limited to patients who could complete the study protocol, whilst those who became too unwell or died were excluded, limiting generalisability and potentially exaggerating treatment effects. Additionally, participants were often required to achieve a highly reproducible pre-treatment value, as variation between tests was often greater than the effect of the study drug, reducing sample sizes and the generalisability of findings (Edelmann, Wachter et al. 2013). Subsequently, the discovery that therapies which improved acute haemodynamics and exercise capacity in the short term could increase the risk of death (Hampton, van Veldhuisen et al. 1997), whilst therapies which had neutral effects on exercise capacity could dramatically improve survival (Lewis, Docherty et al. 2022), led to a mandate that safety be a primary outcome of cardiovascular trials.

Methods to assess exercise capacity objectively include six-minute walk distance, exercise time (using a standardised workload such as the Bruce protocol) and cardiopulmonary exercise testing which provides breath-by-breath analysis of gas exchange. Outcomes such as walk distance, or exercise time may be more relevant to patients than surrogate markers such as LV remodelling. However, these are effort and time dependent, and often improved with placebo or due to familiarisation with the exercise protocol during the study period. Other objective measures obtained by cardiopulmonary exercise testing, such as peak oxygen consumption have prognostic relevance and may be reasonably included. However, a disadvantage of all these metrics is that they are only studied at fixed time points, limiting analysis only to participants who complete the entire study, possibly exaggerating treatment effects by

neglecting those who could not complete the study protocol due to frailty, worsening of the condition, or death.

3.8.2 New York Heart Association classification

The most commonly used tool to assess symptoms in clinical practice, the New York Heart Association (NYHA) classification, divides patients into four categories based upon a subjective assessment of functional status. Patients with class I symptoms have no limitations in physical activity, whereas those with class IV symptoms are breathless at rest (Table 3.1). This simple classification is a fundamental part of the clinical assessment of patients with HFrEF, due to its incorporation in clinical trials and guidelines (Ponikowski, Voors et al. 2016, Yancy, Jessup et al. 2017). There are clear relationships at a population level between the severity of symptoms and outcomes and it is unusual for patients in classes I and II to be regarded as having ‘advanced’ heart failure, even in the presence of severely impaired LV function. However, LV function correlates poorly with NYHA class, and mildly symptomatic patients might still be at increased risk of hospitalisation and death.

3.8.3 American College of Cardiology Foundation/American Heart Association Classification

An alternative scale, the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) classification, combines structural changes of heart disease and symptoms, emphasising the development and progression of disease (Yancy, Jessup et al. 2013), whilst the NYHA classification focusses on exercise capacity and symptoms. Both classification systems can be used to describe individual patients, or patient populations (Table 3.1).

Table 3.1 Comparison of the NYHA functional classification and ACCF/AHA stages of heart failure classification systems

NYHA Functional Classification		ACCF/AHA Stages of Heart Failure	
No equivalent class		A	At high risk of developing CHF, without structural heart disease or symptoms
I	Asymptomatic with no limitation in ordinary physical activity	B	Structural heart disease but without signs or symptoms
II	Mild symptoms and slight limitation during ordinary physical activity	C	Structural heart disease with prior or current symptoms
III	Marked limitation in due to symptoms, comfortable only at rest		
IV	Symptoms present at rest		
IV	Symptoms present at rest	D	Refractory CHF requiring specialist interventions
Adapted from (Yancy, Jessup et al. 2013).			

3.8.4 Health-related quality of life

Physical symptoms such as easy fatiguability, shortness of breath, and oedema, as well as anxiety and depression are common, despite contemporary pharmacological and device therapies (Koshy, Gallivan et al. 2020). Given the challenges of declining event rates, the difficulties in assessing exercise capacity objectively, and the difficulty in assessing changes in complex symptoms using blunt tools such as NYHA classification, the scope of clinical trials has appropriately broadened to incorporate patient-reported outcome measures, including health related quality of life. Numerous tools have been proposed, the most commonly used being the Minnesota Living with Heart Failure Questionnaire (Rector 1987), the Kansas City Cardiomyopathy Questionnaire (Green, Porter et al. 2000), and the generic EuroQol 5D-3L/5L questionnaire and visual analogue scale (Rabin and de Charro 2001), which have generally been assessed in relation to each other. Health status has usually been

reported separately from ‘hard’ endpoints and analysed as second outcomes of the trial (Butler, Filippatos et al. 2022).

3.9 Clinical composite scores and joint modelling

Estimating change in health status appears simple but becomes challenging where there are informatively missing data, particularly relevant for conditions such as CHF where censorship due to death is common. Quality of life assessments are only available for patients who survived the study protocol and were well enough to complete the questionnaires, possibly exaggerating treatment effect estimates since quality of life and survival are closely correlated (Johansson, Joseph et al. 2021). On the other hand, there are inherent limitations in studies which utilise time-to-event analyses. For example, patients who experience an improvement in symptoms, are regarded as being the same as those who remain symptomatic (or worsen) but are not hospitalised and do not die. Additionally, a patient who initially improves but dies later in the trial is counted as having a more favourable outcome than a patient who is hospitalised early, but subsequently stabilises.

To address these limitations, analyses which incorporate health status and adverse outcomes into a single metric have been proposed including hierarchical clinical composite scores (Packer 2001) as has been utilised recently in the Empagliflozin 10mg Compared to Placebo, Initiated in Patients Hospitalised for acUte Heart failure Who Had Been Stabilised (EMPULSE) trial (Voors, Angermann et al. 2022). This approach tackles the issue of mixing endpoints with different clinical (death is more important than hospitalisation) and statistical (earlier deaths are worse than later deaths) weights, whilst including data on improvement or deterioration. The ‘score’

allocates patients into one of three ranks, and interventions are evaluated by testing the differences in rank between study groups, with the overall result determined by ‘win-ratio’.

Table 3.2 Clinical composite score

Rank	Criteria
Improved	Symptoms improve *and* Not hospitalised with heart failure *and* Alive
Worsened	Symptoms worsen *or* Hospitalised with heart failure *or* Dead
Unchanged	Symptoms unchanged *and* Not hospitalised with heart failure *and* Alive
Adapted from (Packer 2016).	

The advantages of such an approach are that, firstly, the clinical composite score combines changes in symptoms and clinical events into a single metric which can be easily understood by a non-statistician. Furthermore, in time-to-event analyses, only patients who experience an event contribute to the statistical power, whereas by using the composite score those who remain unchanged still contribute to the overall outcome. Additional hierarchical ranks are possible, for instance, it is reasonable to rank cardiovascular death more severely than hospitalisation for heart failure, and a deterioration of symptoms as the least severe outcome.

Clinical composite scores can only be applied to participants who have the potential to show a meaningful improvement in symptoms, and so for those with Class I

symptoms, a time-to-event analysis is more appropriate. Furthermore, a composite score might be impossible to interpret if it is feasible that for a given intervention both more patients could improve *and* deteriorate compared to the comparator. Joint modelling has been proposed as an alternative approach which has the advantage of leveraging the raw data from the trial offering the opportunity of considering dependencies between time-to-event data and repeated measurements of longitudinal data such as health status (Ibrahim, Chu et al. 2010). Joint models have been applied successfully in the fields of human immunodeficiency virus and oncology and explored *post hoc* in the setting of transcatheter aortic valve implantation (Spertus, Hatfield et al. 2019). Regardless of the approach taken, results from clinical trials need to be readily understood by non-statisticians, whilst ensuring observed changes in quality of life are 'real' and meaningful to patients.

3.10 Left ventricular remodelling

Remodelling is a progressive change in the structure and function of the LV which occurs in CHF. Pharmacological and device therapies often have favourable effects on LV remodelling, therefore this has sometimes been used as a surrogate outcome measure in clinical studies investigating novel treatments in CHF.

3.10.1 Imaging modalities

Left ventricular remodelling is usually determined by assessing cardiac function non-invasively using echocardiography, also known as cardiac ultrasound. Alternative imaging modalities to assess cardiac structure and function include cardiac magnetic resonance imaging (MRI) and nuclear medicine testing. Echocardiography remains

the primary method of assessing cardiac function due to the ease of use, availability, and relatively lower cost.

3.10.2 Measuring cardiac structure and function using echocardiography

Two-dimensional echocardiography provides a real-time imaging of the geometry of the heart throughout the cardiac cycle. Left ventricular ejection fraction (LVEF) is the most commonly used measure of systolic function and is a fundamental component of risk stratification, with treatments being predicated on LVEF cut-offs to classify patients as having reduced, mildly reduced or preserved ejection fraction (McDonagh, Metra et al. 2021). Other measures such as stroke volume, global longitudinal strain or contractility have prognostic value but have not been validated in clinical trials assessing treatments in CHF. LVEF is calculated by measures of LV internal dimensions and volumes taken at end-diastole and end-systole, determined by simultaneous electrocardiogram. Volumetric measurements are made by manually tracing the endocardial border of the left ventricle, most commonly using the modified Simpson's biplane method of discs, which combines measures taken in apical two-chamber and four-chamber views (Lang, Bierig et al. 2006).

3.10.3 Alternative imaging modalities

Cardiac magnetic resonance (CMR) is regarded as the gold-standard for assessing LV volumes and function, with increased resolution and reduced inter-observer variability compared to echocardiography. Additionally, CMR can provide information on the aetiology of CHF, for example on the presence of myocardial scar, inducible ischaemia, and myocardial viability. However, these investigators are more expensive and time consuming compared to echocardiography, and are contraindicated in

individuals with poor renal function, non-conditional medical devices (including pacemakers and defibrillators), or claustrophobia. Furthermore, there is often a discrepancy between LVEF measured by CMR compared to echocardiogram (often measured as being higher by cardiac MRI (Pellikka, She et al. 2018)), whilst the best evidence to guide practice is derived from clinical trials which have usually used LVEF determined by echocardiogram as inclusion and exclusion criteria. Nuclear medicine imaging is another modality available to assess cardiac structure and function. Equilibrium radionucleotide angiography involves injecting a radiopharmaceutical into a vein and acquiring images of cardiac structure, providing a more reliable and reproducible estimation of LVEF than echocardiography, but with the disadvantage of being invasive and more costly.

3.10.4 Implications of left ventricular remodelling

Whilst LVEF at any given time point correlates poorly with symptoms and outcomes, improvement in LVEF is associated with a favourable prognosis. For example, in recipients of CRT, the extent of LV remodelling is related to improvement in symptoms, freedom from heart failure events and to survival (Ypenburg, van Bommel et al. 2009). For this reason, change in LVEF is commonly used as a surrogate outcome measure in studies assessing interventions in HFrEF, particularly where small sample sizes give limited statistical power to determine differences in cardiovascular outcomes between treatment groups. However, such surrogate measures do not always reliably mirror the clinical status of patients, in terms of symptoms, worsening heart failure events or mortality.

3.11 Conclusions

Measuring response in CHF is difficult due to a variable burden of symptoms and expected decline even in those receiving optimal therapies. Various outcome measures have been proposed including left ventricular remodelling, symptoms, heart failure hospitalisation and death. Each outcome measure has its advantages and disadvantages and may be applied to the study of outcomes in CHF, as long as comparisons are made with a relevant group, the outcomes are pre-specified and relevant to the question being asked.

Chapter 4: Provision of pharmacological therapies and outcomes in multi-morbid patients with heart failure with reduced ejection fraction

Hypothesis: Patients with heart failure with reduced ejection fraction who have co-morbidities derive similar benefits from disease modifying pharmacological therapies as patients without co-morbidities.

4.1 Introduction

The prevalence of chronic heart failure (CHF) continues to rise at least in part owing to the widespread implementation of disease-modifying pharmacological therapies (CIBIS-II 1999, MERIT-HF 1999, Eichhorn and Bristow 2001). As a consequence, patients are living longer with a diagnosis of CHF and are increasingly multi-morbid (Sharma, Zhao et al. 2018). Although use of these agents has been accompanied by changes in the distribution of modes of death, particularly the relative contribution of sudden death (Cubbon, Gale et al. 2011, Shen, Jhund et al. 2017), it remains an important contributor to potentially preventable mortality in patients with heart failure with reduced ejection fraction (HFrEF) (Packer 2020), with those with previous myocardial infarction, severe left ventricular (LV) systolic dysfunction, prior ventricular tachyarrhythmia, and co-existent diabetes mellitus, being at the greatest risk (Myerburg, Mitrani et al. 1998, Cubbon, Adams et al. 2013, Walker and Cubbon 2015).

Co-morbidities not only contribute to disability, impairment of quality of life, and poor outcomes (Sharma, Zhao et al. 2018), but they also complicate management strategies and are associated with more frequent and longer duration of

hospitalisations (Braunstein, Anderson et al. 2003, Mentz and Felker 2013, Mentz, Kelly et al. 2014). It is not known whether multi-morbid patients achieve doses of disease-modifying agents, including angiotensin converting enzyme inhibitors (ACEi) and beta-adrenoceptor antagonists utilised in clinical trials. Furthermore, the effect of these medications of reducing cardiovascular deaths in multi-morbid patients, in whom the competing risk of non-cardiovascular death might mitigate against the favourable effects of these medications is uncertain.

4.2 Objectives

The aims of this analysis were therefore, firstly, to report the real-world provision of pharmacological therapies for people with HFrEF attending specialist heart failure clinics in the United Kingdom with and without co-morbidities. Secondly, I aimed to explore the impact of individual and accrued co-morbidities on modes of death in HFrEF, particularly whether co-morbidities alter the relative risk of sudden death. Finally, I aimed to determine whether multi-morbidity altered the effects of pharmacological therapies in preventing sudden cardiac death due to the aforementioned competing risk of non-cardiovascular death.

4.3 Methods

4.3.1 Study design

The United Kingdom Heart Failure Evaluation and Assessment of Risk Trial (UK-HEART-2) is a prospective cohort study in unselected, ambulatory patients with HFrEF attending specialist cardiology clinics, with the *a priori* aim of describing contributors to outcomes.

4.3.2 Participants

Between June 2006 and December 2014, consecutive patients attending specialist cardiology clinics in four UK hospitals were approached to participate. Inclusion required patients to have stable signs and symptoms of chronic heart failure for at least 3 months, age ≥18 years, and LV ejection fraction (LVEF) ≤ 45% on transthoracic echocardiogram, based upon guidelines for diagnostic and therapeutic criteria in place at the time (Hunt, Abraham et al. 2005, Swedberg, Cleland et al. 2005).

4.3.3 Variables and data sources

At the time of study recruitment, patient demographics, aetiology of LV impairment, past medical history, and functional capacity according to the New York Heart Association (NYHA) classification were collected. A venous blood sample was taken at enrolment and tested for serum haemoglobin, estimated glomerular filtration rate to stage chronic kidney disease (CKD) and serum albumin. Two-dimensional echocardiography was performed. LV end-diastolic diameter (LVEDd), LVEF by Simpson's biplane method, and pulmonary artery systolic pressure were measured, and the presence of regional wall motion abnormality determined by qualitative method according to the American Society of Echocardiography recommendations at the time (Gottdiener, Bednarz et al. 2004). Prescription of ACEi, beta-adrenoceptor antagonist, loop diuretic, and mineralocorticoid receptor antagonist (MRA) were recorded. For the purpose of analysis, doses of ACEi, beta-adrenoceptor antagonist, and loop diuretic are expressed as equivalent doses, relative to the maximum licensed dosages of ramipril, bisoprolol, and furosemide as previously described (Witte, Drozd et al. 2018). Receipt of implantable cardioverter-defibrillator (ICD) or cardiac

resynchronisation therapy (CRT) was assessed during the 6-month period after study recruitment.

4.3.4 Assessment of outcomes

All patients were registered with the UK Office of Population Censuses and Surveys, which provided details of the time of death, with final censorship occurring in November 2018. For this analysis the primary outcome was the mode of death in patients with and without major co-morbidities. Additionally, the association between doses of medication, provision of device therapy, and all-cause mortality and mode specific death were examined.

4.3.5 Definitions

Four key co-morbidities were identified: ischaemic aetiology of heart failure, diabetes mellitus, chronic obstructive pulmonary disease (COPD), and CKD stage IV/V, which were highly prevalent in this population and associated with an increased risk of all-cause mortality. I then used these data to explore the association between co-morbidities and modes of death, which were classified as cardiovascular (including stroke) or non-cardiovascular. Cardiovascular deaths were further divided into progressive heart failure or sudden deaths. Death due to progressive heart failure was a death occurring during decompensation or in patients with refractory symptoms. Sudden deaths were any death, witnessed or unwitnessed, occurring within 1 hour of change in symptoms, or occurring during sleep or whilst the patient was unobserved (Kearney, Fox et al. 2002). Aetiology of LV impairment was classified as either due to

ischaemic heart disease when there was previous myocardial infarction, coronary artery bypass grafting, coronary stenting at index presentation, evidence of inducible ischaemia on non-invasive imaging or scar suggesting infarction on cardiac magnetic resonance imaging, or non-ischaemic cardiomyopathy.

4.3.6 Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 26 (IBM Corporation, Armonk, NY). After normality of distribution was demonstrated, continuous variables are expressed as mean ± standard deviation. Discrete variables are presented as number and percentages in parentheses. Groups were compared using χ^2 for categorical variables and by Student's *t*-test or by one-way analysis of variance for continuous variables, as appropriate. Kaplan–Meier curves were used to plot survival and compared with log-rank test. Age–sex-adjusted and multivariate analyses used Cox proportional hazards regression. In all analyses, statistical significance was defined as $p<0.05$.

4.3.7 Ethical considerations

Ethical approval was given by the Leeds West Research Ethics Committee (07/Q1205/17) and the study was conducted in accordance with the principles outlined in the Declaration of Helsinki. All patients gave informed written consent for inclusion and long-term electronic follow-up.

4.4 Results

4.4.1 Patients

During the study period, a total of 1802 patients with HFrEF were recruited. Of these, five had missing medication doses and eight were missing data on major co-morbidities. The final dataset for this analysis consisted of 1789 patients with an average age of 69.6 ± 12.5 years, of whom 1307 (73%) were male. A total of 472 (26%), 763 (43%), 446 (25%), and 108 (6%) had 0, 1, 2, or ≥3 major co-morbidities, respectively. Ischaemic aetiology of heart failure was the most common co-morbidity, occurring in 1061 (59%) patients; 503 (28%) patients had diabetes mellitus, 283 (16%) had COPD, and 140 (8%) had CKD stage IV/V (Table 4.1).

Table 4.1 Baseline characteristics of patients with 0, 1, 2 or ≥3 major co-morbidities

	All patients (n=1789)	0 (n=472)	1 (n=763)	2 (n=446)	≥3 (n=108)	*p*-value
Demographics						
Age (years)	69.6±12.5	64.4±14.9	70.6±12.0	72.9±9.4	72.7±8.3	**<0.001**
Male sex [n(%)]	1307 (73)	310 (66)	578 (76)	342 (77)	77 (71)	**<0.001**
Major co-morbidities						
Ischaemic aetiology [n(%)]	1061 (59)	0 (0)	537 (70)	417 (94)	107 (99)	**<0.001**
Diabetes mellitus [n(%)]	503 (28)	0 (0)	121 (16)	283 (63)	99 (92)	**<0.001**
COPD [n(%)]	283 (16)	0 (0)	77 (10)	135 (30)	71 (66)	**<0.001**
Observations						
NYHA Class III/IV [n(%)]	550 (31)	92 (20)	238 (31)	166 (37)	54 (50)	**<0.001**
SBP (mmHg)	122.4±21.6	122.4±22.2	122.1±20.9	121.4±21.6	129.2±23.1	**0.02**
DBP (mmHg)	71.5±11.4	73.2±11.9	71.3±10.8	70.2±11.5	70.1±12.1	**0.002**
Heart rate (beats/min)	75.3±17.9	79.2±18.8	73.8±18.0	74.1±16.6	73.3±15.0	**<0.001**
Echocardiogram						
LVEDd (mm)	57.2±8.9	58.5±9.1	57.0±8.8	56.4±8.8	55.8±8.6	**0.001**
LVEF (%)	32.0±9.5	30.6±10.0	32.3±9.3	32.6±9.1	33.7±9.0	**0.001**
PASP (mmHg)	37.0±13.6	34.6±12.7	37.4±13.1	37.0±13.0	44.4±19.6	**0.002**
RWMA [n(%)]	689 (39)	92 (34)	324 (72)	220 (86)	53 (83)	**<0.001**
Blood tests						
Hb (g/L)	13.5±1.8	14.1±1.6	13.4±1.7	13.1±1.8	12.4±1.8	**<0.001**
eGFR (ml/min/1.73m^2)	57.7±19.7	65.4±16.1	58.6±18.3	52.3±20.5	40.9±22.8	**<0.001**
Albumin (g/L)	42.9±3.6	43.4±3.4	43.0±3.7	42.5±3.4	42.4±3.6	**<0.001**
Device therapy						
ICD/CRT-D [n(%)]	209 (12)	23 (5)	117 (15)	62 (14)	7 (7)	**<0.001**
CRT-P [n(%)]	452 (25)	103 (22)	206 (27)	118 (27)	25 (23)	0.19
Medications						
Bisoprolol dose (mg)	3.9±3.4	4.0±3.3	3.9±3.4	3.9±3.4	3.3±3.0	0.26
Maximum bisoprolol dose [n(%)]	271 (15)	71 (15)	122 (16)	66 (15)	12 (11)	0.61
Ramipril dose (mg)	4.9±3.5	4.8±3.4	5.1±3.6	5.0±3.6	3.9±3.4	**0.009**
Maximum ramipril dose [n(%)]	492 (28)	114 (24)	229 (30)	130 (29)	19 (18)	**0.012**
Furosemide dose (mg)	51.3±49.6	41.6±46.1	45.1±43.1	64.7±54.3	82.6±62.3	**<0.001**
MRA [n(%)]	684 (38)	161 (34)	287 (38)	196 (44)	40 (37)	**0.021**

Continuous variables are expressed as mean ± standard deviation, discrete variables are presented as number and percentages in parentheses. Comparisons across groups by ANOVA or Chi-squared for continuous and discrete variables, respectively.

COPD; chronic obstructive pulmonary disease, NYHA; New York Heart Association, SBP; systolic blood pressure, DBP; diastolic blood pressure, LVEDd; left ventricular end-diastolic diameter, LVEF; left ventricular ejection fraction, PASP; pulmonary artery systolic pressure, RWMA; regional wall motion abnormality, Hb; haemoglobin, eGFR; estimated glomerular filtration rate, ICD; implantable cardioverter defibrillator, CRT-D; cardiac resynchronisation therapy defibrillator, CRT-P; cardiac resynchronisation therapy pacemaker, MRA; mineralocorticoid receptor antagonist.

Table 4.2 Baseline characteristics of patients with and without major co-morbidities

	Ischaemic heart failure (n=1061)	Non-ischaemic cardiomyopathy (n=728)	Diabetes mellitus (n=503)	No diabetes mellitus (n=1286)	COPD (n=283)	No COPD (n=1506)	CKD IV/V (n=140)	No CKD (n=1649)
Demographics								
Age (years)	72.2 ± 10.3**	65.9 ± 14.4	70.2 ± 10.7	69.4 ± 13.2	73.2 ± 8.5**	69.0 ± 13.0	74.1 ± 11.8**	69.3 ± 12/5
Male sex [n(%)]	832 (78)**	475 (65)	383 (76)	924 (72)	195 (69)	1112 (74)	85 (61)**	1222 (74)
Observations								
NYHA class III/IV [n(%)]								
SBP (mmHg)	121.9 ± 21.6	123.2 ± 21.7	125.0 ± 21.0**	121.5 ± 21.8	122.9 ± 22.5	122.4 ± 21.5	124.1 ± 23.4	122.3 ± 21.5
DBP (mmHg)	70.5 ± 11.1**	72.9 ± 11.7	71.0 ± 11.2	71.7 ± 11.5	71.3 ± 12.0	71.5 ± 11.3	68.9 ± 11.8*	71.7 ± 11.4
Heart rate (beats/min)	71.9 ± 16.2**	80.3 ± 19.1	75.3 ± 17.2	75.3 ± 18.1	79.2 ± 17.4**	74.6 ± 17.9	73.0 ± 18.0	75.5 ± 17.9
Echocardiogram								
LVEDd (mm)	56.9 ± 8.8	57.6 ± 9.1	56.3 ± 8.8*	57.5 ± 9.0	55.9 ± 8.7*	57.4 ± 8.9	55.3 ± 9.0*	57.3 ± 8.9
LVEF (%)	32.5 ± 9.1*	31.2 ± 10.0	33.1 ± 9.1**	31.5 ± 9.6	32.1 ± 9.6	31.9 ± 9.5	33.1 ± 9.2	31.9 ± 9.5
PASP (mmHg)	37.0 ± 14.0	36.9 ± 13.1	40.8 ± 15.1**	35.8 ± 12.9	38.0 ± 13.8	36.8 ± 13.6	43.4 ± 16.8**	36.4 ± 13.1
RWMA [n(%)]	564 (86)**	125 (33)	193 (72)*	496 (64)	112 (70)	577 (66)	57 (74)	632 (66)
Blood tests								
Hb (g/L)	13.3 ± 1.7**	13.7 ± 1.8	13.0 ± 1.8**	13.6 ± 1.7	13.4 ± 1.8	13.5 ± 1.8	11.8 ± 1.7**	13.6 ± 1.7
eGFR (ml/min/1.73m^2)	54.6 ± 19.3**	62.4 ± 19.3	54.4 ± 20.7**	59.1 ± 19.1	58.1 ± 20.1	57.7 ± 19.6	22.3 ± 6.7**	60.8 ± 17.3
Albumin (g/L)	42.8 ± 3.5	43.0 ± 3.7	42.8 ± 3.4	43.0 ± 3.6	42.4 ± 3.5**	43.0 ± 3.6	40.9 ± 4.1**	43.1 ± 3.5
Device therapy								
ICD/CRT-D [n(%)]	175 (17)**	34 (5)	58 (12)	151 (12)	19 (7)**	190 (13)	10 (7)	199 (12)
CRT-P [n(%)]	295 (28)*	157 (22)	125 (25)	327 (25)	62 (22)	390 (26)	36 (26)	416 (25)
Medications								
Bisoprolol equivalent dose (mg)	3.9 ± 3.4	3.8 ± 3.4	4.2 ± 3.5*	3.7 ± 3.3	2.7 ± 3.0**	4.1 ± 3.4	3.6 ± 3.0	3.9 ± 3.4
Maximum bisoprolol dose [n(%)]	161 (15)	110 (15)	92 (18)*	179 (14)	20 (7)**	251 (17)	17 (12)	254 (15)
Ramipril equivalent dose (mg)	5.0 ± 3.6	4.9 ± 3.5	5.3 ± 3.7**	4.8 ± 3.5	4.5 ± 3.3*	5.0 ± 3.6	3.1 ± 3.2**	5.1 ± 3.5
Maximum ramipril dose [n(%)]	301 (28)	191 (26)	168 (33)**	324 (25)	60 (21)*	432 (29)	18 (13)**	474 (29)
Furosemide equivalent dose (mg)	53.8 ± 50.5*	47.7 ± 48.1	68.3 ± 55.9**	44.7 ± 45.3	58.2 ± 50.0*	50.0 ± 49.5	83.0 ± 62.1**	48.6 ± 47.5
MRA [n(%)]	436 (41)**	248 (34)	216 (43)*	468 (36)	101 (36)	583 (39)	48 (34)	636 (39)

Continuous variables are expressed as mean ± standard deviation, discrete variables are presented as number and percentages in parentheses. Comparisons across groups by ANOVA or Chi-squared for continuous and discrete variables, respectively.

COPD; chronic obstructive pulmonary disease, CKD; chronic kidney disease, NYHA; New York Heart Association, SBP; systolic blood pressure, DBP; diastolic blood pressure, LVEDd; left ventricular end-diastolic diameter, LVEF; left ventricular ejection fraction, PASP; pulmonary artery systolic pressure, RWMA; regional wall motion abnormality, Hb; haemoglobin, eGFR; estimated glomerular filtration rate, ICD; implantable cardioverter defibrillator, CRT-D; cardiac resynchronisation therapy defibrillator, CRT-P; cardiac resynchronisation therapy pacemaker, MRA; mineralocorticoid receptor antagonist.

4.4.2 Utilisation of disease-modifying agents

Overall, patients with multi-morbidity were prescribed lower equivalent doses of beta-adrenoceptor antagonists and ACEi and were less likely to be prescribed the maximum licensed doses (Table 4.1). This was particularly evident in patients with COPD who were prescribed lower doses of beta-adrenoceptor antagonist, and those with CKD IV/V who received lower doses of ACEi (Tables 4.2). The presence of any co-morbidity was associated with a higher furosemide equivalent dose of loop diuretic. In contrast, patients with ischaemic aetiology of heart failure received similar doses of beta-adrenoceptor antagonist and ACEi as those with non-ischaemic cardiomyopathy, and patients with diabetes mellitus were on average prescribed higher doses of both classes of medications. There was no clear relationship between the number of co-morbidities and the prescription of MRA, although those with ischaemic aetiology of heart failure and diabetes mellitus were more likely to be prescribed these agents. The provision of CRT was similar in patients divided by number of major co-morbidities (Table 4.1). Patients with an ischaemic aetiology were more likely to be implanted with CRT or ICD, whilst patients with COPD were less likely to receive an ICD than were those without COPD (Table 4.2).

4.4.3 Mortality and modes of death

During a mean follow-up of 3.8 ± 1.6 years, a total of 737 (41.5%) patients died. Modes of death were available for 713 (97%), and 24 were unclassifiable owing to lack of information. Of the classifiable deaths, progressive heart failure caused 227 (32%)

deaths, whereas 112 (16%) were sudden. Non-cardiovascular death occurred in 314 (44%) patients.

4.4.4 Multi-morbidity and the association with mode of death

There were clear differences in survival between patients who did or did not have the four major co-morbidities of: ischaemic aetiology of heart failure diabetes mellitus, COPD and CKD stage IV/V (Figure 4.1).

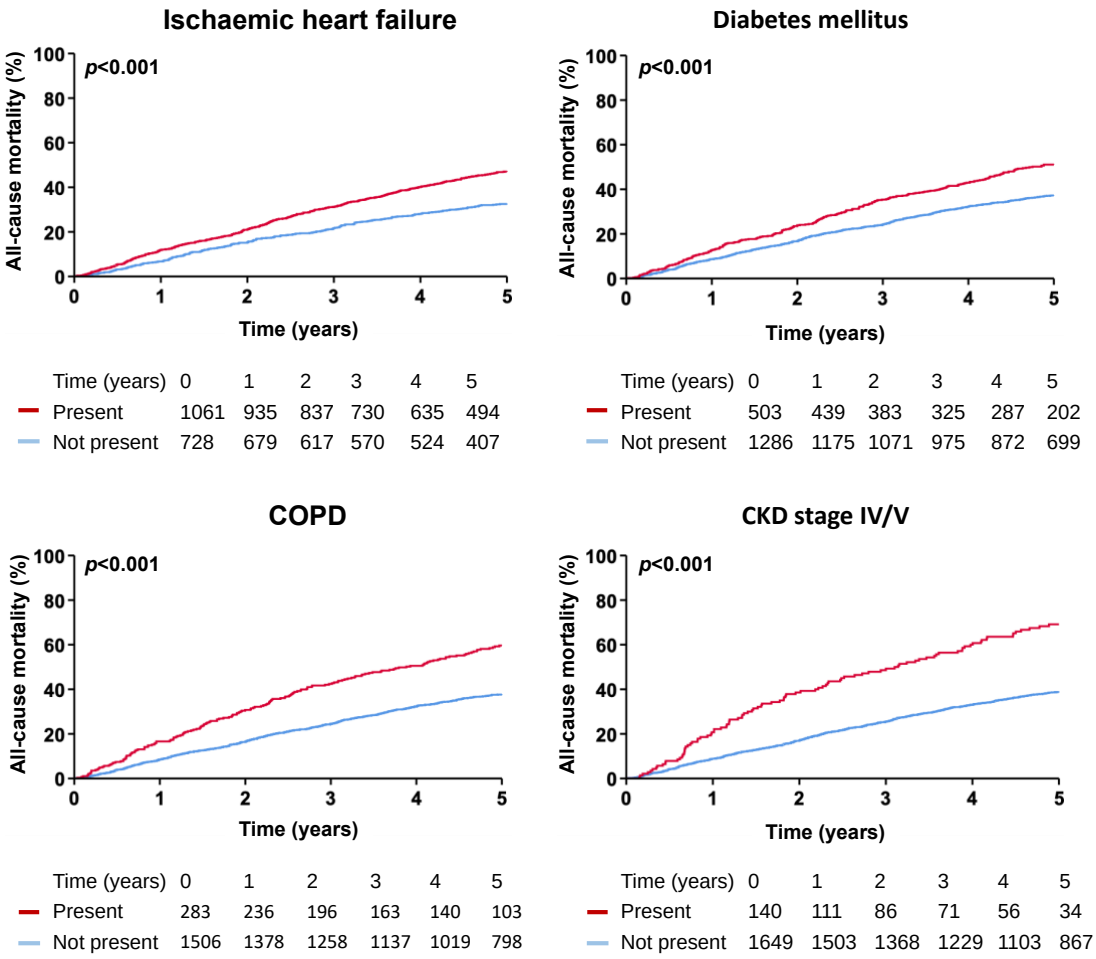


Figure 4.1 Kaplan-Meier plots of all-cause mortality divided by those with and without major co-morbidities.

Reproduced from (Straw, McGinlay et al. 2020) under terms of Creative Commons Attribution Non-Commercial License.

Furthermore, I observed a stepwise increase in the rate of all modes of death in parallel with the number of major co-morbidities (Figure 4.2). When adjusted for age and sex, all major co-morbidities were associated with an increased risk of all-cause mortality (Figure 4.3). COPD was not associated with an increased risk of death from progressive heart failure, although it was associated with a 2.5-fold increased risk of

sudden death. CKD stage IV/V was associated with all-cause mortality and death from progressive heart failure, but the association with sudden death was non-significant. Diabetes mellitus and ischaemic aetiology of heart failure increased the risk of all modes of death.

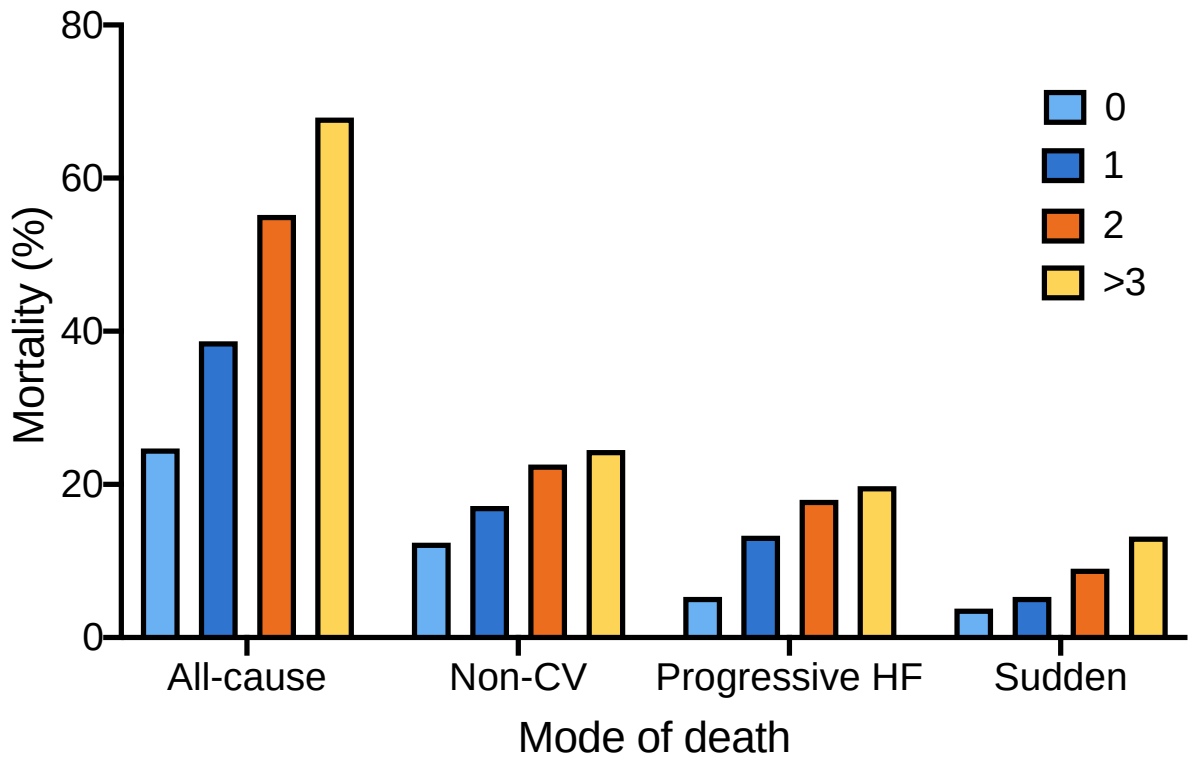


Figure 4.2 Bar chart to show the modes of death in patients with 0, 1, 2 and ≥3 major co-morbidities

Reproduced from (Straw, McGinlay et al. 2020) under terms of Creative Commons Attribution Non-Commercial License.

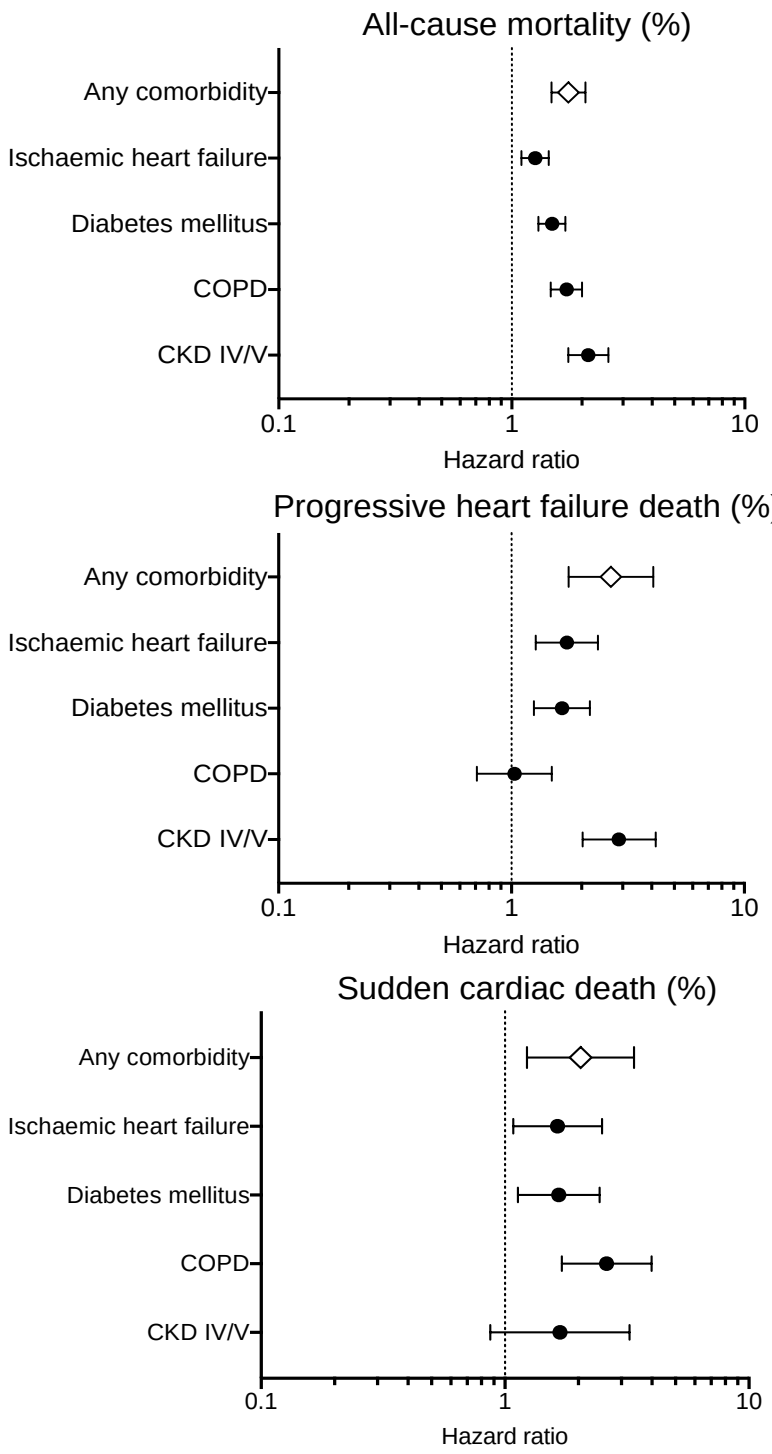


Figure 4.3 Forrest plot showing the hazard of all-cause, progressive heart failure and sudden death in patients with major co-morbidities.

In multivariate analysis, major co-morbidities were associated with all-cause mortality, with the exception of ischaemic aetiology of heart failure (Table 4.3). However, compared with all-cause mortality and progressive heart failure deaths (Table 4.4), sudden deaths were not associated with age, NYHA class III/IV symptoms, or LVEDd but were associated with lower LVEF (as a continuous variable) (Table 4.5).

Table 4.3 Multivariate regression analysis of all-cause mortality in all patients

	Hazard ratio	**95% CI**	***p*-value**
Age (per year)	1.04	1.03-1.05	**<0.001**
Male sex	1.75	1.49-2.06	**<0.001**
Ischaemic heart failure	1.09	0.94-1.26	0.27
Diabetes mellitus	1.32	1.14-1.53	**<0.001**
COPD	1.65	1.40-1.94	**<0.001**
NYHA class III/IV	1.26	1.10-1.45	**0.001**
LVEDd (per mm)	1.00	0.99-1.01	0.73
LVEF (per %)	0.99	0.98-0.99	**<0.001**
Hb (per g/dL)	0.88	0.84-0.92	**<0.001**
eGFR (per ml/min/1.73m^2)	0.99	0.99-1.00	**0.001**
Albumin (per g/L)	0.96	0.94-0.97	**<0.001**
Bisoprolol equivalent dose (per mg)	1.00	0.98-1.02	0.73
Ramipril equivalent dose (per mg)	0.98	0.96-1.00	0.066
Furosemide equivalent dose (per mg)	1.00	1.00-1.00	**<0.001**

CI; confidence interval, COPD; chronic obstructive pulmonary disease, NYHA; New York Heart Association, LVEDd; left ventricular end-diastolic diameter, LVEF; left ventricular ejection fraction, Hb; haemoglobin, eGFR; estimated glomerular filtration rate.

Table 4.4 Multivariate regression analysis of progressive heart failure deaths in all patients

	Hazard ratio	95% CI	*p*-value
Age (per year)	1.05	1.03-1.06	**<0.001**
Male sex	1.78	1.25-2.54	**0.001**
Ischaemic heart failure	1.45	1.04-2.01	**0.028**
Diabetes mellitus	1.32	0.98-1.79	0.072
NYHA class III/IV	1.41	1.06-1.87	**0.019**
LVEDd (per mm)	1.03	1.01-1.05	**0.004**
LVEF (per %)	0.98	0.96-0.99	**0.007**
Hb (per g/dL)	0.88	0.80-0.96	**0.005**
eGFR (per ml/min/1.73m^2)	0.99	0.98-1.00	**0.002**
Albumin (per g/L)	0.96	0.93-1.00	**0.045**
Bisoprolol equivalent dose (per mg)	0.96	0.92-1.01	0.11
Ramipril equivalent dose (per mg)	0.93	0.89-0.97	**0.001**
Furosemide equivalent dose (per mg)	1.01	1.00-1.01	**<0.001**

CI, confidence interval; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; DCM, dilated cardiomyopathy; LVEDd, left ventricular diameter in diastole; PASP, pulmonary artery systolic pressure; Hb, haemoglobin.

Table 4.5 Multivariate regression analysis of sudden death in all patients.

	Hazard ratio	95% CI	*p*-value
Age (per year)	0.99	0.97-1.01	0.33
Male sex	1.83	1.11-3.00	**0.017**
Ischaemic heart failure	1.48	0.95-2.29	0.08
Diabetes mellitus	1.59	1.06-2.38	**0.024**
COPD	2.53	1.64-3.90	**<0.001**
LVEF (per %)	0.97	0.95-0.99	**0.005**
eGFR (per ml/min/1.73m^2)	0.99	0.98-1.00	**0.013**
Bisoprolol equivalent dose (per mg)	0.92	0.86-0.98	**0.009**
CI, confidence interval; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate.			

4.4.5 Disease modifying agents and their association with mode of death

In unadjusted survival analysis, higher doses of beta-adrenoceptor antagonist were associated with lower rates of all-cause, progressive heart failure, and sudden deaths (Figure 4.4), whereas reductions in all-cause mortality with higher doses of ACEi were primarily driven by a reduction in progressive heart failure deaths and not sudden deaths (Figure 4.5). Prescription of MRA was not associated with lower rates of all-cause mortality or sudden deaths; however, there was a lower rate of progressive heart failure deaths.

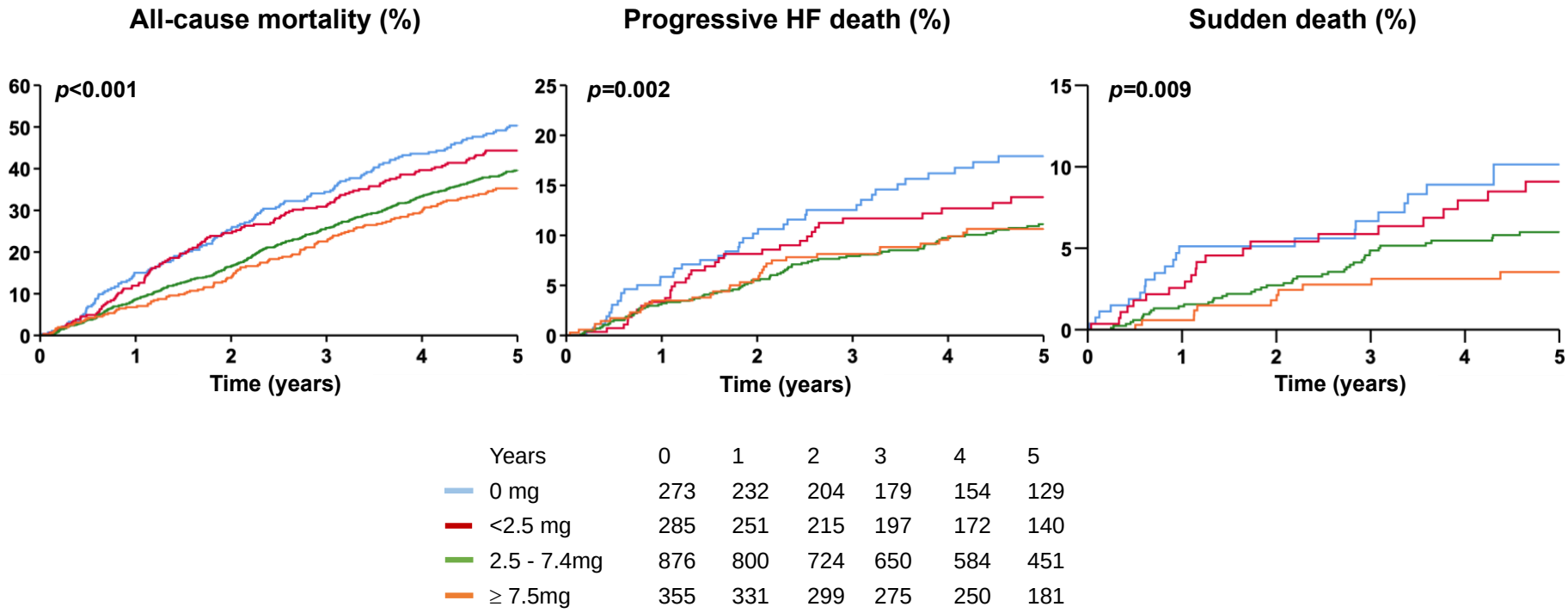


Figure 4.4 Kaplan-Meier plots of all-cause, progressive heart failure, and sudden death stratified by bisoprolol equivalent dose of beta-adrenoceptor antagonist.

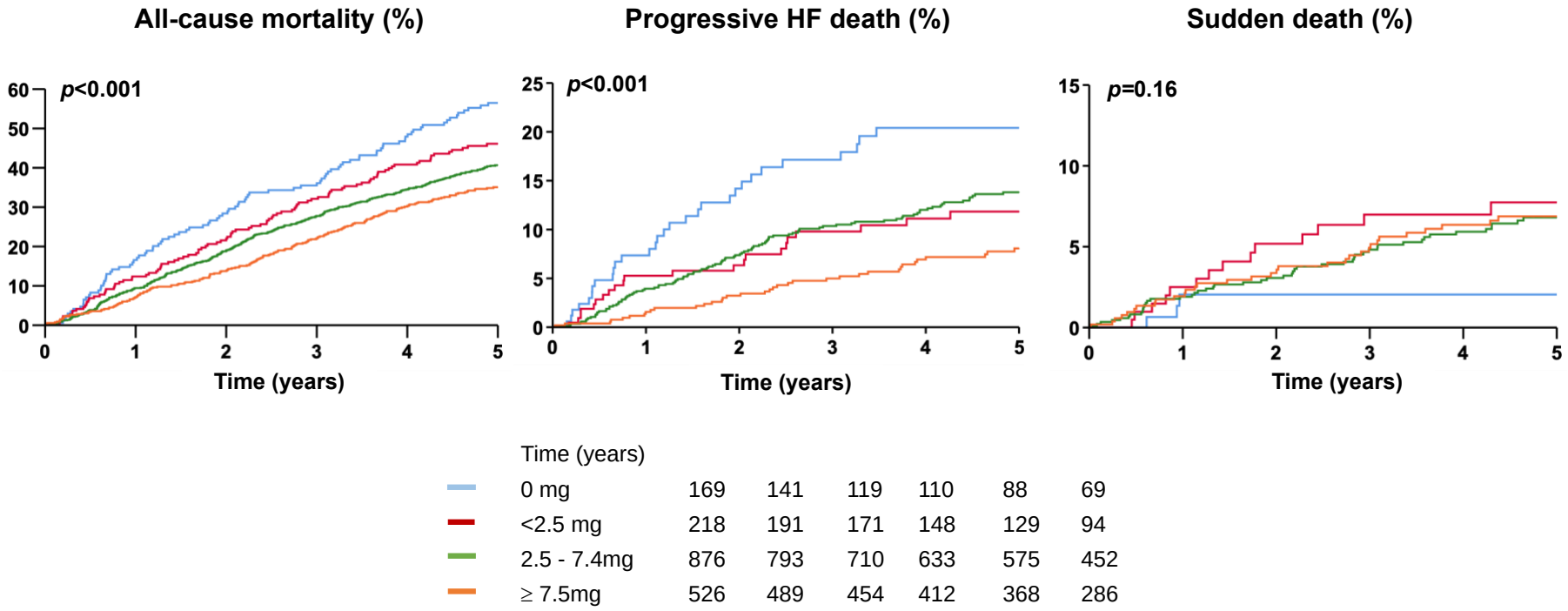


Figure 4.5 Kaplan-Meier plots of all-cause, progressive heart failure, and sudden death stratified by ramipril equivalent dose of angiotensin converting enzyme inhibitor.
Reproduced from (Straw, McGinlay et al. 2020) under terms of Creative Commons Attribution Non-Commercial License.

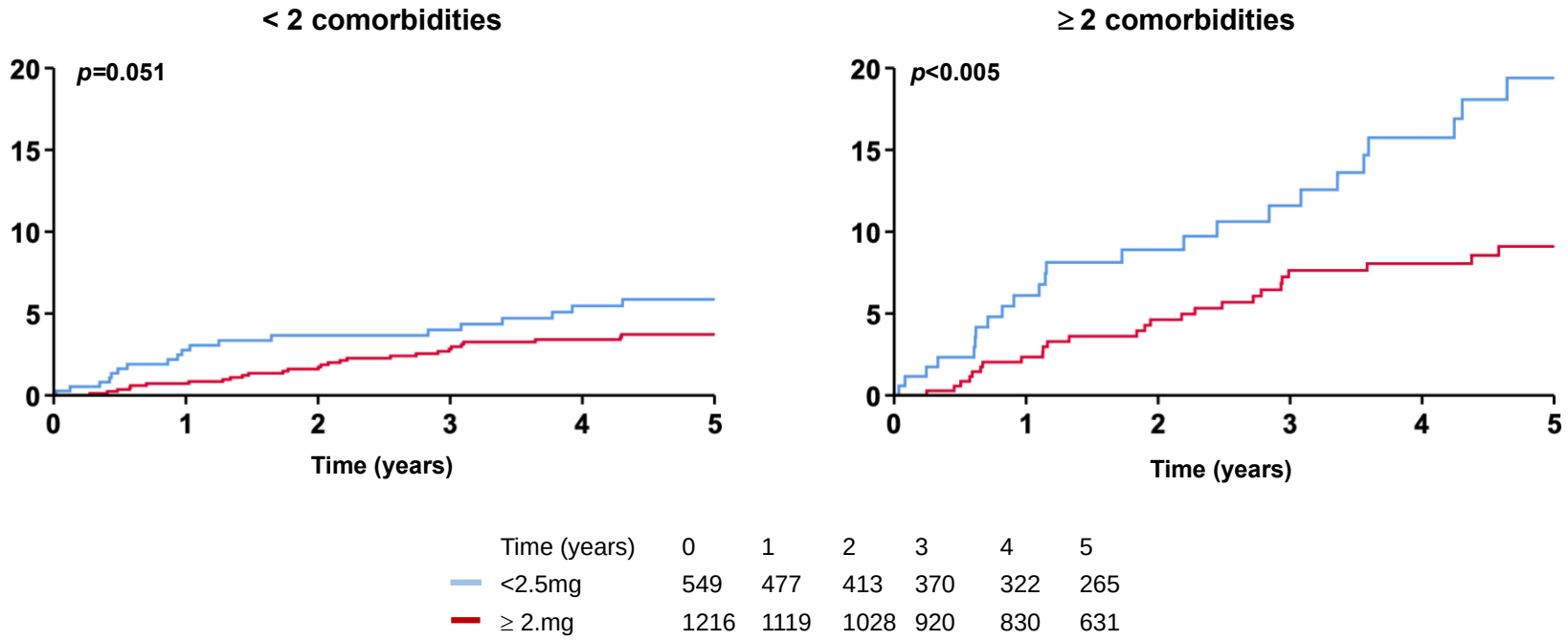


Figure 4.6 Kaplan-Meier plots of sudden death stratified by bisoprolol equivalent dose of beta-adrenoceptor antagonist in patients with <2 and ≥2 major co-morbidities.

There were similar rates in the rates of sudden deaths stratified by the dose of beta-adrenoceptor antagonist in those with and without specific co-morbidities, which were most evident in patients with ≥2 co-morbidities (Figure 3.6). When adjusted for age and sex, there was a relative reduction in sudden death of 9% per milligram bisoprolol equivalent dose of beta-adrenoceptor antagonist (p=0.001), which was 11% (p=0.023) in patients with ≥2 co-morbidities and 8% (p=0.071) in patients with <2 co-morbidities, with the exception of diabetes mellitus, which was associated with a relative reduction in sudden death of 14% per milligram (p=0.005) compared with 7% (p=0.084) in those without diabetes. In the multivariate analysis, dosing of either class of medication was not associated with all-cause mortality or non-cardiovascular deaths (Table 4.3); however, the association between dose of ACEi and progressive heart failure death (Table 4.4) and of beta-adrenoceptor antagonist and sudden death was statistically significant (Table 4.5).

4.5 Discussion

4.5.1 Findings

In this analysis, I have reported the real-world provision of disease-modifying agents in patients with HFrEF attending specialist heart failure clinics in the UK. The novel findings are that multi-morbidity confers an additional risk of all-cause mortality, particularly due to sudden death, despite the competing risk of non-cardiovascular death for these patients. A diagnosis of COPD or diabetes mellitus was associated with >2.5-fold and 1.5-fold increased risk, even when corrected for age, ischaemic aetiology of heart failure, and degree of LV impairment. Patients with multi-morbidity, especially COPD, were on average prescribed lower doses of beta-adrenoceptor

antagonist and less likely to be implanted with ICDs. Higher doses of beta-adrenoceptor antagonists were associated with lower rates of sudden death, especially evident in multi-morbid patients, and there was a modest reduction in sudden death associated with ICD implantation. Cumulatively, these data suggest that there might be a missed opportunity to optimise disease-modifying agents to reduce the risk of sudden death in patients with HFrEF, and that patients with co-morbidity might have the most to gain from targeted dose optimisation and device implantation.

4.5.2 Multi-morbidity and the risk of sudden death in heart failure with reduced ejection fraction

To date, few studies have reported the association between multi-morbidity and modes of death in HFrEF. In one retrospective analysis of an historic cohort including 824 patients, multi-morbidity was found to reduce the risk of sudden death, attributed to the competing risk of non-sudden death (Clarke, Howlett et al. 2011). However, this study was limited by a low rate of sudden deaths (*n*=30), and patients were enrolled between 1998 and 2004, predating the increased penetration of contemporaneous medical therapy in HFrEF. This study also defined multi-morbidity using the Charlson co-morbidity index, which is heavily weighted towards advanced age. In this analysis, I have shown that age is not associated with an increased risk of sudden death in HFrEF but is a major driver of all-cause mortality. This dataset included 112 sudden death events allowing the description of a stepwise increase in the relative risk of sudden death in those with multiple major co-morbidities. My data do not describe the effects of other co-morbidities, such as hypertension and atrial fibrillation on modes of

death; however, there were no significant differences in all-cause mortality in patients with and without these co-morbidities (Mercer, Koshy et al. 2018).

Sudden deaths in patients with HFrEF are often caused by ventricular tachyarrhythmias, one driver of which could be acute coronary syndromes (Watanabe, Tanabe et al. 2014). My findings might therefore be partially explained by a greater burden of coronary artery disease in patients with diabetes mellitus, COPD, and CKD. However, I found that diabetes mellitus and COPD were independent risk factors for sudden death even after correction for ischaemic aetiology of heart failure. Furthermore, clinical trials of statins (Kjekshus, Apetrei et al. 2007, Tavazzi, Maggioni et al. 2008), aspirin, and anticoagulants (Cleland, Findlay et al. 2004, Zannad, Anker et al. 2018), which reduce the incidence of acute coronary syndromes, do not reduce sudden death risk in HFrEF. Alternative contributors could include myocardial fibrosis, which is more common in people with diabetes mellitus, is found in patients with and without ischaemic heart disease (Larghat, Swoboda et al. 2014), and is a substrate for ventricular tachyarrhythmias. Diabetes mellitus increased the risk of sudden death, despite higher doses of beta-adrenoceptor antagonists and ACEi in this cohort and a similar ICD implantation rate as non-diabetic patients. COPD is associated with sudden death and an increased risk of ventricular tachyarrhythmias (Yildiz, Tukek et al. 2002) in patients with and without HFrEF, related to the duration of disease and the frequency of exacerbations (Lahousse, Niemeijer et al. 2015), possibly due to autonomic dysregulation (Stewart, Waterhouse et al. 1995), higher resting heart rates (Jensen, Marott et al. 2013), hypoxia, and chronic systemic inflammation (Lahousse, Niemeijer et al. 2015).

4.5.3 The role of medical and device therapy in preventing sudden death

Contemporary medical and device therapies have resulted in dramatic reductions in sudden deaths in patients with HFrEF between therapeutic eras (Cubbon, Gale et al. 2011). Medical therapy including ACEi (CONSENSUS 1987, SOLVD 1991), beta-adrenoceptor antagonists (CIBIS-II 1999, MERIT-HF 1999), and MRA (Pitt, Zannad et al. 1999, Zannad, McMurray et al. 2011), synergistically reduce all-cause mortality in HFrEF; and in my patients, I observed a clear stepwise reduction in the risk of all-cause mortality in patients receiving the highest doses of ACEi and beta-adrenoceptor antagonists. The association between higher doses of ACEi and all-cause mortality was primarily due to lower rates of progressive heart failure, whereas beta-adrenoceptor antagonists were associated with lower rates of both progressive heart failure and sudden deaths. These observations, in real-world patients are consistent with the pattern of mortality reduction seen in landmark clinical trials, where the effects of ACEi are primarily in preventing progressive pump failure (Garg and Yusuf 1995), with beta-adrenoceptor antagonists preventing both progressive and sudden deaths (MERIT-HF 1999). The prescription of MRA was associated with lower rates of progressive heart failure deaths but not all-cause mortality or sudden deaths.

Multi-morbid patients were on average prescribed lower doses of disease-modifying pharmacotherapies than were patients without co-morbidities; in particular, I observed lower dosing of ACEi in those with CKD and of beta-adrenoceptor antagonists in those with COPD. Although key co-morbidities were associated with lower dosage of pharmacological therapy, qualitative data is lacking on the reasons for failure to up-titrate for patients in whom blood pressure and heart rate allowed (McGinlay, Straw et al. 2022). The prescription of beta-adrenoceptor antagonists for patients with COPD

is typically well tolerated with minimal changes in lung function and improvements in survival even in those with the most severe disease (Short, Lipworth et al. 2011). However, the use of non-selective agents has been shown to increase discontinuation rates, the duration of therapy prior to discontinuation and the risk of heart failure hospitalisation, and so therapies should be tailored for individual patients (Sessa, Mascolo et al. 2018). In this cohort of patients, those with diabetes mellitus were prescribed, on average, higher doses of beta-adrenoceptor antagonists. Historically, there have been concerns about prescribing these medications to those receiving insulin or sulfonylureas owing to perceived risks of masking symptoms of hypoglycaemia or prolonging these episodes (Straw, Witte et al. 2019). However, in clinical trials, rates of hypoglycaemia are not different, and the theoretical risks are far outweighed by the established benefits (MERIT-HF 1999).

In these patients, more severely impaired LV function was strongly associated with an increased risk of sudden death. Treatments such as CRT (Moss, Zareba et al. 2002, Cleland, Daubert et al. 2005) and comprehensive renin-angiotensin-aldosterone system blockade by angiotensin-receptor neprilysin inhibiton (ARNI) reduce the risk of sudden death, primarily by their ability to promote reverse ventricular remodelling. It is possible that beta-adrenoceptor antagonists might also reduce the risk of sudden mechanical failure by facilitating dose-related improvement in LV function (Bristow, Gilbert et al. 1996) and are associated with similar improvements in survival whether target dose or heart rate is achieved (Corletto, Frohlich et al. 2018). However, beta-adrenoceptor antagonists are also protective against ventricular tachyarrhythmias and surges in the autonomic nervous system, which can precipitate electrical and mechanical instability and in part reduce the risk of sudden death, improving survival in those prescribed the highest doses (Packer, Gottlieb et al. 1986).

Patients with COPD are around twice as likely to receive appropriate therapies when implanted with ICDs than are those without (Naksuk, Kunisaki et al. 2013), yet patients with COPD in this cohort were less likely to be implanted. This suggests that implantation should not be avoided in multi-morbid patients who are at still at risk of sudden death and may be partially protected by the targeted implantation of ICDs. However, whilst ICDs have an established role in the prevention of sudden cardiac death in both ischaemic heart failure and non-ischaemic cardiomyopathies (Moss, Zareba et al. 2002, Bardy, Lee et al. 2005, Kober, Thune et al. 2016), in clinical trials, ~50–70% of sudden deaths are not prevented by implantation (Packer 2020). This is confirmed in the present study where ICDs were only modestly protective against sudden death, contrasting with the strong associations with beta-adrenoceptor antagonists. Hence, other mechanisms of sudden death must be at play in HFrEF, which could include rapidly deteriorating pump function.

4.6 Strengths and limitations

This is an analysis of data from a carefully characterised cohort of patients with HFrEF, with long-term follow-up. The study reports the provision of medical and device therapy in a real-world population, with doses achieved similar to other observational studies with similar proportions with major co-morbidities, albeit a lower proportion with COPD (Greene, Butler et al. 2018, Brunner-La Rocca, Linssen et al. 2019). The exclusion of patients with LVEF >45% means that our findings are not generalisable to patients with heart failure with preserved ejection fraction, but they are applicable to many patients with heart failure and mildly reduced ejection fraction. The study was a retrospective analysis of modes of death, and misclassification is a possibility,

although this is unlikely to be biased to a particular mode. The effect of other co-morbidities on modes of death was not analysed, nor the effects of non-cardiovascular medications; however, an analysis of the four most prevalent major co-morbidities in the patient population studied is presented (Sharma, Zhao et al. 2018). The study predated the availability of ARNI and sodium-glucose co-transporter 2 inhibitors, which are associated with additional reductions in progressive heart failure and sudden deaths.

4.7 Conclusions

This study is the first to report the association between the risk of sudden death and the provision of pharmacological therapies in multi-morbid patients with HFrEF. The association between higher doses of beta-adrenoceptor antagonist and lower rate of sudden death was most evident in those with co-morbidities. Patients with COPD who appear to be at the highest risk of sudden death are prescribed the lowest doses of beta-adrenoceptor antagonists and are also less likely to be implanted with ICDs. This might represent a missed opportunity to optimise safe and proven therapies relevant to real-world populations.

Chapter 5: Pharmacological therapies in heart failure with mildly reduced ejection fraction

Hypothesis: Patients with heart failure with mildly reduced ejection fraction derive similar benefits from disease modifying pharmacological therapies as those with heart failure with reduced ejection fraction.

5.1 Introduction

The benefits of disease modifying pharmacological therapies for heart failure with reduced ejection fraction (HFrEF) are well established. Four classes of medications targeting the neurohormonal maladaptations of the syndrome are now proven to reduce heart failure hospitalisations and cardiovascular mortality (Straw, McGinlay et al. 2021). Eligibility for these therapies is largely derived from the inclusion criteria of randomised controlled trials (SOLVD 1991, CIBIS-II 1999, Zannad, McMurray et al. 2011, McMurray, Packer et al. 2014, Borghi and Cicero 2020), which used arbitrary thresholds of left ventricular ejection fraction (LVEF) to identify patients perceived to be at the highest risk, who potentially had the most to gain. Current guidelines recommend pharmacological therapies may be considered for people who have heart failure with mildly reduced ejection fraction (HFmrEF) (LVEF 41-49%) (McDonagh, Metra et al. 2021). However, since this subgroup was not included in the relevant trials, the benefits of these therapies are largely unknown, with these recommendations largely derived from consensus opinion, observational studies, and *post hoc* analyses of randomised controlled trials. There is therefore a need to assess the impact of these recommendations in real-world populations.

5.2 Objectives

To determine the association between the provision of guideline-directed medical therapies and survival in chronic heart failure (CHF), I explored data from two prospective observational studies. Combining these studies permitted the examination of the effects of pharmacological therapies across a broad spectrum of LVEF including patients with HFmrEF, and heart failure with preserved ejection fraction (HFpEF). The aims were firstly, to report prevalence of heart failure with reduced ejection fraction (HFrEF), HFmrEF, and HFpEF amongst a real-world population referred to secondary care with symptoms of chronic heart failure. Secondly, to describe the clinical characteristics and outcomes of patients with HFmrEF compared to HFrEF and HFpEF, and thirdly, to report the provision of pharmacological therapies and explore dose-related associations with outcomes across heart failure classifications.

5.3 Methods

5.3.1 Study design

As described in Chapter 4, the United Kingdom Heart Failure Evaluation and Assessment of Risk Trial (UK-HEART-2) is a prospective, observational study representing a prevalent population of ambulatory patients under the care of four specialist heart failure outpatient clinics. Consecutive patients were approached to participate between July 2006 and December 2014. Inclusion required stable symptoms ± signs of CHF for at least three months, and LVEF ≤45%. The Prospective evaluation of the diagnostic efficacy of the 2010 United Kingdom National Institute for Clinical Excellence Guidelines on Chronic Heart Failure (NICE-CHF) is a prospective, observational cohort study which represents a population of consecutive people newly referred to a specialist heart failure outpatient clinic, from a primary care catchment of

over 750,000 people. In NICE-CHF patients were required to have symptoms ± signs of CHF and elevated natriuretic peptides (N-terminal pro B-type natriuretic peptide [NT-proBNP] ≥125pg/L), and all patients attending between May 2012 and May 2013 were included, regardless of LVEF.

5.3.2 Study procedures

In both studies upon arrival at the outpatient heart failure clinic, demographic details, medical history, blood pressure, and for the UK-HEART-2 cohort functional capacity according to the New York Heart Association classification, were recorded. A venous blood sample was taken at enrolment and tested for full blood count, creatinine, and albumin. For patients included in NICE-CHF, NT-proBNP was measured from samples taken in primary care using the Immulite 2000 assay (Siemens Healthcare Diagnostics, Camberley, UK) in the biochemistry laboratory at the Leeds Teaching Hospitals NHS Trust. The inter-batch coefficient of variation was 8.9% at 350pg/mL and 5.9 at 4100pg/mL. Standard 12-lead electrocardiograms were recorded at 25mm/s and analysed by a senior cardiologist (RMC, MTK, KKW) blinded to patient characteristics. Two-dimensional transthoracic echocardiography was performed by senior cardiac sonographers (JG, MP, JEL), blinded to measurements of NT-proBNP. Left ventricular (LV) dimensions, LVEF, left atrial volumes, and LV Doppler measurements were calculated according to the American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines (Lang, Badano et al. 2015).

5.3.3 Pharmacological therapies

Prescription of beta-adrenoceptor antagonist, angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) and loop diuretic were expressed as equivalent doses, relative to the maximum licensed dosages of bisoprolol, ramipril and furosemide as previously published (Witte, Drozd et al. 2018). For the purpose of analysis, the receipt of beta-adrenoceptor antagonists and ACEi/ARB was divided into patients not receiving these agents, patients prescribed these at low doses (<5mg equivalent dose), and patients prescribed these agents at high doses (≥5mg equivalent dose). In UK-HEART-2 medications were recorded at the time of study enrolment, and in NICE-CHF doses from linked primary care records were recorded. Both studies predated the availability of angiotensin receptor-neprilysin inhibitors (ARNI) and sodium-glucose co-transporter 2 inhibitors (SGLT2i).

5.3.4 Patient classification and assessment of outcomes

Patients were categorised according to the Universal Definition and Classification of Heart Failure as having HFrEF, HFmrEF, HFpEF, or not having CHF (Bozkurt, Coats et al. 2021). HFrEF and HFmrEF required symptoms ± signs of CHF and LVEF ≤40% and 41-49%, respectively. HFpEF required signs ± symptoms of CHF, elevated natriuretic peptides (NT-proBNP ≥125pg/mL), as well as evidence of relevant structural heart disease (for example dilated left atrium or LV hypertrophy), or diastolic dysfunction. Patients without these features were regarded as not having CHF. Vital status data were collected using linked national electronic records from the Hospital Episode Statistics and Office of National Statistical mortality data. Final censorship occurred in November 2018 for UK-HEART-2 and April 2019 for NICE-CHF.

5.3.5 Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 26 (IBM Corporation, Armonk, NY). Normality of distribution was explored visually by distribution plots and confirmed using skewness tests. Continuous variables are presented as mean ± standard deviation if normally distributed, as median (interquartile range) if non-normally distributed, and discrete variables are presented as number (percentage). Groups were compared using two-sided t-tests or one way analysis of covariance for normally distributed continuous data, Mann-Whitey or Kruskal-Wallis H tests for non-normally distributed data, and two-sided Pearson χ^2 for categorical variables. Kaplan Meier analysis was used to plot survival and compared using log-rank test. Age-sex adjusted, and multivariable analyses used Cox proportional hazards regression. In all analyses statistical significance was defined as $p<0.05$.

5.3.6 Ethical considerations

The Health Research Authority provided ethical approval for the studies (UK-HEART-2: 07/Q1205/17; NICE-CHF: CAG8-03(PR1)/2013) which were conducted in accordance with the principles outlined in the Declaration of Helsinki. Participants enrolled in UK-HEART-2 provided informed written consent for inclusion. Ethical approval for NICE-CHF was achieved through a Section 251 application reviewed by the Confidential Advisory Group which allows individual patient data to be used for health service improvement without the need for individual patient consent.

5.4 Results

5.4.1 Classification of heart failure and distribution of ejection fraction

UK-HEART-2 recruited a total of 1802 participants, 47 had insufficient endocardial definition to measure LVEF and five had missing medication doses, leaving 1750 patients, of whom 1423 (81.3%) were classified as having HFrEF and 327 (18.7%) as having HFmrEF. NICE-CHF included 982 patients, of these 22 had insufficient endocardial definition to measure LVEF, 182 did not have CHF and two had missing medication doses, leaving 776 patients, 190 (24.5%) of whom had HFrEF, 123 (15.9%) had HFmrEF and 463 (59.7%) had HFpEF. Following the exclusion of 138 duplicate entries for patients enrolled in both studies (due to inappropriate re-referral of patients enrolled in UK-HEART-2 through the NT-proBNP pathway for a new diagnosis of CHF), the combined dataset consisted of 2388 unique patients, who had a mean age of 73.7 ± 13.3 years and 1525 (63.9%) were male. Within the entire study cohort, LVEF ranged from 5 to 71% (mean 37.2 ± 12.8%) (Figure 1). Overall, 1504 (63.0%) patients were categorised as having HFrEF, 421 (17.6%) as HFmrEF and 463 (19.4%) as HFpEF.

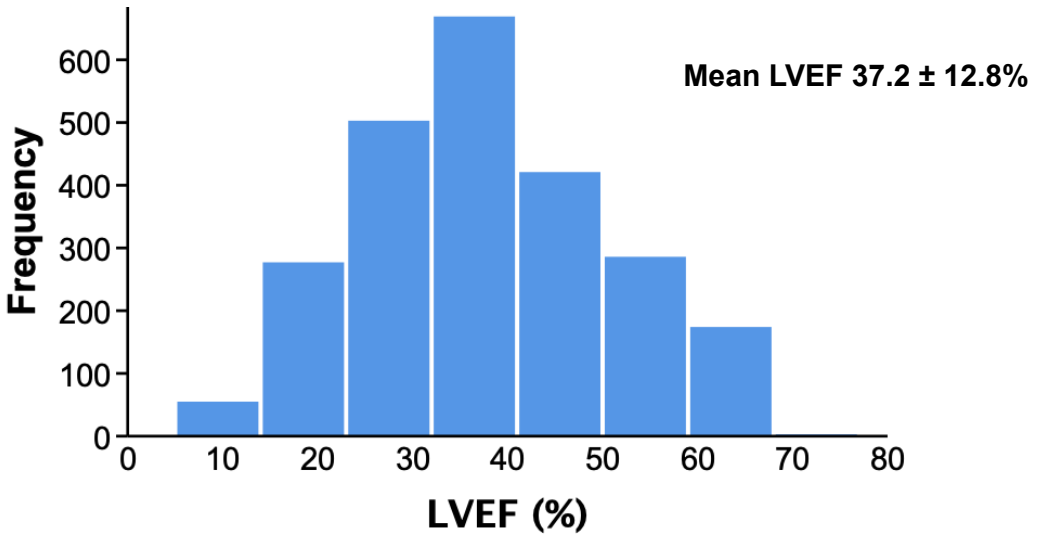


Figure 5.1 Histogram showing distribution of left ventricular ejection fraction within the combined dataset

Reproduced from (Straw, Cole et al. 2023) under terms of Creative Commons Attribution Non-Commercial License.

5.4.2 Clinical characteristics

Descriptive data contrasting patients according to heart failure classification are displayed in Table 1. Patients with HFrEF had a lower mean age and were more likely to be male compared to HFmrEF, although distributions of ischaemic heart disease and diabetes mellitus were similar. Patients with HFpEF were more likely to be older and female, and fewer had a history of ischaemic heart disease. Aside from cardiac dysfunction, there was evidence of differing conventional markers of disease severity across the three classifications, with those with lower LVEF having more impaired renal function, higher NT-proBNP and lower blood pressure. Those with HFrEF were the most symptomatic, being more likely to have New York Heart Association (NYHA) Class III/IV symptoms, compared to HFmrEF (32.1% vs 25.1%;p=0.013 in the UK-

HEART-2 cohort), with higher mean dosing of loop diuretic in those with lower LVEF (p<0.001 in the combined dataset).

5.4.3 Provision of pharmacological therapies

Within the combined dataset, 1875 (78.5%) were prescribed a beta-adrenoceptor antagonists, 1977 (82.8%) an ACEi/ARB and 728 (30.5%) a mineralocorticoid receptor antagonist (MRA) (Table 1). Patients with HFrEF were the most likely to receive a beta-adrenoceptor antagonist (84.7%), ACEi/ARB (86.6%) or MRA (39.9%), whereas those with HFpEF were least likely (59.8%, 62.4% and 7.1%). Patients classified as having HFmrEF usually received a beta-adrenoceptor antagonist (77.0%) and ACEi/ARB (84.6%) but fewer received an MRA (22.6%). Mean dosing of beta-adrenoceptor antagonists and ACEi/ARB was different across the three classifications, with those with HFrEF prescribed the highest doses.

Table 5.1 Clinical characteristics of patients according to classification of chronic heart failure

	All patients (n=2388)	HFrEF (n=1504)	HFmrEF (n=421)	HFpEF (n=463)
Demographics				
Age (years)	73.7 ± 13.2	70.4 ± 13.2	74.2 ± 12.4**	83.8 ± 8.6**
Male sex [n(%)]	1525 (63.9)	1099 (73.1)	266 (63.2)**	160 (34.6)**
NYHA Class III/IV[#]	539 (30.8)	457 (32.1)	82 (25.1)*	-
Co-morbidities				
IHD [n(%)]	1183 (49.5)	847 (56.3)	231 (54.9)	105 (22.7)**
Diabetes mellitus [n(%)]	660 (27.6)	414 (27.5)	134 (31.8)	112 (24.2)
COPD [n(%)]	364 (15.2)	226 (15.0)	74 (17.6)	64 (13.8)
Observations				
SBP (mmHg)	128.2 ± 24.0	122.1 ± 22.0	131.6 ± 22.4**	144.2 ± 23.4**
DBP (mmHg)	72.0 ± 11.8	71.2 ± 11.6	72.7 ± 12.1*	73.8 ± 12.0**
Heart rate (beats/min)	75.2 ± 17.6	76.0 ± 18.5	74.4 ± 17.0	73.5 ± 14.8*
Echocardiogram				
LVEDd (mm)	54.1 ± 9.8	58 (52.8-64)	50.0 ± 7.8**	44.9 ± 6.3**
LVEF (%)	37.2 ± 12.8	30 (24-36)	44.7 ± 1.8**	56.2 ± 4.0**
Blood tests				
Haemoglobin (g/L)	132.6 ± 19.4	134.6 ± 18.8	130.2 ± 20.5**	128.0 ± 19.2**
Creatinine (mmol/L)	102 (80-128)	107 (87-134)	102 (81-129.8)**	79 (66-102.5)**
Albumin (g/L)	42.5 ± 3.6	42.7 ± 3.6	42.6 ± 3.4	41.4 ± 3.5**
NT-proBNP (pg/mL)[#]	1054.5 (508.5-2555)	2511 (1009-5972)	1126 (511-2245)**	845 (438-1705)**
HbA1c (mmol/mol)[#]	45 (41-55)	46 (41-56)	51 (43-58)	44 (40-52.8)
Medications				
Beta-adrenoceptor antagonist [n(%)]	1875 (78.5)	1274 (84.7)	324 (77.0)**	277 (59.8)**
Bisoprolol dose (mg)	3.8 ± 3.4	4.0 ± 3.4	3.5 ± 3.4*	3.2 ± 3.6**
ACEi/ARB [n(%)]	1977 (82.8)	1332 (88.6)	356 (84.6)*	289 (62.4)**
Ramipril dose (mg)	4.5 ± 3.7	4.9 ± 3.6	4.4 ± 3.5*	3.4 ± 3.8**
Loop diuretic [n(%)]	1205 (66.5)	790 (75.3)	191 (63.7)**	224 (48.4)**
Furosemide dose (mg)	42.6 ± 46.7	50.2 ± 49.1	41.0 ± 46.4**	18.8 ± 25.9**
MRA [n(%)]	728 (30.5)	600 (39.9)	95 (22.6)**	33 (7.1)**

p *<0.05, **<0.005 compared to HFrEF
[#]Differences within UK-HEART-2 and NICE-CHF cohorts

IHD; ischaemic heart disease, COPD; chronic obstructive pulmonary disease, NYHA; New York Heart Association, SBP; systolic blood pressure, DBP; diastolic blood pressure, LVEDd; left ventricular end-diastolic diameter, NT-proBNP; N-terminal pro B-type natriuretic peptide, HbA1c; glycosylated haemoglobin, ACEi; angiotensin converting enzyme inhibitor, ARB; angiotensin receptor blocker, MRA; mineralocorticoid receptor antagonist.

5.4.4 Provision of pharmacological therapy and outcomes

During a mean follow-up of 4.8 ± 2.1 years, a total of 1331 (55.7%) patients died. Unadjusted survival was not different between classifications of CHF (log-rank

p=0.98). However, in age-sex adjusted analysis, all-cause mortality risk was lower in HFmrEF (hazard ratio [HR] 0.86 (95% confidence interval [CI] 0.74-0.99);*p*=0.040) and in HFpEF (HR 0.61 (95% CI 0.52-0.71);*p*<0.001) than HFrEF (Figure 5.2). Receipt of beta-adrenoceptor antagonist or ACEi/ARB was associated with better survival in all classifications of heart failure. In age-sex adjusted analysis, these associations remained evident for HFrEF and HFmrEF, but not for HFpEF (Figures 5.3 and 5.4). The receipt of MRA was not associated with survival in HFrEF (*p*=0.48) or HFmrEF (*p*=0.74) but was associated with a worse prognosis in the small proportion of patients with HFpEF who received these agents (*p*=0.001).

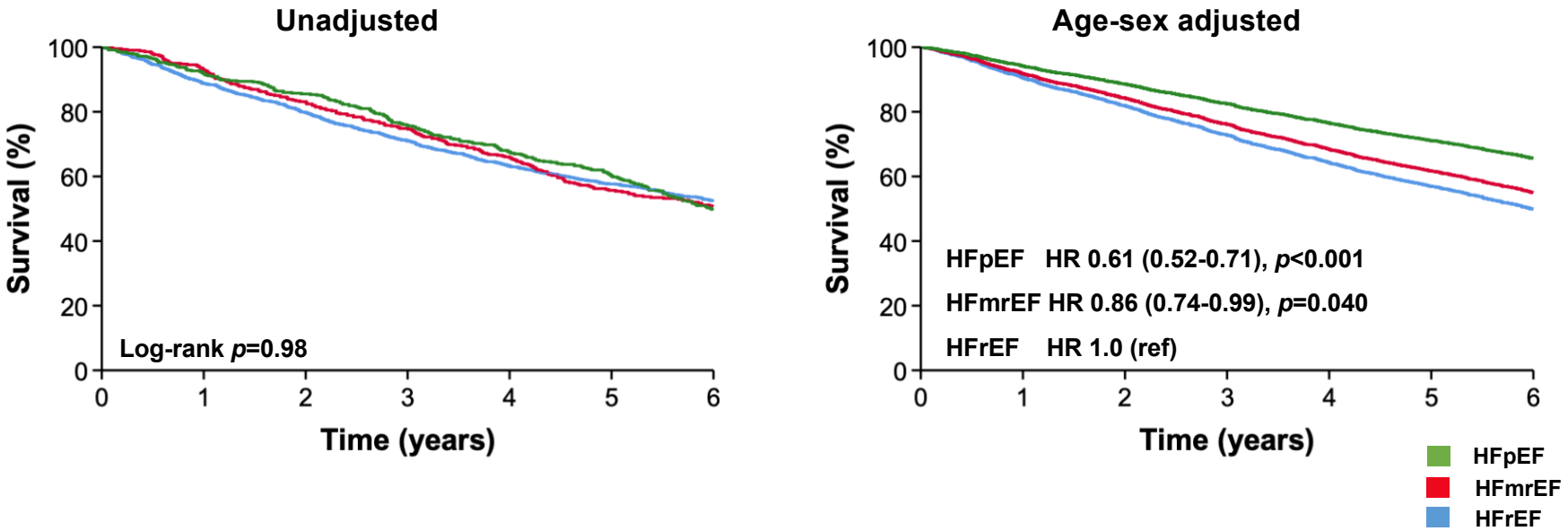


Figure 5.2 Kaplan-Meier and age-sex adjusted survival plots divided by classification of chronic heart failure

Reproduced from (Straw, Cole et al. 2023) under terms of Creative Commons Attribution Non-Commercial License.

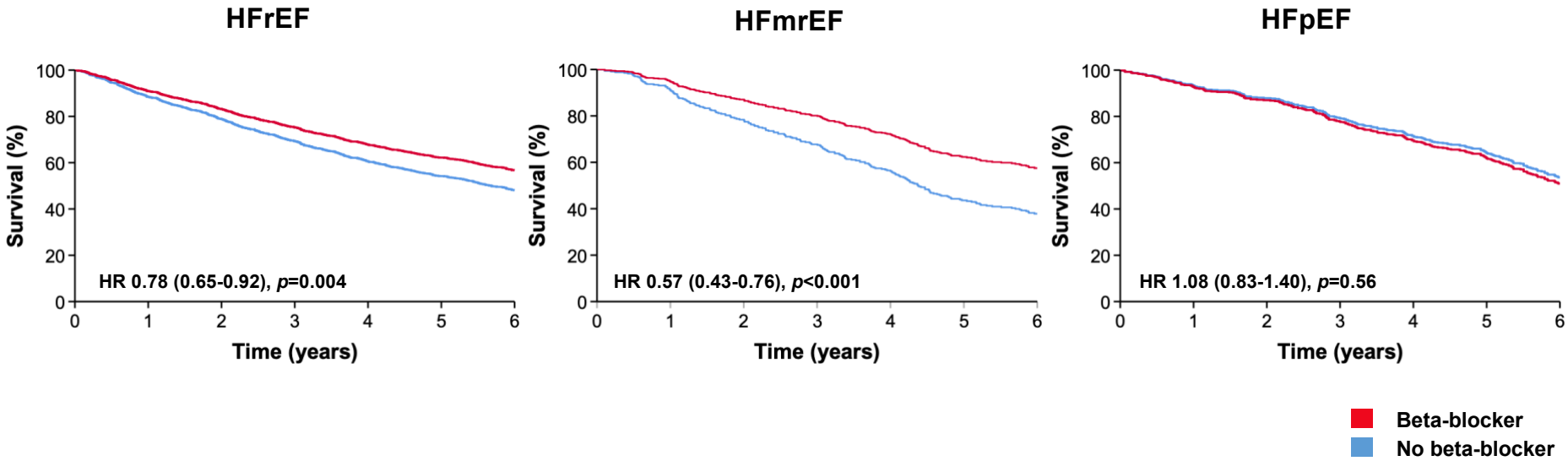


Figure 5.3 Age-sex adjusted survival plot according to receipt of beta-adrenoceptor antagonist divided by classification of chronic heart failure

Reproduced from (Straw, Cole et al. 2023) under terms of Creative Commons Attribution Non-Commercial License.

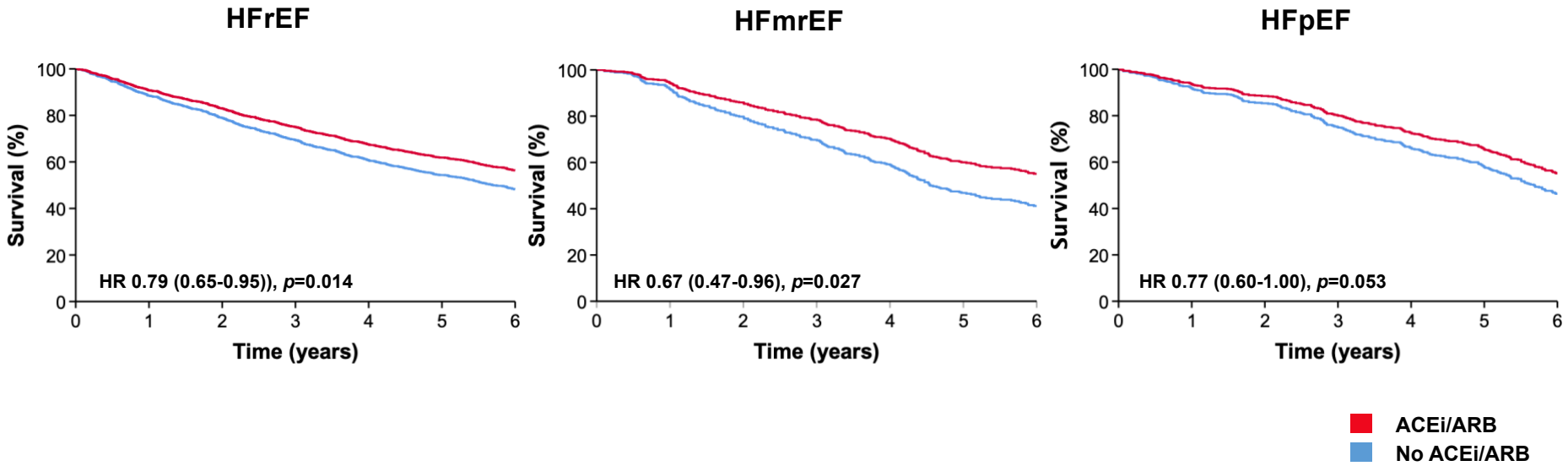


Figure 5.4 Age-sex adjusted survival plot according to receipt of ACEi/ARB divided by classification of chronic heart failure

Reproduced from (Straw, Cole et al. 2023) under terms of Creative Commons Attribution Non-Commercial License.

5.4.5 Dosing of pharmacological therapies and outcomes

I explored the association of the receipt of pharmacological therapies and outcomes further, by dividing patients with HFrEF, HFmrEF, and HFpEF, into those not receiving these agents, those prescribed low doses (<5mg equivalent dose) and those prescribed high doses (≥5mg equivalent dose) of beta-adrenoceptor antagonist and ACEi/ARB. Higher dosing of beta-adrenoceptor antagonist and ACEi/ARBs was associated with lower all-cause mortality risk in patients with HFrEF and HFmrEF, but this was not the case in HFpEF (Figure 5).

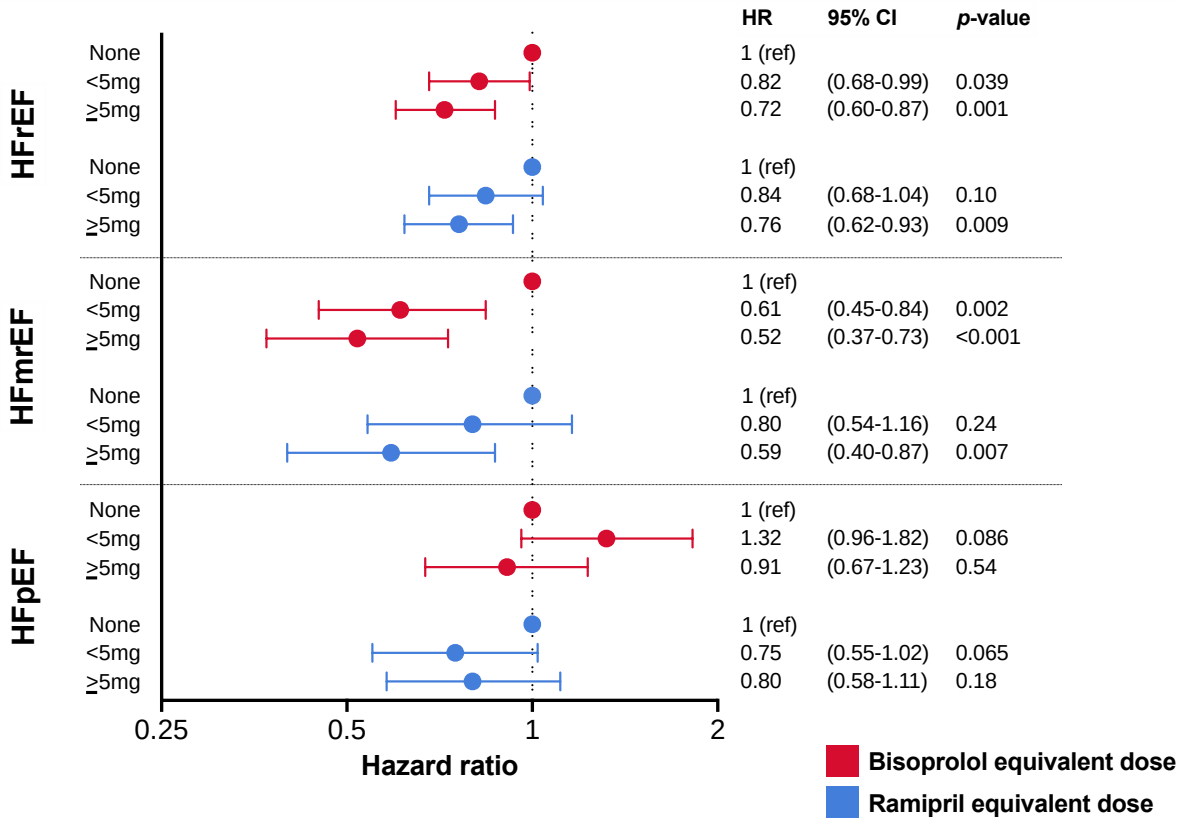


Figure 5.5 Forrest plot showing adjusted hazard ratio of all-cause mortality divided by dosing of beta-adrenoceptor antagonist and ACEi/ARB

Reproduced from (Straw, Cole et al. 2023) under terms of Creative Commons Attribution Non-Commercial License.

There were also clear associations between beta-adrenoceptor antagonist and ACEi/ARB dosing group and patient characteristics, such as age, history of ischaemic heart disease and diabetes, and cardiac dysfunction, although the pattern of these associations were similar between patients with HFrEF and HFmrEF (Tables 5.2 and 5.3).

Table 5.2 Clinical characteristics of patients with HFrEF and HFmrEF divided by dosing of beta-adrenoceptor antagonist

	HFrEF			HFmrEF		
	None (n=229)	<5mg (n=642)	≥5mg (n=631)	None (n=95)	<5mg (n=167)	≥5mg (n=156)
Demographics						
Age (years)	72.6 ± 12.6**	71.1 ± 13.1	68.8 ± 13.3	77.2 ± 12.0**	74.3 ± 11.1	71.8 ± 13.3
Male sex [n(%)]	157 (68.6)*	454 (70.7)	486 (77.0)	54 (56.8)*	112 (67.1)	98 (62.8)
Co-morbidities						
IHD [n(%)]	129 (56.3)	356 (55.5)	362 (57.4)	44 (46.3)	98 (58.7)	86 (55.1)
Diabetes mellitus [n(%)]	60 (26.2)*	153 (23.8)	200 (31.7)	24 (25.3)*	51 (30.5)	59 (37.8)
COPD [n(%)]	64 (27.9)**	104 (16.2)	56 (8.9)	30 (31.6)**	24 (14.4)	19 (12.2)
Observations						
SBP (mmHg)	124.4 ± 21.2	121.0 ± 22.2	122.1 ± 22.0	131.3 ± 22.5	132.4 ± 22.3	130.8 ± 22.7
DBP (mmHg)	71.9 ± 11.3	70.6 ± 11.3	71.6 ± 11.8	73.1 ± 12.3	72.5 ± 12.4	72.6 ± 11.9
Heart rate (beats/min)	79.2 ± 18.9*	75.3 ± 18.3	75.5 ± 18.6	76.2 ± 15.7	73.1 ± 15.6	74.7 ± 19.1
Echocardiogram						
LVEDd (mm)	57.0 ± 9.3	58.3 ± 8.8	58.6 ± 8.3	47.5 ± 8.5**	50.4 ± 7.5	51.2 ± 7.3
LVEF (%)	30.8 ± 7.8**	28.7 ± 8.5	29.4 ± 8.0	45.1 ± 2.1**	44.3 ± 1.6	44.8 ± 1.7
Blood tests						
Haemoglobin (g/L)	132.3 ± 19.4*	133.9 ± 18.7	134.6 ± 18.7	131.7 ± 17.5	129.1 ± 20.8	131.4 ± 20.1
Creatinine (mmol/L)	107 (83.3-135.8)	106 (86-133)	108 (90.8-133.3)	99 (77-124)	107 (83-135)	99 (80-122)
Albumin (g/L)	41.9 ± 3.7**	42.6 ± 3.9	43.2 ± 3.3	42.5 ± 3.7	42.3 ± 3.5	43.1 ± 2.9

*p<0.05, **p<0.005 across three groups

IHD; ischaemic heart disease, COPD; chronic obstructive pulmonary disease, NYHA; New York Heart Association, SBP; systolic blood pressure, DBP; diastolic blood pressure, LVEDd; left ventricular end-diastolic diameter, NT-proBNP; N-terminal pro B-type natriuretic peptide, HbA1c; glycosylated haemoglobin, ACEi; angiotensin converting enzyme inhibitor, ARB; angiotensin receptor blocker, MRA; mineralocorticoid receptor antagonist.

Table 5.3 Clinical characteristics of patients with HFrEF and HFmrEF divided by dosing of ACEi/ARB

	HFrEF			HFmrEF		
	None (n=169)	<5mg (n=514)	≥5mg (n=819)	None (n=65)	<5mg (n=148)	≥5mg (n=206)
Demographics						
Age (years)	75.6 ± 11.7**	70.8 ± 14.0	69.0 ± 12.7	79.5 ± 11.7**	74.3 ± 12.7	72.3 ± 11.9
Male sex [n(%)]	110 (65.1)**	358 (69.6)	630 (76.9)	30 (46.2)**	86 (58.1)	149 (72.3)
Co-morbidities						
IHD [n(%)]	102 (60.4)	277 (53.9)	467 (57.0)	27 (41.5)*	80 (54.1)	124 (60.2)
Diabetes mellitus [n(%)]	45 (26.6)	125 (24.3)	244 (29.8)	19 (29.2)	47 (31.8)	67 (32.5)
COPD [n(%)]	26 (15.4)	81 (15.8)	118 (14.4)	15 (23.1)	31 (20.9)	28 (13.6)
Observations						
SBP (mmHg)	125.1 ± 21.7*	119.6 ± 22.6	123.0 ± 21.5	131.5 ± 21.4	129.8 ± 21.8	133.1 ± 23.2
DBP (mmHg)	71.5 ± 12.1*	70.0 ± 11.1	71.9 ± 11.7	71.4 ± 11.6	72.3 ± 11.9	73.5 ± 12.6
Heart rate (beats/min)	78.2 ± 19.6*	77.3 ± 19.1	74.6 ± 17.8	78.3 ± 18.0*	76.4 ± 17.7	71.8 ± 15.9
Echocardiogram						
LVEDd (mm)	55.7 ± 9.2**	57.9 ± 8.7	58.9 ± 8.5	46.7 ± 7.1**	49.6 ± 8.5	51.3 ± 7.1
LVEF (%)	30.5 ± 7.6	29.0 ± 8.5	29.3 ± 8.4	45.4 ± 2.1**	44.6 ± 1.8	44.5 ± 1.7
Blood tests						
Haemoglobin (g/L)	129.1 ± 18.5**	133.8 ± 18.6	136.2 ± 18.8	124.9 ± 22.5	130.8 ± 18.5	131.4 ± 21.2
Creatinine (mmol/L)	117 (94-167)**	106 (85-134)	106 (87-131)	91 (72.5-140)	98 (78.3-128.8)	105 (86.5-130.5)
Albumin (g/L)	41.5 ± 3.8**	42.3 ± 3.6	43.3 ± 3.5	41.1 ± 3.5**	42.4 ± 3.5	43.3 ± 3.1

*p<0.05, **p<0.005 across three groups

IHD; ischaemic heart disease, COPD; chronic obstructive pulmonary disease, NYHA; New York Heart Association, SBP; systolic blood pressure, DBP; diastolic blood pressure, LVEDd; left ventricular end-diastolic diameter, NT-proBNP; N-terminal pro B-type natriuretic peptide, HbA1c; glycosylated haemoglobin, ACEi; angiotensin converting enzyme inhibitor, ARB; angiotensin receptor blocker, MRA; mineralocorticoid receptor antagonist.

Cox regression was used to further define the association between dosing of beta-adrenoceptor antagonist and ACEi/ARB and all-cause mortality risk in HFrEF and HFmrEF. Interaction analyses suggested that LVEF (as a continuous variable) was not a significant modifier of the effect of the dosing of beta-adrenoceptor antagonist (p=0.83) or ACEi/ARB (p=0.91), in patients with LVEF <50%. Regression models including factors associated with dosing of beta-adrenoceptor antagonist and ACEi/ARB were used to determine the association of dosing of these agents with all-cause mortality risk. In a model including age, sex, diabetes mellitus, chronic obstructive pulmonary disease, heart rate, LVEF, serum haemoglobin, and albumin (which were all associated with dosing of beta-adrenoceptor antagonist), each mg equivalent dose of bisoprolol was associated with incremental reductions in all-cause

mortality risk in HFmrEF (HR 0.95 (95% CI 0.91-1.00);*p*=0.047). Similarly, when adjusted for age, sex, systolic and diastolic blood pressure, heart rate, serum haemoglobin, creatinine, and albumin (which were all associated with dosing of ACEi/ARB), each mg equivalent of ramipril was associated with a similar magnitude of reduction in all-cause mortality risk (HR 0.95 (95% CI 0.90-1.0); *p*=0.044).

5.5 Discussion

5.5.1 Findings

In this pooled analysis of two prospective observational studies, I examined the provision of pharmacological therapies and dosing-related associations with mortality risk across a broad spectrum of LVEF. I was able to show that: 1) HFmrEF is highly prevalent amongst patients presenting to secondary care with symptoms of CHF and elevated natriuretic peptides; 2) clinical characteristics and outcomes varied according to LVEF, but patients with HFmrEF more closely resembled HFrEF, than HFpEF; and 3) higher dosing of beta-adrenoceptor antagonists and ACEi/ARB was associated with better survival in HFrEF and HFmrEF, but not in HFpEF. Taken together, these findings support guideline recommendations extending the indications of pharmacological therapies to all patients with CHF and LV systolic dysfunction.

5.5.2 Prevalence and characteristics of heart failure with mildly reduced ejection fraction

Although the combined dataset included patients enrolled in UK-HEART-2, which excluded people with LVEF >45%, by separately reporting data from the NICE-CHF study I was able to show that in an unselected cohort referred to secondary care with symptoms ± signs of CHF and elevated natriuretic peptides (Gierula, Cubbon et al.

2019), ~75% had LVEF >40%. HFmrEF and HFpEF therefore represent highly prevalent populations, for which therapeutic strategies are required. These findings that a substantial proportion of patients encountered in clinical practice have HFmrEF, are consistent with other registry studies. For example, the prevalence of HFmrEF in the Swedish Heart Failure Registry was around ~25%, although the proportion was only ~8% in the Get with the Guidelines Heart Failure (GWTG-HF) registry (Shah, Xu et al. 2017).

I observed differences in the baseline characteristics of patients with HFmrEF compared to HFrEF. However, although these differences were statistically significant, the numerical differences between groups were relatively small, and the distribution of co-morbidities was similar. Overall, the clinical characteristics of patients with HFmrEF more closely resembled those of HFrEF. The baseline characteristics of patients with HFpEF were more distinct. HFpEF patients were more likely to be older, to be female, and had biomarker evidence of less severe clinical heart failure, for example, lower natriuretic peptides, higher blood pressure and better renal function.

Prior registry and interventional studies have reached conflicting conclusions as to whether patients with HFmrEF more closely resemble HFrEF, HFpEF or are a group with distinct clinical characteristics and outcomes. Earlier studies, for example the GWTG-HF registry, suggest that these patients were more similar to those with HFpEF, and furthermore showed no difference in adjusted survival rates across the heart failure classifications (Shah, Xu et al. 2017). In comparison, in the Candesartan in Heart Failure – Assessment of Reduction in Mortality and Morbidity (CHARM) programme, whilst those with HFrEF and HFmrEF were similar in terms of age, sex

distribution and history of myocardial infarction, those with HFmrEF had a lower risk of cardiovascular death or hospitalisation for heart failure (Lund, Claggett et al. 2018). The Chronic Heart Failure Analysis and Registry in Tohoku District-2 (CHART-2) study suggested that HFmrEF represents an intermediate risk group on the continuity of LVEF, and furthermore made the observation that patients often transitioned to between these groups – especially from HFrEF or HFmrEF to HFpEF due to LV reverse remodelling (Tsuji, Sakata et al. 2017). This approach seems biologically the most plausible. The lack of longitudinal imaging data means that the current study was unable to assess outcomes for patients with heart failure with improved ejection fraction, although it is generally accepted that such patients continue to derive benefit from pharmacological therapies (Halliday, Wassall et al. 2019).

5.5.3 Heart failure classification and outcomes

Consistent with other reports (Fonarow, Stough et al. 2007), unadjusted survival was not different between classifications of heart failure. However, there were significant differences in mean ages and the distribution of sex across heart failure classifications. Compared to HFrEF, in age-sex adjusted analyses, I observed better survival in HFpEF (HR 0.61 [95% CI 0.52-0.71]) and marginally better survival in HFmrEF (HR 0.86 [95% CI 0.74-0.99]). Across all three classifications of heart failure, better survival was observed in unadjusted analyses with the receipt of pharmacological therapies. However, once adjusted for age and sex, these associations were no longer evident in HFpEF.

For the first time, guidelines recommend that pharmacological therapies approved for HFrEF may be considered for those with LVEF 41-49% (McDonagh, Metra et al. 2021), supporting what may have been routine practice in many settings for some time. In the absence of randomised trials, the approach used for this patient population was to administer beta-adrenoceptor antagonists and ACEi/ARB for those presenting with signs and symptoms of CHF and LVEF <50% who were able to tolerate these agents. Consequently, most patients attending the service who had LVEF 41-49% received these medications. Receipt of higher doses of beta-adrenoceptor antagonists and ACEi/ARB was associated with a lower all-cause mortality risk, even after adjusting for confounding variables. These observations suggest benefit in patients with less severely impaired cardiac function, which allies well the hypothesis that heart failure progression can be slowed, halted, or even reversed more effectively during its early stages. On the other hand, consistent with the lack of clinical trial evidence for HFpEF (Pitt, Zannad et al. 1999, Solomon, McMurray et al. 2019), treatments offered to this group attending this service were limited to lifestyle and risk factor modification as well as loop diuretics for alleviation of symptoms of congestion. Hence, the use of disease-modifying agents in those with HFpEF was lower, and I did not observe better outcomes in those receiving these agents.

5.5.4 Pharmacological therapies and outcomes in heart failure with mildly reduced ejection fraction

There are no cardiovascular outcomes trials specifically designed to evaluate the efficacy of pharmacological therapies in HFmrEF (Srivastava, Hsu et al. 2020). Furthermore, patients with HFmrEF have traditionally been excluded from trials in HFrEF. On the other hand, many studies investigating outcomes in HFpEF (especially

more recent trials) have had inclusion criteria overlapping the 41-49% LVEF range, providing insights into the management of patients who would be classified as having HFmrEF according to the proposed universal definition (Bozkurt, Coats et al. 2021). The CHARM programme consisted of three clinical trials evaluating the effects of candesartan. CHARM-Preserved (LVEF >40%) did not demonstrate reductions in mortality with candesartan (Yusuf, Pfeffer et al. 2003). However, in a pooled analysis there were reductions in the primary end-point of cardiovascular death or hospitalisation for heart failure in those with LVEF 40-49% (HR 0.76 [95% CI 0.61-0.96];*p*=0.02) (Lund 2018). Similarly, the Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction (PARAGON-HF) trial assessing the efficacy of sacubitril-valsartan in participants with LVEF ≥45%, did not demonstrate improved outcomes with the novel agent. However, when pooled with the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial (LVEF ≤40%), although the therapeutic effects of sacubitril-valsartan were found to be greatest in those with the most marked LV systolic dysfunction, the benefits did extend to those classified as having HFmrEF (Solomon, Vaduganathan et al. 2020). Finally, in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial (LVEF ≥45%) (Pitt, Pfeffer et al. 2014), patient characteristics and the treatment effect of spironolactone were substantially modified by LVEF, with the greatest benefit (although non-significant) amongst those with LVEF <50% (HR 0.72 [95% CI 0.50-1.05]) (Solomon, Claggett et al. 2016).

For all patients with HFrEF, guidelines recommend four classes of medications proven to reduce hospitalisations and cardiovascular mortality (McDonagh, Metra et al. 2021).

Adherence to guideline recommendations is associated with improved outcomes in real-world populations (Komajda, Lapuerta et al. 2005, Komajda, Schope et al. 2019, Cowie, Schope et al. 2021). However, whether these recommendations for patients with HFmrEF will be translated into meaningful improvements in outcomes is less certain, given that the underpinning data are derived from clinical trials in which the overall results were neutral.

Recent observational studies also lend support to the notion that pharmacological therapies may improve outcomes in HFmrEF. In the Swedish Heart Failure Registry, the provision of an ACEi/ARB was associated with lower all-cause mortality. However, the association for beta-adrenoceptor antagonists was only evident in those with coronary artery disease (Koh, Tay et al. 2017). The CHART-2 registry showed associations with lower mortality with the receipt of beta-adrenoceptor antagonists, but not ACEi/ARB (Tsuji, Sakata et al. 2017). On the other hand, in the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry, beta-adrenoceptor antagonists were not associated with reductions in all-cause mortality in those with LVEF ≥40% (Hernandez, Hammill et al. 2009). Additionally, although recent studies have reported dosing of pharmacological therapies in real-world populations with CHF, these have typically excluded those with LVEF >40% (Brunner-La Rocca, Linssen et al. 2019, Greene, Fonarow et al. 2019, Cowie, Schope et al. 2021), or have not specifically reported outcomes for this population (Fowler, Lottes et al. 2007). By separately reporting the provision of pharmacological therapies and outcomes for patients with HFmrEF, I was able to report the novel observation of incremental reductions in mortality risk amongst

patients receiving the highest doses of these agents, plausibly supporting their efficacy in this setting.

5.6 Strengths and limitations

The analysis included patients from two prospective studies representative of real-world populations of patients with CHF, encompassing a broad spectrum of LVEF and categorised according to guideline recommendations (Bozkurt, Coats et al. 2021). Some limitations should be noted. This was an analysis of observational, non-randomised studies, the data are therefore susceptible to measured and unmeasured confounders. Medications were prescribed at the discretion of the treating cardiologist. The lack of randomisation means causality cannot be inferred and the findings should be regarded as hypothesis generating. Although the intention was to prescribe ACEi/ARB and beta-adrenoceptor antagonists for patients with HFmrEF who could tolerate these agents, the lack of standard operating procedures means that these data may be susceptible to indication bias. Fewer patients who had HFmrEF received these agents compared to HFrEF, although the differences in mean dosing of ACEi/ARB and beta-adrenoceptor antagonists were small, suggesting that once the decision to initiate therapy has been made, titration is generally successful. Although UK-HEART-2 recruited from four centres in the UK, NICE-CHF data originate from one service which may limit generalisability, although the diverse characteristics of the area served by our centre mitigates against this (Witte, Patel et al. 2018). Both studies predate the availability of ARNI and SGLT2i, which may be similarly effective in HFmrEF (Anker, Butler et al. 2019, Solomon, de Boer et al. 2021), and the lack of longitudinal cardiac imaging data means these findings may not be generalisable to those with an improved ejection fraction.

5.7 Conclusions

Patients classified as having HFmrEF according to the Universal Definition and Classification of Heart Failure seem to derive dose-dependent benefits from pharmacological therapies on a par with patients with HFrEF. These findings lend support to guideline recommendations which extend the indications of pharmacological therapies to all patients with symptoms of CHF and LV systolic dysfunction.

Chapter 6: Cardiac contractility index identifies subtle systolic dysfunction in preserved ejection fraction heart failure

Hypothesis: Many individuals with heart failure with a preserved ejection fraction have subtle systolic dysfunction which could be more easily identified by cardiac contractility index.

6.1 Introduction

Chronic heart failure is a clinical syndrome characterised by breathlessness, fatigue, frequent hospitalisation, and premature death (McDonagh, Metra et al. 2021). Current recommendations classify patients by left ventricular ejection fraction (LVEF), the most commonly reported measure of systolic function. Around half of people with heart failure have a preserved ejection fraction (HFpEF), and these individuals have similar symptoms, impairments in quality of life, hospitalisation rates, and mortality risk as those with heart failure with a reduced ejection fraction (HFrEF) (Shah, Xu et al. 2017). As a measure of systolic dysfunction, LVEF has well-known limitations including modest reproducibility, load dependence, and representation of the percentage change in left ventricular (LV) volume rather than myocardial contractility (Park, Park et al. 2018).

Although diastolic dysfunction has been proposed as a key mechanism underpinning the pathophysiology of HFpEF, the presence of subtle or concomitant systolic dysfunction as assessed by strain imaging in those with LVEF ≥50% has been previously suggested (Kraigher-Krainer, Shah et al. 2014). Simply classifying patients as having an ejection fraction which is ‘normal’ may offer limited insight and risk

misclassifying those who have any degree of systolic dysfunction. The ability to more easily identify individuals with HFpEF who actually have concomitant systolic dysfunction could help further refine its phenotypic classification, stratify risk, and identify potential to derive benefit from disease modifying pharmacological therapies.

LV end-systolic pressure to LV end-systolic volume index ratio, or 'cardiac contractility index' (CCI), is a non-invasive measure of LV contractility, validated against invasive haemodynamic studies (Ginzton, Laks et al. 1984, Bombardini, Correia et al. 2003). By incorporating LV end-systolic pressure, CCI is relatively independent of afterload and may therefore more accurately reflect LV contractile force. CCI has been used as a surrogate endpoint in randomised controlled trials assessing pharmacological and device-based therapies in HFrEF, although its prognostic significance in heart failure is unknown (Jamil, Gierula et al. 2016, Gierula, Lowry et al. 2020, Martens, Dupont et al. 2021).

6.2 Objectives

In this study we firstly sought to evaluate whether CCI was associated with all-cause mortality risk in an unselected population with chronic heart failure. Secondly, we aimed to determine its prognostic accuracy compared to LVEF. And, thirdly, we assessed whether CCI could reclassify patients with HFpEF and if these patients had a distinct phenotype and mortality risk.

6.3 Methods

6.3.1 Study design

The prospective evaluation of the diagnostic efficacy of the 2010 United Kingdom National Institute for Clinical Excellence guidelines on Chronic Heart Failure (NICE-CHF) is an observational cohort study including people newly referred to secondary care for suspected heart failure (Straw, Cole et al. 2023). Consecutive unselected patients from a primary care catchment of over 750,000 people between May 2012 and May 2013, who had signs and/or symptoms of chronic heart failure as well as elevated natriuretic peptides (N-terminal pro B-type natriuretic peptide [NT-proBNP] ≥125pg/L), were included.

6.3.2 Study procedures

Patients were evaluated in a secondary care specialist heart failure clinic. Upon arrival, demographic details, medical history, and currently prescribed medications were recorded. Height and weight were measured, and a venous blood sample was taken and tested for full blood count, electrolytes, and assessment of renal and liver function. NT-proBNP had previously been measured at the point of referral using samples collected in primary care, which were analysed at our institution using the Immulite 2000 assay (Siemens Healthcare Diagnostics, Camberley, UK) which has an inter-batch coefficient variation of 8.9% at 350pg/mL and 5.9% at 4100pg/ml. A standard 12-lead electrocardiogram was recorded at 25mm/s and two-dimensional transthoracic echocardiography was performed.

6.3.3 Echocardiography analyses

To determine CCI, systolic blood pressure was used as a surrogate of LV end-systolic pressure as previously described (Haedersdal, Madsen et al. 1993). This was measured using a standard sphygmomanometer placed on the patient's right arm

whilst in a supine position immediately prior to echocardiography. Echocardiographic images were obtained by senior cardiac sonographers according to recommendations of the American Society of Echocardiography and European Association of Cardiovascular Imaging (Lang, Badano et al. 2015). Images were then sent to digital storage media and, for the present analysis were analysed offline using Medcon (McKesson Cardiology, Irving TX, USA) by two senior accredited cardiac sonographers who were blinded to patient characteristics and measurements of NT-proBNP. Where endocardial border definition allowed, LV end-diastolic and end-systolic volumes were measured in apical two and four-chamber views using the biplane method of disks, and indexed for body surface area using the Mosteller equation (Mosteller 1987). CCI was calculated by dividing systolic blood pressure by LV end-systolic volume indexed to body surface area.

6.3.4 Patient classification and ascertainment of outcomes

All patients in the present study had signs and/or symptoms of chronic heart failure and elevated natriuretic peptides (N-terminal B-type natriuretic peptide ≥125pg/mL). We categorised patients according to the most recent European Society of Cardiology guidelines (McDonagh, Metra et al. 2021). For simplicity we categorised all patients with LVEF <50% as having HFrEF, and those with LVEF ≥50% as well as relevant structural heart disease (either left atrial dilatation, LV hypertrophy) or diastolic dysfunction, as having HFpEF (McDonagh, Metra et al. 2021). Patients without these echocardiographic features, including those in whom symptoms were attributable to significant valvular disease were excluded. We divided patients into tertiles based on measures of LV function, to determine the clinical characteristics and outcomes of these groups. The ranges for tertiles one, two and three of LVEF were <46.2%, 46.2-

55.1% and >55.1%; the ranges for tertiles one, two and three of CCI were <3.65mmHg/ml/m^2, 3.65-5.34mmHg/ml/m^2 and >5.34mmHg/ml/m^2. We then subdivided patients into four groups according to whether they were classified as having HFrEF or HFpEF and whether CCI was above or below the median value of 4.43mmHg/ml/m^2. The primary outcome was all-cause mortality according to LVEF and CCI. Vital status data were collected using linked Hospital Episode Statistics and Office of National Statistical mortality data which were available for all patients with final censorship in January 2022.

6.3.5 Statistical analysis

This was an observational study of consecutive cases of newly diagnosed heart failure during one year, and the sample size was not prespecified. Normality of distribution was confirmed using skewness tests. Continuous variables are presented as mean ± standard deviation if normally distributed, or as median (interquartile range) if non-normally distributed, with discrete variables presented as number (percentage). Groups were compared using t-tests or one-way analysis of covariance for normally distributed continuous data, Mann-Whitey or Kruskal-Wallis H tests for non-normally distributed data, and Pearson χ^2 test for categorical variables. Interobserver variability for LV end-diastolic and end-systolic volumes were compared in a random sample of 10% of patients assessed by both observers by inter-observer correlation coefficient and displayed by Bland-Altman plots. We determined the association between LVEF and CCI by Pearson's correlation. We plotted Kaplan Meier curves to illustrate all-cause mortality rates, with significance testing between groups determined by log-rank test.

We found the proportional hazards assumptions were not valid for LVEF and CCI, we therefore estimated mortality rates ratios (IRR) using Poisson regression models. Exposure time was modelled, and we chose four knots for both variables as these provided the best fit assessed by the Akaike and Bayesian information criterion scores. Models including cubic splines with three, four or five knots and first and degree fractional polynomials were compared and found to provide less robust fit. IRRs estimated for LVEF and CCI pertain to specific points (LVEF 20, 30, 40, and 60% compared with 50%, and CCI 2, 4, 6 and 8mmHg/ml/m^2 compared with 4.43mmHg/ml/m^2 which was the median value). Covariates included in a multivariable Poisson regression model were age, sex, ischaemic heart disease, diabetes mellitus, hypertension, systolic blood pressure, heart rate, haemoglobin, creatinine, albumin and NT-proBNP, in which non-normally distributed continuous data were log10 transformed. All tests were two-sided and statistical significance was regarded as $p<0.05$. Statistical analyses were done using Stata/MP (version 16.1, StataCorp LLC, College Station, TX, USA) and PRISM (version 9, GraphPad Software Inc, San Diego, CA).

6.3.6 Ethical considerations

The United Kingdom Health Research Authority provided ethical approval for the study through a Section 251 application reviewed by the Confidential Advisory Group. Approval through a Section 251 application allows individual patient data to be used for health service improvement and waives the requirement for individual patient consent (CAG8-03(PR1)/2013). Appropriate data safeguards were in place and the study complied with the principles outlined in the Declaration of Helsinki.

6.4 Results

6.4.1 Baseline characteristics of the study population

Between May 2012 and May 2013, a total of 982 patients who had suspected heart failure and NTpro-BNP ≥125pg/L were referred for evaluation in secondary care. Of these, 182 did not fulfil diagnostic criteria for chronic heart failure (Table 6.1), whilst for a further 72 patients, calculation of CCI was not possible due to either insufficient endocardial definition or missing height, weight, or systolic blood pressure.

Table 6.1 Final diagnosis in patients who did not have chronic heart failure according to the European Society of Cardiology guidelines definition.

Diagnosis	Frequency
Angina/ischaemic heart disease	10 (5%)
Atrial fibrillation	10 (5%)
Chest infection	3 (2%)
Chronic obstructive pulmonary disease	23 (13%)
Deconditioning	5 (3%)
Dependent oedema	6 (3%)
Diabetes mellitus	2 (1%)
Hypertrophic obstructive cardiomyopathy	2 (1%)
Hypertension	26 (14%)
Lung cancer	2 (1%)
Obesity	10 (5%)
Right heart failure/pulmonary hypertension	42 (23%)
Unascertained	30 (16%)
Valvular heart disease	11 (6%)
Total	182

The final dataset therefore consisted of 728 patients who had a mean age of 82.6 ± 9.2 years, of whom 398 (54.7%) were male. The inter-observer correlation coefficients for LV end-diastolic and end-systolic volumes were 0.99 (95% CI 0.99-1.00) and 0.99 (95% CI 0.99-1.00), respectively (Figure 6.1).

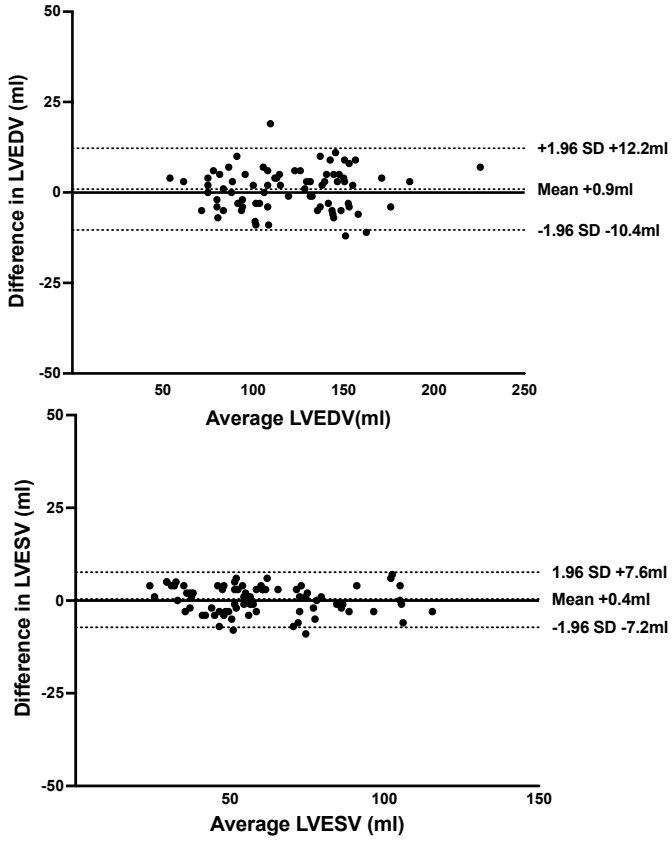


Figure 6.1 Bland Altman plot of inter-observer variability of left ventricular end-diastolic and end-systolic volumes.

Across the entire dataset the mean LVEF was 48.2 ± 11.6% (range 12.7-68.9%) with 293 (40.2%) classified as having HFrEF and 435 (59.8%) as having HFpEF. The mean CCI was 4.55±1.9 mmHg/ml/m^2 (range 0.71-11.3mmHg/ml/m^2) (Figure 6.2).

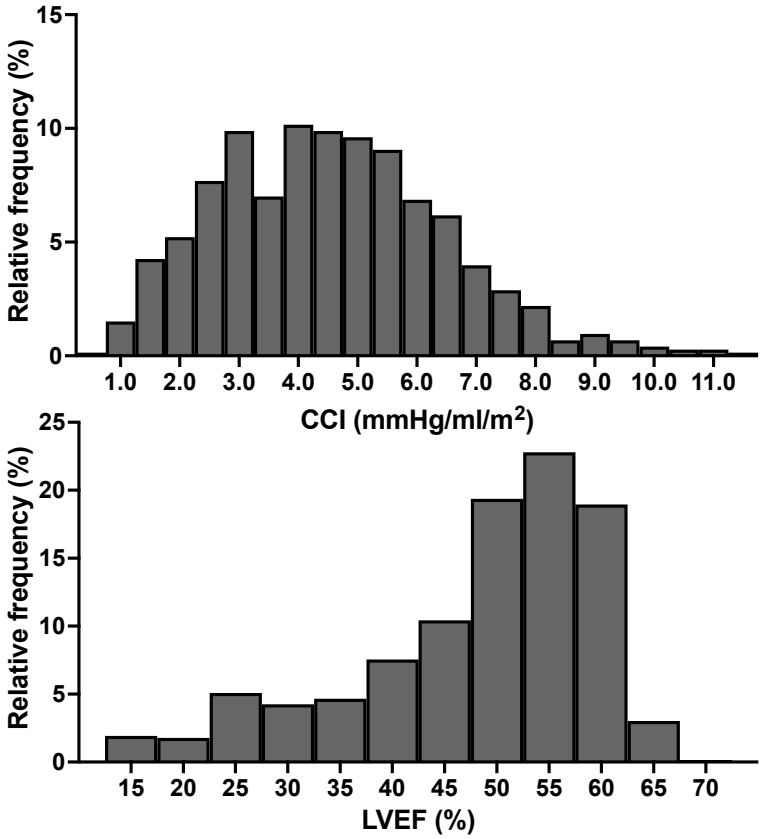


Figure 6.2 Frequency distribution plots of left ventricular ejection fraction and cardiac contractility index

6.4.2 Clinical characteristics according to left ventricular ejection fraction and cardiac contractility index

We divided patients into tertiles of LVEF and CCI to determine differences in the demographic and clinical characteristics between these groups (Tables 6.2 and 6.3). Patients within the lowest tertiles of both LVEF and CCI were more often male, more frequently had ischaemic heart disease and diabetes mellitus, and were less likely to have hypertension. They also had on average greater conventional markers of disease severity including lower systolic blood pressure, higher heart rate, and worse renal function.

Table 6.2 Clinical characteristics of patients divided by tertiles of left ventricular ejection fraction

	All patients (n=728)	Divided by LVEF			
		Tertile 1 <46.2% (n=242)	Tertile 2 46.2-55.1% (n=243)	Tertile 3 >55.1% (n=243)	*p*-value
Demographics					
Age (years)	82.6 ± 9.2	81.4 ± 10.0	83.9 ± 8.5	82.6 ± 8.9	0.012
Male sex [n(%)]	330 (45.3)	148 (44.8)	99 (30.0)	83 (25.2)	<0.001
NYHA Class III/IV [n(%)]	328 (45.1)	98 (40.3)	109 (44.9)	121 (50.0)	0.10
Co-morbidities					
IHD [n(%)]	210 (28.8)	92 (37.9)	64 (26.3)	54 (22.3)	<0.001
Stroke/TIA [n(%)]	62 (8.5)	20 (8.2)	23 (9.5)	19 (7.9)	0.80
Hypertension [n(%)]	490 (67.3)	133 (54.7)	176 (72.4)	181 (74.8)	<0.001
Diabetes mellitus [n(%)]	208 (28.6)	85 (35.0)	64 (26.3)	59 (24.4)	0.023
Atrial fibrillation [n(%)]	263 (36.1)	87 (35.8)	98 (40.3)	78 (32.3)	0.18
CKD [n(%)]	152 (20.9)	45 (18.5)	58 (23.9)	49 (20.2)	0.33
COPD [n(%)]	110 (15.1)	38 (15.6)	38 (15.6)	34 (14.0)	0.85
Observations					
SBP (mmHg)	140.3 ± 22.9	134.7 ± 23.8	141.8 ± 20.9	144.4 ± 22.9	<0.001
Heart rate (beats/min)	76.0 ± 16.9	79.1 ± 19.4	74.7 ± 16.4	74.0 ± 14.2	0.001
Echocardiogram					
LVEDVi (ml/m^2)	65.0 (53.9-81.8)	76.4 (60.1-94.0)	62.3 (50.9-75.1)	61.1 (52.1-72.5)	-
LVESVi (ml/m^2)	31.4 (24.7-43.4)	48.7 (36.4-65.7)	30.2 (24.9-36.7)	24.9 (21.2-29.6)	-
LVEF (%)	48.2 ± 11.6	34.4 ± 9.1	51.3 ± 2.2	58.9 ± 2.5	-
CCI (mmHg/ml/m^2)	4.55 ± 1.92	2.94 ± 1.30	4.81 ± 1.41	5.92 ± 1.68	<0.001
Blood tests					
Haemoglobin (g/L)	130 (119-142)	132 (122-144)	129 (117-141)	129 (119-140)	0.045
Creatinine (mmol/L)	82 (69-104)	86 (74-112)	83 (69-105)	78 (65-94)	<0.001
Sodium	140 (138-143)	140 (138-142)	141 (138-142)	141 (138-143)	0.063
Albumin (g/L)	42 (40-44)	42 (40-44)	41 (39-44)	42 (40-44)	0.030
NT-proBNP (pg/mL)	1066 (503.5-2570)	2119 (810-4827)	1003 (503-2113)	655 (346-1344)	<0.001
HbA1c (mmol/mol)	46 (41-56)	47 (42-56)	46 (40.5-56)	45 (40-54)	0.080
Medications					
Beta-blocker [n(%)]	406 (55.8)	144 (59.3)	131 (53.9)	131 (54.1)	0.41
Bisoprolol dose (mg)	2.9 ± 3.5	2.8 ± 3.4	2.8 ± 3.5	3.0 ± 3.6	0.81
ACEi/ARB [n(%)]	442 (60.7)	158 (65.0)	138 (56.8)	146 (60.3)	0.18
Ramipril dose (mg)	3.4 ± 3.8	3.3 ± 3.7	3.1 ± 3.7	3.6 ± 4.1	0.39
Loop diuretic [n(%)]	338 (46.4)	137 (56.4)	114 (46.9)	87 (36.0)	<0.001
Furosemide dose (mg)	0 (0-40)	20 (0-40)	0 (0-40)	0 (0-20)	<0.001
MRA [n(%)]	29 (4.0)	20 (8.2)	5 (2.1)	4 (1.7)	<0.001

Continuous variables are expressed as mean ± standard deviation, or median (interquartile range) discrete variables as number and percentages in parentheses.

NYHA; New York Heart Association, IHD; ischaemic heart disease, TIA; transient ischaemic attack, CKD; chronic kidney disease, COPD; chronic obstructive pulmonary disease, SBP; systolic blood pressure, LVEDVi; left ventricular end-diastolic volume index, LVESVi, left ventricular end-systolic volume index, LVEF; left ventricular ejection fraction, CCI; cardiac contractility index, NT-proBNP; N-terminal pro B-type natriuretic peptide, HbA1c; glycosylated haemoglobin, ACEi; angiotensin converting enzyme inhibitor, ARB; angiotensin receptor blocker, MRA; mineralocorticoid receptor antagonist.

Table 6.3 Clinical characteristics of patients divided by tertiles of cardiac contractility index

	All patients (n=728)	Divided by cardiac contractility index			
		Tertile 1 <3.65mmHg/ml/m^2 (n=242)	Tertile 2 3.65-5.34mmHg/ml/m^2 (n=243)	Tertile 3 >5.34mmHg/ml/m^2 (n=243)	*p*-value
Demographics					
Age (years)	82.6 ± 9.2	81.7 ± 10.4	82.9 ± 8.8	83.2 ± 8.2	0.16
Male sex [n(%)]	330 (45.3)	154 (46.7)	102 (30.9)	74 (22.4)	<0.001
NYHA Class III/IV [n(%)]	328 (45.1)	104 (42.8)	103 (42.4)	121 (50.0)	0.17
Co-morbidities					
IHD [n(%)]	210 (28.8)	86 (35.4)	70 (28.8)	54 (22.3)	0.006
Stroke/TIA [n(%)]	62 (8.5)	22 (9.1)	26 (10.7)	14 (5.8)	0.14
Hypertension [n(%)]	490 (67.3)	140 (57.6)	166 (68.3)	184 (76.0)	<0.001
Diabetes mellitus [n(%)]	208 (28.6)	85 (35.0)	65 (26.7)	58 (24.0)	0.020
Atrial fibrillation [n(%)]	263 (36.1)	90 (37.0)	92 (37.9)	81 (33.5)	0.57
CKD [n(%)]	152 (20.9)	53 (21.8)	43 (17.7)	56 (23.1)	0.31
COPD [n(%)]	110 (15.1)	39 (16.0)	42 (17.3)	29 (12.0)	0.23
Observations					
SBP (mmHg)	140.3 ± 22.9	129.5 ± 21.7	140.1 ± 20.2	151.4 ± 21.5	-
Heart rate (beats/min)	76.0 ± 16.9	78.1 ± 19.3	74.6 ± 16.4	75.2 ± 14.6	0.049
Echocardiogram					
LVEDVi (ml/m^2)	65.0 (53.9-81.8)	86.5 (73.4-100.6)	65.4 (56.5-74.8)	52.1 (45.3-59.6)	<0.001
LVESVi (ml/m^2)	31.4 (24.7-43.4)	51.2 (42.5-65.7)	31.4 (27.5-35.2)	23.0 (20.2-26.0)	-
LVEF (%)	48.2 ± 11.6	37.2 ± 11.8	51.6 ± 7.1	55.8 ± 5.0	<0.001
CCI (mmHg/ml/m^2)	4.55 ± 1.92	2.51 ± 0.70	4.46 ± 0.49	6.70 ± 1.23	-
Blood tests					
Haemoglobin (g/L)	130 (119-142)	128 (116-141)	130 (119-141)	131 (122-143)	0.21
Creatinine (mmol/L)	82 (69-104)	89 (74-122.5)	80 (68.8-100)	77 (65-96)	<0.001
Sodium	140 (138-143)	140 (138-142)	140.5 (138-143)	141 (139-143)	0.052
Albumin (g/L)	42 (40-44)	42 (39-44)	42 (40-44)	42 (40-44)	0.029
NT-proBNP (pg/mL)	1066 (503.5-2570)	2310 (933-5155)	921 (486-1759)	715 (348-1362)	<0.001
HbA1c (mmol/mol)	46 (41-56)	47 (41-58)	45 (41-53)	46 (40-54.5)	0.31
Medications					
Beta-blocker [n(%)]	406 (55.8)	135 (55.6)	133 (54.7)	138 (57.0)	0.88
Bisoprolol dose (mg)	2.9 ± 3.5	2.5 ± 3.2	3.0 ± 3.6	3.1 ± 3.6	0.10
ACEi/ARB [n(%)]	442 (60.7)	156 (64.2)	134 (55.1)	152 (62.8)	0.089
Ramipril dose (mg)	3.4 ± 3.8	3.4 ± 3.8	3.0 ± 3.6	3.7 ± 4.1	0.11
Loop diuretic [n(%)]	338 (46.4)	143 (58.8)	103 (42.4)	92 (38.0)	<0.001
Furosemide dose (mg)	0 (0-40)	20 (0-40)	0 (0-40)	0 (0-40)	<0.001
MRA [n(%)]	29 (4.0)	19 (7.8)	6 (2.5)	4 (1.7)	0.001

Continuous variables are expressed as mean ± standard deviation, or median (interquartile range) discrete variables as number and percentages in parentheses.

NYHA; New York Heart Association, IHD; ischaemic heart disease, TIA; transient ischaemic attack, CKD; chronic kidney disease, COPD; chronic obstructive pulmonary disease, SBP; systolic blood pressure, LVEDVi; left ventricular end-diastolic volume index, LVESVi, left ventricular end-systolic volume index, LVEF; left ventricular ejection fraction, CCI; cardiac contractility index, NT-proBNP; N-terminal pro B-type natriuretic peptide, HbA1c; glycosylated haemoglobin, ACEi; angiotensin converting enzyme inhibitor, ARB; angiotensin receptor blocker, MRA; mineralocorticoid receptor antagonist.

There was an inverse relationship between NTpro-BNP and both LVEF and CCI as continuous variables. Median NTpro-BNP was 655 (345-1344) pg/mL, 1003 (503-2113) pg/mL and 2119 (810-4827) pg/mL for tertiles one, two and three of LVEF, respectively; and 715 (348-1362) pg/mL, 921 (486-1759) pg/mL and 2310 (933-5155) pg/mL for tertiles one, two and three of CCI, respectively (p<0.0001 for trend in both comparisons) (Figure 6.3). Despite this, the proportion of patients with New York Heart Association class III/IV symptoms was similar across tertiles of LVEF and CCI. Aside from the variables from which these groups were derived (systolic blood pressure and indexed LV volumes), the pattern of these associations was similar across tertiles whether patients were divided by LVEF or CCI.

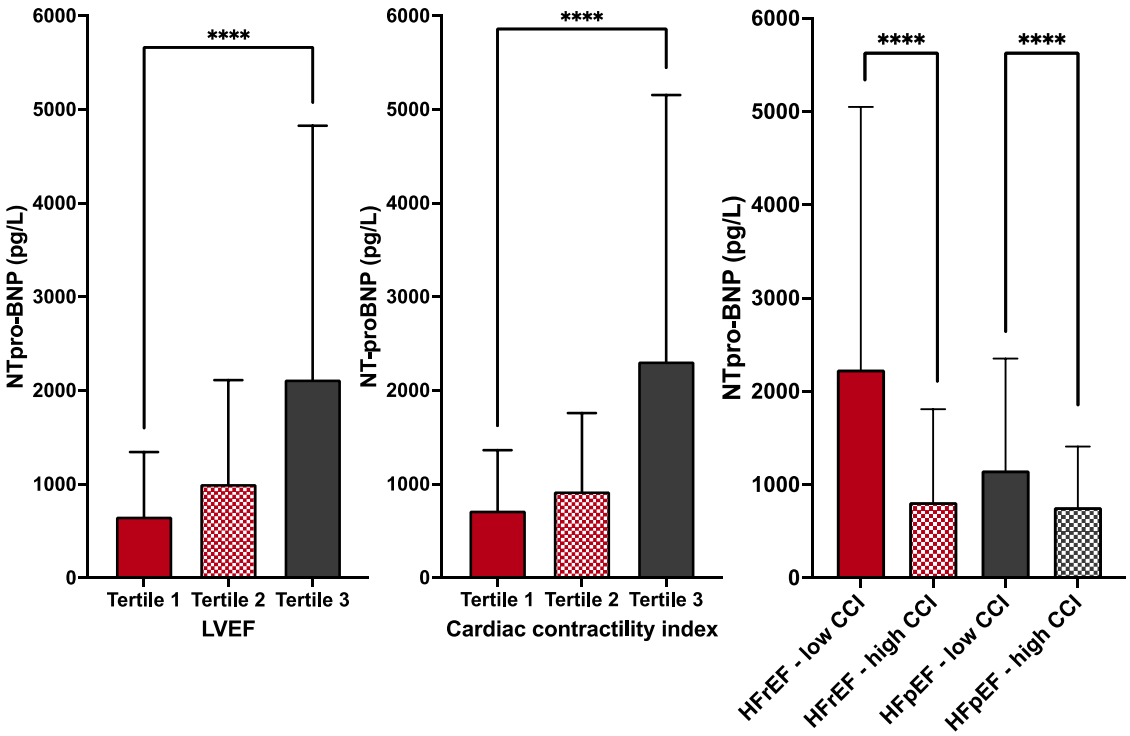


Figure 6.3 Bar charts showing levels of NT-proBNP between groups

6.4.3 Relationship between left ventricular ejection fraction and cardiac contractility index

Although there was a modest, positive correlation between LVEF and CCI (r=0.70 [0.66-0.74], R^2 0.49; *p*<0.0001), the latter was distributed widely for any given value of LVEF, especially evident for those with a preserved ejection fraction (Figure 6.4). To explore the relationship between LVEF and CCI further, we divided patients with HFrEF and HFpEF according to median CCI (≤ or >4.43mmHg/ml/m^2) into four groups. In the HFrEF group, 232 (79.2%) had low contractility and 61 (20.8%) high contractility; of patients with HFpEF, 132 (30.3%) had low contractility and 303 (69.7%) had high contractility.

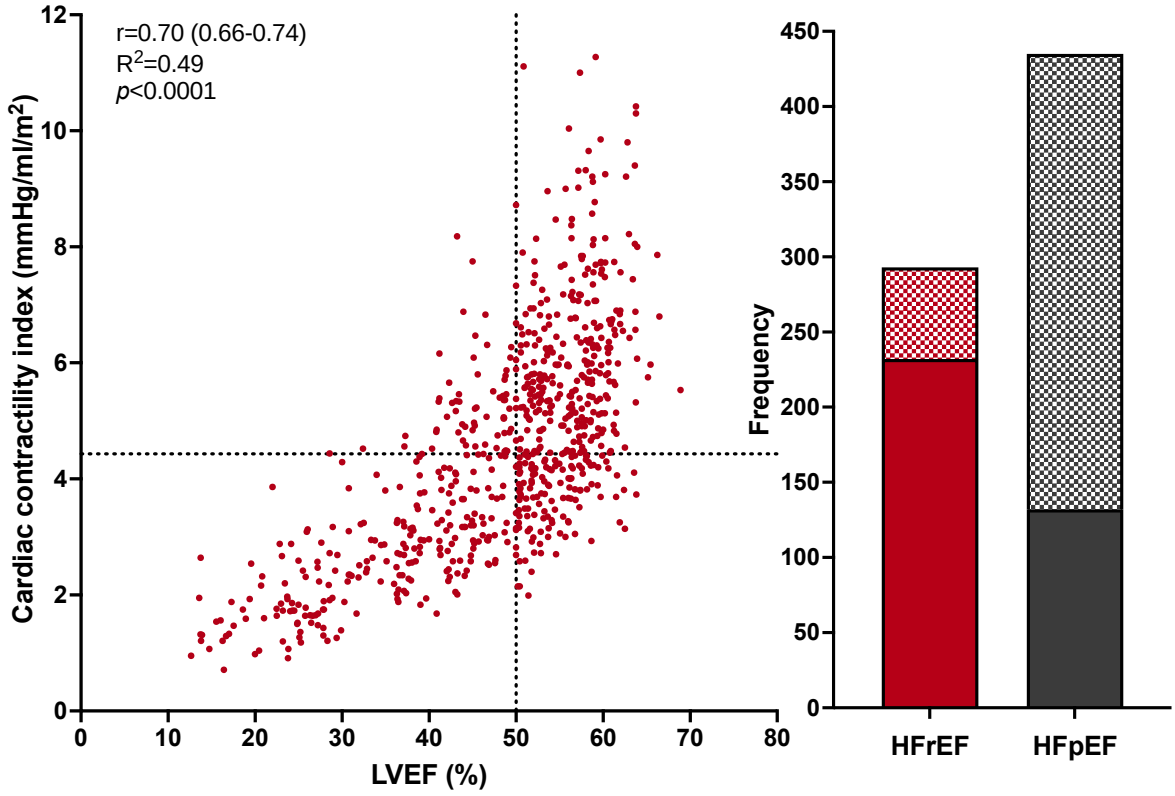


Figure 6.4 Scatter plot of left ventricular ejection fraction and cardiac contractility index, and bar charts showing the proportion of patients with heart

failure with reduced and preserved ejection fraction who had low or high cardiac contractility index

The clinical characteristics of patients with HFrEF and HFpEF divided according to median CCI are displayed in Table 6.4. Patients classified as having HFpEF were on average older, less likely to be male, have ischaemic heart disease or diabetes mellitus and more likely to have hypertension and were receiving lower doses of loop diuretics compared to patients with HFrEF. Within patients classified as having HFpEF, those with low cardiac contractility index were more often male, had ischaemic heart disease and had other markers of risk including lower serum haemoglobin, worse renal function and lower serum albumin compared to those with HFpEF and high contractility. Across these groups, we observed that median NT-proBNP was higher in those with low CCI, regardless of whether they were classified as having HFrEF (2235 [788-5052] and 813 [450-1810] pg/mL) or HFpEF (1153 [503-2353] pg/mL and 761 [401-1409] pg/mL) (Figure 6.4).

Table 6.4 Clinical characteristics of patients with heart failure with reduced and preserved ejection fraction divided by median cardiac contractility index

	All patients (n=728)	HFrEF		HFpEF	
		Low CCI (n=232)	High CCI (n=61)	Low CCI (n=132)	High CCI (n=303)
Demographics					
Age (years)	82.6 ± 9.2	81.1 ± 10.3[#]	83.2 ± 8.5	83.9 ± 8.4[#]	83.1 ± 8.4
Male sex [n(%)]	330 (45.3)	151 (65.1)*[#]	23 (37.7)*	64 (48.5)*[#]	92 (30.4)*
NYHA Class III/IV [n(%)]	328 (45.1)	95 (40.9)	18 (29.5)	55 (41.7)	160 (52.8)
Co-morbidities					
IHD [n(%)]	210 (28.8)	87 (37.5)[#]	25 (41.0)[#]	33 (25.0)[#]	65 (21.5)[#]
Stroke/TIA [n(%)]	62 (8.5)	21 (9.1)	5 (8.2)	12 (9.1)	24 (7.9)
Hypertension [n(%)]	490 (67.3)	123 (53.0)*[#]	42 (68.9)*	94 (71.2)[#]	231 (76.2)
Diabetes mellitus [n(%)]	208 (28.6)	83 (35.8)[#]	19 (31.1)	34 (25.8)[#]	72 (23.8)
Atrial fibrillation [n(%)]	263 (36.1)	81 (34.9)	20 (32.8)	57 (43.2)	105 (34.7)
CKD [n(%)]	152 (20.9)	42 (18.1)	11 (18.0)	31 (23.5)	68 (22.4)
COPD [n(%)]	110 (15.1)	38 (16.4)	10 (16.4)	22 (16.7)	40 (13.2)
Observations					
SBP (mmHg)	140.3 ± 22.9	131.6 ± 22.8*	149.0 ± 20.5*	133.8 ± 20.0*	148.0 ± 21.4*
Heart rate (beats/min)	76.0 ± 16.9	78.7 ± 19.7[#]	79.5 ± 19.3[#]	74.4 ± 15.5[#]	73.8 ± 14.3[#]
Echocardiogram					
LVEDVi (ml/m^2)	65.0 (53.9-81.8)	80.9 (66.0-97.6)*	52.1 (45.4-57.9)*[#]	80.5 (69.9-89.1)*	55.9 (48.1-63.8)*[#]
LVESVi (ml/m^2)	31.4 (24.7-43.4)	51.1 (40.7-67.1)*[#]	29.2 (24.6-32.6)*[#]	35.8 (32.2-41.2)*[#]	24.3 21.2-27.6)*[#]
LVEF (%)	48.2 ± 11.6	34.6 ± 9.6*[#]	45.0 ± 4.1*[#]	54.2 ± 3.5*[#]	56.6 ± 3.8*[#]
CCI (mmHg/ml/m^2)	4.55 ± 1.92	2.64 ± 0.88*[#]	5.31 ± 0.77*[#]	3.69 ± 0.56*[#]	6.24 ± 1.37*[#]
Blood tests					
Haemoglobin (g/L)	130 (119-142)	131 (119-143.8)[#]	132 (123-144)	125.5 (115-138.8)*[#]	130 (120-141)*
Creatinine (mmol/L)	82 (69-104)	86 (74-113)	79 (73.5-100)	83 (69.8-108)*	78 (65-98)*
Sodium	140 (138-143)	140 (138-142)[#]	141 (138-142.5)	141 (138-143)[#]	141 (138-143)
Albumin (g/L)	42 (40-44)	42 (39-43.8)*	43 (41-44.5)*	41 (38-44)*	42 (40-44)*
NT-proBNP (pg/mL)	1066 (503.5-2570)	2235 (788-5052)*[#]	813 (450-1810)*	1153 (503-2353)*[#]	761 (401-1409)*
HbA1c (mmol/mol)	46 (41-56)	47 (42-56)	52 (44-62)[#]	44 (39-54)	45 (40-52.8)[#]
Medications					
Beta-blocker [n(%)]	406 (55.8)	132 (56.9)	35 (57.4)	63 (47.7)*	176 (58.1)*
Bisoprolol dose (mg)	2.9 ± 3.5	2.6 ± 3.3	3.2 ± 3.7	2.6 ± 3.4	3.2 ± 3.6
ACEi/ARB [n(%)]	442 (60.7)	153 (65.9)[#]	34 (55.7)	69 (52.3)[#]	186 (61.4)
Ramipril dose (mg)	3.4 ± 3.8	3.3 ± 3.6	3.2 ± 3.9	2.9 ± 3.7	3.6 ± 4.0
Loop diuretic [n(%)]	338 (46.4)	134 (57.8)*[#]	24 (39.3)*	58 (43.9)[#]	122 (40.3)
Furosemide dose (mg)	0 (0-40)	20 (0-40)*[#]	0 (0-40)*	0 (0-40)[#]	0 (0-40)
MRA [n(%)]	29 (4.0)	19 (8.2)	2 (3.3)	3 (2.3)	5 (1.7)

*represents $p<0.05$ between CCI categories within HFrEF and HFpEF groups.

[#]represents $p<0.05$ between HFrEF and HFpEF within CCI groups.

Continuous variables are expressed as mean ± standard deviation, or median (interquartile range) discrete variables as number and percentages in parentheses.

NYHA; New York Heart Association, IHD; ischaemic heart disease, TIA; transient ischaemic attack, CKD; chronic kidney disease, COPD; chronic obstructive pulmonary disease, SBP; systolic blood pressure, LVEDVi; left ventricular end-diastolic volume index, LVESVi, left ventricular end-systolic volume index, LVEF; left ventricular ejection fraction, CCI; cardiac contractility index, NT-proBNP; N-terminal pro B-type natriuretic peptide, HbA1c; glycosylated haemoglobin, ACEi; angiotensin converting enzyme inhibitor, ARB; angiotensin receptor blocker, MRA; mineralocorticoid receptor antagonist.

6.4.4 Associations with outcomes

During a median follow-up of 5.9 (2.9-9.0) years, a total of 491 (67.4%) patients died. We observed incrementally lower mortality risk across tertiles of CCI, whereas for LVEF, mortality risk was similar comparing patients in tertiles one and two (Figure 6.5).

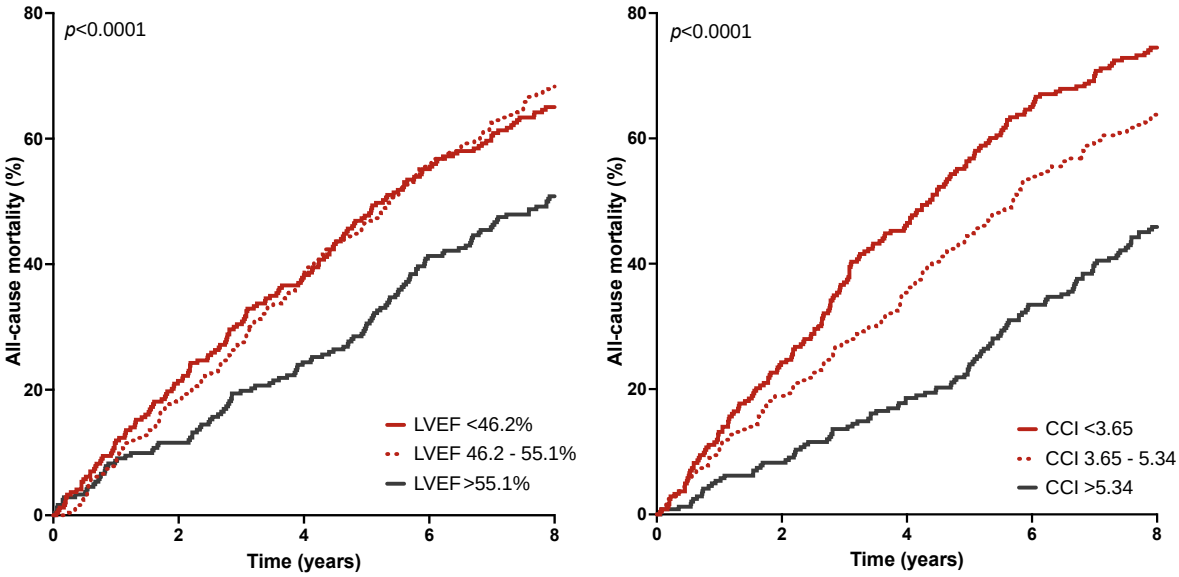


Figure 6.5 Kaplan-Meier plot of all-cause mortality divided by tertiles of left ventricular ejection fraction and cardiac contractility index

All-cause mortality risk was more clearly distinguished between CCI groups than the groups as defined by LVEF regardless of whether divided into two groups, tertiles or quartiles (Figure 6.6).

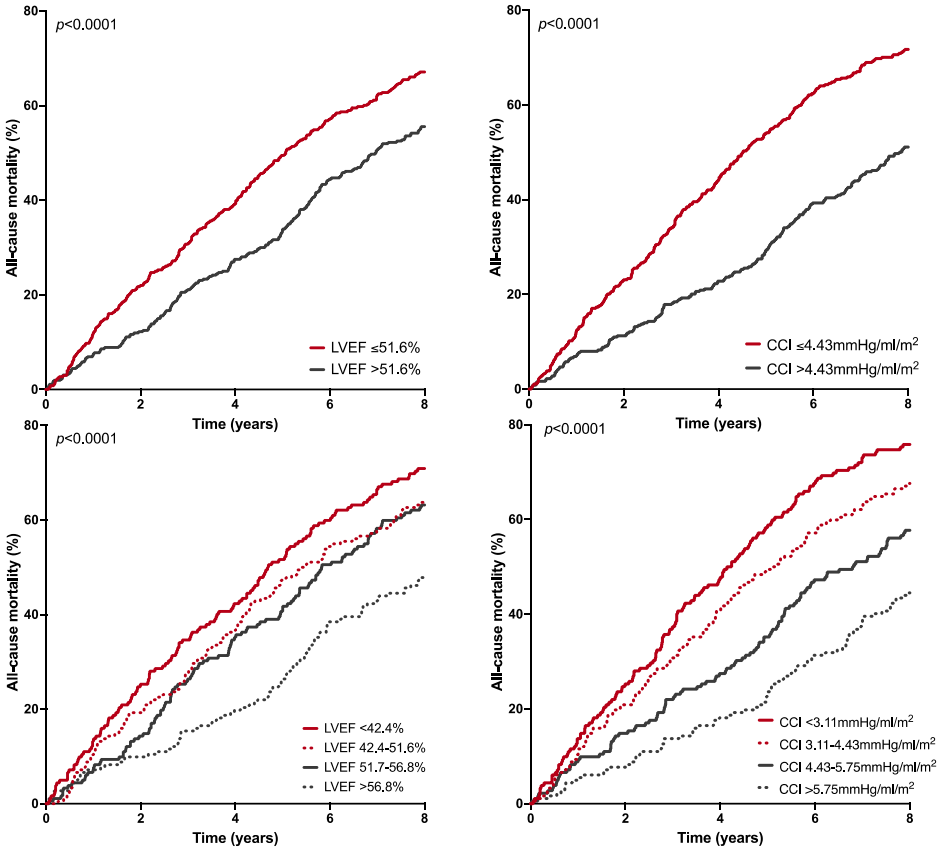


Figure 6.6 Kaplan-Meier plots of all-cause mortality divided by median values or into quartiles of left ventricular ejection fraction and cardiac contractility index

We further evaluated the relationship between mortality and LVEF or CCI by modelling them as continuous variables using restricted cubic splines. We observed a curvi-linear relationship with all-cause mortality risk for CCI, with significantly higher or lower mortality rates across a broad range below or above the median, respectively (Figure 6.7). The relationship with LVEF was more complex, with no clear association with mortality rates across a wide range from 25 to 55%.

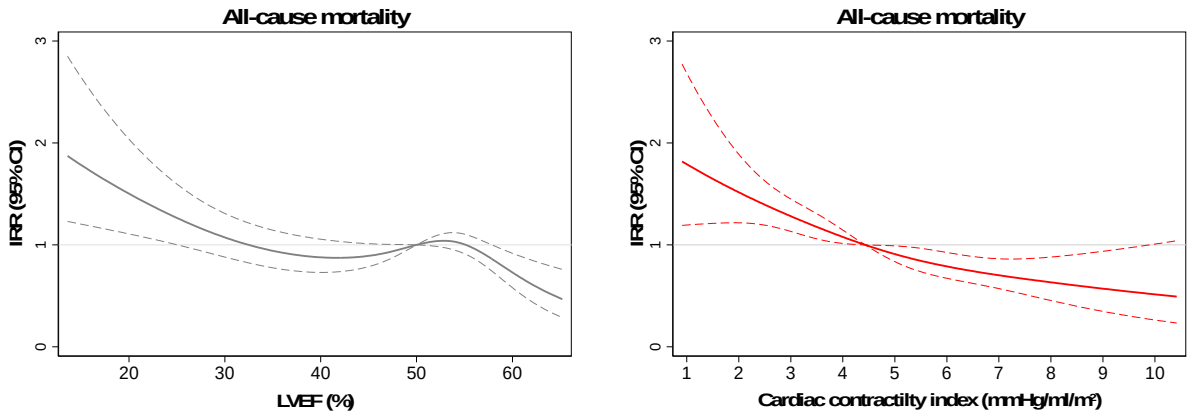


Figure 6.7 Restricted cubic splines displaying incidence rate ratios and 95% confidence intervals of all-cause mortality across left ventricular ejection fraction and cardiac contractility index

Furthermore, in a model including relevant covariates (Table 6.5), the association between LVEF and mortality was no longer evident except for those with the highest LVEF in whom the rate was lower (LVEF 60% IRR 0.69 [0.54-0.88], relative to LVEF 50%). In contrast, the association with all-cause mortality rate remained evident for all specified values of CCI, even after adjusting for prognostically important covariates.

Table 6.5 Unadjusted and adjusted Poisson regression analysis

		Cardiac contractility index	LVEF
	Unadjusted IRR (95% CI)	**Adjusted IRR (95% CI)**	**Adjusted IRR (95% CI)**
Age (per year)	1.06 (1.05-1.07)	1.06 (1.04-1.07)	1.06 (1.04-1.07)
Male	1.19 (0.99-1.42)	1.08 (0.87-1.35)	1.15 (0.93-1.43)
Ischaemic heart disease	1.05 (0.87-1.28)	0.94 (0.76-1.17)	0.96 (0.77-1.19)
Diabetes mellitus	1.09 (0.89-1.32)	1.21 (0.98-1.50)	1.22 (1.00-1.51)
Hypertension	1.00 (0.83-1.21)	1.07 (0.87-1.32)	1.05 (0.85-1.30)
SBP (per mmHg)	1.00 (0.99-1.00)	1.00 (1.00-1.00)	1.00 (0.99-1.00)
HR (per beat/min)	1.01 (1.00-1.01)	1.01 (1.00-1.01)	1.01 (1.00-1.01)
log10 haemoglobin (per g/L)	0.32 (0.17-0.61)	0.87 (0.35-2.19)	0.62 (0.25-1.51)
Log10 creatinine (per μmol/L)	6.61 (3.74-11.67)	1.59 (0.78-3.23)	1.58 (0.77-3.24)
Log10 albumin	0.00 (0.00-0.01)	0.01 (0.00-0.16)	0.01 (0.00-0.14)
Log10 NTpro-BNP	2.19 (1.85-2.59)	1.29 (1.02-1.62)	1.37 (1.09-1.72)
Cardiac contractility index (mmHg/ml/m^2)			
2	1.56 (1.26-1.93)	1.34 (1.03-1.75)	-
4	1.07 (1.01-1.13)	1.06 (1.00-1.13)	-
4.43	1.00	1.00	-
6	0.78 (0.67-0.92)	0.78 (0.66-0.93)	-
8	0.54 (0.39-0.74)	0.61 (0.43-0.85)	-
LVEF (%)			
20	1.69 (1.24-2.29)	-	1.27 (0.89-1.80)
30	1.19 (0.98-1.45)	-	1.01 (0.80-1.28)
40	0.95 (0.79-1.13)	-	0.89 (0.73-1.09)
50	1.00	-	1.00
60	0.66 (0.52-0.84)	-	0.69 (0.54-0.88)

When these two measures of LV systolic function were combined, we observed the all-cause mortality risk was similar for patients classified as having HFrEF, regardless of whether CCI was above or below the median value (p=0.096). However, patients with HFpEF and below median CCI, had an all-cause mortality risk ~40% higher than those patients with CCI above median (p<0.001), which was similar to people with HFrEF (Figure 6.8).

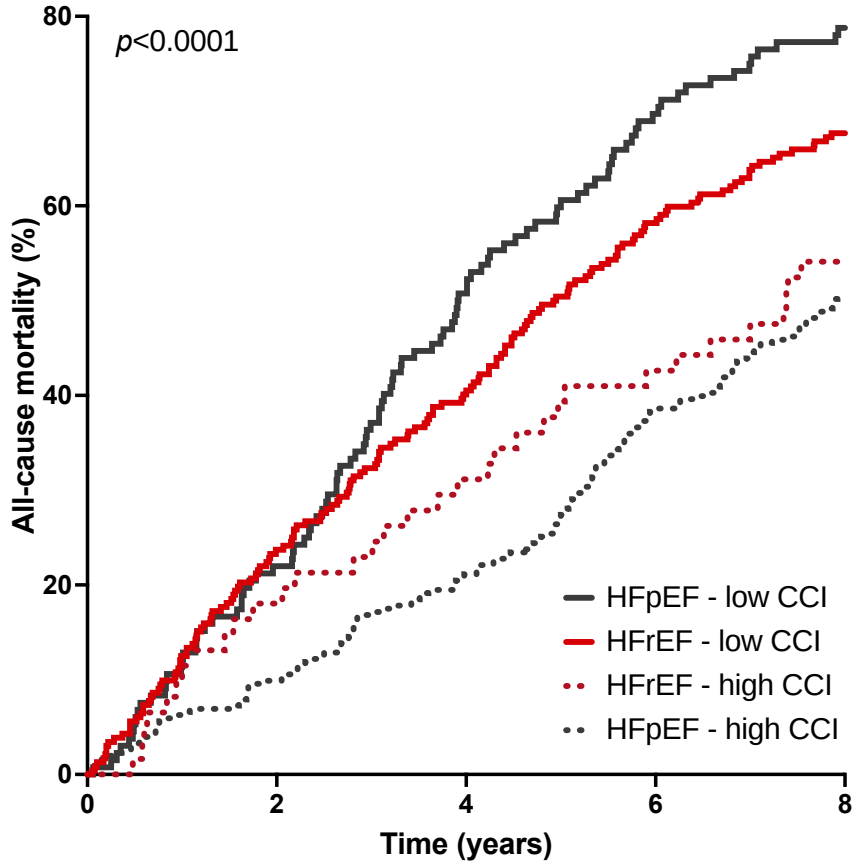


Figure 6.8 Kaplan-Meier plot of all-cause mortality in patients with heart failure with reduced and preserved ejection fraction who had cardiac contractility index below or above the median value

6.5 Discussion

6.5.1 Findings

Our analysis of consecutively presenting patients with *de novo* chronic heart failure has four novel findings. First, we observed a broad range of LV contractility, especially amongst patients classified as having a preserved ejection fraction. Second, we observed a clear relationship between CCI and mortality, which remained evident in a model including conventional markers of risk. Third, the association with all-cause mortality was less clear when patients were classified according to LVEF and was not evident across a broad range of values in adjusted analyses. Fourth, when patients

with HFpEF were reclassified as having low CCI, the all-cause mortality risk was similar to those with HFrEF, despite distinct clinical characteristics. Taken together, these data suggest CCI may help further refine the phenotypic classification of HFpEF by identifying patients with subtle systolic dysfunction who have a worse prognosis.

6.5.2 Left ventricular ejection fraction as an imperfect but essential tool in chronic heart failure

First described over six decades ago (Folse and Braunwald 1962), LVEF is a simple measure of LV systolic function which can be applied across different imaging modalities. Much of current practice is anchored to this simple variable, primarily as landmark trials supporting current guideline-directed therapies enrolled patients below arbitrary thresholds of LVEF who were perceived to be at the highest risk (CIBIS-II 1999, Eichhorn and Bristow 2001). For patients with HFrEF, four classes of medications targeting the neurohormonal maladaptations of the syndrome are proven to reduce hospitalisations and improve survival (Straw, McGinlay et al. 2021). However, with the possible exception of sodium-glucose co-transporter 2 inhibitors (for which there is conflicting evidence) (Anker, Butler et al. 2021, Solomon, McMurray et al. 2022), the benefits of these agents are attenuated for those with higher LVEF (Solomon, Claggett et al. 2016, Solomon, Vaduganathan et al. 2020). Moreover, for the overall population with HFpEF no therapies have been shown to improve survival, with the positive results of recent trials largely driven by reductions in heart failure hospitalisations (Pitt, Pfeffer et al. 2014, Solomon, McMurray et al. 2019). As a result, in clinical practice LVEF persists as an imperfect but necessary tool for diagnosis, risk stratification, and to determine in whom currently available therapies should be applied.

6.5.3 Limitations of left ventricular ejection fraction

Whilst LVEF remains central to our understanding of heart failure, its relative simplicity comes with several well-known limitations, including poor intra and inter-observer reproducibility, depending on the methods and experience of observers (Cole, Dhutia et al. 2015). Furthermore, whilst in the acute setting (for example following myocardial infarction) reduced LVEF may be truly reflective of reduced LV contractility due to the loss of cardiomyocytes, over time LV dilatation means LVEF in chronic heart failure is principally reflective of remodelling in response to loading conditions, and therefore poorly reflects myocardial contractile force (Maurer and Packer 2020). This might be acceptable in conditions such as dilated cardiomyopathy, in which increases in end-diastolic volume parallels reductions in systolic function. In this setting, where stroke volume is initially preserved, dilatation is reflected by a declining LVEF which therefore provides a good approximation of systolic function (Maurer and Packer 2020). However, in other disease states such as restrictive or infiltrative cardiomyopathies, even when myocardial shortening is impaired, there is no resultant increase in LV volumes, such that the measured LVEF is maintained even though systolic function is compromised. In our patients, concomitant systolic dysfunction, determined by low CCI in those with HFpEF was associated with a worse prognosis, independent of clinical characteristics, which were distinct from those with HFrEF.

6.5.4 The potential advantages of cardiac contractility index

A future without LVEF to guide therapy seems improbable, but additional indices of systolic performance which could be incorporated into routine clinical practice may help guide care. The current research landscape of alternative imaging modalities is

dominated by speckle tracking techniques such as myocardial strain and strain rate. Myocardial strain has been shown to better reflect systolic dysfunction amongst patients with HFpEF (Stokke, Hasselberg et al. 2017), and global longitudinal strain is independently associated with mortality risk in hospitalised patients, providing prognostic information not revealed by LVEF (Park, Park et al. 2018). However, barriers exist to its more widespread adoption such as variation between vendors and as yet, no agreed definition of normal ranges. Additionally, there are limited data on the effects of loading conditions on these measurements, whilst the most commonly reported metric, global longitudinal strain, assesses only longitudinal function meaning circumferential and radial dysfunction may be overlooked.

On the other hand, CCI is a simple parameter, with the advantage of being relatively load independent, thereby reflecting changes in LV contractility (Sagawa, Suga et al. 1977). As originally described, CCI requires a measurement of LV volume and pressure at end-systole by invasive ventriculography. However the use of non-invasive systolic blood pressure obtained by standard sphygmomanometer as a surrogate for end-systolic pressure and has been validated against invasive measurements (Haedersdal, Madsen et al. 1993), is already part of a standard echocardiographic assessment, and, in our patients outperformed a conventional assessment of systolic function by LVEF. Low systolic blood pressure is commonly observed in those with advanced systolic heart failure, and these patients seem to derive the greatest benefits from therapies targeting LV contractility (Metra, Pagnesi et al. 2022).

When applied to the current dataset, the relationship with all-cause mortality risk and CCI was curvi-linear and more robust than for LVEF, for which the association with mortality was not evident throughout most of its range. Moreover, by applying CCI to those with HFpEF we were able to show that around a third of patients had reduced contractility, and that these patients had an all-cause mortality risk similar to those with HFrEF. Although dividing patients by the median value of CCI was arbitrary, with as yet no data describing normal values in healthy populations, by doing so we were able to identify a subgroup of people classified as having a normal ejection fraction who were phenotypically distinct and had worse outcomes.

6.6 Strengths and limitations

This analysis includes consecutively referred patients from a prospective study, representative of real-world populations of patients with CHF, encompassing a broad spectrum of LVEF with long-term mortality data (Bozkurt, Coats et al. 2021). Some limitations should be noted. Firstly, this was an observational study conducted in a single centre which may limit generalisability, although the diverse characteristics of the area served by our centre and the inclusion of consecutive patients referred to our service mitigates against this (Witte, Patel et al. 2018). Secondly, the lack of longitudinal imaging data means we cannot determine whether patients with HFpEF went on to develop overt systolic dysfunction (LVEF <50%) in the future and whether low CCI predicted this. Third, normal values of CCI have not been defined and is it therefore unknown how thresholds defined by median values in the present dataset align with those from healthy populations. Fourth, we did not assess the prognostic value of other measurements of LV systolic function such as myocardial strain which may further refine phenotypic classification of patients with heart failure, although the

simplicity of CCI means it could be applied retrospectively to datasets in which myocardial strain or strain-rate were assessed.

6.7 Conclusions

Our findings suggest CCI may provide additional prognostic information, especially for those patients with heart failure and an ejection fraction currently classed as normal. For these patients, the identification of unappreciated systolic dysfunction may help better define risk or refine the phenotypic classification of this heterogenous group. These data could also help refine the inclusion criteria of future randomised controlled trials, potentially allowing us to establish effective therapies for HFpEF patients stratified by their LV contractility. In the meantime, its simplicity means this variable could be easily applied to existing datasets in order to identify who may have derived benefits from therapies in which the overall population did not.

Chapter 7: Identifying patients with chronic heart failure approaching the end-of-life using the 'Surprise Question'

Hypothesis: The 'Surprise Question' can identify patients hospitalised with heart failure who are within the last year of life, and can be used by a diverse range of healthcare professionals involved in their care.

7.1 Introduction

The 'Surprise Question' – "Would you be surprised if this patient died within the next year?" – has been proposed as a screening tool that may identify patients within the last year of life. The Surprise Question aims to guide future care planning and, where appropriate, prompt earlier referral to specialist palliative care services (Murray and Boyd 2011). The importance of palliative and end-of-life care is highlighted in the European Society of Cardiology Guidelines on the diagnosis and treatment of chronic heart failure (CHF) (McDonagh, Metra et al. 2021), and the European Society of Cardiology Heart Failure Association position paper (Hill, Prager Geller et al. 2020), but despite increasing awareness and a clear need, the utilisation of specialist palliative care services for CHF remains low (Janssen, Johnson et al. 2018).

Although the primary driver for referral to specialist palliative care services should be symptoms, it remains the case that prognosis is a key determinant of who accesses these services. As previously discussed, there is doubt as to whether the Surprise Question is an appropriate tool in the setting of CHF, which is a disease characterised by an unpredictable disease trajectory (Figure 2.1), where patients who have suffered

a worsening heart failure event can go on to have remarkably extended periods of relative stability.

7.2 Objectives

The aims of this study were to determine whether the Surprise Question is an appropriate screening tool in the setting of CHF, by firstly determining whether it can identify those with a prognosis of less than one year, and secondly whether the Surprise Question can be used by the diverse range of healthcare professionals involved with their care.

7.3 Methods

7.3.1 Study design

This was a prospective cohort study of patients hospitalised with a primary diagnosis of decompensated heart failure.

7.3.2 Setting

The Department of Cardiology at Leeds Teaching Hospitals NHS Trust, a tertiary referral centre for cardiology and cardiovascular surgery.

7.3.3 Patients

Consecutive patients admitted between 23rd April 2016 and 17th November 2016 were eligible for inclusion. Inclusion and exclusion criteria were deliberately kept minimal to reflect clinical practice, and it was not stipulated whether patients had to have left ventricular (LV) systolic dysfunction. Patients were required to have signs and symptoms of CHF, supported by clear evidence of cardiac dysfunction on

echocardiogram, whether that be left ventricular systolic dysfunction, right ventricular dysfunction, valvular heart disease or diastolic dysfunction. The physician in charge of their care determined the primary diagnosis for the admission, and all patients in whom this was decompensated heart failure were included. Patients with a primary diagnosis other than decompensated heart failure, for example, those with acute heart failure consequent to an acute coronary syndrome at the time of admission, were excluded. Also excluded were patients in whom active medical treatment had been withdrawn due to an existing decision to provide only palliative care at the time of study enrolment.

7.3.4 Participants

Participants were regarded as the healthcare professionals who provided responses to the Surprise Question. These included the responsible cardiologist (specialist physician), the non-specialist trainee-grade doctor (between zero and four years clinical experience), the heart failure specialist nurse, and non-specialist nurse assigned to the care of the patient in question. On each occasion, for each group I sought to identify the individual most familiar with the patient's case. For cardiologists, this was the named physician in charge of the patient's care; for trainee-grade doctors, the doctor who had most recently reviewed the patient's case; for heart failure specialist nurses, the heart failure nurse specialist who had reviewed the patient's case during their admission, and for non-specialist nurses, the nurse assigned to the patient on the day in question.

7.3.5 Study procedures

Healthcare professionals were approached individually and asked the question “would you be surprised if this patient were to die within the next year?”. We asked participants to provide a “surprised” or “not surprised” response. Responders were blinded to the answers given by other healthcare professionals and not required to justify their answer. No time restrictions were stipulated, nor were participants required to review any of the patient’s medical history, laboratory results or imaging, but neither were they blinded to these.

7.3.6 Data sources

In addition, I collected patient demographics including age, sex, co-morbidities and medications, baseline characteristics including blood results (serum haemoglobin, estimated glomerular filtration rate, albumin), most recent echocardiogram, the presence of peripheral or pulmonary oedema, primary diagnosis (as stipulated by the duty cardiologist), and presence or absence of a not-for-resuscitation decision at the time of study recruitment.

7.3.7 Definitions

Peripheral oedema was a clinical diagnosis determined by physical examination. Pulmonary oedema was the presence of rales on auscultation, congestion on chest radiograph, or both. The primary diagnosis was as stipulated by the cardiologist in charge of the patient’s case. Medications were those prescribed prior to admission as recorded in the medical record, and were considered as categorical, except for dosage of loop diuretic which was calculated as furosemide dosage equivalent over 24 hours, where either 40mg of furosemide or 1mg bumetanide was assigned a value of 40.

7.3.8 Assessment of outcomes

Patients were followed up until death or 1-year following study inclusion. The primary outcome was all-cause mortality in those who received a “surprised” response compared to a “not surprised” response. Outcomes data were obtained from the Leeds Teaching Hospitals NHS Trust Patient Pathway Manager Plus (PPM+) electronic care record, which updates mortality events daily directly from the UK Office of National Statistics database, and where possible, dates of death were confirmed from the hospital medical record.

7.3.9 Statistical analyses

Continuous variables are expressed as mean ± standard deviation, categorical as number and percentages. Analysis using 2x2 tables was used to calculate the sensitivity, specificity, positive predictive value, and negative predictive value, of the Surprise Question for each group of healthcare professionals (Figure 7.1 and Table 7.1).

	Dead at 1-year	Alive at 1-year
"Not surprised"	True positive A	False positive B
"Surprised"	False negative C	True negative D

Figure 7.1 2x2 table to showing the sensitivity, specificity, positive predictive value, and negative predictive value of the Surprise Question.

Table 7.1 Sensitivity, specificity, positive predictive value, and negative predictive value for the Surprise Question

Sensitivity	Probability of a patient being identified as "not surprised" who subsequently died	A / A+C
Specificity	Probability of a patient being identified as "surprised" who subsequently survived	D / B+D
Positive predictive value	Probability of death in a patient identified as "not surprised	A / A+B
Negative predictive value	Probability of survival in a patient identified as "surprised"	D / C+D

Additional statistical analyses were performed using SPSS Statistics version 23 for Window (SPSS Inc., Chicago, IL, USA). Survival was determined by Kaplan-Meier plot with differences in survival between those identified as "surprised" and or "not surprised" by their cardiologist determined by log-rank. Differences in baseline characteristics between those identified as "surprised" and "not surprised", and between those who were alive or had died after 1-year were determined by Student's t-test or Chi-squared testing for continuous and categorical variables, respectively.

Multivariable regression was then conducted by Cox regression analysis for characteristics significantly associated with 1-year survival. Age and sex were included in all models, and a *p*-value of <0.05 was regarded as statistically significant. Finally, Kappa agreement statistics were calculated for cases with responses from all participants, and in line with previously publications (Landis and Koch 1977) were graded as poor agreement if <0, fair agreement if 0.21-0.4, moderate agreements if 0.41-0.6, substantial agreement if 0.61-0.8, or near perfect if 0.81-1.

7.3.10 Ethical considerations

No specific funding was provided for the completion of this study, which was sponsored by the University of Leeds and was submitted for ethical review by the Health Research Authority. Following proportionate review by the North East-Tyne and Wear South Research Ethics Committee (IRAS 182067), approval was given along with confirmation that consent from participants (healthcare professionals) was required but consent from patients was not. Each participant was informed of the purpose of the study, provided with a participant information sheet, and offered the opportunity to provide informed, written consent. Healthcare professionals were provided with the opportunity to opt out and advised they did not need to provide reasons for doing so (although none chose to opt out).

7.4 Results

7.4.1 Patients

During the study period, information and responses were collected for 129 consecutively admitted patients with decompensated heart failure, who were followed up until death or 1-year following study enrolment. One patient admitted with

decompensated heart failure was excluded from the study, due to an early decision to provide end-of-life care.

7.4.2 Baseline characteristics

Patients had an average age of 71 ± 14 years, and 81 (63%) were male. In total 108 (84%) of patients had LV systolic dysfunction on their most recent echocardiogram, which was mildly impaired (40-49%) in 23 (18%), moderately impaired (30-39%) in 25 (19%), and severely impaired (<30%) in 60 (47%) patients, whilst 21 (16%) had preserved LV systolic function. The mean number of admissions during the previous year was 0.95 ± 1.4, and the mean length of stay of patients who were admitted was 14 ± 13 days. All patients were cared for in a ward environment, and during the study period none received mechanical ventilation, inotropes, or were admitted to the intensive care unit. At the time of enrolment, 17 patients were in New York Heart Association (NYHA) class II, 101 in class III and 10 in class IV.

Table 7.2 Baseline demographic and clinical characteristics divided by those who survived or had died at 1-year.

Variable	All (n=114)	Survivors (n=75)	Dead at 1-year (n=39)	*p*-value
Age (years)	71 ± 14	68 ± 15	77 ± 10	**0.004**
Male sex [*n* (%)]	73 (64)	52 (61)	29 (66)	0.37
eGFR (ml/min/1.73m^2)	56.4 ± 23.0	61.4 ± 21.9	45.5 ± 21.6	**<0.001**
Haemoglobin (g/L)	121 ± 24	127.6 ± 22.4	109.8 ± 22.3	**<0.001**
Serum albumin (g/L)	32.6 ± 5.4	33.8 ± 5.3	30.2 ± 4.8	**<0.001**
LVEF (%)	34.9 ± 15.1	34.2 ± 15.9	36.3 ± 13.9	0.47
NYHA class >2	97 (85)	65 (87)	32 (82)	0.51
Peripheral oedema [*n* (%)]	95 (83)	68 (80)	41 (93)	**0.039**
Pulmonary oedema [*n* (%)]	66 (58)	61 (72)	17 (39)	**0.001**
IHD [*n* (%)]	35 (31)	20 (24)	21 (48)	**0.005**
Diabetes [*n* (%)]	32 (28)	26 (31)	12 (27)	0.43
COPD [*n* (%)]	11 (10)	6 (7)	8 (18)	0.055
AF [*n* (%)]	60 (53)	45 (53)	23 (52)	0.55
Malignancy [*n* (%)]	7 (6)	2 (2)	6 (14)	**0.034**
DNACPR [*n* (%)]	8 (7)	2 (2)	10 (23)	**<0.001**
Furosemide equivalent dose (mg)	64± 71	43 ± 58	104 ± 78	**<0.001**
Thiazide diuretic [*n* (%)]	8 (7)	4 (5)	5 (11)	0.15
MRA [*n* (%)]	30 (26.3)	19 (22)	17 (39)	**0.041**
Anticoagulation [*n* (%)]	49 (43)	36 (42)	21 (48)	0.35
ACEi/ARB [*n* (%)]	57 (50)	40 (47)	23 (52)	0.35
Beta-adrenoceptor antagonist [*n* (%)]	67 (59)	50 (59)	29 (66)	0.28
Aspirin [*n* (%)]	34 (30)	23 (27)	17 (39)	0.13
Other antiplatelet [*n* (%)]	15 (13)	10 (12)	6 (14)	0.48
Insulin [*n* (%)]	9 (8)	5 (6)	5 (11)	0.22
Oral hypoglycaemic [*n* (%)]	21 (18)	18 (21)	8 (18)	0.44

Continuous variables are expressed as mean ± standard deviation, discrete variables as number and percentages in parentheses.

eGFR; estimated glomerular filtration rate, LVEF; left ventricular ejection fraction, NYHA; New York Heart Association, IHD; ischaemic heart disease, COPD; chronic obstructive pulmonary disease, AF; atrial fibrillation, DNACPR; do not attempt cardiopulmonary resuscitation, MRA; mineralocorticoid receptor antagonist, ACEi; angiotensin converting enzyme inhibitor, ARB; angiotensin receptor blocker.

7.4.3 Outcomes

Electronic follow-up data were available for all patients. After 1-year following study inclusion, a total of 44 (34%) patients had died. Table 7.2 displays demographic and clinical characteristics of patients, divided by whether or not they had died within 1-year. Baseline characteristics associated with all-cause mortality at 1-year were advanced age, poor renal function, anaemia, lower serum albumin, higher dosage of loop diuretic on admission, diagnosis of ischaemic heart disease, history of current or previous malignancy, and presence of a documented not-for-resuscitation decision at the time of study enrolment. LVEF and NYHA class were not associated with all-cause mortality in these hospitalised patients.

7.4.4 Responses to the Surprise Question

The overall response rate to the Surprise Question was 114 (88%) for cardiologists, 128 (100%) for trainee-grade doctors, 89 (67%) for heart failure nurse specialists and 123 (96%) for non-specialist nurses (Table 7.3).

Table 7.3 Total responses from healthcare professionals and number of "surprised" and "not surprised" responses.

		Total	"Surprised"	"Not surprised"
Cardiologist	All	114	50	64
	Alive	75	44	31
	Dead	39	6	33
Trainee-grade doctor	All	128	84	44
	Alive	63	52	11
	Dead	65	32	33
Heart failure nurse	All	89	59	30
	Alive	29	26	3
	Dead	60	33	27
Non-specialist nurse	All	123	79	44
	Alive	73	58	15
	Dead	50	21	29

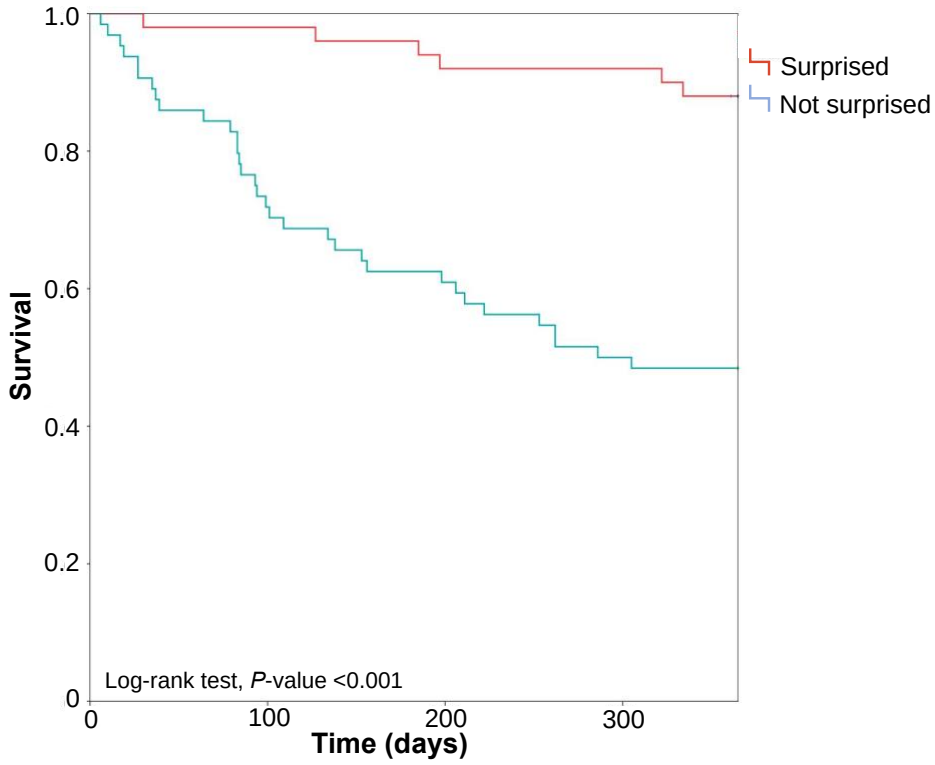
7.4.5 Accuracy of the Surprise Question

Cardiologists were able to identify the majority of those within the last year of life, with a sensitivity of 0.85 and were able to identify those who were unlikely to die within a year, with a negative predictive value of 0.88 (Table 7.4). The positive predictive value of a “not surprised” response was 0.52 and the specificity was 0.59.

Table 7.4 Sensitivity, specify, positive predictive value and negative predictive value of a “not surprised” response.

	Sensitivity	Specificity	PPV	NPV
Cardiologist	0.85	0.59	0.52	0.88
Trainee-grade doctor	0.75	0.62	0.51	0.83
Heart failure nurse	0.90	0.44	0.45	0.90
Non-specialist nurse	0.66	0.73	0.58	0.79
≥2 “not surprised” responses	0.82	0.58	0.50	0.86
≥3 “not surprised” responses	0.70	0.57	0.57	0.83
All “not surprised” responses	0.52	0.66	0.66	0.78
PPV; positive predictive value, NPV; negative predictive value.				

A “not surprised” response was associated with reduced survival at 1-year, relative to a “surprised” response which was statistically significant in unadjusted survival analysis (log-rank test $p<0.001$) (Figure 7.2).



Time (days)	0	100	200	300
'Surprised'	50	49	46	46
'Not surprised'	64	46	39	32

Figure 7.2 Kaplan-Meier plot of all-cause mortality divided by patients who received a "surprised" or "not surprised" response from their cardiologist. Reproduced from (Straw, Byrom et al. 2019) under terms of Creative Commons Attribution Non-Commercial license.

7.4.6 Agreement between participants

The probability of death was increased when there was concordance between participants (Table 7.5). When all participants answered "not surprised", patients were far more likely to die, but this approach reduced the sensitivity, with a trade-off between increasing confidence of a prognosis less than one year and the possibility of not identifying patients at risk of deterioration.

Agreement was substantial between cardiologists and heart failure nurses (Kappa = 0.69, 95% CI 0.52 – 0.86), and moderate with trainee-grade doctors (Kappa = 0.57, 95% CI 0.39 – 0.75). Agreement between trainee grade doctors and heart failure nurses was moderate (Kappa = 0.44, 95% CI 0.25 – 0.63). Agreement between non-specialist nurses was fair with cardiologists and trainee-grade doctors (Kappa = 0.40, 95% CI 0.23 – 0.58 and 0.30, 95% CI 0.09 – 0.50 respectively), and lowest with heart failure specialist nurses (Kappa = 0.21, 95% CI 0.03 – 0.39).

Table 7.5 Kappa coefficient for agreement between respondents to the Surprise Question

Agreement between		Kappa	Kappa SEM	95% CI
Cardiologist	Trainee-grade doctor	0.57	0.091	0.39-0.75
Cardiologist	Heart failure nurse	0.69	0.086	0.52-0.86
Cardiologist	Non-specialist nurse	0.40	0.09	0.23-0.58
Trainee-grade doctor	Heart failure nurse	0.44	0.096	0.25-0.63
Trainee-grade doctor	Non-specialist nurse	0.30	0.11	0.09-0.50
Heart failure nurse	Non-specialist nurse	0.21	0.09	0.03-0.39
SEM; standard error of the mean, CI confidence interval.				

Respondents were not required to justify their response to the Surprise Question, although a “not surprised” response from cardiologist were associated with advanced age, poor renal function, anaemia, low serum albumin, but not LVEF. Table 7.6 shows the baseline demographic and clinical characteristics of these 129 patients, divided by whether they received a “surprised” or “not surprised” response from their cardiologist.

Table 7.6 Baseline demographic and clinical characteristics divided by patients who received a "surprised" or "not surprised" from their cardiologist.

Variable	All (n=114)	"Surprised" (n=50)	"Not surprised" (n=64)	*p*-value
Age (years)	71 ± 14	64 ± 14	77 ± 11	**<0.001**
Male sex [*n* (%)]	73 (64)	33 (66)	40 (63)	0.67
eGFR (ml/min/1.73m^2)	56.4 ± 23.0	65.9± 18.9	49.1 ± 23.5	**<0.001**
Haemoglobin (g/L)	121 ± 24	132.7 ± 21.3	112.3 ± 22.6	**<0.001**
Serum albumin (g/L)	32.6 ± 5.4	33.5 ± 6.4	31.9 ± 4.6	0.14
LVEF (%)	34.9 ± 15.1	32.2 ± 16.8	37.0 ± 13.5	0.096
NYHA class >2	97 (85)	41 (82)	56 (88)	0.41
Peripheral oedema [*n* (%)]	95 (83)	39 (78)	56 (87)	0.23
Pulmonary oedema [*n* (%)]	66 (58)	36 (72)	30 (47)	**0.006**
IHD [*n* (%)]	35 (31)	15 (30)	20 (31)	0.76
Diabetes [*n* (%)]	32 (28)	12 (24)	20 (31)	0.45
COPD [*n* (%)]	11 (10)	3 (6)	8 (12)	0.26
AF [*n* (%)]	60 (53)	27 (54)	33 (51)	0.97
Malignancy [*n* (%)]	7 (6)	1 (2)	6 (9)	0.39
DNACPR [*n* (%)]	8 (7)	1 (2)	7 (11)	**0.013**
Furosemide equivalent dose (mg)	64± 71	52 ± 68	74 ± 73	0.10
Thiazide diuretic [*n* (%)]	8 (7)	4 (8)	4 (6)	0.94
MRA [*n* (%)]	30 (26.3)	11 (22)	19 (30)	0.36
Anticoagulation [*n* (%)]	49 (43)	20 (4)	29 (45)	0.64
ACEi/ARB [*n* (%)]	57 (50)	27 (54)	30 (47)	0.58
Beta-adrenoceptor antagonist [*n* (%)]	67 (59)	29 (58)	38 (59)	0.28
Aspirin [*n* (%)]	34 (30)	13 (26)	21 (33)	0.54
Other antiplatelet [*n* (%)]	15 (13)	4 (8)	11 (17)	0.26
Insulin [*n* (%)]	9 (8)	4 (8)	5 (8)	0.99
Oral hypoglycaemic [*n* (%)]	21 (18)	10 (20)	11 (17)	0.37
Continuous variables are expressed as mean ± standard deviation and discrete variables as numbers with percentages in parentheses.				
eGFR; estimated glomerular filtration rate, LVEF; left ventricular ejection fraction, NYHA; New York Heart Association, IHD; ischaemic heart disease, COPD; chronic obstructive pulmonary disease, AF; atrial fibrillation, DNACPR; do not attempt cardiopulmonary resuscitation, MRA; mineralocorticoid receptor antagonist, ACEi; angiotensin converting enzyme inhibitor, ARB; angiotensin receptor blocker.				

In regression analysis, a “not surprised” response from the cardiologist was significantly associated with reduced survival (hazard ratio (HR) 4.6, 95% confidence interval (CI) 1.8-11.8, *p*=0.001) as were lower eGFR, haemoglobin, serum albumin, history of cancer and not-for-resuscitation decision; whilst a presentation with pulmonary oedema was associated with better survival (Table 7.7).

Table 7.7 Survival analysis of baseline characteristics adjusted for age and sex

Variable	Hazard ratio	95% CI	*p*-value
eGFR (per ml/min/1.73m^2)	0.98	0.96 – 0.99	**0.001**
Hb (per g/L)	0.98	0.97 – 1.0	**0.014**
Alb (per g/L)	0.90	0.84 – 0.96	**0.001**
Peripheral oedema	2.9	0.88 – 9.3	0.081
Pulmonary oedema	0.34	0.18 – 0.65	**0.001**
IHD	1.7	0.90 – 3.4	0.102
Malignancy	4.9	2.0 – 12.0	**0.001**
DNACPR	4.1	1.7 – 9.8	**0.002**
Furosemide equivalent dose (per 40mg)	1.5	1.3 – 1.7	**<0.001**
MRA	1.8	0.9 – 3.5	0.083
‘Not surprised’ cardiologist	4.6	1.8 – 11.9	**0.001**

CI, confidence interval; eGFR, estimated glomerular filtration rate; Hb, serum haemoglobin; Alb, serum albumin; IHD, ischaemic heart disease; Furosemide equivalent dose per 24 hours (40mg furosemide = 1mg bumetanide); DNACPR, do not attempt cardiopulmonary resuscitation decision; MRA, mineralocorticoid receptor antagonist.

The response to the Surprise Question was then adjusted for important clinical covariates which were associated with survival at 1-year in unadjusted analysis, which were age, sex, eGFR, albumin, and furosemide equivalent dose. In this multivariable model, the association between a “not surprised” response to the Surprise Question and survival remained significant (HR 2.8, 95% CI 1.0-7.9, *p*-0.046) (Table 7.8).

Table 7.8 Multivariate survival analysis of important clinical covariates and the Surprise Question

Variable	Hazard ratio	95% CI	*p* value
Age (per year)	1.0	1.0 – 1.1	0.063
Male sex	1.2	0.6 – 2.4	0.57
eGFR (per ml/min/1.73m^2)	0.99	0.98 – 1.0	0.30
Serum albumin (per g/L)	0.92	0.86 – 0.98	**0.010**
Furosemide equivalent dose (per 40mg)	1.3	1.1 – 1.6	**0.002**
'Not surprised' cardiologist	2.8	1.0 – 7.9	**0.046**
CI, confidence interval; eGFR, estimated glomerular filtration rate; Alb, serum albumin; Furosemide equivalent dose per 24 hours (40mg furosemide = 1mg bumetanide).			

There were similar levels of accuracy across all four groups of healthcare professionals with high sensitivity and negative predictive values, although overall there was an over-classification of patients as "not surprised".

7.5 Discussion

7.5.1 Findings

The results presented here demonstrate that for patients hospitalised with decompensated heart failure, the Surprise Question predicted all-cause mortality at 1 year, and did so independently of important clinical variables known to be associated with a poor prognosis. Overall, there was also substantial or moderate agreement between groups of participants, with the exception of specialist team members with non-specialist nurses, where agreement was fair.

7.5.2 Accuracy of the Surprise Question

Overall, characteristics that predicted mortality were consistent with those associated with a ‘not surprised’ response, perhaps reflecting an awareness amongst specialists of the predictors of poor outcomes in this patient population (Tables 6.2 and 6.6). In the present study, pulmonary oedema was associated with a favourable outcome compared to those admitted with peripheral oedema, and NYHA class was not associated with survival. That patients who were comfortable at rest had a worse prognosis goes against conventional thinking, however it is consistent with other studies (Shoaib, Waleed et al. 2014). Mortality in the current study is higher than in most contemporary interventional studies: the patients had high rates of renal dysfunction and were older than those in many datasets (Konstam, Gheorghiade et al. 2007, Gheorghiade, Bohm et al. 2013). The present prospective study was an investigation of the prediction of mortality, with a view to potentially providing additional health and social care and was *a priori* not designed to assess cause of death.

To date, four studies have reported on the accuracy of the Surprise Question for patients with cardiac diagnoses including heart failure. One study reported the accuracy of the Surprise Question from a large cohort of general practice patients, and found that the Surprise Question had a sensitivity of 79% and a specificity of 61% (Barnes, Gott et al. 2008). One community-based study investigated whether fulfilling the Gold Standards Framework criteria for end-of-life care (at least two indicators out of: a ‘not surprised’ response to the Surprise Question, NYHA class III or IV symptoms, repeated hospitalisation, symptoms despite maximally tolerated therapy), predicted survival at 1 year. This study assessed responses from heart failure nurses and found that the Surprise Question greatly overestimated the mortality rate in this patient

cohort, possibly explained by an appreciation that patients with heart failure are at risk of unpredictable deterioration (Haga, Murray et al. 2012). A further study including heart failure specialist nurses reported data for patients who prompted a ‘not surprised’ response, but did not report the accuracy of responses for patients who generated a ‘surprised’ response (Johnson, Nunn et al. 2012). One study assessed the Surprise Question in hospitalised patients initially admitted with an acute coronary syndrome, meaning it is unlikely to be generalisable to the chronic heart failure population (Fenning, Woolcock et al. 2012).

7.5.3 The Surprise Question can be used by a variety of healthcare professionals

Whether the Surprise Question can be used by different healthcare professionals has been infrequently reported. One study looked at responses by consensus within a multidisciplinary team, but did not test responses from individuals independently (Feyi, Klinger et al. 2015), whilst another study recorded responses by doctors and nurses independently, finding that physicians were more likely to record a ‘not surprised’ response, and that where physicians and nurses agreed upon a ‘not surprised’ response this was highly predictive of a poor prognosis (Da Silva Gane, Braun et al. 2013). These studies were consistent with the findings here, in that specialists were more likely to be pessimistic about patient prognosis and agreement improves accuracy.

The present study is the first to investigate the predictive power of the Surprise Question for patients hospitalised with heart failure whilst assessing responses from a number of allied healthcare professionals. Of the patients who died within 1 year,

85% had been identified by the Surprise Question, and patients for whom there was a ‘surprised’ response were far less likely to die. Cardiologists were on balance better at identifying patients within the last year of life, and where there was consensus with other healthcare professionals the accuracy was superior. However, there was a trade-off between higher levels of accuracy and not identifying patients within the last year of life, which in clinical practice is undesirable. Agreement between participants was moderate or substantial, except for comparisons with non-specialist nurses (Landis and Koch 1977). The highest agreement was between cardiologists and heart failure nurses, perhaps reflecting a shared perspective between healthcare professionals who spend the most time managing heart failure patients. The lowest agreement was between heart failure nurses and non-specialist nurses, who were less likely to classify patients as ‘not surprised’ and therefore identify patients in the last year of life.

7.5.4 Using the Surprise Question in clinical practice

Overall, there was an over-classification of patients into the ‘not surprised’ category, with only half of patients identified as such dying within 1 year. This perhaps reflects the unpredictable trajectory of heart failure (Downar, Goldman et al. 2017, White, Kupeli et al. 2017). It could be argued that prognostication is less important here, as those patients identified as ‘not surprised’ are still likely to benefit from a palliative and symptom-orientated approach, or the inclusion on a specialist palliative care registry regardless of survival at 1 year. When engaging with patients and families regarding future care planning, discussions would need to address this limitation of the Surprise Question.

Despite an appreciation of the unpredictability of prognosis for patients diagnosed with heart failure, there seemed to be a low rate of not-for-resuscitation decisions made during this study. Only 7 out of 64 patients who received a ‘not surprised’ response from their cardiologist, had a do-not-attempt-resuscitation decision in place at time of study enrolment, although it is possible this may have changed later during their admission following further discussions with patients and relatives about their prognosis.

The present study provides strong evidence, consistent with other literature, that clinicians are good at identifying patients who will survive, suggesting that it is unlikely specialist palliative care services would be withheld from those who need this if the Surprise Question were to be used to aid decision making. Furthermore, active treatment for patients with severe heart failure is largely symptomatic and therefore complimentary to palliative care. Patients with decompensated heart failure are frequently hospitalised during crisis periods. However, where resources permit, interventions such as intravenous diuretic therapy and monitoring of renal function could be delivered in the community. Perhaps for patients identified by a “not surprised” response, this approach would be complimentary with what is primarily palliative, symptom-guided therapy.

7.6 Strengths and limitations

This was a prospective cohort study, conducted in a relevant population showing the Surprise Question can be used to identify individuals within the last year of life, and additionally that this simple and intuitive question can be used by other healthcare professionals. Some limitations should be noted. Firstly, prognostication is not the only

concern when considering referral to specialist palliative care services, and the present study does not investigate when it is appropriate to adopt a palliative approach and who might benefit. Even if the Surprise Question could reliably predict time to death, this is only one factor involved in such a decision. Instead, the focus should be on symptoms, patient preferences, and social circumstances, although it seems likely a poor prognosis will remain a major driver of these decisions. Whilst data on pulmonary congestion and NYHA class were collected during the recruitment phase, data on frailty and fatigue were not collected, although these variables are likely to be encapsulated within the holistic framework of the Surprise Question.

European guidelines recommend an early consideration of a symptom focused approach, and point towards indicators such as repeated hospitalisation and frailty as drivers for such decisions (Ponikowski, Voors et al. 2016). Up to a quarter of patients hospitalised with heart failure may require specialist palliative care services, and a short remaining life span remains a major driver in their delivery (Small, Gardiner et al. 2010, Lakin, Robinson et al. 2016, Campbell, Petrie et al. 2018, Janssen, Johnson et al. 2018). The effect of the Surprise Question on the delivery and impact on specialist palliative care services was not assessed by this study. Prospective, randomised studies are required to investigate whether predictive mortality models can improve patient access to specialist palliative care services without unfavourably influencing the management of patients identified as “not surprised” but still alive at 1 year. However, patients with heart failure and ongoing symptoms should receive palliation of those symptoms with a range of treatments, including angiotensin-converting enzyme inhibitors, beta-adrenoceptor antagonists, and diuretics. Therefore, identifying patients as ‘not surprised’ is unlikely to be detrimental to their care.

This study was limited by a small sample size, single centre setting, and small number of events. Another limitation was the possible confusing phrasing of the Surprise Question. To address this concern, participants were offered an information sheet and given a verbal explanation of the question prior to response. The study also did not assess participants' attitudes towards the question, however previous qualitative research has demonstrated that the question is feasible and acceptable amongst healthcare professionals and families (Haydar, Almeder et al. 2017). Furthermore, the Leeds Cardiovascular Patient and Public Involvement and Engagement group found the question acceptable and was actively engaged in the design of this study.

The predictive power of the Surprise Question compared to other inpatient prediction tools was not assessed by the current study. Being simple, intuitive, and quick to do, the Surprise Question might have an advantage over more complex inpatient tools, although this requires assessment in future studies. Having described the accuracy of the Surprise Question in a cohort of heart failure patients, it would be intriguing to compare the utility and ease of use of this simple approach against more complex tools in a large patient cohort. Furthermore, whether the Surprise Question may allow a structured method for all members of the multidisciplinary team to contribute to advanced care planning would have to be tested in prospective studies.

7.7 Conclusions

The Surprise Question might be a useful adjunct to assist in the care planning of patients with heart failure who may be entering the last year of life. In the present study cohort, the Surprise Question identified nearly all patients who were in the last year of life. There was, however, an over-classification of patients into the "not surprised"

category, with only around half dying within 1 year. If validated, the Surprise Question could be used by all members of the multidisciplinary team, such that any member could prompt discussions around resuscitation status, establishing goals of care and, where appropriate, referral to specialist palliative care services.

Chapter 8: Ceiling of care decisions and their associations with clinical characteristics and outcomes

Hypothesis: Where treating teams are supported to do so, advanced care planning can become a routine part of clinical care and not associated with worse outcomes in patients unsuitable for full intensive care-based treatments.

8.1 Introduction

In Chapter 6, the ability of the Surprise Question to predict mortality in patients hospitalised with heart failure, was assessed. The prognosis following heart failure hospitalisation was poor, with 34% of patients having died within 1-year of admission. A low rate of advanced care planning was observed, evidenced by a small proportion of patients having a not-for-resuscitation decision documented at the time of study enrolment. Despite this, hospitalisation might present an ideal opportunity to begin these discussions, however whether this could become a routine part of clinical care or might in fact be detrimental to outcomes is unknown.

In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified as the cause of a cluster of viral pneumonia cases in Wuhan City, China (Ghinai, McPherson et al. 2020). SARS-CoV-2 can result in a broad spectrum of illness, from asymptomatic or paucisymptomatic infection to coronavirus disease 2019 (COVID-19), a viral pneumonia resulting in high rates of hospitalisation, intensive care unit (ICU) admission, and requirement for mechanical ventilation (Grasselli, Zangrillo et al. 2020, Huang, Wang et al. 2020). Risk factors for severe disease include age (Wang, He et al. 2020), cardiovascular co-morbidities (Yang, Zheng et al. 2020),

obesity (Docherty, Harrison et al. 2020), and non-white ethnicity (Pareek, Bangash et al. 2020). Observational data have resulted in contradictory findings as to the associations with these risk factors and outcomes, possibly owing to heterogeneous outcome measures with hospitalisation, ICU admission (Hippisley-Cox, Young et al. 2020, Huang, Wang et al. 2020, Wang, Hu et al. 2020), receipt of mechanical ventilation (Guan, Ni et al. 2020), or death (Wu, Chen et al. 2020, Zhou, Yu et al. 2020), proposed as defining 'severe disease'.

Advanced care planning became an integral part of the response in the UK, supported by national recommendations that discussions of the risk, benefits, and likely outcomes of different treatment modalities should be undertaken for all hospitalised patients. During the first wave of the pandemic at the Leeds Teaching Hospitals NHS Trust (LTHT), treating teams were encouraged to utilise the Recommended Summary Plan for Emergency Care and Treatment (ReSPECT) process (RCUK 2020) to document patient and carers' wishes regarding ceiling of care and resuscitation decisions at the point of admission. The COVID-19 pandemic therefore presented a framework to explore the hypothesis that advanced care planning could become a routine part of the clinical care for hospitalised patients, and would be acceptable to those with cardiovascular disease who seemed to be at the highest risk.

8.2 Objectives

The aims of this analysis were firstly, to report the pre-emptive ceiling of care and cardiopulmonary resuscitation decisions in patients admitted during the COVID-19 pandemic utilising the ReSPECT process. Secondly, the analysis aimed to explore the demographic and clinical characteristics associated with these decisions in a unique

setting where advanced care planning was routine. And finally, to determine the association of these characteristics with outcomes, to explore how ceiling of care decisions might be confounding variables in observational datasets aiming to determine predictors of outcomes in COVID-19 and other diseases.

8.3 Methods

8.3.1 Study design

A retrospective, observational study was performed to explore factors associated with outcomes in COVID-19 at the LTHT. As one of the largest university teaching hospitals in Europe, LTHT comprises two large and four smaller facilities, providing over 1800 inpatient beds, serving a secondary care population of more than 750,000 people, and hence is well placed to report the outcomes of such an approach.

8.3.2 Patients

All patients aged ≥18 years with laboratory confirmed SARS-CoV-2 infection, hospitalised at LTHT between 5th March and 7th May 2020, were included. Consistent with World Health Organisation (WHO) guidance, laboratory confirmation for SARS-CoV-2 was defined as a positive result of real-time reverse transcriptome-polymerase chain reaction assay of nasal or pharyngeal swabs, or lower respiratory tract aspirates (WHO 2020). Patients who tested positive, but admitted for other reasons or were infected with SARS-CoV-2 during hospitalisation, were excluded, as were those who were assessed in the Emergency Department but not hospitalised.

8.3.3 Data sources and definitions

Clinical data and outcomes were obtained from the Leeds Patient Pathway Manager Plus (PPM+) electronic care record, which updates mortality events daily directly from the UK Office of National Statistics database. Ceiling of care and cardiopulmonary resuscitation (CPR) decisions were standardised and documented electronically using the ReSPECT process (RCUK 2020). Demographic data include age, sex, and ethnicity. Ethnicity was self-reported and classified according to the 2011 Census for England, Northern Ireland and Wales as White-European, South-Asian, East-Asian, Black-African, mixed race and other ethnicities, and, for the purpose of analysis, was dichotomised as White-European or Black, Asian and minority ethnic (BAME). Clinical data include major co-morbidities, frailty, and the prescription of medical therapy. Major co-morbidities were any of: hypertension, diabetes mellitus, chronic kidney disease (CKD) stage III-V, atrial fibrillation, chronic obstructive pulmonary disease (COPD), ischaemic heart disease (IHD), heart failure with reduced ejection fraction (HFrEF), history of stroke or transient ischaemic attack (TIA), and active malignancy. Frailty was classified by the Canadian Study of Health and Aging Clinical Frailty Scale (CFS) (Rockwood, Song et al. 2005) according to national recommendations (NICE 20 March 2020), which, during the COVID-19 pandemic was mandatory for all patients assessed in the Emergency Department at LTHT. Pre-admission medical therapy was obtained by regular prescription information from electronic primary care records. The prescription of renin-angiotensin-aldosterone (RAAS) inhibitors, beta-adrenoceptor antagonists, calcium channel blockers, diuretics, statins, antiplatelets and anticoagulants, medications for diabetes mellitus and immunosuppression, were recorded. Clinical markers of disease severity at the time of hospitalisation, including laboratory investigations, chest radiography, and clinical observations were also

recorded. Laboratory investigations included full blood count, renal function, and blood tests to stratify disease severity, which were C-reactive protein, ferritin, D-dimer and procalcitonin. All chest radiographs were interpreted by a radiologist and graded as either being consistent with, indeterminant for, or inconsistent with COVID-19 pneumonia. Clinical observations included heart rate, blood pressure, tympanic temperature, peripheral oxygen saturations, and respiratory rate, and were obtained from the earliest assessment of physiology, usually recorded by paramedic crew or on arrival in the Emergency Department.

8.3.4 Assessment of outcomes

Patients were followed-up until discharge from hospital, or death. Outcomes data include treatments administered during hospitalisation, maximum level of care received, and death prior to discharge. Administered treatments were oxygen therapy, continuous positive airway pressure (CPAP), mechanical ventilation, circulatory support (vasopressors or inotropes), or new requirement for renal replacement therapy. Level one care was hospitalisation without need for organ support (but including oxygen therapy) and delivered in a ward setting; level two care was single organ support (usually CPAP), but excluding mechanical ventilation, and delivered in either in a ward, high-dependency unit or ICU setting; level three care was multi-organ support or mechanical ventilation, and delivered on the ICU.

8.3.5 Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 26 (IBM Corporation, Armonk, NY). After testing for normality of distribution, continuous variables are expressed as mean ± standard deviation or median (interquartile range),

as appropriate. Discrete variables are presented as number (percentage), and ordinal data as median (interquartile range). Groups were compared using Student's t-test or one-way analysis of variance for normally distributed continuous data, by Mann-Whitney U test or Kruskal-Wallis H-test for non-normally distributed continuous data and by Pearson χ^2 tests for categorical data. Age-sex adjusted, and multivariable analyses were performed using binary logistic regression analysis. All tests were two-sided and statistical significance was defined as $p < 0.05$.

8.3.6 Ethical considerations

Approval was given following institutional governance review, and, in view of the retrospective nature, individual patient consent was waived as appropriate data protection safeguards were in place.

8.4 Results

8.4.1 Patient demographics

Between 5th March and 7th May 2020, a total of 599 patients tested positive for SARS-CoV-2 in LTHT and of these, 65 were admitted for reasons other than COVID-19, 38 were not hospitalised, five were aged < 18 years, and six tests were subsequently amended as negative following quality control. The final dataset therefore consisted of 485 patients, with a mean age of 71.2 ± 16.9 years of whom 259 (53.4%) were male. Self-reported ethnicity was available for 475 patients (97.9%), of whom 402 (84.6%) classified themselves as White-European, 31 (6.5) as South-Asian, 19 (4.0%) as Black-African, two (0.4%) as East-Asian and 21 (4.4%) as either mixed or other ethnicities.

8.4.2 Cardiovascular co-morbidities

Cardiovascular co-morbidities were highly prevalent; the most common being hypertension, which was present in 222 (45.8%) patients, whilst 147 (30.3%) had diabetes mellitus, 87 (21.3%) had atrial fibrillation, 62 (15.2%) had IHD, 51 (12.5%) had pre-existing HFrEF and 48 (11.7%) had history of prior stroke/TIA (Table 8.1). A total of 109 (22.5%), 130 (26.8%), 105 (21.6%) and 141 (29.1%) patients had zero, one, two, and three or more major co-morbidities, respectively.

Table 8.1 Baseline clinical characteristics of patients divided by ceiling of care decisions.

	All patients (n=409)	Level 1 (n=208)	Level 2 (n=75)	Level 3 (n=126)	*p*-value
Demographics					
Age (years)	73·1 ± 15·3	81·9 ± 9·4	75·4 ± 9·9	57·6 ± 12·8	**<0·001**
Male sex [n(%)]	211 (54)	103 (49·5)	43 (57·3)	75 (59·5)	0·17
BMI (kg/m^2)	26·3 (22·1-30·8)	23·2 (20·5-27·1)	27·6 (22·0-31·8)	29·4 (25·8-34·0)	**<0·001**
BAME [n(%)]	56 (13·7)	12 (5·8)	8 (10·7)	36 (28·6)	**<0·001**
Clinical Frailty Scale	5 (3-6)	6 (5-7)	4 (3-5)	2 (2-3)	**<0·001**
Co-morbidities					
HFrEF [n(%)]	51 (12·5)	34 (16·3)	13 (17·3)	4 (3·2)	**0·001**
IHD [n(%)]	62 (15·2)	39 (18·8)	15 (20·0)	8 (6·3)	**0·004**
Hypertension [n(%)]	191 (46·7)	99 (47·6)	44 (58·7)	48 (38·1)	**0·017**
AF [n(%)]	87 (21·3)	60 (28·8)	17 (22·7)	10 (7·9)	**<0·001**
Diabetes mellitus [n(%)]	125 (30·6)	67 (32·2)	32 (42·7)	26 (20·6)	**0·004**
Stroke/TIA [n(%)]	48 (11·7)	34 (16·3)	10 (13·3)	4 (3·2)	**0·001**
CKD [n(%)]	103 (25·2)	69 (33·2)	29 (38·7)	5 (4·0)	**<0·001**
COPD [n(%)]	64 (15·6)	41 (19·7)	16 (21·3)	7 (5·6)	**0·001**
Malignancy [n(%)]	33 (8·1)	22 (10·6)	7 (9·3)	4 (3·2)	**0·050**
Medications					
ACEi [n(%)]	74 (18·1)	30 (14·4)	23 (30·7)	21 (16·7)	**0·007**
ARB [n(%)]	32 (7·8)	10 (4·8)	8 (10·7)	14 (11·1)	0·069
BB [n(%)]	99 (24·2)	61 (29·3)	22 (29·3)	16 (12·7)	**0·001**
CCB [n(%)]	68 (16·6)	27 (13·0)	20 (26·7)	21 (16·7)	**0·024**
Loop diuretic [n(%)]	64 (15·6)	50 (24·0)	12 (16·0)	2 (1·6)	**<0·001**
MRA [n(%)]	16 (3·9)	11 (5·3)	3 (4·0)	2 (1·6)	0·24
Statin [n(%)]	171 (41·8)	85 (40·4)	49 (65·3)	38 (30·2)	**<0·001**
Antiplatelet [n(%)]	105 (25·7)	57 (27·4)	23 (30·7)	25 (19·8)	0·17
Anticoagulant [n(%)]	57 (13·9)	42 (20·2)	11 (14·7)	4 (3·2)	**<0·001**
Metformin [n(%)]	50 (12·2)	23 (11·1)	14 (18·7)	13 (10·3)	0·17
Sulphonylurea [n(%)]	20 (4·9)	5 (2·4)	8 (10·7)	7 (5·6)	**0·016**
Corticosteroid [n(%)]	21 (5·1)	12 (5·8)	3 (4·0)	6 (4·8)	0·82
Immunosuppression [n(%)]	21 (5·1)	9 (4·3)	5 (6·7)	7 (5·6)	0·71

Continuous variables are expressed as mean ± standard deviation or median and interquartile range in parentheses, discrete variables as number and percentages in parentheses.

BMI; body mass index, BAME; Black Asian and minority ethnic, BMI; body mass index, HFrEF; heart failure with reduced ejection fraction, IHD; ischaemic heart disease, AF; atrial fibrillation, CKD; chronic kidney disease, COPD; chronic obstructive pulmonary disease, ACEi; angiotensin converting enzyme inhibitor, ARB; angiotensin II receptor blocker, BB; beta-adrenoceptor antagonist, CCB; calcium channel blocker, MRA; mineralocorticoid receptor antagonist.

8.4.3 Ceiling of care and cardiopulmonary resuscitation decisions

Bar charts showing ceiling of care decisions divided by patient demographics are displayed in Figure 8.1. Patients in the present study were often elderly, frail and were multi-morbid. Following consultation with patients, their next-of-kin and surrogate decision makers, pre-emptive ceiling of care decisions were documented for 409 (84.3%) patients hospitalised with SARS-CoV-2 infection. Of patients in whom these decisions were made, 208 (50.9%), 75 (18.3%) and 126 (30.8%) patients were deemed suitable for a maximum of level one, two or three care, respectively. CPR decisions were made for 451 (93.0%) patients, of whom 336 (74.5%) were deemed not for CPR in event of cardiac arrest, with CPR deemed appropriate in 115 (25.5%).

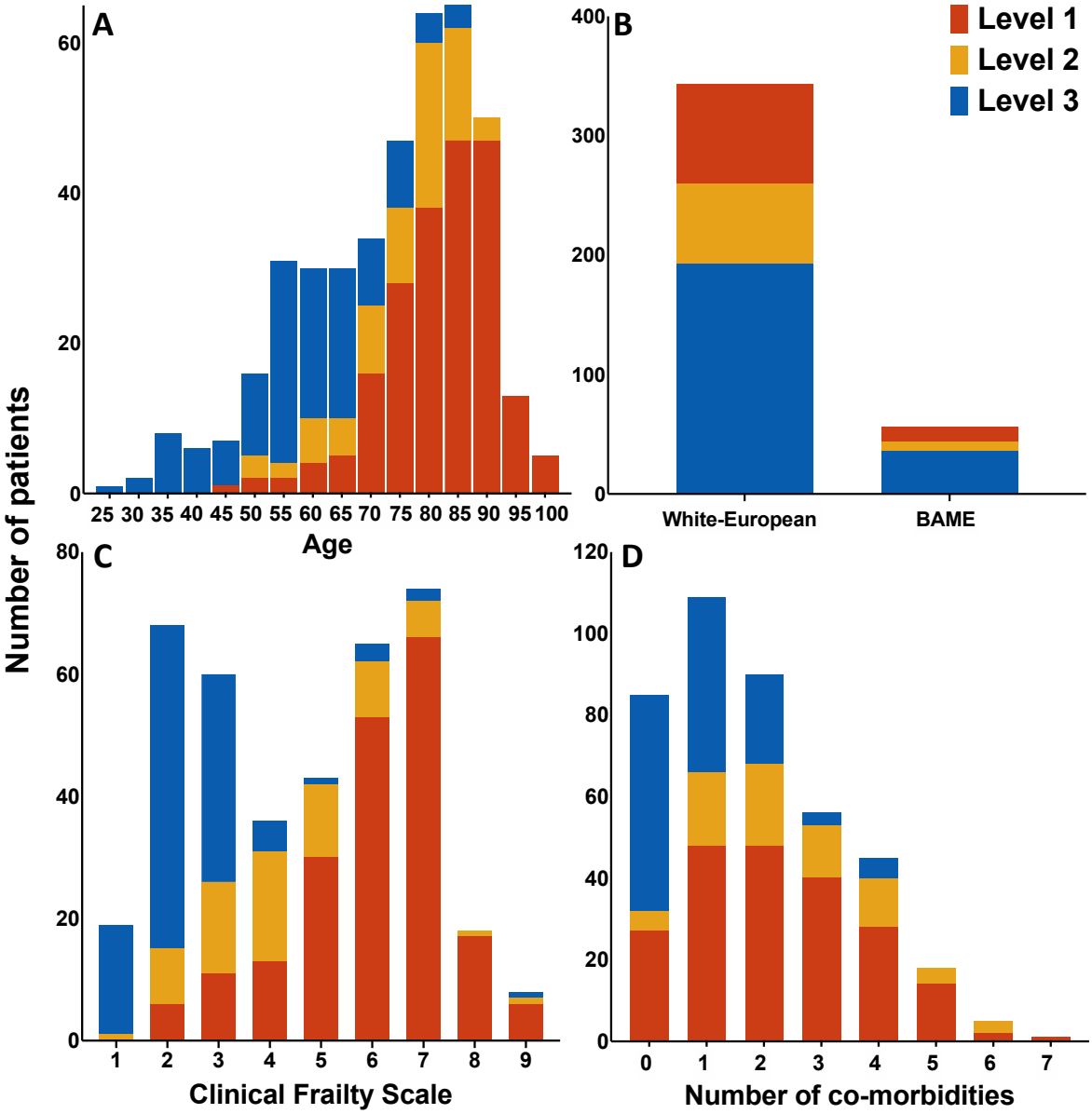


Figure 8.1 Bar charts showing A: age, B: ethnicity, C: Clinical Frailty Score and D: co-morbidities in patients deemed appropriate for level one, two or three care.

8.4.4 Association between ceiling of care decisions and patient characteristics

Patients considered suitable for escalation of treatment were younger, less frail, and had fewer major co-morbidities. There were associations between treatment escalation decisions and age, frailty, and burden of co-morbidities. In unadjusted analysis, age was strongly associated with treatment escalation decisions, most evident in patients over 85 years of age (odds ratio (OR) 0.004, 95% confidence interval (CI) 0.001–0.017, $p < 0.001$). Other variables associated with ceiling of care decisions were higher CFS, lower body mass index (BMI), a diagnosis of any major co-morbidity, the prescription of cardiovascular medications and White-European ethnicity (Figure 8.2).

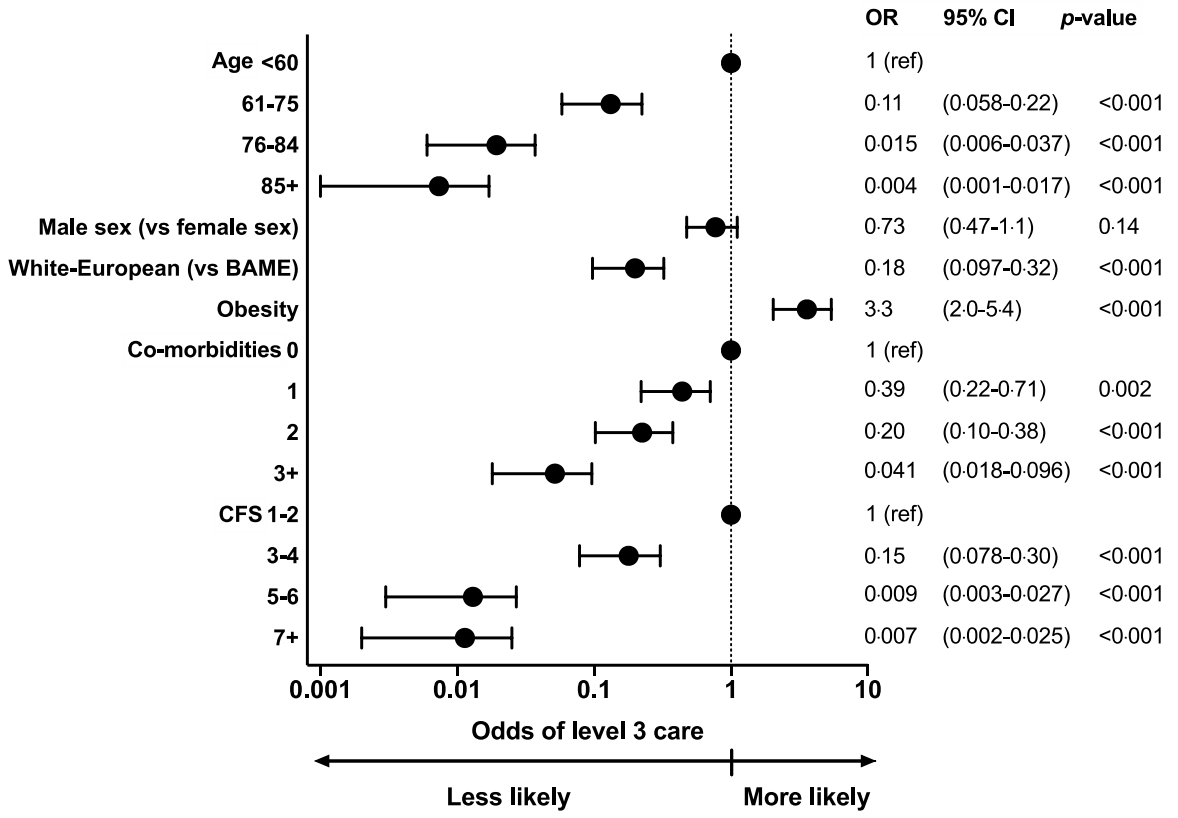


Figure 8.2 Forrest plot showing unadjusted odds ratio of appropriateness of level three care associated with demographic and clinical variables.
Reproduced from (Straw, McGinlay et al. 2021) under terms of Creative Commons Attribution 4.0 International License.

Compared to White-European patients, BAME patients were on average younger (58.0 ± 15·4 vs 73.7 ± 16.0 years, $p < 0.001$), had fewer major co-morbidities (1 (0,2) vs 2 (1, 3), $p = 0.037$), and were less frail (CFS 2 (2, 4) vs 5 (3, 7), $p < 0.001$). When adjusted for age and sex, ethnicity was not associated with ceiling of care decisions, nor were there associations between ceiling of care decisions and lower BMI or the prescription of most cardiovascular medications. Associations between a ceiling of care decision of less than level three and frailty, a diagnosis of diabetes mellitus, COPD, CKD, history of stroke or TIA, and prescription of loop diuretic or statin remained when adjusted for age and sex. In multivariable regression analysis,

predictors of ceiling of care decisions were advanced age (OR 1·1 per year, 95% CI 1.1–1.2, $p < 0.001$) and higher CFS (OR 2.1, 95% CI 1.7–2.7, $p < 0.001$) (Table 8.2).

Table 8.2 Multivariable binary regression analysis of clinical characteristics and ceiling of care decisions (with individual co-morbidities).

	Odds ratio	**95% CI**	***p*-value**
Age (per year)	0·89	0·86-0·92	**<0·001**
Male sex	1·8	0·81-4·0	0·15
CFS (per nodal point)	0·47	0·37-0·60	**<0·001**
Diabetes	0·49	0·20-1·2	0·11
COPD	0·60	0·19-1·9	0·38
CKD	0·31	0·093-1·1	0·062
Stroke/TIA	1·1	0·25-5·1	0·88
Loop diuretic	0·27	0·031-2·3	0·23
Statin	0·68	0·30-1·5	0·35
CI; confidence interval, CFS; Clinical Frailty Scale, COPD; chronic obstructive pulmonary disease, CKD; chronic kidney disease, TIA; transient ischaemic attack.			

No other clinical or demographic variables were independently associated with the decision to limit the maximal care level provided. No individual co-morbidities featured as part of a multivariable analysis although there was a significant association between the cumulative number of major co-morbidities and ceiling of care decisions (OR 1.4 per co-morbidity, 95% CI 1.0–1.9, $p = 0.048$) (Table 8.3).

Table 8.3 Multivariable binary regression analysis of clinical characteristics and ceiling of care decisions (with cumulative number of co-morbidities).

	Odds ratio	95% CI	*p*-value
Age (per year)	0.89	0.86-0.93	**<0.001**
Male sex	1.75	0.79-3.8	0.17
CFS (per nodal point)	0.48	0.38-0.60	**<0.001**
Co-morbidities (per co-morbidity)	0.72	0.52-1.0	**0.048**
Loop diuretic	0.23	0.026-2.1	0.19
Statin	0.65	0.30-1.4	0.28
CI; confidence interval, CFS; Clinical Frailty Scale.			

8.4.5 Association between ceiling of care decisions and clinical markers of disease severity

Patients deemed inappropriate for level three care had on average fewer markers of severe SARS-CoV-2 infection at the time of presentation, compared to those who were (Table 8.4). Laboratory markers of systemic inflammation such as C-reactive protein and serum ferritin were more often abnormal in patients deemed eligible for escalation to level three care, as were assessments of physiology such as respiratory rate, heart rate, and tympanic temperature. Chest radiography data were available for 471 (97.1%) patients at the time of hospitalisation, of which 217 (44.7%) were reported as consistent with, 151 (31.1%) were indeterminate for, and 103 (21.2%) inconsistent with, COVID-19. Patients who were considered appropriate for level three care were more likely to have chest radiography consistent with COVID-19 compared to those who were not ($p < 0.001$), suggesting a higher severity of disease in these patients.

Table 8.4 Markers of severity of disease divided by ceiling of care decisions

	All patients (n=409)	**Level 1 (n=208)**	**Level 2 (n=75)**	**Level 3 (n=126)**	***p*-value**
Laboratory findings					
Hb	129·2 ± 20·7	126·6 ± 21·8	125·0 ± 21·6	135·9 ± 16·5	**<0·001**
WCC	7·0 (5·4-9·4)	7·2 (5·4-10·0)	6·5 (5·0-9·1)	7·1 (5·6-9·5)	0·23
ANC	5·4 (4·0-8·0)	5·7 (4·0-8·9)	5·1 (3·9-7·8)	5·6 (4·2-8·3)	0·38
Lymphocyte count	0·8 (0·5-1·1)	0·7 (0·5-1·1)	0·7 (0·5-1·0)	0·8 (0·6-1·1)	0·12
Na^{2+}	138 (136-141)	140 (136-145)	137 (135·8-140)	137 (135-139)	**<0·001**
K^{+}	4·0 (3·7-4·4)	4·0 (3·7-4·5)	4·2 (3·7-4·5)	3·9 (3·7-4·2)	**0·034**
Creatinine	81 (63-117)	95 (68-143)	86·5 (65·8-129·5)	74 (60·3-89·8)	**<0·001**
CRP	90 (45-169)	77·5 (34·8-159·8)	106 (72·3-187·3)	110 (68-192)	**0·001**
Ddimer	467 (258·5-1035·3)	496 (266-1978)	671 (387-1042)	373 (223-924)	0·068
hsTNI	20·5 (8·1-60)	40·0 (17·2-94·3)	25·5 (9·9-70·5)	8·5 (4·6-22·2)	**<0·001**
Ferritin	460 (220-982)	365 (143·8-671·5)	510 (261·3-946)	674 (338·5-1458)	**<0·001**
Procalcitonin	0·15 (0·08-0·38)	0·17 (0·08-0·52)	0·14 (0·08-0·32)	0·15 (0·09-0·40)	0·60
Clinical observations					
RR (min^{-1})	22 (18-28)	20 (18-28)	22·5 (20-28)	24 (20-29)	**0·026**
O_2 saturations (%)	94·5 (89-96)	95 (90-97)	94 (88-96)	94 (89-96)	0·065
Heart rate (min^{-1})	90 (76-103)	89 (73-102·8)	89 (79-101·3)	96 (86-108·5)	**0·001**
SBP (mmHg)	129·2 ± 23·5	130·4 ± 25·5	131·2 ± 24·4	126·2 ± 18·8	0·21
Temperature (°C)	37·7 ± 1·1	37·4 ± 1·1	37·7 ± 1·1	38·0 ± 1·0	**<0·001**
Chest radiography					
COVID-19 [n(%)]	190 (47·4)	61 (29·6)	40 (55·6)	89 (72·4)	**<0·001**
Indeterminate [n(%)]	125 (31·2)	79 (38·2)	22 (30·6)	24 (19·5)	
Non-COVID-19 [n(%)]	86 (21·4)	66 (32·0)	10 (13·9)	10 (8·1)	

Hb; haemoglobin, WCC, white cell count, ANC; absolute neutrophil count, Na^{2+}; sodium, K^{+}; potassium, CRP; C-reactive protein, hsTNI; high-sensitivity troponin-I, RR; respiratory rate, O_2; oxygen, SBP; systolic blood pressure.

8.4.6 Treatments administered during hospitalisation

During hospitalisation, a total of 383 (79.0%) patients required oxygen therapy, 88 (18.1%) received CPAP, 38 (7.8%) received mechanical ventilation, renal replacement therapy was used in 11 (2.3%), and 28 (5.8%) patients required inotropes or vasopressors. CPAP was delivered in a ward setting for 6 (6.8%), on the high-dependency unit for 13 (14.8%), and on ICU for 69 (78.4%). All patients who required mechanical ventilation were cared for in an ICU setting. Overall, 92 (19.0%) patients were admitted to ICU, 61 (81.3%) of whom were deemed suitable for level three care, whilst 14 (18.7%) were suitable for, and received, level two care.

8.4.7 Outcomes

At the time of censorship, a total of 307 (63.3%) patients had been discharged from hospital following a mean hospital stay of 12.7 ± 10.5 days. Overall, 159 (32.8%) patients died prior to discharge with a mean follow-up of 12.6 ± 11.2 days after admission, whilst 19 (3.9%) remained in hospital. Despite on average having more markers of disease severity, patients deemed to be suitable for level three care were more likely to be discharged, and less likely to have died during hospitalisation ($p < 0.001$) (Figure 8.3). Of the 20 (16%) patients eligible for level three care who died during the study period, all were admitted to ICU and received mechanical ventilation prior to death. Overall, including patients in whom ceiling of care decisions were not documented, 38 (7.8%) received mechanical ventilation during the study period and of these seven (18.4%) had been discharged, nine (23.7%) remained in hospital, and 22 (57.9%) had died.

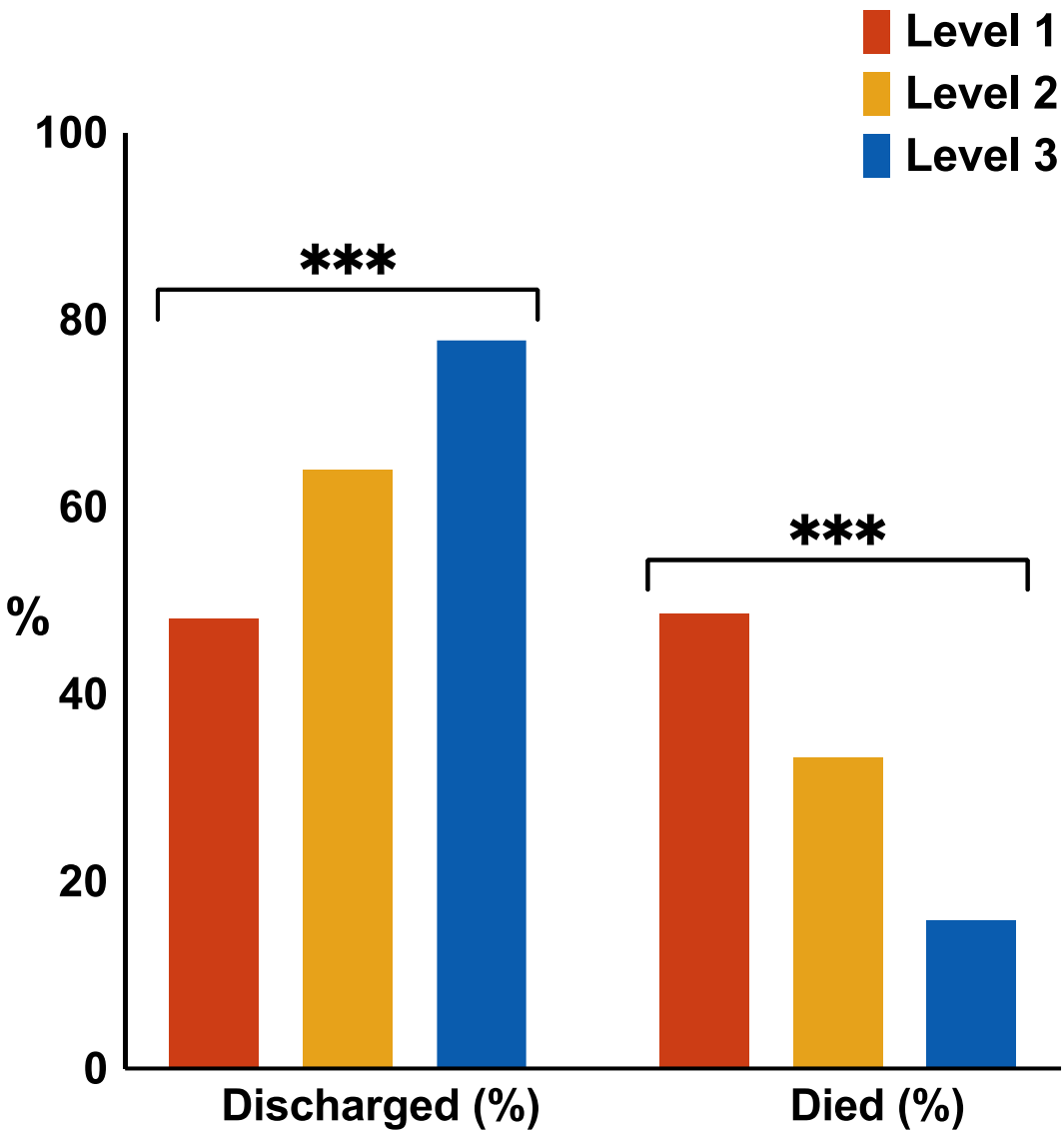


Figure 8.3 Bar charts showing outcomes of patients appropriate for level one, two or three care.

p-value <0.05*, <0.01**, <0.001***

Death during admission was associated with advanced age, White-European ethnicity, higher CFS, a diagnosis of HFrEF, atrial fibrillation, CKD or COPD and the prescription of anticoagulant (Table 8.5). When adjusted for age and sex, associations between death during admission and higher CFS remained (OR 1.2, 95% CI 1.1–

1.4, $p = 0.001$), but not the associations with White-European ethnicity, any individual cardiovascular or non-cardiovascular co-morbidity or medication. In a multivariable model including age, CFS and maximum level of care receiving during admission, receipt of level two (OR 2.6, 95% CI 1.1–11.6, $p = 0.033$) or level three care (OR 8.1, 95% CI 3.7–17.8, $p < 0.001$) were associated with an increased risk of death during hospitalisation.

Table 8.5 Baseline clinical characteristics of patients divided by those who were alive or had died during the study period.

	All patients (n=485)	**Alive (n=326)**	**Dead (n=159)**	***p*-value**
Demographics				
Age (years)	71·6 ± 16·3	68·4 ± 17·4	78·1 ± 11·5	**<0·001**
Male sex [n(%)]	259 (53·4)	168 (51·5)	91 (57·3)	0·24
BMI (kg/m^2)	26·3 (22·1-30·8)	26·7 (22·2-31·4)	25·5 (21·9-29·9)	0·13
BAME [n(%)]	73 (15·4)	59 (18·6)	14 (8·9)	**0·006**
Clinical Frailty Scale	5 (3-6)	3 (2-6)	6 (3-7)	**<0·001**
Co-morbidities				
HFrEF [n(%)]	59 (12·2)	31 (9·5)	28 (17·6)	**0·010**
IHD [n(%)]	69 (14·2)	46 (14·1)	23 (14·5)	0·92
Hypertension [n(%)]	222 (45·8)	155 (47·5)	67 (42·1)	0·26
AF [n(%)]	97 (20·0)	52 (16·0)	45 (28·3)	**0·001**
Diabetes mellitus [n(%)]	147 (30·3)	90 (27·6)	57 (35·8)	0·064
Stroke/TIA [n(%)]	53 (10·9)	32 (9·8)	21 (13·2)	0·26
CKD [n(%)]	119 (24·5)	71 (21·8)	48 (30·2)	**0·043**
COPD [n(%)]	69 (14·2)	37 (11·3)	32 (20·1)	**0·009**
Malignancy [n(%)]	37 (7·6)	23 (7·1)	14 (8·8)	0·50
Medications				
ACEi [n(%)]	84 (17·3)	57 (17·5)	27 (17·0)	0·89
ARB [n(%)]	41 (8·5)	31 (9·5)	10 (6·3)	0·23
BB [n(%)]	113 (23·3)	75 (23·0)	38 (23·9)	0·83
CCB [n(%)]	80 (16·5)	57 (17·5)	23 (14·5)	0·40
Loop diuretic [n(%)]	74 (15·3)	47 (14·4)	27 (17·0)	0·46
MRA [n(%)]	18 (3·7)	12 (3·7)	6 (3·8)	0·96
Statin [n(%)]	200 (41·2)	136 (41·7)	64 (40·3)	0·76
Antiplatelet [n(%)]	115 (23·7)	75 (23·0)	40 (25·2)	0·60
Anticoagulant [n(%)]	67 (13·8)	38 (11·7)	29 (18·2)	**0·049**
Metformin [n(%)]	61 (12·6)	39 (12·0)	22 (13·8)	0·56
Sulphonylurea [n(%)]	23 (4·7)	18 (5·7)	5 (3·2)	0·23
Corticosteroid [n(%)]	24 (4·9)	14 (4·3)	10 (6·4)	0·34
Immunosuppression [n(%)]	22 (4·5)	13 (4·0)	9 (5·7)	0·41

Continuous variables are presented as mean ± standard deviation, or median and interquartile range in parentheses, discrete variables as number and percentages in parentheses.

BMI; body mass index, BAME; Black Asian and minority ethnic, BMI; body mass index, HFrEF; heart failure with reduced ejection fraction, IHD; ischaemic heart disease, AF; atrial fibrillation, CKD; chronic kidney disease, COPD; chronic obstructive pulmonary disease, ACEi; angiotensin converting enzyme inhibitor, ARB; angiotensin II receptor blocker, BB; beta-adrenoceptor antagonist, CCB; calcium channel blocker, MRA; mineralocorticoid receptor antagonist.

8.5 Discussion

8.5.1 Findings

In this study, data are presented regarding pre-emptive advanced care planning, in patients admitted with SARS-CoV-2 infection during the COVID-19 pandemic according to national recommendations (NICE 20 March 2020). In contrast to usual clinical care, these decisions were made for the majority of hospitalised patients, who were often elderly, frail and frequently had cardiovascular co-morbidities. Advanced age, higher CFS, and the accrued number of co-morbidities, were independently associated with a decision to limit the ceiling of care below full intensive care-based treatment (level three). In contrast, only age and frailty were associated with death during hospitalisation, and in a multivariate model including age, CFS and maximum level of care receipt of level two or three care, were associated with worse outcomes.

Taken together these data suggest that firstly, decisions to limit care below full intensive care treatment was not associated with worse outcomes in patients deemed unsuitable for these treatments. Secondly, these decisions were associated with accrued number of major co-morbidities, which are known to be highly prevalent in people with CHF and associated with worse outcomes. Finally, where supported to do so, treating teams are generally comfortable initiating ceiling of care decisions, and patients, their next-of-kin and surrogate decisions makers receptive to them.

8.5.2 Addressing goals of care

Early reports from Wuhan (Wang, Hu et al. 2020, Wu and McGoogan 2020, Yang, Yu et al. 2020) and Lombardy (Grasselli, Greco et al. 2020) highlighted the risks to patients due to demand for ICU care surpassing surge capacity (Murthy, Gomersall et

al. 2020, Savulescu, Vergano et al. 2020). Considerable focus on preparedness in the United Kingdom has therefore included timely and patient-centred pre-emptive discussions, addressing goals of care in the setting of a potentially fatal illness, which disproportionately effects the elderly and those with cardiovascular co-morbidities. The priorities of such decisions were to avoid intensive and distressing treatments in patients who would not want to receive them, and to manage patients appropriately according to the likelihood of benefit from intensive treatment (Curtis, Kross et al. 2020).

Advanced care planning can be challenging for patients and healthcare professionals. It is essential that such discussions occur at an appropriate time and are framed within the individual patient's beliefs and wishes (Pitcher, Fritz et al. 2017). At LTHT, establishing and documenting goals of care was facilitated by the availability of the ReSPECT process (RCUK 2020). This simple electronic documentation is standardised across care settings, and is recognised regionally by hospitals, primary care practices, and ambulance services, and facilitates timely shared decision-making amongst patients, their next-of-kin, and surrogate decision makers. The data presented here suggest that whilst advanced care planning has not been a routine part of clinical care, as evidenced by the low rate of advanced care planning in Chapter 7, where treating teams are supported to do so, they are generally comfortable initiating discussions of goals of care, with a remarkable rate of advanced care documentation during the first wave of the pandemic.

The COVID-19 pandemic continues to challenge healthcare systems globally, and has raised important ethical issues, particularly the need to prioritise access to limited resources to those with the greatest chance of survival and anticipated shorter

recovery (Curtis, Kross et al. 2020, Savulescu, Vergano et al. 2020). The majority of LTHT patients were considered inappropriate for escalation of care to an ICU setting, or for CPR. Although this could imply that decisions were influenced by a drive to protect resources, ICU and ward bed occupancy at LTHT was below surge capacity throughout the study period and a local database monitored and disseminated this information to treating teams daily. Hence, although a higher proportion of patients had the ReSPECT process completed during the peak months of the pandemic than would usually be expected, LTHT did not experience a severe shortage of ICU bed capacity, making it unlikely that the outcomes of these assessments were biased towards a particular decision by the capacity to provide care. The high rate of not-for-resuscitation and ceiling of care decisions therefore probably reflects the demographics and clinical characteristics of patients in the present study who were often elderly, frail, and had major cardiovascular and non-cardiovascular co-morbidities. Furthermore, in a multivariable model adjusted for age and CFS, receipt of level two or three care were associated with an increased risk of death, reflecting baseline differences in disease severity in patients who were considered appropriate for intensive treatments. It is feasible, however, that a more challenging environment including the requirement for appropriate personal protective equipment prior to CPR, risks of transmission to healthcare professionals (Kramer, Lo et al. 2020), and the limited effectiveness of cardiopulmonary resuscitation in the setting of COVID-19 (Shao, Xu et al. 2020) may have influenced these decisions.

8.5.3 Demographic and clinical characteristics and their association with ceiling of care decisions

In appreciation that a high proportion of patients admitted with SARS-CoV-2 infection were elderly and frail, and therefore potentially unlikely to benefit from intensive treatments, even in the absence of COVID-19 infection, on 20th March 2020 the National Institute for Health and Care Excellence (NICE) produced guidance that included the CFS as a framework with which to begin discussions with patients and carers around advanced care planning and suitability for ICU care in the event of deterioration (NICE 20 March 2020). The CSF is a nine-point scale which provides healthcare professionals with a simple screening tool for measuring frailty. The CSF has been validated in frail patients receiving ICU care, in which it reliably predicts outcomes (Muscedere, Waters et al. 2017, Moug, Carter et al. 2020). In patients in the current study, frailty was a strong predictor of ceiling of care decisions, which is likely to reflect both the known poor prognosis in frail patients receiving ICU care, and also the aforementioned national recommendations. As would be expected, advanced age was strongly associated with these decisions, with patients aged over 85 years being far more likely to be deemed ineligible for level three care compared to those under 65.

BAME patients were more likely than White-European patients to be considered appropriate for level three care (OR 5.7, 95% CI 3.1–10.4, $p < 0.001$), however they were on average younger, less frail and had fewer major co-morbidities. In age-sex adjusted analysis, ethnicity was not associated with ceiling of care decisions, nor was it associated with survival. Together these findings suggest that these decisions are unlikely to have contributed to the worse outcomes in BAME patients reported elsewhere.

8.5.4 Receipt of cardiovascular medications are not associated with worse outcomes where appropriate definitions are applied

The low rate of public testing for SARS-CoV-2 infection in many countries during the first wave of the pandemic meant that studies have often been limited to hospitalised patients which have not considered the confounding effects of advanced care planning, such that a valid picture of risk factors for severe disease in elderly, frail and multi-morbid populations is unknown. Studies investigating risk factors in COVID-19 have often classified ICU admission as a marker of severe disease, either in recognition of poor outcomes in these patients or where mortality data were not yet available. For example, a population based study in the UK found that the receipt of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin-II-receptor blocker (ARB) was associated with a reduced risk (except in Black-African patients) of severe disease (Hippisley-Cox, Young et al. 2020). However, without accounting for the confounding effects of ceiling of care decisions, admission to ICU or receipt of mechanical ventilation might be associated with *better* prognosis when compared with conservative management for patients in whom these treatments were considered inappropriate or futile (Straw and Witte 2020). Furthermore, these observations have not been confirmed in studies restricted to patients already on ICU, in which death was the primary endpoint (Grasselli, Greco et al. 2020, Gupta, Hayek et al. 2020).

In the current cohort of patients, prescription of ACEi (but not ARB) was associated with reduced likelihood of being considered appropriate for level three care, but was not associated with an increased risk of death during hospitalisation. These observations may be a result of biases introduced by pre-emptive ceiling of care decisions where those with cardiovascular co-morbidities are not considered for ICU

care, and the relative risk of severe disease therefore appears less where this definition is applied. Admission to ICU, in the present study, was guided by these pre-emptive decisions in addition to severity of illness, however, the setting of care was not consistent for all patients. For example, some patients who were deemed inappropriate for mechanical ventilation received CPAP in an ICU setting, whilst others received these treatments in a ward or high-dependency unit.

A further paradox revealed by this data is that whilst patients deemed appropriate for level three care were more unwell at presentation, as evidenced by more abnormal laboratory values, chest radiography and physiological assessment, when compared to patients suitable for level one or two care, outcomes were favourable with the vast majority surviving until discharge. In this analysis, all those patients deemed appropriate for level three care who subsequently died, did so following escalation of their care to an ICU setting and mechanical ventilation. Overall, 14 (18.7%) of patients deemed eligible for level two and 61 (48.8%) of those deemed eligible for level three care, were admitted to an ICU setting allowing for delivery of key treatments for COVID-19 of CPAP and mechanical ventilation. Including patients in whom ceiling of care decisions were not made, 38 (7.8%) patients received mechanical ventilation. This rate was low compared to earlier reports from Wuhan and Lombardy, but similar to contemporary reports from the UK (Docherty, Harrison et al. 2020). Despite an average age of 57.8 ± 13.2 years, more than half of these patients had died at follow-up, with fewer than one in five having been discharged and, at the time of reporting, almost a quarter still in hospital. It might therefore be reasonable to regard mechanical ventilation as a surrogate marker of severe disease in patients who remain in hospital at the time of censorship, due to the poor anticipated prognosis in this group.

8.6 Strengths and limitations

This is an analysis of a carefully characterised cohort of consecutively admitted patients with SARS-2-CoV infection in whom standardised documentation of ceiling of care decisions was routine, and completed in the majority of cases. The principal limitations are inherent to the retrospective design and single centre setting, and the findings should be interpreted in light of this. Recommendations to assist treating teams making ceiling of care decisions were available (NICE 20 March 2020), however these have not been validated in COVID-19, nor are there randomised data supporting their use. These decisions were not standardised, rather they were made between patients, their next-of-kin or surrogate decision makers, following discussions regarding their goals of care. Whilst it is recognised that there is a risk of undertreatment with this approach, it is also the case that undertreatment from a medical perspective may not equate to undertreatment from the perspective of patients or their relatives.

Although the majority of patients in the present study had cardiovascular co-morbidities (including diabetes), the associations with clinical characteristics and outcomes in patients with CHF were not specifically investigated. Additional limitations include the availability of ICU beds (Rhodes, Ferdinande et al. 2012), demographic and cultural differences between countries which may limit the generalisability of the findings. Finally, receipt of oxygen therapy is an imprecise measure of disease severity (although in line with other observational and interventional studies in COVID-19 (Horby, Lim et al. 2021) and the follow-up time was relatively short.

8.7 Conclusions

As far as is known, this study is the first to report ceiling of care and CPR decisions for hospitalised patients in a setting where these decisions were routine. These decisions were made for most patients and broadly in line with known poor predictors of poor outcomes. Taken together, the study findings suggest that when supported to do so, treating teams are generally comfortable initiating these discussions, and in those deemed unsuitable for full intensive care treatment, this was not associated with worse outcomes.

Chapter 9: Discussion

Despite significant progress, chronic heart failure (CHF) remains a disease associated with poor quality of life and reduced longevity. Additional improvements might be possible beyond the therapies which most patients receive, by employing a comprehensive disease modifying programme and, in selected patients, by adopting an early, integrated palliative care approach.

9.1 Simplify to progress

In chapter 1 I explored how CHF is associated with a prognosis similar to many forms of cancer, in which any delays have the possibility to cost lives. I presented a novel conceptual framework in which the implementation of the ‘Four pillars’ of pharmacological therapies for CHF might improve outcomes.

9.2 Prioritise symptoms

Our efforts to improve the lives of those with CHF should not be limited to implementing therapies which extend life. Increasing numbers of people die with symptoms of CHF, and offering palliative care as an early, integral part of their care could yield further benefits.

9.3 Move beyond ‘response’

Chapter 3 explored the concept of response, and how measuring outcomes in CHF is difficult due to the variable burden of symptoms and unpredictable disease trajectory. Various outcome measures can be utilised in studies of CHF, including mortality,

worsening heart failure events, left ventricular remodelling, symptoms, and quality of life.

9.4 Utilise proven therapies for those with the most to gain

In chapter 4 I presented data from a prospective cohort study, showing that despite the competing risk of non-cardiovascular death, those with co-morbidities were at higher risk of progressive heart failure and sudden death, and were prescribed lower doses of disease modifying pharmacological therapies. Those with co-morbidities have the most to gain, suggesting a need to enhance the delivery of therapies for these patients.

9.5 Optimise therapies for those with ‘mild’ heart failure

Guideline indications for pharmacological and device therapies have until very recently been limited to those with HFrEF. However, as shown in Chapter 5, a large proportion of patients with CHF have heart failure with mildly reduced ejection fraction. These patients may derive similar benefit from pharmacological therapies as those with heart failure with reduced ejection fraction, supporting guideline recommendations extending the indications of these agents to this population.

9.6 Identify systolic dysfunction in all classifications of heart failure

Therapies for heart failure with a preserved ejection fraction are currently limited, however a significant proportion of patients with an ejection fraction currently classified as ‘normal’ have systolic dysfunction. These patients may derive benefit from pharmacological therapies currently applied to heart failure with reduced ejection

fraction, and simpler tool to identify these patients such as cardiac contractility index may improve the phenotypic classification of this heterogenous group.

9.7 Identify those approaching the end-of-life

The Surprise Question has been proposed as a method of identifying those within the last year of life who might benefit from the early adoption of a palliative care approach. Despite being incorporated into the United Kingdom Gold Standards Framework and national guidelines, the approach has not been tested in the setting of CHF. In a prospective cohort study, I demonstrated that the Surprise Question was able to identify nearly all patients within the last year of life, whilst also being able to reliably identify those who would survive. There was an over classification of patients into the "not surprised" category, and the low positive predictive value of the question might limit its use in routine clinical practice. However, there is no evidence that this might cause harm to those identified as possibly being able to benefit from palliative care interventions, although a nocebo effect is feasible.

9.8 Make advanced care planning an integrated part of heart failure care

Hospitalisation for heart failure is associated with a dismal prognosis. Despite this I observed a low rate of advanced care planning, as evidenced by a low rate of not-for-resuscitation decisions in Chapter 7. The coronavirus disease 2019 pandemic permitted the examination of how the Recommended Summary Plan for Emergency Care and Treatment (ReSPECT) process could be used to incorporate advanced care planning into routine clinical care. I observed that nearly all patients were offered advanced care planning, avoiding distressing and inappropriate interventions in those who would not benefit from them. My data suggests that when encouraged to do so,

physicians are generally comfortable initiating these conversations and patients receptive to them.

List of References

Abraham, W. T., W. G. Fisher, A. L. Smith, D. B. Delurgio, A. R. Leon, E. Loh, D. Z. Kocovic, M. Packer, A. L. Clavell, D. L. Hayes, M. Ellestad, R. J. Trupp, J. Underwood, F. Pickering, C. Truex, P. McAtee, J. Messenger and M. S. G. M. I. R. C. Evaluation (2002). "Cardiac resynchronization in chronic heart failure." N Engl J Med **346**(24): 1845-1853.

Afilalo, J., K. P. Alexander, M. J. Mack, M. S. Maurer, P. Green, L. A. Allen, J. J. Popma, L. Ferrucci and D. E. Forman (2014). "Frailty assessment in the cardiovascular care of older adults." J Am Coll Cardiol **63**(8): 747-762.

Alemzadeh-Ansari, M. J., M. M. Ansari-Ramandi and N. Naderi (2017). "Chronic Pain in Chronic Heart Failure: A Review Article." J Tehran Heart Cent **12**(2): 49-56.

Amro, O. W., M. Ramasamy, J. A. Strom, D. E. Weiner and B. L. Jaber (2016). "Nephrologist-Facilitated Advance Care Planning for Hemodialysis Patients: A Quality Improvement Project." Am J Kidney Dis **68**(1): 103-109.

Anker, S. D., J. Butler, G. Filippatos, J. P. Ferreira, E. Bocchi, M. Bohm, H. P. Brunner-La Rocca, D. J. Choi, V. Chopra, E. Chuquiure-Valenzuela, N. Giannetti, J. E. Gomez-Mesa, S. Janssens, J. L. Januzzi, J. R. Gonzalez-Juanatey, B. Merkely, S. J. Nicholls, S. V. Perrone, I. L. Pina, P. Ponikowski, M. Senni, D. Sim, J. Spinar, I. Squire, S. Taddei, H. Tsutsui, S. Verma, D. Vinereanu, J. Zhang, P. Carson, C. S. P. Lam, N. Marx, C. Zeller, N. Sattar, W. Jamal, S. Schnaidt, J. M. Schnee, M. Brueckmann, S. J. Pocock, F. Zannad, M. Packer and E. M.-P. T. Investigators

(2021). "Empagliflozin in Heart Failure with a Preserved Ejection Fraction." N Engl J Med **385**(16): 1451-1461.

Anker, S. D., J. Butler, G. S. Filippatos, W. Jamal, A. Salsali, J. Schnee, K. Kimura, C. Zeller, J. George, M. Brueckmann, F. Zannad, M. Packer, E. M.-P. T. Committees and Investigators (2019). "Evaluation of the effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: rationale for and design of the EMPEROR-Preserved Trial." Eur J Heart Fail **21**(10): 1279-1287.

Anker, S. D., A. Negassa, A. J. Coats, R. Afzal, P. A. Poole-Wilson, J. N. Cohn and S. Yusuf (2003). "Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study." Lancet **361**(9363): 1077-1083.

Arena, R., J. Myers and M. Guazzi (2008). "The clinical and research applications of aerobic capacity and ventilatory efficiency in heart failure: an evidence-based review." Heart Fail Rev **13**(2): 245-269.

Austin, J., D. Hockey, W. R. Williams and S. Hutchison (2013). "Assessing parenteral diuretic treatment of decompensated heart failure in the community." Br J Community Nurs **18**(11): 528, 530-524.

Bardy, G. H., K. L. Lee, D. B. Mark, J. E. Poole, D. L. Packer, R. Boineau, M. Domanski, C. Troutman, J. Anderson, G. Johnson, S. E. McNulty, N. Clapp-Channing, L. D. Davidson-Ray, E. S. Fraulo, D. P. Fishbein, R. M. Luceri, J. H. Ip

and I. Sudden Cardiac Death in Heart Failure Trial (2005). "Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure." N Engl J Med **352**(3): 225-237.

Barnes, S., M. Gott, S. Payne, C. Parker, D. Seamark, S. Gariballa and N. Small (2008). "Predicting mortality among a general practice-based sample of older people with heart failure." Chronic Illn **4**(1): 5-12.

Beattie, J. M. and M. J. Johnson (2012). "Subcutaneous furosemide in advanced heart failure: has clinical practice run ahead of the evidence base?" BMJ Support Palliat Care **2**(1): 5-6.

Bekelman, D. B., E. P. Havranek, D. M. Becker, J. S. Kutner, P. N. Peterson, I. S. Wittstein, S. H. Gottlieb, T. E. Yamashita, D. L. Fairclough and S. M. Dy (2007). "Symptoms, depression, and quality of life in patients with heart failure." J Card Fail **13**(8): 643-648.

Bekelman, D. B., J. S. Rumsfeld, E. P. Havranek, T. E. Yamashita, E. Hutt, S. H. Gottlieb, S. M. Dy and J. S. Kutner (2009). "Symptom burden, depression, and spiritual well-being: a comparison of heart failure and advanced cancer patients." J Gen Intern Med **24**(5): 592-598.

Benjamin, E. J., S. S. Virani, C. W. Callaway, A. M. Chamberlain, A. R. Chang, S. Cheng, S. E. Chiuve, M. Cushman, F. N. Delling, R. Deo, S. D. de Ferranti, J. F. Ferguson, M. Fornage, C. Gillespie, C. R. Isasi, M. C. Jimenez, L. C. Jordan, S. E. Judd, D. Lackland, J. H. Lichtman, L. Lisabeth, S. Liu, C. T. Longenecker, P. L.

Lutsey, J. S. Mackey, D. B. Matchar, K. Matsushita, M. E. Mussolino, K. Nasir, M. O'Flaherty, L. P. Palaniappan, A. Pandey, D. K. Pandey, M. J. Reeves, M. D. Ritchey, C. J. Rodriguez, G. A. Roth, W. D. Rosamond, U. K. A. Sampson, G. M. Satou, S. H. Shah, N. L. Spartano, D. L. Tirschwell, C. W. Tsao, J. H. Voeks, J. Z. Willey, J. T. Wilkins, J. H. Wu, H. M. Alger, S. S. Wong, P. Muntner, E. American Heart Association Council on, C. Prevention Statistics and S. Stroke Statistics (2018). "Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association." Circulation **137**(12): e67-e492.

Berg, D. D., P. S. Jhund, K. F. Docherty, S. A. Murphy, S. Verma, S. E. Inzucchi, L. Kober, M. N. Kosiborod, A. M. Langkilde, F. A. Martinez, O. Bengtsson, P. Ponikowski, M. Sjostrand, S. D. Solomon, J. J. V. McMurray and M. S. Sabatine (2021). "Time to Clinical Benefit of Dapagliflozin and Significance of Prior Heart Failure Hospitalization in Patients With Heart Failure With Reduced Ejection Fraction." JAMA Cardiol **6**(5): 499-507.

Bhatt, D. L., M. Szarek, P. G. Steg, C. P. Cannon, L. A. Leiter, D. K. McGuire, J. B. Lewis, M. C. Riddle, A. A. Voors, M. Metra, L. H. Lund, M. Komajda, J. M. Testani, C. S. Wilcox, P. Ponikowski, R. D. Lopes, S. Verma, P. Lapuerta, B. Pitt and S.-W. T. Investigators (2021). "Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure." N Engl J Med **384**(2): 117-128.

Blacher, M., A. Zimerman, P. H. B. Engster, E. Grespan, C. A. Polanczyk, M. M. Rover, J. A. F. Neto, L. C. Danzmann, E. G. Bertoldi, M. V. Simoes, L. Beck-da-Silva, A. Biolo and L. E. Rohde (2020). "Revisiting heart failure assessment based on objective measures in NYHA functional classes I and II." Heart.

Blacher, M., A. Zimerman, P. H. B. Engster, E. Grespan, C. A. Polanczyk, M. M. Rover, J. A. F. Neto, L. C. Danzmann, E. G. Bertoldi, M. V. Simoes, L. Beck-da-Silva, A. Biolo and L. E. Rohde (2021). "Revisiting heart failure assessment based on objective measures in NYHA functional classes I and II." Heart **107**(18): 1487-1492.

Blinderman, C. D., P. Homel, J. A. Billings, R. K. Portenoy and S. L. Tennstedt (2008). "Symptom distress and quality of life in patients with advanced congestive heart failure." J Pain Symptom Manage **35**(6): 594-603.

Bombardini, T., M. J. Correia, C. Cicerone, E. Agricola, A. Ripoli and E. Picano (2003). "Force-frequency relationship in the echocardiography laboratory: a noninvasive assessment of Bowditch treppe?" J Am Soc Echocardiogr **16**(6): 646-655.

Borghi, C. and A. F. G. Cicero (2020). "Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction." N Engl J Med **382**(10): 972.

Bozkurt, B., A. J. S. Coats, H. Tsutsui, C. M. Abdelhamid, S. Adamopoulos, N. Albert, S. D. Anker, J. Atherton, M. Bohm, J. Butler, M. H. Drazner, G. Michael Felker, G. Filippatos, M. Fiuzat, G. C. Fonarow, J. E. Gomez-Mesa, P. Heidenreich, T. Imamura, E. A. Jankowska, J. Januzzi, P. Khazanie, K. Kinugawa, C. S. P. Lam, Y. Matsue, M. Metra, T. Ohtani, M. Francesco Piepoli, P. Ponikowski, G. M. C. Rosano, Y. Sakata, P. Seferovic, R. C. Starling, J. R. Teerlink, O. Vardeny, K. Yamamoto, C. Yancy, J. Zhang and S. Zieroth (2021). "Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart

Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association." Eur J Heart Fail **23**(3): 352-380.

Braunstein, J. B., G. F. Anderson, G. Gerstenblith, W. Weller, M. Niefeld, R. Herbert and A. W. Wu (2003). "Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure." J Am Coll Cardiol **42**(7): 1226-1233.

Bristow, M. R., E. M. Gilbert, W. T. Abraham, K. F. Adams, M. B. Fowler, R. E. Hershberger, S. H. Kubo, K. A. Narahara, H. Ingersoll, S. Krueger, S. Young and N. Shusterman (1996). "Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators." Circulation **94**(11): 2807-2816.

Bristow, M. R., L. A. Saxon, J. Boehmer, S. Krueger, D. A. Kass, T. De Marco, P. Carson, L. DiCarlo, D. DeMets, B. G. White, D. W. DeVries, A. M. Feldman, P. Comparison of Medical Therapy and I. Defibrillation in Heart Failure (2004). "Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure." N Engl J Med **350**(21): 2140-2150.

Brunner-La Rocca, H. P., G. C. Linssen, F. J. Smeele, A. A. van Drimmelen, H. J. Schaafsma, P. H. Westendorp, P. C. Rademaker, H. J. van de Kamp, A. W. Hoes, J. J. Brugts and C.-H. Investigators (2019). "Contemporary Drug Treatment of Chronic

Heart Failure With Reduced Ejection Fraction: The CHECK-HF Registry." JACC Heart Fail **7**(1): 13-21.

Butler, J., G. Filippatos, T. Jamal Siddiqi, M. Brueckmann, M. Bohm, V. K. Chopra, J. Pedro Ferreira, J. L. Januzzi, S. Kaul, I. L. Pina, P. Ponikowski, S. J. Shah, M. Senni, O. Vedin, S. Verma, B. Peil, S. J. Pocock, F. Zannad, M. Packer and S. D. Anker (2022). "Empagliflozin, Health Status, and Quality of Life in Patients With Heart Failure and Preserved Ejection Fraction: The EMPEROR-Preserved Trial." Circulation **145**(3): 184-193.

Campbell, R. T., M. C. Petrie, C. E. Jackson, P. S. Jhund, A. Wright, R. S. Gardner, P. Sonecki, A. Pozzi, P. McSkimming, A. McConnachie, F. Finlay, P. Davidson, M. A. Denvir, M. J. Johnson, K. J. Hogg and J. J. V. McMurray (2018). "Which patients with heart failure should receive specialist palliative care?" Eur J Heart Fail **20**(9): 1338-1347.

Cazeau, S., C. Leclercq, T. Lavergne, S. Walker, C. Varma, C. Linde, S. Garrigue, L. Kappenberger, G. A. Haywood, M. Santini, C. Bailleul, J. C. Daubert and I. Multisite Stimulation in Cardiomyopathies Study (2001). "Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay." N Engl J Med **344**(12): 873-880.

Cheung, W. Y., K. Schaefer, C. W. May, R. J. Glynn, L. H. Curtis, L. W. Stevenson and S. Setoguchi (2013). "Enrollment and events of hospice patients with heart failure vs. cancer." J Pain Symptom Manage **45**(3): 552-560.

Christakis, N. A. and E. B. Lamont (2000). "Extent and determinants of error in physicians' prognoses in terminally ill patients: prospective cohort study." West J Med **172**(5): 310-313.

Chua, T. P., D. Harrington, P. Ponikowski, K. Webb-Peploe, P. A. Poole-Wilson and A. J. Coats (1997). "Effects of dihydrocodeine on chemosensitivity and exercise tolerance in patients with chronic heart failure." J Am Coll Cardiol **29**(1): 147-152.

CIBIS-II (1999). "The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial." Lancet **353**(9146): 9-13.

Clarke, B., J. Howlett, J. Sapp, P. Andreou and R. Parkash (2011). "The effect of comorbidity on the competing risk of sudden and nonsudden death in an ambulatory heart failure population." Can J Cardiol **27**(2): 254-261.

Cleland, J. G., J. C. Daubert, E. Erdmann, N. Freemantle, D. Gras, L. Kappenberger, L. Tavazzi and I. Cardiac Resynchronization-Heart Failure Study (2005). "The effect of cardiac resynchronization on morbidity and mortality in heart failure." N Engl J Med **352**(15): 1539-1549.

Cleland, J. G., I. Findlay, S. Jafri, G. Sutton, R. Falk, C. Bulpitt, C. Prentice, I. Ford, A. Trainer and P. A. Poole-Wilson (2004). "The Warfarin/Aspirin Study in Heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure." Am Heart J **148**(1): 157-164.

Cohen, L. M., R. Ruthazer, A. H. Moss and M. J. Germain (2010). "Predicting six-month mortality for patients who are on maintenance hemodialysis." Clin J Am Soc Nephrol **5**(1): 72-79.

Cohn, J. N., G. Johnson, S. Ziesche, F. Cobb, G. Francis, F. Tristani, R. Smith, W. B. Dunkman, H. Loeb, M. Wong and et al. (1991). "A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure." N Engl J Med **325**(5): 303-310.

Cole, G. D., N. M. Dhutia, M. J. Shun-Shin, K. Willson, J. Harrison, C. E. Raphael, M. Zolgharni, J. Mayet and D. P. Francis (2015). "Defining the real-world reproducibility of visual grading of left ventricular function and visual estimation of left ventricular ejection fraction: impact of image quality, experience and accreditation." Int J Cardiovasc Imaging **31**(7): 1303-1314.

Connerney, I. and P. A. Shapiro (2011). "Assessment of depression in heart failure patients: what is the role for cardiology?" J Am Coll Cardiol **57**(4): 424-426.

Conrad, N., A. Judge, J. Tran, H. Mohseni, D. Hedgecott, A. P. Crespillo, M. Allison, H. Hemingway, J. G. Cleland, J. J. V. McMurray and K. Rahimi (2018). "Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals." Lancet **391**(10120): 572-580.

CONSENSUS (1987). "Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)." N Engl J Med **316**(23): 1429-1435.

Corletto, A., H. Frohlich, T. Tager, M. Hochadel, R. Zahn, C. Kilkowski, R. Winkler, J. Senges, H. A. Katus and L. Frankenstein (2018). "Beta blockers and chronic heart failure patients: prognostic impact of a dose targeted beta blocker therapy vs. heart rate targeted strategy." Clin Res Cardiol **107**(11): 1040-1049.

Cowie, M. R., J. Schope, S. Wagenpfeil, L. Tavazzi, M. Bohm, P. Ponikowski, S. D. Anker, G. S. Filippatos, M. Komajda and Q. Investigators (2021). "Patient factors associated with titration of medical therapy in patients with heart failure with reduced ejection fraction: data from the QUALIFY international registry." ESC Heart Fail **8**(2): 861-871.

Cubbon, R. M., B. Adams, A. Rajwani, B. N. Mercer, P. A. Patel, G. Gherardi, C. P. Gale, P. D. Batin, R. Ajjan, L. Kearney, S. B. Wheatcroft, R. J. Sapsford, K. K. Witte and M. T. Kearney (2013). "Diabetes mellitus is associated with adverse prognosis in chronic heart failure of ischaemic and non-ischaemic aetiology." Diab Vasc Dis Res **10**(4): 330-336.

Cubbon, R. M., C. P. Gale, L. C. Kearney, C. B. Schechter, W. P. Brooksby, J. Nolan, K. A. Fox, A. Rajwani, W. Baig, D. Groves, P. Barlow, A. C. Fisher, P. D. Batin, M. B. Kahn, A. G. Zaman, A. M. Shah, J. A. Byrne, S. J. Lindsay, R. J. Sapsford, S. B. Wheatcroft, K. K. Witte and M. T. Kearney (2011). "Changing characteristics and mode of death associated with chronic heart failure caused by left ventricular systolic dysfunction: a study across therapeutic eras." Circ Heart Fail **4**(4): 396-403.

Cubbon, R. M. and K. K. Witte (2009). "Cardiac resynchronisation therapy for chronic heart failure and conduction delay." BMJ **338**: b1265.

Curtis, J. R., E. K. Kross and R. D. Stapleton (2020). "The Importance of Addressing Advance Care Planning and Decisions About Do-Not-Resuscitate Orders During Novel Coronavirus 2019 (COVID-19)." JAMA **323**(18): 1771-1772.

Da Silva Gane, M., A. Braun, D. Stott, D. Wellsted and K. Farrington (2013). "How robust is the 'surprise question' in predicting short-term mortality risk in haemodialysis patients?" Nephron Clin Pract **123**(3-4): 185-193.

Daniels, L. B. and A. S. Maisel (2007). "Natriuretic peptides." J Am Coll Cardiol **50**(25): 2357-2368.

DIG (1997). "The effect of digoxin on mortality and morbidity in patients with heart failure." N Engl J Med **336**(8): 525-533.

Docherty, A. B., E. M. Harrison, C. A. Green, H. E. Hardwick, R. Pius, L. Norman, K. A. Holden, J. M. Read, F. Dondelinger, G. Carson, L. Merson, J. Lee, D. Plotkin, L. Sigfrid, S. Halpin, C. Jackson, C. Gamble, P. W. Horby, J. S. Nguyen-Van-Tam, A. Ho, C. D. Russell, J. Dunning, P. J. Openshaw, J. K. Baillie, M. G. Semple and I. C. investigators (2020). "Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study." BMJ **369**: m1985.

Doughty, R. N., S. MacMahon and N. Sharpe (1994). "Beta-blockers in heart failure: promising or proved?" J Am Coll Cardiol **23**(3): 814-821.

Downar, J., R. Goldman, R. Pinto, M. Englesakis and N. K. Adhikari (2017). "The "surprise question" for predicting death in seriously ill patients: a systematic review and meta-analysis." CMAJ **189**(13): E484-E493.

Drozd, M., E. Garland, A. M. N. Walker, T. A. Slater, A. Koshy, S. Straw, J. Gierula, M. Paton, J. Lowry, R. Sapsford, K. K. Witte, M. T. Kearney and R. M. Cubbon (2020). "Infection-Related Hospitalization in Heart Failure With Reduced Ejection Fraction: A Prospective Observational Cohort Study." Circ Heart Fail **13**(5): e006746.

Drozd, M., S. D. Relton, A. M. N. Walker, T. A. Slater, J. Gierula, M. F. Paton, J. Lowry, S. Straw, A. Koshy, M. McGinlay, A. D. Simms, V. K. Gatenby, R. J. Sapsford, K. K. Witte, M. T. Kearney and R. M. Cubbon (2021). "Association of heart failure and its comorbidities with loss of life expectancy." Heart **107**(17): 1417-1421.

Edelmann, F., R. Wachter, A. G. Schmidt, E. Kraigher-Krainer, C. Colantonio, W. Kamke, A. Duvinage, R. Stahrenberg, K. Durstewitz, M. Loffler, H. D. Dungen, C. Tschope, C. Herrmann-Lingen, M. Halle, G. Hasenfuss, G. Gelbrich, B. Pieske and D. H. F. I. Aldo (2013). "Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial." JAMA **309**(8): 781-791.

Eichhorn, E. J. and M. R. Bristow (2001). "The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial." Curr Control Trials Cardiovasc Med **2**(1): 20-23.

Fenning, S., R. Woolcock, K. Haga, J. Iqbal, K. A. Fox, S. A. Murray and M. A. Denvir (2012). "Identifying acute coronary syndrome patients approaching end-of-life." PLoS One **7**(4): e35536.

Feyi, K., S. Klinger, G. Pharro, L. McNally, A. James, K. Gretton and M. K. Almond (2015). "Predicting palliative care needs and mortality in end stage renal disease: use of an at-risk register." BMJ Support Palliat Care **5**(1): 19-25.

Folse, R. and E. Braunwald (1962). "Determination of fraction of left ventricular volume ejected per beat and of ventricular end-diastolic and residual volumes. Experimental and clinical observations with a precordial dilution technic." Circulation **25**: 674-685.

Fonarow, G. C., W. G. Stough, W. T. Abraham, N. M. Albert, M. Gheorghiade, B. H. Greenberg, C. M. O'Connor, J. L. Sun, C. W. Yancy, J. B. Young, O.-H. Investigators and Hospitals (2007). "Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry." J Am Coll Cardiol **50**(8): 768-777.

Fowler, M. B., S. R. Lottes, J. J. Nelson, M. A. Lukas, E. M. Gilbert, B. Greenberg, B. M. Massie, W. T. Abraham, J. A. Franciosa and C. P. Physicians (2007). "Beta-

blocker dosing in community-based treatment of heart failure." Am Heart J **153**(6): 1029-1036.

Freedland, K. E., R. M. Carney, M. W. Rich, B. C. Steinmeyer and E. H. Rubin (2015). "Cognitive Behavior Therapy for Depression and Self-Care in Heart Failure Patients: A Randomized Clinical Trial." JAMA Intern Med **175**(11): 1773-1782.

Garg, R. and S. Yusuf (1995). "Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials." JAMA **273**(18): 1450-1456.

Gheorghiade, M., M. Bohm, S. J. Greene, G. C. Fonarow, E. F. Lewis, F. Zannad, S. D. Solomon, F. Baschiera, J. Botha, T. A. Hua, C. R. Gimpelewicz, X. Jaumont, A. Lesogor, A. P. Maggioni, A. Investigators and Coordinators (2013). "Effect of aliskiren on postdischarge mortality and heart failure readmissions among patients hospitalized for heart failure: the ASTRONAUT randomized trial." JAMA **309**(11): 1125-1135.

Ghinai, I., T. D. McPherson, J. C. Hunter, H. L. Kirking, D. Christiansen, K. Joshi, R. Rubin, S. Morales-Estrada, S. R. Black, M. Pacilli, M. J. Fricchione, R. K. Chugh, K. A. Walblay, N. S. Ahmed, W. C. Stoecker, N. F. Hasan, D. P. Burdsall, H. E. Reese, M. Wallace, C. Wang, D. Moeller, J. Korpics, S. A. Novosad, I. Benowitz, M. W. Jacobs, V. S. Dasari, M. T. Patel, J. Kauerauf, E. M. Charles, N. O. Ezike, V. Chu, C. M. Midgley, M. A. Rolfes, S. I. Gerber, X. Lu, S. Lindstrom, J. R. Verani, J. E. Layden and C.-I. T. Illinois (2020). "First known person-to-person transmission of severe

acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the USA." Lancet **395**(10230): 1137-1144.

Gierula, J., R. M. Cubbon, M. F. Paton, R. Byrom, J. E. Lowry, S. F. Winsor, M. McGinlay, E. Sunley, E. Pickles, L. C. Kearney, A. Koshy, T. A. Slater, H. K. Chumun, H. A. Jamil, K. M. Bailey, J. H. Barth, M. T. Kearney and K. K. Witte (2019). "Prospective evaluation and long-term follow-up of patients referred to secondary care based upon natriuretic peptide levels in primary care." Eur Heart J Qual Care Clin Outcomes **5**(3): 218-224.

Gierula, J., J. E. Lowry, M. F. Paton, C. A. Cole, R. Byrom, A. O. Koshy, H. Chumun, L. C. Kearney, S. Straw, T. S. Bowen, R. M. Cubbon, A. M. Keenan, D. D. Stocken, M. T. Kearney and K. K. Witte (2020). "Personalized Rate-Response Programming Improves Exercise Tolerance After 6 Months in People With Cardiac Implantable Electronic Devices and Heart Failure: A Phase II Study." Circulation **141**(21): 1693-1703.

Ginzton, L. E., M. M. Laks, M. Brizendine, R. Conant and I. Mena (1984). "Noninvasive measurement of the rest and exercise peak systolic pressure/end-systolic volume ratio: a sensitive two-dimensional echocardiographic indicator of left ventricular function." J Am Coll Cardiol **4**(3): 509-516.

Godfrey, C., M. B. Harrison, J. Medves and J. E. Tranmer (2006). "The symptom of pain with heart failure: a systematic review." J Card Fail **12**(4): 307-313.

Gold, M. R., J. Rickard, J. C. Daubert, P. Zimmerman and C. Linde (2021). "Redefining the Classifications of Response to Cardiac Resynchronization Therapy: Results From the REVERSE Study." JACC Clin Electrophysiol **7**(7): 871-880.

Goodlin, S. J., P. J. Hauptman, R. Arnold, K. Grady, R. E. Hershberger, J. Kutner, F. Masoudi, J. Spertus, K. Dracup, J. F. Cleary, R. Medak, K. Crispell, I. Pina, B. Stuart, C. Whitney, T. Rector, J. Teno and D. G. Renlund (2004). "Consensus statement: Palliative and supportive care in advanced heart failure." J Card Fail **10**(3): 200-209.

Goodlin, S. J., R. Trupp, P. Bernhardt, K. L. Grady and K. Dracup (2007). "Development and evaluation of the "Advanced Heart Failure Clinical Competence Survey": a tool to assess knowledge of heart failure care and self-assessed competence." Patient Educ Couns **67**(1-2): 3-10.

Goodlin, S. J., S. Wingate, N. M. Albert, S. J. Pressler, J. Houser, J. Kwon, J. Chiong, C. P. Storey, T. Quill, J. R. Teerlink and P.-H. Investigators (2012). "Investigating pain in heart failure patients: the pain assessment, incidence, and nature in heart failure (PAIN-HF) study." J Card Fail **18**(10): 776-783.

Gottdiener, J. S., J. Bednarz, R. Devereux, J. Gardin, A. Klein, W. J. Manning, A. Morehead, D. Kitzman, J. Oh, M. Quinones, N. B. Schiller, J. H. Stein, N. J. Weissman and E. American Society of (2004). "American Society of Echocardiography recommendations for use of echocardiography in clinical trials." J Am Soc Echocardiogr **17**(10): 1086-1119.

Granger, C. B., J. J. McMurray, S. Yusuf, P. Held, E. L. Michelson, B. Olofsson, J. Ostergren, M. A. Pfeffer, K. Swedberg, C. Investigators and Committees (2003). "Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial." Lancet **362**(9386): 772-776.

Grasselli, G., M. Greco, A. Zanella, G. Albano, M. Antonelli, G. Bellani, E. Bonanomi, L. Cabrini, E. Carlesso, G. Castelli, S. Cattaneo, D. Cereda, S. Colombo, A. Coluccello, G. Crescini, A. Forastieri Molinari, G. Foti, R. Fumagalli, G. A. Iotti, T. Langer, N. Latronico, F. L. Lorini, F. Mojoli, G. Natalini, C. M. Pessina, V. M. Ranieri, R. Rech, L. Scudeller, A. Rosano, E. Storti, B. T. Thompson, M. Tirani, P. G. Villani, A. Pesenti, M. Cecconi and C.-L. I. Network (2020). "Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy." JAMA Intern Med **180**(10): 1345-1355.

Grasselli, G., A. Zangrillo, A. Zanella, M. Antonelli, L. Cabrini, A. Castelli, D. Cereda, A. Coluccello, G. Foti, R. Fumagalli, G. Iotti, N. Latronico, L. Lorini, S. Merler, G. Natalini, A. Piatti, M. V. Ranieri, A. M. Scandroglio, E. Storti, M. Cecconi, A. Pesenti and C.-L. I. Network (2020). "Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy." JAMA **323**(16): 1574-1581.

Green, C. P., C. B. Porter, D. R. Bresnahan and J. A. Spertus (2000). "Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure." J Am Coll Cardiol **35**(5): 1245-1255.

Greene, S. J., J. Butler, N. M. Albert, A. D. DeVore, P. P. Sharma, C. I. Duffy, C. L. Hill, K. McCague, X. Mi, J. H. Patterson, J. A. Spertus, L. Thomas, F. B. Williams, A. F. Hernandez and G. C. Fonarow (2018). "Medical Therapy for Heart Failure With Reduced Ejection Fraction: The CHAMP-HF Registry." J Am Coll Cardiol **72**(4): 351-366.

Greene, S. J., G. C. Fonarow, A. D. DeVore, P. P. Sharma, M. Vaduganathan, N. M. Albert, C. I. Duffy, C. L. Hill, K. McCague, J. H. Patterson, J. A. Spertus, L. Thomas, F. B. Williams, A. F. Hernandez and J. Butler (2019). "Titration of Medical Therapy for Heart Failure With Reduced Ejection Fraction." J Am Coll Cardiol **73**(19): 2365-2383.

Gros, C., A. Souque, J. C. Schwartz, J. Duchier, A. Cournot, P. Baumer and J. M. Lecomte (1989). "Protection of atrial natriuretic factor against degradation: diuretic and natriuretic responses after in vivo inhibition of enkephalinase (EC 3.4.24.11) by acetorphan." Proc Natl Acad Sci U S A **86**(19): 7580-7584.

Guan, W. J., Z. Y. Ni, Y. Hu, W. H. Liang, C. Q. Ou, J. X. He, L. Liu, H. Shan, C. L. Lei, D. S. C. Hui, B. Du, L. J. Li, G. Zeng, K. Y. Yuen, R. C. Chen, C. L. Tang, T. Wang, P. Y. Chen, J. Xiang, S. Y. Li, J. L. Wang, Z. J. Liang, Y. X. Peng, L. Wei, Y. Liu, Y. H. Hu, P. Peng, J. M. Wang, J. Y. Liu, Z. Chen, G. Li, Z. J. Zheng, S. Q. Qiu, J. Luo, C. J. Ye, S. Y. Zhu, N. S. Zhong and C. China Medical Treatment Expert Group for (2020). "Clinical Characteristics of Coronavirus Disease 2019 in China." N Engl J Med **382**(18): 1708-1720.

Gupta, S., S. S. Hayek, W. Wang, L. Chan, K. S. Mathews, M. L. Melamed, S. K. Brenner, A. Leonberg-Yoo, E. J. Schenck, J. Radbel, J. Reiser, A. Bansal, A. Srivastava, Y. Zhou, A. Sutherland, A. Green, A. M. Shehata, N. Goyal, A. Vijayan, J. C. Q. Velez, S. Shaefi, C. R. Parikh, J. Arunthamakun, A. M. Athavale, A. N. Friedman, S. A. P. Short, Z. A. Kibbelaar, S. Abu Omar, A. J. Admon, J. P. Donnelly, H. B. Gershengorn, M. A. Hernan, M. W. Semler, D. E. Leaf and S.-C. Investigators (2020). "Factors Associated With Death in Critically Ill Patients With Coronavirus Disease 2019 in the US." JAMA Intern Med **180**(11): 1436-1447.

Haedersdal, C., J. K. Madsen and K. Saunamaki (1993). "The left ventricular end-systolic pressure and pressure-volume index. Comparison between invasive and auscultatory arm pressure measurements." Angiology **44**(12): 959-964.

Haga, K., S. Murray, J. Reid, A. Ness, M. O'Donnell, D. Yellowlees and M. A. Denvir (2012). "Identifying community based chronic heart failure patients in the last year of life: a comparison of the Gold Standards Framework Prognostic Indicator Guide and the Seattle Heart Failure Model." Heart **98**(7): 579-583.

Halliday, B. P., R. Wassall, A. S. Lota, Z. Khalique, J. Gregson, S. Newsome, R. Jackson, T. Rahneva, R. Wage, G. Smith, L. Venneri, U. Tayal, D. Auger, W. Midwinter, N. Whiffin, R. Rajani, J. N. Dungu, A. Pantazis, S. A. Cook, J. S. Ware, A. J. Baksi, D. J. Pennell, S. D. Rosen, M. R. Cowie, J. G. F. Cleland and S. K. Prasad (2019). "Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial." Lancet **393**(10166): 61-73.

Hamano, J., T. Morita, S. Inoue, M. Ikenaga, Y. Matsumoto, R. Sekine, T. Yamaguchi, T. Hirohashi, T. Tajima, R. Tatara, H. Watanabe, H. Otani, C. Takigawa, Y. Matsuda, H. Nagaoka, M. Mori, N. Yamamoto, M. Shimizu, T. Sasara and H. Kinoshita (2015). "Surprise Questions for Survival Prediction in Patients With Advanced Cancer: A Multicenter Prospective Cohort Study." Oncologist **20**(7): 839-844.

Hampton, J. R., D. J. van Veldhuisen, F. X. Kleber, A. J. Cowley, A. Ardia, P. Block, A. Cortina, L. Cserhalmi, F. Follath, G. Jensen, J. Kayanakis, K. I. Lie, G. Mancia and A. M. Skene (1997). "Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure. Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME II) Investigators." Lancet **349**(9057): 971-977.

Haydar, S. A., L. Almeder, L. Michalakes, P. K. J. Han and T. D. Strout (2017). "Using the Surprise Question To Identify Those with Unmet Palliative Care Needs in Emergency and Inpatient Settings: What Do Clinicians Think?" J Palliat Med **20**(7): 729-735.

Heerspink, H. J. L., B. V. Stefansson, R. Correa-Rotter, G. M. Chertow, T. Greene, F. F. Hou, J. F. E. Mann, J. J. V. McMurray, M. Lindberg, P. Rossing, C. D. Sjostrom, R. D. Toto, A. M. Langkilde, D. C. Wheeler, D.-C. T. Committees and Investigators (2020). "Dapagliflozin in Patients with Chronic Kidney Disease." N Engl J Med **383**(15): 1436-1446.

Hernandez, A. F., B. G. Hammill, C. M. O'Connor, K. A. Schulman, L. H. Curtis and G. C. Fonarow (2009). "Clinical effectiveness of beta-blockers in heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) Registry." J Am Coll Cardiol **53**(2): 184-192.

Hicks, K. A., K. W. Mahaffey, R. Mehran, S. E. Nissen, S. D. Wiviott, B. Dunn, S. D. Solomon, J. R. Marler, J. R. Teerlink, A. Farb, D. A. Morrow, S. L. Targum, C. A. Sila, M. T. Thanh Hai, M. R. Jaff, H. V. Joffe, D. E. Cutlip, A. S. Desai, E. F. Lewis, C. M. Gibson, M. J. Landray, A. M. Lincoff, C. J. White, S. S. Brooks, K. Rosenfield, M. J. Domanski, A. J. Lansky, J. J. V. McMurray, J. E. Tcheng, S. R. Steinhubl, P. Burton, L. Mauri, C. M. O'Connor, M. A. Pfeffer, H. M. J. Hung, N. L. Stockbridge, B. R. Chaitman, R. J. Temple and I. Standardized Data Collection for Cardiovascular Trials (2018). "2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials." J Am Coll Cardiol **71**(9): 1021-1034.

Hill, L., T. Prager Geller, R. Baruah, J. M. Beattie, J. Boyne, N. de Stoutz, G. Di Stolfo, E. Lambrinou, A. K. Skibelund, I. Uchmanowicz, F. H. Rutten, J. Celutkiene, M. F. Piepoli, E. A. Jankowska, O. Chioncel, T. Ben Gal, P. M. Seferovic, F. Ruschitzka, A. J. S. Coats, A. Stromberg and T. Jaarsma (2020). "Integration of a palliative approach into heart failure care: a European Society of Cardiology Heart Failure Association position paper." Eur J Heart Fail **22**(12): 2327-2339.

Hippisley-Cox, J., D. Young, C. Coupland, K. M. Channon, P. S. Tan, D. A. Harrison, K. Rowan, P. Aveyard, I. D. Pavord and P. J. Watkinson (2020). "Risk of severe

COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: cohort study including 8.3 million people." Heart **106**(19): 1503-1511.

Horby, P., W. S. Lim, J. R. Emberson, M. Mafham, J. L. Bell, L. Linsell, N. Staplin, C. Brightling, A. Ustianowski, E. Elmahi, B. Prudon, C. Green, T. Felton, D. Chadwick, K. Rege, C. Fegan, L. C. Chappell, S. N. Faust, T. Jaki, K. Jeffery, A. Montgomery, K. Rowan, E. Juszczak, J. K. Baillie, R. Haynes and M. J. Landray (2021). "Dexamethasone in Hospitalized Patients with Covid-19." N Engl J Med **384**(8): 693-704.

Horne, G. and S. Payne (2004). "Removing the boundaries: palliative care for patients with heart failure." Palliat Med **18**(4): 291-296.

Hsia, D. S., O. Grove and W. T. Cefalu (2017). "An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus." Curr Opin Endocrinol Diabetes Obes **24**(1): 73-79.

Huang, C., Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang and B. Cao (2020). "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China." Lancet **395**(10223): 497-506.

Hui, D. (2015). "Prognostication of Survival in Patients With Advanced Cancer: Predicting the Unpredictable?" Cancer Control **22**(4): 489-497.

Hunt, S. A., W. T. Abraham, M. H. Chin, A. M. Feldman, G. S. Francis, T. G. Ganiats, M. Jessup, M. A. Konstam, D. M. Mancini, K. Michl, J. A. Oates, P. S. Rahko, M. A. Silver, L. W. Stevenson, C. W. Yancy, E. M. Antman, S. C. Smith, Jr., C. D. Adams, J. L. Anderson, D. P. Faxon, V. Fuster, J. L. Halperin, L. F. Hiratzka, A. K. Jacobs, R. Nishimura, J. P. Ornato, R. L. Page, B. Riegel, C. American College of, G. American Heart Association Task Force on Practice, P. American College of Chest, H. International Society for, T. Lung and S. Heart Rhythm (2005). "ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society." Circulation **112**(12): e154-235.

Ibrahim, J. G., H. Chu and L. M. Chen (2010). "Basic concepts and methods for joint models of longitudinal and survival data." J Clin Oncol **28**(16): 2796-2801.

Jaarsma, T., J. M. Beattie, M. Ryder, F. H. Rutten, T. McDonagh, P. Mohacsi, S. A. Murray, T. Grodzicki, I. Bergh, M. Metra, I. Ekman, C. Angermann, M. Leventhal, A. Pitsis, S. D. Anker, A. Gavazzi, P. Ponikowski, K. Dickstein, E. Delacretaz, L. Blue, F. Strasser, J. McMurray and H. F. A. o. t. E. S. C. Advanced Heart Failure Study Group of the (2009). "Palliative care in heart failure: a position statement from the palliative care workshop of the Heart Failure Association of the European Society of Cardiology." Eur J Heart Fail **11**(5): 433-443.

Jamil, H. A., J. Gierula, M. F. Paton, R. Byrom, J. E. Lowry, R. M. Cubbon, D. A. Cairns, M. T. Kearney and K. K. Witte (2016). "Chronotropic Incompetence Does Not Limit Exercise Capacity in Chronic Heart Failure." J Am Coll Cardiol **67**(16): 1885-1896.

Janssen, D. J. A., M. J. Johnson and M. A. Spruit (2018). "Palliative care needs assessment in chronic heart failure." Curr Opin Support Palliat Care **12**(1): 25-31.

Javier, A. D., R. Figueroa, E. D. Siew, H. Salat, J. Morse, T. G. Stewart, R. Malhotra, M. Jhamb, J. O. Schell, C. Y. Cardona, C. A. Maxwell, T. A. Ikizler and K. Abdel-Kader (2017). "Reliability and Utility of the Surprise Question in CKD Stages 4 to 5." Am J Kidney Dis **70**(1): 93-101.

Jensen, M. T., J. L. Marott, P. Lange, J. Vestbo, P. Schnohr, O. W. Nielsen, J. S. Jensen and G. B. Jensen (2013). "Resting heart rate is a predictor of mortality in COPD." Eur Respir J **42**(2): 341-349.

Jiang, W., J. Alexander, E. Christopher, M. Kuchibhatla, L. H. Gaulden, M. S. Cuffe, M. A. Blazing, C. Davenport, R. M. Califf, R. R. Krishnan and C. M. O'Connor (2001). "Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure." Arch Intern Med **161**(15): 1849-1856.

Johansson, I., P. Joseph, K. Balasubramanian, J. J. V. McMurray, L. H. Lund, J. A. Ezekowitz, D. Kamath, K. Alhabib, A. Bayes-Genis, A. Budaj, A. L. L. Dans, A. Dzudie, J. L. Probstfield, K. A. A. Fox, K. M. Karaye, A. Makubi, B. Fukakusa, K. Teo, A. Temizhan, T. Wittlinger, A. P. Maggioni, F. Lanas, P. Lopez-Jaramillo, J.

Silva-Cardoso, K. Sliwa, H. Dokainish, A. Grinvalds, T. McCready, S. Yusuf and G. C. Investigators (2021). "Health-Related Quality of Life and Mortality in Heart Failure: The Global Congestive Heart Failure Study of 23 000 Patients From 40 Countries." Circulation **143**(22): 2129-2142.

Johnson, M., A. Nunn, T. Hawkes, S. Stockdale and A. Daley (2012). "Planning for end-of-life care in heart failure: experience of two integrated cardiology-palliative care teams." Br J Cardiol. **19**: 71-75.

Johnson, M. J., T. A. McDonagh, A. Harkness, S. E. McKay and H. J. Dargie (2002). "Morphine for the relief of breathlessness in patients with chronic heart failure--a pilot study." Eur J Heart Fail **4**(6): 753-756.

Kahn, J. C., M. Patey, J. L. Dubois-Rande, P. Merlet, A. Castaigne, C. Lim-Alexandre, J. M. Lecomte, D. Duboc, C. Gros and J. C. Schwartz (1990). "Effect of sinorphan on plasma atrial natriuretic factor in congestive heart failure." Lancet **335**(8681): 118-119.

Kearney, M. T., K. A. Fox, A. J. Lee, R. J. Prescott, A. M. Shah, P. D. Batin, W. Baig, S. Lindsay, T. S. Callahan, W. E. Shell, D. L. Eckberg, A. G. Zaman, S. Williams, J. M. Neilson and J. Nolan (2002). "Predicting death due to progressive heart failure in patients with mild-to-moderate chronic heart failure." J Am Coll Cardiol **40**(10): 1801-1808.

Kindermann, I., D. Fischer, J. Karbach, A. Link, K. Walenta, C. Barth, C. Ukena, F. Mahfoud, V. Kollner, M. Kindermann and M. Bohm (2012). "Cognitive function in

patients with decompensated heart failure: the Cognitive Impairment in Heart Failure (CogImpair-HF) study." Eur J Heart Fail **14**(4): 404-413.

Kjekshus, J., E. Apetrei, V. Barrios, M. Bohm, J. G. Cleland, J. H. Cornel, P. Dunselman, C. Fonseca, A. Goudev, P. Grande, L. Gullestad, A. Hjalmarson, J. Hradec, A. Janosi, G. Kamensky, M. Komajda, J. Korewicki, T. Kuusi, F. Mach, V. Mareev, J. J. McMurray, N. Ranjith, M. Schaufelberger, J. Vanhaecke, D. J. van Veldhuisen, F. Waagstein, H. Wedel, J. Wikstrand and C. Group (2007). "Rosuvastatin in older patients with systolic heart failure." N Engl J Med **357**(22): 2248-2261.

Kober, L., J. J. Thune, J. C. Nielsen, J. Haarbo, L. Videbaek, E. Korup, G. Jensen, P. Hildebrandt, F. H. Steffensen, N. E. Bruun, H. Eiskjaer, A. Brandes, A. M. Thogersen, F. Gustafsson, K. Egstrup, R. Videbaek, C. Hassager, J. H. Svendsen, D. E. Hofsten, C. Torp-Pedersen, S. Pehrson and D. Investigators (2016). "Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure." N Engl J Med **375**(13): 1221-1230.

Koh, A. S., W. T. Tay, T. H. K. Teng, O. Vedin, L. Benson, U. Dahlstrom, G. Savarese, C. S. P. Lam and L. H. Lund (2017). "A comprehensive population-based characterization of heart failure with mid-range ejection fraction." Eur J Heart Fail **19**(12): 1624-1634.

Komajda, M., P. Lapuerta, N. Hermans, J. R. Gonzalez-Juanatey, D. J. van Veldhuisen, E. Erdmann, L. Tavazzi, P. Poole-Wilson and C. Le Pen (2005).

"Adherence to guidelines is a predictor of outcome in chronic heart failure: the MAHLER survey." Eur Heart J **26**(16): 1653-1659.

Komajda, M., J. Schope, S. Wagenpfeil, L. Tavazzi, M. Bohm, P. Ponikowski, S. D. Anker, G. S. Filippatos, M. R. Cowie and Q. Investigators (2019). "Physicians' guideline adherence is associated with long-term heart failure mortality in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry." Eur J Heart Fail **21**(7): 921-929.

Konstam, M. A., M. Gheorghiade, J. C. Burnett, Jr., L. Grinfeld, A. P. Maggioni, K. Swedberg, J. E. Udelson, F. Zannad, T. Cook, J. Ouyang, C. Zimmer, C. Orlandi and I. Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (2007). "Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial." JAMA **297**(12): 1319-1331.

Koshy, A. O., E. R. Gallivan, M. McGinlay, S. Straw, M. Drozd, A. G. Toms, J. Gierula, R. M. Cubbon, M. T. Kearney and K. K. Witte (2020). "Prioritizing symptom management in the treatment of chronic heart failure." ESC Heart Fail **7**(5): 2193-2207.

Kraigher-Krainer, E., A. M. Shah, D. K. Gupta, A. Santos, B. Claggett, B. Pieske, M. R. Zile, A. A. Voors, M. P. Lefkowitz, M. Packer, J. J. McMurray, S. D. Solomon and P. Investigators (2014). "Impaired systolic function by strain imaging in heart failure with preserved ejection fraction." J Am Coll Cardiol **63**(5): 447-456.

Kramer, D. B., B. Lo and N. W. Dickert (2020). "CPR in the Covid-19 Era - An Ethical Framework." N Engl J Med **383**(2): e6.

Lahousse, L., M. N. Niemeijer, M. E. van den Berg, P. R. Rijnbeek, G. F. Joos, A. Hofman, O. H. Franco, J. W. Deckers, M. Eijgelsheim, B. H. Stricker and G. G. Brusselle (2015). "Chronic obstructive pulmonary disease and sudden cardiac death: the Rotterdam study." Eur Heart J **36**(27): 1754-1761.

Lakin, J. R., M. G. Robinson, R. E. Bernacki, B. W. Powers, S. D. Block, R. Cunningham and Z. Obermeyer (2016). "Estimating 1-Year Mortality for High-Risk Primary Care Patients Using the "Surprise" Question." JAMA Intern Med **176**(12): 1863-1865.

Landis, J. R. and G. G. Koch (1977). "The measurement of observer agreement for categorical data." Biometrics **33**(1): 159-174.

Lang, R. M., L. P. Badano, V. Mor-Avi, J. Afilalo, A. Armstrong, L. Ernande, F. A. Flachskampf, E. Foster, S. A. Goldstein, T. Kuznetsova, P. Lancellotti, D. Muraru, M. H. Picard, E. R. Rietzschel, L. Rudski, K. T. Spencer, W. Tsang and J. U. Voigt (2015). "Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging." J Am Soc Echocardiogr **28**(1): 1-39 e14.

Lang, R. M., L. P. Badano, V. Mor-Avi, J. Afilalo, A. Armstrong, L. Ernande, F. A. Flachskampf, E. Foster, S. A. Goldstein, T. Kuznetsova, P. Lancellotti, D. Muraru, M.

H. Picard, E. R. Rietzschel, L. Rudski, K. T. Spencer, W. Tsang and J. U. Voigt (2015). "Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging." Eur Heart J Cardiovasc Imaging **16**(3): 233-270.

Lang, R. M., M. Bierig, R. B. Devereux, F. A. Flachskampf, E. Foster, P. A. Pellikka, M. H. Picard, M. J. Roman, J. Seward, J. Shanewise, S. Solomon, K. T. Spencer, M. St John Sutton, W. Stewart, N. American Society of Echocardiography's, C. Standards, Q. Task Force on Chamber, C. American College of Cardiology Echocardiography, A. American Heart and E. S. o. C. European Association of Echocardiography (2006). "Recommendations for chamber quantification." Eur J Echocardiogr **7**(2): 79-108.

Larghat, A. M., P. P. Swoboda, J. D. Biglands, M. T. Kearney, J. P. Greenwood and S. Plein (2014). "The microvascular effects of insulin resistance and diabetes on cardiac structure, function, and perfusion: a cardiovascular magnetic resonance study." Eur Heart J Cardiovasc Imaging **15**(12): 1368-1376.

Lewis, G. D., K. F. Docherty, A. A. Voors, A. Cohen-Solal, M. Metra, D. J. Whellan, J. A. Ezekowitz, P. Ponikowski, M. Bohm, J. R. Teerlink, S. B. Heitner, S. Kupfer, F. I. Malik, L. Meng and G. M. Felker (2022). "Developments in Exercise Capacity Assessment in Heart Failure Clinical Trials and the Rationale for the Design of METEORIC-HF." Circ Heart Fail: CIRCHEARTFAILURE121008970.

Lund, L. H. (2018). "Heart Failure with Mid-range Ejection Fraction: Lessons from CHARM." Card Fail Rev **4**(2): 70-72.

Lund, L. H., B. Claggett, J. Liu, C. S. Lam, P. S. Jhund, G. M. Rosano, K. Swedberg, S. Yusuf, C. B. Granger, M. A. Pfeffer, J. J. V. McMurray and S. D. Solomon (2018). "Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum." Eur J Heart Fail **20**(8): 1230-1239.

MacIver, J., V. Rao, D. H. Delgado, N. Desai, J. Ivanov, S. Abbey and H. J. Ross (2008). "Choices: a study of preferences for end-of-life treatments in patients with advanced heart failure." J Heart Lung Transplant **27**(9): 1002-1007.

Malhotra, R., X. Tao, Y. Wang, Y. Chen, R. H. Apruzzese, P. Balter, Q. Xiao, L. A. Usvyat, P. Kotanko and S. Thijssen (2017). "Performance of the Surprise Question Compared to Prediction Models in Hemodialysis Patients: A Prospective Study." Am J Nephrol **46**(5): 390-396.

Martens, P., M. Dupont, J. Dauw, P. Nijst, L. Herbots, P. Dendale, P. Vandervoort, L. Bruckers, W. H. W. Tang and W. Mullens (2021). "The effect of intravenous ferric carboxymaltose on cardiac reverse remodelling following cardiac resynchronization therapy-the IRON-CRT trial." Eur Heart J **42**(48): 4905-4914.

Maurer, M. S. and M. Packer (2020). "How Should Physicians Assess Myocardial Contraction?: Redefining Heart Failure With a Preserved Ejection Fraction." JACC Cardiovasc Imaging **13**(3): 873-878.

McDonagh, T. A., M. Metra, M. Adamo, R. S. Gardner, A. Baumbach, M. Bohm, H. Burri, J. Butler, J. Celutkiene, O. Chioncel, J. G. F. Cleland, A. J. S. Coats, M. G. Crespo-Leiro, D. Farmakis, M. Gilard, S. Heymans, A. W. Hoes, T. Jaarsma, E. A. Jankowska, M. Lainscak, C. S. P. Lam, A. R. Lyon, J. J. V. McMurray, A. Mebazaa, R. Mindham, C. Muneretto, M. Francesco Piepoli, S. Price, G. M. C. Rosano, F. Ruschitzka, A. Kathrine Skibelund and E. S. C. S. D. Group (2021). "2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure." Eur Heart J **42**(36): 3599-3726.

McGinlay, M., S. Straw, R. Byrom-Goulthorp, S. D. Relton, J. Gierula, R. M. Cubbon, M. T. Kearney and K. K. Witte (2022). "Suboptimal Dosing of beta-Blockers in Chronic Heart Failure: A Missed Opportunity?" J Cardiovasc Nurs **37**(6): 589-594.

McIlvennan, C. K. and L. A. Allen (2016). "Palliative care in patients with heart failure." BMJ **353**: i1010.

McMurray, J. J., J. Ostergren, K. Swedberg, C. B. Granger, P. Held, E. L. Michelson, B. Olofsson, S. Yusuf, M. A. Pfeffer, C. Investigators and Committees (2003). "Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial." Lancet **362**(9386): 767-771.

McMurray, J. J., M. Packer, A. S. Desai, J. Gong, M. P. Lefkowitz, A. R. Rizkala, J. L. Rouleau, V. C. Shi, S. D. Solomon, K. Swedberg, M. R. Zile, P.-H. Investigators and Committees (2014). "Angiotensin-neprilysin inhibition versus enalapril in heart failure." N Engl J Med **371**(11): 993-1004.

McMurray, J. J. V., S. D. Solomon, S. E. Inzucchi, L. Kober, M. N. Kosiborod, F. A. Martinez, P. Ponikowski, M. S. Sabatine, I. S. Anand, J. Belohlavek, M. Bohm, C. E. Chiang, V. K. Chopra, R. A. de Boer, A. S. Desai, M. Diez, J. Drozdz, A. Dukat, J. Ge, J. G. Howlett, T. Katova, M. Kitakaze, C. E. A. Ljungman, B. Merkely, J. C. Nicolau, E. O'Meara, M. C. Petrie, P. N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D. L. DeMets, K. F. Docherty, P. S. Jhund, O. Bengtsson, M. Sjostrand, A. M. Langkilde, D.-H. T. Committees and Investigators (2019). "Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction." N Engl J Med **381**(21): 1995-2008.

Mentz, R. J. and G. M. Felker (2013). "Noncardiac comorbidities and acute heart failure patients." Heart Fail Clin **9**(3): 359-367, vii.

Mentz, R. J., J. P. Kelly, T. G. von Lueder, A. A. Voors, C. S. Lam, M. R. Cowie, K. Kjeldsen, E. A. Jankowska, D. Atar, J. Butler, M. Fiuzat, F. Zannad, B. Pitt and C. M. O'Connor (2014). "Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction." J Am Coll Cardiol **64**(21): 2281-2293.

Mercer, B. N., A. Koshy, M. Drozd, A. M. N. Walker, P. A. Patel, L. Kearney, J. Gierula, M. F. Paton, J. E. Lowry, M. T. Kearney, R. M. Cubbon and K. K. Witte (2018). "Ischemic Heart Disease Modifies the Association of Atrial Fibrillation With Mortality in Heart Failure With Reduced Ejection Fraction." J Am Heart Assoc **7**(20): e009770.

MERIT-HF (1999). "Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)." Lancet **353**(9169): 2001-2007.

Metra, M., M. Pagnesi, B. L. Claggett, R. Diaz, G. M. Felker, J. J. V. McMurray, S. D. Solomon, D. Bonderman, J. C. Fang, C. Fonseca, E. Goncalvesova, J. G. Howlett, J. Li, E. O'Meara, Z. M. Miao, S. A. Abbasi, S. B. Heitner, S. Kupfer, F. I. Malik and J. R. Teerlink (2022). "Effects of omecamtiv mecarbil in heart failure with reduced ejection fraction according to blood pressure: the GALACTIC-HF trial." Eur Heart J **43**(48): 5006-5016.

Moroni, M., D. Zocchi, D. Bolognesi, A. Abernethy, R. Rondelli, G. Savorani, M. Salera, F. G. Dall'Olio, G. Galli, G. Biasco and S. U. Q. P. g. on behalf of the (2014). "The 'surprise' question in advanced cancer patients: A prospective study among general practitioners." Palliat Med **28**(7): 959-964.

Moss, A. H., J. Ganjoo, S. Sharma, J. Gansor, S. Senft, B. Weaner, C. Dalton, K. MacKay, B. Pellegrino, P. Anantharaman and R. Schmidt (2008). "Utility of the "surprise" question to identify dialysis patients with high mortality." Clin J Am Soc Nephrol **3**(5): 1379-1384.

Moss, A. H., J. R. Lunney, S. Culp, M. Auber, S. Kurian, J. Rogers, J. Dower and J. Abraham (2010). "Prognostic significance of the "surprise" question in cancer patients." J Palliat Med **13**(7): 837-840.

Moss, A. J., W. Zareba, W. J. Hall, H. Klein, D. J. Wilber, D. S. Cannom, J. P. Daubert, S. L. Higgins, M. W. Brown, M. L. Andrews and I. I. I. Multicenter Automatic Defibrillator Implantation Trial (2002). "Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction." N Engl J Med **346**(12): 877-883.

Mosteller, R. D. (1987). "Simplified calculation of body-surface area." N Engl J Med **317**(17): 1098.

Moug, S., B. Carter, P. K. Myint, J. Hewitt, K. McCarthy and L. Pearce (2020). "Decision-Making in COVID-19 and Frailty." Geriatrics (Basel) **5**(2).

Mullens, W., A. Auricchio, P. Martens, K. Witte, M. R. Cowie, V. Delgado, K. Dickstein, C. Linde, K. Vernooy, F. Leyva, J. Bauersachs, C. W. Israel, L. H. Lund, E. Donal, G. Boriani, T. Jaarsma, A. Berruezo, V. Traykov, Z. Yousef, Z. Kalarus, J. Cosedis Nielsen, J. Steffel, P. Vardas, A. Coats, P. Seferovic, T. Edvardsen, H. Heidbuchel, F. Ruschitzka and C. Leclercq (2020). "Optimized implementation of cardiac resynchronization therapy: a call for action for referral and optimization of care: A joint position statement from the Heart Failure Association (HFA), European Heart Rhythm Association (EHRA), and European Association of Cardiovascular Imaging (EACVI) of the European Society of Cardiology." Eur J Heart Fail **22**(12): 2349-2369.

Mullens, W., J. Dauw, P. Martens, F. H. Verbrugge, P. Nijst, E. Meekers, K. Tartaglia, F. Chenot, S. Moubayed, R. Dierckx, P. Blouard, P. Troisfontaines, D. Derthoo, W. Smolders, L. Bruckers, W. Droogne, J. M. Ter Maaten, K. Damman, J.

Lassus, A. Mebazaa, G. Filippatos, F. Ruschitzka, M. Dupont and A. S. Group (2022). "Acetazolamide in Acute Decompensated Heart Failure with Volume Overload." N Engl J Med **387**(13): 1185-1195.

Muntwyler, J., G. Abetel, C. Gruner and F. Follath (2002). "One-year mortality among unselected outpatients with heart failure." Eur Heart J **23**(23): 1861-1866.

Murray, S. and K. Boyd (2011). "Using the 'surprise question' can identify people with advanced heart failure and COPD who would benefit from a palliative care approach." Palliat Med **25**(4): 382.

Murthy, S., C. D. Gomersall and R. A. Fowler (2020). "Care for Critically Ill Patients With COVID-19." JAMA **323**(15): 1499-1500.

Muscedere, J., B. Waters, A. Varambally, S. M. Bagshaw, J. G. Boyd, D. Maslove, S. Sibley and K. Rockwood (2017). "The impact of frailty on intensive care unit outcomes: a systematic review and meta-analysis." Intensive Care Med **43**(8): 1105-1122.

Myerburg, R. J., R. Mitrani, A. Interian, Jr. and A. Castellanos (1998). "Interpretation of outcomes of antiarrhythmic clinical trials: design features and population impact." Circulation **97**(15): 1514-1521.

Naksuk, N., K. M. Kunisaki, D. G. Benditt, V. Tholakanahalli and S. Adabag (2013). "Implantable cardioverter-defibrillators in patients with COPD." Chest **144**(3): 778-783.

NICE. (20 March 2020). "COVID-19 rapid guidelines: critical care in adults." Retrieved 24.06.2020, from www.nice.org.uk/guidance/ng159.

Northridge, D. B., A. G. Jardine, C. T. Alabaster, P. L. Barclay, J. M. Connell, H. J. Dargie, S. G. Dilly, I. N. Findlay, A. F. Lever and G. M. Samuels (1989). "Effects of UK 69 578: a novel atriopeptidase inhibitor." Lancet **2**(8663): 591-593.

O'Connor, C. M., W. Jiang, M. Kuchibhatla, S. G. Silva, M. S. Cuffe, D. D. Callwood, B. Zakhary, W. G. Stough, R. M. Arias, S. K. Rivelli, R. Krishnan and S.-C. Investigators (2010). "Safety and efficacy of sertraline for depression in patients with heart failure: results of the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) trial." J Am Coll Cardiol **56**(9): 692-699.

O'Leary, N., N. F. Murphy, C. O'Loughlin, E. Tiernan and K. McDonald (2009). "A comparative study of the palliative care needs of heart failure and cancer patients." Eur J Heart Fail **11**(4): 406-412.

Oh, S. W. and S. Y. Han (2015). "Loop Diuretics in Clinical Practice." Electrolyte Blood Press **13**(1): 17-21.

Oxberry, S. G., D. J. Torgerson, J. M. Bland, A. L. Clark, J. G. Cleland and M. J. Johnson (2011). "Short-term opioids for breathlessness in stable chronic heart failure: a randomized controlled trial." Eur J Heart Fail **13**(9): 1006-1012.

Packer, M. (2001). "Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure." J Card Fail **7**(2): 176-182.

Packer, M. (2016). "Development and Evolution of a Hierarchical Clinical Composite End Point for the Evaluation of Drugs and Devices for Acute and Chronic Heart Failure: A 20-Year Perspective." Circulation **134**(21): 1664-1678.

Packer, M. (2020). "What causes sudden death in patients with chronic heart failure and a reduced ejection fraction?" Eur Heart J **41**(18): 1757-1763.

Packer, M., S. D. Anker, J. Butler, G. Filippatos, S. J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Bohm, D. J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J. R. Gonzalez Juanatey, S. Kaul, H. P. Brunner-La Rocca, B. Merkely, S. J. Nicholls, S. Perrone, I. Pina, P. Ponikowski, N. Sattar, M. Senni, M. F. Seronde, J. Spinar, I. Squire, S. Taddei, C. Wanner, F. Zannad and E. M.-R. T. Investigators (2020). "Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure." N Engl J Med **383**(15): 1413-1424.

Packer, M., J. Butler, F. Zannad, G. Filippatos, J. P. Ferreira, S. J. Pocock, P. Carson, I. Anand, W. Doehner, M. Haass, M. Komajda, A. Miller, S. Pehrson, J. R. Teerlink, S. Schnaidt, C. Zeller, J. M. Schnee and S. D. Anker (2021). "Effect of Empagliflozin on Worsening Heart Failure Events in Patients With Heart Failure and Preserved Ejection Fraction: EMPEROR-Preserved Trial." Circulation **144**(16): 1284-1294.

Packer, M., R. M. Califf, M. A. Konstam, H. Krum, J. J. McMurray, J. L. Rouleau and K. Swedberg (2002). "Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE)." Circulation **106**(8): 920-926.

Packer, M., S. S. Gottlieb and P. D. Kessler (1986). "Hormone-electrolyte interactions in the pathogenesis of lethal cardiac arrhythmias in patients with congestive heart failure. Basis of a new physiologic approach to control of arrhythmia." Am J Med **80**(4A): 23-29.

Packer, M., P. A. Poole-Wilson, P. W. Armstrong, J. G. Cleland, J. D. Horowitz, B. M. Massie, L. Ryden, K. Thygesen and B. F. Uretsky (1999). "Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group." Circulation **100**(23): 2312-2318.

Pang, W. F., B. C. Kwan, K. M. Chow, C. B. Leung, P. K. Li and C. C. Szeto (2013). "Predicting 12-month mortality for peritoneal dialysis patients using the "surprise" question." Perit Dial Int **33**(1): 60-66.

Pareek, M., M. N. Bangash, N. Pareek, D. Pan, S. Sze, J. S. Minhas, W. Hanif and K. Khunti (2020). "Ethnicity and COVID-19: an urgent public health research priority." Lancet **395**(10234): 1421-1422.

Park, J. J., J. B. Park, J. H. Park and G. Y. Cho (2018). "Global Longitudinal Strain to Predict Mortality in Patients With Acute Heart Failure." J Am Coll Cardiol **71**(18): 1947-1957.

Pellikka, P. A., L. She, T. A. Holly, G. Lin, P. Varadarajan, R. G. Pai, R. O. Bonow, G. M. Pohost, J. A. Panza, D. S. Berman, D. L. Prior, F. M. Asch, S. Borges-Neto, P. Grayburn, H. R. Al-Khalidi, K. Miszalski-Jamka, P. Desvigne-Nickens, K. L. Lee, E. J. Velazquez and J. K. Oh (2018). "Variability in Ejection Fraction Measured By Echocardiography, Gated Single-Photon Emission Computed Tomography, and Cardiac Magnetic Resonance in Patients With Coronary Artery Disease and Left Ventricular Dysfunction." JAMA Netw Open **1**(4): e181456.

Penrod, J. D., P. Deb, C. Dellenbaugh, J. F. Burgess, Jr., C. W. Zhu, C. L. Christiansen, C. A. Luhrs, T. Cortez, E. Livote, V. Allen and R. S. Morrison (2010). "Hospital-based palliative care consultation: effects on hospital cost." J Palliat Med **13**(8): 973-979.

Pitcher, D., Z. Fritz, M. Wang and J. A. Spiller (2017). "Emergency care and resuscitation plans." BMJ **356**: j876.

Pitt, B., M. A. Pfeffer, S. F. Assmann, R. Boineau, I. S. Anand, B. Claggett, N. Clausell, A. S. Desai, R. Diaz, J. L. Fleg, I. Gordeev, B. Harty, J. F. Heitner, C. T. Kenwood, E. F. Lewis, E. O'Meara, J. L. Probstfield, T. Shaburishvili, S. J. Shah, S. D. Solomon, N. K. Sweitzer, S. Yang, S. M. McKinlay and T. Investigators (2014). "Spironolactone for heart failure with preserved ejection fraction." N Engl J Med **370**(15): 1383-1392.

Pitt, B., F. Zannad, W. J. Remme, R. Cody, A. Castaigne, A. Perez, J. Palensky and J. Wittes (1999). "The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators." N Engl J Med **341**(10): 709-717.

Ponikowski, P., A. A. Voors, S. D. Anker, H. Bueno, J. G. Cleland, A. J. Coats, V. Falk, J. R. Gonzalez-Juanatey, V. P. Harjola, E. A. Jankowska, M. Jessup, C. Linde, P. Nihoyannopoulos, J. T. Parissis, B. Pieske, J. P. Riley, G. M. Rosano, L. M. Ruilope, F. Ruschitzka, F. H. Rutten, P. van der Meer and M. Authors/Task Force (2016). "2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC." Eur Heart J **37**(27): 2129-2200.

Ponikowski, P., A. A. Voors, S. D. Anker, H. Bueno, J. G. F. Cleland, A. J. S. Coats, V. Falk, J. R. Gonzalez-Juanatey, V. P. Harjola, E. A. Jankowska, M. Jessup, C. Linde, P. Nihoyannopoulos, J. T. Parissis, B. Pieske, J. P. Riley, G. M. C. Rosano, L. M. Ruilope, F. Ruschitzka, F. H. Rutten, P. van der Meer and E. S. C. S. D. Group (2016). "2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC." Eur Heart J **37**(27): 2129-2200.

Punnoose, L. R., M. M. Givertz, E. F. Lewis, P. Pratibhu, L. W. Stevenson and A. S. Desai (2011). "Heart failure with recovered ejection fraction: a distinct clinical entity." J Card Fail **17**(7): 527-532.

Rabin, R. and F. de Charro (2001). "EQ-5D: a measure of health status from the EuroQol Group." Ann Med **33**(5): 337-343.

RCUK. (2020). "The ReSPECT Process." Retrieved 24.06.2020, from https://www.resus.org.uk/respect/health-and-care-professionals/.

Rector, T. K. S. C. J. (1987). "Patients' self-assessment of their congestive heart failure: content, reliability and validity of a new measure—the Minnesota Living with Heart Failure questionnaire." Heart Failure **3**: 198-209.

Rhee, J. and J. M. Clayton (2015). "The 'surprise' question may improve the accuracy of GPs in identifying death in patients with advanced stage IV solid-cell cancer." Evid Based Med **20**(2): 71.

Rhodes, A., P. Ferdinande, H. Flaatten, B. Guidet, P. G. Metnitz and R. P. Moreno (2012). "The variability of critical care bed numbers in Europe." Intensive Care Med **38**(10): 1647-1653.

Rice, J., L. Hunter, A. T. Hsu, M. Donskov, T. Luciani, D. Toal-Sullivan, V. Welch and P. Tanuseputro (2018). "Using the "Surprise Question" in Nursing Homes: A Prospective Mixed-Methods Study." J Palliat Care **33**(1): 9-18.

Rockwood, K., X. Song, C. MacKnight, H. Bergman, D. B. Hogan, I. McDowell and A. Mitnitski (2005). "A global clinical measure of fitness and frailty in elderly people." CMAJ **173**(5): 489-495.

Rogers, A., J. M. Addington-Hall, A. S. McCoy, P. M. Edmonds, A. J. Abery, A. J. Coats and J. S. Gibbs (2002). "A qualitative study of chronic heart failure patients' understanding of their symptoms and drug therapy." Eur J Heart Fail **4**(3): 283-287.

Rogers, J. G., C. B. Patel, R. J. Mentz, B. B. Granger, K. E. Steinhauser, M. Fiuzat, P. A. Adams, A. Speck, K. S. Johnson, A. Krishnamoorthy, H. Yang, K. J. Anstrom, G. C. Dodson, D. H. Taylor, Jr., J. L. Kirchner, D. B. Mark, C. M. O'Connor and J. A. Tulsky (2017). "Palliative Care in Heart Failure: The PAL-HF Randomized, Controlled Clinical Trial." J Am Coll Cardiol **70**(3): 331-341.

Romeiro, F. G., K. Okoshi, L. A. Zornoff and M. P. Okoshi (2012). "Gastrointestinal changes associated to heart failure." Arq Bras Cardiol **98**(3): 273-277.

Rutledge, T., V. A. Reis, S. E. Linke, B. H. Greenberg and P. J. Mills (2006). "Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes." J Am Coll Cardiol **48**(8): 1527-1537.

Sagawa, K., H. Suga, A. A. Shoukas and K. M. Bakalar (1977). "End-systolic pressure/volume ratio: a new index of ventricular contractility." Am J Cardiol **40**(5): 748-753.

Savulescu, J., M. Vergano, L. Craxi and D. Wilkinson (2020). "An ethical algorithm for rationing life-sustaining treatment during the COVID-19 pandemic." Br J Anaesth **125**(3): 253-258.

Selby, D., A. Chakraborty, T. Lilien, E. Stacey, L. Zhang and J. Myers (2011). "Clinician accuracy when estimating survival duration: the role of the patient's performance status and time-based prognostic categories." J Pain Symptom Manage **42**(4): 578-588.

Selman, L., T. Beynon, I. J. Higginson and R. Harding (2007). "Psychological, social and spiritual distress at the end of life in heart failure patients." Curr Opin Support Palliat Care **1**(4): 260-266.

Sessa, M., A. Mascolo, R. N. Mortensen, M. P. Andersen, G. M. C. Rosano, A. Capuano, F. Rossi, G. Gislason, H. Enghusen-Poulsen and C. Torp-Pedersen (2018). "Relationship between heart failure, concurrent chronic obstructive pulmonary disease and beta-blocker use: a Danish nationwide cohort study." Eur J Heart Fail **20**(3): 548-556.

Shah, K. S., H. Xu, R. A. Matsouaka, D. L. Bhatt, P. A. Heidenreich, A. F. Hernandez, A. D. Devore, C. W. Yancy and G. C. Fonarow (2017). "Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes." J Am Coll Cardiol **70**(20): 2476-2486.

Shao, F., S. Xu, X. Ma, Z. Xu, J. Lyu, M. Ng, H. Cui, C. Yu, Q. Zhang, P. Sun and Z. Tang (2020). "In-hospital cardiac arrest outcomes among patients with COVID-19 pneumonia in Wuhan, China." Resuscitation **151**: 18-23.

Shapiro, P. A. (2009). "Treatment of depression in patients with congestive heart failure." Heart Fail Rev **14**(1): 7-12.

Sharma, A., X. Zhao, B. G. Hammill, A. F. Hernandez, G. C. Fonarow, G. M. Felker, C. W. Yancy, P. A. Heidenreich, J. A. Ezekowitz and A. D. DeVore (2018). "Trends in Noncardiovascular Comorbidities Among Patients Hospitalized for Heart Failure: Insights From the Get With The Guidelines-Heart Failure Registry." Circ Heart Fail **11**(6): e004646.

Shen, L., P. S. Jhund, M. C. Petrie, B. L. Claggett, S. Barlera, J. G. F. Cleland, H. J. Dargie, C. B. Granger, J. Kjekshus, L. Kober, R. Latini, A. P. Maggioni, M. Packer, B. Pitt, S. D. Solomon, K. Swedberg, L. Tavazzi, J. Wikstrand, F. Zannad, M. R. Zile and J. J. V. McMurray (2017). "Declining Risk of Sudden Death in Heart Failure." N Engl J Med **377**(1): 41-51.

Shoaib, A., M. Waleed, S. Khan, A. Raza, M. Zuhair, X. Kassianides, A. Djahit, K. Goode, K. Wong, A. Rigby, A. Clark and J. Cleland (2014). "Breathlessness at rest is not the dominant presentation of patients admitted with heart failure." Eur J Heart Fail **16**(12): 1283-1291.

Short, P. M., S. I. Lipworth, D. H. Elder, S. Schembri and B. J. Lipworth (2011). "Effect of beta blockers in treatment of chronic obstructive pulmonary disease: a retrospective cohort study." BMJ **342**: d2549.

Small, N., C. Gardiner, S. Barnes, M. Gott, S. Payne, D. Seamark and D. Halpin (2010). "Using a prediction of death in the next 12 months as a prompt for referral to palliative care acts to the detriment of patients with heart failure and chronic obstructive pulmonary disease." Palliat Med **24**(7): 740-741.

Sobanski, P. Z., B. Alt-Epping, D. C. Currow, S. J. Goodlin, T. Grodzicki, K. Hogg, D. J. A. Janssen, M. J. Johnson, M. Krajnik, C. Leget, M. Martinez-Selles, M. Moroni, P. S. Mueller, M. Ryder, S. T. Simon, E. Stowe and P. J. Larkin (2020). "Palliative care for people living with heart failure: European Association for Palliative Care Task Force expert position statement." Cardiovasc Res **116**(1): 12-27.

Solomon, S. D., B. Claggett, E. F. Lewis, A. Desai, I. Anand, N. K. Sweitzer, E. O'Meara, S. J. Shah, S. McKinlay, J. L. Fleg, G. Sopko, B. Pitt, M. A. Pfeffer and T. Investigators (2016). "Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction." Eur Heart J **37**(5): 455-462.

Solomon, S. D., R. A. de Boer, D. DeMets, A. F. Hernandez, S. E. Inzucchi, M. N. Kosiborod, C. S. P. Lam, F. Martinez, S. J. Shah, D. Lindholm, U. Wilderang, F. Ohrn, B. Claggett, A. M. Langkilde, M. Petersson and J. J. V. McMurray (2021). "Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial." Eur J Heart Fail **23**(7): 1217-1225.

Solomon, S. D., J. J. V. McMurray, I. S. Anand, J. Ge, C. S. P. Lam, A. P. Maggioni, F. Martinez, M. Packer, M. A. Pfeffer, B. Pieske, M. M. Redfield, J. L. Rouleau, D. J. van Veldhuisen, F. Zannad, M. R. Zile, A. S. Desai, B. Claggett, P. S. Jhund, S. A. Boytsov, J. Comin-Colet, J. Cleland, H. D. Dungen, E. Goncalvesova, T. Katova, J. F. Kerr Saraiva, M. Lelonek, B. Merkely, M. Senni, S. J. Shah, J. Zhou, A. R. Rizkala, J. Gong, V. C. Shi, M. P. Lefkowitz, P.-H. Investigators and Committees (2019). "Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction." N Engl J Med **381**(17): 1609-1620.

Solomon, S. D., J. J. V. McMurray, B. Claggett, R. A. de Boer, D. DeMets, A. F. Hernandez, S. E. Inzucchi, M. N. Kosiborod, C. S. P. Lam, F. Martinez, S. J. Shah, A. S. Desai, P. S. Jhund, J. Belohlavek, C. E. Chiang, C. J. W. Borleffs, J. Comin-Colet, D. Dobreanu, J. Drozdz, J. C. Fang, M. A. Alcocer-Gamba, W. Al Habeeb, Y. Han, J. W. Cabrera Honorio, S. P. Janssens, T. Katova, M. Kitakaze, B. Merkely, E. O'Meara, J. F. K. Saraiva, S. N. Tereshchenko, J. Thierer, M. Vaduganathan, O. Vardeny, S. Verma, V. N. Pham, U. Wilderang, N. Zaozerska, E. Bachus, D. Lindholm, M. Petersson, A. M. Langkilde, D. T. Committees and Investigators (2022). "Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction." N Engl J Med **387**(12): 1089-1098.

Solomon, S. D., A. R. Rizkala, J. Gong, W. Wang, I. S. Anand, J. Ge, C. S. P. Lam, A. P. Maggioni, F. Martinez, M. Packer, M. A. Pfeffer, B. Pieske, M. M. Redfield, J. L. Rouleau, D. J. Van Veldhuisen, F. Zannad, M. R. Zile, A. S. Desai, V. C. Shi, M. P. Lefkowitz and J. J. V. McMurray (2017). "Angiotensin Receptor Neprilysin Inhibition in Heart Failure With Preserved Ejection Fraction: Rationale and Design of the PARAGON-HF Trial." JACC Heart Fail **5**(7): 471-482.

Solomon, S. D., M. Vaduganathan, L. C. B, M. Packer, M. Zile, K. Swedberg, J. Rouleau, A. P. M, A. Desai, L. H. Lund, L. Kober, I. Anand, N. Sweitzer, G. Linssen, B. Merkely, J. Luis Arango, D. Vinereanu, C. H. Chen, M. Senni, A. Sibulo, S. Boytsov, V. Shi, A. Rizkala, M. Lefkowitz and J. J. V. McMurray (2020). "Sacubitril/Valsartan Across the Spectrum of Ejection Fraction in Heart Failure." Circulation **141**(5): 352-361.

SOLVD (1991). "Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure." N Engl J Med **325**(5): 293-302.

Spertus, J. V., L. A. Hatfield, D. J. Cohen, S. V. Arnold, M. Ho, P. G. Jones, M. Leon, B. Zuckerman and J. A. Spertus (2019). "Integrating Quality of Life and Survival Outcomes in Cardiovascular Clinical Trials." Circ Cardiovasc Qual Outcomes **12**(6): e005420.

Srivastava, P. K., J. J. Hsu, B. Ziaeian and G. C. Fonarow (2020). "Heart Failure With Mid-range Ejection Fraction." Curr Heart Fail Rep **17**(1): 1-8.

Stewart, A. G., J. C. Waterhouse and P. Howard (1995). "The QTc interval, autonomic neuropathy and mortality in hypoxaemic COPD." Respir Med **89**(2): 79-84.

Stokke, T. M., N. E. Hasselberg, M. K. Smedsrud, S. I. Sarvari, K. H. Haugaa, O. A. Smiseth, T. Edvardsen and E. W. Remme (2017). "Geometry as a Confounder When Assessing Ventricular Systolic Function: Comparison Between Ejection Fraction and Strain." J Am Coll Cardiol **70**(8): 942-954.

Straw, S., R. Byrom, J. Gierula, M. F. Paton, A. Koshy, R. Cubbon, M. Drozd, M. Kearney and K. K. Witte (2019). "Predicting one-year mortality in heart failure using the 'Surprise Question': a prospective pilot study." Eur J Heart Fail **21**(2): 227-234.

Straw, S., C. A. Cole, M. McGinlay, M. Drozd, T. A. Slater, J. E. Lowry, M. F. Paton, E. Levelt, R. M. Cubbon, M. T. Kearney, K. K. Witte and J. Gierula (2023). "Guideline-directed medical therapy is similarly effective in heart failure with mildly reduced ejection fraction." Clin Res Cardiol **112**(1): 111-122.

Straw, S., J. Gierula and K. K. Witte (2022). "Designing clinical trials in heart failure with preserved ejection fraction: quality over quantity?" Eur J Heart Fail **24**(5): 851-854.

Straw, S., M. McGinlay, M. Drozd, T. A. Slater, A. Cowley, S. Kamalathasan, N. Maxwell, R. A. Bird, A. O. Koshy, M. Prica, P. A. Patel, S. D. Relton, J. Gierula, R. M. Cubbon, M. T. Kearney and K. K. Witte (2021). "Advanced care planning during the COVID-19 pandemic: ceiling of care decisions and their implications for observational data." BMC Palliat Care **20**(1): 10.

Straw, S., M. McGinlay, S. D. Relton, A. O. Koshy, J. Gierula, M. F. Paton, M. Drozd, J. E. Lowry, C. Cole, R. M. Cubbon, K. K. Witte and M. T. Kearney (2020). "Effect of disease-modifying agents and their association with mortality in multi-morbid patients with heart failure with reduced ejection fraction." ESC Heart Fail **7**(6): 3859-3870.

Straw, S., M. McGinlay and K. K. Witte (2021). "Four pillars of heart failure: contemporary pharmacological therapy for heart failure with reduced ejection fraction." Open Heart **8**(1).

Straw, S. and K. K. Witte (2020). "Observational data during the COVID-19 pandemic: opportunity with uncertainty." Heart **106**(19): 1461-1462.

Straw, S., K. K. Witte and M. T. Kearney (2019). "Heart failure: A preventable and treatable complication of type 2 diabetes." J Diabetes **11**(7): 613-616.

Straw, S., K. K. Witte and M. T. Kearney (2021). End-stage congestive heart failure. Textbook of Palliative Care. E. Bruera, Taylor and Francis. **Third Edition**.

Swedberg, K., J. Cleland, H. Dargie, H. Drexler, F. Follath, M. Komajda, L. Tavazzi, O. A. Smiseth, A. Gavazzi, A. Haverich, A. Hoes, T. Jaarsma, J. Korewicki, S. Levy, C. Linde, J. L. Lopez-Sendon, M. S. Nieminen, L. Pierard, W. J. Remme, D. Task Force for the and C. Treatment of Chronic Heart Failure of the European Society of (2005). "Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology." Eur Heart J **26**(11): 1115-1140.

Swedberg, K., M. Komajda, M. Bohm, J. S. Borer, I. Ford, A. Dubost-Brama, G. Lerebours, L. Tavazzi and S. Investigators (2010). "Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study." Lancet **376**(9744): 875-885.

Tang, A. S., G. A. Wells, M. Talajic, M. O. Arnold, R. Sheldon, S. Connolly, S. H. Hohnloser, G. Nichol, D. H. Birnie, J. L. Sapp, R. Yee, J. S. Healey, J. L. Rouleau and I. Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (2010). "Cardiac-resynchronization therapy for mild-to-moderate heart failure." N Engl J Med **363**(25): 2385-2395.

Tavazzi, L., A. P. Maggioni, R. Marchioli, S. Barlera, M. G. Franzosi, R. Latini, D. Lucci, G. L. Nicolosi, M. Porcu, G. Tognoni and H. F. I. Gissi (2008). "Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial." Lancet **372**(9645): 1231-1239.

Taylor, A. L., S. Ziesche, C. Yancy, P. Carson, R. D'Agostino, Jr., K. Ferdinand, M. Taylor, K. Adams, M. Sabolinski, M. Worcel, J. N. Cohn and I. African-American Heart Failure Trial (2004). "Combination of isosorbide dinitrate and hydralazine in blacks with heart failure." N Engl J Med **351**(20): 2049-2057.

Tomasoni, D., M. Adamo, M. S. Anker, S. von Haehling, A. J. S. Coats and M. Metra (2020). "Heart failure in the last year: progress and perspective." ESC Heart Fail **7**(6): 3505-3530.

Tracy, C. M., A. E. Epstein, D. Darbar, J. P. DiMarco, S. B. Dunbar, N. A. Estes, 3rd, T. B. Ferguson, Jr., S. C. Hammill, P. E. Karasik, M. S. Link, J. E. Marine, M. H. Schoenfeld, A. J. Shanker, M. J. Silka, L. W. Stevenson, W. G. Stevenson, P. D. Varosy, M. Writing Committee, A. E. Epstein, J. P. DiMarco, K. A. Ellenbogen, N. A. Estes, 3rd, R. A. Freedman, L. S. Gettes, A. M. Gillinov, G. Gregoratos, S. C. Hammill, D. L. Hayes, M. A. Hlatky, L. K. Newby, R. L. Page, M. H. Schoenfeld, M. J.

Silka, L. W. Stevenson, M. O. Sweeney, A. A. T. F. Members, J. L. Anderson, A. K. Jacobs, J. L. Halperin, N. M. Albert, M. A. Creager, D. DeMets, S. M. Ettinger, R. A. Guyton, J. S. Hochman, F. G. Kushner, E. M. Ohman, W. Stevenson, C. W. Yancy, F. American College of Cardiology, G. American Heart Association Task Force on Practice, S. American Association for Thoracic, A. Heart Failure Society of and S. Society of Thoracic (2012). "2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines." J Thorac Cardiovasc Surg **144**(6): e127-145.

Tsuji, K., Y. Sakata, K. Nochioka, M. Miura, T. Yamauchi, T. Onose, R. Abe, T. Oikawa, S. Kasahara, M. Sato, T. Shiroto, J. Takahashi, S. Miyata, H. Shimokawa and C.-. Investigators (2017). "Characterization of heart failure patients with mid-range left ventricular ejection fraction-a report from the CHART-2 Study." Eur J Heart Fail **19**(10): 1258-1269.

Turgeon, R. D., M. R. Kolber, P. Loewen, U. Ellis and J. P. McCormack (2019). "Higher versus lower doses of ACE inhibitors, angiotensin-2 receptor blockers and beta-blockers in heart failure with reduced ejection fraction: Systematic review and meta-analysis." PLoS One **14**(2): e0212907.

Vaduganathan, M., B. L. Claggett, P. S. Jhund, J. W. Cunningham, J. Pedro Ferreira, F. Zannad, M. Packer, G. C. Fonarow, J. J. V. McMurray and S. D. Solomon (2020). "Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection

fraction: a comparative analysis of three randomised controlled trials." Lancet **396**(10244): 121-128.

van Riet, E. E., A. W. Hoes, A. Limburg, M. A. Landman, H. van der Hoeven and F. H. Rutten (2014). "Prevalence of unrecognized heart failure in older persons with shortness of breath on exertion." Eur J Heart Fail **16**(7): 772-777.

Voors, A. A., C. E. Angermann, J. R. Teerlink, S. P. Collins, M. Kosiborod, J. Biegus, J. P. Ferreira, M. E. Nassif, M. A. Psotka, J. Tromp, C. J. W. Borleffs, C. Ma, J. Comin-Colet, M. Fu, S. P. Janssens, R. G. Kiss, R. J. Mentz, Y. Sakata, H. Schirmer, M. Schou, P. C. Schulze, L. Spinarova, M. Volterrani, J. K. Wranicz, U. Zeymer, S. Zieroth, M. Brueckmann, J. P. Blatchford, A. Salsali and P. Ponikowski (2022). "The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial." Nat Med **28**(3): 568-574.

Wachter, R., M. Senni, J. Belohlavek, E. Straburzynska-Migaj, K. K. Witte, Z. Kobalava, C. Fonseca, E. Goncalvesova, Y. Cavusoglu, A. Fernandez, S. Chaaban, E. Bohmer, A. C. Pouleur, C. Mueller, C. Tribouilloy, E. Lonn, A. L. B. J, J. Gniot, M. Mozheiko, M. Lelonek, A. Noe, H. Schwende, W. Bao, D. Butylin, D. Pascual-Figal and T. Investigators (2019). "Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study." Eur J Heart Fail **21**(8): 998-1007.

Walker, A. M. and R. M. Cubbon (2015). "Sudden cardiac death in patients with diabetes mellitus and chronic heart failure." Diab Vasc Dis Res **12**(4): 228-233.

Walker, A. M. N., M. Drozd, M. Hall, P. A. Patel, M. Paton, J. Lowry, J. Gierula, R. Byrom, L. Kearney, R. J. Sapsford, K. K. Witte, M. T. Kearney and R. M. Cubbon (2018). "Prevalence and Predictors of Sepsis Death in Patients With Chronic Heart Failure and Reduced Left Ventricular Ejection Fraction." J Am Heart Assoc **7**(20): e009684.

Wang, D., B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, B. Wang, H. Xiang, Z. Cheng, Y. Xiong, Y. Zhao, Y. Li, X. Wang and Z. Peng (2020). "Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China." JAMA **323**(11): 1061-1069.

Wang, L., W. He, X. Yu, D. Hu, M. Bao, H. Liu, J. Zhou and H. Jiang (2020). "Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up." J Infect **80**(6): 639-645.

Watanabe, E., T. Tanabe, M. Osaka, A. Chishaki, B. Takase, S. Niwano, I. Watanabe, K. Sugi, T. Katoh, K. Takayanagi, K. Mawatari, M. Horie, K. Okumura, H. Inoue, H. Atarashi, I. Yamaguchi, S. Nagasawa, K. Moroe, I. Kodama, T. Sugimoto and Y. Aizawa (2014). "Sudden cardiac arrest recorded during Holter monitoring: prevalence, antecedent electrical events, and outcomes." Heart Rhythm **11**(8): 1418-1425.

Weissman, D. E. and D. E. Meier (2011). "Identifying patients in need of a palliative care assessment in the hospital setting: a consensus report from the Center to Advance Palliative Care." J Palliat Med **14**(1): 17-23.

White, N., N. Kupeli, V. Vickerstaff and P. Stone (2017). "How accurate is the 'Surprise Question' at identifying patients at the end of life? A systematic review and meta-analysis." BMC Med **15**(1): 139.

WHO. (2020). "Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected: interim guidance, 28 January 2020. World Health Organisation.", from Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected: interim guidance, 28 January 2020.

Williams, S. G., D. J. Wright, P. Marshall, A. Reese, B. H. Tzeng, A. J. Coats and L. B. Tan (2003). "Safety and potential benefits of low dose diamorphine during exercise in patients with chronic heart failure." Heart **89**(9): 1085-1086.

Witte, K. K., M. Drozd, A. M. N. Walker, P. A. Patel, J. C. Kearney, S. Chapman, R. J. Sapsford, J. Gierula, M. F. Paton, J. Lowry, M. T. Kearney and R. M. Cubbon (2018). "Mortality Reduction Associated With beta-Adrenoceptor Inhibition in Chronic Heart Failure Is Greater in Patients With Diabetes." Diabetes Care **41**(1): 136-142.

Witte, K. K., P. A. Patel, A. M. N. Walker, C. B. Schechter, M. Drozd, A. Sengupta, R. Byrom, L. C. Kearney, R. J. Sapsford, M. T. Kearney and R. M. Cubbon (2018). "Socioeconomic deprivation and mode-specific outcomes in patients with chronic heart failure." Heart **104**(12): 993-998.

Wolsk, E., D. Kaye, J. Komtebedde, S. J. Shah, B. A. Borlaug, D. Burkhoff, D. W. Kitzman, C. S. P. Lam, D. J. van Veldhuisen, P. Ponikowski, M. C. Petrie, C.

Hassager, J. E. Moller and F. Gustafsson (2019). "Central and Peripheral Determinants of Exercise Capacity in Heart Failure Patients With Preserved Ejection Fraction." JACC Heart Fail **7**(4): 321-332.

Wood, N., S. Straw, M. Scalabrin, L. D. Roberts, K. K. Witte and T. S. Bowen (2021). "Skeletal muscle atrophy in heart failure with diabetes: from molecular mechanisms to clinical evidence." ESC Heart Fail **8**(1): 3-15.

Wu, C., X. Chen, Y. Cai, J. Xia, X. Zhou, S. Xu, H. Huang, L. Zhang, X. Zhou, C. Du, Y. Zhang, J. Song, S. Wang, Y. Chao, Z. Yang, J. Xu, X. Zhou, D. Chen, W. Xiong, L. Xu, F. Zhou, J. Jiang, C. Bai, J. Zheng and Y. Song (2020). "Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China." JAMA Intern Med **180**(7): 934-943.

Wu, Z. and J. M. McGoogan (2020). "Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention." JAMA **323**(13): 1239-1242.

Xue, Q. L. (2011). "The frailty syndrome: definition and natural history." Clin Geriatr Med **27**(1): 1-15.

Yancy, C. W., M. Jessup, B. Bozkurt, J. Butler, D. E. Casey, Jr., M. M. Colvin, M. H. Drazner, G. S. Filippatos, G. C. Fonarow, M. M. Givertz, S. M. Hollenberg, J. Lindenfeld, F. A. Masoudi, P. E. McBride, P. N. Peterson, L. W. Stevenson and C.

Westlake (2017). "2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America." Circulation **136**(6): e137-e161.

Yancy, C. W., M. Jessup, B. Bozkurt, J. Butler, D. E. Casey, Jr., M. H. Drazner, G. C. Fonarow, S. A. Geraci, T. Horwich, J. L. Januzzi, M. R. Johnson, E. K. Kasper, W. C. Levy, F. A. Masoudi, P. E. McBride, J. J. McMurray, J. E. Mitchell, P. N. Peterson, B. Riegel, F. Sam, L. W. Stevenson, W. H. Tang, E. J. Tsai and B. L. Wilkoff (2013). "2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines." Circulation **128**(16): 1810-1852.

Yang, J., Y. Zheng, X. Gou, K. Pu, Z. Chen, Q. Guo, R. Ji, H. Wang, Y. Wang and Y. Zhou (2020). "Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis." Int J Infect Dis **94**: 91-95.

Yang, X., Y. Yu, J. Xu, H. Shu, J. Xia, H. Liu, Y. Wu, L. Zhang, Z. Yu, M. Fang, T. Yu, Y. Wang, S. Pan, X. Zou, S. Yuan and Y. Shang (2020). "Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study." Lancet Respir Med **8**(5): 475-481.

Yildiz, P., T. Tukek, V. Akkaya, A. B. Sozen, A. Yildiz, F. Korkut and V. Yilmaz (2002). "Ventricular arrhythmias in patients with COPD are associated with QT dispersion." Chest **122**(6): 2055-2061.

Yim, C. K., Y. Barron, S. Moore, C. Murtaugh, A. Lala, M. Aldridge, N. Goldstein and L. P. Gelfman (2017). "Hospice Enrollment in Patients With Advanced Heart Failure Decreases Acute Medical Service Utilization." Circ Heart Fail **10**(3).

Ypenburg, C., R. J. van Bommel, C. J. Borleffs, G. B. Bleeker, E. Boersma, M. J. Schalij and J. J. Bax (2009). "Long-term prognosis after cardiac resynchronization therapy is related to the extent of left ventricular reverse remodeling at midterm follow-up." J Am Coll Cardiol **53**(6): 483-490.

Yusuf, S., M. A. Pfeffer, K. Swedberg, C. B. Granger, P. Held, J. J. McMurray, E. L. Michelson, B. Olofsson, J. Ostergren, C. Investigators and Committees (2003). "Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial." Lancet **362**(9386): 777-781.

Zannad, F., S. D. Anker, W. M. Byra, J. G. F. Cleland, M. Fu, M. Gheorghiade, C. S. P. Lam, M. R. Mehra, J. D. Neaton, C. C. Nessel, T. E. Spiro, D. J. van Veldhuisen, B. Greenberg and C. H. Investigators (2018). "Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease." N Engl J Med **379**(14): 1332-1342.

Zannad, F., J. J. McMurray, H. Krum, D. J. van Veldhuisen, K. Swedberg, H. Shi, J. Vincent, S. J. Pocock, B. Pitt and E.-H. S. Group (2011). "Eplerenone in patients with systolic heart failure and mild symptoms." N Engl J Med **364**(1): 11-21.

Zhou, F., T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, J. Xiang, Y. Wang, B. Song, X. Gu, L. Guan, Y. Wei, H. Li, X. Wu, J. Xu, S. Tu, Y. Zhang, H. Chen and B. Cao (2020).

"Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study." Lancet **395**(10229): 1054-1062.

Zinman, B., C. Wanner, J. M. Lachin, D. Fitchett, E. Bluhmki, S. Hantel, M. Mattheus, T. Devins, O. E. Johansen, H. J. Woerle, U. C. Broedl, S. E. Inzucchi and E.-R. O. Investigators (2015). "Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes." N Engl J Med **373**(22): 2117-2128.