Sudden death and pump failure death in heart failure

Li Shen
BMED, MMED

Submitted in fulfilment of the requirements for the degree of PhD

University of Glasgow
College of Medical, Veterinary and Life Sciences
Institute of Cardiovascular & Medical Sciences

Summary

Sudden death and pump failure death are two major modes of death in patients with heart failure and reduced ejection fraction (HF-REF) and in patients with heart failure and preserved ejection fraction (HF-PEF). There have been advances in evidence-based treatments in patients with HF-REF over the last two decades, along with the changing patient characteristics in both HF-REF and HF-PEF populations. It is of great interest and significance to discover if these changes have translated into temporal changes (and corresponding trends over time) in the risks of sudden death and pump failure death in both populations. Apart from examining any changes in the rates of mode-specific death in population level, it is also of interest and importance to estimate the risks for sudden death and pump failure death in individual patients. Accurate risk prediction can aid in better risk stratification. In patients with HF-REF, identifying high-risk subgroups would help target the device therapy to those most likely to benefit and identifying low-risk subgroups would avoid unnecessary implantation, thus improving the cost-effectiveness of the therapy. In patients with HF-PEF, identifying high-risk subgroups would enable further research into the efficacy of device therapy in this population. The aims of this work were to examine the trends in the rates of sudden death and pump failure death over time in patients with HF-REF and in patients with HF-PEF, and to separately develop validated models to predict sudden death and pump failure death in both populations.

Given that there are limited data on mode-specific death from community-based studies, I used data from clinical trials which have more detailed and standardised sub-classification and adjudication of mortal events. Besides, compared to community-based studies, clinical trials have more detailed baseline characterisation, which allows more complete multivariable adjustment to account for confounding and between-study differences. Therefore, a cohort of 46,163 patients with HF-REF enrolled in 13 clinical trials conducted between 1995-2015 and a cohort of 10,517 patients with HF-PEF in 3 clinical trials over the period 1999-2013 were included in this thesis. Multiple linear regression analysis was used to examine the trends in the rates of sudden death and pump failure death over time in both populations respectively. The cumulative

incidences for sudden death and pump failure death in each trial at different time points during follow-up were calculated with the cumulative incidence function method, counting the competing risk of death from other causes. The risk for each mode of death across trial arms and by HF duration was examined using the Cox regression models, with further adjustment for a number of confounding variables. The models to predict sudden death and pump failure death in patients with HF-REF were separately developed in PARADIGM-HF and validated in ATMOSPHERE. Models for both modes of death in HF-PEF were developed in I-PRESERVE and validated in CHARM-Preserved as well as TOPCAT. These models were constructed using a competing risk approach with the Fine-Gray sub-distributional hazards regression analysis. Model performance was examined by assessing calibration (i.e. the agreement between the observed and predicted cumulative incidences over time) and discrimination (i.e. the ability to separate patients at higher risk from those at lower risk).

I found that the risks of sudden death and pump failure death in patients with HF-REF have fallen across 13 clinical trials over the period 1995-2015, consistent with a cumulative use of evidence-based therapies in this population. The absolute rates of sudden death and pump failure death were very low in the early follow-up after randomisation in patients with HF-REF who received modern evidence-based treatment. Longer standing HF was associated with greater risks of sudden death and, particularly, pump failure death in HF-REF.

The risks of sudden death and pump failure death were consistently low across the 3 largest clinical trials in patients with HF-PEF, with little difference by experimental treatment in any trial. There was a downward trend in the rates of sudden death and pump failure death across these trials over time, in parallel with a changing characteristic of patients enrolled in these trials. Nevertheless, sudden death and pump failure death remained the most common modes of death, altogether accounting for the majority of CV death. The absolute rates of sudden death and pump failure death in patients with HF-PEF were extremely low in the early follow-up after randomisation. Longer standing HF was associated with a slightly higher risk of sudden death and a substantially higher risk of pump failure death in HF-PEF.

The sudden death and pump failure death models in patients with HF-REF I developed in the largest and most contemporary cohort (PARADIGM-HF), included a number of variables collected in routine clinical practice, and accounted for the prognostic impact of the competing risk of death from other causes. The discriminating ability was modest for the sudden death model but excellent for the pump failure death model. Both models showed good calibration and were robust when externally validated in ATMOSPHERE.

The prognostic models in patients with HF-PEF I developed in I-PRESERVE, using simple demographic and clinical variables, showed good discrimination and calibration for both sudden death and pump failure death, and were robust in external validation in CHARM-Preserved and TOPCAT. The performance of both models was further improved with the inclusion of NT-proBNP.

In conclusion, I have found that the risks of sudden death and pump failure death have declined over time both in patients with HF-REF and in patients with HF-PEF based on clinical trial data. The patterns of change in the rates of both modes of death over time need to be examined in community-based populations. The prognostic models for both modes of death, showing reasonable performance, can be considered for use in risk stratification for mode-specific death in both populations, aiding in decision making in device therapy in similar patients in HF-REF and helping with patient selection for device interventions in future trials in HF-PEF.

Table of Contents

List of Tables

List of Figures

Publications related to work in this thesis

Shen L, Jhund PS, Petrie MC, Claggett BL, Barlera S, Cleland JGF, Dargie HJ, Granger CB, Kjekshus J, Køber L, Latini R, Maggioni AP, Packer M, Pitt B, Solomon SD, Swedberg K, Tavazzi L, Wikstrand J, Zannad F, Zile MR, McMurray JJV. Declining Risk of Sudden Death in Heart Failure. *New Engl J Med 2017; 377:41-51.*

Shen L, Jhund PS, Shi VC, Rouleau JL, Solomon SD, Swedberg K, Zile MR, Packer M, McMurray JJV and on behalf of PARADIGM-HF Executive Committee. Predicting sudden death and pump failure death in patients with heart failure and reduced ejection fraction: competing risk regression analyses of the PARADIGM-HF trial [Abstract]. *Eur Heart J (2016) 37 (suppl_1): 21.*

Shen L, Jhund PS, Pitt B, Zannad F, McMurray JJV. Temporal trends in sudden death in patients with heart failure and reduced ejection fraction: an analysis of the RALES and EMPHASIS-HF trials [Abstract]. *European Journal of Heart Failure (2015) 17 (Suppl. 1): 266.*

Presentations to learned societies

ESC Congress 2016, Rome, Italy. 27-31th August 2016. Shen L, Jhund PS, Shi VC, Rouleau JL, Solomon SD, Swedberg K, Zile MR, Packer M, McMurray JJV and on behalf of PARADIGM-HF Executive Committee. Predicting sudden death and pump failure death in patients with heart failure and reduced ejection fraction: competing risk regression analyses of the PARADIGM-HF trial. *Moderate Poster*.

ESC Heart Failure Congress 2015 and the 2nd World Congress on Acute Heart Failure, Seville, Spain. 23rd-26th May, 2015. Shen L, Jhund PS, Pitt B, Zannad F, McMurray JJV. Temporal trends in sudden death in patients with heart failure and reduced ejection fraction: an analysis of the RALES and EMPHASIS-HF trials. *Rapid Fire Abstract*.

Acknowledgements

Firstly I would like to thank Professor John McMurray, who accepted me as his PhD student and offered me his mentorship. This work would not have been possible without his guidance and support. I am grateful for the training opportunities he has provided to develop my transferable skills, and for his thoughtfulness and help during my life as an international student. His insights into and passion towards scientific research has always inspired me to do more.

I would also like to thank my co-supervisor Dr Pardeep Jhund for being an excellent teacher who has combined teaching and guidance perfectly, for introducing me into the world of statistics, and believing in my potential and pushing me towards it, for his expertise and valuable advice on research governance, and for his encouragement and support to help me overcome the hurdles in research and life.

Special thanks to Dr Kieran Docherty for proofreading and his timely help. Many thanks to the colleagues who work in the heart failure research group, particularly, Eugene, Jane, Ross, and Jo for their support.

In addition to the people who participated in the clinical trials, I would like to thank all those involved in these studies; their work and efforts made these invaluable data available for the work in this thesis.

I am grateful to the China Scholarship Council for supporting this work through a doctorate research scholarship.

Finally, I would like to thank my family. To my aunt, Jody, for staying in touch and having been my best counsellor throughout this research. To my beloved parents, for their selfless love and unconditional support; although they hardly understood what research I worked on, they have always believed in me and provided me with the liberty to pursue my chosen path. Special thanks to my parents-in-law, for their love and moral support. Lastly, thanks to my dearest husband, Xin, for his love, for abiding my absence, for always being there during the happy and difficult moments, for showing faith in me and giving me strength during my pursuit of PhD degree.

Author's declaration

I declare that, except where explicit reference is made to the contribution of others, this thesis is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

Li Shen

Abbreviations

95% CI - 95% confidence interval

123I-MIBG - Iodine-123 meta-iodobenzylguanidine

AAA – abdominal aortic aneurysm

ACCF - American College of Cardiology Foundation

ACEI - angiotensin converting enzyme inhibitor

ADMIRE-ICD - the International Study to Determine if AdreView Heart Function Scan Can be Used to Identify Patients With Mild or Moderate Heart Failure (HF) That Benefit From Implanted Medical Device

AF - atrial fibrillation

AHA - American Heart Association

ALAT - alanine transaminase

ANOVA - analysis of variance

ANP - atrial natriuretic peptide

ARB - angiotensin receptor blocker

Apo A-I - apolipoprotein A-I

Apo B - apolipoprotein B

ATLAS - Assessment of Treatment with Lisinopril And Survival trial

ATMOSPHERE - the Aliskiren Trial to Minimize OutcomeS in Patients with HEart failure

BEST - the Beta-Blocker Evaluation of Survival

BMI - body mass index

BNP - B-type natriuretic peptide

BP - blood pressure

BUN - blood urea nitrogen

CABG - coronary artery bypass grafting

CAD - coronary artery disease

CARE-HF - Cardiac REsynchronization-Heart Failure

CHARM - Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity

CHART - Chronic Heart failure Analysis and Registry in Tohoku district

CIBIS-II - the Cardiac Insufficiency Bisoprolol Study II

CIF - cumulative incidence function

CK - creatine kinase

CMR - cardiovascular magnetic resonance
CMR GUIDE - the Cardiovascular magnetic resonance-GUIDEd management of mild to moderate left ventricular systolic dysfunction
COMPANION - Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure
CONSORT - Consolidated Standards of Reporting Trials
COPD - chronic obstructive pulmonary disease
CORONA - the Controlled Rosuvastatin Multinational Trial in Heart Failure
CRT - cardiac resynchronisation therapy
CRT-D - cardiac resynchronization therapy with defibrillator
CRT-P - cardiac resynchronization therapy with pacemaker
CV – cardiovascular
DANISH - DANish study to assess the efficacy of ICDs in patients with non-ischemic Systolic Heart failure on mortality
DBP - diastolic blood pressure
DEFINITE - Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation
DIG-ancillary - Digitalis Investigation Group ancillary trial
ECG - electrocardiogram
eGFR - estimated glomerular filtration rate
ELITE2 - Evaluation of Losartan in the Elderly
EMPHASIS-HF - the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure
EQ-5D - EuroQol five dimensions questionnaire
ER - emergency room
FDA - Food and Drug Administration
FS - fractional shortening
GGT - Gamma-glutamyl transpeptidase
GISSI-HF - the Gruppo Italiano per lo studio della sopravvivenza nell'Insufficienza cardiaca Heart failure
HDL-C - high density lipoprotein cholesterol
HF - heart failure
HF-ACTION - Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training
IVCD - intraventricular conduction defect
hsCRP - high-sensitivity C-reactive protein

HF-MREF – heart failure with mid-range ejection fraction

HF-PEF – heart failure with preserved ejection fraction

HF-REF – heart failure with reduced ejection fraction

HR - hazard ratio

HRV - heart rate variability

ICD - implantable cardioverter defibrillator

IDC - idiopathic dilated cardiomyopathy

I-PRESERVE - the Irbesartan in Heart Failure with Preserved Ejection Fraction Study

J-CHF - the Japanese Diastolic Heart Failure Study

KM - Kaplan-Meier

LBBB - left bundle branch block

LDL-C - low-density lipoprotein cholesterol

LVEDD - left ventricular end diastolic diameter

LVEF - left ventricular ejection fraction

LVH - left ventricular hypertrophy

LVSD - left ventricular systolic dysfunction

MADIT-II - Multicenter Automatic Defibrillator Implantation Trial II

MERIT-HF - the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure

MI - myocardial infarction

MR - mitral regurgitation

MRA - mineralocorticoid receptor antagonist

MUSIC - MUerte Subita en Insuficiencia Cardiaca study

MUSTT - Multicenter Unsustained Tachycardia Trial

NP - natriuretic peptides

NR - not reported

NSVT- nonsustained ventricular tachycardia

NT-proBNP - N-terminal pro-B-type natriuretic peptide

NYHA - New York Heart Association

PAD - peripheral artery disease

PARADIGM-HF - the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure

PARAGON-HF - Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction

PARAMOUNT - Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion

PCI - percutaneous coronary intervention

PEP-CHF - Perindopril in Elderly People with Chronic Heart Failure

PH - proportional hazards

PRAISE - Prospective Randomized Amlodipine Survival Evaluation

PROMISE - Prospective Randomized Milrinone Survival Evaluation

PTCA - percutaneous transluminal coronary angioplasty

QALY - quality-adjusted life years

RALES - Randomized Aldactone Evaluation Study

RCT - randomised controlled trial

RENAISSANCE - Randomized Enbrel North American Strategy to Study Antagonism of Cytokines

RESET-SCD - REevaluation of optimal treatment Strategies for prEvenTion of Sudden Cardiac Death in patients with ischemic cardiomyopathy

ROC AUC - area under the curve of receiver operating characteristic curve

SBP - systolic blood pressure

SCD-HeFT - the Sudden Cardiac Death in Heart Failure trial

SDNN - standard deviation of all normal-to-normal RR intervals

SENIORS - the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure

SHFM - Seattle Heart Failure Model

SPRM - Seattle Proportional Risk Model

TOPCAT - Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist

TSH - thyroid-stimulating hormone

UK - United Kingdom

UK-HEART - United Kingdom-heart failure evaluation and assessment of risk trial

US - United States

VAD - ventricular assist device

Val-HeFT - the Valsartan Heart Failure Trial

VPB - ventricular premature beat

VT - ventricular tachycardia

VF - ventricular fibrillation

Chapter 1 Introduction and literature review

In this thesis, I will examine the risks of sudden death and pump failure death over time in patients with heart failure and reduced ejection fraction (HF-REF) and heart failure and preserved ejection fraction (HF-PEF). I will develop and validate models to predict sudden death and pump failure death separately in both populations.

In the first chapter I will give an overview of heart failure (HF), and the two major modes of death, i.e. sudden death and pump failure death, in heart failure. Thereafter, I will review the literature on prognostic models that have been published for sudden death and pump failure death in heart failure.

In the second chapter I will introduce and describe the datasets and study populations used to derive and validate the models before describing the statistical methods used for the analyses in this thesis.

In Chapter 3 I will describe the risks of sudden death and pump failure death over time in patients with HF-REF enrolled in the major clinical trials of therapies for HF-REF. I will develop risk models to predict sudden death and pump failure death separately in patients with HF-REF in Chapter 4 and validate them in an independent cohort in Chapter 5.

In Chapter 6 I will examine the risks of sudden death and pump failure death over time in patients with HF-PEF enrolled in the clinical trials in this population. I will construct models to predict sudden death and pump failure death separately in patients with HF-PEF, and externally validate them in independent cohorts in Chapter 7.

Finally, I will discuss my findings and their implications in Chapter 8.

1.1 Overview of heart failure

1.1.1 Definition and diagnosis of heart failure

The European Society of Cardiology defines heart failure (HF) as "an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues, despite normal filling pressures (or only at the expense of increased filling pressures)",[1] while the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) defines HF as "a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood".[2]

Irrespective of the definition, clinically, HF is widely recognised as a syndrome with typical symptoms (e.g. dyspnoea, fatigue and exercise intolerance) and/or signs (e.g. peripheral oedema, elevated jugular venous pressure, pulmonary crackles) caused by an abnormality of cardiac structure and/or function.[1-3] These symptoms and signs can be identified based on medical history and physical examination, but many of them are non-specific and, therefore, are of limited diagnostic value; besides, before clinical symptoms/signs become apparent, patients can present with left ventricular dysfunction i.e. asymptomatic structural or functional cardiac abnormality, which is associated with increased risk of HF and death.[4] Consequently, determination of an underlying cardiac cause is pivotal to the diagnosis of HF, and this evidence can be obtained from plasma natriuretic peptides (NPs) measurements, electrocardiographic (ECG) and echocardiographic evaluation.[1-3]

1.1.2 Classification of heart failure

The left ventricular ejection fraction (LVEF) is central to the classification of patients with HF, not only because of different underlying aetiologies, demographics, comorbidities, prognosis and response to treatment, but also because most clinical trials selected patients based on LVEF. Mathematically, LVEF is the stroke volume (the end-diastolic volume minus the end-systolic volume) divided by the end-diastolic volume in the left ventricle, which is usually measured using echocardiography, radionuclide techniques, ventricular angiography or cardiac magnetic resonance imaging; a normal LVEF is generally considered to be >50%.

Based on LVEF, HF is typically classified as HF with reduced ejection fraction (HF-REF), HF with preserved ejection fraction (HF-PEF), and HF with mid-range ejection fraction (HF-MREF), respectively.[2, 3] HF-REF has been variably classified as LVEF ≤35%, ≤40%, and <40% in guidelines;[1-3] randomised controlled trials (RCTs) in HF-REF have mainly enrolled patients with an LVEF ≤35%[5, 6] or ≤40%.[7, 8] The diagnosis of HF-PEF requires LVEF ≥50% according to the latest guidelines,[2, 3] and patients with LVEF between 40% and 49% are considered to have HF-MREF.[2, 3] However, historically, the HF-PEF trials used different cut-off values of LVEF including >40%[9, 10], ≥45%[11, 12] and >45%,[13] in other words, patients with HF-MREF have generally been included in the trials of HF-PEF. The diagnosis of HF-PEF is more difficult than the diagnosis of HF-REF because it is largely one of exclusion of other potential non-cardiac causes of symptoms suggestive of HF. Patients with HF-PEF generally do not have a dilated left ventricle or markedly reduced contractility (i.e. systolic dysfunction), but instead have an increase in left ventricular wall thickness and left atrial size (reflecting diastolic dysfunction). Patients with HF-PEF tend to be older, more often female and obese with a history of hypertension and are less likely to have coronary heart disease, compared to patients with HF-REF. Overall, prognosis is better in patients with HF-PEF than those with HF-REF, although it is only in patients with HF-REF that therapies have been shown to reduce morbidity and mortality; none of the experimental therapies from RCTs has been demonstrated efficacy in patients with HF-PEF to date.

1.1.3 Incidence and prevalence of heart failure

The incidence of HF varies largely across studies reflecting difference in the diagnostic criteria applied and population studied (demographic composition, geographic region and time frame); in general, the reported incidence ranges from 1 to 9 cases per 1000 person-years.[14-18] Overall, HF occurs more frequently in the elderly than in a young population, and the incidence is higher in men than in women.[19] Data on temporal trends suggest that the incidence of HF may have stabilised and possibly be declining over time in both Europe and the United states (US). A Swedish study, based on a health register in Stockholm comprising 2.1 million people, reported an age- and sex-adjusted HF incidence of 3.8/1000 person-years in 2010 with a 24% decline compared to their national health data in 2006.[17] This result was echoed by a Scottish national-level study based on 5.1 million people, which showed the age-standardised incidence of first HF hospitalisation declined from 1.62/1000 person-years in 1994 to 1.05/1000 person-years in 2003 in men (a very similar trend for women).[20] Likewise, in the Olmsted County cohort from the US, the age- and sex-adjusted incidence of HF decreased substantially from 3.2 to 2.2 per 1000 person-years between 2000 and 2010, a 37.5% decrease over the decade.[16] A decline in the incidence was observed both for HF-REF and HF-PEF, but less pronounced in HF-PEF.[16]

HF affects about 1-3% of the adult population in the developed countries: an estimated 900,000 people live with HF in the United Kingdom (UK),[21] and this figure is about 6.5 million (2.5%) in the US.[22] Similarly, the estimated prevalence of HF is 2.2% in Sweden.[17] Overall, the estimated prevalence of HF is over 37.7 million worldwide.[14] The prevalence of HF increases with age, rising from 1.4-1.9% among those aged 40-59 years to 13.4-14.1% among those ≥80 years of age based on the 2011-2014 US National Health and Nutrition Examination Survey.[22] These numbers are commensurate with the previous data from the Rotterdam study.[23] Despite promising data suggesting the HF incidence is possibly decreasing, the prevalence of HF continues to rise, probably driven by the aging population, better prognosis of coronary heart disease, and improved survival as a result of better treatment and management of this disease.[2, 3, 22] The reported prevalence of HF-PEF varies from 22% to 73% of all HF cases, depending partly on the definition used and population studied, and based on the available data. Studies have reported that the proportion of patients with HF-PEF is increasing over time.[16, 24, 25]

1.1.4 Treatment of heart failure

The goals of treatment in patients with HF are to relieve symptoms, improve functional capacity and quality of life, prevent hospital admission and improve survival.

Some pharmacological therapies have proven to reduce hospitalisation and mortality in patients with symptomatic [New York Heart Association (NYHA) functional class II-IV] HF-REF. These include three pivotal neurohumoral antagonists, that is, angiotensin converting enzyme inhibitors (ACEI) [or an angiotensin receptor blocker (ARB)], a beta-blocker and a mineralocorticoid receptor antagonist (MRA), which can modify HF progression and have been recommended for treatment in every patient with HF-REF, unless not tolerated or contraindicated.[1-3] Very recently, in the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF), LCZ696 or sacubitril/valsartan, a combination of a neprilysin inhibitor and an ARB, has demonstrated superiority over enalapril (an ACEI) in reducing the risks of both mortality and HF hospitalisation, and is recommended as a replacement of ACEIs or ARBs in patients who remain symptomatic despite optimal medical therapy and who meet the trial criteria.[3, 26, 27] Ivabradine, a sinoatrial node modulator, reduces heart rate and has been shown to reduce the risk of cardiovascular (CV) death or HF hospitalisation, and has been recommended in selected patients with HF-REF in sinus rhythm with a resting heart rate ≥70 beats/min.[3, 26, 28] In conjunction with these evidence-based medications, diuretics are recommended and commonly used to alleviate the symptoms of congestion,[2, 3] although the effect of diuretics on morbidity and long-term survival in patients with HF has yet to be examined.

For device therapies, cardiac resynchronisation therapy (CRT) has been demonstrated to reduce all-cause mortality and hospitalisation for CV causes, and relieve symptoms and improve quality of life in selected patients with HF-REF.[29, 30] Accordingly, CRT is recommended in patients with HF-REF and QRS duration ≥130 ms and more specific indications are noted in the guidelines.[2, 3]

Implantable cardioverter defibrillators (ICDs) are highly effective in correcting lethal ventricular tachyarrhythmias. Two landmark trials have provided data on the primary prevention of sudden death by an ICD in patients with HF-REF, i.e. the Multicenter Automatic Defibrillator Implantation Trial-II (MADIT-II) in 2002 and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) in 2005.[31, 32] In detail, MADIT-II included 1232 patients with a prior myocardial infarction and a LVEF ≤30%, and use of an ICD was associated with a 31% reduced risk of overall mortality [Hazard ratio (HR) 0.69, 95% confidence interval (CI) 0.51-0.93, p=0.016] and an absolute decrease in the mortality rate of 9% after 3 years (from 31% to 22%).[31] In SCD-HeFT, ICD treatment reduced all-cause death by 23% (HR 0.77, 95% CI 0.62-0.96, p=0.007) in patients with NYHA class II-III HF and a LVEF ≤35%, with an absolute reduction in the mortality rate of 7% in 5 years (from 36% to 29%).[32] The effect on all-cause death did not vary according to the cause of HF (p value for interaction 0.68), but there was only a trend in the reduction of all-cause death either in the ischaemic (HR 0.79, 97.5% CI 0.60-1.04, p=0.05) or non-ischaemic (HR 0.73, 97.5% CI 0.50-1.07, p=0.06) subgroup.[32] One year before the publication of SCD-HeFT, the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) study did not find a significant survival benefit of ICD (HR 0.65, 95% CI 0.40-1.06, p=0.08) in 458 patients with non-ischaemic cardiomyopathy who had a LVEF <36% and NYHA class I-III symptoms.[33] Nevertheless, in a meta-analysis by Desai *et al.* of 5 trials including 1854 patients with non-ischaemic HF, use of an ICD was associated with a 31% decreased risk of all-cause death (HR 0.69, 95% CI 0.55-0.87, p=0.002).[34] These decade-old studies are the basis of the evidence for the recommendations of ICD implantation in the current guidelines.[2, 3] However, there is an inconsistency in the level of evidence for non-ischaemic cardiomyopathy between the current American and European guidelines.[2, 3] In the American guidelines, the findings from the SCD-HeFT and MADIT-II led to class IA recommendations of ICD implantation for primary prevention of sudden death in patients with NYHA class II-III symptomatic HF and a LVEF ≤35%, with no difference between patients with ischaemic and non-ischaemic causes.[2] By contrast, in the European guidelines, findings from the DEFINITE trial, the subgroup analysis of the SCD-HeFT and the meta-analysis by Desai *et al.* altogether led to class IB recommendation for patients with non-ischaemic HF, as opposed to class IA recommendation for patients with ischaemic HF.[3]

It is worth to mention that since the publication of SCD-HeFT, there has been an increasing use of evidence-based therapies including beta-blockers, MRAs and CRT. In SCD-HeFT, only 69% of patients received a beta-blocker at baseline, and 19% received a MRA and none received CRT.[32] Very recently, in the DANish study to assess the efficacy of ICDs in patients with non-ischemic Systolic Heart failure on mortality (DANISH), more than 90% of patients received a beta-blocker at baseline and nearly 60% received a MRA and 58% received CRT.[35] After a median 67.6 months of follow-up, the study did not find a significant survival benefit of ICD (HR 0.87, 95% CI 0.68-1.12, p=0.28). However, there was an interaction between the ICD effect and age (p value for interaction 0.009). Use of an ICD was associated with a 36% lower risk of all-cause death in patients younger than 68 years (HR 0.64, 95% CI 0.45-0.90, p=0.01), but not in patients ≥68 years (HR 1.19, 95% CI 0.81-1.73, p=0.38). The effect of ICD treatment on all-cause death was the same regardless of CRT status (p value for interaction 0.73). In the subgroup of patients without CRT, ICD did not reduce the risk of all-cause mortality, and this was also the case in the CRT subgroup. In patients who received a CRT defibrillator (CRT-D) there was no difference in survival compared to patients who received a CRT pacemaker alone (CRT-P) (HR 0.91, 95% CI 0.64-1.29, p=0.59).[35] Likewise, in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) study,[30] CRT-D was not superior to CRT-P (p =0.12) in reducing the risk of all-cause death in later analyses of the data by independent authors,[36] although both reduced the risk of mortality compared to optimal medical therapy.[30]

In patients with HF-PEF, none of the medical treatments tested, including candesartan, irbesartan, perindopril and spironolactone, have been shown to reduce morbidity and mortality,[9-12] and the efficacy of device therapies has yet to be examined. Diuretics are used to relieve symptoms of congestion as in HF-REF. Adequate management of comorbidities, such as atrial fibrillation, hypertension, myocardial ischaemia and dysglycaemia, is considered important in HF-PEF, though there is limited evidence in guide what specific treatment approaches are most effective.[2, 3] On the basis of the favourable effects in PARADIGM-HF in HF-REF and in a phase II trial in HF-PEF,[27, 37] sacubitril/valsartan is under examination in the ongoing Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction (PARAGON-HF) trial.[38] There is another ongoing trial to evaluate the benefit of ICD therapy in patients with relatively preserved ejection fraction (LVEF 36-50%) and the presence of late gadolinium enhancement on cardiovascular magnetic resonance (CMR) imaging (CMR-Guide trial, ClincalTrial.gov number NCT01918215).[2, 3]

Ventricular assist devices (VADs) have emerged as a viable therapeutic option for patients with end-stage HF who are refractory to optimal medical therapy. VADs are typically used as a bridge to recovery or a bridge to transplantation, and are increasingly used as destination therapy.[2, 3] Bridge to recovery is for patients who only need temporary support after which the heart recovers and the VAD is then removed. Bridge to transplantation is for patients who are eligible for heart transplantation and to keep them alive until a donor heart becomes available. Destination therapy is for patients with end-stage HF who are ineligible for transplantation, or as a permanent alternative for heart transplantation for patients long-term waiting for transplant.[2, 3] Heart transplantation is the gold standard treatment in carefully selected patients with refractory end-stage HF, which has been shown to improve long term survival and increase functional status and quality of life.[2, 3] Nevertheless, heart transplantation is a limited treatment option for patients with end-stage HF, given that the number of patients on the transplant waiting list exceeds the availability of donor hearts. Besides, issues with rejection and the consequences of long-term immunosuppressive therapy after transplant remain problematic.[2, 3] Accordingly, for patients eligible for transplantation, VADs, initially used as a short-term bridge to transplant, have increasingly been used as a permanent alternative to heart transplant.

1.1.5 Prognosis of heart failure

Although community-based studies suggest that overall survival in patients with HF has improved over time, prognosis remains poor with a mortality rate of 40-60% within 5 years of diagnosis.[19, 39] Survival is generally better in patents with HF-PEF than in HF-REF,[25, 40] but the trend in improvement of survival has been primarily observed in those with HF-REF but not in HF-PEF,[25] which has been attributed to the advances in therapies and their implementation in the HF-REF population.[2, 3]

The majority of patients with HF die from CV causes, and the proportion varies with study design (trial or population-based), study population and time period of study; [3, 41] in general, deaths attributed to non-CV causes are proportionally higher in community-based studies and among patients with HF-PEF, and there has been an increase in the proportion of non-CV deaths over time both in HF-

REF and HF-PEF.[16, 42, 43] The shift in the distribution of death toward non-CV causes may reflect the cumulative benefit of HF therapies in reducing CV death in HF-REF, and the increasing comorbidity burden due to the elderly nature in HF-PEF. The risk of CV death is generally decreasing but remains significant, and sudden death and pump failure death account for the majority of CV death in HF.[3, 41, 44] I will summarise the definitions, incidences and treatment available for both modes of death in the next section.

1.2 Sudden death and pump failure death in heart failure

1.2.1 Classification of mode-specific death

Historically, there has existed heterogeneity in the definitions of sudden death and a lack of reporting or detailed information on the definitions of pump failure death in HF studies before mid-1990s.[45] Thereafter, a framework was proposed for classification of mode of death in HF, calling for recording detailed information on (A) activity and place of death, (C) cause of death, (M) mode of death and (E) events associated with death.[45] Despite its anticipated value in characterising death events, systematically collecting this information would be resource intensive and hard to achieve. Consequently, over the last two decades, definitions for each mode of death used among HF studies were broadly similar, but not uniform in terms of details regarding timing of the event, presence of a witness and clinical conditions before death. More recently, consensus efforts have been made by the ACCF and AHA in collaboration with the US Food and Drug Administration (FDA) to standardise definitions of cardiovascular endpoint events used in clinical trials.[46] Sudden death has been defined in a more detailed way: “death that occurs unexpectedly, not following an acute MI; death witnessed and occurring without new or worsening symptoms; death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI; death witnessed and attributed to an identified arrhythmia (e.g., captured on an ECG recording, witnessed on a monitor, or unwitnessed but found on ICD review); death after unsuccessful resuscitation from cardiac arrest; death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac aetiology; or unwitnessed death in a subject seen alive and clinically stable ≤24 hours prior to being found dead without any evidence supporting a specific non-CV cause of death (information regarding the patient's clinical status preceding death should be provided, if available)". Pump failure death has been defined as "death associated with clinically worsening symptoms and/or signs of HF, regardless of HF aetiology (deaths due to HF can have various aetiologies, including single or recurrent myocardial infarctions, ischaemic or non-ischaemic cardiomyopathy, hypertension, or valvular disease)". Worsening symptoms due to HF include dyspnoea, decreased exercise tolerance, fatigue, worsened end-organ perfusion and volume overload. And worsening signs of HF include peripheral oedema, increasing abdominal distention or ascites, pulmonary rales/crackles/crepitations, increased jugular venous pressure and/or hepatojugular reflux, S3 gallop, and clinical significant or rapid weight gain thought to be related to fluid retention.

Standardisation of endpoint definitions is of great importance to achieve uniform event reporting and data collection. It should help reduce the bias of event adjudication within a trial between central endpoint committee members, and enhance the event consistency across trials and across health care systems thus facilitating combined or comparative analyses.

1.2.2 Risk of mode-specific death in heart failure

The rates of mode-specific death have varied across studies in terms of study design, study population (e.g. HF type, disease severity, demographics, comorbidity burden), classification of mortal events (definition and case ascertainment) and time (the calendar year of study and the duration of follow-up).

Looking at study design, compared to clinical trials, population-based studies, generally, are less likely to present specific breakdown of death events from CV and non-CV causes, and if provided, death events were less often adjudicated by a central endpoint committee. Besides, population-based studies are highly variable in terms of setting of enrolment (e.g. primary care, outpatient clinic, hospital discharge/admission), study sample size (and events), and follow-up duration. Accordingly, data on mode-specific death from population-based studies are scarce and variable. Among patients with HF-REF, a Japanese cardiac register study reported that 23% of total mortality among the hospitalised HF patients was attributed to sudden death, and 37% due to pump failure and 18% due to non-CV causes.[47] Rather consistent rates of sudden death (18% and 20%) and pump failure death (34% and 33%) were reported from another two cohort studies, although the contribution of non-CV death to the overall mortality was variable (47% and 28%).[48, 49] In patients with HF-PEF, sudden death accounted for about 7-15% of total mortality, whereas the proportions of deaths attributed to pump failure and non-CV causes varied widely, ranging from 17% to 60% and from 17% to 86% respectively.[44] Based on clinical trial studies, in patients with HF-REF, sudden death was reported to account for average 42% (range 23-58%) of total mortality, followed by pump failure death at 36% (range 27-56%), whereas non-CV death accounted for a smaller proportion at 14% (range 4-20%).[50] In patients with HF-PEF, sudden death accounted for average 25% (range 21-28%) of overall mortality, pump failure death at 15% (range 13-21%) and non-CV death at 32% (29-37%).[50]

There are several observational studies that have performed point-to-point comparisons of the risks of mode-specific death in patients with HF between different therapeutic periods. Cubbon R *et al*. reported a significant reduction in sudden death (from 34% to 13%) and a concomitant increase in non-CV death (11% to 41%), with negligible change in pump failure death (41% to 37%) as a proportion of total mortality among patients with ambulant HF-REF recruited between 1993-1995 and 2006-2009 in the same geographic region in the UK.[51] Similarly, a decrease in the contribution of sudden death and an increase in non-CV death to overall mortality was also observed among patients with severe HF awaiting heart transplantation in a single centre in the US and among patients with HF with mixed LVEF in the Tohoku district of Japan.[52, 53] However, the temporal trends in rates of mode-specific death over time have yet to be examined, in particular with adjustment for detailed patient characteristics at baseline.

1.2.3 Effects of heart failure treatment on mode-specific death

The currently recommended neurohumoral therapies for HF-REF, including ACEIs or ARBs,[54, 55] beta-blockers,[56] and MRAs,[57] all reduce the risk of sudden death. Evidence from meta-analyses of RCTs demonstrated that, compared to placebo, ACEIs reduced the risk of sudden death by 20% (odds ratio 0.80, 95% CI 0.70-

0.92, p≤0.001),[54] beta-blockers by 31% (odds ratio 0.69, 95% CI 0.62-0.77, p<0.00001) and MRAs by 23% (odds ratio 0.77, 95% CI 0.66-0.89, p=0.001).[56, 57] A study of Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) programs showed that candesartan (an ARB) reduced sudden death by 15% compared to placebo (HR 0.85, 95% CI 0.73-0.99, p=0.036).[55] In the PARADIGM-HF, sacubitril/valsartan reduced the risk of sudden death by 20% compared with enalapril (HR 0.80, 95% CI 0.68-0.94, P=0.008) in patients who were receiving guideline recommended medications including a beta-blocker and a MRA.[58] Ivabradine did not reduce the risk of sudden death.[28]

With the cumulative use of these neurohumoral therapies, the residual risk of sudden death may be decreasing, and the overall survival benefit of ICD may have diminished to non-significant levels. However, ICDs have been shown to be effective in reducing the risk of sudden death in HF-REF, irrespective of aetiology. Use of an ICD led to a 67% reduction in sudden death (HR 0.33, 95% CI 0.20-0.59, p<0.001) in patients with ischaemic HF in MADIT-II,[59] and a 80% reduction (HR 0.20, 95% CI 0.06-0.71, p=0.006) in patients with non-ischaemic cardiomyopathy in DEFINITE, although in the latter trial this effect was based upon a tiny number of events.[33] Likewise, in SCD-HeFT an ICD reduced the risk of sudden death in the ischaemic (HR 0.43, 95% CI 0.27-0.67) and non-ischaemic (HR 0.34, 95% CI 0.17-0.70) causes of HF.[60] In the very recent DANISH study, ICD treatment reduced sudden death by 50% in patients with non-ischaemic cardiomyopathy (HR 0.50, 95% CI 0.31-0.82, p=0.005).

CRT had a neutral effect on sudden death compared to optimal medical therapy (HR 1.04, 95% CI 0.73-1.46, p=0.84) based on the evidence from a meta-analysis of 5 RCTs,[61] although individual trials had mixed results. In an extended report from the Cardiac REsynchronization-Heart Failure (CARE-HF) trial, CRT-P reduced sudden death by 46% (HR 0.54, 95% CI 0.35-0.84, p=0.006),[62] while in the COMPANION trial CRT-P had no effect on sudden death (HR 1.21, 95% CI 0.70-2.07, p=0.485), but CRT-D reduced sudden death by 56% (HR 0.44, 95% CI 0.23-0.86, p=0.02).[63] This may reflect that CRTs modify left ventricular remodelling and improve cardiac function which may have the paradoxical effect of appearing to increase death due to arrhythmia. Beneficial left ventricular remodelling can reduce the arrhythmia burden, but can also lead to greater exposure to the risk of sudden death by reducing the rate of pump failure death.[3] It is unclear if the reduction in sudden death with an ICD is independent of CRT status. Although in the DANISH there was no difference in the overall survival benefit of an ICD between patients with and without an CRT, the interaction was not reported for mode-specific death.[35]

Based on individual studies, both enalapril and candesartan reduced the risk of pump failure death by 22% compared to placebo (HR 0.78, 95% CI 0.65-0.94, p <0.01).[55, 64] In PARADIGM-HF, sacubitril/valsartan reduced the risk of pump failure death by 21% compared to enalapril (HR 0.79, 95% CI 0.64-0.98, p=0.034).[58] The effect of beta-blockers on pump failure death had mixed results from individual studies and no meta-analysis is yet available to provide a synthesised estimate.[65] This is also the case for the effect of MRAs on pump failure death: spironolactone reduced pump failure death by 36% compared to placebo (HR 0.64, 95% CI 0.51-0.80, p<0.001) in patients with severe HF, while eplerenone only showed a trend in reduction (HR 0.77, 95% CI 0.55-1.08, p=0.12) in patients with mild symptomatic HF who were already receiving an ACEI/ARB and a beta-blocker.[66, 67] Ivabradine reduced the risk of pump failure death by 26% compared to placebo (HR 0.74, 95% CI 0.58-0.94, p=0.014).[28] CRT, either alone or in combination with an ICD, reduced the risk of pump failure death compared to optimal medical therapy.[62, 63] In a meta-analysis of 5 RCTs, use of CRT led to a 38% reduction of pump failure death (HR 0.62, 95% CI 0.46-0.85, p=0.003).[61] ICD treatment alone had no effect on the risk of pump failure death in SCD-HeFT,[60] and the effect of ICDs on pump failure death was not reported in the other ICD trials (of course, an ICD would not be expected to reduce pump failure death).[33, 35, 59]

In HF-PEF, none of the examined neurohumoral therapies, including ARBs[50, 55] and MRAs,[12] reduced the risk of sudden death or pump failure death. The effect of a beta-blocker on either mode of death was not reported, probably due to small study size and few events.[10] Device therapies have yet to be examined in this population.

1.2.4 Summary

The last two decades have witnessed advances in, and implementation of evidence-based therapies in patients with HF-REF, along with the changing risk profiles and comorbidities in both HF-REF and HF-PEF populations. It is of great interest and importance to discover if these changes have translated into temporal changes (and corresponding trends over time) in the risks of sudden death and pump failure death in both populations. There are limited data on mode-specific death from population-based studies which tend to vary greatly in terms of study participants, study size and follow-up duration, and which have relatively sparse patient characterisation at baseline. By contrast, cohorts from clinical trials have more detailed baseline characterisation, which allows more complete multivariable adjustment, and more standardised follow-up and event sub-classification and adjudication, which may reduce the bias and variation within a study. Accordingly, I will examine the trends in the risks of sudden death and pump failure death over time in patients with HF-REF enrolled in 13 clinical trials conducted between 1995-2015 and in patients with HF-PEF from 3 clinical trials over the period 1999-2013 respectively.

Apart from examining the rate of mode-specific death in population level, it would be of interest and importance to predict the risk of mode-specific death in individual patients. Accurate risk prediction for mode-specific death in individual patients can help with better risk stratification and aid clinicians and patients in decision making. Among patients with HF-REF, identification of high-risk subgroups would help target costly interventions, such as ICDs and LVADs, to those most in need, and identifying low-risk subgroups would avoid unnecessary treatment and improve the cost-effectiveness of these interventions. Among patients with HF-PEF, knowledge of prognosis would facilitate further research into the efficacy of specific interventions in this population, e.g. designing randomised controlled trials in selected patients with high risks. Existing risk stratification models focus on predicting all-cause mortality in HF patients, which have been systematically reviewed.[68-70] Fewer models have been developed to predict mode-specific death, i.e. sudden death and pump failure death, and their characteristics and performance have not been appraised. Therefore, in the next section I will perform a systematic review to identify published models to predict sudden death and pump failure death in patients with chronic ambulatory HF, to summarise and compare their characteristics and performance, and to evaluate their clinical utility.

1.3 Prognostic models for sudden death and pump failure death in heart failure

1.3.1 Methods

1.3.1.1 Search strategy

A systematic search was performed in the electronic databases MEDLINE and Embase, limited to adult human subjects and English language. Relevant key search terms were combined including “heart failure” and “ambulatory” and “mortality” or “survival” or “sudden death” or “pump failure death” and “model” or “predict”. The search terms and search strategy in detail are presented in Appendix Table 1 and Appendix Table 2. The search was last updated on 17 April 2017. Bibliographic references of eligible studies and relevant reviews were hand searched to identify additional studies.

1.3.1.2 Review methods and selection criteria

Retrieved articles from MEDLINE and Embase databases were combined in the reference manager Endnote (Version X7). After eliminating duplicate papers, I screened the titles and abstracts of the retrieved publications, and then examined full-text versions of all publications considered potentially relevant. Studies were eligible if they enrolled adult (≥18 years) patients with chronic ambulatory HF, reported multivariable analysis (≥2 predictors) to predict sudden death, pump failure death or both. There were no restrictions on study design, LVEF or geographic regions. Studies were excluded if they enrolled patients exclusively during a hospital admission, i.e. patients with acutely decompensated heart failure. For studies based on the same study cohorts, those with shorter follow-up or smaller sample size were excluded if they provided no additional information.

1.3.1.3 Data extraction and data analysis

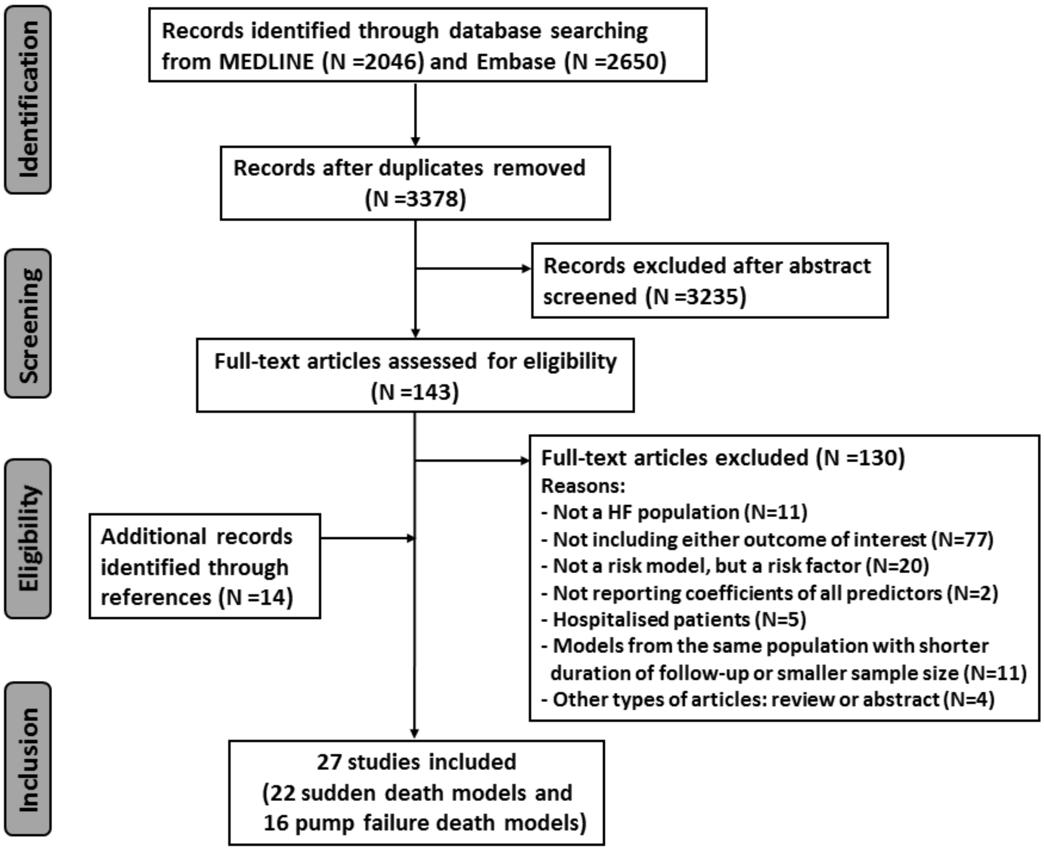
Data extraction was undertaken by outcome (i.e. sudden death or pump failure death). For each included study, the information collected is outlined in detail in Appendix Table 3, which mainly included the aspects of study characteristics, patient characteristics, outcome of interest, model construction, model validity, model performance and handling of missing data. Data were summarised and analysed according to these elements, with a focus on model construction (modelling approach, model assumption, individual predictors and the ratio of number of predictors and number of events) and model performance (discrimination, calibration and validation).

Overfitting refers to a scenario of having too many variables relative to the number of observations/events in a regression model, which may lead to random error or noise. To avoid overfitting, there is a rule of thumb that there should be at least 10 events for each final prediction variable of a multivariable model.[71] Model discrimination, known as "separation", refers to the ability to distinguish individuals who develop an event from those who do not, and is commonly examined using C statistics, e.g. ROC AUC (area under the curve of receiver operating characteristic curve) or Harrell's C statistic.[72] C statistics generally range from 0.5 (random concordance) to 1 (perfect concordance), the higher the C statistic, the better the model discrimination. Model calibration is also known as 'prediction accuracy', refers to the magnitude of agreement between predicted and observed event rates at a population level.[72] Model validation examines the reliability of model performance when a model is applied to another cohort.[73] These three aspects are indispensable in evaluating a model. I will explain these concepts in detail in the Chapter 2 Methods. Finally, I will select the best existing models for mode-specific death and point out their limitations if any.

1.3.2 Results

A total of 2046 citations were identified from MEDLINE and 2650 from Embase. After removing duplicate records, the titles and abstracts of 3378 citations were screened, and 143 full-text articles were further assessed for eligibility with additional 14 publications identified through references. In total, 27 studies were finally included in this analysis,[74-100] comprising 22 models to predict sudden death[74-82, 84-86, 89, 91-93, 95-100] and 16 models for pump failure death,[75, 78-80, 82-85, 87, 88, 90, 91, 94, 98-100] all of which were published between 1994 and 2015. The diagram of study selection process is displayed in Figure 1-1.

Figure 1-1 Diagram of study selection process in the literature review



1.3.2.1 Study characteristics

For the models that predicted sudden death, the majority, 11 (50%) studies, were based on prospective cohort data, 6 (27%) from clinical trial databases, 2 (9%) from the combination of trial databases and registry data, 1 (5%) from retrospective patient records and 2 (9%) were unspecified (Table 1-1). Most studies, 12 (55%), developed models that used data collected from European cohorts, only 1 (5%) used data from North America, 4 (18%) were derived from data from Japan and the remaining 5 (23%) used clinical trial databases that randomised patients across the world. Of these clinical trial databases most randomised patients were from North America and Europe. The sample size of the studies varied largely: 11 (50%) studies included <500 participants, and only 7 (32%) studies had a sample size of ≥1000 patients. Of the 16 (73%) studies reporting the calendar time of data collection, most, 10 (67%) studies, used data collected by the year 2000, before the broad use of modern guideline-recommended treatments such as beta-blockers and MRAs. The average duration of follow-up ranged from 6.1 months to 11.7 years, with the majority in the range of 2 to 4 years.

Of the models to predict pump failure death, most, 10 (63%) studies, were based on prospective cohort data, 3 (19%) used clinical trial databases, and 1 (6%) was based on the combination of registry data and trial databases, leaving 2 (12%) unspecified (Table 1-2). 9 (56%) studies used data collected from European cohorts, 3 (19%) from Japanese cohorts, only 1 (6%) from the US and the remaining 3 (19%) used data from clinical trials that randomised patients worldwide but most from Europe and North America. The majority, 10 (63%) studies, had a sample size of <500 participants, and only 3 (19%) studies included over 1000 participants. 11 (69%) studies reported data collection time, about half (45%) of which were collected by the year 2000. The average duration of follow-up ranged from 6 months to 6.9 years, and the majority were within the range of 2-4 years.

Table 1-1 Study and patient characteristics for sudden death models

Publication	Study characteristics					Patient characteristics		
	Data source	**Country (No. centres)**	**Sample size**	**Study period**	**Follow-up duration**	**HF subtype**	**Patient population (age, sex, LVEF, and NYHA class III-IV)**	**Baseline medication**
Kawai,[75] 2015	Prospective cohort study	Japan (1)	81	NR	Mean 6.9 years	HF-REF	Mean age 63 years, men (77%), LVEF<35% and mean LVEF 26%, NYHA class III-IV (26%)	ACEI/ARB (85%), beta-blocker (67%), MRA (64%)
Shadman,[74] 2015	Registry + trial database (PRAISE, Val-HeFT, COMET, Italian HF Registry, University of Washington cohort)	International (NR)	9885	NR	Mean 28 months	Mixed	Median age 64 years, men (79%), median LVEF 27%, NYHA class III-IV (49%)	ACEI/ARB (96%), beta-blocker (47%), MRA (6%)
Adabag,[76] 2014	Trial database (I-PRESERVE)	International (293)	4128	2002-2008	Mean 49.5 months	HF-PEF	Age >60 years and mean age 72 years, men (40%), LVEF ≥45% and mean LVEF 60%, NYHA class III-IV (79%)	ACEI (25%), beta-blocker (58%), MRA (15%)
Furukawa,[77] 2013	Patient records (retrospective)	Japan (1)	132	1995-2002	Mean 6.7 years	HF-REF	Mean age 63 years, men (80%), LVEF <40% and mean LVEF 30%, NYHA class III-IV (18%)	ACEI/ARB (85%), beta-blocker (69%), MRA (56%)
Smilde,[81] 2009	Trial database (Dutch ibopamine multicenter trial)	Netherlands (NR)	90	1989-2002	Mean 11.7 years	HF-REF	Mean age 60 years, men (85%), LVEF <45% and mean LVEF 29%, NYHA class III-IV (20%)	NR
Tamaki,[80] 2009	Prospective cohort study	Japan (1)	106	NR	Mean 65 months	HF-REF	Mean age 64 years, men (76%), LVEF <40% and mean LVEF 30%, NYHA class III-IV (22%)	ACEI (70%), beta-blocker (75%), MRA (NR)
Vazquez,[79] 2009	Prospective cohort study (MUSIC study)	Spain (8)	992	2003-2007	Median 44 months	Mixed EF>45% (25%)	Mean age 65 years, men (72%), LVEF 10-70% and mean LVEF 37%, NYHA class III-IV (22%)	ACEI/ARB (74/17%), beta-blocker (68%), MRA (38%)
Wedel,[78] 2009	Trial database (CORONA)	International (371)	3342	2003-2007	Median 32.8 months	HF-REF	Age ≥60 years and mean age 73 years, men (75%), LVEF≤40% (≤35% if NYHA class II) and mean LVEF 31%, NYHA class III-IV (63%), ischaemic aetiology (100%)	ACEI/ARB (92%), beta-blocker (77%), MRA (39%), ICD (2.3%)
Uretsky,[82] 2008	Trial database (CARE-HF)	Europe (82)	813	2001-2005	Mean 36.4 months	HF-REF	Median age 67 years, men (74%), LVEF≤35% and mean LVEF 25%, NYHA class III-IV (100%), cardiac dyssynchrony (100%)	ACEI/ARB (95%), beta-blocker (72%), MRA (56%)
Guazzi,[85] 2007	NR	Italy (NR)	156	NR	Mean 23.6 months	Unspecified	Mean age 61 years, men (80%), mean LVEF 35%, NYHA class III-IV (29%)	ACEI (76%), beta-blocker (46%), MRA (39%)

Mozaffarian,[84] 2007	Registry + trial database (PRAISE, ELITE2, Val-HeFT, RENAISSANCE, Italian HF Registry, University of Washington cohort)	International (NR)	10538	NR	Mean 1.6 years	Mixed	Mean age 65 years, men (76%), mean LVEF 28%, NYHA class III-IV (51%)	ACEI/ARB (80/39%), beta-blocker (31%), MRA (NR)
Watanabe,[86] 2006	Prospective cohort study (CHART study)	Japan (26)	680	2000-2004	Mean 26 months	HF-REF	Mean age 66 years, men (69%), LVEF <50% and mean LVEF 42%, NYHA class III-IV (19%)	ACEI/ARB (71%), beta-blocker (39%), MRA (20%)
Kearney,[89] 2004	Prospective cohort study (UK-HEART study)	UK (8)	553	1993-2000	5 years	Mixed	Mean age 63 years, men (76%), mean LVEF 42% and LVEF >45% (36%), NYHA class III-IV (39%)	ACEI/ARB (81%), beta-blocker (8%), MRA (NR)
Isnard,[93] 2003	Prospective cohort study	France (1)	250	1996-2000	Median 584 days	HF-REF	Mean age 54 years, men (NR), LVEF <45% and mean LVEF 29%, NYHA class III-IV (55%)	ACEI (89%), beta-blocker (21%), MRA (14%)
La Rovere MT,[92] 2003	Prospective cohort study	Italy (NR)	202	1991-1995	Mean 3 years	HF-REF	Mean age 54 years, men (87%), LVEF 23%, NYHA Class II-III (88%)	ACEI/ARB (90%), beta-blocker (6%), MRA (NR)
Poole-Wilson,[91] 2003	Trial database (ATLAS)	International (287)	3164	1992-1997	Median 46 months	HF-REF	Mean age 64 years, men (80%), LVEF ≤30% and mean LVEF 23%, NYHA class III-IV (84%)	ACEI/ARB (100%), beta-blocker (11%), MRA (NR)
Baldasseroni,[96] 2002	Prospective cohort study	Italy (150)	5517	1995-2000	1 year	Unspecified	Mean age 63 years, men (76%), LVEF (NR), NYHA class III-IV (28%)	ACEI/ARB (84%), beta-blocker (18%), MRA (NR)
Berger,[95] 2002	Prospective cohort study	Austria (1)	452	1995-2000	Mean 592 days	HF-REF	Mean age 54 years, men (87%), LVEF ≤35% and mean LVEF 20%, NYHA class III-IV (54%)	ACEI/ARB (89/5%), beta-blocker (30%), MRA (NR)
Teerlink,[97] 2000	Trial database (PROMISE)	The US and Canada (119)	1080	1989-1990	6.1 months	HF-REF	Mean age 64 years, men (78%), LVEF ≤35% and mean LVEF 21%, NYHA class III-IV (100%)	ACEI/ARB (100%), beta-blocker (NR), MRA (NR)
Madsen,[99] 1997	Prospective cohort study	Denmark (1)	190	1988-1990	Median 24.5 months	Unspecified	Mean age 66 years, men (72%), median LVEF 30%, NYHA class III-IV (46%)	ACEI/ARB (33%), beta-blocker (4%), MRA (NR)
Szabo,[98] 1997	NR	Netherlands (1)	159	NR	Mean 23 months	HF-REF	Mean age 60 years, men (NR), LVEF <40% and mean LVEF 27%, NYHA class III-IV (38%)	NR
Szabo,[100] 1994	Prospective cohort study	Netherlands (1)	211	1988-1992	Mean 21 months	HF-REF	Mean age 63 years, men (76%), LVEF <45% and mean LVEF 26%, NYHA class III-IV (NR)	ACEI (42%), beta-blocker (15%), MRA (NR)

CARE-HF, Cardiac Resynchronization in Heart Failure; CHART, Chronic Heart failure Analysis and Registry in Tohoku district; ELITE2, Evaluation of Losartan in the Elderly; NR, not reported; PRAISE, Prospective Randomized Amlodipine Survival Evaluation; PROMISE, Prospective Randomized Milrinone Survival Evaluation; RENAISSANCE, Randomized Enbrel North American Strategy to Study Antagonism of Cytokines.

Table 1-2 Study and patient characteristics for pump failure death models

Publication	Study characteristics					Patient characteristics		
	Data source	Country (No. centres)	Sample size	Study period	Follow-up duration	HF subtype	Patient population	Baseline medication
Kawai,[75] 2015	Prospective cohort study	Japan (1)	81	NR	Mean 6.9 years	HF-REF	Mean age 63 years, men (77%), LVEF<35% and mean LVEF 26%, NYHA class III-IV (26%)	ACEI/ARB (85%), beta-blocker (67%), MRA (64%)
Tamaki,[80] 2009	Prospective cohort study	Japan (1)	106	NR	Mean 65 months	HF-REF	Mean age 64 years, men (76%), LVEF <40% and mean LVEF 30%, NYHA class III-IV (22%)	ACEI (70%), beta-blocker (75%), MRA (NR)
Vazquez,[79] 2009	Prospective cohort study (MUSIC study)	Spain (8)	992	2003-2007	Median 44 months	Mixed	Mean age 65 years, men (72%), LVEF 10-70% and mean LVEF 37% and LVEF >45% (25%), NYHA class III-IV (22%)	ACEI/ARB (74/17%), beta-blocker (68%), MRA (38%)
Wedel,[78] 2009	Trial database (CORONA)	International (371)	3342	2003-2007	Median 32.8 months	HF-REF	Age ≥60 years and mean age 73 years, men (75%), LVEF≤40% (≤35% if NYHA class II) and mean LVEF 31%, NYHA class III-IV (63%), ischaemic aetiology (100%)	ACEI/ARB (92%), beta-blocker (77%), MRA (39%)
Mehta,[83] 2008	Prospective cohort study	UK (2)	396	2004-2006	Median 370 days	Mixed	Median age 75 years, men (61%), mean LVEF 38%, NYHA class III-IV (88%)	ACEI/ARB (72/7%), beta-blocker (31%), MRA (20%)
Uretsky,[82] 2008	Trial database (CARE-HF)	Europe (82)	813	2001-2005	Mean 36.4 months	HF-REF	Median age 67 years, men (74%), LVEF≤35% and mean LVEF 25%, NYHA class III-IV (100%), cardiac dyssynchrony (100%)	ACEI/ARB (95%), beta-blocker (72%), MRA (56%)
Guazzi,[85] 2007	NR	Italy (NR)	156	NR	Mean 23.6 months	Unspecified	Mean age 61 years, men (80%), mean LVEF 35%, NYHA class III-IV (29%)	ACEI (76%), beta-blocker (46%), MRA (39%)

Mozaffarian,[84] 2007	Registry + trial database (PRAISE, RENAISSANCE, ELITE2, Val-HeFT, Italian HF Registry, University of Washington cohort)	International (NR)	10538	NR	Mean 1.6 years	Mixed	Mean age 65 years, men (76%), mean LVEF 28%, NYHA class III-IV (51%)	ACEI/ARB (80/39%), beta-blocker (31%), MRA (NR)
Berger,[87] 2005	Prospective cohort study	Austria (1)	452	1995-2000	Mean 592 days	HF-REF	Mean age 54 years, men (87%), LVEF ≤35% and mean LVEF 20%, NYHA class III-IV (54%)	ACEI/ARB (89/5%), beta-blocker (30%), MRA (NR)
Kyuma,[88] 2004	Prospective cohort study	Japan (1)	158	1999-2001	16 months	Mixed	Mean age 64 years, men (70%), mean LVEF 41% and LVEF ≥50% (20%), NYHA class III-IV (39%)	ACEI/ARB (64%), beta-blocker (55%), MRA (39%), ICD (8%)
Poole-Wilson,[91] 2003	Trial database (ATLAS)	International (287)	3164	1992-1997	Median 46 months	HF-REF	Mean age 64 years, men (80%), LVEF ≤30% and mean LVEF 23%, NYHA class III-IV (84%)	ACEI/ARB (100%), beta-blocker (11%), MRA (NR)
Vrtovec,[90] 2003	Prospective cohort study	US (1)	241	2001	6 months	HF-REF	Mean age 67 years, men (59%), mean LVEF 27%, NYHA class III-IV (100%)	ACEI (87%), beta-blocker (73%), MRA (NR)
Kearney,[89] 2002	Prospective cohort study (UK-HEART study)	UK (8)	553	1993-2000	5 years	Mixed	Mean age 63 years, men (76%), mean LVEF 42% and LVEF >45% (36%), NYHA class III-IV (39%)	ACEI/ARB (81%), beta-blocker (8%), MRA (NR)
Madsen,[99] 1997	Prospective cohort study	Denmark (1)	190	1988-1990	Median 24.5 months	Unspecified	Mean age 66 years, men (72%), median LVEF 30%, NYHA class III-IV (46%)	ACEI/ARB (33%), beta-blocker (4%), MRA (NR)
Szabo,[98] 1997	NR	Netherlands (1)	159	NR	Mean 23 months	HF-REF	Mean age 60 years, men (NR), LVEF <40% and mean LVEF 27%, NYHA class III-IV (38%)	NR
Szabo,[100] 1994	Prospective cohort study	Netherlands (1)	211	1988-1992	Mean 21 months	HF-REF	Mean age 63 years, men (76%), LVEF <45% and mean LVEF 26%, NYHA class III-IV (NR)	ACEI (42%), beta-blocker (15%), MRA (NR)

Abbreviations are same as Table 1-1.

1.3.2.2 Patient characteristics

For sudden death, 14 (64%) models were derived from patients with HF-REF and only 1 (5%) model from patients with HF-PEF;[76] the remaining 7 (32%) studies included all HF patients regardless of LVEF or did not specify the left ventricular systolic function further (Table 1-1). The average age of the patients in these studies ranged from 54 to 73 years, with the majority at about 64 years. The predominance of men (≥70%) was observed in all studies, except the model in the HF-PEF patients in which the proportion of men was 40%.[76] The proportion of patients with NYHA class III or IV symptoms varied greatly across these studies ranging from 18% to 100%. There were 2 (9%) studies that did not report the use of ACEIs/ARBs,[81, 98] of the remaining studies the use of ACEIs/ARBs was consistently high, except 2 studies in which data were collected before 1992[99, 100] and 1 study in patients with HF-PEF.[76] The use of beta-blockers was not reported in 3 (14%) studies,[81, 97, 98] and only 7 (32%) studies had over 50% of patients treated with beta-blockers, and the proportion was below 50% in 12 (55%) studies. The use of MRAs was not reported in 12 (55%) studies, and only 3 (14%) studies had over 50% of patients having received MRAs,[75, 77, 82] leaving 7 (32%) studies with the proportion below 50%. Of the studies with the use of beta-blockers and MRAs below 50% or not reported, most had collected data before the year 2000.

For pump failure death models, 9 (56%) studies included HF patients with reduced EF, and the remainder either included HF patients with a full range of LVEFs or made no reference to LVEF; none of the models were developed specifically in patients with HF-PEF (Table 1-2). Patients in all studies were predominantly male. The distributions of the average age and the proportion of patients with NYHA class III-IV across the studies for pump failure death models was similar to those for sudden death models. The use of ACEIs/ARBs and beta-blockers was not reported in one study,[98] in the rest of the studies, the use of ACEIs/ARBs was consistently high, except 2 studies in which data were collected before 1992;[99, 100] the use of beta-blockers was over 50% of patients in 7 (44%) studies and below 50% in 8 (50%) studies. The use of MRAs was not reported in 9 (56%) studies, and only 2 (13%) studies had over 50% of patients having received MRAs,[75, 82] leaving 5 (31%) studies with the proportion below 50%. Likewise, in the studies with the use of beta-blockers and MRAs below 50% or not reported, data collection was mainly performed before the year 2000.

1.3.2.3 Outcomes of interest

The definitions of sudden death were broadly similar across these studies, despite 6 (27%) studies having included witnessed cardiac arrest[75, 77, 80, 85, 93, 95] and 1 further (5%) study included appropriate ICD discharge for ventricular tachycardia or fibrillation[92] (Table 1-3). The sudden death events were adjudicated by an endpoint committee in 10 (45%) studies, most of which were derived from clinical trials except 3 from observational studies, i.e., the MUSIC (MUerte Subita en Insuficiencia Cardiaca) study,[79] the UK-HEART (United Kingdom-heart failure evaluation and assessment of risk trial) study,[89] and one cohort from Italy;[85] the remaining 12 (55%) studies either included investigator-reported events or did not specify this further. Most, 12 (55%) studies, had less than 50 sudden death events; only 7 studies had over 100 events, most of which were based on trial databases, except one based on the Italian Network on HF Registry cohort.[96]

The definition for pump failure death used was generally similar across the studies, whereas 2 studies, i.e. the MUSIC study[79] and the ATLAS (assessment of treatment with lisinopril and survival) trial,[91] also included heart transplantation as a pump failure death, which contributed to 16% (N=20) and 9% (N=39) of the overall pump failure deaths respectively (Table 1-4). Half of the models were based on endpoint-committee adjudicated events, the Seattle HF model (SHFM) study, based on multiple cohorts, used a mix of adjudicated and investigator-report events,[84] and the remaining studies either used investigator-reported events or made no reference to event identification. Over two thirds of the studies had less than 50 pump failure death events, and only 5 studies had over 100 events, all of which were from clinical trials except the one based on the MUSIC study.[79]

Table 1-3 Event number and definition, and model construction and performance for sudden death models

	Outcome of interest	Model construction					Model performance		
Publication	**Number and definition for SD (Event adjudication)**	**No. final/candidate variables (final in bold)**	**Analytic method**	**Over-fitting**	**Model assumption**	**Missing data**	**Discrimination**	**Calibration**	**Validation**
Kawai,[75] 2015	(N=16 including witnessed cardiac arrest) Witnessed cardiac arrest or death within 1 hr of the onset of acute symptoms, unexpected or unwitnessed death in a patient known to have been well within the previous 24 hrs. (NR)	2/6 **MIBG score,** washout rate of cardiac MIBG, heart to mediastinum MIBG uptake ratio on delayed image, **uric acid**, norepinephrine, LVEDD.	Cox regression	Yes	NR	NR	Sensitivity, specificity, predictive accuracy	NR	No
Shadman,[74] 2015 (SPRM)	(N=1225) Unexpected death in a clinically stable patient or death from documented or presumed cardiac arrhythmia without a clear non-CV cause. (Investigator report or endpoint committee adjudication)	10/17 **Sex, age**, ischaemic aetiology, **diabetes, LVEF,** LVEDD, **SBP, creatinine, serum sodium**, log NT-proBNP, **NYHA class, BMI**, diuretic dose, statin, beta-blocker, ACEI/ARB, **digoxin.**	multinomial logistic regression	No	No	NR	NR	NR	No
Adabag,[76] 2014 (I-PRESERVE)	(N=231) Unexpected death in a previously clinically stable patient and included patients who had an unsuccessful attempted resuscitation, all having a human contact within 24 hrs before the event. (Endpoint committee adjudication)	6/18 **Age, sex,** LVEF, BMI, ischaemic aetiology, history of ischaemic heart disease, **diabetes, MI,** AF, chronic kidney disease, **LBBB on ECG,** pulmonary congestion on chest X-ray, creatinine, albumin, neutrophil count, **ln NT-proBNP**, loop diuretic, ACEI.	Cox regression with stepwise selection	No	PH assumption examined	NR	Harrell's C (0.75)	observed vs. predicted plot	No
Furukawa,[77] 2013	(N=26 including witnessed cardiac arrest) Witnessed cardiac arrest or death within 1 hr of the onset of acute symptoms, unexpected or unwitnessed death in a patient who was known to have been well within the previous 24 hrs. (NR)	3/14 **Early repolarization pattern, LVEF,** QRS duration, ventricular late potential, **duration of filtered QRS complex,** age, sex, aetiology, NYHA class, heart rate, SBP, DBP, LVEDD, total counts of VPBs on Holter monitoring.	Cox regression with stepwise selection	Yes	NR	NR	Sensitivity, specificity, predictive accuracy	NR	No
Smilde,[81] 2009	(N=28) Unexpected death that occurred within 1 hr of new or more serious symptoms, or during sleep or while unobserved, in the absence of increasing angina or progressive HF. (Investigator report)	2/13 **LVEF <30%, VPBs >20/h**, sex, VT, mean NN <750ms, SDNN <110ms, SDNN <50ms, SDANN <100ms, RMSSD <25ms, TP <2500 ms^2, VLFP <1500 ms^2, LFP <300 ms^2 and HFP <100 ms^2.	Cox regression	No	NR	NR	NR	NR	No

Tamaki,[80] 2009	(N=18 including witnessed cardiac arrest) Witnessed cardiac arrest or death within 1 hr of the onset of acute symptoms, unexpected or unwitnessed death in a patient known to have been well within the previous 24 hrs. (NR)	2/6 **Washout rate of cardiac MIBG**, heart to mediastinum MIBG uptake ratio on delayed image, uric acid, norepinephrine, **LVEF,** heart to mediastinum MIBG uptake ratio on early image.	Cox regression with stepwise selection	Yes	NR	NR	Sensitivity, specificity, predictive accuracy	NR	No
Vazquez,[79] 2009 (MUSIC)	(N=90) A witnessed death occurring within 1 hr from onset of new symptoms, unless a cause other than cardiac was obvious, or an unwitnessed death (<24 hrs) in the absence of pre-existing progressive circulatory failure or other causes of death, or a death during attempted resuscitation. (Endpoint committee adjudication)	5/12 **Prior AVE**, Echo (**LA size >26 mm**, LVEDD ≥33mm, MR grade 3/4, LVEF≤35%, restrictive filling pattern), ECG & Holter (AF, **LBBB/IVCD, NSVT + frequent VPBs**), eGFR<60 ml/min/1.73 m^2, **NT-proBNP >1000 pg/ml,** Troponin positive. (AVE denotes atherosclerotic vascular event, which included previous MI, stroke or lower limb ischemia).	Cox regression with stepwise selection	No	NR	>5% excluded; <5% median imputation	Harrell's C statistic (0.77)	Predicted vs. observed survival in deciles of their risk scores	Bootstrap resampling
Wedel,[78] 2009 (CORONA)	(N=407) Witnessed instantaneous death in the absence of any acute symptoms, and also in the absence of progressive circulatory failure, the latter lasting for ≥60 min; unwitnessed death in the absence of pre-existing progressive circulatory failure or other modes of death; patients resuscitated from a cardiac arrest in the absence of pre-existing circulatory failure or other modes of death and who die within 28 days without a non-CV cause being identified; or a similar patient who dies during an attempted resuscitation; death within 60 min from the onset of new symptoms unless other cause than cardiac is obvious. (Endpoint committee adjudication)	8/29 **Log NT-proBNP, LVEF, age, Apo A-I, CABG, diabetes, AF, sex**, NYHA class, creatinine, SBP, pacemaker, intermittent claudication, stroke, CK, PTCA/PCI, BMI, MI, ALAT, hsCRP, ICD, Apo B, aortic aneurysm, hypertension, angina, smoking, heart rate, TSH, triglycerides.	Cox regression	No	NR	Complete case analysis	ROC AUC (NR)	NR	No
Uretsky,[82] 2008 (CARE-HF)	(N=71) Witnessed sudden unexpected collapse with or without documented arrhythmia, or unwitnessed sudden unexpected death in the CV category. (Endpoint committee adjudication)	2/8 **Index of MR severity*** , **CRT**, log BNP*, end-diastolic volume index*, SBP*, IDC, EQ-5D*, interventricular mechanical delay*. (*Included time-dependent covariates with the values measured at 3 months replacing the	Cox regression with stepwise selection	No	PH assumption examined	NR	NR	NR	No

		baseline value in the model for those still at risk after 3 months).							
Guazzi,[85] 2007	(N=17 including witnessed cardiac arrest) A witnessed cardiac arrest or death within 1 hr of the onset of acute symptoms, or an unexpected unwitnessed death in a patient known to have been well within the previous 24 hrs. (Adjudication from a panel of 3 physicians)	2/6 Peak VO2, VE/VCO2 slope, **exercise oscillatory breathing, LV mass,** left ventricular end-systolic volume, LVEF.	Cox regression with stepwise selection	Yes	NR	NR	NR	NR	No
Mozaffarian,[84] 2007 (SHFM)	(N=1014) Unexpected death in a clinically stable patient or death from documented or presumed cardiac arrhythmia without a clear non-CV cause. (Investigator report or endpoint committee adjudication)	14/17 **Age, sex**, BMI, **NYHA class, LVEF, ischaemic aetiology, SBP**, **diuretic dose, allopurinol, statin, sodium,** creatinine, **cholesterol,** white blood cell, **haemoglobin, lymphocytes, uric acid**.	Cox regression with stepwise selection	No	NR	Complete case analysis	ROC AUC (0.68)	NR	No
Watanabe,[86] 2006 (CHART)	(N=36) Sudden, unexpected death without worsening HF. It included witnessed sudden collapse and death, and unwitnessed deaths which were unexpected and which could not be explained by non-cardiac causes. (Investigator report)	5/16 Age, sex, prior HF hospitalisation, underlying heart diseases, NYHA class, **diabetes,** hypertension**, NSVT**, AF, ACEI/ARB, beta-blocker, digitalis, spironolactone, **BNP >200 pg/ml, LVEF <30%**, **and LVEDD>60 mm**. (After including the number of risk markers as a covariate, only number of risk markers ≥3 included)	Cox regression with stepwise selection	Yes	NR	NR	Sensitivity, specificity	NR	No
Kearney,[89] 2004 (UK-HEART)	(N=67) Death occurred within 1 hr of a change in symptoms or during sleep or while the patient was unobserved and had previously been clinically stable. (Endpoint committee adjudication)	4/16 Age, sex, **NSVT,** LVH, LVEDD, LVSDD, LVEF, sodium, potassium, urea, creatinine, **log cardiothoracic ratio**, ln QTc dispersion, **QTc dispersion across leads V1-V6**, maximum QTc interval, and **QRS dispersion across leads V1-V6.**	Cox regression with stepwise selection	No	NR	Multiple imputation	ROC AUC (0.71)	NR	Bootstrap resampling
Isnard,[93] 2003	(N=19 including witnessed cardiac arrest) Witnessed cardiac arrest, a death within 1 hr of worsening symptoms, or an	1/13 NYHA class, heart rate, SBP, LVEDD, LVEF, sodium, ANP, NT-ANP, **BNP**, norepinephrine,	Cox regression with stepwise selection	No	NR	NR	NR	NR	No

	unexpected death during sleep without worsening symptoms the day before. (NR)	endothelin, peak VO2, and percent predicted VO2 consumption.							
La Rovere MT,[92] 2003	(N=19 including ICD discharge for VT/VF) Death occurring within 1 hr of onset of symptoms in a medically stable patient, death during sleep, unwitnessed death occurring within 1 hr of the patient last being seen alive, or appropriate and documented ICD discharge for fast VT/VF. (NR)	2/9 LVEF ≤21%, **LVEDD ≥77 mm,** VPBs ≥86/h, BUN ≥57 mg/dl, Bilirubin ≥1.03 mg/dl, HRV (Baseline SDNN ≤21 ms, Baseline LFP ≤11 ms^2, Baseline LFP/HFP ≤0.37, **Controlled-breathing LFP ≤13 ms^2**).	Cox regression	Yes	NR	NR	NR	NR	Run a new model in an external cohort
Poole-Wilson,[91] 2003 (ATLAS)	(N=589) Observed arrhythmic deaths and sudden deaths not attributable to intractable MI or any other identifiable cause. These deaths were also recorded as “witnessed” or “unwitnessed”. Patients with sudden loss of consciousness who were resuscitated but later died. (Endpoint committee adjudication)	8/22 Lisinopril treatment, **age**, sex, **ischaemic heart disease**, **LVEF**, NYHA, SBP, DBP, heart rate, sodium, potassium, **creatinine, haemoglobin,** antidiabetic agent, aspirin, **beta-blocker, long acting nitrates**, short acting nitrates, **previous ACEI, anti-arrhythmic agent**, calcium channel blocker, anticoagulant/warfarin.	competing risk Cox regression	No	NR	NR	NR	NR	No
Baldasseroni,[96] 2002	(N=306) NR. (NR)	10/23 **age, ischaemic heart disease, prior HF hospitalisation, NYHA class, SBP, 3rd heart sound, chronic AF, VT, beta-blocker, LBBB**, sex, cardiothoracic ratio, LVEF, heart rate, renal failure, ACEI, diuretic, digoxin, nitrates, amiodarone, calcium antagonist, other antiarrhythmic agent and antiplatelet.	Cox regression	No	NR	NR	NR	NR	No

Berger,[95] 2002	(N=44 including witnessed cardiac arrest) Witnessed cardiac arrest or death within 1 hr of the onset of acute symptoms or unexpected, unwitnessed death (i.e. during sleep) in a patient known to have been well within previous 24 hrs. (Investigator report)	1/16 **log BNP**, log NT-ANP, LVEF, log NT-BNP, SBP, big endothelin, NYHA class, ARB, beta-blocker, rhythm, amiodarone, heart rate, ACEI, diabetes, CAD, hypertension.	Cox regression with stepwise selection	No	NR	NR	ROC AUC (0.66)	NR	No
Teerlink,[97] 2000 (PROMISE)	(N=139) Unexpected circulatory collapse resulting in death within 1 hr in a previous clinically stable patient. (Endpoint committee adjudication)	4/10 **LVEF**, NYHA class, CAD, **age, milrinone,** SBP, **NSVT episodes,** PVBs, NSVT, NSVT beats.	Cox regression with stepwise selection	No	NR	NR	ROC AUC (0.69)	NR	No
Madsen,[99] 1997	(N=20) Death within 1 hr of the onset of new symptoms or unobserved but assumed based on the clinical setting. (Investigator report)	5/8 **VT ≥4 beats, sodium ≤137 mmol/L, magnesium ≤0.8 mmol/L, creatinine ≥121 umol/L, the increase in heart rate during exercise ≤35 beats/min,** LVEF, noradrenaline, serum urea >7.6 mmol/L.	Cox regression with stepwise selection	Yes	NR	NR	NR	NR	No
Szabo,[98] 1997	(N=16) Death that occurred within 1 hr of onset of symptoms or during sleep in the absence of increasing angina or acute worsening of HF. (Investigator report)	1/3 **LVEF <27%**, SDNN <108 ms, percent difference between successive normal to normal NN intervals >50ms.	Cox regression	No	NR	NR	NR	NR	No
Szabo,[100] 1994	(N=23) Unexpected death within 1 hr of the onset of new signs/symptoms or during sleep, in the absence of increasing angina or overt HF. (Investigator report)	2/4 **LVEF ≤27%, presence of VT**, Frequency VT ≥144 beats/min, length VT ≥2s.	Cox regression	No	NR	NR	NR	NR	No

AF, atrial fibrillation; ALAT, Alanine transaminase; ANP, atrial natriuretic peptide; Apo A-I, Apolipoprotein A-I; Apo B, Apolipoprotein B; CK, creatine kinase; DBP, diastolic blood pressure; FS, fractional shortening; GGT, gamma-glutamyl transpeptidase; EQ-5D, EuroQol five dimensions questionnaire; HFP, high frequency power; HRV, heart rate variability; hsCRP, high-sensitivity C-reactive protein; IDC, idiopathic dilated cardiomyopathy; IVCD, intraventricular conduction defect; LA, left atrial; LFP, low frequency power; LV, left ventricular; LVEDD, left ventricular end diastolic diameter; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction; MIBG, metaiodobenzylguanidine; MR, mitral regurgitation; NR, not reported; NSVT, nonsustained ventricular tachycardia; PTCA, percutaneous transluminal coronary angioplasty; SBP, systolic blood pressure; SDNN, standard deviation of all normal-to-normal RR intervals; TP, all frequencies total power; TSH, thyroid-stimulating hormone; VLFP, very low frequency power; VPB, ventricular premature beat; VT, ventricular tachycardia; VF, ventricular fibrillation.

Table 1-4 Event number and definition, and model construction and performance for pump failure death models

	Outcome of interest	Model construction					Model performance		
Publication	**Number and definition for PFD (Event adjudication)**	**No. final/candidate variables (final in bold)**	**Analytic method**	**Over-fitting**	**Model assumption**	**Missing data**	**Discrimination**	**Calibration**	**Validation**
Kawai,[75] 2015	(N=11) Death because of progressively reduced cardiac output and failed organ perfusion. (NR)	3/6 **MIBG score**, washout rate of cardiac MIBG, **creatinine**, uric acid, LVEDD, **LVEF**	Cox regression	Yes	NR	NR	sensitivity, specificity, predictive accuracy	NR	No
Tamaki,[80] 2009	(N=11) NR. (NR)	4/7 **LVEDD, washout rate of cardiac MIBG, LVEF, creatinine,** uric acid, heart to mediastinum MIBG uptake ratio on delayed image, left atrial dimension	Cox regression with stepwise selection	Yes	NR	NR	sensitivity, specificity, predictive accuracy	NR	No
Vazquez,[79] 2009 (MUSIC)	(N=123 including 20 heart transplant) Death occurring in hospitals as a result of refractory progressive end-stage HF or heart transplantation. (Endpoint committee adjudication)	6/18 Age ≥65, BMI <25, Echo (**LA size >26 mm**, LVEDD ≥33 mm, MR grade 3/4, **LVEF ≤35%**, restrictive filling pattern), ECG & Holter (AF, heart rate >80 beats/min, QRS duration >120 ms, LBBB/IVCD, NSVT + frequent VPBs), **eGFR <60 ml/min/1.73 m^2, hyponatremia ≤138 mmol/L, NT-proBNP >1000 pg/ml, troponin-positive**, haemoglobin <120 g/L, GGT >50 IU/L	Cox regression with stepwise selection	No	NR	>5% excluded; <5% median imputation	Harrell's C (0.80)	Predicted versus observed survival in deciles of their risk scores	Bootstrap resampling
Wedel,[78] 2009 (CORONA)	(N=230) Cardiogenic shock; pulmonary oedema sufficient to cause tachypnoea and distress. HF symptoms or signs requiring intravenous therapy or oxygen administration. Confinement to bed but only if this is due to HF	10/29 **Log NT-proBNP, age, diabetes, CABG, NYHA class, heart rate, AF, SBP, LVEF, intermittent claudication**, BMI, smoking, creatinine, hypertension, CK, angina, stroke, Apo A-I, sex, PTCA/PCI, pacemaker, aortic aneurysm, ICD, ALAT, triglyceride, Apo B, TSH, MI, hsCRP	Cox regression	No	NR	Complete case analysis	ROC AUC (0.80)	Predicted versus observed	No

	symptoms. Sudden death during hospitalisation for aggravated HF. (Endpoint committee adjudication)								
Uretsky,[82] 2008 (CARE-HF)	(N=102) Death due to progressive failure of the heart to pump adequately to sustain life. (Endpoint committee adjudication)	3/8 **Log BNP, SBP, CRT,** interventricular mechanical delay, end-diastolic volume index, index of MR severity, EQ-5D, IDC	Cox regression with stepwise selection	No	PH assumption examined	NR	NR	NR	No
Mehta,[83] 2008	(N=31) Worsening HF, manifest by an increase in symptoms and HF medications and usually including hospitalization, in the week preceding death (including cardiogenic shock, pulmonary oedema, HF symptoms/signs requiring intravenous therapy or O_2, confinement at home due to HF, cases described as end stage HF in which therapy was felt to be futile and progressive HF cases in which terminal arrhythmias were documented). (Adjudication from a panel of 3 cardiologists)	5/28 **Age**, sex, race, CAD aetiology, acute MI aetiology, NYHA class, outpatient vs. inpatient assessment, **SBP <115 mmHg**, heart rate, AF history, **QRS duration >100 ms**, lung crackles beyond bases, cardiothoracic ratio, **sodium**, urea ≥10 mmol/L, creatinine ≥100 umol/L, haemoglobin, Troponin T, LVEDD, LVESD, FS, LVEF, global left ventricular systolic function, **ACEI***, ACEI/ARB*, beta-blocker*, beta-blocker and ACEI or ARB*, MRA*. (*drug therapy at the time of discharge or death)	Cox regression with stepwise selection	Yes	NR	NR	NR	NR	No
Guazzi,[85] 2007	(N=17) Deaths resulting from HF deterioration with progression of congestive symptoms. (Adjudication from a panel of 3 physicians)	3/6 **LV mass, left ventricular end-systolic volume, VE/VCO2 slope,** peak VO2, exercise oscillatory breathing, LVEF.	Cox regression with stepwise selection	Yes	NR	NR	NR	NR	No
Mozaffarian,[84] 2007 (SHFM)	(N=684) Death due to progressively reduced cardiac output and failure of organ perfusion. (Investigator report or endpoint committee adjudication)	14/17 **Age, male sex**, BMI, **NYHA class, LVEF, ischaemic aetiology, SBP**, **diuretic dose, allopurinol, statin, sodium,** creatinine, **cholesterol,** white blood cell, **haemoglobin, lymphocytes, uric acid.**	Cox regression with stepwise selection	No	No	Complete case analysis	ROC AUC (0.85)	NR	No

Berger,[87] 2005	(N=31) Death due to pump failure owing to progressive deterioration of ventricular function with worsening HF symptoms even if the terminal episode was an arrhythmia. (Investigator report)	3/16 **Log NT-ANP**, big endothelin, **log BNP**, log NT-BNP, NYHA class, diabetes, **CAD**, ACEI, LVEF, SBP, heart rate, rhythm, amiodarone, beta-blocker, ARB, hypertension.	Cox regression with stepwise selection	No	NR	NR	ROC AUC (0.88)	NR	No
Kyuma,[88] 2004	(N=15) Death due to deterioration of congestive HF. (NR)	1/6 **BNP,** age, cardiac 123I-MIBG activity (late heart to mediastinum ratio), nitrate, diabetes, chronic renal dysfunction.	Cox regression	No	NR	NR	NR	NR	No
Poole-Wilson,[91] 2003 (ATLAS)	(N=445 including 39 heart transplant) Patients with intractable HF, even if the terminal event was an arrhythmia; heart transplantation was included. (Endpoint committee adjudication)	10/22 Lisinopril treatment, **age,** sex, **ischaemic heart disease, LVEF**, NYHA class, **SBP**, DBP, **heart rate, sodium,** potassium, **creatinine, haemoglobin,** antidiabetic agent, **aspirin,** beta-blocker, long acting nitrates, short acting nitrates, previous ACEI, **anti-arrhythmic agent**, calcium channel blocker, anticoagulant/warfarin	Competing risk Cox regression	No	NR	NR	NR	NR	No
Vrtovec,[90] 2003	(N=24) Death resulting from multiorgan failure caused by HF progression. (NR)	2/21 **QTc interval >440ms, BNP>1000pg/ml,** BNP<700pg/ml, BNP 701-1000 pg/ml, QRS >120ms, age, sex, ischaemic aetiology, NYHA class, heart rate, SBP, DBP, LVEF, LVEDD, sodium, creatinine, inotropes, diuretic, digoxin, ACEI, beta-blocker.	Cox regression with stepwise selection	No	NR	NR	NR	NR	No
Kearney,[89] 2002 (UK-HEART)	(N=76) Death occurred after a documented period of symptomatic or hemodynamic deterioration. (Endpoint committee adjudication)	3/17 Age, sex, NSVT, LVH, LVEDD, LVSDD, LVEF, **sodium**, potassium, urea, **creatinine**, ln cardiothoracic ratio, ln **SDNN**, ln VLEP, ln LFP, ln HFP and ln TP.	Cox regression with stepwise selection	No	NR	NR	ROC AUC (0.77)	NR	No
Madsen,[99] 1997	(N=29) Death due to progressive pump failure after a period of severe HF even if the terminal episode was an arrhythmia. (Investigator report)	7/9 Sodium≤137 mmol/L, the increase in heart rate during exercise≤35 beats/min, **NYHA class, maximal heart rate difference during 24h ≤50, LVEF, plasma noradrenaline, potassium, urea, exercise time ≤4 min.**	Cox regression with stepwise selection	Yes	NR	NR	NR	NR	No

Szabo,[98] 1997	(N=14) Death due to progressive pump failure included all fatalities occurring after a period of deterioration of HF symptoms. (Investigator report)	3/4 **LVEF <27%,** SDNN <108 ms, **percent differences between successive normal to normal NN intervals >50ms, LFP>14ms^2.**	Cox regression	Yes	NR	NR	NR	NR	No
Szabo,[100] 1994	(N=22) Death occurring in the presence of progressively worsening pump function despite maximal treatment. (Investigator report)	2/3 **LVEF ≤27%, presence of VT,** VPB ≥353/24hrs.	Cox regression	No	NR	NR	NR	NR	No

Abbreviations are same as Table 1-3.

1.3.2.4 Model construction

Apart from one study using logistic regression,[74] all sudden death models were developed using Cox regression analysis. Only 2 studies examined the proportional hazards assumptions[76, 82] (Table 1-3). All models for pump failure death used the Cox regression analysis, with only one study examining the proportional hazards assumption[82] (Table 1-4).

Overall, most studies considered routinely obtained variables for risk prediction including demographics, clinical assessments, comorbidities, treatment, and 12-lead ECG, echocardiography, chest X-ray, routine laboratory measures, as well as natriuretic peptides. Some studies further incorporated other measures that are not routinely collected such as data from signal-averaged ECGs,[77, 80] 24h ambulatory ECGs (including heart rate variability parameters),[75, 77, 79, 81, 89, 92, 94, 96-100] cardiac Iodine-123 meta-iodobenzylguanidine (^{123}I-MIBG) imaging,[75, 80, 88] cardiopulmonary exercise testing,[85, 93, 99] quality of life[82] and other neurohormonal tests (e.g. noradrenaline, endothelin).[80, 87, 93, 95, 99] The number of candidate predictors varied generally from 3 to 29 for both the sudden death and pump failure death models (Table 1-3 and 1-4).

Accordingly, the final models showed a great variety in number and type of prediction variables across these studies (Table 1-3 and 1-4). The number of final predictors for the sudden death models ranged from 1 to 14 (median 3.5); nearly identical findings were observed for the pump failure death models. Of note, overfitting (i.e. one predictive variable is studied for less than 10 events) was observed in 7 sudden death models and 6 pump failure death models, respectively. A few variables have emerged as the most consistent predictors for sudden death across these studies: LVEF was included in 11 models, in 7 of which LVEF was used as a continuous variable[74, 77, 78, 80, 84, 91, 97] and in 4 of which LVEF was categorised by the value of 30%[81, 86] or 27%[98, 100] respectively; age was included in 7 studies as a continuous variable;[74, 76, 78, 84, 91, 96, 97] B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) was included in 6 studies and in 1 as a continuous variable,[93] 3 as a continuous variable with log transformation,[76, 78, 95] and 2 as a categorical variable;[79, 86] sex[74, 76, 78, 84] and a history of diabetes[74, 76, 78, 86] were included in 4 studies. Likewise, a few predictors for pump failure death emerged consistently: LVEF was included in 9 studies, in 6 of which LVEF was used as a continuous variable[75, 78, 80, 84, 91, 99] and in 3 studies LVEF was categorised by the value of 27%[98, 100] or 35%;[79] BNP or NT-proBNP was included in 6 studies with 1 using it as a continuous variable,[88] 3 as a continuous variable with log transformation,[78, 82, 87] and 2 using categories;[79, 90] and systolic blood pressure was included in 4 studies as a continuous variable[78, 82, 84, 91] and in one study with the categorisation at 115 mmHg;[83] serum sodium was included in 4 studies as a continuous variable[83, 84, 91, 94] and in one study with the categorisation at 138 mmol/L;[79] age [78, 83, 84, 91] and serum creatinine[75, 80, 91, 94] were included in 4 studies as a continuous variable.

1.3.2.5 Model performance

Model discrimination was examined only in 7 (32%) models for sudden death using C statistics (i.e. ROC AUC and Harrell's C),[76, 78, 79, 84, 89, 95, 97] ranging from 0.66 to 0.77 (Table 1-3); similarly, C statistics were only evaluated in 5 (31%) models for pump failure death,[78, 79, 84, 87, 94] which were consistently high ranging from 0.77 to 0.88 (Table 1-4). In the remaining studies for sudden death or pump failure death, model discrimination was either unspecified or examined with the use of the measures of sensitivity and specificity which subjectivity involved in the selection of the cut-off values and were typically used in diagnostic tests. Model calibration was largely unexamined, except 2 sudden death models[76, 79] and 2 pump failure death models.[78, 79] In general, model validation was poorly performed across these studies. For sudden death models only 2 had internal validation using bootstrap resampling method,[79, 89] and one had 'external validation'[92] which involved developing a new model in another cohort rather than external validation (Table 1-3). Only one pump failure death model had internal validation[79] (Table 1-4).

1.3.2.6 The best existing models and their limitations

In patients with HF-REF, the SHFM, originally designed to predict all-cause death,[101] was reported to have good discrimination when applied to predict sudden death (ROC AUC 0.68) and, particularly, pump failure death (ROC AUC 0.85).[84] However, the SHFM was significantly less discriminatory for both sudden death and pump failure death in patients who had receiving beta-blockers than those did not.[84] Besides, the predictive variables in the SHFM may more reflect overall survival, and lack specificity for mode-specific death. Based on the same population, the SHFM authors recently developed the Seattle Proportional Risk Model (SPRM) to predict the proportion of deaths due to sudden death rather than the absolute risk.[74] However, data were collected in the study cohorts before the widespread use of beta-blockers and MRAs. It is unclear whether these models still perform well when applied to a contemporary cohort receiving modern guideline recommended therapies. Models developed in the CORONA (the Controlled Rosuvastatin Multinational Trial in Heart Failure) trial showed good discrimination and calibration in predicting sudden death as well as pump failure death.[78] Most patients had received guideline recommended therapies, but this cohort had exclusive ischaemic cause of HF. Besides, some routine biochemical measurements, such as serum chloride and albumin, were not considered in the model construction. Models developed in the MUSIC study also showed good calibration and discrimination to predict sudden death and pump failure death with C statistics of 0.77 and 0.80, respectively.[79] Although a substantial number of patients in this study had received current guideline recommended therapies, this cohort included HF patients with full range of LVEFs, and about 25% had a LVEF ≥45%, i.e., they are not exclusively HF-REF patients. Besides, despite the mortality events having been adjudicated by an endpoint committee, which is unusual in prospective cohort studies, the number of events was relatively small, i.e. 90 sudden deaths and 123 pump failure deaths including 20 heart transplantations. More importantly, none of the models abovementioned have been validated in other independent cohorts, or has taken into account the competing risk of death from other causes (which is frequent).

In patients with HF-PEF, no models have been developed to predict pump failure death, and there is only one model available to predict sudden death, which was based on the I-PRESERVE (the Irbesartan in Heart Failure with Preserved Ejection Fraction Study) trial,[76] the largest trial in HF-PEF by far. All sudden death events were adjudicated by a central endpoint committee and the large number of events avoided model overfitting. The model simply consisted of 6 variables including age, male sex, history of diabetes, history of myocardial infarction, LBBB on ECG and natural log transformed NT-proBNP, and showed good discrimination (Harrell's C 0.75) and calibration. Nevertheless, the model has not been validated in an independent cohort. Moreover, the modelling approach did not consider the competing risk of death from other causes, which was large accounting for 74% of total mortality.

1.3.3 Summary

I have summarised separately the published models to predict sudden death and pump failure death in patients with HF, and undertook a critical appraisal of the available models in the aspects of study and patient characteristics, the number and adjudication of events, and model construction and model performance (i.e. discrimination, calibration and validation).

These existing models are mainly developed in patients with HF-REF or in patients with HF where the LVEF was not specified; only one model has been developed to predict sudden death in patients with HF-PEF and none for pump failure death. These models all have some features that would limit the consideration of their use in clinical practice: many models were developed before the wide use of modern guideline-recommended medications, including beta-blockers and MRAs; most were based on a relatively small study size and few events, commonly leading to model overfitting; about half of the models used the individual investigator-reported events, in which inter-investigator bias may arise; more importantly, model performance, in particular model calibration and model validation, were largely unexamined. In other words, most models terminated at the phase of model construction, leaving the model quality and robustness unevaluated and unknown. These limitations may in part explain the reality that none of these models have been used in routine clinical practice.

Consequently, there is a need to develop models to predict sudden death and pump failure death in patients with HF-REF and HF-PEF separately based on a large cohort with a great use of modern guideline recommended therapies, which account for the prognostic influence of the competing risk of death from other causes, and more importantly, to examine the discrimination and calibration ability of the developed models, and to examine the model robustness by validating in an independent cohort. I will develop models that meet these requirements in this thesis. In addition, I will examine if the classic

SHFM and the new SPRM still perform well in contemporary cohorts on optimal medical therapies.

This will be achieved through the aims and objectives outlined in the next chapter.

Aims and Objectives

Aims

Following introduction and the results of the literature review the following aims of this thesis were developed:

- To describe the trends in the rates of sudden death and pump failure death over time in patients with HF-REF and in patients with HF-PEF.

- To develop and validate models to predict sudden death and pump failure death in patients with HF-REF and in patients with HF-PEF.

These aims were translated into the following objectives:

Objectives

- To describe the rates of sudden death and pump failure death in patients with HF-REF enrolled in 13 clinical trials over the period 1995-2015.

- To examine how the risks of sudden death and pump failure death have changed between 1995 and 2015, with the cumulative introduction of disease modifying medications in patients with HF-REF enrolled in 13 clinical trials.

- To calculate the cumulative incidences of sudden death and pump failure death during follow-up, particularly early after randomisation, in patients with HF-REF enrolled in 13 clinical trials.

- To examine if the risks of sudden death and pump failure death differ by the length of time between HF diagnosis and randomisation in patients with HF-REF enrolled in 13 clinical trials.

- To develop models to predict sudden death and pump failure death in a large contemporary cohort of patients with HF-REF enrolled in PARADIGM-HF, accounting for the competing risk of death from other causes.

- To validate the models developed in this thesis in another modern cohort of patients with HF-REF enrolled in ATMOSPHERE.

- To validate the existing SHFM for predicting sudden death and pump failure death and the SPRM for predicting sudden death in the contemporary PARADIGM-HF and ATMOSPHERE cohorts.

- To describe the rates of sudden death and pump failure death in patients with HF-PEF enrolled in 3 clinical trials over the period 1999-2013.

- To examine how the risks of sudden death and pump failure death have changed over 1999-2013 in patients with HF-PEF enrolled in 3 clinical trials.

- To calculate the cumulative incidences of sudden death and pump failure death during follow-up, particularly early after randomisation, in patients with HF-PEF enrolled in 3 clinical trials.

- To examine if the risks of sudden death and pump failure death differ by the length of time between HF diagnosis and randomisation in patients with HF-PEF enrolled in 3 clinical trials.

- To develop models to predict sudden death and pump failure death in a large cohort of patients with HF-PEF enrolled in I-PRESERVE, accounting for the competing risk of death from other causes.

- To validate the models for sudden death and pump failure death developed in this thesis in other two cohorts of patients with HF-PEF enrolled in CHARM-Preserved and TOPCAT.

Chapter 2 Methods

2.1 Study population

I will perform the analyses based on the individual patient-level data from 16 RCTs in patients with chronic HF. Thirteen of these trials enrolled patients with HF-REF, which included the Randomized Aldactone Evaluation Study (RALES),[66] the Beta-blocker Evaluation of Survival (BEST) trial,[102] the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II),[5] the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF),[7] the Valsartan Heart Failure (Val-HeFT) trial,[103] the SCD-HeFT trial,[32] the Alternative trial and the Added trial of the CHARM programme,[104, 105] the CORONA trial,[8] the Gruppo Italiano per lo studio della sopravvivenza nell'Insufficienza cardiaca Heart failure (GISSI-HF) trial,[106] the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF),[67] the PARADIGM-HF trial,[27] and the Aliskiren Trial to Minimize OutcomeS in Patients with HEart failure (ATMOSPHERE) trial.[6] The remaining 3 trials were conducted in patients with HF-PEF including the preserved trial of the CHARM programme (CHARM-Preserved),[9] the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE),[11] and the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial.[12]

All trials were approved by the institutional review boards or ethic committees at each of the participating centres and all patients provided written informed consent for participation in these trials. The design and results of these trials have been published and their main characteristics are summarised in Table 2-1 and Table 2-2.

Table 2-1 Design of the included clinical trials in HF-REF

	RALES (N=1663)	**BEST (N=2708)**	**CIBIS-II (N=2647)**	**MERIT-HF (N=3991)**	**Val-HeFT (N=5010)**	**SCD-HeFT (N=2521)**	**CHARM-Alternative (N=2028)**
Comparison	Spironolactone 25mg o.d. Placebo	Bucindolol 100mg b.i.d. Placebo	Bisoprolol 10mg o.d. Placebo	Metoprolol CR/XL 200mg o.d. Placebo	Valsartan 160mg b.i.d. Placebo	Shock-only, single-lead ICD Amiodarone 400 mg o.d. Placebo	Candesartan 32mg o.d. Placebo
Study period	1995-1998	1995-1999	1995-1998	1997-1998	1997-2000	1997-2003	1999-2003
Follow-up duration	Mean 24 months	Mean 2.0 years	Mean 1.3 years	Mean 1.0 year	Mean 23 months	Median 45.5 months	Median 33.7 months
Site distribution	195 centres in 15 countries	90 centres in the US and Canada	274 hospitals in 18 countries in western and eastern Europe	313 sites in 13 European countries and in the US	302 centres in 16 countries	95 centres in the US	618 centres in 26 countries
Inclusion criteria							
Age -years	-	≥18	18-80	40-80	≥18	≥18	≥18
NYHA class	III-IV	III-IV	III-IV	II-IV	II-IV	II-III	II-IV
LVEF-%	≤35	≤35	≤35	≤40 (max walking distance ≤450m for 6 min walk test if 36-40)	<40 with LVIDD/BSA >2.9 cm/m^2	≤35	≤40
Prior HF hospitalisation	No	No	No	No	No	No	Hospitalisation for a cardiac reason within the previous 6 months if NYHA class II
Exclusion criteria							
BP -mmHg	-	Systolic BP <80	Uncontrolled hypertension, systolic BP <100	Systolic BP <100	-	-	Symptomatic hypotension
Potassium -mmol/L	>5.0	-	-	-	-	-	≥5.5
Serum creatinine	>221umol/L	≥265 umol/L	≥300 umol/L	-	>221umol/L	>221umol/L	≥265 umol/L
Others	-	Heart rate <50 beats/min	Heart rate <60 beats/min	-	-	Pacemaker implanted	Intolerance to ACEIs

	CHARM-Added (N=2548)	**CORONA (N=5011)**	**GISSI-HF (N=4574)**	**EMPHASIS-HF (N=2737)**	**PARADIGM-HF (N=8399)**	**ATMOSPHERE (N=7016)**
Comparison	Candesartan 32mg o.d. Placebo	Rosuvastatin 10mg o.d. Placebo	Rosuvastatin 10mg o.d. Placebo	Eplerenone 50mg o.d. Placebo	Sacubitril/valsartan (LCZ696) 200mg b.i.d. Enalapril 10mg b.i.d.	Aliskiren/enalapril Aliskiren 300mg o.d. Enalapril 5-10mg b.i.d.
Study period	1999-2003	2003-2007	2002-2008	2006-2010	2009-2014	2009-2015
Follow-up duration	Median 41 months	Median 32.8 months	Median 3.9 years	Median 21 months	Median 27 months	Median 36.6 months
Site distribution	618 centres in 26 countries	371 sites in 19 European countries, Russia, and South Africa	357 centres in Italy	278 centres in 29 countries	1043 centres in 47 countries	789 centres in 43 countries
Inclusion criteria						
Age -years	≥18	≥60	≥18	≥55	≥18	≥18
NYHA class	II-IV	II-IV	II-IV	II	II-IV	II-IV
LVEF-%	≤40	≤40 (≤35 if NYHA class II)	≤40, or >40 if hospitalised for HF in the previous year	≤30 (30-35 if QRS duration >130 ms)	≤40/≤35 (since December 2012)	≤35
Prior HF hospitalisation	Hospitalisation for a cardiac reason within previous 6 months if NYHA class II	No	HF hospitalisation within previous 12 months if LVEF >40%	Cardiovascular hospitalisation within prior 6 months; if not, BNP ≥250pg/ml or NT-proBNP ≥500pg/ml in men and ≥750pg/ml in women.	If HF hospitalisation within prior 12 months, BNP ≥100 pg/ml or NT-proBNP ≥400pg/ml; if not, BNP ≥150pg/ml or NT-proBNP ≥600pg/ml	If HF hospitalisation within prior 12 months, BNP ≥100 pg/ml or NT-proBNP ≥400pg/ml; if not, BNP ≥150pg/ml or NT-proBNP ≥600pg/ml
Exclusion criteria						
BP -mmHg	Symptomatic hypotension	-	-	Uncontrolled hypertension or symptomatic hypotension, or systolic BP <85	Symptomatic hypotension, systolic BP <100 at screening or <95 at randomisation	Symptomatic hypotension, systolic BP <95 at visit 1 or <90 at randomisation
Potassium -mmol/L	≥5.5	-	-	>5.0 within 24 hours prior to randomisation	>5.2 at screening, or >5.4 at randomisation	≥5.0 at screening, or ≥5.2 at randomisation

Renal function Serum creatinine - umol/L eGFR -ml/min/1.73m^2	Creatinine ≥265	Creatinine >221	Creatinine >221	eGFR <30 at randomisation	eGFR <30 at screening, or <35 at randomisation	eGFR <40 at screening, or <35 at randomisation, or eGFR decrease >25% from screening to randomisation
Others	-	Ischaemic aetiology	-	Haemoglobin <10 g/dl	A history of angioedema, or intolerant of ACEIs or ARBs	A history of inability to take ACEIs

Table 2-2 Design of the included clinical trials in HF-PEF

	CHARM-Preserved (N=3023)	I-PRESERVE (N=4128)	TOPCAT (N=3445)
Comparison	Candesartan 32 mg o.d. Placebo	Irbesartan 300 mg o.d. Placebo	Spironolactone 15-45 mg o.d. Placebo
Study period	1999-2003	2002-2008	2006-2013
Follow-up duration	Median 36.6 months	Mean 49.5 months	Mean 3.3 years
Site distribution	618 centres in 26 countries	293 sites in 25 countries	233 sites in 6 countries
Inclusion criteria			
Age -years	≥18	≥60	≥50
NYHA class	II-IV	II-IV	-
LVEF-%	>40	≥45	≥45
Prior HF hospitalisation	Hospitalisation for a cardiac reason within previous 6 months if NYHA class II	HF hospitalisation within previous 6 months; if not, ongoing class III or IV symptoms with corresponding evidence	HF hospitalisation within prior 12 months; if not, a BNP ≥100 pg/ml or NT-proBNP ≥360 pg/ml within 60 days before randomisation
Exclusion criteria			
BP -mmHg	Symptomatic hypotension	Systolic BP <100, or systolic BP >160 or diastolic BP >95 despite antihypertensive therapy	Systolic BP >160
Renal function	Serum creatinine ≥265 umol/L	Serum creatinine >221 umol/L	Serum creatinine ≥221 umol/L, or eGFR <30 ml/min/1.73m^2
Potassium -mmol/L	≥5.5	-	≥5.0
Others	-	Intolerant of ARBs, previous LVEF <40%, haemoglobin <11 g/dl	-

2.2 Outcomes of interest

In this thesis, sudden death and pump failure death are the outcomes of interest. Adjudication of these events in each trial was carried out by an independent endpoint committee in a blinded fashion using pre-specified criteria. The definitions of both outcomes used in these trials are presented in Table 2-3. Similar, but not identical criteria, were used in most of these trials. To increase consistency across the trials, death occurring suddenly but accompanied by preceding HF worsening in BEST and Val-HeFT was considered as pump failure death rather than sudden death.

Table 2-3 Definitions of sudden death and pump failure death used in the included trials

Trial	**Definition of sudden death**	**Definition of pump failure death**
RALES	Witnessed death from cardiac causes heralded by abrupt loss of consciousness within 1 hour after the onset of symptoms in a patient in whom death was unexpected.	Deaths due to worsening HF (defined as increasing symptoms or signs requiring an increase treatment).
BEST	Sudden death either with or without preceding changes in HF symptoms.	Death due to pump failure with or without secondary arrhythmic death.
CIBIS-II	Death occurring within 1 hour without previous worsening of symptoms of HF, including unexpected deaths occurring during sleep to be sudden when patients were found dead by family members sharing the same room in the morning.	Death occurred as a consequence of progressive deterioration of HF, acute pulmonary oedema, or cardiogenic shock.
MERIT-HF	Witnessed instantaneous death in the absence of progressive circulatory failure lasting for ≥60 minutes, unwitnessed death in the absence of pre-existence progressive circulatory failure or other causes of death, death within 28 days after resuscitation from cardiac arrest in the absence of pre-existing circulatory failure or other causes of death, death during attempted resuscitation, or death within 60 minutes from the onset of new symptoms unless a cause other than cardiac was obvious.	Death from HF, which was any of cardiogenic shock, pulmonary edema, heart-failure symptoms or signs requiring intravenous therapy or oxygen, confinement to bed because of HF symptoms, or sudden death during hospital stay for aggravated HF.
Val-HeFT	Observed or unobserved death that was apparently sudden and unexpected and usually out of the hospital.	Deaths occurred in the setting of worsening symptoms of HF, usually in the hospital or after a recent hospitalization for worsening HF.
SCD-HeFT	Death occurred suddenly and presumed to cardiac causes including tachyarrhythmia, bradyarrhythmia and HF.	Death occurring in a subject with progressively worsening HF over the preceding 3 to 4 months, in whom long-term survival was not expected, was considered to be due to HF even when death was sudden or associated with a terminal ventricular tachyarrhythmia event. This adjudication required the absence of evidence that the cause of progressive HF was not a sustained supraventricular or ventricular tachyarrhythmia. Events deemed related to HF therapy such as those triggered by digoxin toxicity or inotrope-related ventricular tachyarrhythmia were also characterized as being due to HF.
CHARM-Alternative, CHARM-Added ***and*** CHARM-Preserved	Death that occurred unexpectedly in an otherwise stable patient. Examples may include: the time of death is unknown; for identified arrhythmic death; in the absence of medical care; patient is unable to be resuscitated from cardiac arrest; and patient who later dies from an attempted resuscitation.	Death occurring within the context of clinically worsening symptoms and/or signs of HF without evidence of another cause of death. If worsening HF is secondary to MI, then MI should be listed as the primary cause of death given that the patient suffered a MI within 14 days of death.

CORONA	Sudden death refers to sudden cardiac death and includes the following deaths: 1. Witnessed instantaneous death in the absence of any acute symptoms; and also in the absence of progressive circulatory failure, the latter lasting for 60 minutes or more. 2. Unwitnessed death in the absence of pre-existing progressive circulatory failure or other modes of death. 3. Patients resuscitated from a cardiac arrest in the absence of pre-existing circulatory failure; or other modes of death and who die within 28 days without a non-cardiovascular cause (e.g. suicide, accident) being identified; or a similar patient who dies during an attempted resuscitation. 4. Death within 60 minutes from the onset of new symptoms unless other cause than cardiac is obvious.	Pump failure death included the following deaths: Cardiogenic shock (defined as hypotension resulting in a failure to maintain normal renal or cerebral function for >60 minutes prior to death). Pulmonary oedema sufficient to cause tachypnoea and distress. HF symptoms or signs requiring iv therapy or oxygen administration. Confinement to bed but only if this is due to HF symptoms. Sudden death during hospitalisation for aggravated HF.
GISSI-HF	Sudden death from cardiac cause occurring within 1 hour from symptom onset.	Not reported.
EMPHASIS-HF	Witnessed/unwitnessed instantaneous or near instantaneous death that occurred without warning, or within 24 hours of non-diagnostic symptoms. The cause of death has to be considered cardiac in origin and not due to another adjudicated cause including AMI, arrhythmias or progressive HF. No sudden symptoms: Patient was observed by anyone in his/her usual state of health within 24 hours of death. Sudden symptoms: Patient experienced abrupt loss of consciousness within 1 hour of the onset of at least 1 of the following new or worsened symptoms: chest pain, dyspnoea at rest, dyspnoea with exertion, palpitations, syncope/near syncope, other.	Diagnosis of HF by at least 1 of each of the following 2 criteria: 1. Symptoms: newly developed or worsening increasing dyspnoea at rest or with exertion, newly developed or worsening orthopnoea, or newly developed or worsening paroxysmal nocturnal dyspnoea. 2. Signs: newly developed or worsening increasing peripheral oedema, newly developed or worsening pulmonary basilar crackles/post-tussive rales, newly developed or worsening jugular venous distension, newly developed or worsening third heart sound or gallop rhythm, chest x-ray evidence of pulmonary venous congestion, renal hypoperfusion (worsening renal function) with no other apparent cause, or pleural effusion. And if time allows, change in HF medication (new or additional oral diuretic, intravenous diuretic, intravenous vasodilator, intravenous inotrope, intravenous digitalis/digitoxin or other) or supportive measures (continuous positive airway pressure, mechanical ventilation, mechanical support, e.g. intra-aortic balloon pump and ventricular assist device or other). No evidence of other primary cause of death (e.g. AMI based on negative biochemical markers of cardiac myocyte necrosis).
PARADIGM-HF ***and*** ATMOSPHERE	Death occurring unexpectedly in an otherwise stable subject. Further sub-classification of sudden death is as follows: 1. Death witnessed or subject last seen alive <1 hour previously or 2. Subject last seen alive ≥1 hour and < 24 hours previously.	Death occurring in the context of clinically worsening symptoms and/or signs of HF without evidence of another cause of death. Death occurring as a complication of the implantation of a ventricular assist device, cardiac transplant, or other surgery primarily for refractory HF. Death occurring after referral to hospice specifically for progressive HF.

		Note: If worsening HF is secondary to MI, then MI should be listed as the primary cause of death if the subject suffered an MI within 14 days of death.
I-PRESERVE	Unexpected death in a previously stable patient. This includes patients who were comatose then died after attempted resuscitation. Patients in this category should have had recent human contact before the event. Patients who die who have been out of contact for prolonged or unknown periods of time will be classified as unknown.	Death from worsening/intractable HF which generally occur during hospitalization but can occur at home during hospice care. Terminal arrhythmias associated with pump failure deaths will be classified as a pump failure death. Pump failure secondary to a recent myocardial infarction will be classified as an MI death.
TOPCAT	Death that occurred unexpectedly in an otherwise stable subject. Further sub-classification of sudden death will be as follows: witnessed ***or*** last seen ≥1 and <24 hours.	Death occurring within the context of clinically worsening symptoms and/or signs of HF without evidence of another cause of death. If worsening HF is secondary to MI, then MI should be listed as the primary cause of death given that the subject had an MI within 14 days of death.

2.3 Statistical analyses

I analysed the data in several ways, in line with the objectives of my thesis.

2.3.1 Descriptive statistics

I examined the baseline characteristics of the total population, patients with and without sudden death (i.e. those who died from other non-sudden causes and those alive) and patients with and without pump failure death (i.e. those who died from other causes than pump failure death and those alive) in each trial, respectively. These included patient demographics, clinical assessment, medical history, medical treatment and device, and 12-lead ECG findings and laboratory measurements if available. Continuous variables that were normally distributed (e.g. age, LVEF) were summarised as means and standard deviations and compared using Student's t-test between 2 subgroups or one-way ANOVA among ≥3 subgroups. Continuous variables that were not normally distributed, e.g. NT-proBNP, were summarised using medians and interquartile ranges, and analysed using the non-parametric Mann-Whitney U test for comparison of 2 subgroups or the Kruskal-Wallis test for comparison of ≥3 subgroups. Categorical variables were presented as numbers and percentages and analysed with a chi-square test or the Fisher's exact test if cells have an expected frequency of ≤5.

2.3.2 Handling missing data

Missing data occur when no data value is available for a variable in an observation. Rubin defined three main forms of missingness including missing completely at random (i.e. the probability of data being missing does not depend on the observed or unobserved data), missing at random (i.e. the probability of data being missing does not depend on the unobserved data, conditional on the observed data), and missing not at random (the probability of data being missing does depend on the unobserved data, conditional on the observed data).[107] There are several methods to handle missing data.[108] One is complete case analysis, i.e. to include only those patients for whom all variables involved in the analysis are observed, which is commonly used especially when the volume of missing is not large. Another popular method is the imputation technique, including simple imputation and multiple imputation, which is appropriate when data are missing (completely) at random.[109] The third is the missing-indicator method, which does not impute missing values, instead, missing observations are set to a certain value with an additional dummy variable to indicate these missing; this method allows all patients to be included in the analysis, thus maintaining statistical power.

Analyses in this thesis were based on complete case analysis approach, except for the scenario described below. Estimated glomerular filtration rate (eGFR) and NT-proBNP are important prognostic factors but were not available in all patients. Measurements of eGFR were available in all trials except the CHARM programme, where it was only recorded in North American patients. NT-proBNP was recorded only in a subset of patients in Val-HeFT (81% available), CORONA (73%), GISSI-HF (15%), PARADIGM-HF (99.8%), ATMOSPHERE (91%), I-PRESERVE (84%) and TOPCAT (18%), and was not recorded in the rest of trials (i.e. completely missing). To examine the additional prognostic effect of eGFR and NT-proBNP on the risk of each mode of death, sensitivity analyses were performed using the missing-indicator method, in addition to the primary complete case analysis. Details were described in Chapter 3 and Chapter 6.

2.3.3 Survival data and censoring

In clinical research, it is very common that the outcome is the time from a defined point to the occurrence of a given event, e.g. time to CV death after some treatment intervention, or time to tumour recurrence after surgery. This type of outcome provides more information than simply whether or not an event has occurred. Data with time-to-event outcomes are known as survival data, or more precisely, time-to-event data.[110] A distinctive feature of survival data is censoring, which refers to those subjects in whom an event is not observed within the follow-up and thus they provide only partial information on when the event would occur.[111] There are three types of censoring: ‘left censoring’ where the event occurred prior to certain time but not exactly when, ‘interval censoring’ where the event occurred within some window of time, and most commonly, ‘right censoring’ where the event has yet to occur.[110] In this thesis I focused on ‘right-censoring’ since all events are observed exactly or right censored. ‘Right censoring’ occurs when the follow-up of a subject ends before an event can be observed, which can be due to loss to follow-up (e.g. the patient moves away), withdrawal due to a side effect, or the subject does not experience an event by the end of the study (administrative censoring) or the subject has another event that precludes the occurrence of the primary one (a competing risk). However, these censored subjects cannot be excluded in the analysis since the amount of time they go through without experiencing an event itself is informative and must be accounted for.

2.3.4 Overview of survival analysis: conventional vs. competing risk methods

Survival analysis refers to a set of statistical methods to analyse survival data and handle censoring, i.e. allowing censored subjects to contribute information until they leave the study for a variety of reasons.

Conventional methods for analysing survival data make the important assumption of independent or non-informative censoring.[112, 113] This means that censoring occurs randomly, and if these subjects could be followed beyond the time points they were censored, they would have the same future risk for the occurrence of a given event as the non-censored counterparts. These methods are appropriate when the outcome of interest is overall survival, but are problematic if the outcome of interest is mode-specific death or a non-fatal event since competing risks arise in this case.[112, 113]

Specifically, a competing risk is an event whose occurrence precludes the occurrence of the outcome of primary interest. To illustrate this, assume that the outcome of interest is CV death, but clearly a subject could die from a non-CV cause, in this case non-CV death serves as a competing risk. A subject who dies due to a non-CV cause is no longer at risk for CV death no matter how long the duration of follow-up is extended. This setting violates the assumption of ‘independent censoring’, which assumes that a patient dying from a non-CV cause still has the same chance of having a CV death as those who remain alive. This only exists in an imaginary world where a subject could not die from other causes but a CV cause. In the example of non-fatal events, death serves as a competing risk which precludes the occurrence of non-fatal events.

In the presence of competing risks, censoring subjects when a competing event occurs, as conventional survival analysis does, is inappropriate. A more appropriate approach is to acknowledge the presence of competing risks and to make inference for the primary outcome accounting for competing risks; this method is known as competing risk analysis.[112]

2.3.5 Estimation of the event probability (or cumulative incidence)

The initial description of survival data is often to graphically present and estimate the probability (or risk) of a given event over a certain time interval. There are several fundamental concepts to define.[114] One of the most important concepts is the *survival function S(t)*, which is the probability of survival or remaining event free to a certain time t. Another important concept is the *failure function F(t)*, which can be estimated by one minus the *survival function*, *1-S(t)*, estimating the probability of having an event by time t, given that a subject has not had an event just prior to that time. In the absence of competing risk, the Kaplan-Meier (KM) estimate is commonly used to estimate the *survival function S(t)*.[115] Using the product limit method, it computes the survival probability at a certain time interval multiplied by any earlier computed probabilities to get the final estimate, given that the probability of survival at the end of the interval on condition that the subject was a survivor at the beginning of the interval (conditional probability). The survival probability at any particular time t is calculated by the formula given below:

$$S(t) = \frac{\text{number of subjects at risk prior to time t} - \text{number of subjects having an event}}{\text{number of subjects at risk prior to time t}}$$

Only those remaining event-free and uncensored at time t are counted as at risk, i.e. those censored by time t are not counted in the calculation. Under independent censoring, making inference on the completely observed population can be feasible, those at risk are representative for those censored, i.e. the censored subjects are not at high or low risk of having an event. However, censorings can also be caused by competing risks, and these censored subjects will certainly not experience the primary event any longer. Since subjects that will never fail are treated as if they could fail, the naïve estimate of event probability based on KM estimate is upwards biased, especially if the competing risk is large.[116] A more appropriate estimate takes into account the possibility that a subject is at risk for the primary outcome of interest, but can also be removed from the risk because of competing events. This estimate refers to the cumulative incidence function (CIF).[114, 116] The CIF for *k*th cause is defined as $CIF_k(t)$, which denotes the probability of experiencing the *k*th event before time t and before the occurrence of other competing events. I omit the details here as they are not essential for a qualitative understanding of the CIF and have been described in many publications.[114, 116]

In this thesis, sudden death and pump failure death are the outcomes of interest, and deaths from other causes, i.e. non-sudden deaths and deaths other than due to worsening HF, serve as competing risks respectively. I calculated the CIF for mode-specific death at different time points during follow-up and plotted the CIF curves over time, counting death from other causes as a competing risk.

2.3.6 Regression models for survival data

Another fundamental concept in survival analysis is *hazard function h(t)*, which denotes the instantaneous rate of occurrence of the event at time *t* among subjects who are still at risk to time *t*.[114] Hazard function regression models allow examination of the effect of a set of covariates on survival or the risk of a given event. Cox proportional hazards regression models are most popularly used in survival analysis and Fine-Gray sub-distribution proportional hazards regression models are increasingly used in the context of competing risks.[112, 117, 118]

2.3.6.1 Cox proportional hazards regression model

Cox proportional hazards regression models are used with the assumption that the covariates have a multiplicative effect on the hazard and this effect is constant over time. This can be written as $h(t)=h_0(t)\exp(X\beta)$, where $h_0(t)$ denotes the baseline hazard function (i.e. the hazard function when all covariates are set to zero), X denotes a set of covariates, and β denotes their corresponding coefficients; the exponentiation of a beta-coefficient for a certain covariate is the corresponding hazard ratio (HR), which denotes the relative change in the hazard function by increasing the covariate by one unit holding other covariates constant. A hazard ratio reflects whether, and to what the extent, the rate of outcome of interest is affected by a certain covariate. A HR =1 implies no association between the covariate and the rate, a HR >1 implies that an increase in the covariate value is associated with a higher rate, whereas a HR <1 implies that an increase in the covariate value is associated with a lower rate. Moreover, the further away the HR is from 1, the larger the effect in that covariate.

Under independent censoring, the cumulative hazard function *H(t)* can be estimated by 'Nelson-Aalen estimate', which is based on the same calculation information of the KM estimate.[114] There is a 'one-to-one' relationship between the hazard function and incidence: a risk factor associated with a higher hazard of a given event is also associated with a higher incidence.[114] The relation is:

$$S(t) = e^{-H(t)} \text{ or } F(t) = 1 - e^{-H(t)}\ or\ S(t) = S0(t)^{\exp(X\beta)}$$

However, in the presence of competing risks, there is no longer direct correspondence between the hazard of the event of interest and its cumulative incidence, as the cumulative incidence of a given event depends not only on the hazard itself but also on the hazard of competing events.[114] Regression models in the context of competing risks are detailed below.

2.3.6.2 Models in the presence of competing risks: cause-specific hazards and sub-distribution hazards

To accommodate competing risks, there mainly exist two modelling methods: one models the association of covariates on the cause-specific hazard function, and the other models the association of covariates on the CIF.[114] Both methods are valid and the choice of the appropriate approach depends on the research question: the former is preferred for aetiological questions and the latter is preferred for prognostic research.[112]

Assuming the research question is to assess the effect of experimental treatment compared with placebo on sudden death, then non-sudden deaths serve as competing events. If the treatment reduced the rate of sudden death but did not affect the rate of non-sudden deaths, the treatment would reduce the absolute risk of sudden death, but this reduced risk would leave more patients at risk for non-sudden death. Thus, although the treatment did not affect the rate of non-sudden death, we would expect to observe an increase in the absolute risk of non-sudden death associated with the treatment. Similarly, if the treatment only modestly reduced the rate of sudden death but dramatically reduced the rate of non-sudden death, the absolute risk of sudden death would increase merely because the lowered incidence of non-sudden death leaves more patients vulnerable to sudden death. In this case, the over-compensation could conceal the moderate rate reduction of sudden death associated with the treatment. If it is an aetiological research question (e.g. does the treatment decrease the rate of the event of interest?), cause-specific hazards regression models are preferred, and if it is relevant to prognosis (e.g. does the treatment decrease the absolute risk of the event of interest?), models on CIF are recommended.[112]

Regression on the cause-specific hazard function can be achieved by a Cox proportional cause-specific hazards regression model. This model assumes the same functional association between covariates and the cause-specific hazard function, as the popular Cox model for overall survival in the absence of competing risks does for the association between covariates and the overall hazard. It is technically valid that a cause-specific hazards model for a specific event can be fitted in a standard Cox regression treating competing events as if they were censored.

Several models for regression on CIF have been introduced and the most popular model of this kind is the Fine-Gray sub-distribution proportional hazards model.[116, 118] It builds a direct correspondence between covariates and cumulative incidence of a cause-specific event, as does the popular Cox model for the incidence of all-cause mortality.[114] The resulting estimate for the effect of each covariate is known as sub-distribution hazard ratio (sHR). The numerical interpretation of sHR is same as the HR, and the difference is that the effect of the former is on CIF while the latter is on rate.[114]

In this thesis, I used the Cox cause-specific hazards regression model to assess the rates of mode-specific death across trial arms and by HF duration, and used Fine-Gray sub-distribution hazards model for model development and validation.

2.3.7 Model validity assessment

2.3.7.1 Overfitting

Overfitting refers to a scenario that random error or noise is fitted in a regression model resulting in unstable coefficients and it occurs when a model is excessively complex, such as having too many parameters relative to the number of observations/events. To avoid overfitting, there is a rule of thumb that there should be at least 10 events for each final prediction variable of a multivariable model.[71]

2.3.7.2 Linearity assumption for continuous variables

The linearity assumption refers to an equal change of a continuous variable will have an equal effect on outcome. A variety of non-linear relationships are possible. It is inappropriate to put a continuous variable into a model without examining its linearity, since any non-linearity may lead to a loss of efficiency and introduce bias underlying the association.[71] I used restricted cubic spline method with 5 knots to examine the linearity for a continuous variable with outcome.[119, 120] If the relationship appears non-linear, certain cutoff values or mathematical transformation were applied based on the spline curves and clinical relevance.

2.3.7.3 Distributional assumption

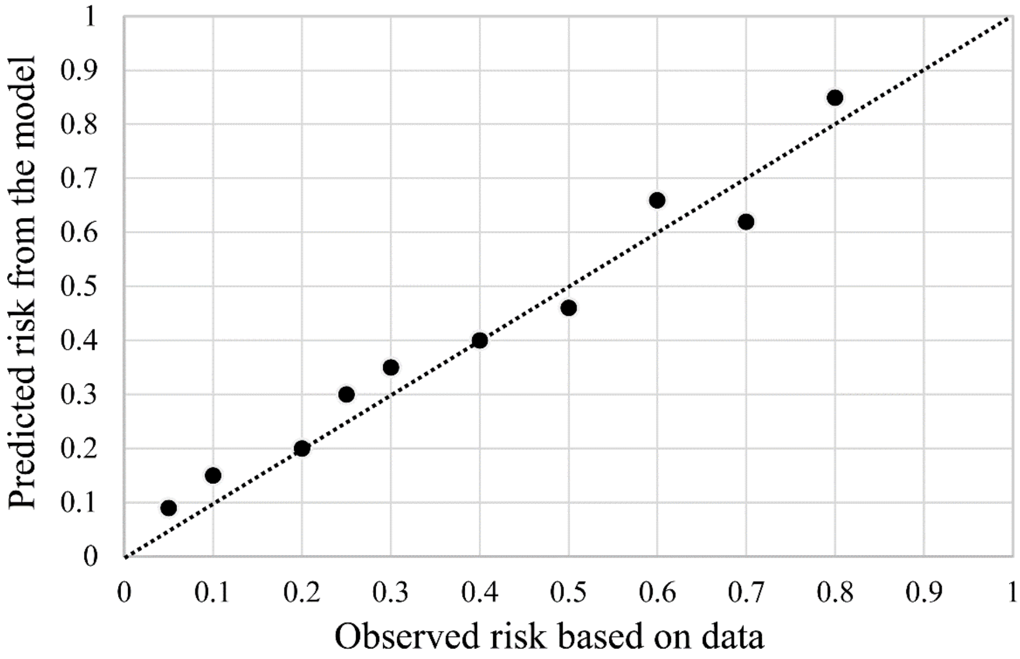
For a certain regression analysis to be valid, the distributional assumption must be true. The Cox model makes a key assumption of proportional hazards, which refers to the survival functions for two strata must have hazards that are proportional over time, i.e. the relative hazard is constant. This assumption is commonly examined by testing Schoenfeld residuals with the null hypothesis of a zero slope in a generalised linear model on time, and by visually assessing the parallelism of curves from log-log survival plots.[121] For the Fine-Gray model in the competing risk settings, an equivalent to the hazard for the Cox model is the sub-distribution hazard, which refers to the hazard for an individual who either fails from cause k or does not, and in the latter case has an infinite failure time for cause k, given that with mutually exclusive event types, those who fail from one cause are no longer at risk for failing from other causes. Like the Cox model, the Fine-Gray model makes a proportional assumption for the sub-distribution hazards, i.e. they are constant over time or time-independent.[118] The assumption can be examined by adding time varying terms of the covariates in the model. The proportional sub-distribution hazards assumption is valid if none of the time-dependent covariates are statistically significant.[122]

2.3.8 Model performance assessment

When developing, or validating a model, we need to quantify how good the prediction from a model is, that is model performance. There are two fundamental aspects of model performance: calibration and discrimination.[123]

Calibration, sometimes known as ‘prediction accuracy’, is the magnitude of agreement between predicted and observed event rates at a population level, with better models having smaller differences in-between. Calibration can be assessed graphically with the prediction on the x-axis and observation on the y-axis, and perfect prediction should be on the 45-degree line. For a binary outcome, the y-axis (observation) only contains 0 and 1 values, and thus smoothing techniques, e.g. loess algorithm, are routinely used to estimate the observed probabilities corresponding to the predicted probabilities. We can also plot the results for patients with similar predicted risks to identify mis-calibration in certain risk subgroups. For example, we can plot the observed outcome by deciles of prediction risks, which is a graphical depiction of the Hosmer-Lemeshow goodness-of-fit test.[124] For survival data, we can plot the observed vs. predicted probabilities of an event across different risk subgroups over certain time interval to identify mis-calibration in certain risk subgroups or at certain timepoints.[72]

Figure 2-1 Calibration graph - an example



Each circle corresponds to observed risk based on data (x axis) and predicted risk from the model (y axis) in each risk subgroup. The dotted line is the 45-degree line which indicates perfect prediction.

Discrimination, also known as ‘separation’, refers to the ability of a model to distinguish patients who develop an event (‘case’) from those who do not (‘control’). In time-to-event settings, discrimination is the ability to separate who will develop an event earlier from who will develop an event later or not at all.[72, 123] The concordance (C) statistic is routinely used to quantify the discrimination ability of prognostic models with binary and survival outcomes. In general, C statistic ranges from 0.5 (random concordance) to 1 (perfect concordance). For a binary outcome, C statistic is identical to the area under the receiver operating characteristic curve (ROC AUC),[125] which plots sensitivity (proportion of ‘cases’ for whom the model predicts are at high risk) against 1-specificity (proportion of ‘controls’ for whom the model predicts are high risk) for consecutive cutoffs for the probability of an outcome. The area indicates an estimated probability that for any possible pair of ‘case’ and ‘control’, the ‘case’ has a higher predicted risk than the ‘control’ (i.e. concordant pair). For time-to-event outcomes, C statistic is a rank-order measure, in which a pair of patients is called concordant if the event occurs earlier in the patient who has the higher risk predicted by a model, or vice versa. In the presence of right censoring, a pair of patients cannot be ordered if both are event-free and which one will first develop an event is unknown. The C statistic proposed by Harrell, known as Harrell's C, ignores the pairs that cannot be ordered and only use 'orderable' pairs to calculate the concordant pairs among them.[126] Harrell's C depends on the study-specific censoring distribution, to accommodate for this a modified C index is proposed using the inverse of the probability of censoring weighted estimator.[127]

Figure 2-2 ROC curve - an example

A point in the upper left corner or coordinate (0,1) of the ROC space indicates a perfect classification with an area under ROC curve of 1.0, which represents 100% sensitivity (no false negatives) and 100% specificity (no false positives). The dotted diagonal line gives an area under ROC curve of 0.5 which represents a random guess i.e. no-discrimination. The more the points move towards the upper left direction, the better the discrimination is. The example given here has an excellent discrimination with an area under the ROC curve of 0.89.

It can be argued that discrimination ability is more important than calibration since inadequate calibration can be adjusted (i.e. re-calibrated) whereas poor discrimination cannot be altered.[72]

2.3.9 Model validation

Validation refers to the process of assessing the performance of a predefined model in new data. It is worth noting that there are two misconceptions of the validation practice including repeating the whole modelling process in the validation cohort (which leads to new predictors and their corresponding coefficients), and refitting to the validation cohort the predictors from the derivation model (same predictors but different coefficients), both of which will lead to a new model other than validating the existing model, and as such, would themselves need validation.[72] In terms of the independence of the validation cohort, validation can be divided into two subtypes: internal validation, which reuses a subset or all of the cohort in which a model was developed, and external validation, which uses a different cohort from the one for model derivation. In general, internal validation is used to assess and correct for the sampling variation of the derivation model, and bootstrapping is the most commonly used technique;[73] whereas, external validation examines the replicability or generalisability of a developed model to a different but plausibly related cohort, which is crucial and a first step towards the introduction of a new model for consideration to use in clinical practice.[73]

In this thesis, external validation was performed for all the derived models to predict sudden death and pump failure death in both the HF-REF and HF-PEF populations. The performances of the existing SHFM[84] and SPRM[74] were also examined externally in the contemporary PARADIGM-HF and ATMOSPHERE cohorts.[6, 27]

2.3.10 Individual risk estimation

To estimate the absolute risk (i.e. CIF) for mode-specific death in individual patients using the models to be developed, the risk score was first calculated as the sum of the products of each predictor coefficient from each model and the corresponding predictor value in an individual patient.[101] The derived risk score was to compute the corresponding incidence of mode-specific death at a given follow-up time by using the formula below:

Estimated CIF (t) =1 – [1 - CIF_0 (t)]**exp(risk score) =1 - S_0(t)**exp(risk score)

2.3.11 Statistical software packages

The cumulative incidence function and C index were achieved using the *'cmprsk'* and *'pec'* packages in R project (version 3.2.3). Other data analyses were performed using the Stata (version 14, Stata Corp, College Station, TX, US). All tests of statistical significance were two-tailed at a significant level of 0.05 ($p < 0.05$).

Chapter 3 Rates of sudden death and pump failure death over time in HF-REF

In this chapter I will describe the rates of sudden death and pump failure death separately in patients with HF-REF enrolled in 13 clinical trials over the period 1995-2015. I will examine how the risks of sudden death and pump failure death have changed over this period with the cumulative use of evidence based medications, the cumulative incidence of each mode of death during follow-up, particularly early after randomisation, and whether these risks differ by the length of time from HF diagnosis to randomisation. The cumulative incidence function method will be used to calculate the incidences of sudden death and pump failure death during follow-up counting the competing risk of death from other causes, the linear regression analysis will be used to examine the rate of each mode of death with the calendar year, and the conventional Cox regression analysis will be used to compute the annual rates and hazard ratios for each mode of death across trial arms and by HF duration.

3.1 Methods

3.1.1 Study population

I attempted to obtain all major randomised clinical trials which supported guideline recommendations in patients with stable chronic HF-REF (with a LVEF ≤40% and NYHA class II-IV symptoms) conducted over the last two decades. Among the 43 trials identified, 21 trials were excluded as the reasons indicated in Figure 3-1. A total of 22 trials were eligible for this analysis, but data were not obtained in 9 trials, and their characteristics are summarised in Appendix Table 4. Therefore, 13 RCTs available were included in the analysis, namely, RALES, BEST, CIBIS-II, MERIT-HF, Val-HeFT, SCD-HeFT, CHARM-Alternative, CHARM-Added, CORONA, GISSI-HF, EMPHASIS-HF, PARADIGM-HF and ATMOSPHERE.[5-8, 27, 32, 66, 67, 102-106] The design and results of these trials have been reported in detail and their main characteristics are outlined in Table 2-1.

Figure 3-1 CONSORT diagram for trial selection in HF-REF

Chronic HF-REF trials supporting guideline recommendations [N=43]

Excluded [N=21]:
- **Small sample size (<1000)[N=12]:** CONSENSUS, V-HeFT I, V-HeFT II, V-HeFT III (outcomes not adjudicated), TIM-HF, CHAMPION, ECHO-CRT, IN-TIME (a high proportion of defibrillator use), COMPANION (after excluding ICD arm), DEFINITE, CARE-HF, ANDROMEDA;
- **Not broadly representative[N=2]:** A-HeFT(African Americans), RED-HF (anaemia);
- **ICD in many or all patients in both arms [N=3]:** MADIT-CRT, RAFT, HF-ACTION;
- **Outcomes not adjudicated [N=3]:** SOLVD-P, SOLVD-T, DIG;
- **Not exclusively HF-REF [N=1]:** SENIORS.

Eligible but not available/obtained [N=9]:
PRAISE 1+2, ELITE II, COPERNICUS, COMET, AF-CHF, ATLAS, SHIFT, HEAAL, STICH.

Eligible and included [N=13]:
RALES, BEST, CIBIS-II, MERIT-HF, Val-HeFT, SCD-HeFT, CHARM-Alternative, CHARM-Added, CORONA, GISSI-HF, EMPHASIS-HF, PARADIGM-HF, ATMOSPHERE.

3.1.2 Outcomes of interest

I examined the annual rates and the proportions of sudden death and pump failure death separately in each trial, the cumulative incidences of each mode of death at different time points from randomisation (30 days, 60 days, 90 days, 180 days, 1 year, 2 years and 3 years), and the risks of each mode of death according to the length of time between diagnosis of HF and randomisation (≤3 months, >3-6 months, >6-12 months, >1-2 years, >2-5 years, and >5 years). In each trial, an independent endpoint committee blindly adjudicated death events using pre-specified criteria. Similar but not identical criteria were used in these trials (Table 2-2). In BEST and Val-HeFT, sudden death events included those with preceding HF symptoms, and to ensure consistency these events were counted as pump failure death other than sudden death in this analysis.

3.1.3 Adjustment for potential confounding variables

The confounding effect of a number of variables on the risks of sudden death and pump failure death was examined including age, sex, LVEF, NYHA class, ischaemic aetiology, and a history of myocardial infarction, hypertension and diabetes, which had been collected in all trials. The measurements of eGFR were available in all trials except CHARM (measured only in North American patients). Plasma NT-proBNP levels were measured only in Val-HeFT, CORONA, GISSI-HF, PARADIGM-HF and ATMOSPHERE. The additional prognostic influence of eGFR and NT-proBNP on each mode of death was examined in patients with full data and after missing data imputation.

3.1.4 Statistical analyses

Baseline characteristics of all patients in each trial were summarised as means with standard deviations for continuous variables and percentages for categorical variables. Baseline characteristics of patients having a sudden death and the remaining patients (i.e. those alive and those dying non-suddenly) in each trial were also summarised and compared using Student's t-test for continuous variables and chi square test for categorical variables. Likewise, baseline characteristics in patients with pump failure death and the rest (i.e. those survived and those died without worsening HF) in each trial were summarised and compared. NT-proBNP was presented as median and interquartile range and analysed using the Mann-Whitney U test, because of violating the assumption of normal distribution.

The cumulative incidences for sudden death and pump failure death in each trial were calculated separately at the time points of 30 days, 60 days, 90 days, 180 days, 1 year, 2 years and 3 years from randomisation, counting death from other causes as a competing risk, and were also outlined using cumulative incidence curves. The annual rates of each mode of death in each trial and in each arm of each trial were calculated per 100 patient-years. The hazard ratio for each mode of death in each trial arm was calculated using cause-specific Cox proportional hazards model using the placebo arm of the earliest trial, RALES, as the reference. In a Cox model, the association between calendar year and the risk for each mode of death was then examined with adjustment for randomisation arm and with trial as a random effect. These models were then further adjusted for the confounding variables listed above. For models further adjusting for eGFR and NT-proBNP, complete case analysis was performed as the primary analysis, together with a sensitivity analysis based on the missing-indicator method using single imputation for a missing value in those trials where data were not completely missing with a further covariate indicating missing data.[108] The associations between calendar year and the annual rates of sudden death and pump failure death were assessed separately in a multiple linear regression model with the randomisation year and randomisation arm as covariates, weighted by the inverse-variance of the annual rate with trial as a random effect. A multivariate linear regression analysis was also undertaken for all-cause death to assess whether apparent outliers from the overall trends may result from the patients themselves enrolled in a specific trial or the misclassification of death events.

The duration between HF diagnosis and randomisation was collected in BEST, Val-HeFT, SCD-HeFT, CHARM-Alternative, CHARM-Added, CORONA, GISSI-HF, EMPHASIS-HF, PARADIGM-HF and ATMOSPHERE, but not in RALES, CIBIS-II or MERIT-HF. To assess the effect of HF duration on the risk of each mode of death, patients with data available were merged and further divided into 6 groups: diagnosis within 3 months, >3-6 months, >6-12 months, >1-2 years, >2-5 years, and >5 years. According to these duration groups, cumulative incidence curves for each mode of death were produced and were compared using the Gray's test,[128] and hazard ratios for each mode of death were calculated employing patients with new-onset HF (within 3 months of diagnosis before randomisation) as reference, with adjustment for the confounding variables listed above and counting within-trial clustering.

3.2 Results

This analysis consisted of 46,163 patients randomised in the 13 clinical trials conducted in patients with HF-REF over the past two decades (1995-2015), after excluding patients having an ICD or CRT-D (N=4228) at baseline and patients with a LVEF greater than 40% in GISSI-HF (N=461). Of the analysable patients, 10,857 (23.5% of total population) died during follow-up, and 4190 (9.1%) were attributed to sudden death and 2973 (6.4%) were due to pump failure death. The levels of eGFR were measured in 43,060 (93%) patients and both eGFR and plasma NT-proBNP were available in 20,730 (45%) patients.

3.2.1 Baseline characteristics of study population

The key characteristics of patients in each trial are summarised in Table 3-1. There was a higher mean age in CORONA (73 years) and EMPHASIS-HF (69 years) compared to the other trials, because both set a minimum age threshold for inclusion (60 and 55 years respectively). Most patients were men across the trials; the proportion was highest in CIBIS-II (81%) and lowest in CHARM-Alternative (68%). By design, all patients had NYHA class III-IV (predominantly class III) symptoms in RALES, BEST and CIBIS-II; all were in class II-III in SCD-HeFT (mainly class II) and all were in class II in EMPHASIS-HF. The remaining trials enrolled patients mainly in NYHA class II and III. The mean LVEF varied greatly by trial, ranging from 23% in BEST to 32% in GISSI-HF. CORONA by design only enrolled patients with an ischaemic aetiology; ischaemic aetiology was predominant in the remaining trials except GISSI-HF (40%). The proportion of patients with a history of hypertension was much higher in the more recent trials and this was also the case but to a lesser extent for the prevalence of diabetes. The proportion of patients with renal dysfunction (defined as eGFR <60 ml/min/1.73 m^2) varied across the trials ranging from 25% in ATMOSPHERE to 57% in CORONA. The use of ACEIs/ARBs was consistently high (over 90%) across these trials, except CHARM-Alternative in which all patients were intolerant to ACEIs. Rates of treatment with a beta-blocker and a MRA were substantially higher in the more contemporary trials.

Table 3-1 Baseline characteristics of patients in the included trials in HF-REF

	Missing data No. (%)	RALES (N=1663)	BEST (N=2617)	CIBIS-II (N=2647)	MERIT-HF (N=3991)	Val-HeFT (N=5010)	SCD-HeFT (N=1692)
Age -years	0	65.2±11.9	60.2±12.4	60.9±10.5	63.3±9.7	62.7±11.1	58.9±11.9
Male (%)	0	73.2	77.9	80.5	77.5	80.0	76.5
Race (%)	3860 (8.4)						
White		86.6	69.4	99.0	94.1	90.3	76.4
Black		7.2	23.5	0.3	5.2	6.9	16.2
Asian		1.9	-	0.6	0.4	-	1.2
Other		4.3	7.1	0.2	0.3	2.8	6.2
LVEF -%	112 (0.2)	25.4±6.7	23.1±7.3	27.4±6.0	27.7±6.9	26.7±7.2	23.9±6.9
NYHA class (%)	12 (<0.1)						
I		0.1	0	0	0	0.1	0
II		0.4	0	0	41	61.8	70.6
III		70.5	91.7	83.2	55.4	36.2	29.4
IV		29.0	8.3	16.8	3.6	1.9	0
Ischaemic aetiology (%)	8 (<0.1)	54.6	58.0	49.8	65.3	57.2	52.0
Blood pressure -mmHg							
Systolic	20 (<0.1)	122.2±20.1	117.3±18.0	129.7±19.4	129.8±17.2	123.8±18.5	120.0±19.4
Diastolic	29 (<0.1)	74.6±11.6	71.1±11.2	79.7±11.1	78.3±9.2	75.5±10.6	71.2±11.3
Heart rate -beats/min	18 (<0.1)	80.9±14.2	81.7±13.2	80.5±15.0	82.5±10.2	73.4±12.6	74.6±13.9
Body mass index	1810 (3.9)	-	28.0±5.9	26.9±4.1	27.2±4.7	26.9±4.5	-
Medical history (%)							
Current smoking	6677 (14.5)	-	17.8	16.6	14.5	-	15.6
Previous HF hospitalisation	22498 (48.7)	-	-	-	-	-	-
Angina	6641 (14.4)	6.7	51.7	-	39.7	21.2	30.5
Myocardial infarction	4 (<0.1)	28.4	41.8	55.0	48.2	46.9	44.3
PCI	10668 (23.1)	-	15.2	4.4	8.0	-	21.1
CABG	4314 (9.3)	-	28.3	-	20.9	23.2	26.8
Hypertension	1 (<0.1)	23.5	59.2	43.5	43.8	40.9	56.0
Diabetes	0	22.2	36.1	11.7	24.7	25.5	30.4
Atrial fibrillation	4315 (9.3)	-	23.9	-	16.7	12.1	14.7
Stroke	4308 (9.3)	-	-	7.4¶	7.9	6.9	7.2
Laboratory tests							
eGFR -ml/min/1.73m^2	3103 (6.7)	64.9±23.0	70.1±24.7	77.5±31.3	66.6±19.6	61.4±15.6	70.9±22.2
eGFR <60 ml/min/1.73m^2 (%)	3086 (6.7)	47.8	35.7	31.6	36.8	46.9	32.3
Creatinine -mg/dl	3084 (6.7)	1.24±0.36	1.24±0.41	1.18±0.33	1.21±0.37	1.28±0.31	1.21±0.74
NT-proBNP -pg/ml	25419 (55.1)	-	-	-	-	901a [377-1990]	-
Treatment (%)							
Digitalis	14 (<0.1)	73.5	92.1	52.0	63.6	67.3	71.1
Diuretics	14 (<0.1)	100	93.4	98.5	90.3	85.5	83.5
ACEI	14 (<0.1)	94.5	91.4	96.0	89.5	92.7	85.6
ARB	9199 (19.9)	-	6.2	-	6.6	NA	14.8
ACEI/ARB	2678 (5.8)	-	96.6	-	95.7	96.4	97.5
Beta-blocker	14 (<0.1)	10.6	NA	NA	NA	34.9	68.7
MRA	9001 (19.5)	NA	3.3	10.9	0.2	5.0	19.3
Pacemaker	15008 (32.5)	-	7.9	-	3.9	-	0
CRT-P	30723 (66.6)	-	-	-	-	-	-
Treatment arm	0	49.4	50.0	50.1	49.9	50.1	49.9

	CHARM-Alternative (N=1960)	CHARM-Added (N=2448)	CORONA (N=4875)	GISSI-HF (N=3820)	EMPHASIS-HF (N=2316)	PARADIGM-HF (N=7156)	ATMOSPHERE (N=5968)
Age -years	66.1±10.8	63.6±11.0	72.7±7.1	67.2±10.8	68.7±7.7	63.7±11.6	63.1±12.1
Male (%)	67.6	78.4	76.0	79.0	76.1	76.7	76.5
Race (%)							
White	88.4	90.5	98.6	-	81.2	62.6	61.7
Black	3.7	5.0	0.3	-	2.2	4.8	1.6
Asian	6.6	3.6	0.7	-	13.3	20.7	28.9
Other	1.3	0.9	0.4	-	3.3	11.9	7.8
LVEF -%	30.0±7.4	28.1±7.5	30.1± 6.4	31.6±6.2	26.4± 4.4	29.9±6.1	28.8±5.5
NYHA class (%)							
I	0	0	0	0	0	4.9	0
II	48.0	24.1	37.1	63.1	100	69.8	61.4
III	48.5	72.9	61.5	34.8	0	24.6	36.4
IV	3.5	2.9	1.5	2.2	0	0.8	2.2
Ischaemic aetiology (%)	67.8	62.5	100	40.1	68.1	58.7	54.2
Blood pressure -mmHg							
Systolic	130.4±18.7	125.6±18.6	129.5±16.4	126.5±18.0	125.0±16.8	122.0±15.4	124.4±18.2
Diastolic	76.8±10.7	75.2±10.7	76.3±8.9	77.1±9.8	75.3±10.2	74.2±10.0	77.6±11.0
Heart rate -beats/min	74.5±13.7	73.7±13.1	71.8±11.2	73.2±13.6	72.3±12.7	72.9±12.1	72.4±12.7
Body mass index	27.4±4.8	27.8±5.3	27.2±4.6	27.0±4.5	27.5±4.9	27.9±5.5	27.2±5.3
Medical history (%)							
Current smoking	13.7	17.1	8.7	14.9	10.7	14.1	12.4
Previous HF hospitalisation	68.2	77.0	-	44.4	51.2	62.3	58.5
Angina	58.1	52.6	72.7	11.4	43.5	27.2	23.7
Myocardial infarction	61.0	55.2	59.4	32.9	48.2	40.8	37.3
PCI	15.7	14.3	11.2	8.1	18.6	18.1	16.3
CABG	24.5	24.1	16.5	13.9	15.6	13.2	11.6
Hypertension	49.8	48.1	63.9	52.7	67.2	71.3	62.4
Diabetes	27.0	30.2	29.5	25.9	31.6	33.6	27.3
Atrial fibrillation	25.3	26.4	40.9	18.8	30.7	36.6	33.5
Stroke	8.4	8.4	12.5	4.5	9.4	8.3	7.0
Laboratory tests							
eGFR -ml/min/1.73m^2	68.5±26.7b	73.3±26.9c	57.8±15.1	69.9±21.8	71.4±21.8	68.8±20.3	75.1±24.7
eGFR <60 ml/min/1.73m^2 (%)	41.5b	32.5c	57.0	33.9	32.1	34.4	24.6
Creatinine -mg/dl	1.21±0.45b	1.16±0.40c	1.30±0.32	1.15±0.34	1.14±0.30	1.10±0.29	1.02±0.27
NT-proBNP -pg/ml	-	-	1480d [618-3156]	884e [381-1980]	-	1640 [888-3342]	1204f [630-2285]
Treatment (%)							
Digitalis	45.4	57.9	33.1	40.1	28.2	31.2	32.5
Diuretics	85.3	90.0	88.2	81.5	86.4	79.8	79.0
ACEI	0	100	80.2	78.1	78.5	77.2	66.9
ARB	NA	NA	12.7	18.1	19.0	23.0	1.4
ACEI/ARB	NA	NA	91.8	93.7	94.4	99.8	67.3
Beta-blocker	54.2	54.7	75.0	63.3	86.0	92.4	90.9
MRA	23.5	16.8	38.9	39.8	NA	55.5	35.3
Pacemaker	8.0	7.9	10.6	10.4	8.4	7.2	4.1
CRT-P	-	-	-	-	2.3	1.9	1.8
Treatment arm	49.6	50.2	50.1	50.0	50.3	49.8	66.6

¶ Cerebrovascular diseases.

The letters denote the number of patients available: a=4067(81%), b=618(32%), c=872(36%), d= 3555(73%), e=570(15%), f=5408(91%).

3.2.2 Baseline characteristics of patients with sudden death

There were some differences in baseline characteristics between patients with and without sudden death (Table 3-2). Overall, those who died suddenly were older, more often male, and were more likely to have worse HF symptoms, lower LVEF or an ischaemic aetiology than those who had not died suddenly. Patients with sudden death tended to have a lower blood pressure, a higher heart rate, and were more likely to have prior myocardial infarction, a history of diabetes and renal dysfunction, but were less likely to have undergone coronary revascularisation. The NT-proBNP levels were substantially higher in patients having a sudden death in the trials with data available. There was a less use of a beta-blocker but a greater use of a diuretic, digitalis or MRA in patients having a sudden death.

Table 3-2 Baseline characteristics of patients with and without sudden death in the included trials in HF-REF

	RALES		BEST		CIBIS-II		MERIT-HF	
	SD (N=192)	**Others (N=1471)**	**SD (N=294)**	**Others (N=2323)**	**SD (N=131)**	**Others (N=2516)**	**SD (N=211)**	**Others (N=3780)**
Age -years	66.5±10.1	65.1±12.1	61.0±12.2	60.1±12.4	61.1±10.0	60.9±10.6	63.3±9.9	63.3±9.7
Male (%)	81.8**	72.1	79.3	77.7	83.2	80.4	83.4*	77.2
LVEF-%	24.4±6.7*	25.5±6.7	21.3±7.0***	23.3±7.3	26.2±6.3*	27.5±6.0	25.7±7.0***	27.8±6.9
NYHA class (%)							*	
I	0	0.1	0	0	0	0	0	0
II	0.5	0.3	0	0	0	0	31.3	41.5
III	74.5	70.0	91.2	91.8	81.7	83.3	64.5	54.9
IV	25.0	29.6	8.8	8.2	18.3	16.7	4.3	3.6
Ischaemic aetiology (%)	60.9	53.8	68.7***	56.7	48.9	49.8	72.0*	64.9
Race (%)	*							
White	89.1	86.3	66.3	69.8	99.2	99	91.9	94.3
Black	4.2	7.6	26.2	23.2	0	0.3	7.1	5.1
Asian	4.2	1.6	0	0	0.8	0.6	0.5	0.4
Other	2.6	4.5	7.5	7.0	0	0.2	0.5	0.2
BP -mmHg								
Systolic	122.9±21.0	122.1±20.0	116.1±16.8	117.5±18.2	126.5±18.3	129.9±19.4	125.7±17.4***	130.0±17.1
Diastolic	74.3±12.3	74.6±11.5	69.8±11.0*	71.3±11.2	78.4±10.0	79.8±11.1	77.3±9.4	78.3±9.2
Heart rate -beats/min	79.0±14.2	81.1±14.2	81.3±13.3	81.8±13.2	82.2±14.2	80.4±15.0	83.7±11.1	82.5±10.1
BMI	-	-	27.8±5.8	28.0±5.9	26.4±3.8	26.9±4.1	26.7±4.9	27.3±4.7
Medical history (%)								
Current smoking	-	-	13.3*	18.3	13.0	16.8	15.2	14.4
HF hospitalisation	-	-			-	-	-	-
Angina	8.3	6.5	53.7	51.4	-	-	-	-
Myocardial infarction	32.3	27.9	48.6*	40.9	53.4	55.1	53.6	47.9
PCI	-	-	15.6	15.2	3.1	4.5	-	-
CABG	-	-	29.9	28.1	-	-	15.6	21.2
Hypertension	32.3**	22.4	63.3	58.6	45.8	43.3	43.1	43.8
Diabetes	25.0	21.8	38.4	35.9	13.0	11.7	24.2	24.7
Atrial fibrillation	-	-	23.8	23.9	-	-	21.8*	16.4
Stroke	-	-	-	-	16.0¶***	7.0¶	10.9	7.7
Laboratory tests								
eGFR – ml/min/1.73m^2	61.0±22.1*	65.4±23.0	66.2±21.3**	70.7±25.0	72.0±26.5*	77.7±31.5	65.2±20.9	66.7±19.5
eGFR <60 ml/min/1.73m^2 (%)	52.6	47.1	41.0*	35.1	35.1	31.5	40.3	36.4
Creatinine -mg/dl	1.33±0.39***	1.23±0.36	1.29±0.37*	1.23±0.41	1.23±0.31	1.17±0.33	1.26±0.37*	1.21±0.37
NT-proBNP -pg/ml	-	-	-	-	-	-	-	-
Treatment (%)								
Digitalis	74.0	73.0	95.9*	91.6	67.9***	50.8	74.9***	63.0
Diuretics	-	-	96.3*	93.1	-	-	93.8	90.1
ACEI	95.3	93.4	92.9	91.3	97.7	94.6	89.6	89.5
ARB	-	-	3.7	6.5	-	-	6.2	6.6
ACEI/ARB	-	-	96.3	96.7	-	-	95.7	95.7
Beta-blocker	8.3	10.9	NA	NA	NA	NA	NA	NA
MRA	NA	NA	4.8	3.1	12.2	10.8	-	-
Pacemaker	-	-	8.8	7.7	-	-	-	-
CRT-P	-	-	-	-	-	-	-	-
Treatment arm	42.7*	50.3	44.6*	50.7	36.6**	50.8	37.4***	50.6

	Val-HeFT		SCD-HeFT		CHARM-Alternative	
	SD (N=442)	**Others (N=4568)**	**SD (N=168)**	**Others (N=1524)**	**SD (N=186)**	**Others (N=1774)**
Age -years	63.3±10.8	62.6±11.1	59.0±11.3	58.8±12.0	67.6±10.9	66.0±10.8
Male (%)	86.7***	79.3	83.3*	75.7	74.2*	66.9
LVEF-%	24.8±7.2***	26.9±7.1	23.0±6.5	24.0±6.9	28.4±7.7**	30.1±7.3
NYHA class (%)	**		*		*	
I	0	0.1	0	0	0	0
II	55.4	62.4	63.7	71.4	38.2	49.0
III	41.0	35.7	36.3	28.6	56.5	47.6
IV	3.6	1.8	0	0	5.4	3.3
Ischaemic aetiology (%)	64.0**	56.5	64.3***	50.6	77.4**	66.7
Race (%)						
White	89.6	90.4	76.8	76.3	86.6	88.6
Black	7.2	6.8	17.3	16.1	2.2	3.8
Asian	-	-	1.2	1.2	9.1	6.3
Other	3.2	2.8	4.8	6.4	2.2	1.2
BP -mmHg						
Systolic	123.2±18.6	123.8±18.5	118.5±19.6	120.1±19.4	128.5±18.9	130.6±18.7
Diastolic	74.5±10.1*	75.6±10.6	69.7±11.2	71.4±11.3	76.0±11.2	76.9±10.6
Heart rate -beats/min	74.7±13.4*	73.3±12.5	74.9±13.8	74.6±14.0	75.3±13.7	74.4±13.7
BMI	26.9±4.6	27.0±4.5	-	-	26.7±5.0*	27.5±4.8
Medical history (%)						
Current smoking	-	-	13.1	15.9	15.6	13.5
HF hospitalisation	-	-			73.7	67.6
Angina	22.4	21.1	38.7*	29.6	57.5	58.1
Myocardial infarction	52.9**	46.3	60.1***	42.6	69.4*	60.1
PCI	-	-	22.6	20.9	14.5	15.8
CABG	25.3	23.0	30.4	26.4	24.2	24.6
Hypertension	43.9	40.6	60.7	55.4	50.5	49.8
Diabetes	27.8	25.2	39.3**	29.4	33.9*	26.3
Atrial fibrillation	14.5	11.9	16.1	14.6	31.7*	24.6
Stroke	6.8	6.9	8.3	7.1	7.5	8.5
Laboratory tests						
eGFR -ml/min/1.73m^2	61.0±16.0	61.4±15.6	69.9±21.9	71.0±22.2	59.1±20.8**c	69.4±27.0d
eGFR <60 ml/min/1.73m^2 (%)	46.9	46.8	31.0	32.4	58.5**c	39.8d
Creatinine -mg/dl	1.31±0.31*	1.28±0.31	1.23±0.38	1.21±0.77	1.34±0.36*c	1.20±0.45d
NT-proBNP -pg/ml	1335***a [571-3034]	867b [363-1909]	-	-	-	-
Treatment (%)						
Digitalis	73.8**	66.7	78.0*	70.3	57.5***	44.1
Diuretics	90.7***	85.0	92.3**	82.5	91.9**	84.6
ACEI	93.4	92.6	85.1	85.7	0	0.2
ARB	NA	NA	17.9	14.4	NA	NA
ACEI/ARB	96.4	96.4	98.8	97.3	NA	NA
Beta-blocker	31.0	35.3	72.0	68.3	50.5	54.6
MRA	-	-	17.9	19.5	29.0	22.9
Pacemaker	-	-	-	-	9.7	7.8
CRT-P	-	-	-	-	-	-
Treatment arm	52.0	49.9	45.2	50.5	40.9*	50.6

	CHARM-Added		CORONA		GISSI-HF	
	SD (N=311)	**Others (N=2137)**	**SD (N=631)**	**Others (N=4244)**	**SD (N=367)**	**Others (N=3453)**
Age -years	65.8±10.4***	63.3±11.1	73.7±7.6***	72.6±7.0	70.2±9.2***	66.9±10.9
Male (%)	81.0	78.1	82.6***	75.1	80.4	78.9
LVEF-%	26.6±7.3***	28.3±7.5	29.3±6.7***	31.2±6.4	30.5±6.1***	31.7±6.2
NYHA class (%)	*		**		***	
I	0	0	0	0	0	0
II	18.3	25.0	33.6	37.6	52.9	64.2
III	77.8	72.2	63.7	61.1	43.3	33.9
IV	3.9	2.8	2.7	1.3	3.8	2.0
Ischaemic aetiology (%)	67.2	61.8	100	100	50.4***	39.0
Race (%)						
White	90.7	90.5	98.1	98.7	-	-
Black	3.2	5.2	0	0.3	-	-
Asian	4.8	3.5	1.1	0.7	-	-
Other	1.3	0.8	0.8	0.4	-	-
BP -mmHg						
Systolic	123.7±17.1	125.9±18.8	127.1±17.5***	129.8±16.3	126.9±18.8	126.5±18.0
Diastolic	74.4±10.7	75.4±10.7	74.6±9.1***	76.5±8.8	77.0±9.6	77.1± 9.8
Heart rate -beats/min	74.0±13.2	73.6±13.1	72.5±11.1	71.7±11.2	73.7±12.7	73.1±13.7
BMI	27.5±5.2	27.9±5.3	26.5±4.5***	27.3±4.6	26.8±4.4	27.1±4.5
Medical history (%)						
Current smoking	17.7	17.0	7.8	8.8	11.7	15.3
HF hospitalisation	77.2	76.9	-	-	47.4	44.1
Angina	53.7	52.4	71.6	72.8	14.7*	11.0
Myocardial infarction	59.2	54.7	65.5***	58.5	39.2**	32.2
PCI	10.0*	14.9	9.7	11.5	6.5	8.2
CABG	24.1	24.1	15.7	16.6	14.7	13.8
Hypertension	48.2	48.1	61.2	64.3	52.9	52.7
Diabetes	36.0*	29.3	32.5	29.1	29.2	25.5
Atrial fibrillation	24.8	26.7	44.1	40.4	23.2*	18.3
Stroke	9.3	8.2	13.5	12.3	5.7	4.4
Laboratory tests						
eGFR -ml/min/1.73m^2	71.4±29.9e	73.5±26.5f	55.1±15.0***	58.2±15.1	64.3±21.2***	70.5±21.8
eGFR <60 ml/min/1.73m^2 (%)	38.8e	31.6f	64.1***	55.6	43.6***	32.9
Creatinine -mg/dl	1.20±0.41e	1.15±0.40f	1.38±0.34***	1.29±0.31	1.24±0.40***	1.14±0.33
NT-proBNP -pg/ml	-	-	2894***g [1263-5326]	1352h [562-2803]	1659***i [829-3092]	840j [353-1767]
Treatment (%)						
Digitalis	62.4	57.3	37.1*	32.5	51.5***	38.8
Diuretics	93.9*	89.5	92.1**	87.6	88.0***	80.8
ACEI	100	99.9	80.8	80.1	77.1	78.2
ARB	NA	NA	-	-	17.7	18.2
ACEI/ARB	NA	NA	90.8	91.9	92.4	93.9
Beta-blocker	50.5	55.3	73.1	75.2	58.9	63.8
MRA	18.0	16.6	43.9**	38.2	39.0	39.9
Pacemaker	8.4	7.9	10.0	10.7	14.7**	9.9
CRT-P	-	-	-	-	-	-
Treatment arm	47.3	50.6	49.4	50.2	53.1	49.6

	EMPHASIS-HF		PARADIGM-HF		ATMOSPHERE	
	SD (N=125)	**Others (N=2191)**	**SD (N=525)**	**Others (N=6631)**	**SD (N=607)**	**Others (N=5361)**
Age -years	69.9±8.4	68.6±7.6	63.0±12.2	63.7±11.6	63.2±12.5	63.1±12.1
Male (%)	80.8	75.9	82.9***	76.3	84.0***	75.6
LVEF-%	25.8±5.0	26.4±4.4	29.1±6.5**	29.9±6.1	28.1±5.5**	28.8±5.5
NYHA class (%)			***		***	
I	0	0	4.0	4.9	0	0
II	100	100	63.0	70.3	50.6	62.6
III	0	0	31.8	24.0	45.5	35.4
IV	0	0	1.1	0.7	4.0	2.0
Ischaemic aetiology (%)	78.2*	67.5	65.1**	58.2	57.5	53.8
Race (%)	*		***		**	
White	73.6	81.6	54.1	63.3	55.8	62.4
Black	2.4	2.2	6.1	4.7	1.7	1.6
Asian	21.6	12.8	29.0	20.0	35.6	28.2
Other	2.4	3.4	10.9	12.0	7.0	7.8
BP -mmHg						
Systolic	123.3±16.4	125.1±16.8	120.8±15.7	122.1±15.3	121.3±16.9***	124.7±18.3
Diastolic	74.8±9.0	75.3±10.3	73.9±10.5	74.2±10.0	76.9±10.8	77.7±11.0
Heart rate -beats/min	74.0±11.9	72.2±12.7	73.6±11.7	72.9±12.2	73.1±12.8	72.3±12.7
BMI	26.7±5.3	27.5±4.9	27.2±5.7**	28.0±5.5	26.2±5.2***	27.3±5.3
Medical history (%)						
Current smoking	11.2	10.6	13.7	14.1	11.9	12.5
HF hospitalisation	55.6	50.9	65.0	62.1	59.0	58.4
Angina	45.2	43.4	30.5	26.9	24.7	23.6
Myocardial infarction	56.5	47.8	48.2***	40.2	38.4	37.2
PCI	17.7	18.6	13.1**	18.5	13.5*	16.7
CABG	15.3	15.6	12.0	13.3	11.4	11.7
Hypertension	68.8	67.1	69.7	71.4	59.1	62.8
Diabetes	36.8	31.3	35.4	33.5	22.7**	27.8
Atrial fibrillation	35.5	30.4	32.8	36.9	31.6	33.8
Stroke	16.3**	9.0	9.0	8.3	8.7	6.8
Laboratory tests						
eGFR -ml/min/1.73m^2	69.6±21.3	71.5±21.8	68.6±19.8	68.8±20.3	75.4±22.1	75.0±24.9
eGFR <60 ml/min/1.73m^2 (%)	34.4	32.0	34.7	34.4	24.9	24.6
Creatinine -mg/dl	1.18±0.31	1.14±0.30	1.13±0.29	1.10±0.29	1.03±0.27	1.02±0.27
NT-proBNP -pg/ml	-	-	2444*** [1256-5198]	1580 [870-3133]	1801***k [903-3183]	1142m [607-2149]
Treatment (%)						
Digitalis	41.1**	27.5	35.4*	30.9	42.0***	31.4
Diuretics	90.3	86.1	81.7	79.6	84.2***	78.4
ACEI	82.3	78.2	79.2	77.1	67.9	66.8
ARB	13.7	19.3	21.0	23.2	1.6	1.4
ACEI/ARB	94.4	94.4	100	100	68.5	67.2
Beta-blocker	80.6	86.3	89.9*	92.6	89.5	91.0
MRA	NA	NA	55.8	55.4	37.2	35.1
Pacemaker	2.4*	8.7	5.3	7.3	4.0	4.2
CRT-P	0.8	2.4	1.0	2.0	1.3	1.8
Treatment arm	44.8	50.6	45.3	50.2	67.2	66.6

*P<0.05, **p<0.01, *** p<0.001

The letters denote the number of patients available: a=352 (80%), b=3715(81%), c=53(28%), d=567(32%), e=103(33%), f=769(36%), g=422(67%), h=3133(74%), i=49 (13%), j=521 (15%), k =573 (94%), m=4835 (90%).

SD denotes sudden death.

3.2.3 Baseline characteristics of patients with pump failure death

The characteristics of patients with and without pump failure death in each trial are outlined in Table 3-3. In general, patients having a pump failure death tended to be older, have more severe HF symptoms, lower LVEF and blood pressure. They were more likely to have previous hospital admission for worsening HF, a history of diabetes, atrial fibrillation or renal dysfunction. Similar to patients dying suddenly, patients having a pump failure death were less likely to be treated with a beta-blocker, but were more likely to receive a diuretic, digitalis or MRA and have a pacemaker or CRT-P implantation. Likewise, NT-proBNP levels were substantially higher in patients with a pump failure death than in those without.

Table 3-3 Baseline characteristics of patients with and without pump failure death in the included trials in HF-REF

	RALES		BEST		CIBIS-II		MERIT-HF	
	PFD (N=316)	**Others (N=1347)**	**PFD (N=336)**	**Others (N=2281)**	**PFD (N=83)**	**Others (N=2564)**	**PFD (N=88)**	**Others (N=3903)**
Age -years	67.3±11.9***	64.7±11.8	63.7±11.8***	59.6±12.4	64.0±11.7**	60.8±10.5	68.0±7.0***	63.2±9.7
Male (%)	72.8	73.3	83.3*	77.1	92.8**	80.1	83.0	77.4
LVEF-%	24.1±6.9***	25.7±6.6	20.6±7.4***	23.4±7.2	25.4±6.8**	27.5±5.9	24.4±6.9***	27.8±6.9
NYHA class (%)	***		***		***		***	
I	0	0.1	0	0	0	0	0	0
II	0	0.4	0	0	0	0	13.6	41.6
III	53.2	74.6	83.3	92.9	65.1	83.8	69.3	55.1
IV	46.8	24.9	16.7	7.1	34.9	16.2	17.0	3.3
Ischaemic aetiology (%)	54.7	54.6	70.5	56.2	51.8	49.7	73.9	65.1
Race (%)								
White	87.0	86.5	72.6	69.0	100	98.9	96.6	94.1
Black	8.2	7.0	22.3	23.7	0	0.3	2.3	5.3
Asian	0.6	2.2	4.8	5.6	0	0.6	1.1	0.4
Other	4.1	4.3	0.3	1.8	0	0.2	0	0.3
BP -mmHg								
Systolic	113.8±17.0***	124.2±20.2	111.0±16.9***	118.3±18.0	119.8±15.9***	130.0±19.4	118.5±13.3***	130.0±17.1
Diastolic	70.8±10.8***	75.5±11.6	67.6±10.2***	71.6±11.3	74.5±8.5***	79.8±11.1	73.2±8.4***	78.4±9.2
Heart rate -beats/min	81.8±14.1	80.6±14.2	82.1±13.5	81.7±13.2	82.1±17.0	80.4±14.9	85.5±11.3**	82.5±10.2
BMI	-	-	26.7±5.4***	28.2±6.0	26.3±4.2	26.9±4.1	24.9±3.7***	27.3±4.7
Medical history (%)								
Current smoking	-	-	14.9	18.2	18.1	16.6	11.4	14.6
HF hospitalisation	-	-	-	-	-	-	-	-
Angina	6.0	6.8	57.1*	50.9	-	-	-	-
Myocardial infarction	28.2	28.4	51.8***	40.3	57.8	54.9	56.8	48.0
PCI	-	-	15.2	5.2	7.2	4.3	-	-
CABG	-	-	34.8**	27.4	-	-	25.0	20.8
Hypertension	13.9***	25.8	61.3	58.8	32.5*	43.8	40.9	43.8
Diabetes	21.5	22.3	45.2***	34.8	18.1	11.5	38.6**	24.3
Atrial fibrillation	-	-	33.0***	22.6	-	-	18.2	16.6
Stroke	-	-	-	-	10.8¶	7.3¶	8.0	7.9
Laboratory tests								
eGFR -ml/min/1.73m^2	59.8±21.3***	66.1±23.2	59.1±27.8***	71.7±23.8	61.4±32.2***	78.0±31.1	55.3±17.4***	66.9±19.5
eGFR <60 ml/min/1.73m^2 (%)	59.7***	45.0	59.6***	32.3	56.6***	30.8	59.3***	36.3
Creatinine -mg/dl	1.32±0.37***	1.22±0.36	1.47±0.49***	1.21±0.38	1.48±0.49***	1.17±0.32	1.48±0.77***	1.20±0.36
NT-proBNP -pg/ml	-	-	-	-	-	-	-	-
Treatment (%)								
Digitalis	81.0***	71.3	95.2*	91.7	62.7*	51.3	77.3**	63.3
Diuretics	-	-	98.2***	92.7	-	-	96.6*	90.2
ACEI	93.0	93.2	89.9	91.7	91.6	94.8	89.8	89.5
ARB	-	-	4.2	6.5	-	-	3.4	6.6
ACEI/ARB	-	-	93.8**	97.1	-	-	93.2	95.7
Beta-blocker	5.1***	11.5	NA	NA	43.4	50.4	NA	NA
MRA	NA	NA	4.5	3.2	20.5**	10.6	-	-
Pacemaker	-	-	10.4	7.5	-	-	-	-
CRT-P	-	-	-	-	-	-	-	-
Treatment arm	40.2***	51.6	49.4	50.1	43.4	50.4	34.1**	50.2

	Val-HeFT		SCD-HeFT		CHARM-Alternative	
	PFD (N=321)	Others (N=4689)	PFD (N=125)	Others (N=1567)	PFD (N=151)	Others (N=1809)
Age -years	67.5±10.7***	62.4±11.0	64.8±10.4***	58.4±11.9	70.6±10.1***	65.7±10.8
Male (%)	80.4	80.0	83.2	75.9	66.2	67.7
LVEF-%	24.5±6.9***	26.9±7.1	22.2±6.0**	24.1±7.0	27.2±7.3***	30.2±7.3
NYHA class (%)	***		***		***	
I	0	0.1	0	0	0	0
II	34.6	63.6	44.8	72.7	26.5	49.8
III	59.5	34.6	55.2	27.3	61.6	47.4
IV	5.9	1.7	0	0	11.9	2.8
Ischaemic aetiology (%)	65.4**	56.6	68.0***	50.7	69.5	67.6
Race (%)						
White	92.5	90.2	78.4	76.2	88.1	88.4
Black	4.7	7.0	14.4	16.3	3.3	3.7
Asian	-	-	1.6	1.2	6.6	6.6
Other	2.8	2.8	5.6	6.3	2.0	1.3
BP -mmHg						
Systolic	117.2±17.9***	124.2±18.5	114.5±18.8**	120.4±19.4	124.1±18.1***	130.9±18.7
Diastolic	71.3±10.2***	75.8±10.6	65.8±10.7***	71.7±11.3	72.6±10.7***	77.2±10.6
Heart rate -beats/min	75.1±12.1*	73.3±12.6	76.5±14.5	74.4±13.9	78.0±12.2**	74.2±13.8
BMI	25.9±4.4***	27.0±4.5	-	-	26.5±5.5*	27.5±4.8
Medical history (%)						
Current smoking	-	-	9.6	16.1	11.9	13.9
HF hospitalisation	-	-	-	-	90.7***	66.3
Angina	28.3**	20.7	32.0	30.4	56.3	58.2
Myocardial infarction	50.8	46.6	55.2*	43.5	66.2	60.6
PCI	-	-	22.4	21.0	10.6	16.1
CABG	29.6**	22.8	39.2**	25.8	21.2	24.8
Hypertension	43.9	40.7	68.8**	54.9	47.7	50.0
Diabetes	30.5*	25.1	46.4***	29.1	43.7***	25.6
Atrial fibrillation	14.6	11.9	25.6***	13.8	35.1**	24.4
Stroke	10.3*	6.6	7.2	7.2	10.6	8.2
Laboratory tests						
eGFR - ml/min/1.73m^2	51.0±15.7***	62.1±15.3	59.1±17.8***	71.8±22.3	51.5±29.4***c	69.6±26.1d
eGFR <60 ml/min/1.73m^2 (%)	76.6***	44.8	52.0***	30.7	74.4***c	39.2d
Creatinine -mg/dl	1.51±0.38***	1.27±0.30	1.39±0.46**	1.19±0.75	1.63±0.58***c	1.18±0.42d
NT-proBNP -pg/ml	2375a [1040-4366]	843b [356-1849]	-	-	-	-
Treatment (%)						
Digitalis	77.9***	66.6	82.4**	70.2	57.0**	44.4
Diuretics	96***	84.8	95.2***	82.5	98.7***	84.2
ACEI	90.3	92.9	86.4	85.6	0	0
ARB	NA	NA	13.6	14.9	NA	NA
ACEI/ARB	93.8**	96.6	98.4	97.4	NA	NA
Beta-blocker	20.2***	35.9	59.2*	69.4	37.1***	55.6
MRA	-	-	25.6	18.8	39.7***	22.1
Pacemaker	-	-	-	-	12.6*	7.6
CRT-P	-	-	-	-	-	-
Treatment arm	46.7	50.4	50.4	49.9	44.4	50.1

	CHARM-Added		CORONA		GISSI-HF	
	PFD (N=200)	**Others (N=2248)**	**PFD (N=372)**	**Others (N=4503)**	**PFD (N=321)**	**Others (N=3499)**
Age -years	68.6±11.0***	63.2±10.9	75.3±7.2***	72.5±7.1	71.9±8.6***	66.8±10.9
Male (%)	80.5	78.2	76.3	76.0	81.6	78.8
LVEF-%	25.3±7.3***	28.4±7.4	29.0±6.9***	31.1±6.4	29.2±6.9***	31.8±6.1
NYHA class (%)	***		***		***	
I	0	0	0	0	0	0
II	15.0	25.0	26.3	38.0	41.4	65.1
III	75.0	72.7	70.4	60.7	52.0	33.2
IV	10.0	2.3	3.2	1.3	6.5	1.7
Ischaemic aetiology (%)	66.0	62.2	100	100	49.2***	39.3
Race (%)						
White	92.0	90.3	98.4	98.6	-	-
Black	3.0	5.2	0	0.3	-	-
Asian	4.5	3.6	1.1	0.7	-	-
Other	0.5	0.9	0.5	0.4	-	-
BP -mmHg						
Systolic	121.0±18.0***	126.0±18.6	123.4±16.3***	130.0±16.4	120.9±17.1***	127.0±18.0
Diastolic	72.7±10.7***	75.5±10.7	73.2±8.5***	76.5±8.9	74.0±9.4***	77.4±9.8
Heart rate -beats/min	76.0±12.5**	73.4±13.2	74.8±11.7***	71.5±11.1	75.0±13.1*	73.0±13.7
BMI	26.3±5.0***	27.9±5.3	26.1±4.4***	27.3±4.6	25.7±4.4***	27.1±4.5
Medical history (%)						
Current smoking	14.5	17.3	4.8**	9.0	9.3**	15.4
HF hospitalisation	85.5**	76.2	-	-	61.1***	42.9
Angina	53.5	52.5	73.1	72.6	13.1	11.2
Myocardial infarction	58.5	54.9	61.6	59.2	42.4***	32.0
PCI	7.5**	14.9	8.6	11.5	7.8	8.1
CABG	25.5	23.9	14.0	16.7	20.6***	13.3
Hypertension	44.5	48.4	59.7	64.3	46.7*	53.3
Diabetes	35.5	29.7	37.6***	28.8	34.9***	25.0
Atrial fibrillation	37.5***	25.5	48.9**	40.2	26.8***	18.1
Stroke	9.5	8.3	15.1	12.3	7.2*	4.3
Laboratory tests						
eGFR - ml/min/1.73m^2	55.4±18.9***e	74.9±27.0f	51.1±15.0***	58.4±15.0	59.7±22.1***	70.8±21.6
eGFR <60 ml/min/1.73m^2 (%)	62.5***e	29.8f	74.3***	55.6	57.4***	31.8
Creatinine -mg/dl	1.43±0.43***e	1.14±0.39f	1.45±0.37***	1.29±0.31	1.34±0.44***	1.13±0.32
NT-proBNP -pg/ml	-	-	3404g [1722-6753]	1373h [579-2894]	2035i [1170-4236]	819j [347-1702]
Treatment (%)						
Digitalis	72.5***	56.6	47.0***	32.0	59.2***	38.3
Diuretics	99.0***	89.2	97.8***	87.4	94.7***	80.3
ACEI	100	99.9	73.1***	80.8	74.8	78.4
ARB	NA	NA	-	-	19.9	17.9
ACEI/ARB	NA	NA	87.1***	92.2	91.9	93.9
Beta-blocker	37.0***	56.2	64.8***	75.8	49.2***	64.6
MRA	24.5**	16.1	51.3***	37.9	53.0***	38.6
Pacemaker	16.5***	7.2	14.8**	10.3	19.9***	9.5
CRT-P	-	-	-	-	-	-
Treatment arm	44.0	50.8	49.7	50.1	47.0	50.2

	EMPHASIS-HF		PARADIGM-HF		ATMOSPHERE	
	PFD (N=94)	**Others (N=2222)**	**PFD (N=261)**	**Others (N=6895)**	**PFD (N=305)**	**Others (N=5663)**
Age -years	71.6±7.9***	68.5±7.6	65.3±13.0*	63.6±11.6	65.4±13.4***	63.0±12.0
Male (%)	80.9	75.9	80.1	76.6	82.3*	76.2
LVEF-%	24.9±4.5**	26.4±4.4	28.2±6.6***	29.9±6.1	27.0±5.8***	28.9±5.5
NYHA class (%)			**			
I	0	0	1.9	5.0	0	0
II	100	100	63.6	70.0	55.1	61.8
III	0	0	33.7	24.2	41.6	36.1
IV	0	0	0.8	0.8	3.3	2.1
Ischaemic aetiology (%)	74.2	67.8	49.0**	59.1	45.9**	54.6
Race (%)					***	
White	71.3	81.6	57.9	62.8	63.8	61.6
Black	4.3	2.2	3.8	4.8	4.9	1.4
Asian	18.1	13.1	21.5	20.7	23.7	29.2
Other	6.4	3.2	16.9	11.7	7.6	7.8
BP -mmHg						
Systolic	117.6±16.3***	125.3±16.7	118.0±14.8***	122.1±15.4	118.8±18.3***	124.7±18.2
Diastolic	72.0±11.7**	75.4±10.1	71.5±9.9***	74.3±10.0	73.8±10.8***	77.8±11.0
Heart rate -beats/min	75.3±13.9*	72.1±12.6	74.8±12.9*	72.9±12.1	73.5±13.7	72.3±12.6
BMI	25.2±4.2***	27.6±4.9	27.1±5.4**	28.0±5.5	26.6±5.4	27.2±5.3
Medical history (%)						
Current smoking	11.7	10.6	9.6*	14.3	11.5	12.5
HF hospitalisation	74.5***	50.2	69.0*	62.1	71.8***	57.8
Angina	39.4	43.7	19.5**	27.5	20.3	23.9
Myocardial infarction	63.8**	47.6	38.7	40.9	33.4	37.5
PCI	14.9	18.8	13.4*	18.3	12.8	16.5
CABG	16.0	15.6	12.3	13.2	11.5	11.7
Hypertension	62.8	67.4	63.6**	71.6	57.7	62.7
Diabetes	44.7**	31.1	39.5*	33.4	22.3*	27.6
Atrial fibrillation	36.2	30.4	41.8	36.4	41.6**	33.1
Stroke	11.7	9.3	12.3*	8.2	8.9	6.9
Laboratory tests						
eGFR - ml/min/1.73m^2	61.2±20.1***	71.8±21.7	63.4±24.9***	69.0±20.0	70.6±26.1**	75.3±24.5
eGFR <60 ml/min/1.73m^2 (%)	52.1***	31.3	49.0***	33.9	37.0***	23.9
Creatinine -mg/dl	1.26±0.32***	1.13±0.30	1.22±0.35***	1.10±0.29	1.11±0.32***	1.02±0.26
NT-proBNP -pg/ml	-	-	3645*** [1795-6704]	1591 [877-3157]	2236***k [1081-4241]	1168m [616-2174]
Treatment (%)						
Digitalis	44.1***	27.5	41.0***	30.8	45.9***	31.8
Diuretics	95.7**	86.0	88.5***	79.4	85.9**	78.6
ACEI	72.0	78.7	72.4	77.4	63.0	67.1
ARB	20.4	19.0	28.0	22.8	1.0	1.4
ACEI/ARB	92.5	94.5	100	100	63.0	67.6
Beta-blocker	79.6	86.3	88.9*	92.5	89.5	90.9
MRA	43.6	50.6	59.4	55.3	42.0*	35.0
Pacemaker	14.9*	8.1	14.6***	6.9	6.9*	4.0
CRT-P	5.3*	2.1	5.0***	1.8	4.3***	1.7
Treatment arm	43.6	50.6	44.8	50.0	71.5	66.4

*P<0.05, **p<0.01, *** p<0.001.

a=258 (80%), b=3809 (81%), c=39(26%), d=581(32%), e=72(36%), f=800 (36%), g=256 (69%), h=3299 (73%), i=47 (15%), j=523 (15%), k=292 (96%), m=5116 (90%).

PFD denotes pump failure death.

3.2.4 Sudden death rates in each trial and in each arm of each trial

Compared to the earlier trials, the rate of sudden death was lower in the more recent trials which had a higher adoption of disease-modifying therapies, except for CORONA which enrolled patients aged ≥60 years with an ischaemic aetiology only (Figure 3-2 and Table 3-4). The annual rate of sudden death declined from 6.5% in the oldest RALES to 3.3% in the latest ATMOSPHERE, although CORONA lay above the trend with a rate of 5.2%, p for trend=0.001 (Table 3-4 and Figure 3-3). There was a similar pattern in the rates of death from any cause across the trials, suggesting that the higher sudden death rate in CORONA was likely to be due to the underlying risk of patients in the trial itself (Figure 3-4). Unsurprisingly, the proportion of sudden death relative to total mortality did not fall across trials, given that the downward trend in sudden death rates was in line with the falling overall mortality rates (Figure 3-5).

Figure 3-2 Cumulative incidence curves for sudden death by trials in HF-REF

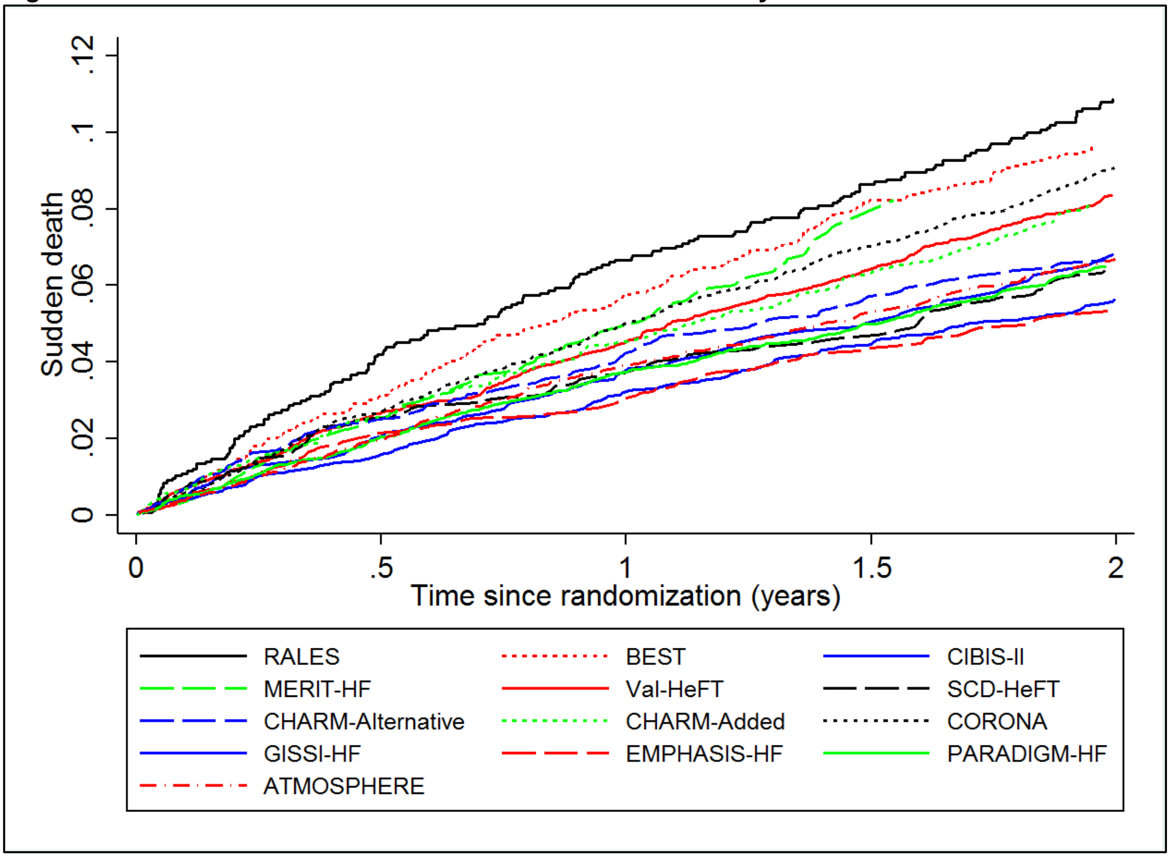


Table 3-4 Annual rates and cumulative incidences of sudden death at different time points in the included trials in HF-REF (treatment arms combined)

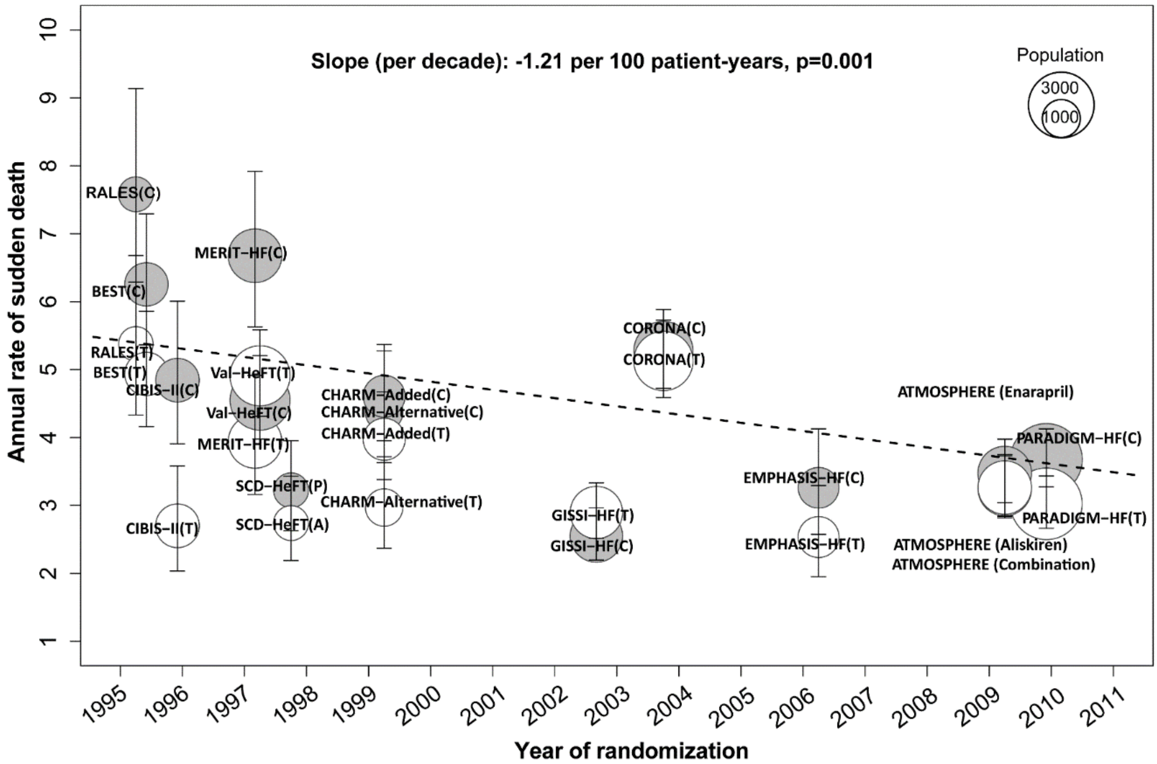
	RALES (N=1663)	**BEST (N=2617)**	**CIBIS-II (N=2647)**	**MERIT-HF (N=3991)**	**Val-HeFT (N=5010)**
No. of sudden death	192	294	131	211	442
Annual rate (95% CI)	6.5 (5.6-7.4)	5.6 (5.0-6.3)	3.8 (3.2-4.5)	5.3 (4.6-6.1)	4.7 (4.3-5.2)
Cumulative incidence (95% CI)					
30 days	1.0 (0.5-1.5)	0.5 (0.2-0.8)	0.4 (0.1-0.6)	0.3 (0.1-0.5)	0.6 (0.4-0.8)
60 days	1.5 (0.9-2.0)	1.1 (0.7-1.6)	0.9 (0.6-1.3)	0.7 (0.4-0.9)	1.0 (0.7-1.3)
90 days	2.4 (1.6-3.1)	1.8 (1.3-2.3)	1.3 (0.9-1.7)	1.3 (0.9-1.6)	1.3 (1.0-1.7)
180 days	4.2 (3.2-5.2)	3.1 (2.4-3.7)	2.0 (1.5-2.5)	2.5 (2.0-3.0)	2.6 (2.2-3.1)
1 year	6.7 (5.5-7.9)	5.8 (4.9-6.7)	3.8 (3.0-4.5)	5.0 (4.3-5.7)	4.5 (3.9-5.1)
2 years	10.9 (9.3-12.4)	9.7 (8.5-10.9)	6.8 (5.4-8.2)	-	8.4 (7.5-9.2)
3 years	13.4 (11.4-15.4)	13.5 (12.0-15.1)	-	-	12.2 (10.6-13.9)

	SCD-HeFT (N=1692)	**CHARM-Alternative (N=1960)**	**CHARM-Added (N=2448)**	**CORONA (N=4875)**
No. of sudden death	168	186	311	631
Annual rate (95% CI)	3.0 (2.6-3.5)	3.7 (3.2-4.2)	4.3 (3.8-4.8)	5.2 (4.8-5.6)
Cumulative incidence (95% CI)				
30 days	0.5 (0.2-0.9)	0.6 (0.2-0.9)	0.6 (0.3-0.9)	0.5 (0.3-0.7)
60 days	0.9 (0.4-1.3)	1.1 (0.6-1.5)	1.0 (0.6-1.4)	0.9 (0.6-1.1)
90 days	1.4 (0.9-2.0)	1.6 (1.1-2.2)	1.5 (1.0-1.9)	1.3 (1.0-1.7)
180 days	2.5 (1.7-3.2)	2.5 (1.8-3.2)	2.5 (1.9-3.2)	2.6 (2.2-3.1)
1 year	3.7 (2.8-4.6)	4.2 (3.3-5.1)	4.5 (3.7-5.3)	5.0 (4.4-5.6)
2 years	6.4 (5.2-7.5)	6.7 (5.6-7.8)	8.2 (7.1-9.3)	9.1 (8.3-9.9)
3 years	8.7 (7.4-10.1)	9.5 (8.1-10.8)	11.2 (9.9-12.4)	13.2 (12.2-14.2)

	GISSI-HF (N=3820)	**EMPHASIS-HF (N=2316)**	**PARADIGM-HF (N=7156)**	**ATMOSPHERE (N=5968)**
No. of sudden death	367	125	525	607
Annual rate (95% CI)	2.7(2.5-3.0)	2.9 (2.4-3.4)	3.3 (3.1-3.6)	3.3 (3.1-3.6)
Cumulative incidence (95% CI)				
30 days	0.3 (0.2-0.5)	0.3 (0.1-0.5)	0.4 (0.3-0.6)	0.3 (0.2-0.5)
60 days	0.6 (0.3-0.8)	0.7 (0.3-1.0)	0.7 (0.5-0.9)	0.6 (0.4-0.8)
90 days	1.0 (0.7-1.3)	1.0 (0.6-1.5)	1.0 (0.8-1.3)	1.0 (0.7-1.2)
180 days	1.5 (1.2-1.9)	2.1 (1.5-2.7)	2.0 (1.7-2.3)	1.9 (1.6-2.3)
1 year	3.2 (2.6-3.8)	3.0 (2.3-3.7)	3.7 (3.3-4.2)	3.9 (3.4-4.4)
2 years	5.6 (4.9-6.4)	5.3 (4.3-6.4)	6.5 (5.9-7.1)	6.7 (6.0-7.3)
3 years	7.6 (6.7-8.4)	7.4 (6.0-8.7)	8.8 (8.0-9.5)	9.3 (8.5-10.0)

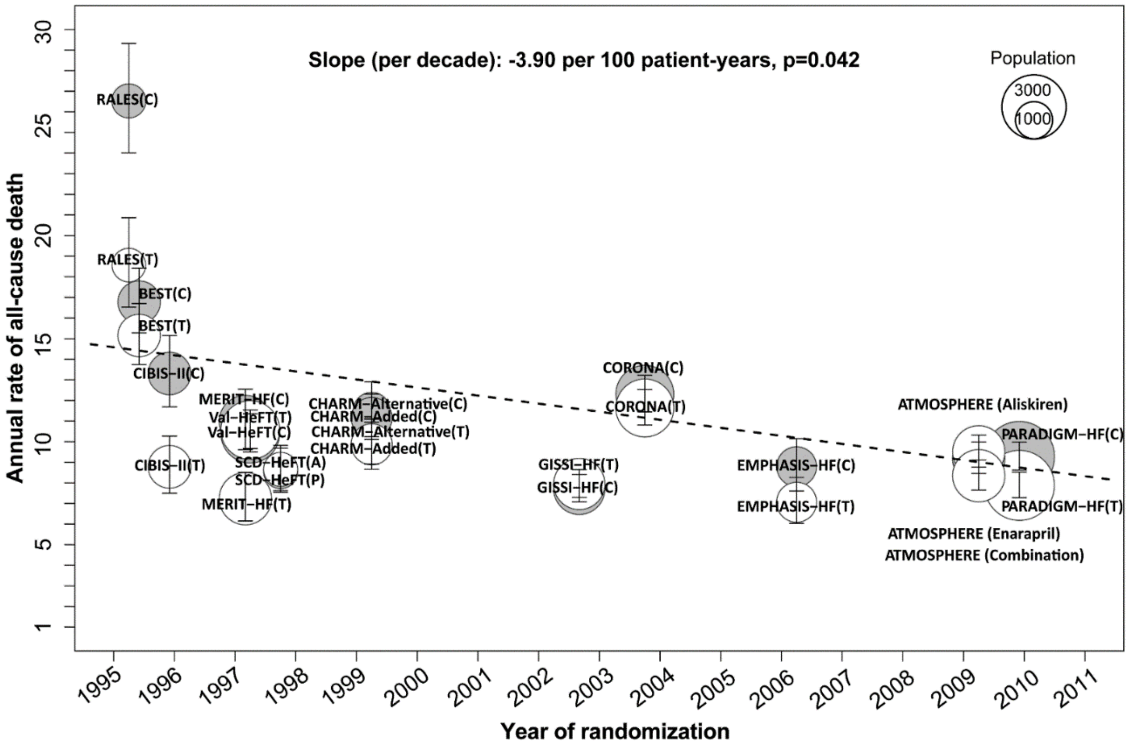
Annual rates are shown as sudden death per 100 patient-years. Cumulative incidences are presented as percent. '-' denotes data not available.

Figure 3-3 Trends in the sudden death rate across trial arms over time in HF-REF



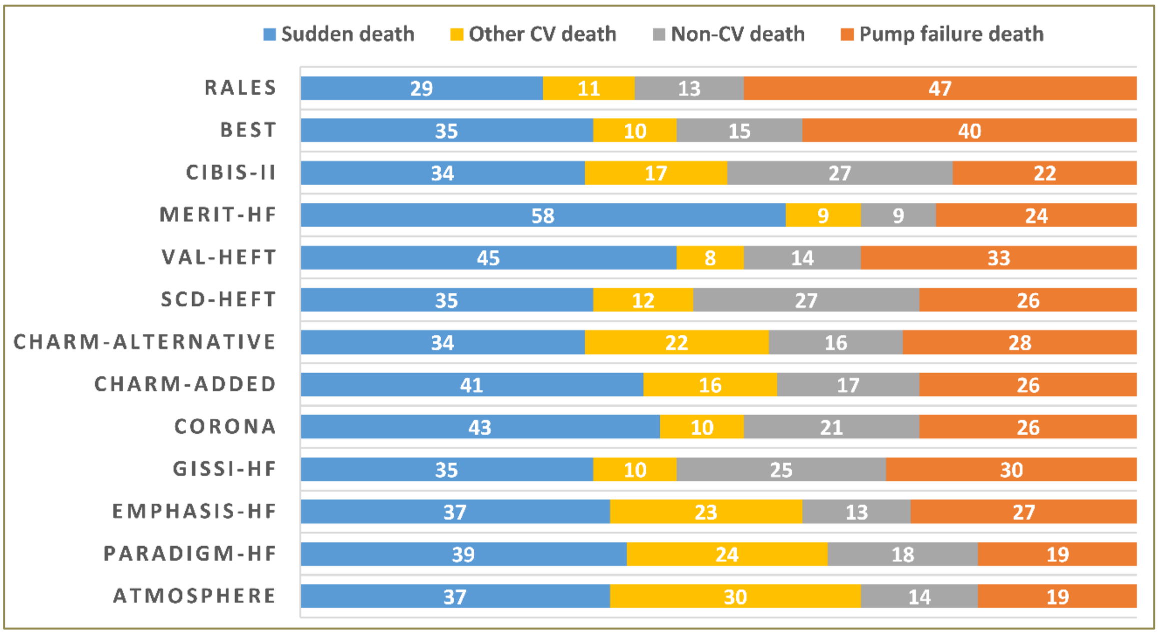
Annual rates are shown as sudden death per 100 patient-years. The black dotted line is based on the multiple linear regression of the annual rate in each trial arm with the randomisation year and randomisation arm as covariates, weighted by its inverse-variance and with trial as a random effect. P for slope represents the p value for randomisation year based on the linear model. Each circle represents each trial arm as labelled, with the control arm in each trial illustrated in gray and the experimental arm in white. The centre of each circle corresponds to randomisation year (x axis) and the annual rate (y axis) in each arm, the error bars in each circle correspond to the 95% confidence interval of the annual rate. The area of each circle represents the sample size in each arm (reference size shown in the upper right corner). C denotes control arm; T, experimental treatment arm; P, placebo arm; A, amiodarone arm.

Figure 3-4 Trends in the all-cause death rate across trial arms over time in HF-REF



Annual rates are shown as all-cause death per 100 patient-years. Other notes and abbreviations are same as those in Figure 3-3.

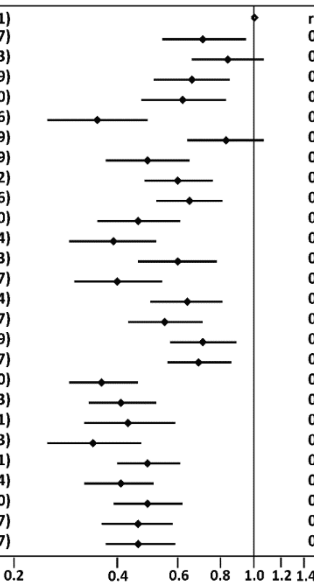
Figure 3-5 Proportions of sudden death and pump failure death relative to overall mortality across the trials in HF-REF



The rate of sudden death was lower in the experimental therapy group in all trials, with the exceptions of Val-HeFT and GISSI-HF, where the opposite, albeit to a minimal extent, was true (Figure 3-3). Adjusting for randomisation treatment, with trial as a random effect, there was a 41% decline in the risk of sudden death over the past 20 years (HR 0.59, 95% CI 0.37-0.92, p=0.021). The fall in risk over time was attenuated when additionally adjusting for conventional confounding variables, but randomisation treatment remained significantly associated with a lower risk of sudden death (HR 0.87, 95% CI 0.82-0.93, p <0.001). When examining the risk of sudden death by individual trial arm, compared to the placebo arm of RALES, the risks of sudden death were 59% and 54% lower in the treatment arm of PARADIGM-HF and in the combination therapy arm of ATMOSPHERE, respectively (Figure 3-6). These differences were attenuated somewhat but remained highly significant after adjustment for conventional confounding covariates (adjusted HR 0.65, 95% CI 0.51-0.83, p<0.001; 0.70, 0.55-0.89, p=0.004, respectively [Figure 3-7]). A similar result was observed with further adjustment for eGFR (Figure 3-8). In the subset of patients with both eGFR and NT-proBNP available, compared with the placebo arm of Val-HeFT, the risk of sudden death in the treatment arm of PARADIGM-HF and in the combination therapy arm of ATMOSPHERE were slightly lower (16% and 10% respectively) with adjustment for the conventional covariates but was markedly lower (43% and 25% respectively) further adjusting for NT-proBNP (Figure 3-9). Imputation of missing values made little change in these findings (Figure 3-8 and Figure 3-9).

Figure 3-6 Hazard ratio for sudden death across the trial arms in HF-REF with incremental use of evidence-based medications

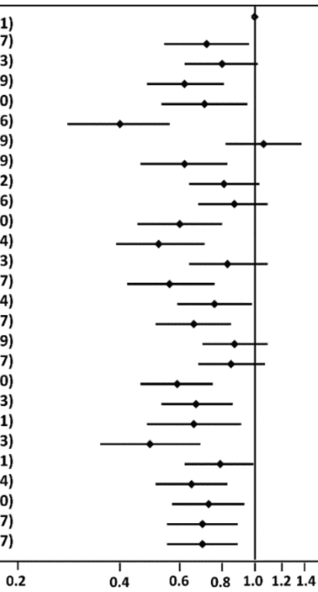
Trial arm	Medication	Annual rate	HR (95% CI)	p value
RALES(C)	ACEI(94%)+BB(10%)	7.6 (6.3–9.1)	reference	–
RALES(T)	ACEI(95%)+BB(11%)+MRA(100%)	5.4 (4.3–6.7)	0.71 (0.54, 0.95)	0.020
BEST(C)	ACEI/ARB(97%)+MRA(4%)	6.3 (5.4–7.3)	0.84 (0.66, 1.07)	0.150
BEST(T)	ACEI/ARB(96%)+BB(100%)+MRA(3%)	4.9 (4.2–5.9)	0.66 (0.51, 0.85)	0.001
CIBIS–II(C)	ACEI(96%)+MRA(10%)	4.8 (3.9–6.0)	0.62 (0.47, 0.83)	0.001
CIBIS–II(T)	ACEI(96%)+BB(100%)+MRA(11%)	2.7 (2.0–3.6)	0.35 (0.25, 0.49)	<0.001
MERIT–HF(C)	ACEI/ARB(96%)+MRA(8%)	6.7 (5.6–7.9)	0.83 (0.64, 1.07)	0.147
MERIT–HF(T)	ACEI/ARB(95%)+BB(100%)+MRA(7%)	3.9 (3.2–4.9)	0.49 (0.37, 0.65)	<0.001
Val–HeFT(C)	ACEI/ARB(93%)+BB(35%)+MRA(5%)	4.6 (4.0–5.2)	0.60 (0.48, 0.76)	<0.001
Val–HeFT(T)	ACEI/ARB(100%)+BB(35%)+MRA(5%)	4.9 (4.3–5.6)	0.65 (0.52, 0.81)	<0.001
SCD–HeFT(P)	ACEI/ARB(98%)+BB(69%)+MRA(19%)	3.2 (2.6–4.0)	0.46 (0.35, 0.61)	<0.001
SCD–HeFT(A)	ACEI/ARB(97%)+BB(69%)+MRA(20%)	2.7 (2.2–3.4)	0.39 (0.29, 0.52)	<0.001
CHARM–Alternative(C)	BB(54%)+MRA(23%)	4.4 (3.6–5.3)	0.60 (0.46, 0.78)	<0.001
CHARM–Alternative(T)	ARB(100%)+BB(54%)+MRA(24%)	3.0 (2.4–3.7)	0.40 (0.30, 0.54)	<0.001
CHARM–Added(C)	ACEI(100%)+BB(55%)+MRA(16%)	4.6 (4.0–5.4)	0.64 (0.50, 0.81)	<0.001
CHARM–Added(T)	ACEI/ARB(100%)+BB(54%)+MRA(17%)	4.0 (3.4–4.7)	0.55 (0.43, 0.71)	<0.001
CORONA(C)	ACEI/ARB(92%)+BB(75%)+MRA(39%)	5.3 (4.7–5.9)	0.71 (0.57, 0.89)	0.002
CORONA(T)	ACEI/ARB(91%)+BB(75%)+MRA(39%)	5.1 (4.6–5.7)	0.69 (0.56, 0.86)	0.001
GISSI–HF(C)	ACEI/ARB(93%)+BB(63%)+MRA(41%)	2.5 (2.2–3.0)	0.36 (0.29, 0.46)	<0.001
GISSI–HF(T)	ACEI/ARB(94%)+BB(64%)+MRA(39%)	2.9 (2.5–3.3)	0.41 (0.33, 0.52)	<0.001
EMPHASIS–HF(C)	ACEI/ARB(93%)+BB(86%)	3.3 (2.6–4.1)	0.43 (0.32, 0.59)	<0.001
EMPHASIS–HF(T)	ACEI/ARB(94%)+BB(85%)+MRA(100%)	2.5 (2.0–3.3)	0.34 (0.25, 0.47)	<0.001
PARADIGM–HF(C)	ACEI/ARB(100%)+BB(92%)+MRA(57%)	3.7 (3.3–4.1)	0.49 (0.40, 0.61)	<0.001
PARADIGM–HF(T)	ACEI/ARB(100%)+BB(93%)+MRA(54%)+LCZ696	3.0 (2.7–3.4)	0.41 (0.32, 0.51)	<0.001
ATMOSPHERE (Enarapril)	ACEI/ARB(100%)+BB(91%)+MRA(36%)	3.5 (3.0–4.0)	0.49 (0.39, 0.62)	<0.001
ATMOSPHERE (Aliskiren)	ACEI/ARB(2%)+BB(90%)+MRA(35%)+Aliskiren	3.2 (2.8–3.7)	0.46 (0.36, 0.58)	<0.001
ATMOSPHERE (Combination)	ACEI/ARB(100%)+BB(91%)+MRA(35%)+Aliskiren	3.3 (2.8–3.7)	0.46 (0.37, 0.59)	<0.001



Annual rates are shown as sudden death per 100 patient-years. Hazard ratios shown are compared to the placebo arm of RALES (N=46,151). C denotes control arm; T, experimental treatment arm; P, placebo arm; A, amiodarone arm.

Figure 3-7 Hazard ratio for sudden death across the trial arms in HF-REF with incremental use of evidence-based medications, with adjustment for 8 conventional covariates

Trial arm	Medication	Annual rate	HR (95% CI)	p value
RALES(C)	ACEI(94%)+BB(10%)	7.6 (6.3–9.1)	reference	–
RALES(T)	ACEI(95%)+BB(11%)+MRA(100%)	5.4 (4.3–6.7)	0.72 (0.54, 0.96)	0.023
BEST(C)	ACEI/ARB(97%)+MRA(4%)	6.3 (5.4–7.3)	0.80 (0.62, 1.02)	0.072
BEST(T)	ACEI/ARB(96%)+BB(100%)+MRA(3%)	4.9 (4.2–5.9)	0.62 (0.48, 0.81)	<0.001
CIBIS–II(C)	ACEI(96%)+MRA(10%)	4.8 (3.9–6.0)	0.71 (0.53, 0.95)	0.020
CIBIS–II(T)	ACEI(96%)+BB(100%)+MRA(11%)	2.7 (2.0–3.6)	0.40 (0.28, 0.56)	<0.001
MERIT–HF(C)	ACEI/ARB(96%)+MRA(8%)	6.7 (5.6–7.9)	1.06 (0.82, 1.37)	0.676
MERIT–HF(T)	ACEI/ARB(95%)+BB(100%)+MRA(7%)	3.9 (3.2–4.9)	0.62 (0.46, 0.83)	0.001
Val–HeFT(C)	ACEI/ARB(93%)+BB(35%)+MRA(5%)	4.6 (4.0–5.2)	0.81 (0.64, 1.03)	0.088
Val–HeFT(T)	ACEI/ARB(100%)+BB(35%)+MRA(5%)	4.9 (4.3–5.6)	0.87 (0.68, 1.09)	0.227
SCD–HeFT(P)	ACEI/ARB(98%)+BB(69%)+MRA(19%)	3.2 (2.6–4.0)	0.60 (0.45, 0.80)	<0.001
SCD–HeFT(A)	ACEI/ARB(97%)+BB(69%)+MRA(20%)	2.7 (2.2–3.4)	0.52 (0.39, 0.71)	<0.001
CHARM–Alternative(C)	BB(54%)+MRA(23%)	4.4 (3.6–5.3)	0.83 (0.64, 1.09)	0.187
CHARM–Alternative(T)	ARB(100%)+BB(54%)+MRA(24%)	3.0 (2.4–3.7)	0.56 (0.42, 0.76)	<0.001
CHARM–Added(C)	ACEI(100%)+BB(55%)+MRA(16%)	4.6 (4.0–5.4)	0.76 (0.59, 0.98)	0.031
CHARM–Added(T)	ACEI/ARB(100%)+BB(54%)+MRA(17%)	4.0 (3.4–4.7)	0.66 (0.51, 0.85)	0.001
CORONA(C)	ACEI/ARB(92%)+BB(75%)+MRA(39%)	5.3 (4.7–5.9)	0.87 (0.70, 1.09)	0.239
CORONA(T)	ACEI/ARB(91%)+BB(75%)+MRA(39%)	5.1 (4.6–5.7)	0.85 (0.68, 1.07)	0.157
GISSI–HF(C)	ACEI/ARB(93%)+BB(63%)+MRA(41%)	2.5 (2.2–3.0)	0.59 (0.46, 0.75)	<0.001
GISSI–HF(T)	ACEI/ARB(94%)+BB(64%)+MRA(39%)	2.9 (2.5–3.3)	0.67 (0.53, 0.86)	0.001
EMPHASIS–HF(C)	ACEI/ARB(93%)+BB(86%)	3.3 (2.6–4.1)	0.66 (0.48, 0.91)	0.011
EMPHASIS–HF(T)	ACEI/ARB(94%)+BB(85%)+MRA(100%)	2.5 (2.0–3.3)	0.49 (0.35, 0.69)	<0.001
PARADIGM–HF(C)	ACEI/ARB(100%)+BB(92%)+MRA(57%)	3.7 (3.3–4.1)	0.79 (0.62, 0.99)	0.043
PARADIGM–HF(T)	ACEI/ARB(100%)+BB(93%)+MRA(54%)+LCZ696	3.0 (2.7–3.4)	0.65 (0.51, 0.83)	<0.001
ATMOSPHERE (Enarapril)	ACEI/ARB(100%)+BB(91%)+MRA(36%)	3.5 (3.0–4.0)	0.73 (0.57, 0.93)	0.009
ATMOSPHERE (Aliskiren)	ACEI/ARB(2%)+BB(90%)+MRA(35%)+Aliskiren	3.2 (2.8–3.7)	0.70 (0.55, 0.89)	0.003
ATMOSPHERE (Combination)	ACEI/ARB(100%)+BB(91%)+MRA(35%)+Aliskiren	3.3 (2.8–3.7)	0.70 (0.55, 0.89)	0.004

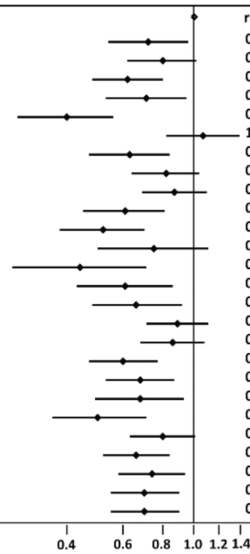


Annual rates are shown as sudden death per 100 patient-years. Hazard ratios are adjusted for conventional covariates including age, sex, NYHA class, LVEF, ischaemic aetiology, previous myocardial infarction, and a history of hypertension and diabetes (N= 46,019). Hazard ratios shown are compared to the placebo arm of RALES. C denotes control arm; T, experimental treatment arm; P, placebo arm; A, amiodarone arm.

Figure 3-8 Hazard ratio for sudden death across the trial arms in HF-REF with incremental use of evidence-based medications, with adjustment for 8 conventional covariates and eGFR

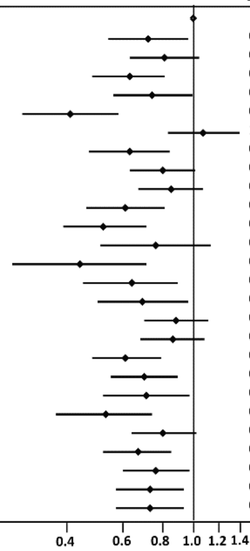
A

Trial arm	Medication	Annual rate	HR (95% CI)	p value
RALES(C)	ACEI(94%)+BB(10%)	7.6 (6.3–9.1)	reference	–
RALES(T)	ACEI(95%)+BB(11%)+MRA(100%)	5.4 (4.3–6.7)	0.72 (0.54, 0.96)	0.024
BEST(C)	ACEI/ARB(97%)+MRA(4%)	6.3 (5.4–7.3)	0.80 (0.62, 1.02)	0.074
BEST(T)	ACEI/ARB(96%)+BB(100%)+MRA(3%)	4.9 (4.2–5.9)	0.62 (0.48, 0.80)	<0.001
CIBIS–II(C)	ACEI(96%)+MRA(10%)	4.8 (3.9–6.0)	0.71 (0.53, 0.95)	0.020
CIBIS–II(T)	ACEI(96%)+BB(100%)+MRA(11%)	2.7 (2.0–3.6)	0.40 (0.28, 0.56)	<0.001
MERIT–HF(C)	ACEI/ARB(96%)+MRA(8%)	6.7 (5.6–7.9)	1.07 (0.82, 1.39)	0.615
MERIT–HF(T)	ACEI/ARB(95%)+BB(100%)+MRA(7%)	3.9 (3.2–4.9)	0.63 (0.47, 0.84)	0.002
Val–HeFT(C)	ACEI/ARB(93%)+BB(35%)+MRA(5%)	4.6 (4.0–5.2)	0.82 (0.64, 1.04)	0.095
Val–HeFT(T)	ACEI/ARB(100%)+BB(35%)+MRA(5%)	4.9 (4.3–5.6)	0.87 (0.69, 1.10)	0.259
SCD–HeFT(P)	ACEI/ARB(98%)+BB(69%)+MRA(19%)	3.2 (2.6–4.0)	0.61 (0.45, 0.81)	0.001
SCD–HeFT(A)	ACEI/ARB(97%)+BB(69%)+MRA(20%)	2.7 (2.2–3.4)	0.52 (0.38, 0.70)	<0.001
CHARM–Alternative(C)	BB(54%)+MRA(23%)	4.4 (3.6–5.3)	0.75 (0.50, 1.11)	0.144
CHARM–Alternative(T)	ARB(100%)+BB(54%)+MRA(24%)	3.0 (2.4–3.7)	0.44 (0.27, 0.71)	0.001
CHARM–Added(C)	ACEI(100%)+BB(55%)+MRA(16%)	4.6 (4.0–5.4)	0.61 (0.43, 0.86)	0.005
CHARM–Added(T)	ACEI/ARB(100%)+BB(54%)+MRA(17%)	4.0 (3.4–4.7)	0.66 (0.48, 0.92)	0.015
CORONA(C)	ACEI/ARB(92%)+BB(75%)+MRA(39%)	5.3 (4.7–5.9)	0.89 (0.71, 1.11)	0.298
CORONA(T)	ACEI/ARB(91%)+BB(75%)+MRA(39%)	5.1 (4.6–5.7)	0.86 (0.68, 1.08)	0.193
GISSI–HF(C)	ACEI/ARB(93%)+BB(63%)+MRA(41%)	2.5 (2.2–3.0)	0.60 (0.47, 0.77)	<0.001
GISSI–HF(T)	ACEI/ARB(94%)+BB(64%)+MRA(39%)	2.9 (2.5–3.3)	0.68 (0.53, 0.87)	0.002
EMPHASIS–HF(C)	ACEI/ARB(93%)+BB(86%)	3.3 (2.6–4.1)	0.68 (0.49, 0.93)	0.016
EMPHASIS–HF(T)	ACEI/ARB(94%)+BB(85%)+MRA(100%)	2.5 (2.0–3.3)	0.50 (0.36, 0.71)	<0.001
PARADIGM–HF(C)	ACEI/ARB(100%)+BB(92%)+MRA(57%)	3.7 (3.3–4.1)	0.80 (0.63, 1.01)	0.055
PARADIGM–HF(T)	ACEI/ARB(100%)+BB(93%)+MRA(54%)+LCZ696	3.0 (2.7–3.4)	0.66 (0.52, 0.84)	0.001
ATMOSPHERE (Enarapril)	ACEI/ARB(100%)+BB(91%)+MRA(36%)	3.5 (3.0–4.0)	0.74 (0.58, 0.94)	0.012
ATMOSPHERE (Aliskiren)	ACEI/ARB(2%)+BB(90%)+MRA(35%)+Aliskiren	3.2 (2.8–3.7)	0.70 (0.55, 0.90)	0.005
ATMOSPHERE (Combination)	ACEI/ARB(100%)+BB(91%)+MRA(35%)+Aliskiren	3.3 (2.8–3.7)	0.70 (0.55, 0.90)	0.005



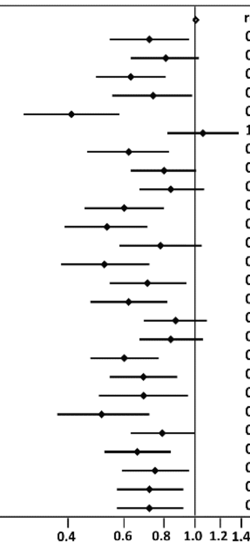
B

Trial arm	Medication	Annual rate	HR (95% CI)	p value
RALES(C)	ACEI(94%)+BB(10%)	7.6 (6.3–9.1)	reference	–
RALES(T)	ACEI(95%)+BB(11%)+MRA(100%)	5.4 (4.3–6.7)	0.72 (0.54, 0.96)	0.026
BEST(C)	ACEI/ARB(97%)+MRA(4%)	6.3 (5.4–7.3)	0.81 (0.63, 1.04)	0.093
BEST(T)	ACEI/ARB(96%)+BB(100%)+MRA(3%)	4.9 (4.2–5.9)	0.63 (0.48, 0.81)	<0.001
CIBIS–II(C)	ACEI(96%)+MRA(10%)	4.8 (3.9–6.0)	0.74 (0.56, 0.99)	0.041
CIBIS–II(T)	ACEI(96%)+BB(100%)+MRA(11%)	2.7 (2.0–3.6)	0.41 (0.29, 0.58)	<0.001
MERIT–HF(C)	ACEI/ARB(96%)+MRA(8%)	6.7 (5.6–7.9)	1.07 (0.83, 1.39)	0.607
MERIT–HF(T)	ACEI/ARB(95%)+BB(100%)+MRA(7%)	3.9 (3.2–4.9)	0.63 (0.47, 0.84)	0.002
Val–HeFT(C)	ACEI/ARB(93%)+BB(35%)+MRA(5%)	4.6 (4.0–5.2)	0.80 (0.63, 1.01)	0.061
Val–HeFT(T)	ACEI/ARB(100%)+BB(35%)+MRA(5%)	4.9 (4.3–5.6)	0.85 (0.67, 1.07)	0.173
SCD–HeFT(P)	ACEI/ARB(98%)+BB(69%)+MRA(19%)	3.2 (2.6–4.0)	0.61 (0.46, 0.81)	0.001
SCD–HeFT(A)	ACEI/ARB(97%)+BB(69%)+MRA(20%)	2.7 (2.2–3.4)	0.52 (0.39, 0.71)	<0.001
CHARM–Alternative(C)	BB(54%)+MRA(23%)	4.4 (3.6–5.3)	0.76 (0.51, 1.13)	0.178
CHARM–Alternative(T)	ARB(100%)+BB(54%)+MRA(24%)	3.0 (2.4–3.7)	0.44 (0.27, 0.71)	0.001
CHARM–Added(C)	ACEI(100%)+BB(55%)+MRA(16%)	4.6 (4.0–5.4)	0.64 (0.45, 0.89)	0.009
CHARM–Added(T)	ACEI/ARB(100%)+BB(54%)+MRA(17%)	4.0 (3.4–4.7)	0.69 (0.50, 0.96)	0.028
CORONA(C)	ACEI/ARB(92%)+BB(75%)+MRA(39%)	5.3 (4.7–5.9)	0.88 (0.70, 1.11)	0.274
CORONA(T)	ACEI/ARB(91%)+BB(75%)+MRA(39%)	5.1 (4.6–5.7)	0.86 (0.68, 1.08)	0.181
GISSI–HF(C)	ACEI/ARB(93%)+BB(63%)+MRA(41%)	2.5 (2.2–3.0)	0.61 (0.48, 0.79)	<0.001
GISSI–HF(T)	ACEI/ARB(94%)+BB(64%)+MRA(39%)	2.9 (2.5–3.3)	0.70 (0.55, 0.89)	0.004
EMPHASIS–HF(C)	ACEI/ARB(93%)+BB(86%)	3.3 (2.6–4.1)	0.71 (0.52, 0.97)	0.032
EMPHASIS–HF(T)	ACEI/ARB(94%)+BB(85%)+MRA(100%)	2.5 (2.0–3.3)	0.53 (0.37, 0.74)	<0.001
PARADIGM–HF(C)	ACEI/ARB(100%)+BB(92%)+MRA(57%)	3.7 (3.3–4.1)	0.80 (0.64, 1.02)	0.067
PARADIGM–HF(T)	ACEI/ARB(100%)+BB(93%)+MRA(54%)+LCZ696	3.0 (2.7–3.4)	0.67 (0.52, 0.85)	0.001
ATMOSPHERE (Enarapril)	ACEI/ARB(100%)+BB(91%)+MRA(36%)	3.5 (3.0–4.0)	0.76 (0.60, 0.97)	0.027
ATMOSPHERE (Aliskiren)	ACEI/ARB(2%)+BB(90%)+MRA(35%)+Aliskiren	3.2 (2.8–3.7)	0.73 (0.57, 0.93)	0.012
ATMOSPHERE (Combination)	ACEI/ARB(100%)+BB(91%)+MRA(35%)+Aliskiren	3.3 (2.8–3.7)	0.73 (0.57, 0.93)	0.011



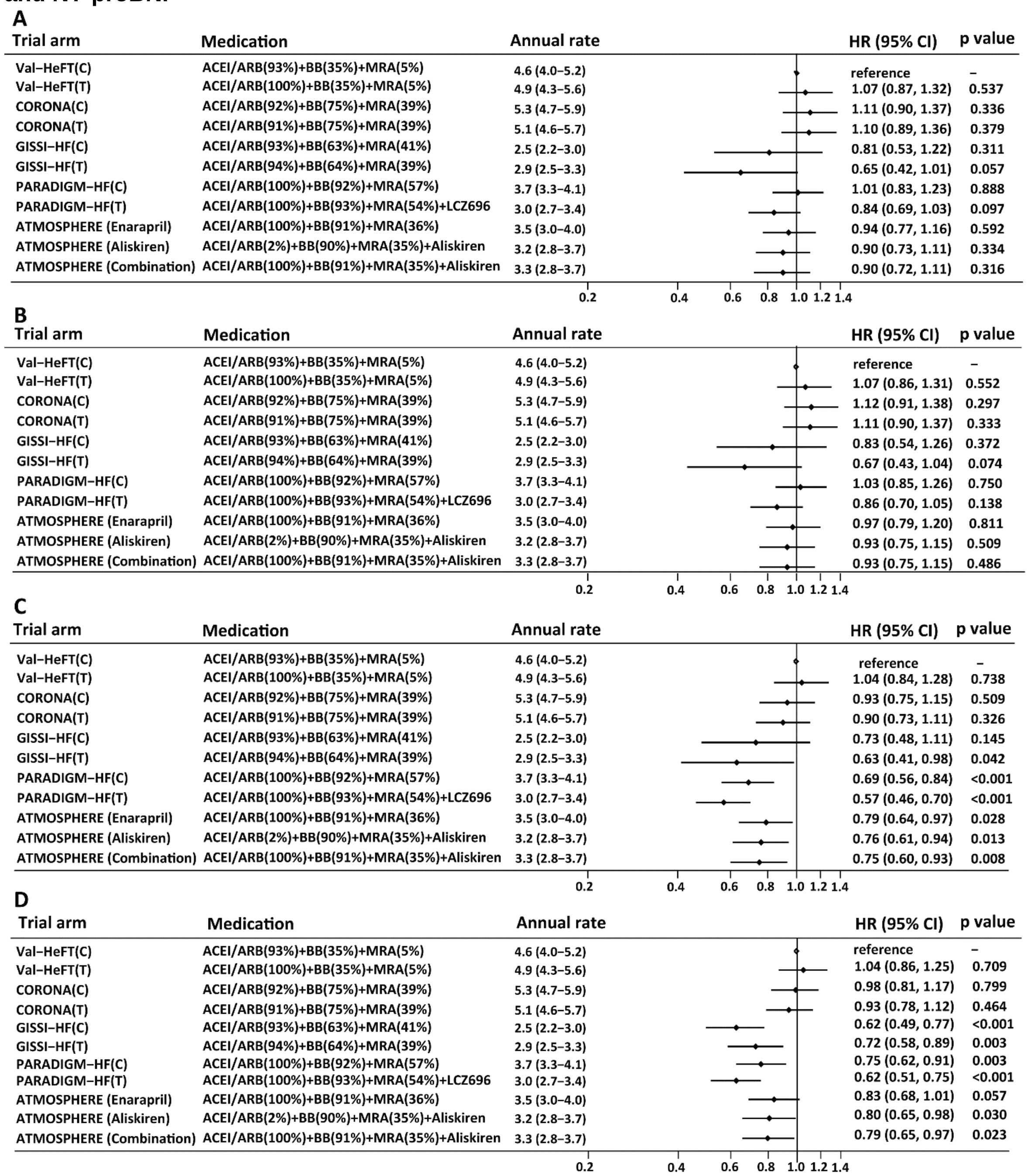
C

Trial arm	Medication	Annual rate	HR (95% CI)	p value
RALES(C)	ACEI(94%)+BB(10%)	7.6 (6.3–9.1)	reference	–
RALES(T)	ACEI(95%)+BB(11%)+MRA(100%)	5.4 (4.3–6.7)	0.72 (0.54, 0.96)	0.025
BEST(C)	ACEI/ARB(97%)+MRA(4%)	6.3 (5.4–7.3)	0.81 (0.63, 1.03)	0.085
BEST(T)	ACEI/ARB(96%)+BB(100%)+MRA(3%)	4.9 (4.2–5.9)	0.63 (0.49, 0.81)	<0.001
CIBIS–II(C)	ACEI(96%)+MRA(10%)	4.8 (3.9–6.0)	0.74 (0.55, 0.98)	0.038
CIBIS–II(T)	ACEI(96%)+BB(100%)+MRA(11%)	2.7 (2.0–3.6)	0.41 (0.29, 0.58)	<0.001
MERIT–HF(C)	ACEI/ARB(96%)+MRA(8%)	6.7 (5.6–7.9)	1.06 (0.82, 1.37)	0.670
MERIT–HF(T)	ACEI/ARB(95%)+BB(100%)+MRA(7%)	3.9 (3.2–4.9)	0.62 (0.46, 0.83)	0.001
Val–HeFT(C)	ACEI/ARB(93%)+BB(35%)+MRA(5%)	4.6 (4.0–5.2)	0.80 (0.63, 1.01)	0.059
Val–HeFT(T)	ACEI/ARB(100%)+BB(35%)+MRA(5%)	4.9 (4.3–5.6)	0.84 (0.67, 1.07)	0.154
SCD–HeFT(P)	ACEI/ARB(98%)+BB(69%)+MRA(19%)	3.2 (2.6–4.0)	0.60 (0.45, 0.80)	0.001
SCD–HeFT(A)	ACEI/ARB(97%)+BB(69%)+MRA(20%)	2.7 (2.2–3.4)	0.53 (0.39, 0.71)	<0.001
CHARM–Alternative(C)	BB(54%)+MRA(23%)	4.4 (3.6–5.3)	0.78 (0.58, 1.05)	0.099
CHARM–Alternative(T)	ARB(100%)+BB(54%)+MRA(24%)	3.0 (2.4–3.7)	0.52 (0.38, 0.72)	<0.001
CHARM–Added(C)	ACEI(100%)+BB(55%)+MRA(16%)	4.6 (4.0–5.4)	0.71 (0.54, 0.94)	0.016
CHARM–Added(T)	ACEI/ARB(100%)+BB(54%)+MRA(17%)	4.0 (3.4–4.7)	0.62 (0.47, 0.82)	0.001
CORONA(C)	ACEI/ARB(92%)+BB(75%)+MRA(39%)	5.3 (4.7–5.9)	0.87 (0.69, 1.09)	0.213
CORONA(T)	ACEI/ARB(91%)+BB(75%)+MRA(39%)	5.1 (4.6–5.7)	0.84 (0.67, 1.06)	0.142
GISSI–HF(C)	ACEI/ARB(93%)+BB(63%)+MRA(41%)	2.5 (2.2–3.0)	0.60 (0.47, 0.77)	<0.001
GISSI–HF(T)	ACEI/ARB(94%)+BB(64%)+MRA(39%)	2.9 (2.5–3.3)	0.69 (0.54, 0.88)	0.003
EMPHASIS–HF(C)	ACEI/ARB(93%)+BB(86%)	3.3 (2.6–4.1)	0.69 (0.50, 0.95)	0.021
EMPHASIS–HF(T)	ACEI/ARB(94%)+BB(85%)+MRA(100%)	2.5 (2.0–3.3)	0.51 (0.37, 0.72)	<0.001
PARADIGM–HF(C)	ACEI/ARB(100%)+BB(92%)+MRA(57%)	3.7 (3.3–4.1)	0.79 (0.63, 1.00)	0.052
PARADIGM–HF(T)	ACEI/ARB(100%)+BB(93%)+MRA(54%)+LCZ696	3.0 (2.7–3.4)	0.66 (0.52, 0.84)	0.001
ATMOSPHERE (Enarapril)	ACEI/ARB(100%)+BB(91%)+MRA(36%)	3.5 (3.0–4.0)	0.75 (0.59, 0.96)	0.021
ATMOSPHERE (Aliskiren)	ACEI/ARB(2%)+BB(90%)+MRA(35%)+Aliskiren	3.2 (2.8–3.7)	0.72 (0.57, 0.92)	0.009
ATMOSPHERE (Combination)	ACEI/ARB(100%)+BB(91%)+MRA(35%)+Aliskiren	3.3 (2.8–3.7)	0.72 (0.57, 0.92)	0.008



Annual rates are shown as sudden death per 100 patient-years. Panel A, HRs are adjusted for conventional confounding variables in the subset of patients with eGFR measurements available (N=42,920); Panel B, adjustment for conventional covariates and eGFR in the subset of patients with eGFR measurement available (N=42,920); Panel C, adjustment for conventional covariates and eGFR with simple imputation of eGFR levels (N=46,019). HRs shown are compared to the placebo arm of RALES. C denotes control arm; T, experimental treatment arm; P, placebo arm; A, amiodarone arm.

Figure 3-9 Hazard ratio for sudden death across the trial arms in HF-REF with incremental use of evidence-based medications, with adjustment for 8 conventional covariates, eGFR and NT-proBNP



Annual rates are shown as sudden death per 100 patient-years. Panel A, adjustment for conventional confounding variables in the subset of patients with NT-proBNP available [N=20,715]; Panel B, adjustment for conventional covariates and eGFR in the subset of patients with NT-proBNP available [N=20,715]; Panel C, adjustment for conventional covariates, eGFR and log transformed NT-proBNP in the subset of patients with NT-proBNP available [N=20,715]; Panel D, adjustment for conventional covariates, eGFR and log transformed NT-proBNP with simple imputation of eGFR and NT-proBNP in the trials with NT-proBNP collected (i.e. not complete missing) [N=26,809]. HRs shown are compared to the placebo arm of Val-HeFT. C denotes control arm; T, experimental treatment arm.

3.2.5 Pump failure death rates in each trial and in each arm of each trial

Similar to the trend in the sudden death rates across trials, the rate of pump failure death was substantially lower in the more recent trials compared to the earlier trials (Table 3-5 and Figure 3-10). The annual rate of pump failure death was quite high at 10.6% in the oldest trial (RALES) and was 6.4% in BEST, but later seemed to be starting to plateau, with a rate of 1.7% in the latest trials (PARADIGM-HF and ATMOSPHERE) (Table 3-5 and Figure 3-11). Overall, there was a downward trend in the rate of pump failure death across these trials with a slope of 3.47% per decade, p for trend =0.027 (Figure 3-11). It seemed the downward trend was driven by the high rates in the earliest trials of RALES and BEST, which randomised patients with severe HF; in a sensitivity analysis with the exclusion of both trials, the falling trend was attenuated but remained significant, with a slope of 0.92% per decade, p for trend =0.004 (Figure 3-12). There was a smaller proportion of pump failure death relative to total mortality in more recent trials (Figure 3-5).

Table 3-5 Annual rates and cumulative incidences of pump failure death at different time points in the included trials in HF-REF (treatment arms combined)

	RALES (N=1663)	BEST (N=2617)	CIBIS-II (N=2647)	MERIT-HF (N=3991)	Val-HeFT (N=5010)
No. of pump failure death	316	336	83	88	321
Annual rate (95% CI)	10.6 (9.5-11.8)	6.4 (5.7-7.1)	2.4 (1.9-2.9)	2.2 (1.8-2.7)	3.4 (3.1-3.8)
Cumulative incidence (95% CI)					
30 days	1.0 (0.5-1.4)	0.2 (0.0-0.4)	0.1 (0.0-0.2)	0.1 (0.0-0.2)	0.1 (0.0-0.2)
60 days	2.7 (1.9-3.5)	0.6 (0.3-0.9)	0.4 (0.1-0.6)	0.3 (0.1-0.4)	0.3 (0.1-0.4)
90 days	3.5 (2.6-4.4)	1.0 (0.6-1.4)	0.7 (0.4-1.0)	0.4 (0.2-0.6)	0.5 (0.3-0.7)
180 days	5.6 (4.5-6.7)	2.4 (1.9-3.0)	1.1 (0.7-1.4)	1.0 (0.7-1.3)	1.1 (0.8-1.4)
1 year	10.5 (9.0-12.0)	5.2 (4.4-6.1)	2.2 (1.6-2.7)	2.1 (1.7-2.6)	2.6 (2.2-3.0)
2 years	17.8 (15.9-19.6)	10.9 (9.7-12.2)	4.4 (3.3-5.5)	-	6.0 (5.3-6.7)
3 years	21.7 (19.3-24.0)	15.2 (13.6-16.8)	-	-	9.9 (8.1-11.7)

	SCD-HeFT (N=1692)	CHARM-Alternative (N=1960)	CHARM-added (N=2448)	CORONA (N=4875)
No. of pump failure death	125	151	200	372
Annual rate (95% CI)	2.2 (1.9-2.6)	3.0 (2.5-3.5)	2.8 (2.4-3.2)	3.1 (2.8-3.4)
Cumulative incidence (95% CI)				
30 days	0.0	0.5 (0.2-0.8)	0.1 (0.0-0.2)	0.1 (0.0-0.2)
60 days	0.3 (0.0-0.6)	0.6 (0.3-1.0)	0.3 (0.1-0.5)	0.4 (0.2-0.5)
90 days	0.3 (0.0-0.6)	0.8 (0.4-1.2)	0.6 (0.3-0.9)	0.6 (0.4-0.9)
180 days	0.7 (0.3-1.0)	1.7 (1.2-2.3)	1.1 (0.7-1.5)	1.5 (1.2-1.9)
1 year	1.4 (0.8-1.9)	3.0 (2.3-3.8)	2.5 (1.8-3.1)	2.5 (2.1-3.0)
2 years	3.3 (2.5-4.2)	5.8 (4.7-6.8)	4.7 (3.9-5.6)	5.2 (4.6-5.8)
3 years	5.4 (4.3-6.5)	7.2 (6.0-8.4)	7.3 (6.2-8.3)	7.7 (6.9-8.5)

	GISSI-HF (N=3820)	EMPHASIS-HF (N=2316)	PARADIGM-HF (N=7156)	ATMOSPHERE (N=5968)
No. of pump failure death	321	94	261	305
Annual rate (95% CI)	2.4 (2.1-2.7)	2.2 (1.8-2.7)	1.7 (1.5-1.9)	1.7 (1.5-1.9)
Cumulative incidence (95% CI)				
30 days	0.2 (0.0-0.3)	0.2 (0.0-0.3)	0.1 (0.0-0.1)	0.1 (0.0-0.1)
60 days	0.2 (0.1-0.4)	0.3 (0.1-0.5)	0.1 (0.1-0.2)	0.1 (0.0-0.2)
90 days	0.4 (0.2-0.7)	0.5 (0.2-0.8)	0.2 (0.1-0.3)	0.2 (0.1-0.3)
180 days	1.0 (0.7-1.3)	1.1 (0.7-1.6)	0.5 (0.3-0.7)	0.5 (0.4-0.7)
1 year	2.1 (1.6-2.6)	1.9 (1.3-2.5)	1.5 (1.2-1.8)	1.3 (1.0-1.6)
2 years	4.4 (3.8-5.1)	3.5 (2.7-4.4)	3.0 (2.6-3.4)	2.7 (2.3-3.1)
3 years	6.2 (5.5-7.0)	5.5 (4.3-6.7)	4.5 (3.9-5.0)	4.3 (3.7-4.8)

Annual rates are shown as pump failure death per 100 patient-years. Cumulative incidences are presented as percent. '-' denotes data not available.

Figure 3-10 Cumulative incidence curves for pump failure death by trials in HF-REF

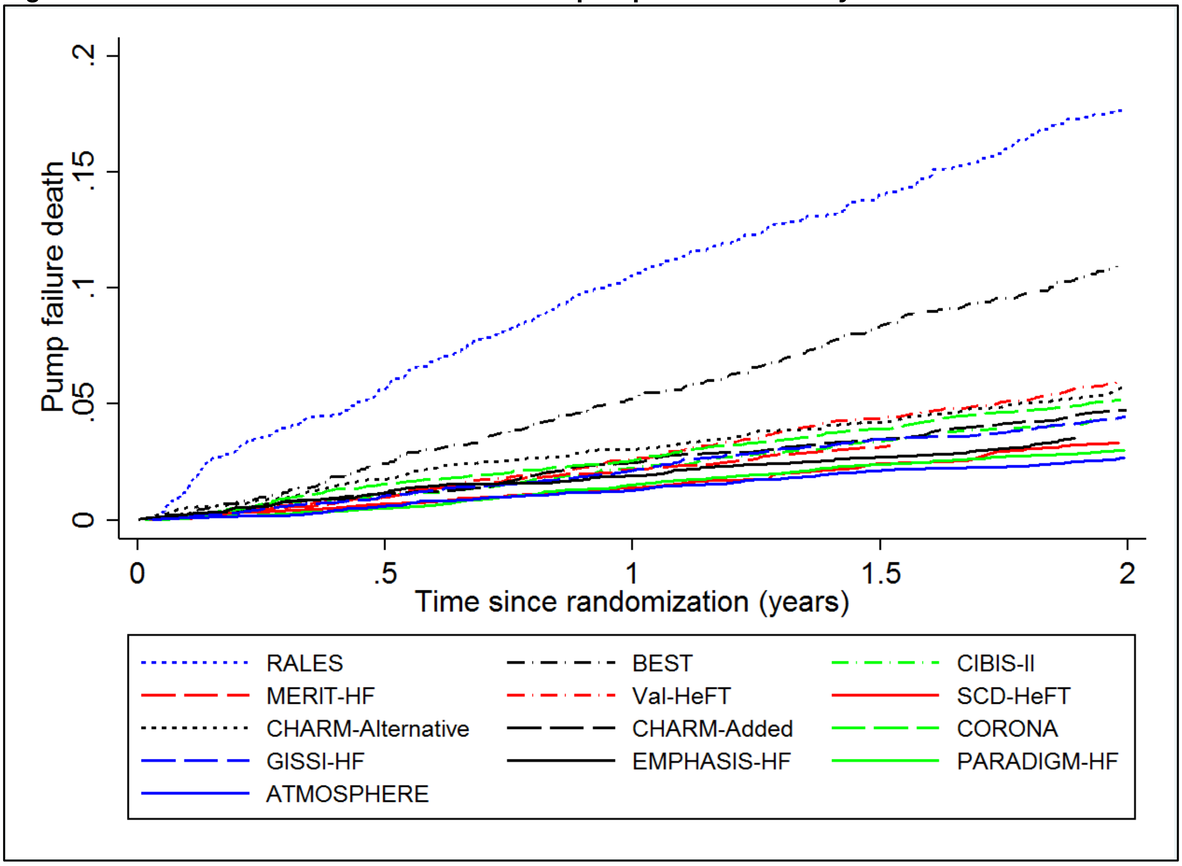
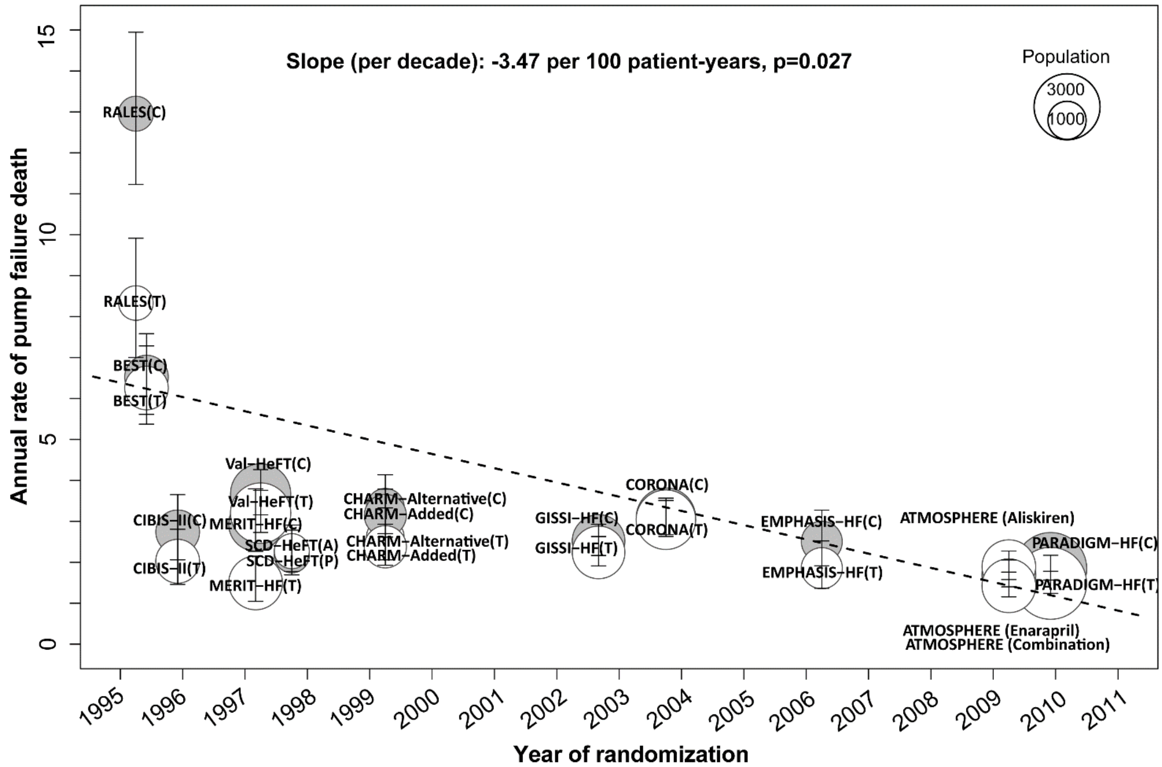
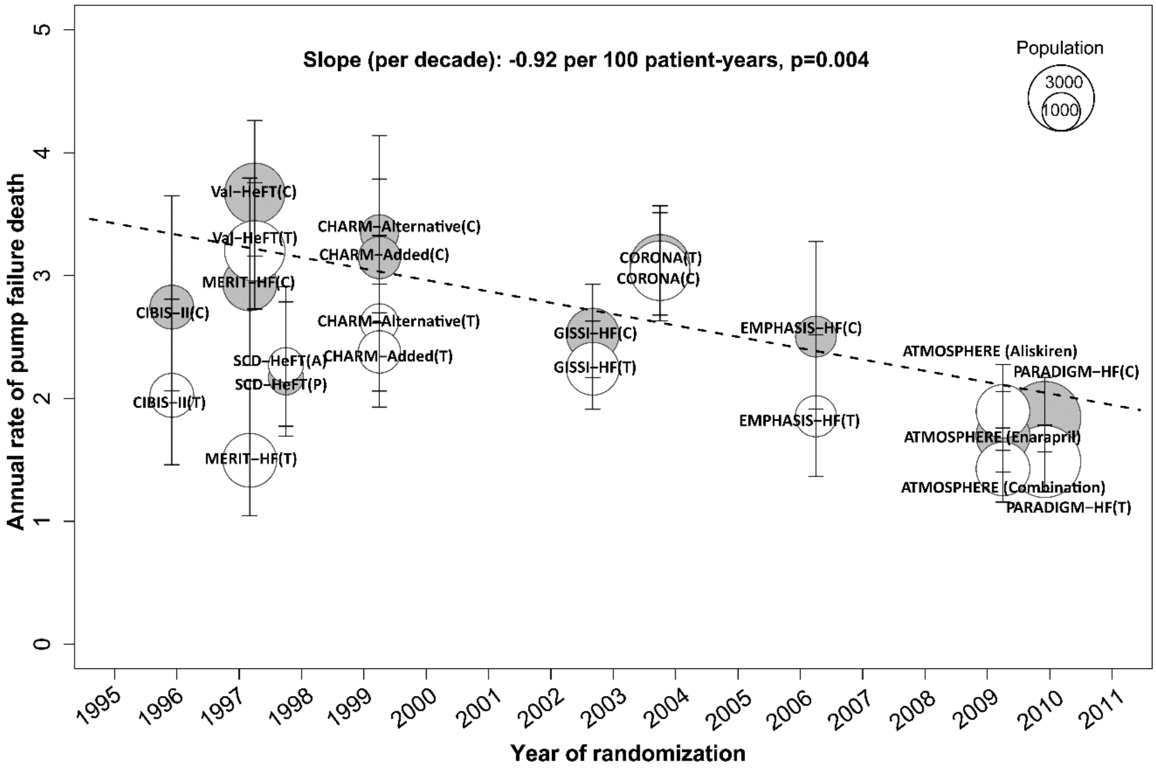


Figure 3-11 Trends in the pump failure death rate across trial arms over time in HF-REF



Annual rates are shown as pump failure death per 100 patient-years. The black dotted line is based on the multiple linear regression of the annual rate in each trial arm with the randomisation year and randomisation arm as covariates, weighted by its inverse-variance and with trial as a random effect. P for slope represents the p value for randomisation year based on the linear model. Each circle represents each trial arm as labelled, with the control arm in each trial illustrated in gray and the experimental arm in white. The centre of each circle corresponds to randomisation year (x axis) and the annual rate (y axis) in each arm, the error bars in each circle correspond to the 95% confidence interval of the annual rate. The area of each circle represents the sample size in each arm (reference size shown in the upper right corner). C denotes control arm; T, experimental treatment arm; P, placebo arm; A, amiodarone arm.

Figure 3-12 Trends in the pump failure death rate across trial arms over time in HF-REF, with the exclusion of RALES and BEST

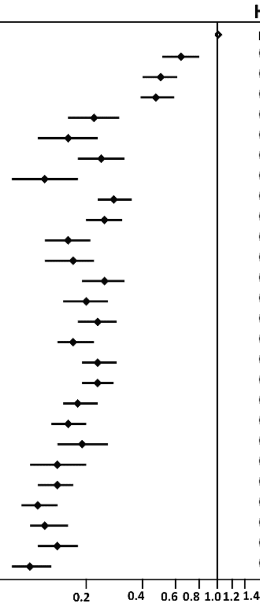


Annual rates are shown as pump failure death per 100 patient-years. Other notes and abbreviations are same as those in Figure 3-11.

The rate of pump failure death was lower in the experimental treatment group in all trials, with the exceptions of SCD-HeFT and ATMOSPHERE (Figure 3-11). There was a substantial decline in the risk of pump failure death of 80% over the past two decades (HR 0.20, 95% CI 0.09-0.47, p<0.001), adjusting for randomisation treatment with trial as a random effect. In a sensitivity analysis with the exclusion of RALES and BEST, the size of risk reduction of pump failure death over time was attenuated to 50% but remained significant (HR 0.50, 95% CI 0.33-0.78, p=0.002). With further adjustment for conventional covariates, the risk reduction over time was attenuated in both primary and sensitivity analyses, but randomisation treatment remained significantly related to a lower risk of pump failure death (HR 0.84, 95% CI 0.78-0.91, p<0.001). When examining the risk of pump failure death by individual trial arm, compared to the placebo arm of RALES, the risk of pump failure death was 89% and 90% lower in the treatment arm of PARADIGM-HF and in the combination therapy arm of ATMOSPHERE, respectively (Figure 3-13). These differences were slightly attenuated but remained pronounced after adjustment for conventional confounding covariates (adjusted HR 0.34, 95% CI 0.26-0.43, p<0.001; 0.27, 0.21-0.36, p<0.001, respectively [Figure 3-14]). Further adjustment for eGFR gave a similar result (Figure 3-15). In the cohort with both measurements available in eGFR and NT-proBNP, compared to the placebo arm of Val-HeFT, the risk of pump failure death in the treatment arm of PARADIGM-HF and in the combination therapy arm of ATMOSPHERE were substantially lower (43% and 50% respectively) with adjustment for the conventional covariates, and continued to fall (63% and 53% respectively) with further adjustment for NT-proBNP (Figure 3-16). Imputation of missing values gave similar results (Figure 3-15 and Figure 3-16).

Figure 3-13 Hazard ratio for pump failure death across the trial arms in HF-REF with incremental use of evidence-based medications

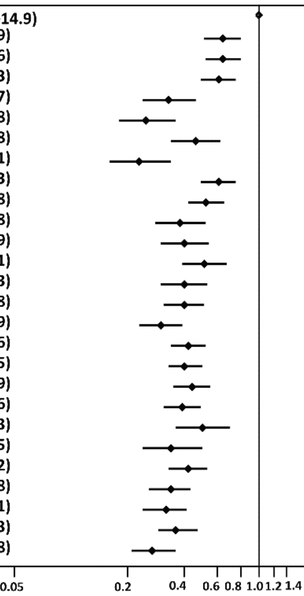
Trial arm	Medication	Annual rate	HR (95% CI)	p value
RALES(C)	ACEI(94%)+BB(10%)	13.0 (11.2–14.9)	reference	–
RALES(T)	ACEI(95%)+BB(11%)+MRA(100%)	8.3 (7.0–9.9)	0.64 (0.51, 0.80)	<0.001
BEST(C)	ACEI/ARB(97%)+MRA(4%)	6.5 (5.6–7.6)	0.50 (0.40, 0.61)	<0.001
BEST(T)	ACEI/ARB(96%)+BB(100%)+MRA(3%)	6.3 (5.4–7.3)	0.47 (0.39, 0.59)	<0.001
CIBIS–II(C)	ACEI(96%)+MRA(10%)	2.7 (2.1–3.7)	0.22 (0.16, 0.30)	<0.001
CIBIS–II(T)	ACEI(96%)+BB(100%)+MRA(11%)	2.0 (1.5–2.8)	0.16 (0.11, 0.23)	<0.001
MERIT–HF(C)	ACEI/ARB(96%)+MRA(8%)	2.9 (2.3–3.8)	0.24 (0.18, 0.32)	<0.001
MERIT–HF(T)	ACEI/ARB(95%)+BB(100%)+MRA(7%)	1.5 (1.0–2.1)	0.12 (0.08, 0.18)	<0.001
Val–HeFT(C)	ACEI/ARB(93%)+BB(35%)+MRA(5%)	3.7 (3.2–4.3)	0.28 (0.23, 0.35)	<0.001
Val–HeFT(T)	ACEI/ARB(100%)+BB(35%)+MRA(5%)	3.2 (2.7–3.8)	0.25 (0.20, 0.31)	<0.001
SCD–HeFT(P)	ACEI/ARB(98%)+BB(69%)+MRA(19%)	2.2 (1.7–2.8)	0.16 (0.12, 0.21)	<0.001
SCD–HeFT(A)	ACEI/ARB(97%)+BB(69%)+MRA(20%)	2.3 (1.8–2.9)	0.17 (0.12, 0.22)	<0.001
CHARM–Alternative(C)	BB(54%)+MRA(23%)	3.3 (2.7–4.1)	0.25 (0.19, 0.32)	<0.001
CHARM–Alternative(T)	ARB(100%)+BB(54%)+MRA(24%)	2.6 (2.1–3.3)	0.20 (0.15, 0.26)	<0.001
CHARM–Added(C)	ACEI(100%)+BB(55%)+MRA(16%)	3.1 (2.6–3.8)	0.23 (0.18, 0.29)	<0.001
CHARM–Added(T)	ACEI/ARB(100%)+BB(54%)+MRA(17%)	2.4 (1.9–2.9)	0.17 (0.14, 0.22)	<0.001
CORONA(C)	ACEI/ARB(92%)+BB(75%)+MRA(39%)	3.1 (2.7–3.6)	0.23 (0.19, 0.29)	<0.001
CORONA(T)	ACEI/ARB(91%)+BB(75%)+MRA(39%)	3.0 (2.6–3.5)	0.23 (0.19, 0.28)	<0.001
GISSI–HF(C)	ACEI/ARB(93%)+BB(63%)+MRA(41%)	2.5 (2.2–2.9)	0.18 (0.15, 0.23)	<0.001
GISSI–HF(T)	ACEI/ARB(94%)+BB(64%)+MRA(39%)	2.2 (1.9–2.6)	0.16 (0.13, 0.20)	<0.001
EMPHASIS–HF(C)	ACEI/ARB(93%)+BB(86%)	2.5 (1.9–3.3)	0.19 (0.14, 0.26)	<0.001
EMPHASIS–HF(T)	ACEI/ARB(94%)+BB(85%)+MRA(100%)	1.9 (1.4–2.5)	0.14 (0.10, 0.20)	<0.001
PARADIGM–HF(C)	ACEI/ARB(100%)+BB(92%)+MRA(57%)	1.8 (1.6–2.2)	0.14 (0.11, 0.17)	<0.001
PARADIGM–HF(T)	ACEI/ARB(100%)+BB(93%)+MRA(54%)+LCZ696	1.5 (1.2–1.8)	0.11 (0.09, 0.14)	<0.001
ATMOSPHERE (Enarapril)	ACEI/ARB(100%)+BB(91%)+MRA(36%)	1.7 (1.4–2.1)	0.12 (0.10, 0.16)	<0.001
ATMOSPHERE (Aliskiren)	ACEI/ARB(2%)+BB(90%)+MRA(35%)+Aliskiren	1.9 (1.6–2.3)	0.14 (0.11, 0.18)	<0.001
ATMOSPHERE (Combination)	ACEI/ARB(100%)+BB(91%)+MRA(35%)+Aliskiren	1.4 (1.2–1.8)	0.10 (0.08, 0.13)	<0.001



Annual rates are shown as pump failure death per 100 patient-years. Hazard ratios shown are compared to the placebo arm of RALES (N=46,151). C denotes control arm; T, experimental treatment arm; P, placebo arm; A, amiodarone arm.

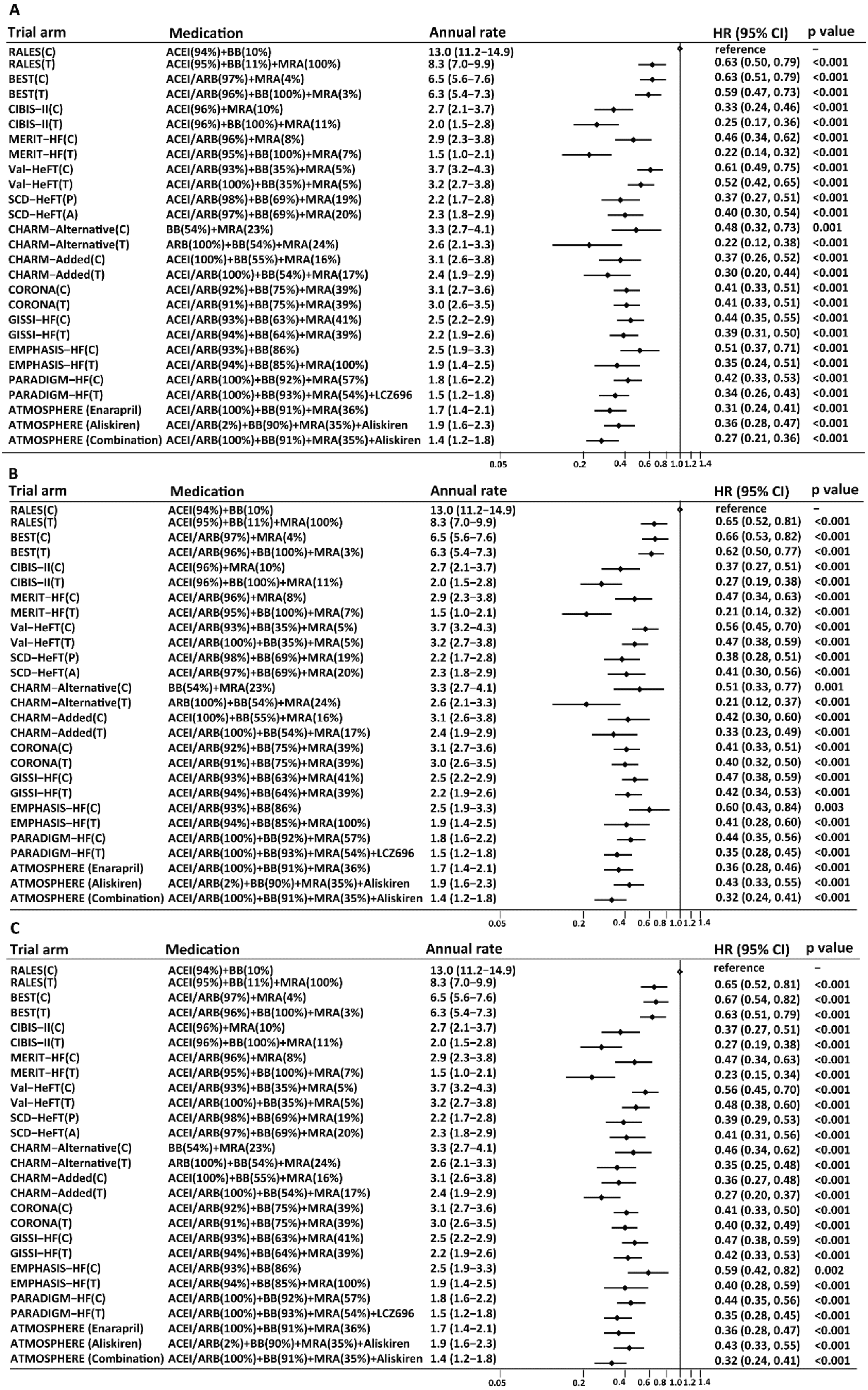
Figure 3-14 Hazard ratio for pump failure death across the trial arms in HF-REF with incremental use of evidence-based medications, with adjustment for 8 conventional covariates

Trial arm	Medication	Annual rate	HR (95% CI)	p value
RALES(C)	ACEI(94%)+BB(10%)	13.0 (11.2–14.9)	reference	–
RALES(T)	ACEI(95%)+BB(11%)+MRA(100%)	8.3 (7.0–9.9)	0.64 (0.51, 0.80)	<0.001
BEST(C)	ACEI/ARB(97%)+MRA(4%)	6.5 (5.6–7.6)	0.64 (0.52, 0.80)	<0.001
BEST(T)	ACEI/ARB(96%)+BB(100%)+MRA(3%)	6.3 (5.4–7.3)	0.61 (0.49, 0.75)	<0.001
CIBIS–II(C)	ACEI(96%)+MRA(10%)	2.7 (2.1–3.7)	0.33 (0.24, 0.46)	<0.001
CIBIS–II(T)	ACEI(96%)+BB(100%)+MRA(11%)	2.0 (1.5–2.8)	0.25 (0.18, 0.36)	<0.001
MERIT–HF(C)	ACEI/ARB(96%)+MRA(8%)	2.9 (2.3–3.8)	0.46 (0.34, 0.62)	<0.001
MERIT–HF(T)	ACEI/ARB(95%)+BB(100%)+MRA(7%)	1.5 (1.0–2.1)	0.23 (0.16, 0.34)	<0.001
Val–HeFT(C)	ACEI/ARB(93%)+BB(35%)+MRA(5%)	3.7 (3.2–4.3)	0.61 (0.49, 0.75)	<0.001
Val–HeFT(T)	ACEI/ARB(100%)+BB(35%)+MRA(5%)	3.2 (2.7–3.8)	0.52 (0.42, 0.65)	<0.001
SCD–HeFT(P)	ACEI/ARB(98%)+BB(69%)+MRA(19%)	2.2 (1.7–2.8)	0.38 (0.28, 0.52)	<0.001
SCD–HeFT(A)	ACEI/ARB(97%)+BB(69%)+MRA(20%)	2.3 (1.8–2.9)	0.40 (0.30, 0.54)	<0.001
CHARM–Alternative(C)	BB(54%)+MRA(23%)	3.3 (2.7–4.1)	0.51 (0.39, 0.67)	<0.001
CHARM–Alternative(T)	ARB(100%)+BB(54%)+MRA(24%)	2.6 (2.1–3.3)	0.40 (0.30, 0.53)	<0.001
CHARM–Added(C)	ACEI(100%)+BB(55%)+MRA(16%)	3.1 (2.6–3.8)	0.40 (0.31, 0.51)	<0.001
CHARM–Added(T)	ACEI/ARB(100%)+BB(54%)+MRA(17%)	2.4 (1.9–2.9)	0.30 (0.23, 0.39)	<0.001
CORONA(C)	ACEI/ARB(92%)+BB(75%)+MRA(39%)	3.1 (2.7–3.6)	0.42 (0.34, 0.52)	<0.001
CORONA(T)	ACEI/ARB(91%)+BB(75%)+MRA(39%)	3.0 (2.6–3.5)	0.40 (0.33, 0.50)	<0.001
GISSI–HF(C)	ACEI/ARB(93%)+BB(63%)+MRA(41%)	2.5 (2.2–2.9)	0.44 (0.35, 0.55)	<0.001
GISSI–HF(T)	ACEI/ARB(94%)+BB(64%)+MRA(39%)	2.2 (1.9–2.6)	0.39 (0.31, 0.49)	<0.001
EMPHASIS–HF(C)	ACEI/ARB(93%)+BB(86%)	2.5 (1.9–3.3)	0.50 (0.36, 0.70)	<0.001
EMPHASIS–HF(T)	ACEI/ARB(94%)+BB(85%)+MRA(100%)	1.9 (1.4–2.5)	0.34 (0.24, 0.50)	<0.001
PARADIGM–HF(C)	ACEI/ARB(100%)+BB(92%)+MRA(57%)	1.8 (1.6–2.2)	0.42 (0.33, 0.53)	<0.001
PARADIGM–HF(T)	ACEI/ARB(100%)+BB(93%)+MRA(54%)+LCZ696	1.5 (1.2–1.8)	0.34 (0.26, 0.43)	<0.001
ATMOSPHERE (Enarapril)	ACEI/ARB(100%)+BB(91%)+MRA(36%)	1.7 (1.4–2.1)	0.32 (0.24, 0.41)	<0.001
ATMOSPHERE (Aliskiren)	ACEI/ARB(2%)+BB(90%)+MRA(35%)+Aliskiren	1.9 (1.6–2.3)	0.36 (0.29, 0.47)	<0.001
ATMOSPHERE (Combination)	ACEI/ARB(100%)+BB(91%)+MRA(35%)+Aliskiren	1.4 (1.2–1.8)	0.27 (0.21, 0.36)	<0.001



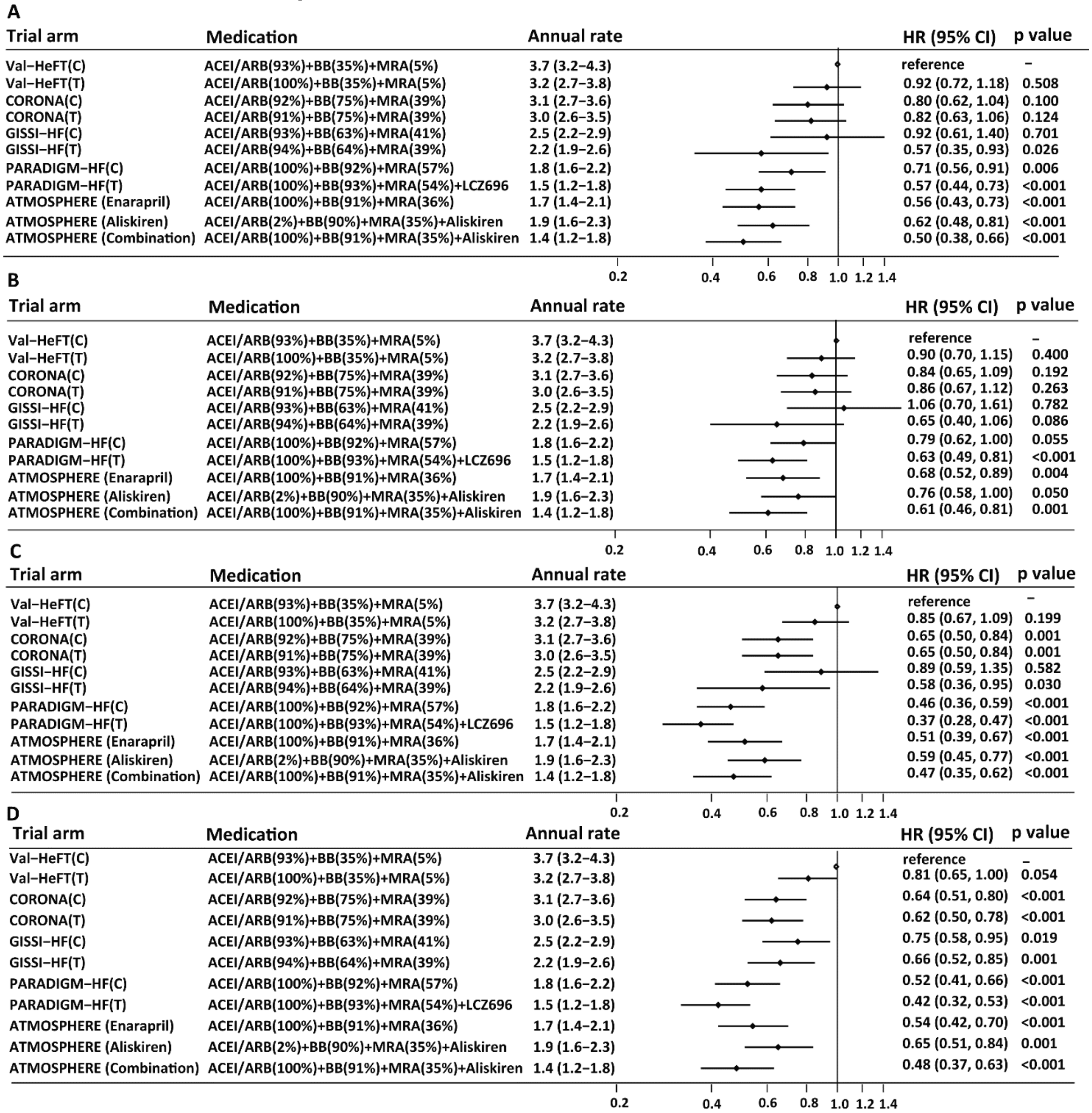
Annual rates are shown as pump failure death per 100 patient-years. Hazard ratios are adjusted for conventional covariates including age, sex, NYHA class, LVEF, ischaemic aetiology, previous myocardial infarction, and a history of hypertension and diabetes (N= 46019). Hazard ratios shown are compared to the placebo arm of RALES. C denotes control arm; T, experimental treatment arm; P, placebo arm; A, amiodarone arm.

Figure 3-15 Hazard ratio for pump failure death across the trial arms in HF-REF with incremental use of evidence-based medications, with adjustment for 8 conventional covariates and eGFR



Annual rates are shown as pump failure death per 100 patient-years. Panel A, HRs are adjusted for conventional confounding variables in the subset of patients with eGFR measurements available (N=42,920); Panel B, adjustment for conventional covariates and eGFR in the subset of patients with eGFR measurements available (N=42,920); Panel C, adjustment for conventional covariates and eGFR with simple imputation of eGFR levels (N=46,019). HRs shown are compared to the placebo arm of RALES. C denotes control arm; T, experimental treatment arm; P, placebo arm; A, amiodarone arm.

Figure 3-16 Hazard ratio for pump failure death across the trial arms in HF-REF with incremental use of evidence-based medications, with adjustment for 8 conventional covariates, eGFR and NT-proBNP



Annual rates are shown as pump failure death per 100 patient-years. Panel A, adjustment for conventional confounding variables in the subset of patients with NT-proBNP available [N=20,715]; Panel B, adjustment for conventional covariates and eGFR in the subset of patients with NT-proBNP available [N=20,715]; Panel C, adjustment for conventional covariates, eGFR and log transformed NT-proBNP in the subset of patients with NT-proBNP available [N=20,715]; Panel D, adjustment for conventional covariates, eGFR and log transformed NT-proBNP with simple imputation of eGFR and NT-proBNP in the trials with NT-proBNP collected (i.e. not complete missing) [N=26,809]. HRs shown are compared to the placebo arm of Val-HeFT. C denotes control arm; T, experimental treatment arm.

3.2.6 Sudden death at different time points during follow-up

The cumulative incidences of sudden death at 90 days were consistently low across these trials ranging from 2.4% (95% CI 1.6-3.1%) in RALES to 1.0% (95% CI 0.7-1.2%) in ATMOSPHERE (Table 3-4 and Figure 3-2). At 180 days, in general, the cumulative incidence of sudden death was nearly double that at 90 days in each trial, but it remained low in absolute terms, at around 2% in contemporary trials such as PARADIGM-HF and ATMOSPHERE. At 1 year, the cumulative incidence reached 6.7% in RALES and was 5.8% in BEST or lower in the other trials. At 3 years, the cumulative sudden death rate reached over 13% in RALES, BEST and CORONA (13.4%, 13.5% and 13.2% respectively), but was much lower in the more recent trials (around 7.4-9.3%).

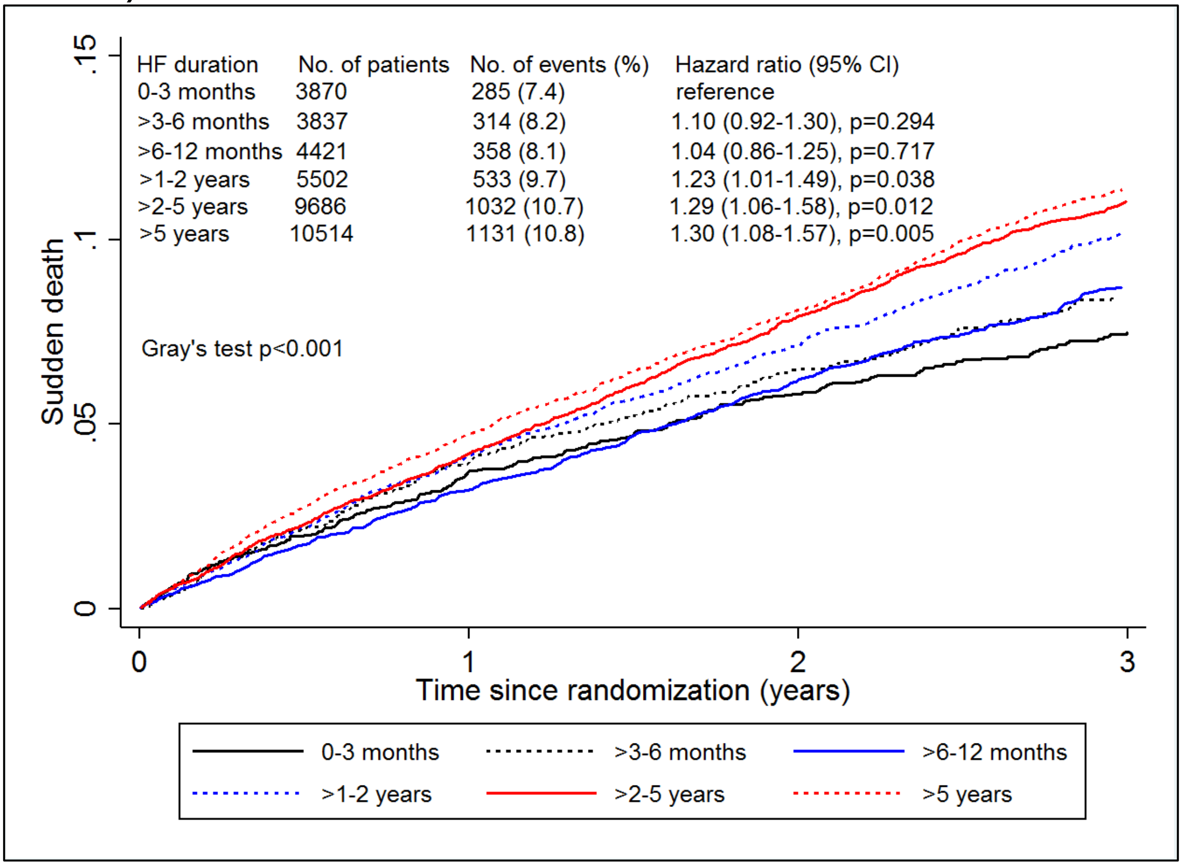
3.2.7 Pump failure death at different time points during follow-up

The cumulative incidences of pump failure death at 90 days were consistently low at 1.0% or lower across these trials, except for RALES with a value of 3.5% (95% CI 2.6-4.4%) (Table 3-5 and Figure 3-10). At 180 days, the cumulative incidence of pump failure death was almost double that at 90 days in each trial, but it remained low in absolute terms at 0.5% in the contemporary PARADIGM-HF and ATMOSPHERE. At 1 year, the cumulative incidence reached 10.5% in RALES and 5.2% in BEST and was 3.0% in CHARM-Alternative or lower in the other trials. At 3 years, the cumulative incidence of pump failure death reached over 21% in RALES and 15% in BEST, but was substantially lower in the more recent trials (about 4.3-6.2%).

3.2.8 Sudden death according to HF duration

The cumulative risk of sudden death during follow-up was plotted according to the length of time from the diagnosis of HF to randomisation based on the merged data from ten trials with this information available (Figure 3-17). There was a significant overall difference among patients with different HF durations (Gray's test $p<0.001$), where longer history of HF carried higher risk of sudden death, especially in the later period of follow-up. There was no evidence that the risk of sudden death in patients with recent-onset HF (within 3 months before randomisation) was higher than those with longer-standing HF.

Figure 3-17 Cumulative incidence curves for sudden death over time in HF-REF according to the length of time between diagnosis of HF and randomisation (trials with data available combined)

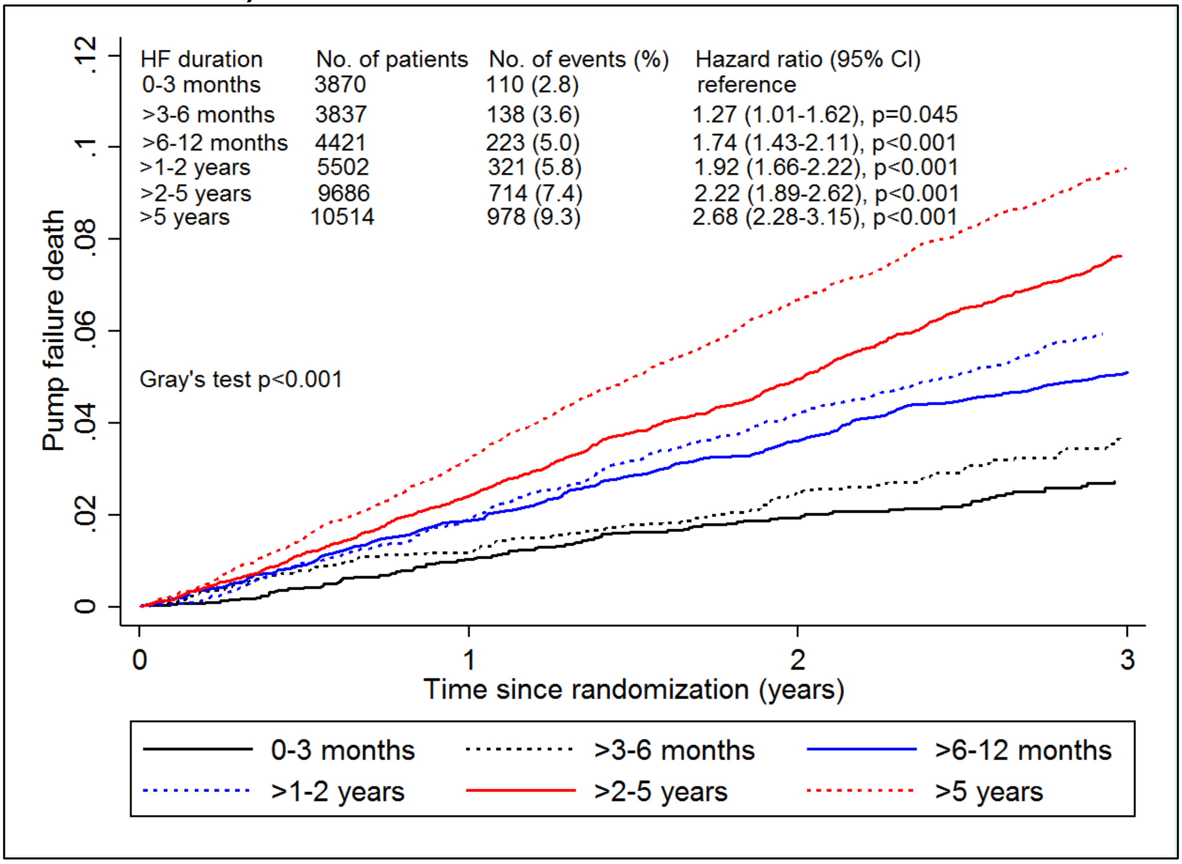


Hazard ratios for sudden death are shown for patients diagnosed within 3 months compared to those diagnosed with HF for >3-6 months, >6-12 months, >1-2 years, >2-5 years and >5 years respectively. These hazard ratios are adjusted for age, sex, NYHA class, LVEF, ischaemic aetiology, previous myocardial infarction and a history of diabetes and hypertension and are counted for within-trial clustering (N=37,706). Data were available in BEST, Val-HeFT, SCD-HeFT, CHARM-Alternative, CHARM-Added, CORONA, GISSI-HF, EMPHASIS-HF, PARADIGM-HF and ATMOSPHERE (N= 37,830).

3.2.9 Pump failure death according to HF duration

As shown in Figure 3-18, the cumulative incidence curves for pump failure death during follow-up were outlined by HF duration. Overall, a significant difference in the risk of pump failure death was observed among patients with different HF durations (Gray's test $p<0.001$). Patients with longer-standing HF carried a higher risk of pump failure death: compared to patients with recent-onset HF, the risk of pump failure death was about 90%, 120% and 170% higher in those with a diagnosis of HF of >1-2 years, >2-5 years and over 5 years respectively.

Figure 3-18 Cumulative incidence curves for pump failure death over time in HF-REF according to the length of time between diagnosis of HF and randomisation (trials with data available combined)



Hazard ratios for pump failure death are shown for patients diagnosed within 3 months compared to those diagnosed for >3-6 months, >6-12 months, >1-2 years, >2-5 years and >5 years respectively. These hazard ratios are adjusted for age, sex, NYHA class, LVEF, ischaemic aetiology, previous myocardial infarction and a history of diabetes and hypertension and are counted for within-trial clustering (N=37,706). Data were available in BEST, Val-HeFT, SCD-HeFT, CHARM-Alternative, CHARM-Added, CORONA, GISSI-HF, EMPHASIS-HF, PARADIGM-HF and ATMOSPHERE (N= 37,830).

3.3 Discussion

This analysis of individual patient-level data from 46,163 patients randomised in 13 clinical trials showed that the rates of sudden death and pump failure death in patients with HF-REF have fallen by 41% and by 80% respectively over the last 20 years between the start of RALES and the completion of ATMOSPHERE. The declining rates over this period are in parallel with a cumulative use of disease modifying therapies known to reduce both modes of death. Now in patients with a high adoption of modern disease-modifying treatment in HF-REF, the absolute rate is relatively low for sudden death at around 2% at 6 months and 9% by 3 years, and is even lower for pump failure death with the corresponding rates of 0.5% and 4.5% respectively. Of note, a longer history of HF was associated with higher risks of sudden death and, in particular, pump failure death, especially in the later period of follow-up.

This analysis found that the risk of sudden death has declined across trials over the last two decades, and this was coincident with a cumulative use of disease modifying therapies including beta-blockers and MRAs over the same time frame. Concerns may arise that the falling risk may be driven by the diverse study design and different levels of comorbidity burden across these trials. For example, patients enrolled in the more recent trials were more likely to have a history of hypertension and diabetes, and tended to have a lower blood pressure and heart rate than those in the older trials. However, the downward trend persisted after adjustment for major difference across the trials and key prognostic factors. Besides, the estimate of the falling risk of sudden death over time may be conservative. The plasma NT-proBNP, an important prognostic factor, was only measured in a subset of patients, but based on the cohort with data available, additional adjustment for NT-proBNP gave a substantially lower risk of sudden death in the more recent trials and treatment arms. Reassuringly, the observation of the falling trend in the sudden death rate was echoed by the finding from a study based on less selected patients over a similar time span.[52]

A more pronounced reduction was observed in the risk of pump failure death across the same period, compared to sudden death or death from any cause; accordingly, pump failure death made a smaller contribution to overall mortality over time. Although both risks of sudden death and pump failure death increased with progression of HF, pump failure death was more common, as a proportion of total mortality, in patients with more advanced HF.[7, 84] It is arguable that the falling trend in the rate of pump failure death may be due to an unfair comparison given that patients enrolled in the earlier trials, i.e. RALES and BEST, had more severe HF than those in the more recent trials. However, after excluding patients in RALES and BEST in a sensitivity analysis, the falling trend persisted, although attenuated, and this was also the case with adjustment for the severity of HF including NYHA class and LVEF and other prognostic factors. This may reflect the cumulative use of disease modifying therapies, given the evidence from individual clinical trials that pharmacotherapies including beta-blockers and MRAs improved pump function and lowered the risk of pump failure death,[7, 66, 67] which was reinforced by the observation in this analysis that randomisation treatment was significantly associated with a lower risk of pump failure death. Another possible reason could be the improved management of acute worsening of HF, which would otherwise have led to a mortal event. Nevertheless, the observation of a declining risk of pump failure death over time stands in contrast to some observational studies in which only a modest reduction or even an increase was observed in the risk of pump failure death over time.[51, 52] The reason for the discrepancy is uncertain, but it may result from the difference in the study population, since patients in this analysis were selected for trial participation, who were more likely to be younger and stable or have less severe symptoms, and who were different from those with newly diagnosed HF or hospitalised patients in observational studies. Besides, patients enrolled in the clinical trials were more likely to have comprehensive health care involving more frequent patient contact and better and timely management of HF aggravation than those in observational studies.

Encouragingly, the cumulative incidences of sudden death are low at 3 months, and even at 6 months, in the more recent trials, in concert with a recent report of the national experience of wearable cardioverter defibrillators in the United States.[129] Current guidelines have recommended the use of evidence-based medications for at least 3 months before device implantation.[3, 130] However, in newly diagnosed patients initiation and up-titration of three neurohumoral blockers may take many weeks and there is evidence that reverse-remodelling is both dose-dependent and greater with multiple drugs than one or two agents.[131-

[135] Moreover, decreases in left ventricular volumes and increases in LVEF may still occur between 6 and 12 months after treatment initiation. Consequently, 3 months may be too short a period to wait to see whether there is sufficient recovery of LVEF to obviate the need for an ICD. For example, in one study, 66% of potential ICD candidates demonstrated an increase in LVEF above the threshold for implantation after optimisation of medical therapy over an average of 5.4 months.[136] This analysis has shown that the rate of sudden death remains low (≤2%) for at least 6 months after randomisation in the trials analysed. It is unlikely that a clinically meaningful mortality benefit will be obtained with an ICD in patients with a sudden death rate of 1-2%,[137] especially over the first 6 months after implantation, as the clinical trials showed no discernible benefit using ICDs in that period.[31, 32] This view is reinforced by a recent study in which no reduction in overall mortality was observed in patients with non-ischemic cardiomyopathy with high adoption of modern pharmacological treatment and cardiac resynchronization therapy.[35] Furthermore, in a recent nationwide analysis of complications after primary prevention ICD implantation in ambulatory patients in the US, the device-related mortality rate was reported to be 0.73% at 30 days (with a total serious complication rate of 8.4%).[138] It seems unlikely from the present findings that the mortality related to device implantation could be offset by a reduction in sudden death within 6 months. This result, therefore, highlights the need for better risk stratification of sudden death to benefit from ICD therapy in a cost-effective manner.

The mortality rates due to progressive heart failure were quite low at early follow-up in the contemporary trials, e.g. at about 0.5% and 1.0% at 3 and 6 months respectively. A different picture was outlined in population-based studies, where a high rate of pump failure death at early follow-up was observed.[83] This inconsistency was not surprising given that patients enrolled in clinical trials often have established HF, i.e. survivors of early high-risk phase of this disease, in which death due to worsening HF makes a greater contribution.

Patients with newly diagnosed HF did not have a higher risk for sudden death than those with a longer history of HF, if anything, the opposite is true, especially at later periods of follow-up. The association of a longer history of HF with a higher risk was also observed for pump failure death, with a greater magnitude of the association and a wider separation by HF duration. This observation may be due the fact that patients with a longer standing of HF more often have advanced HF, in whom death from worsening HF is more common than sudden death.[7]

There are several limitations to this analysis. Firstly, the study is a post-hoc analysis based on clinical trial data rather than "real-world" cohorts in which patients tend to be older, have more co-morbidity and be treated with fewer and less optimal doses of guide recommended medications.[139-141] However, compared to the "real-world" unselected cohorts, cohorts from clinical trials have detailed characterisation and follow-up, which allows more complete multivariable adjustment. Moreover, it is in patients similar to those in this analysis that ICDs are most clearly indicated. Secondly, the definitions for mode-specific death were not uniform despite being broadly similar across these trials. This is not surprising given that there were no standardised definitions for mode-specific death until very recently when the US ACCF and AHA in collaboration with the FDA made a consensus on the definitions of cardiovascular endpoint events used in clinical trials.[46] Besides, accurate classification of modes of death not only requires specific and detailed definitions, but also needs to capture the specific characteristics surrounding death and collect this information in a standardised way. Use of clinical trials has another strength that mortality events are sub-classified and cause of death is adjudicated in a careful and standardised way, and this could reduce the bias and variation within a trial. Thirdly, in this analysis time since randomisation instead of time since HF diagnosis was used as the underlying time scale, in other words, the patients examined were the "natural survivors" by the time of randomisation. This may be less likely to reflect the risks of sudden death and pump failure death in the time course of HF progression. However, ten out of the 13 trials provided information on the length of time between diagnosis of HF and randomisation.

3.4 Summary

The risks of sudden death and pump failure death in patients with HF-REF enrolled in clinical trials have fallen over the last two decades, in parallel with a cumulative use of disease modifying therapies on both modes of death. The absolute rates of sudden death and pump failure death were particularly low in the early follow-up after randomisation in pharmacologically well-treated patients in the contemporary trials. A longer standing HF was associated with greater risks of sudden death and, particularly, pump failure death.

Given the falling risks of both modes of death, it is of great importance to identify a high-risk subgroup to target costly devices to those most in need and to identify a low-risk subgroup to avoid unnecessary treatment, thereby improving the cost effectiveness of device treatment. In the next chapter, I will develop prognostic models to estimate the individual risks for sudden death and pump failure death in patients with HF-REF.

Chapter 4 Developing models to predict sudden death and pump failure death in HF-REF

In this chapter I will develop prognostic models for sudden death and pump failure death separately in patients with HF-REF enrolled in PARADIGM-HF using a competing risk approach with Fine-Gray sub-distributional hazards regression models, accounting for the prognostic influence of death from other causes.[27, 118] The performance of the derived models will be examined by assessing the calibration ability, i.e. the agreement between the predicted and observed cumulative incidences, and discrimination ability, i.e. separating patients with a higher risk from those with a lower risk, respectively. An individual's risk score for each mode of death will be calculated and the corresponding cumulative incidence will be predicted.

4.1 Methods

4.1.1 Study population

The models were developed in a subset of patients with HF-REF randomised in PARADIGM-HF who did not have an ICD or CRT-D implanted at baseline.[27]

4.1.2 Candidate prediction variables

A broad spectrum of baseline variables (N=58) were assessed to identify predictors for each mode of death separately; the variables included demographics, clinical feathures of HF, medical history, treatment, 12-lead ECG, routine biochemical tests and NT-proBNP (Appendix Table 5). A full set of baseline variables were collected in most patients, and patients with missing values (<5.0%) were excluded in this analysis (Appendix Table 5). No difference was observed between the cohort with all baseline variables available and the overall population (all p values >0.7).

4.1.3 Statistical analysis

The prognostic influence of each candidate predictor on the cumulative incidence of each mode of death was first assessed by a univariate Fine-Gray sub-distribution hazards regression analysis.[118] For each continuous variable, linearity was examined using the restricted cubic spline method. If the response appeared nonlinear, certain cut-off values or transformation were applied based on the spline curves and clinical relevance. For categorical variables, appropriate dummy variables were used. For each variable, the statistical strength for predicting each mode of death was quantified by X^2 values with one degree of freedom (the larger X^2, the more powerful the predictor). For each outcome, univariate predictors significant at a $p < 0.20$ level were entered into a multivariable Fine-Gray model with a backward stepwise selection at the exclusion p value of 0.05. The proportional sub-distribution hazards assumption for the derived models was examined using time varying terms.

For each mode of death, an individual's risk score was calculated as the sum of each predictor value multiplied by its corresponding coefficient from the final multivariable model. Model calibration was assessed by comparing the predicted cumulative incidence curve with observed Aalen-Johansen estimator in each quartile of the risk score (the closer the better). Model discrimination was assessed by visually examining the distribution of each set of curves (the wider the better), together with by computing the Harrell's C statistic and C index at 1, 2, and 3 years counting for right censoring.[127]

4.2 Results

4.2.1 Patient characteristics and mortality events

This analysis included 7156 patients with HF-REF enrolled in PARADIGM-HF after excluding 1243 patients with an ICD or CRT-D at baseline. The average age was 63.7 years and 77% were men. The mean LVEF was 29.9%, most were in NYHA class II-III (predominantly in class II [69.8%]) and the majority had an ischaemic aetiology (58.7%). There was substantial use of guideline-recommended medications including beta-blockers (92.4%) and MRAs (55.5%). The baseline characteristics are shown in Table 4-1.

During a median 27 months of follow-up, 1344 death events occurred including 525 sudden deaths and 261 pump failure deaths. The corresponding annual rates for sudden death and pump failure death were 3.4 (95% CI 3.1-3.7) and 1.7 (95% CI 1.5-1.9) per 100 patient-years, respectively.

Table 4-1 Baseline characteristics in PARADIGM-HF and ATMOSPHERE

	PARADIGM-HF (N=7156)	ATMOSPHERE N=5968	p value
Age -years	63.7±11.6	63.1±12.1	0.01
Male sex - no. (%)	5492 (76.7)	4565 (76.5)	0.73
Race - no. (%)			<0.001
White	4480 (62.6)	3659 (61.7)	
Black	344 (4.8)	95 (1.6)	
Asian	1480 (20.7)	1716 (28.9)	
Other	852 (11.9)	460 (7.8)	
Region - no. (%)			<0.001
North America	275 (3.8)	81 (1.4)	
Latin America	1372 (19.2)	1077 (18.0)	
Western Europe	1423 (19.9)	1225 (20.5)	
Central Europe	2625 (36.7)	1737 (29.1)	
Asia or Pacific region	1461 (20.4)	1848 (31.0)	
Body mass index	28.0±5.5	27.2±5.3	<0.001
Blood pressure -mmHg			
Systolic	122.0±15.4	124.4±18.2	<0.001
Diastolic	74.2±10.0	77.6±11.0	<0.001
Heart rate -beats/min	72.9±12.1	72.4±12.7	0.008
LVEF -%	29.9±6.1	28.8±5.5	<0.001
NYHA class - no. (%)			<0.001
II	4988 (69.8)	4030 (67.5)	
III	1756 (24.6)	1718 (28.8)	
IV	54 (0.8)	56 (0.9)	
Ischaemic aetiology - no. (%)	4204 (58.7)	3232 (54.2)	<0.001
HF duration - no. (%)			<0.001
within 1 year	2391 (33.4)	2229 (37.4)	
>1-5 years	2781 (38.9)	2197 (36.8)	
>5 years	1984 (27.7)	1538 (25.8)	
Medical history - no. (%)			
Current smoking	1008 (14.1)	741 (12.4)	0.005
Previous HF hospitalisation	4459 (62.3)	3490 (58.5)	<0.001
Myocardial infarction	2919 (40.8)	2228 (37.3)	<0.001
Angina	1944 (27.2)	1415 (23.7)	<0.001
CABG or PCI	1951 (27.3)	1475 (24.7)	0.001
Hypertension	5101 (71.3)	3725 (62.4)	<0.001
Diabetes	2406 (33.6)	1629 (27.3)	<0.001
Atrial fibrillation	2621 (36.6)	2002 (33.5)	<0.001
Stroke	596 (8.3)	419 (7.0)	0.005
Cancer	320 (4.5)	186 (3.1)	<0.001
Asthma	249 (3.5)	179 (3.0)	0.12
COPD	876 (12.2)	625 (10.5)	0.002
PAD	610 (8.5)	461 (7.7)	0.10
Medication - no. (%)			
Digoxin	2232 (31.2)	1940 (32.5)	0.11
Diuretics	5709 (79.8)	4713 (79.0)	0.25
ACEI or ARB	7156 (100.0)	4019 (67.3)	<0.001
Beta-blocker	6610 (92.4)	5423 (90.9)	0.002
MRA	3969 (55.5)	2109 (35.3)	<0.001
Any antiplatelet agent	3988 (55.7)	3251 (54.5)	0.15
Aspirin	3653 (51.0)	3021 (50.6)	0.63

Anticoagulant	2173 (30.4)	1633 (27.4)	<0.001
Statin	3796 (53.0)	2893 (48.5)	<0.001
Pacemaker	513 (7.2)	358 (6.0)	0.007
CRT-P	136 (1.9)	107 (1.8)	0.65
12-lead ECG - no. (%)			
QRS duration -ms	114.3±31.6	114.5±31.6	0.78
Atrial fibrillation	1866 (26.1)	1434 (24.3)	0.02
Bundle branch block	1965 (27.5)	1659 (28.1)	0.43
Left bundle branch block	1440 (20.1)	1245 (21.1)	0.18
Right bundle branch block	552 (7.7)	441 (7.5)	0.59
Q wave	1247 (17.4)	1108 (18.8)	0.05
Left ventricular hypertrophy	1423 (19.9)	1189 (20.1)	0.73
Laboratory measurement			
eGFR <60 ml/min/1.73 m^2 - no. (%)	2462 (34.4)	1467 (24.6)	<0.001
eGFR -ml/min/1.73 m^2	68.8±20.3	75.1±24.7	<0.001
Creatinine -mg/dl	1.10±0.29	1.02±0.27	<0.001
BUN -mmol/L	7.2±2.9	7.2±2.9	0.09
Albumin -g/L	42.8±3.2	43.2±3.6	<0.001
Haemoglobin -g/L	139.4±16.2	137.4±16.6	<0.001
Potassium -mmol/L	4.51±0.48	4.46±0.47	<0.001
Sodium -mmol/L	141.5±3.0	139.7±3.3	<0.001
Chloride -mmol/L	103.9±3.4	103.8±3.6	0.24
Calcium -mmol/L	2.32±0.11	2.33±0.12	0.06
Total cholesterol -mmol/L	4.59±1.16	4.54±1.20	0.005
HDL-C -mmol/L	1.24±0.37	1.24±0.38	0.50
LDL-C -mmol/L	2.58±0.95	2.52±1.00	<0.001
Triglyceride-mmol/L	1.71±1.18	1.75±1.21	0.077
NT-proBNP -pg/ml¶	1640 (888-3342)	1204 (630-2285)	<0.001

¶ NT-proBNP measurements were available in 5408 (90.6%) patients in ATMOSPHERE.

4.2.2 Derivation of the model to predict sudden death

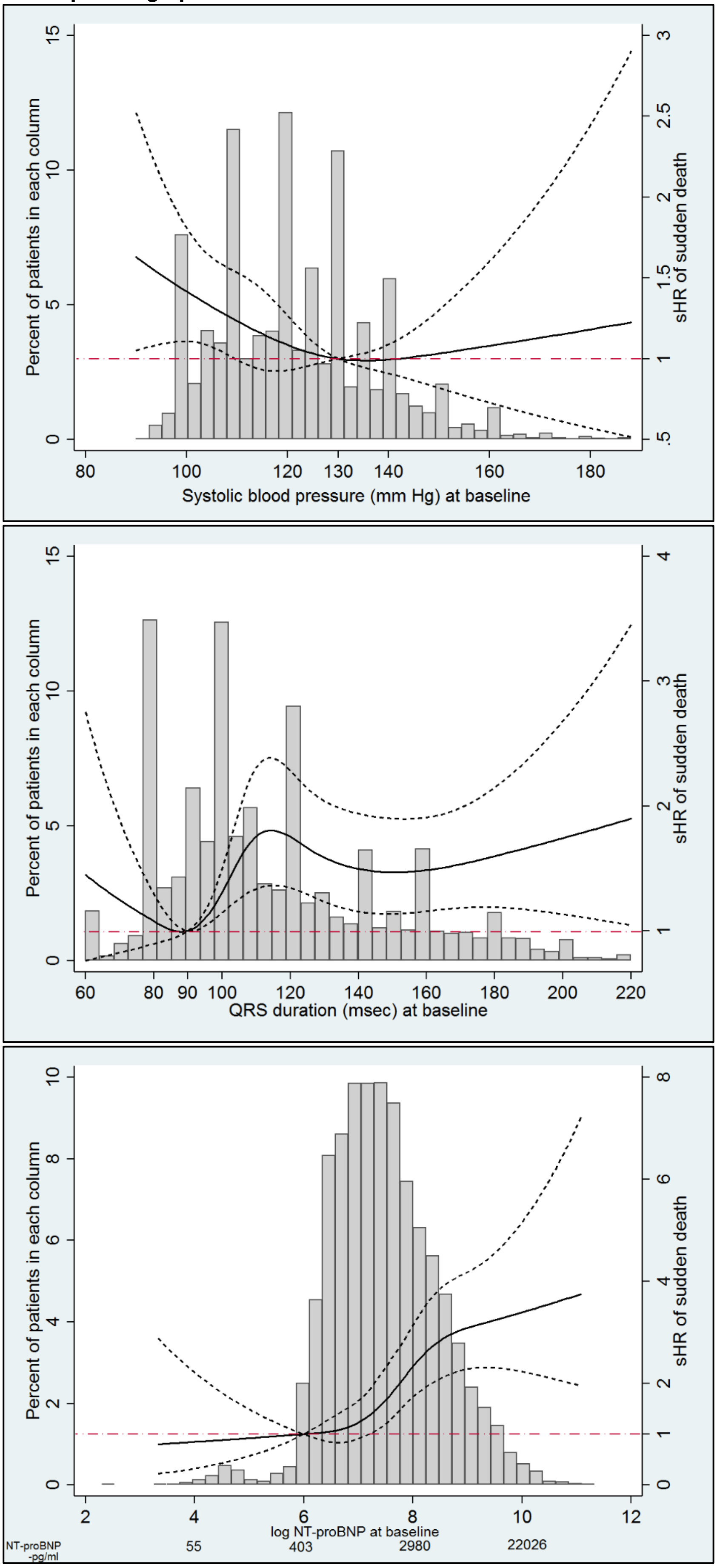
Table 4-2 lists the 25 most powerful prediction variables for sudden death from the univariate analysis in a descending order of predictive strength, and the top 5 variables were NT-proBNP, Asian race, LVEF, NYHA class and BMI. A total of 10 variables were finally included in the multivariable model. Male sex, Asian race, advanced NYHA class (III-IV vs. I-II), ischaemic aetiology, lower systolic BP, left ventricular hypertrophy (LVH) on ECG, prolonged QRS duration and a higher NT-proBNP level were independently associated with a higher risk of sudden death, while prior CABG or PCI and a history of cancer were associated with a lower risk of sudden death. There was no further trend for systolic BP with values >130 mmHg, for QRS duration with values <90 ms or >120 ms, or for log transformed NT-proBNP with values <6 (equivalent to NT-proBNP around 400 pg/ml) (Figure 4-1).

Table 4-2 Univariate and multivariable predictors for sudden death in PARADIGM-HF

	Univariate analysis*			Multivariable model			
	sHR (95% CI)	**p value**	**X^2 score**	**sHR (95% CI)**	**coefficient**	**p value**	**X^2 score**
Log NT-proBNP -pg/mL (from 6), per 1 log unit increase	1.50 (1.38-1.62)	<0.001	96.2	1.42 (1.31-1.54)	0.348	<0.001	70.4
Asian race vs. Caucasian race	1.71 (1.40-2.08)	<0.001	28.5	1.54 (1.26-1.89)	0.434	<0.001	17.7
LVEF 25-35%, per 1% increase	0.95 (0.93-0.97)	<0.001	19.5				
NYHA class III/IV vs. I/II	1.48 (1.23-1.77)	<0.001	17.6	1.35 (1.12-1.64)	0.302	0.002	9.4
BMI 17-28 kg/m^2, per 1 kg/m^2 increase	0.94 (0.92-0.97)	<0.001	16.1				
QRS duration 90-120 ms, per 5 ms increase	1.07 (1.03-1.10)	<0.001	14.0	1.07 (1.04-1.11)	0.069	<0.001	15.4
Triglycerides up to 2.3 mmol/L, per 1 mol/L increase	0.74 (0.62-0.87)	<0.001	14.0				
Myocardial infarction history (yes vs. no)	1.35 (1.14-1.61)	0.001	12.0				
CABG or PCI (yes vs. no)	0.70 (0.56-0.86)	0.001	11.5	0.64 (0.51-0.81)	-0.444	<0.001	14.5
Male vs. female sex	1.47 (1.18-1.85)	0.001	11.2	1.44 (1.14-1.81)	0.365	0.002	9.7
Cancer history (yes vs. no)	0.31 (0.16-0.63)	0.001	10.6	0.36 (0.18-0.72)	-1.033	0.004	8.3
Left ventricular hypertrophy on ECG (yes vs. no)	1.36 (1.12-1.66)	0.002	9.5	1.29 (1.06-1.58)	0.257	0.013	6.2
Ischaemic aetiology (yes vs. no)	1.30 (1.09-1.56)	0.004	8.4	1.58 (1.30-1.93)	0.460	<0.001	21.2
Albumin 30-45 g/L, per 1 g/L increase	0.96 (0.92-0.99)	0.004	8.4				
Haemoglobin A1C 5.7-12.0%, per 1% increase	1.09 (1.03-1.16)	0.004	8.3				
Systolic BP up to 130 mmHg, per 5 mmHg increase	0.95 (0.91-0.98)	0.005	8.0	0.95 (0.91-0.99)	-0.049	0.018	5.6
Black race vs. Caucasian race	1.69 (1.17-2.44)	0.005	7.9				
Serum potassium up to 4.0 mmol/L, per 0.1mmol/L increase	0.92 (0.82-0.98)	0.006	7.4				
Bundle branch block on ECG (yes vs. no)	1.28 (1.06-1.53)	0.009	6.9				
Digoxin use (yes vs. no)	1.23 (1.03-1.47)	0.024	5.1				
Beta-blocker use (yes vs. no)	0.73 (0.55-0.97)	0.031	4.7				
LCZ696 vs. enalapril	0.83 (0.70-0.98)	0.032	4.6				
Asthma history (yes vs. no)	0.51 (0.28-0.95)	0.033	4.5				
Atrial fibrillation history (yes vs. no)	0.82 (0.68-0.98)	0.033	4.5				
Left bundle branch block on ECG (yes vs. no)	1.23 (1.01-1.50)	0.043	4.1				

*The 25 strongest prediction variables for sudden death from the univariate analysis are presented in a descending order of predictive strength.

Figure 4-1 Histograms of systolic BP (A), QRS duration (B) and log NT-proBNP (C) and the corresponding spline curves with the risk of sudden death in PARADIGM-HF



4.2.3 Derivation of the model to predict pump failure death

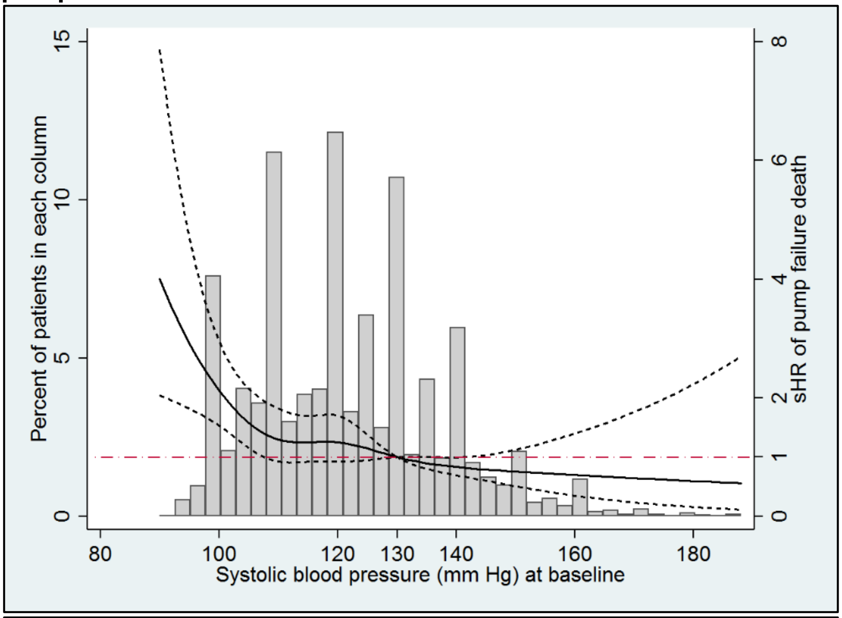
Table 4-3 shows the 25 strongest prediction variables for pump failure death from the univariate analysis in a descending order of predictive strength, and the top 5 variables were NT-proBNP, serum albumin, BUN, creatinine and eGFR. A total of 11 variables were included in the multivariable model, that is, systolic BP, advanced NYHA class, LVEF, ischaemic aetiology, longer history of HF (diagnosed either >1-5 years or >5 years), bundle branch block on ECG, serum albumin, creatinine and chloride, and NT-proBNP (log transformed). No further trend was observed for systolic BP above 130 mmHg, albumin below 30 or above 45 g/L, creatinine below 1.0 or above 2.5 mg/dl, chloride below 90 or above 106 mmol/L, and log transformed NT-proBNP below 6 (equivalent to NT-proBNP around 400 pg/ml) (Figure 4-2).

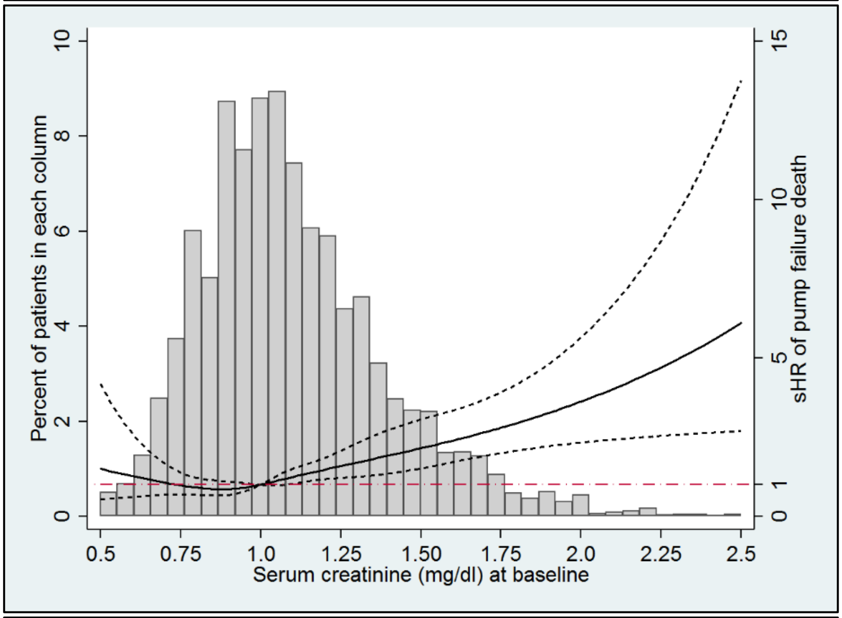
Table 4-3 Univariate and multivariable predictors for pump failure death in PARADIGM-HF

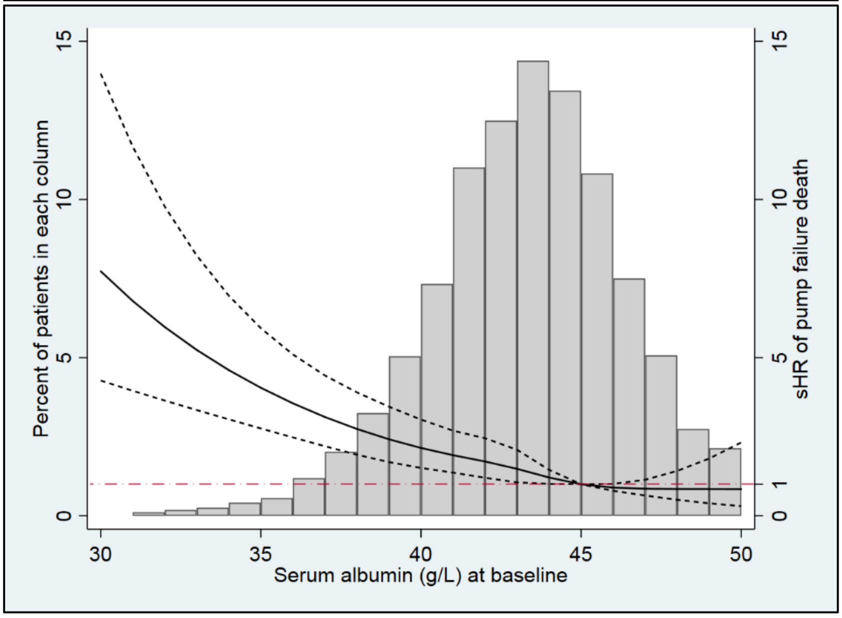
	Univariate analysis*			**Multivariable model**			
	sHR (95% CI)	**p value**	**X^2 score**	**sHR (95% CI)**	**coefficient**	**p value**	**X^2 score**
Log NT-proBNP -pg/ml (from 6), per 1 log unit increase	2.00 (1.78-2.24)	<0.001	142.3	1.61 (1.41-1.84)	0.477	<0.001	49.4
Albumin 30-45 g/L, per 1g/L decrease	1.16 (1.12-1.20)	<0.001	62.7	1.10 (1.06-1.15)	0.100	<0.001	26.5
BUN 6-16 mmol/L, per 1mmol/L increase	1.17 (1.12-1.22)	<0.001	54.6				
Creatinine 1.0-2.5 mg/dL, per 0.1 mg/dL increase	1.15 (1.10-1.19)	<0.001	48.9	1.08 (1.03-1.13)	0.075	0.001	11.4
eGFR up to 60 ml/min/1.73 m^2, per 1ml/min/1.73 m^2 increase	0.96 (0.94-0.97)	<0.001	42.1				
Serum chloride 90-106 mmol/L, per 1 mmol/L decrease	1.12 (1.08-1.16)	<0.001	38.3	1.09 (1.06-1.13)	0.091	<0.001	24.3
HF duration >5 years vs. ≤ 1 year	2.71 (1.94-3.80)	<0.001	34.0	2.58 (1.81-3.68)	0.948	<0.001	27.5
LVEF up to 40%, per 1% decrease	1.05 (1.03-1.07)	<0.001	30.0	1.02 (1.00-1.04)	0.020	0.032	4.6
Haemoglobin 90-140 g/L, per 1 g/L increase	0.97 (0.96-0.98)	<0.001	26.9				
Systolic BP up to 130 mmHg, per 5 mmHg decrease	1.14 (1.08-1.21)	<0.001	22.8	1.10 (1.04-1.17)	0.098	0.001	12.1
QRS duration 90-220 ms, per 5 ms increase	1.05 (1.03-1.06)	<0.001	22.8				
Pacemaker implanted (yes vs. no)	2.29 (1.62-3.23)	<0.001	22.0				
Diastolic BP -mmHg, per 1 mmHg increase	0.97 (0.96-0.98)	<0.001	19.7				
Bundle branch block on ECG (yes vs. no)	1.72 (1.34-2.21)	<0.001	18.5	1.45 (1.12-1.87)	0.369	0.005	8.1
Cardiac resynchronization therapy (yes vs. no)	2.96 (1.68-5.22)	<0.001	14.1				
Age 70-96 years, per 1 year increase	1.05 (1.02-1.08)	<0.001	14.1				
Serum sodium -mmol/L, per 1 mmol/L	0.93 (0.89-0.97)	<0.001	12.8				
Digoxin use (yes vs. no)	1.56 (1.22-1.99)	<0.001	12.4				
Diuretics use (yes vs. no)	1.97 (1.35-2.88)	<0.001	12.3				
NYHA class III/IV vs. I/II	1.57 (1.22-2.03)	0.001	12.1	1.42 (1.08-1.86)	0.350	0.011	6.5
Ischaemic aetiology (yes vs. no)	0.66 (0.52-0.84)	0.001	11.4	0.70 (0.54-0.90)	-0.357	0.005	7.7
Haemoglobin A1C -%, per 1% increase	1.11 (1.04-1.18)	0.001	10.4				
Right bundle branch block on ECG (yes vs. no)	1.81 (1.26-2.59)	0.001	10.3				
HF duration >1-5 years vs. ≤ 1 year	1.73 (1.23-2.43)	0.002	9.9	1.73 (1.21-2.47)	0.549	0.003	9.1
Heart rate above 70 beats/min, per 1 beat/min increase	1.02 (1.01-1.03)	0.002	9.7				

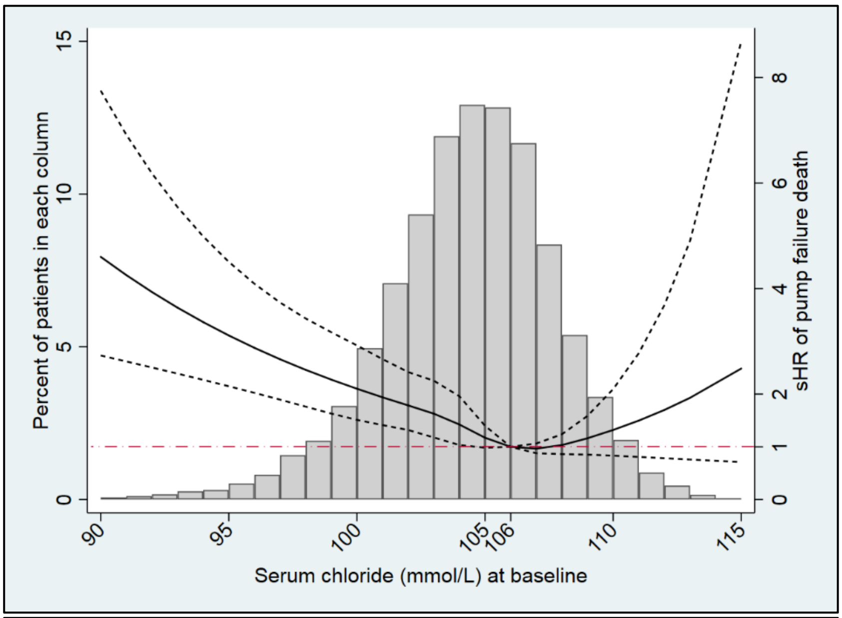
*The 25 strongest variables for pump failure death from the univariate analysis are presented in a descending order of predictive strength.

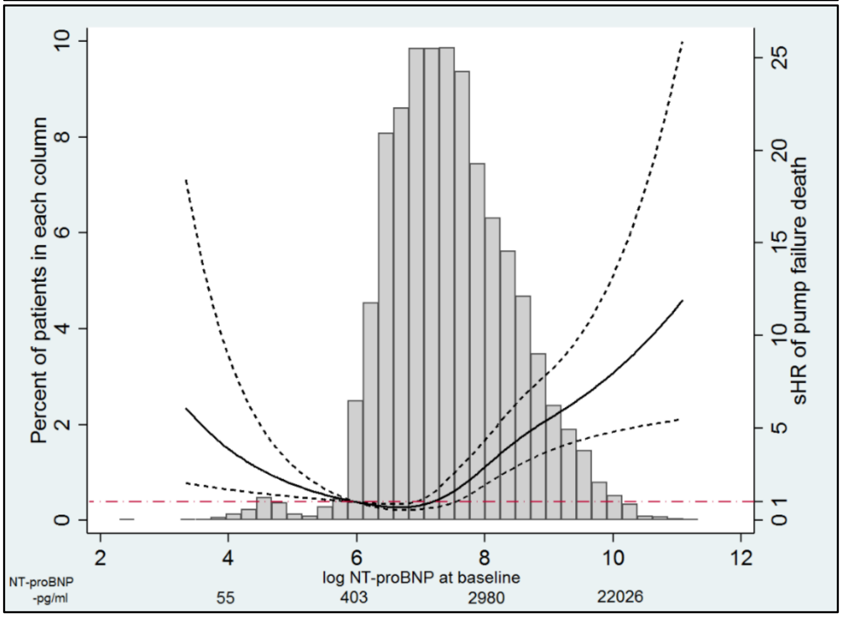
Figure 4-2 Histograms of systolic BP (A), serum creatinine (B), serum albumin (C), serum chloride (D) and log NT-proBNP (E) and the corresponding spline curves with the risk of pump failure death in PARADIGM-HF







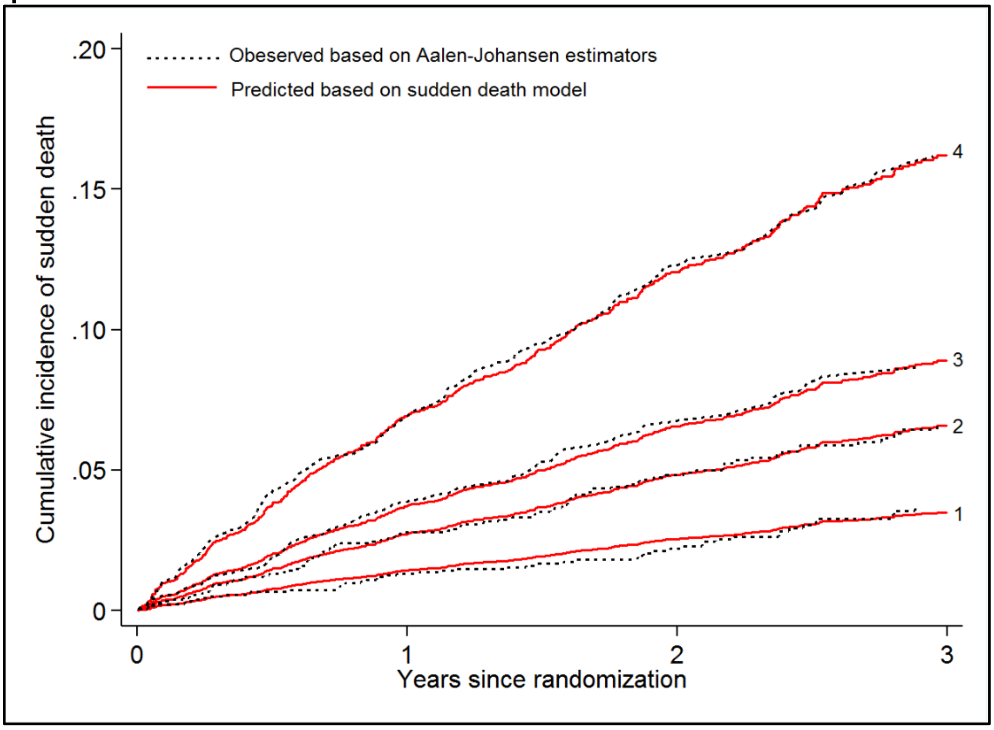

Percent of patients in each column
sHR of pump failure death
Serum chloride (mmol/L) at baseline


Percent of patients in each column
sHR of pump failure death
log NT-proBNP at baseline
NT-proBNP
-pg/ml
55
403
2980
22026

4.2.4 Performance of the models

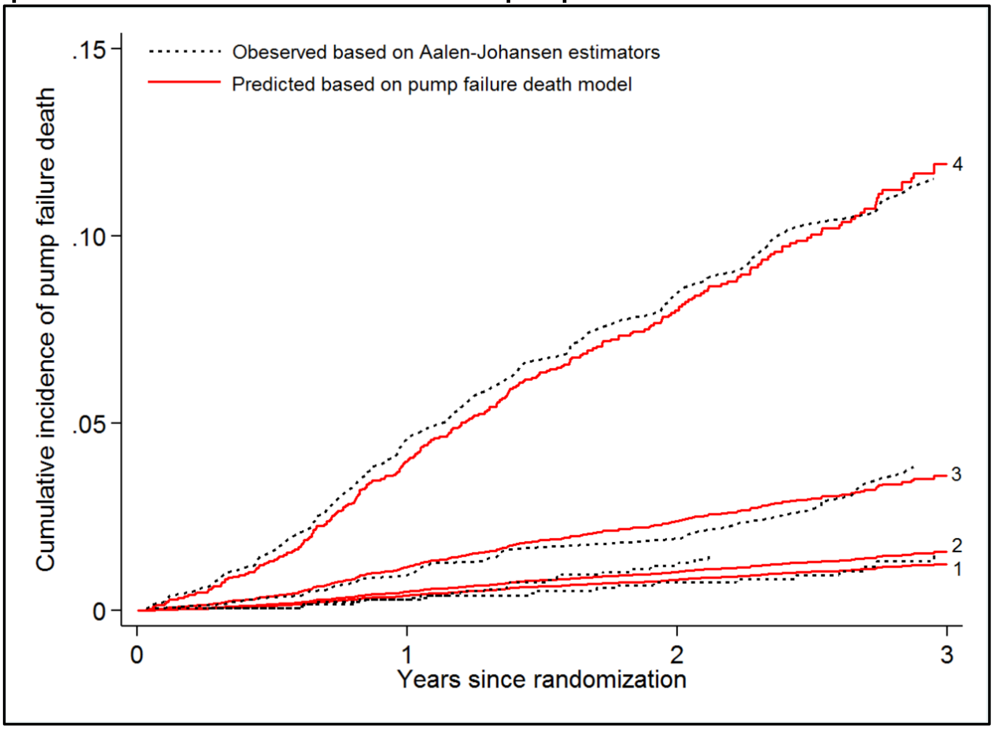
As can be seen from Figure 4-3 the sudden death model was well calibrated: the curves for observed Aalen-Johansen estimators and predicted cumulative incidences were almost identical in each quartile of the risk score over time based on the model. In addition, each set of the four curves were well separated, indicating good discrimination. This was confirmed by a reasonable value of Harrell's C statistic of 0.68 (95% CI 0.66-0.70) and C index of 0.67, 0.68 and 0.66 at 1, 2 and 3 years, respectively.

Figure 4-3 Observed vs. predicted cumulative incidence curves for sudden death by quartiles of the risk score based on the sudden death model in PARADIGM-HF



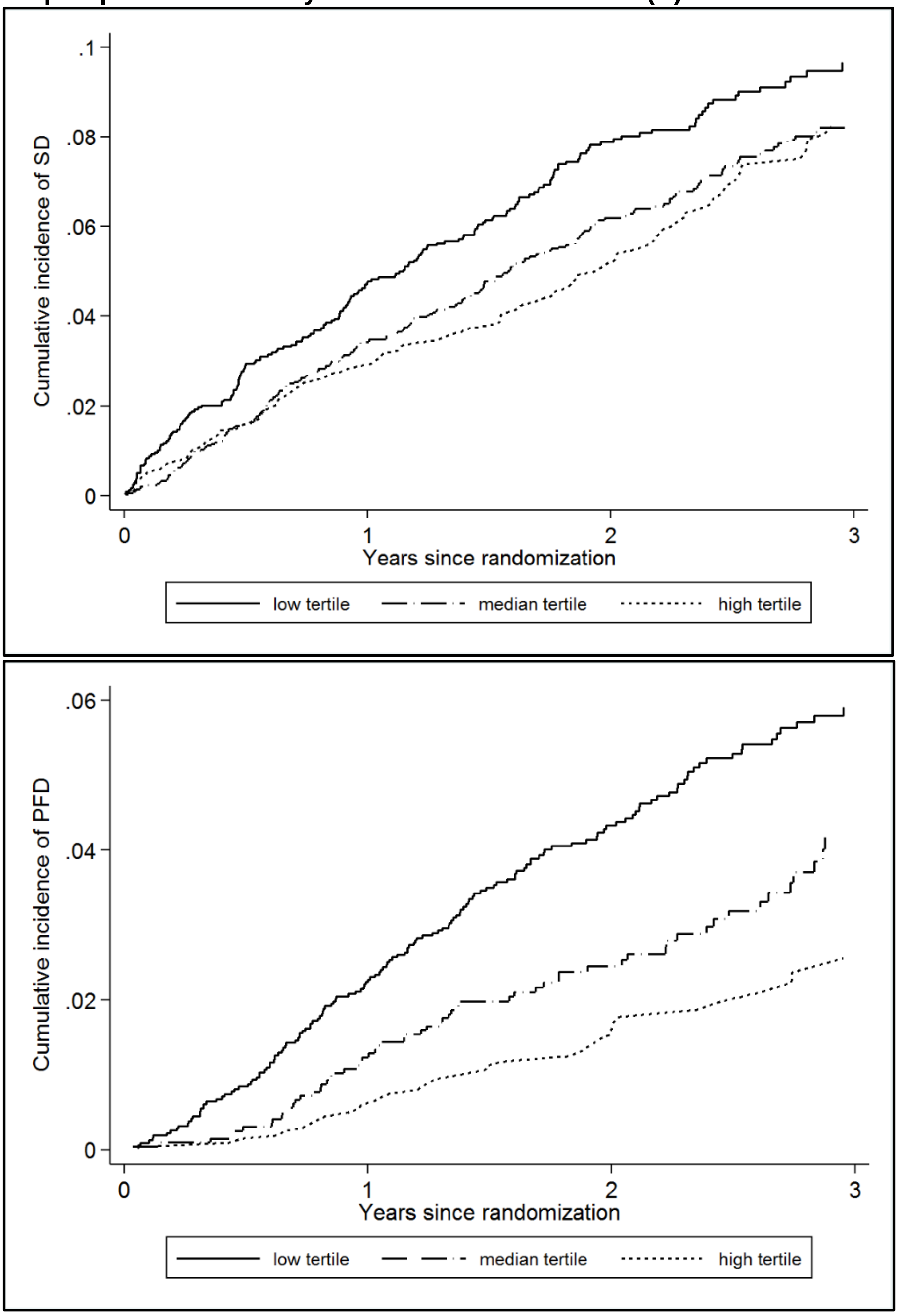
For the pump failure death model, the curves for the predicted cumulative incidence agreed well with the corresponding observed ones by quartiles of the risk score, suggesting good calibration (Figure 4-4). The model appeared less able to discriminate the lower two quartiles, but the model identified the highest and the second highest quartiles which exhibited over 10 times and 3 times the risk of the lowest quartile at 3 years respectively. The excellent discrimination was also quantified by C statistics with Harrell's C of 0.79 (95% CI 0.76-0.82) and C index of 0.82, 0.79 and 0.76 at 1-, 2- and 3-year, respectively.

Figure 4-4 Observed vs. predicted cumulative incidence curves for pump failure death by quartiles of the risk score based on the pump failure death model in PARADIGM-HF



There was some violation of proportional sub-distribution hazards assumption for systolic BP (p=0.01) in sudden death model and for albumin (p=0.02) in pump failure death model. When graphically displaying the cumulative incidences by tertiles of each predictor, the curves do not cross over time, suggesting that while statistically significant this was not relevant to the performance of the model (Figure 4-5).

Figure 4-5 Cumulative incidence curves for sudden death by tertiles of systolic BP (A) and for pump failure death by tertiles of serum albumin (B) in PARADIGM-HF



4.2.5 Predicting an individual's risk

The multivariable models presented in Table 4-2 and Table 4-3 can be used to calculate an individual's risk score for sudden death and for pump failure death respectively, by summing the products of the value and their corresponding coefficient of each predictor from each model. Based on the obtained risk scores, the corresponding cumulative incidence for each mode of death within 3 years can be estimated using the curves outlined in Figure 4-6 and Figure 4-7. These figures show the distribution of the risk scores for sudden death and pump failure death and its association with the corresponding predicted cumulative incidence by 3 years, respectively.

Figure 4-6 Distribution of the risk score for sudden death and its relation to the cumulative incidence of sudden death within 3 years in PARADIGM-HF

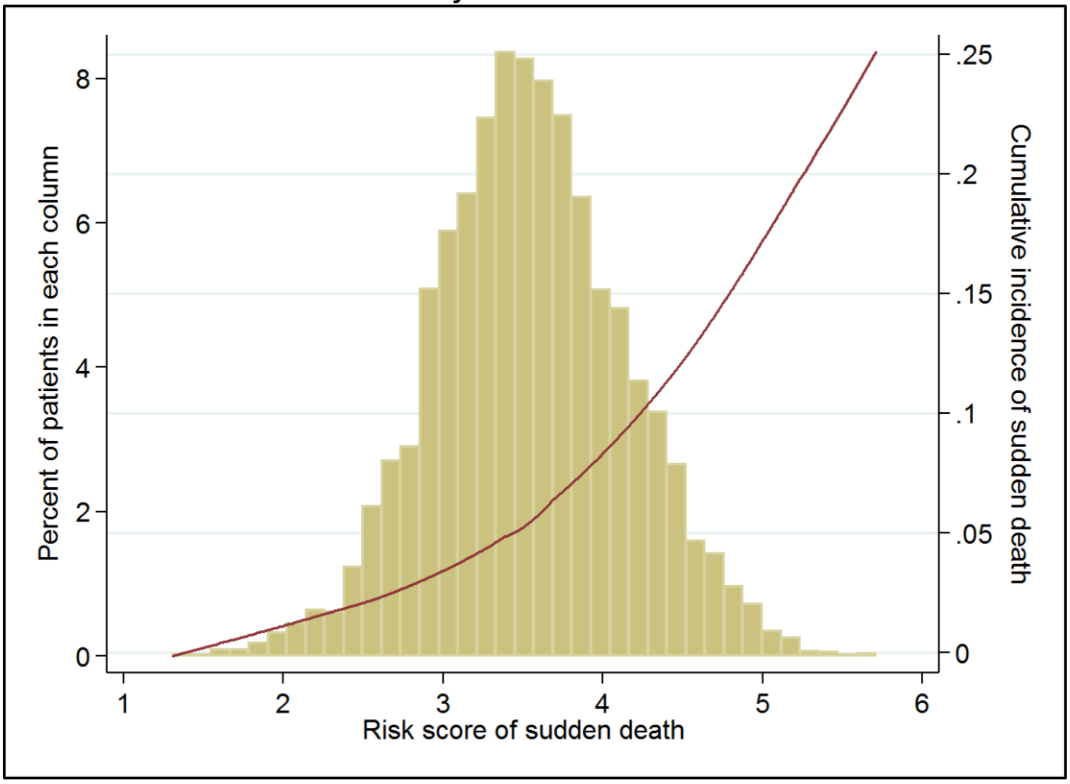
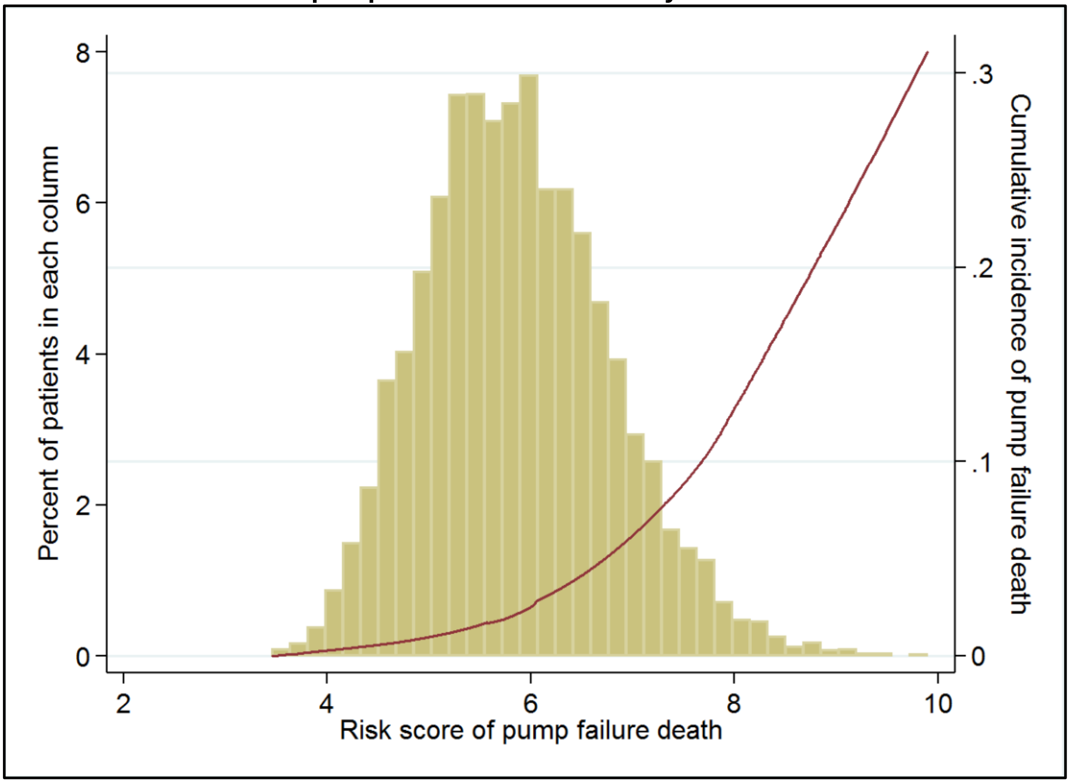


Figure 4-7 Distribution of the risk score for pump failure death and its relation to the cumulative incidence of pump failure death within 3 years in PARADIGM-HF



Given below is an example of using the derived models to calculate the individual's risk scores and cumulative incidences for sudden death and pump failure death respectively.

Consider a white male patient, who has been diagnosed with HF of an ischaemic cause for 2 years, with a LVEF of 30% and NYHA functional class II and a systolic blood pressure 125 mmHg, who has previous PCI intervention and no other comorbidities, with a QRS duration of 110 ms and no other abnormalities on ECG, and with serum levels of albumin 40 g/L, chloride 96 mmol/L, creatinine 1.2 mg/dl, and NT-proBNP 750 pg/ml.

Based on Table 4-2, the risk score for sudden death is 0.365 + 0.460 -0.444 + (125/5)*(-0.049)+ 110/5*0.069 +ln(750)*0.348 =2.978. Figure 4-6 indicates that this patient is at low risk for sudden death with a probability of 3.5% by 3 years.

Based on Table 4-3, the risk score for pump failure death is (130-125)/5*(0.098) +(40-30)*0.020 -0.357 +0.549+1.2*10*0.075 +(45-40)*(0.100) +(106-96)*(0.091) +ln(750)*0.477 = 5.958. Based on Figure 4-7, this patient is at low risk for pump failure death with a probability of 2.6% by 3 years.

4.3 Discussion

I developed prognostic models to predict the risks of sudden death and pump failure death separately, using a competing risk analysis approach, in patients with HF-REF enrolled in PARADIGM-HF, the largest and most contemporary positive trial in HF. Both derived models demonstrated good discrimination and calibration.

The clinical benefits of quantifying the risk of mode-specific death in individual patients with HF-REF have been discussed, and there already exist several predictive models for sudden death and pump failure death in HF as summarised in the Chapter 1 Introduction and literature review. However, they all have limitations and none has gained widespread acceptance in current clinical practice. Earlier models were developed before the widespread use of modern guideline recommended therapies including beta-blockers and MRAs.[89, 91, 94] More recently, separate risk models for mode-specific death were developed in patients with HF and unspecified left ventricular function in the MUSIC study.[79] Although the models exhibited excellent discrimination for both sudden death and pump failure death with C statistics of 0.77 and 0.80 respectively, they were based on few events (90 sudden deaths and 123 pump failure deaths) and narrow spectrum of candidate predictors. Predictive models for sudden death and pump failure death were also developed in the cohort randomised in CORONA, where only patients with an ischaemic aetiology were included;[78] additionally, routinely collected variables such as serum chloride and albumin were not examined. Investigators of the HF-ACTION trial only evaluated the incremental prognostic values for mode-specific death gained from new biomarkers, i.e. NT-proBNP, galectin-3 and soluble ST2, in addition to a clinical model for all-cause death in the same cohort developed previously.[142, 143] No predictive model or risk score was provided and over 46% of the patients in HF-ACTION had an ICD at baseline. Importantly, none of these models aforementioned has accounted for the prognostic influence of the competing risk of death from other causes.

The models I developed here have particular strengths. First, they were constructed in a large contemporary HF population with a great number of patients having received modern guideline-recommended medications. Besides, the cohort was geographically and ethnically diverse, indicating these models potentially can be generalisable to a broad range of modern patients with HF-REF. Secondly, a wide variety of candidate variables, which are currently assessed in clinical practice, were examined including demographics, clinical assessment, medical history, treatment, ECG, routine biochemical tests and NT-proBNP. Thirdly, death from other causes was counted as a competing risk instead of non-informative censoring, which can diminish its bias on the prognosis of each mode of death.[113]

Each model has included some variables that have been previously identified to estimate prognosis for sudden death, such as male sex,[78] NYHA class,[96, 144] ischaemic aetiology,[91, 96] systolic BP[96] and NT-proBNP,[78, 79] and for pump failure death such as LVEF,[78, 79] NYHA class,[78] systolic BP,[78] creatinine,[94] albumin[145] and NT-proBNP,[78, 79] respectively. Although LVEF is a well-known prognostic factor for sudden death and has been used as a key criterion for selecting ICD recipients,[3, 146] it was not independently associated with the risk of sudden death. This observation may reflect the relatively narrow range of LVEF in patients enrolled in PARADIGM-HF and, possibly, the inclusion of NT-proBNP, a related and more powerful predictor. This analysis also showed that Asian race was associated with a 50% higher risk of sudden death compared to other ethnicities (predominantly white). The reason for this is unknown, and apart from the difference in the clusters of baseline prognostic factors, it is possible due to an underlying genetic predisposition across races (e.g. the prevalence of atrial fibrillation is lower among Asians than Western caucasians).[147] LBBB has been reported as a risk factor of sudden death,[79, 96] but I found other ECG parameters, i.e. LVH and prolonged QRS duration (within a cut-off value of 120 milliseconds above which there was no further trend) were more powerful and thus included in the multivariable model. Findings from previous studies have shown that both LBBB and RBBB were associated with a higher risk of pump failure death (somewhat stronger with RBBB).[148] This was also the case in this analysis. The combination of LBBB and RBBB (namely BBB) increased the prediction power and thus were included in the multivariable model. Serum chloride was identified as a more powerful predictor than sodium for pump failure death, standing in contrast to the SHFM and the MUSIC risk score in which hyponatremia was a key component.[79, 101] Of note, serum chloride levels were not analysed in these models. When both being assessed simultaneously, the superiority of serum chloride over sodium in prognosis prediction was observed as reported previously.[149, 150] The mechanism of higher prognostic value of serum chloride than sodium in predicting pump failure death is uncertain, and one possible explanation is that decongestive therapies such as loop diuretics lead to electrolyte wasting, while may limit reabsorption of chloride more potently than sodium, in other words, serum chloride may serve as a better surrogate for decongestive therapy use and intensity. Besides, chloride also serves as one of the major charge-balancing anions in the serum along with bicarbonate and albumin, and hypochloraemia may be associated with the pathophysiological states of high serum bicarbonate, low potassium and albumin.[151, 152] Surprisingly, neither model included age or diabetes, two well-established risk factors in HF. This may reflect that advanced age and diabetes are not exclusively related to sudden death and pump failure death, but also associated with death from other CV or non-CV causes, thus their prognostic value failed to maintain when using competing risk approach.

There were some limitations in this analysis. First, these models were constructed in patients from a clinical trial rather than in a “real-world” cohort, in other words, patients tended to be healthier, have less co-morbidity and receive more and higher doses of evidence-based treatment. However, it is in patients similar to those in this analysis that ICDs are most clearly indicated. Secondly, in line with previous findings,[79, 84] the sudden death model was less discriminative than the pump failure death model. This suggests that there is a need for improvement in the prediction of sudden death. Some variables had been identified predictive of sudden death, but were not available in most patients in PARADIGM-HF such as echocardiographic parameters, 24-h Holter monitoring,[79] and other biomarkers, e.g. apolipoprotein A-1,[78] ST2 and galectin-3.[143] The addition of these predictors may further improve the model discrimination ability. Nevertheless, these parameters are not available in routine clinical practice; therefore, even if their addition improves model discrimination, it remains to be examined if the addition would improve the decision making to a degree that would justify the additional costs and complexity. Thirdly, in a given patient, the mode of death can be changed by implanting a defibrillator. Although patients with a defibrillator at baseline were excluded, I cannot rule out the potential confounding influence of ICDs implanted after randomisation, although there were few such cases (2.7%). Lastly, even if mode-specific death were appropriately classified and accurately estimated, a difference may still lie in between the predicted risk and the response to treatment.

4.4 Summary

The prognostic models developed can separately estimate the risks of sudden death and pump failure death with good discrimination and calibration in the derivation cohort of patients with HF-REF. In the next chapter, I will validate both models externally in ATMOSPHERE. If both models remain robust in validation, they may be useful in risk stratification for mode-specific death, which aid decision making in device therapies and help with the selection of patients for specific interventions in future trials.

Chapter 5 Validating models to predict sudden death and pump failure death in HF-REF

In this chapter I will separately examine the performance of the prognostic models for sudden death and pump failure death derived from PARADIGM-HF by external validation in ATMOSPHERE. I will also examine the model performance of the Seattle Heart Failure Model (SHFM)[84] and Seattle Proportional Risk Model (SPRM),[74] developed in a historic population in which beta-blockers and MRAs were not widely used, in the contemporary PARADIGM-HF and ATMOSPHERE cohorts. Validation will be performed by fitting a univariate regression analysis on the risk score which is the sum of the products of predictor coefficients from the derivation model and its corresponding predictor values in the validation cohort. For consistency, the same regression approach (i.e. Fine-Gray competing risk, Cox proportional hazards or logistic regression) in the model derivation process will be correspondingly used in the validation process.

5.1 Methods

5.1.1 The prognostic models to be validated

Validation was undertaken for the sudden death model derived from PARADIGM-HF which consisted of 10 prediction variables including sex, Asian race, systolic BP, ischaemic aetiology, NYHA class, cancer history, prior CABG or PCI, left ventricular hypertrophy on ECG, QRS duration and NT-proBNP; for the pump failure death derived from PARADIGM-HF including systolic BP, NYHA class, LVEF, ischaemic aetiology, HF duration (>1-5 years and >5 years), bundle branch block on ECG, serum albumin, creatinine, chloride and NT-proBNP; for SHFM which included age, sex, NYHA class, 100/LVEF, ischaemic aetiology, systolic BP, weight-adjusted diuretic dose, allopurinol, statin, sodium, 100/cholesterol, haemoglobin, percent lymphocytes, uric acid, ACEIs, beta-blockers, ARBs, K-sparing diuretics and devices; and for the SPRM which consisted of age, sex, LVEF, NYHA class, systolic BP, BMI, a history of diabetes, digoxin use, and serum creatinine and sodium (Appendix Table 6 and Appendix Table 7).[74, 84]

5.1.2 The validation cohorts

After excluding patients with an ICD or CRT-D at baseline, patients enrolled in ATMOSPHERE (N=5968) and patients in PARADIGM-HF (N=7156) comprised the two validation cohorts.[6, 27] The sudden death model and pump failure death model derived from PARADIGM-HF were validated in the ATMOSPHERE cohort. All predictive variables were available in most patients (missing observations <3%) except NT-proBNP (9.4% missing); accordingly, the sudden death and pump failure death models were validated in 5234 (87.7%) and 5356 (89.7%) patients in ATMOSPHERE respectively, using the complete case analysis approach (Appendix Table 6). The SHFM model was validated both in PARADIGM-HF and ATMOSPHERE, and all prediction variables were available in most patients (missing observations ≤5%) except weight-adjusted diuretic dose (21.1% missing in PARADIGM-HF and 22.8% missing in ATMOSPHERE), leaving 5320 (74.3%) patients in PARADIGM-HF and 4223 (74.1%) in ATMOSPHERE for validation. All prediction variables for the SPRM were available in most patients (missing observations <2%) in PARADIGM-HF and ATMOSPHERE, with corresponding 7007 (98.9%) and 5951 (99.7%) patients with complete data included in the validation (Appendix Table 7).

5.1.3 Statistical analysis

For each model to be validated, an individual's risk score was calculated as the sum of predictor coefficients from each derivation model multiplied by its corresponding predictor values in the validation cohort. The obtained risk score of each model was fitted into a regression model using the same approach as the model derivation procedure for consistency, and model performance was examined using the same approach as the derivation procedure for valid comparison.

To validate the models to predict sudden death and pump failure death derived from PARADIGM-HF, the individual's risk score for each mode of death was fitted into a univariate Fine-Gray regression analysis.[118] Model calibration was examined by comparing the predicted and observed cumulative incidences over time in each quartile of the risk score. Model discrimination was examined by visually evaluating the distribution of each set of cumulative incidence curves, as well as by calculating the Harrell's C statistic and C index at 1-, 2-, and 3-year accounting for right censoring.[127]

To validate the SHFM, the same risk score was fitted into a Cox proportional hazards model for sudden death, pump failure death and all-cause death, respectively.[84] The discrimination ability was examined using the Harrell's C statistic, and the calibration was examined by comparing the observed Kaplan-Meier survival estimator with the predicted event free probability (based on Cox model for consistency) in each quartile of the risk score.

To validate the SPRM, a logistic regression analysis was fitted for sudden death and the discrimination was examined using the ROC AUC at 1 year, an equivalent to Harrell's C.[74] In the same paper, a bi-modal system was proposed to provide individual estimates of the proportion of mortality due to sudden death for any given SHFM estimated mortality rate, which intended to identify the subset of patients who were at a disproportionately higher risk of sudden death but a lower absolute rate of dying from other causes, i.e. presumably benefit most from an ICD.[74] This bimodal system, which consisted of the SPRM for the proportion of sudden death relative to total mortality and the SHFM for the absolute 1-year all-cause mortality rate, was also validated in the PARADIGM-HF and ATMOSPHERE cohorts.

5.2 Results

5.2.1 Patient characteristics and events in ATMOSPHERE (versus PARADIGM-HF)

A total of 5968 patients with HF-REF in ATMOSPHERE comprised the validation cohort after excluding 1048 patients with an ICD or CRT-D at baseline. As can be seen from Table 4-1, the patient characteristics at baseline in ATMOSPHERE were similar, for the most part, to PARADIGM-HF: predominantly male, mean age of 63 years, similar pattern of NYHA class distribution (mainly class II), over half with an ischaemic cause of HF and a very high use rate of beta-blockers (>90%). However, some differences were also noted. Compared to PARADIGM-HF, ATMOSPHERE had a higher proportion of Asian patients (29% vs. 21%), but a smaller proportion of patients with a history of hypertension (62% vs. 71%) or diabetes (27% vs. 34%). Mean serum creatinine level was lower in ATMOSPHERE than in PARADIGM-HF (1.02 mg/dl vs. 1.10 mg/dl). Correspondingly, the proportion of patients with renal dysfunction (eGFR <60 mL/min/1.73m^2) was lower in ATMOSPHERE than in PARADIGM-HF (25% vs. 35%). Notably, substantially fewer patients were treated with a MRA in ATMOSPHERE than in PARADIGM-HF (35% vs. 55%), and the median plasma NT-proBNP level was much lower in ATMOSPHERE compared to PARADIGM-HF (1204 pg/ml vs. 1640 pg/ml).

In ATMOSPHERE, there were 1644 death events including 607 sudden deaths and 305 pump failure deaths over a median 37.7 months of follow-up. The annual rate of mode-specific death was identical to PARADIGM-HF, at 3.4 (95% CI 3.1-3.7) per 100 patient-years for sudden death and 1.7 (95% CI 1.5-1.9) per 100 patient-years for pump failure death.

5.2.2 Validation of the models derived from PARADIGM-HF

As shown in Figure 5-1, the distribution of the risk score for sudden death in ATMOSPHERE was almost identical to PARADIGM-HF, with a mean ± standard deviation of 3.4 ± 0.6 and 3.5 ± 0.6, respectively.

Figure 5-1 Distribution of the individual risk score for sudden death in ATMOSPHERE (A) and PARADIGM-HF (B)

Each figure shows the distribution of the risk score based on the box plot (the upper) and the histogram (the lower).

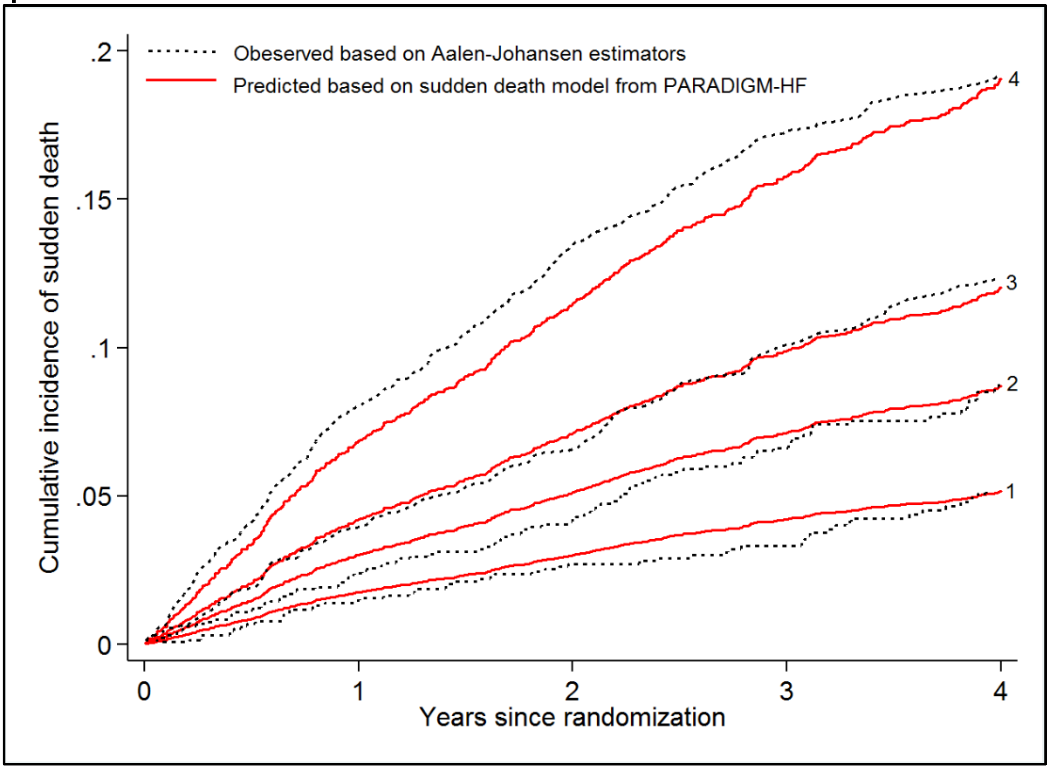
Likewise, the distribution of the risk score for pump failure death in ATMOSPHERE agreed well with that in PARADIGM-HF (5.6 ± 0.9 vs. 5.8 ± 0.9) (Figure 5-2).

Figure 5-2 Distribution of the individual risk score for pump failure death in ATMOSPHERE (A) and PARADIGM-HF (B)

Each figure shows the distribution of the risk score based on the box plot (the upper) and the histogram (the lower).

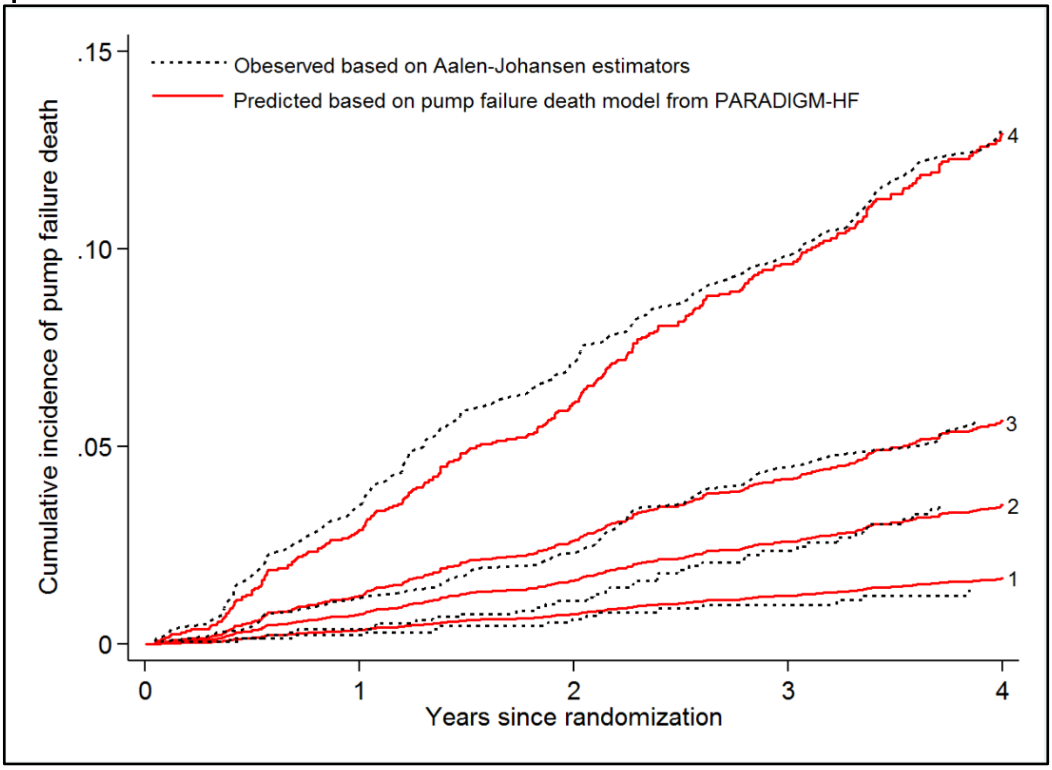
For the sudden death model, discrimination ability in ATMOSPHERE was equally good as in PARADIGM-HF with a Harrell's C of 0.68 (95% CI 0.65-0.70) and C-index of 0.70, 0.69 and 0.68 at 1 year, 2 years and 3 years, respectively. Figure 5-3 shows the predicted and observed cumulative incidence curves by quartiles of the risk score in ATMOSPHERE. Each set of the observed and predicted curves was well separated between the neighbouring quartiles, visually confirming the discrimination ability concluded above. Moreover, each pair of the observed and predicted cumulative incidences in each quartile was fairly close over time except in the highest one, where the validation model under-estimated the risk of sudden death consistently over time.

Figure 5-3 Observed vs. predicted cumulative incidence curves for sudden death by quartiles of the risk score in ATMOSPHERE



For the pump failure death model, there was a slight decrease in discrimination ability when validated in ATMOSPHERE, but it remained excellent with a Harrell's C of 0.75 (95% CI 0.72-0.78) and C-index of 0.78, 0.76 and 0.73 at 1-, 2- and 3-year respectively. As presented in Figure 5-4, both the observed and predicted cumulative incidence curves were widely separated by quartiles of the risk score in ATMOSPHERE. Besides, the figure shows that the model was well calibrated in validation: the predicted cumulative incidence curve agreed well with the observed one in each quartile of the risk score, apart from the highest quartile where an under-estimation for pump failure death was observed in the early period of follow-up.

Figure 5-4 Observed vs. predicted cumulative incidence curves for pump failure death by quartiles of the risk score in ATMOSPHERE



5.2.3 Validation of SHFM in ATMOSPHERE and PARADIGM-HF

As can be seen from Table 5-1, there were some similarities in baseline characteristics between the SHFM cohort and the contemporary PARADIGM-HF and ATMOSPHERE cohorts including the proportion of men, the distributions of age, serum sodium, haemoglobin, uric acid and lymphocyte percent. However, some notable differences were also observed: the SHFM cohort included patients with mixed left ventricular dysfunction, while the contemporary cohorts only included patients with HF-REF, although the average LVEF was similar; the proportion of patients with advanced NYHA class (III-IV) was higher in the SHFM cohort than the two contemporary cohorts, this was also the case for the proportion of patients with an ischaemic aetiology; the proportion of patients having received potassium sparing diuretics, statins or, in particular, beta-blockers were much higher, while the average cholesterol and creatinine levels were somewhat lower in the contemporary cohorts, compared to the SHFM cohort.

Table 5-1 Baseline characteristics in the SHFM cohort and in ATMOSPHERE and PARADIGM-HF

	SHFM (N=10538)	**ATMOSPHERE (N=5968)**	**PARADIGM-HF (N=7156)**
Age -years	65 (18-96)	63 (19-95)	64 (18-96)
Male sex (%)	76	76	77
NYHA class (%)			
II	49	67	70
III	37	29	25
IV	14	1	1
LVEF -%	28 (1-75)	29 (5-35)	30 (5-42)
Ischaemic aetiology (%)	62	54	59
Systolic BP -mmHg	125 (70-210)	124 (85-200)	122 (90-188)
ACEI (%)	80	67	89
ARB (%)	39	1	61
Beta-blocker (%)	31	91	92
K-Sparing diuretic (%)	13a	36	56
Allopurinol (%)	8b	7	9
Statin (%)	25	48	53
Serum sodium -mmol/L	140 (120-175)	140 (110-154)	141 (116-159)
Creatinine -mg/dl	1.3 (0.1-8.2)	1.02 (0.1-3.2)	1.10 (0.2-3.7)
Cholesterol -mg/dl	201 (33-600)	175 (54-451)c	178 (65-572)f
Uric acid -g/dl	7.3 (0.1-20)	7.4 (1.6-16.6)	6.8 (0.3-17.1)g
Haemoglobin -g/dl	13.8 (5.0-21.1)	13.7 (5.6-22.9)d	13.9 (6-20.1) h
Lymphocyte -%	25 (1-91)	27 (3-76)e	28 (3-87)i

The letter denotes the number of patients with data available: a=9775 (92.8%), b=5617 (53.3%), c=5759 (96.5%), d=5928 (99.3%), e=5920 (99.2%), f=6995 (97.8%), g=6996 (97.8%), h=6927 (96.8%), i=6800 (95.0%). Data were presented as mean (range) or proportion in consistent with the data shown in the SHFM cohort from the paper by Mozaffarian D *et al* 2007.[84]

During a mean 1.6 years of follow up, there were 2014 death events including 1014 sudden deaths with an annual rate of 6.1 per 100 patient-years and 684 pump failure deaths with an annual rate of 4.1 per 100 patient-years in the SHFM cohort, nearly double those in the validation cohorts.

The SHFM had good discrimination for sudden death with a 1-year C statistic of 0.68 (95% CI 0.65-0.70) in the original cohort. However, when using SHFM to predict sudden death in the contemporary cohorts, its discrimination ability decreased in ATMOSPHERE and particularly in PARADIGM-HF, with the corresponding C statistics of 0.62 (95% CI 0.58-0.66) and 0.55 (95% CI 0.51-0.59) at 1 year, respectively (Table 5-2).

Table 5-2 Discrimination ability of SHFM in the validation cohorts (versus the derivation cohort)

	Derivation cohort	ATMOSPHERE	PARADIGM-HF
Sudden death			
1 year	0.68 (0.65-0.70)	0.62 (0.58-0.66)	0.55 (0.51-0.59)
3 years	-	0.63 (0.60-0.66)	0.57 (0.54-0.60)
Overall	-	0.63 (0.60-0.65)	0.57 (0.54-0.60)
Pump failure death			
1 year	0.85 (0.83-0.87)	0.69 (0.62-0.76)	0.70 (0.65-0.75)
3 years	-	0.64 (0.59-0.68)	0.67 (0.63-0.70)
Overall	-	0.64 (0.60-0.67)	0.67 (0.63-0.70)
All-cause death			
1 year	0.73 (0.71-0.74)	0.64 (0.61-0.67)	0.60 (0.58-0.63)
3 years	-	0.62 (0.60-0.64)	0.60 (0.59-0.62)
Overall	-	0.62 (0.60-0.63)	0.60 (0.59-0.62)

Results are presented as values of Harrell's C (95% confidence interval).

The SHFM had excellent discrimination for pump failure death with a 1-year C statistic of 0.85 (95% CI 0.83-0.87) in the original cohort. When it was used to predict pump failure death in ATMOSPHERE, its discriminative ability declined substantially by 0.16 with a 1-year C statistic of 0.69 (95% CI 0.62-0.76). A similar size of decrease in discrimination was also observed when validated in PARADIGM-HF (Table 5-2).

Given that the SHFM was originally designed to predict all-cause mortality, I also examined its discrimination for all-cause death in ATMOSPHERE and PARADIGM-HF. Compared to its derivation cohort (C statistic 0.73, 95% CI 0.71-0.74), the discrimination ability at 1 year was much lower either in ATMOSPHERE (0.64, 95% CI 0.61-0.67) or in PARADIGM-HF (0.60, 95% CI 0.58-0.63) (Table 5-2).

Surprisingly, the calibration ability was good when predicting sudden death, pump failure death or all-cause death either in ATMOSPHERE (Figure 5-5) or in PARADIGM-HF (Figure 5-6).

Figure 5-5 Observed vs. predicted probabilities for sudden death, pump failure death and all-cause death by quartiles of the SHFM risk score in ATMOSPHERE

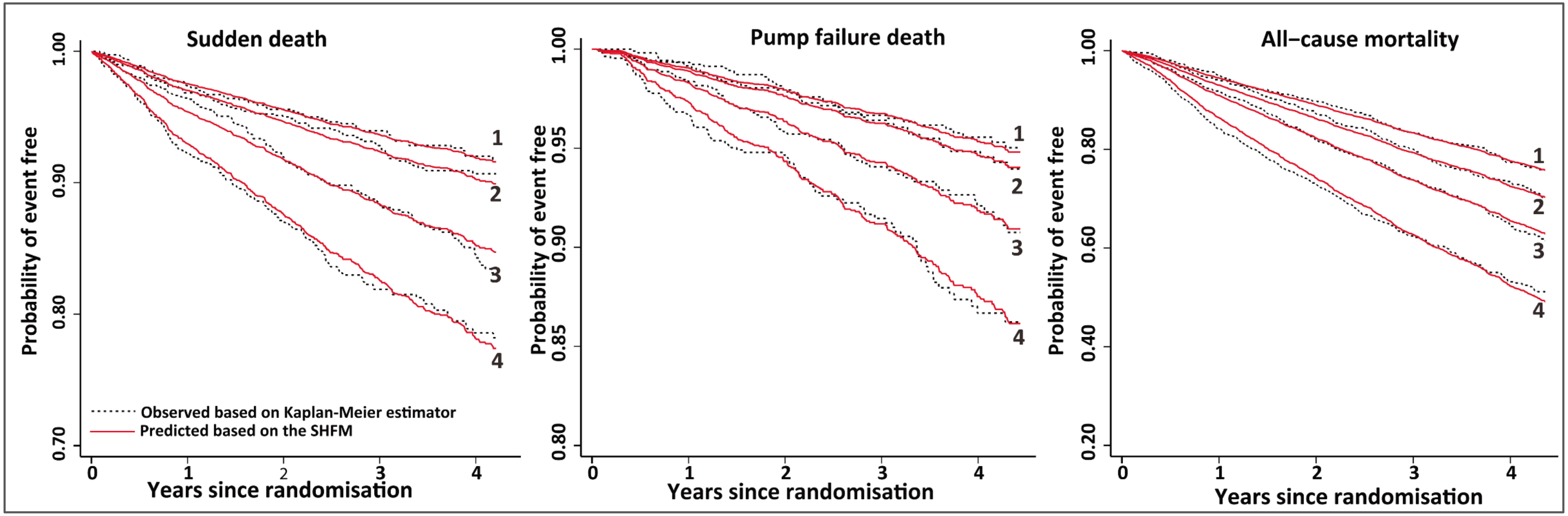
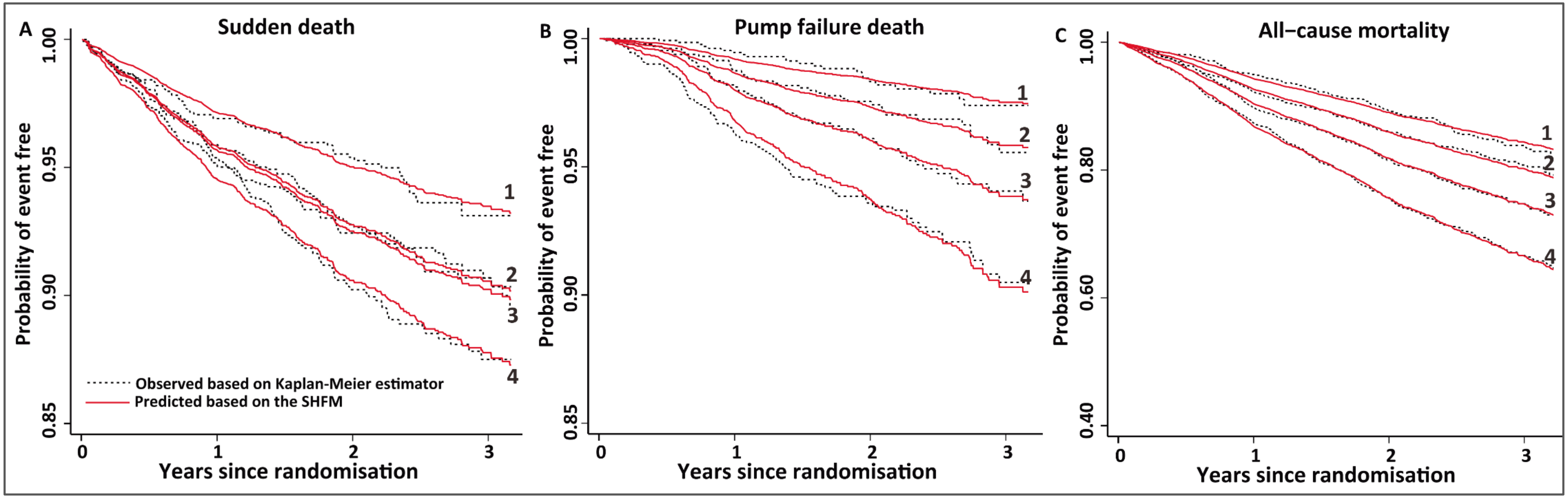


Figure 5-6 Observed vs. predicted probabilities for sudden death, pump failure death and all-cause death by quartiles of the SHFM risk score in PARADIGM-HF



5.2.4 Validation of SPRM in ATMOSPHERE and PARADIGM-HF

There were 9885 patients with HF in the cohort for the derivation of SPRM. Table 5-3 shows some baseline characteristics in the SPRM cohort and in the validation cohorts of ATMOSPHERE and PARADIGM-HF. The mean age, proportion of men, and proportions of patients with an ischaemic aetiology and a history of diabetes were largely similar across these cohorts, but some differences were observed. Compared to the two validation cohorts, the SPRM cohort tended to have worse cardiac function, i.e. lower mean LVEF and a higher proportion of patients with NYHA class III-IV symptoms, and worse renal function, but had a much lower average level of NT-proBNP. The rate of use of statins, and, in particular, beta-blockers was much lower while digoxin use was much higher in the SPRM cohort than in the validation cohorts.

Table 5-3 Baseline characteristics in the SPRM cohort and in ATMOSPHERE and PARADIGM-HF

	SPRM (N=9885)	ATMOSPHERE (N=5968)	PARADIGM-HF (N=7156)
Age -years	64±15	63±12	64±12
Male sex -no. (%)	7806 (79.0)	4565 (76.5)	5492 (76.7)
BMI	26.5±5.3	27.2±5.3	28.0±5.5
LVEF -%	27±11	29±6	30±6
Systolic BP -mmHg	121±25	124±18	122±15
NYHA class -no. (%)			
II	5071 (51.3)	4030 (67.5)	4988 (69.8)
III	3436 (34.8)	1718 (28.8)	1756 (24.6)
IV	1378 (13.9)	56 (0.9)	54 (0.8)
Ischaemic aetiology -no. (%)	5512 (55.8)	3232 (54.2)	4204 (58.7)
Diabetes -no. (%)	2591 (26.2)	1629 (27.3)	2406 (33.6)
Digoxin -no. (%)	6627 (67.0)	1940 (32.5)	2232 (31.2)
Statin -no. (%)	2464 (24.9)	2893 (48.5)	3796 (53.0)
ACEI or ARB -no. (%)	9533 (96.4)	4019 (67.3)	7156 (100)
Beta-blocker -no. (%)	4616 (46.7)	5423 (90.9)	6610 (92.4)
Diuretic dose -mg/kg	0.50±0.83	0.62±0.57b	0.66±0.69d
Serum sodium -mmol/L	140±3	140±3	142±3e
Creatinine -mg/dl	1.21±0.3	1.02±0.27	1.10±0.29
NT-proBNP -pg/ml	895±1616a	1934±2519c	2964±4121

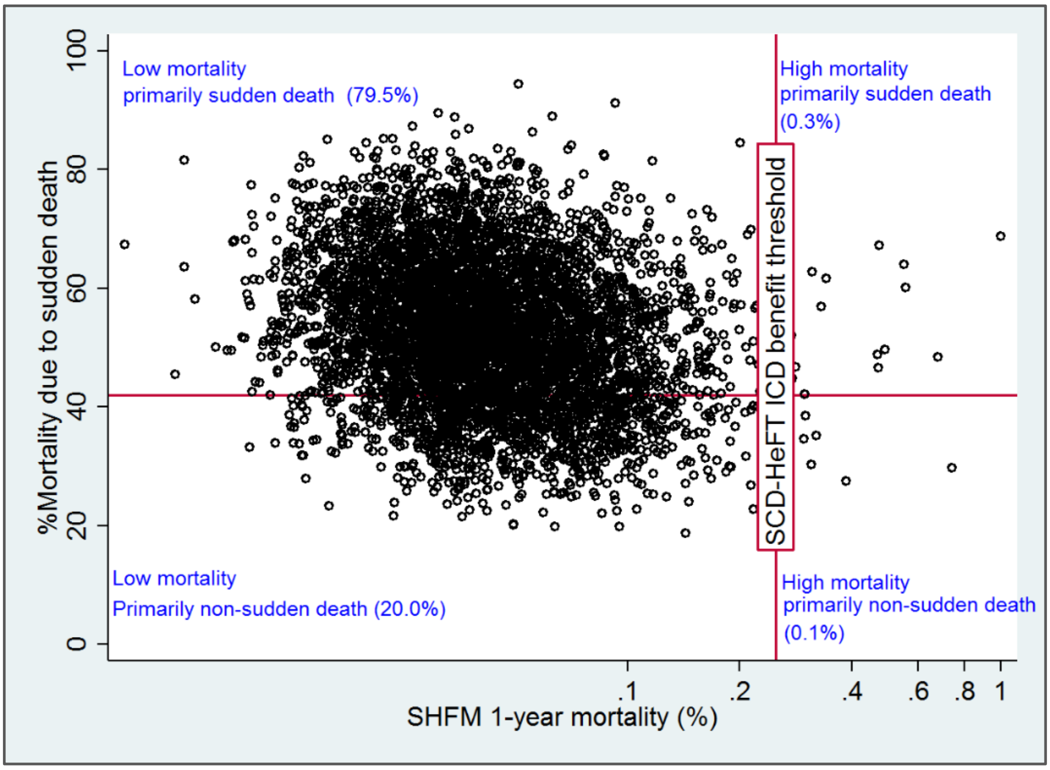
The letters denote the number of patients with data available: a=4028 (40.7%), b=4606 (77.2%), c=5408 (90.6%), d=5652 (79%), e=7026 (98.2%).

Data were presented as mean ± standard deviation or number (percent) in consistent with the data shown in the SPRM cohort from the paper by Shadman R *et al* 2015.[74]

There were 2552 death events during a mean 28 months of follow up in the SPRM derivation cohort, including 1225 sudden deaths with an annual rate of 4.2 per 100 patient-years.

The SPRM was designed to predict the proportion of sudden death relative to total mortality other than the absolute risk. Overall, the model over-estimated the proportion of deaths that were sudden in ATMOSPHERE (predicted vs. observed proportions were 53.6% vs. 36.9%) as well as in PARADIGM-HF (52.5% vs. 39.1%). A decrease in discrimination ability was observed when applying it to ATMOSPHERE and PARADIGM-HF (1-year ROC AUC 0.54 and 0.57, respectively), compared to 0.64 in the derivation cohort of SPRM. As can be seen from Figure 5-7, using a threshold of 42% of proportion of mortality due to sudden death and 25% of 1-year mortality rate (used by the SPRM investigators to identify patients most likely to benefit from an ICD), this bimodal system allocated the majority patients to the upper left quadrant, low risk of mortality which was primarily attributable to sudden death, either in ATMOSPHERE (81.5%) or in PARADIGM-HF (79.5%). In other words, this model predicted that most patients would have an indication for ICD.

Figure 5-7. Validation of Seattle Proportional Risk model in ATMOSPHERE (A) and in PARADIGM-HF (B).



An annual all-cause mortality rate of below 25% and a predicted proportion of mortality due to sudden death of over 42% were used to identify the subset of patients in the left upper quadrant who are assumed to benefit most from ICD (according to the Seattle Proportional Risk model). Data were available for calculating the risk scores of SHFM and SPRM in 4417 (74.0%) patients in ATMOSPHERE (Panel A) and 5320 (74.3%) patients in PARADIGM-HF (Panel B).

5.3 Discussion

I externally validated the prognostic models for sudden death and pump failure death derived from PARADIGM-HF in ATMOSPHERE. Generally, the discrimination and calibration ability of both models developed in PARADIGM-HF were good and robust in ATMOSPHERE. I also examined the model performance of the SHFM and SPRM in the contemporary PARADIGM-HF and ATMOSPHERE cohorts. Despite reasonable calibration, the SHFM had a large decrease in the discrimination ability to predict sudden death, pump failure death and even all-cause death in both modern cohorts. The SPRM showed poor discrimination and calibration, and assigned most patients into the category who had a low mortality but primarily due to sudden death, i.e. meriting ICD implantation, in both contemporary cohorts.

5.3.1 What is external validation?

Validation refers to examining the performance of a predefined model (identical predictors and their coefficients) in an independent cohort, other than repeating the whole modelling process in new data, or re-estimating the effects of predictors from the original model in new data. The latter two approaches would lead to new models, and therefore, would themselves need external validation.[72] It is noteworthy that external validation is not exclusive to newly developed models, but also can be carried out in existing models developed in a historic population since which treatment or prognosis has largely changed.[153]

Discrimination and calibration are two key aspects of evaluating and thus validating model performance. Discrimination is the ability to separate patients with differing prognosis. Patients predicted to be at greater risk should have higher event rates than those estimated to be at lower risk. Calibration examines the prediction accuracy, i.e. the agreement between the predicted and observed risks. Sometimes a model may systematically over-/under-predict the risk (poor calibration), but it may separate well between patients with high and low risks (good discrimination). The model may be still useful in risk stratification if the incompetence in calibration can be improved by recalibration strategies.[72, 154] On the other hand, a model with poor discrimination assigns patients to a high or low risk similar to a random guess: a low-risk patient may be predicted at high risk, leading to unnecessary treatment, and a high-risk patient may be predicted at low risk, which would result in missed treatment. Moreover, the poor discrimination cannot be altered with post-modelling techniques. Therefore, a model with poor discrimination would have little clinical value in risk stratification, regardless of its calibration ability.[72]

5.3.2 Why is external validation necessary?

The performance of a prognostic model is generally better in the derivation cohort than in a new cohort. It is possible that a promising prediction model performs poorly outside the derivation cohort. Therefore, it is of fundamental importance to verify the robustness and generalisability of a newly-developed model in one or more independent cohorts before it can be considered for use to inform prognosis for a wide range of patients in clinical practice.[155] In a way, external validation can be regarded as a pilot trial of applying a model to target populations, and good performance in validation may serve as a reassurance for the consideration of model use. On the other hand, a poor performance could suggest further means of improvement for a derived model. If a model appears poorly calibrated (under-/over-prediction) in the validation cohort, the model should be recalibrated before it can be considered for use in similar populations; otherwise, an under-prediction would lead to appropriate patients missing out on certain beneficial treatments, while an over-prediction would result in inappropriate patients receiving certain treatments which are unnecessary. If a model has poor discrimination in validation, further improvement in the original model should be made, such as adding potential interaction between predictors, including more advanced forms of association between continuous predictors and outcomes, and including more powerful predictors. If not, patients would be wrongly assigned to a high or low risk, and a poorly discriminatory model would have little clinical value in risk stratification.

Due to a lack of cohorts besides those used for model derivation, internal validation has been commonly used as an alternative.[153] However, internal validation is no substitute for external validation. Because this approach is neither statistically efficient since cross-validation and split-sampling techniques typically make a sacrifice of the cohort size for model derivation and use smaller cohorts (and numbers of events) for model validation, nor methodologically sound given that there is no material difference between derivation and validation cohorts other than randomly by chance, thus no guarantee for generalisability.[155]

5.3.3 Validation of models for mode-specific death derived from PARADIGM-HF

When validating in ATMOSPHERE, the discrimination ability maintained for the sudden death model but slightly decreased for the pump failure death model derived from PARADIGM-HF. Nevertheless, in absolute terms, the discrimination ability was moderate for the sudden death model with C-statistic slightly below 0.7, but excellent for pump failure death model with C-statistic around 0.75. Although both models were well-calibrated in the validation cohort, there was a slight under-prediction in the highest quartile. If the models were used to guide decision making in device therapy, it may lead to appropriate patients missing out on device therapy, since patients with a high risk may be predicted to have a lower risk below the threshold for the indication of device therapy. Although a decrease in performance in validation is conceivable, the reason for the decrease is uncertain. However, it is unlikely caused by the difference in the baseline risk between the derivation and validation cohorts, since both cohorts were from clinical trial setting with similar eligibility criteria and reflected similar treatment strategies within nearly overlapped study periods, and consequently the corresponding incidences for mode-specific death were almost identical. One possible explanation is the variation in the distribution of individual predictor values between cohorts. For example, compared to PARADIGM-HF, NT-proBNP, the most powerful predictor in both models, was systematically lower in ATMOSHERE, and this was also the case for serum creatinine, a predictor for pump failure death; while the prevalence of Asian race, a predictor for sudden death, was higher in ATMOSPHERE. This variation may result in a mixed contribution of individual predictors to the overall risk score, which may cumulatively lead to a difference in the model performance, even if the underlying predictor effects were consistent. Another possibility is the inconsistency in the underlying predictor effects between the derivation and validation cohorts, since I cannot rule out there may exist unexamined interactions between covariates or more complicated relationships between covariates and the outcome. Nevertheless, the sudden death and pump failure death models remained robust when externally validated in the similar population, and these models can be considered for use in risk stratification and aiding decision making in device therapy.

5.3.4 Validation of SHFM in the modern cohorts

The SHFM was reported to have good discrimination for sudden death and particularly for pump failure death comparable to the models I developed in PARADIGM-HF. When applied to the contemporary PARADIGM-HF and ATMOSPHERE cohorts, the SHFM was well-calibrated, but had a substantial decrease in discrimination in either cohort. The reason for the decrease in discrimination is unknown, and one possible explanation is that the baseline risks for mode-specific death in the contemporary cohorts were in the lower spectrums of the risks in the SHFM derivation cohort, i.e. narrower but within the spectrums, leading to less separated prognosis but within the prediction range for the contemporary cohorts. As can be seen where the annual rates for sudden death and pump failure death were 3.4 and 1.7 per 100 patient-years respectively in the modern validation cohorts, and the corresponding rates were much higher as 6.1 and 4.1 per 100 patient-years respectively in the SHFM derivation cohort. The decrease in discrimination and maintenance in calibration were also observed in the original SHFM for all-cause death, in which good agreement between the observed and predicted mortality was observed in the derivation as well as 5 validation cohorts, but the 1-year ROC AUC ranged from 0.68 to 0.81 across these cohorts with different case-mix variations.[101] In the derivation cohort, the SHFM was significantly less discriminatory for both sudden death and pump failure death in patients who had received beta-blockers than those did not.[84] Accordingly, another explanation for the decrease in discrimination can be due to a universal use of beta-blockers (over 90%) in both contemporary validation cohorts.[6, 27] Consequently, the SHFM may have little clinical significance in risk stratification for mode-specific death in patients receiving contemporary evidence-based therapies.

5.3.5 Validation of SPRM in the modern cohorts

The SPRM was developed to predict the proportion of sudden death relative to total mortality rather than the absolute risk.[74] With a combination of the predicted risk of annual total mortality derived from SHFM, the investigators attempted to identify a subset of patients who would benefit most from ICD: a high risk of sudden death but a low risk of dying from other causes. Applying this bi-modal system to PARADIGM-HF and ATMOSPHERE, it yielded poor discrimination and over-estimated the proportional risk of sudden death. Consequently, the bi-model system allocated majority patients in the category who had low mortality rate but disproportionally high risk of sudden death, in other words, the majority of patients in the modern cohorts were predicted to have indications for an ICD. The reason for the poor performance of the SPRM in the modern cohorts is uncertain, but this may reflect the heterogeneity in proportion of sudden death as to overall mortality between the validation cohorts (<40%) and the derivation cohort (48%), suggesting an underlying difference in the baseline risk across cohorts. Thus, the intercept from the original SPRM may not be transportable, and a direct application may lead to the predicted proportional risk being systematically higher in the validation cohorts. In keeping with this observation, a study showed that the SPRM overestimated the proportional risk of sudden death in patients with an ICD (predicted vs. actual proportion of sudden death: 56% vs. 31%) in the HF-ACTION cohort, in which the baseline risk for sudden death was presumably lower compared to the derivation cohort.[156]

Very recently, two studies have shown that the SPRM was able to classify different magnitudes of the survival benefit from ICD in the HF-ACTION cohort and in an observational cohort including patients from an ICD registry and HF registries/clinical trials, but neither was a randomised clinical trial for primary prevention ICDs and both shared great differences in the baseline characteristics between the ICD and non-ICD subgroups.[156, 157] Moreover, the SPRM was used to estimate the relative risk of sudden death as a proportion of total mortality, other than the absolute risk (i.e. cumulative incidence) of sudden death. The proportional risk may be useful at a population level for policy making, but not at an individual level for decision making.

5.4 Summary

The sudden death and pump failure death models developed in PARADIGM-HF remained robust in ATMOSPHERE. These models can be considered for use in risk stratification for mode-specific death and aiding decision making in device therapy in similar populations. Despite good calibration, the SHFM had a substantial decrease in discrimination to predict sudden death, pump failure death and even all-cause death in the modern cohorts. Therefore, the SHFM may have limited clinical value in risk stratification for sudden death and pump failure death in contemporary patients if not modified and re-validated. The SPRM showed poor discrimination and over-estimated the actual proportional risk of sudden death, and consequently, together with the SHFM, the bimodal system assigned most patients into the category of meriting an ICD in both contemporary cohorts.

Chapter 6 Rates of sudden death and pump failure death over time in HF-PEF

In this section I will describe the rates of sudden death and pump failure death in patients with HF-PEF enrolled in three clinical trials over the time period between 1999 and 2013. I will examine the rates of sudden death and pump failure death in each trial and the cumulative incidences of each mode of death at different time intervals during follow-up, and the cumulative incidences for each mode of death according to the duration between HF diagnosis and randomisation. The analyses will be undertaken using the conventional survival analysis to calculate the annual rates for mode-specific death, and using the cumulative incidence function method to calculate their cumulative incidences during follow-up counting death from other causes as a competing risk. The relationship between the rate of mode-specific death and the calendar year will be examined using the multivariable linear regression analysis. The risk of mode-specific death with the calendar year, by trial arm and by HF duration will be examined using the cause-specific Cox regression analysis.

6.1 Methods

6.1.1 Study population

I attempted to obtain all major clinical trials in patients with chronic HF-PEF conducted over the last two decades. The majority of clinical trials in HF-PEF enrolled cohorts with small sample sizes (ranging from 40 to 426 participants) and examined the structural and functional outcomes including exercise capacity, 6-min walking distance, quality of life, changes in echocardiographic parameters and plasma natriuretic peptides levels over a short period of follow-up (ranging from 1 week to 12 months),[37, 158-163] and the key characteristics and results of these trials have been summarised in a recent systematic review.[164] Among the 7 trials identified examining mortality outcomes, 4 trials were excluded, i.e. the Digitalis Investigation Group ancillary trial (DIG- ancillary) [N=988] given that the outcomes were not adjudicated by an endpoint committee and only pump failure death events were reported,[13] the secondary analysis of the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure (SENIORS) because of small cohort size (N=752) with only sudden death (N=27) having been reported,[165] and the Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial and the Japanese Diastolic Heart Failure Study (J-CHF) because of small cohort size (N=245 and N=850 respectively) with neither mode of death having been reported. Their design and main characteristics are summarised in Appendix Table 8.[10, 166] Finally, 3 RCTs were included in the analysis, namely CHARM-Preserved, I-PRESERVE and TOPCAT.[9, 11, 12] The design and results of the included trials have been published previously and their main characteristics are summarised in Table 2-2.

6.1.2 Outcomes of interest

The outcomes of interest were the proportions and the rates of sudden death and pump failure death in each trial, and the cumulative incidences of each mode of death at different time intervals since randomisation (30 days, 60 days, 90 days, 180 days, 1 year, 2 years and 3 years), and the risks of each mode of death according to the length of time between diagnosis of HF and randomisation (≤1 year, >1-5 years and >5 years). In each trial, all death events were blindly adjudicated by an independent endpoint committee using pre-specified criteria, which were similar across the trials (Table 2-3).

6.1.3 Adjustment for potential confounding variables

I examined the confounding effects of conventional covariates on the risks of sudden death and pump failure death including age, sex, LVEF, NYHA class, systolic BP, HF hospitalisation within the past 6 months, and a history of myocardial infarction, hypertension or diabetes, which were available in all trials. The eGFR measurements were recorded in all trials, except CHARM-Preserved in which eGFR was only available in North American patients. Plasma NT-proBNP was available only in the subset of patients in I-PRESERVE (84% available) and TOPCAT (18% available). The additional prognostic effects of eGFR and NT-proBNP on each mode of death was examined in patients with complete data and after imputation of missing values.

6.1.4 Statistical analyses

Baseline characteristics of all patients in each trial were summarised as means with standard deviations for continuous variables and percentages for categorical variables. Baseline characteristics of patients with sudden death and without sudden death (i.e. those alive and those dying non-suddenly) in each trial were also summarised and compared using Student's t-test for continuous variables and chi square test for categorical variables. Likewise, baseline characteristics in patients with and without pump failure death in each trial were summarised and compared. NT-proBNP was not normally distributed and thus was presented as median and interquartile range and analysed using the Mann-Whitney U test.

The annual rates of sudden death and pump failure death in each trial and in each arm of each trial were calculated using conventional survival analysis as per 100 patient-years. The cumulative incidences for each mode of death at different time points of 30 days, 60 days, 90 days, 180 days, 1 year, 2 years and 3 years from randomisation were calculated and plotted using the cumulative incidence function method counting death from other causes as a competing risk.[118, 128] The hazard ratio for each mode of death in each trial arm was calculated using cause-specific Cox proportional hazards model using the placebo arm of CHARM-Preserved as the reference. In a Cox model, the association between calendar year and the risk for each mode of death was then examined with adjustment for randomisation arm and with trial as a random effect. These models were then further adjusted for the confounding variables listed above. For models further adjusting for eGFR and NT-proBNP, the complete case analysis was performed as the primary analysis, together with a sensitivity analysis based on missing-indicator method using single imputation for a missing value in those trials where data were not completely missing, i.e. I-PRESERVE and TOPCAT, with a further covariate indicating missing data.[108] The association between calendar year and the annual rate of each mode of death was examined in a multiple linear regression model with the randomisation year and randomisation arm as covariates, weighted by the inverse-variance of the annual rate with trial as a random effect. To account for the inconsistency in the threshold of LVEF used in CHARM-Preserved (>40%) and I-PRESERVE and TOPCAT (both ≥45%), sensitivity analyses were performed after excluding patients with a LVEF below 45% in CHARM-Preserved. To examine the changes in risks of total mortality and death due to non-CV causes across these trials, annual rates for both outcomes in each trial and in each arm of each trial were also calculated, and their associations with the calendar year were examined using the multiple linear regression analysis as described above.

The length of time between HF diagnosis and randomisation was collected in CHARM-Preserved and I-PRESERVE, but not in TOPCAT. To assess the effect of HF duration on the risk of each mode of death, patients with data available were merged and further divided into 3 groups (based on the collected data): diagnosis within 1 year, >1-5 years and >5 years. According to these duration groups, cumulative incidence curves for each mode of death were produced and were compared using the Gray's test,[128] and HRs for each mode of death were calculated using patients within 1-year diagnosis of HF as reference, adjusting for the confounding variables listed above and counting for within-trial clustering.

6.2 Results

There were only 3 large clinical trials in patients with HF-PEF, and all were included in this analysis, which consisted of 10,517 patients after excluding patients having an ICD or CRT-D at baseline (N=79). Of these patients, 1876 (17.8% of total population) died during follow-up, including 474 (4.5%) having a sudden death, 288 (2.7%) dying from pump failure, and 598 (5.7%) dying from non-CV causes.

There were 444 (14.8%) patients with a LVEF below 45% in CHARM-Preserved. The eGFR levels were measured in 8500 (81%) patients and both eGFR and plasma NT-proBNP were available in 4063 (39%) patients.

6.2.1 Baseline characteristics of study population

The key characteristics of patients at baseline in each trial are shown in Table 6-1. The mean age was higher in I-PRESERVE and TOPCAT (72 and 69 years respectively) than in CHARM-Preserved (67 years), because I-PRESERVE and

TOPCAT set minimum age thresholds for inclusion (60 and 50 years respectively). Likewise, both set a higher LVEF threshold for inclusion (≥45%) compared to CHARM-Preserved (>40%), accordingly, the average LVEF was higher in I-PRESERVE and TOPCAT (59% and 57% respectively) than in CHARM-Preserved (54%). There was a female predominance in TOPCAT (52%) and particularly in I-PRESERVE (60%), but not in CHARM-Preserved (40%). All trials enrolled patients mainly with NYHA class II and III symptoms with a preponderance of class III in I-PRESERVE and class II in CHARM-Preserved and TOPCAT. The patients were typically obese with a higher level of mean BMI in TOPCAT compared to I-PRESERVE and CHARM-Preserved (32.1 kg/m^2 versus 29.6 kg/m^2 and 29.2 kg/m^2). Comorbidities were common: about 30-40% of patients had diabetes, atrial fibrillation, or renal dysfunction (defined as an eGFR <60 ml/min/1.73m^2), the prevalence of which were all higher in TOPCAT than in CHARM-Preserved and I-PRESERVE. The majority had coronary artery disease and hypertension; the proportion of patients with coronary artery disease was much higher in CHARM-Preserved than in I-PRESERVE and TOPCAT (72% versus 51% and 59%), but a substantially higher prevalence of hypertension was observed in TOPCAT and I-PRESERVE compared to CHARM-Preserved (91% and 89% versus 64%). However, the mean systolic blood pressure was 7 mmHg lower in TOPCAT than the other two trials (129 mmHg versus 136 mmHg and 136 mmHg). There was a higher rate of treatment with an ACEI/ARB, a beta-blocker or MRA in TOPCAT. NT-proBNP measurements were available in a subset of patients in TOPCAT (18%) and I-PRESERVE (84%), with substantially higher median levels in TOPCAT than in I-PRESERVE (843 pg/ml versus 339 pg/ml).

Table 6-1 Baseline characteristics of patients in the included trials in HF-PEF

	CHARM-Preserved (N=3000)	**I-PRESERVE (N=4116)**	**TOPCAT (N=3401)**
Age -years	66.7±11.1	71.6±6.9	68.5±9.6
Female sex (%)	1204 (40.1)	2485 (60.4)	1760 (51.8)
Race (%)			
White	2745 (91.5)	3847 (93.5)	3028 (89.0)
Black	125 (4.2)	82 (2.0)	294 (8.6)
Asian	71 (2.4)	35 (0.9)	18 (0.5)
Other	59 (2.0)	152 (3.7)	61 (1.8)
Blood pressure -mmHg			
Systolic	136.2±18.4	136.4±15.0	129.3±13.9
Diastolic	77.8±10.7	78.8±9.1	75.9±10.6
Heart rate -beats/min	71.3±12.4	71.4±10.5	69.0±10.6
Body mass index	29.2±5.8	29.6±5.3	32.1±7.1
LVEF -%	54.1±9.4	59.4±9.2	57.1±7.4

NYHA class (%)			
I-II	1825 (60.8)	869 (21.1)	2282 (67.2)
III-IV	1175 (39.2)	3246 (78.9)	1116 (32.8)
Aetiology (%)			
Ischaemic	1692 (56.4)	1033 (25.1)	-
Hypertensive	682 (22.7)	2616 (63.6)	-
Others	626 (20.9)	467 (11.3)	-
HF duration (%)			
≤1 year	1272 (42.4)	1991 (48.4)	-
>1 and ≤ 5 years	1114 (37.1)	1504 (36.6)	-
>5 years	613 (20.4)	617 (15.0)	-
Medical history (%)			
Current smoking	406 (13.5)	-	357 (10.5)
HF hospitalisation within the previous 6 months	1063 (35.4)	1809 (44.0)	1787 (52.5)
Myocardial infarction	1325 (44.2)	963 (23.4)	873 (25.7)
Angina	1807 (60.2)	1773 (43.1)	1598 (47.0)
CABG or PCI	994 (33.1)	542 (13.2)	791 (23.3)
Coronary artery disease	2151 (71.7)	2087 (50.7)	1993 (58.6)
Hypertension	1932 (64.4)	3645 (88.6)	3109 (91.5)
Diabetes	851 (28.4)	1128 (27.4)	1096 (32.3)
Atrial fibrillation	874 (29.1)	1199 (29.1)	1192 (35.1)
Stroke	267 (8.9)	394 (9.6)	260 (7.7)
Pacemaker	214 (7.1)	245 (6.0)	247 (7.3)
COPD or asthma	-	386 (9.4)	543 (16.0)
Dyslipidaemia	-	1801 (43.8)	2039 (60.0)
Treatment (%)			
Digitalis	831 (27.7)	556 (13.5)	337 (9.9)
Diuretic	2240 (74.7)	3407 (82.8)	2778 (81.9)
Loop	1860 (62.0)	2140 (52.0)	1764 (52.0)
Thiazide	410 (13.7)	1552 (37.7)	1394 (41.1)
ACEI or ARB	1775 (59.2)	2572 (62.5)	2863 (84.2)
ACEI	563 (18.8)	1048 (25.5)	2231 (65.8)
ARB	1503 (50.1)	2062 (50.1)	680 (20.0)
Beta-blocker	1668 (55.6)	2423 (58.9)	2637 (77.7)
MRA	350 (11.7)	631 (15.3)	1698 (49.9)
Calcium channel blocker	938 (31.3)	1634 (39.7)	1284 (37.8)
Antiarrhythmic agent	291 (9.7)	355 (8.6)	289 (8.5)
Antiplatelet	1849 (61.6)	2412 (58.6)	2292 (67.6)
Aspirin	1752 (58.4)	2249 (54.7)	2220 (65.4)
Oral anticoagulant	735 (24.5)	783 (19.0)	774 (22.8)
Lipid lowering agent	1248 (41.6)	1272 (30.9)	1816 (53.5)
Anti-diabetic agent	-	922 (22.4)	943 (27.8)
Laboratory tests			
Creatinine -mg/dl	1.12±0.41a	1.00±0.32b	1.09±0.30
eGFR -ml/min/1.73m^2	72.3±26.9a	72.6±22.5b	67.7±20.2
eGFR <60 ml/min/1.73m^2 (%)	370 (34.5)a	1239 (30.8)b	1307 (38.5)
NT-proBNP -pg/ml	-	339 [133-960]c	843 [463-1727]d

The letters denote the number of patients available: a=1074 (36%), b=4027 (98%), c=3470 (84%), d=615 (18%).

"-" denotes data having not been recorded.

6.2.2 Baseline characteristics of patients with sudden death

The characteristics of patients with and without sudden death in each trial are shown in Table 6-2. Overall, patients with sudden death were more often elderly, male, had lower LVEF and more advanced HF symptoms. They were more likely to have previous hospital admission for HF worsening, a history of myocardial infarction, diabetes or atrial fibrillation, and have been treated with loop diuretics. The average level of eGFR was lower, and correspondingly the proportion of patients with renal dysfunction was higher in patients with sudden death. Compared to patients without sudden death, the median level of NT-proBNP in patients with sudden death was substantially higher in I-PRESERVE, but slightly lower in TOPCAT.

Table 6-2 Baseline characteristics of patients with and without sudden death in the included trials in HF-PEF

	CHARM-Preserved		I-PRESERVE		TOPCAT	
	SD (N=134)	**Others (N=2866)**	**SD (N=230)**	**Others (N=3886)**	**SD (N=110)**	**Others (N=3291)**
Age -years	70.0±10.5***	66.5±11.1	73.7±7.4***	71.5±6.9	68.6±9.0	68.5±9.6
Male sex (%)	90 (67.2)	1706 (59.5)	127 (55.2)***	1504 (38.7)	78 (70.9)***	1563 (47.5)
Race (%)						
White	117 (87.3)***	2628 (91.7)	220 (95.7)	3627 (93.3)	96 (87.3)	2932 (89.1)
Black	2 (1.5)	123 (4.3)	5 (2.2)	77 (2.0)	9 (8.2)	285 (8.7)
Asian	8 (6.0)	63 (2.2)	0 (0.0)	35 (0.9)	0 (0.0)	18 (0.5)
Other	7 (5.2)	52 (1.8)	5 (2.2)	147 (3.8)	5 (4.5)	56 (1.7)
Blood pressure -mmHg						
Systolic	136.6±16.8	136.2±18.5	135.8±15.8	136.4±14.9	128.5±16.0	129.3±13.8
Diastolic	77.9±10.1	77.8±10.7	77.9±8.3	78.8±9.1	73.6±12.5*	75.9±10.5
Heart rate -beats/min	73.2±12.1	71.2±12.4	73.3±10.3**	71.3±10.4	69.6±10.7	69.0±10.6
Body mass index	28.6±5.5	29.2±5.8	28.6±5.1**	29.7±5.3	32.7±7.7	32.0±7.1
LVEF -%	52.9±9.3	54.1±9.4	56.7±9.2***	59.6±9.1	54.0±7.4***	57.2±7.4
NYHA class III-IV (%)	57 (42.5)	1118 (39.0)	181 (78.7)	3065 (78.9)	38 (34.5)	1078 (32.8)
Aetiology (%)						
Ischaemic	80 (59.7)	1612 (56.2)	88 (38.3)***	945 (24.3)	-	-
Hypertensive	27 (20.1)	655 (22.9)	115 (50.0)	2501 (64.4)	-	-
Other	27 (20.1)	599 (20.9)	27 (11.7)	440 (11.3)	-	-
HF duration (%)						
≤1 year	52 (38.8)	1220 (42.6)	107 (46.5)	1884 (48.5)	-	-
>1 and ≤ 5 years	46 (34.3)	1068 (37.3)	81 (35.2)	1423 (36.7)	-	-
>5 years	36 (26.9)	577 (20.1)	42 (18.3)	575 (14.8)	-	-
Medical history (%)						
Current smoking	26 (19.4)*	380 (13.3)	-	-	14 (12.7)	343 (10.4)
HF hospitalisation within the previous 6 months	57 (42.5)	1006 (35.1)	128 (55.7)***	1681 (43.3)	59 (53.6)	1728 (52.5)

Coronary artery disease	92 (68.7)	2059 (71.8)	143 (62.2) ***	1944 (50.0)	67 (60.9)	1926 (58.5)
Myocardial infarction	63 (47.0)	1262 (44.0)	81 (35.2)***	882 (22.7)	41 (37.3)**	832 (25.3)
Angina	70 (52.2)	1737 (60.6)	110 (47.8)	1663 (42.8)	46 (41.8)	1552 (47.2)
CABG or PCI	36 (26.9)	958 (33.4)	36 (15.7)	506 (13.0)	36 (32.7)*	755 (23.0)
Hypertension	96 (71.6)	1836 (64.1)	199 (86.5)	3446 (88.7)	100 (90.9)	3009 (91.5)
Diabetes	57 (42.5)***	794 (27.7)	86 (37.4)***	1042 (26.8)	43 (39.1)	1053 (32.0)
Atrial fibrillation	47 (35.1)	827 (28.9)	85 (37.0)**	1114 (28.7)	39 (35.5)	1153 (35.1)
Stroke	19 (14.2)*	248 (8.7)	26 (11.3)	368 (9.5)	9 (8.2)	251 (7.6)
Pacemaker	11 (8.2)	203 (7.1)	19 (8.3)	226 (5.8)	6 (5.5)	241 (7.3)
COPD or asthma	-	-	37 (16.1)***	349 (9.0)	20 (18.2)	523 (15.9)
Dyslipidaemia	-	-	87 (37.8)	1714 (44.1)	66 (60.0)	1973 (60.0)
Treatment (%)						
Digitalis	51 (38.1)**	780 (27.2)	47 (20.4)**	509 (13.1)	12 (10.9)	325 (9.9)
Diuretics	117 (87.3)***	2123 (74.1)	200 (87.0)	3207 (82.6)	95 (86.4)	2683 (81.7)
Loop	101 (75.4)**	1759 (61.4)	146 (63.5)***	1994 (51.4)	77 (70.0)***	1687 (51.4)
Thiazide	19 (14.2)	391 (13.6)	73 (31.7)	1479 (38.1)	38 (34.5)	1356 (41.3)
ACEI or ARB	85 (63.4)	1690 (59.0)	145 (63.0)	2427 (62.4)	94 (85.4)	2769 (84.1)
ACEI	35 (26.1)*	528 (18.4)	70 (30.4)	978 (25.2)	73 (66.4)	2158 (65.7)
ARB	69 (51.5)	1434 (50.0)	113 (49.1)	1949 (50.2)	24 (21.8)	656 (20.0)
Beta-blocker	60 (44.8)**	1608 (56.1)	132 (57.4)	2291 (59.0)	89 (80.9)	2548 (77.6)
MRA	15 (11.2)	335 (11.7)	51 (22.2)**	580 (14.9)	56 (50.9)	1642 (49.9)
Calcium channel blocker	42 (31.3)	896 (31.3)	72 (31.3)**	1562 (40.2)	38 (34.5)	1246 (38.0)
Antiarrhythmic agent	7 (5.2)	284 (9.9)	28 (12.2)*	327 (8.4)	11 (10.0)	278 (8.5)
Antiplatelet	74 (55.2)	1775 (61.9)	136 (59.1)	2276 (58.6)	73 (66.4)	2219 (67.6)
Aspirin	70 (52.2)	1682 (58.7)	123 (53.5)	2126 (54.8)	71 (64.5)	2149 (65.5)
Oral anticoagulant	32 (23.9)	703 (24.5)	53 (23.0)	730 (18.8)	22 (20.0)	752 (22.9)
Lipid lowering agent	44 (32.8)*	1204 (42.0)	63 (27.4)	1209 (31.1)	57 (51.8)	1759 (53.6)
Anti-diabetic agent	-	-	73 (31.7)***	849 (21.9)	40 (36.4)*	903 (27.5)
Laboratory tests						
Creatinine -mg/dl	1.19±0.38a	1.12±0.42b	1.09±0.38***c	0.99±0.31d	1.20±0.32***	1.09±0.30
eGFR -ml/min/1.73m^2	66.6±22.2a	72.5±27.1b	69.8±23.9c	72.7±22.4d	65.0±21.0	67.8±20.2
eGFR <60 ml/min/1.73m^2	17 (42.5)a	353 (34.1)b	80 (34.9)c	1159 (30.5)d	54 (49.1)*	1253 (38.1)
NT-proBNP -pg/ml	-	-	944e [353-2032]***	320f [130-908]	659g [515-2582]	844h [461-1708]

*P<0.05, **p<0.01, *** p<0.001

SD denotes sudden death, "-" denotes data having not been collected.

The letters denote the number of patients available: a=40 (30%), b=1034 (36%), c=229 (100%), d=3798 (98%), e=195 (85%), f=3275 (84%), g=22 (20%), h=593 (18%).

6.2.3 Baseline characteristics of patients with pump failure death

There were some notable differences in baseline characteristics between patients with and without pump failure death (Table 6-3). In general, compared to patients without pump failure death, patients who died from progressive pump failure were more likely to be older, have worse HF symptoms, lower blood pressure or BMI, and have higher heart rate. These patients with pump failure death tended to have longer standing HF, and have more comorbidities including previous HF hospitalisation, diabetes, atrial fibrillation, COPD or asthma and renal dysfunction, but were less likely to have hypertension. There was a higher rate of the use of digitalis, loop diuretics, oral anticoagulants or pacemaker, but a lower rate of use of antiplatelets in patients with pump failure death. The average level of eGFR was substantially lower and the median plasma NT-proBNP concentration was substantially higher in patients with pump failure death than those without pump failure death.

Table 6-3 Baseline characteristics of patients with and without pump failure death in the included trials in HF-PEF

	CHARM-Preserved		**I-PRESERVE**		**TOPCAT**	
	PFD (N=100)	Others (N=2900)	PFD (N=123)	Others (N=3993)	PFD (N=65)	Others (N=3336)
Age -years	75.8±8.2***	66.4±11.0	75.5±7.0***	71.5±6.9	75.3±8.8***	68.4±9.5
Male sex (%)	58 (58.0)	1738 (59.9)	62 (50.4)*	1569 (39.3)	32 (49.2)	1609 (48.2)
Race (%)						
White	93 (93.0)	2652 (91.4)	115 (93.5)	3732 (93.5)	57 (87.7)	2971 (89.1)
Black	2 (2.0)	123 (4.2)	4 (3.3)	78 (2.0)	5 (7.7)	289 (8.7)
Asian	1 (1.0)	70 (2.4)	2 (1.6)	33 (0.8)	1 (1.5)	17 (0.5)
Other	4 (4.0)	55 (1.9)	2 (1.6)	150 (3.8)	2 (3.1)	59 (1.8)
Blood pressure -mmHg						
Systolic	134.4±20.4	136.3±18.4	134.6±19.6	136.4±14.8	125.2±15.9*	129.3±13.8
Diastolic	72.4±11.5***	78.0±10.6	75.2±9.4***	78.9±9.0	70.4±10.3***	76.0±10.6
Heart rate -beats/min	72.8±10.9	71.3±12.4	74.2±11.1**	71.3±10.4	71.4±10.7	68.9±10.6
Body mass index	26.9±5.0***	29.3±5.8	29.1±6.4	29.7±5.2	30.2±6.5*	32.1±7.1
LVEF -%	54.7±10.3	54.0±9.4	56.7±9.0***	59.5±9.1	56.5±7.1	57.1±7.5
NYHA class III-IV (%)	61 (61.0)***	1114 (38.4)	97 (78.9)	3149 (78.9)	34 (52.3)***	1082 (32.5)
Aetiology (%)						
Ischaemic	50 (50.0)	1642 (56.6)	44 (35.8)**	989 (24.8)	-	-
Hypertensive	21 (21.0)	661 (22.8)	59 (48.0)	2557 (64.0)	-	-
Other	29 (29.0)	597 (20.6)	20 (16.3)	447 (11.2)	-	-
HF duration (%)						
within 1 year	25 (25.0)***	1247 (43.0)	46 (37.4)*	1945 (48.8)	-	-
>1 and ≤5 years	36 (36.0)	1078 (37.2)	54 (43.9)	1450 (36.3)	-	-
>5 years	39 (39.0)	574 (19.8)	23 (18.7)	594 (14.9)	-	-

Medical history (%)						
Current smoking	10 (10.0)	396 (13.7)	-	-	7 (10.8)	350 (10.5)
HF hospitalisation within the previous 6 months	56 (56.0)***	1007 (34.7)	73 (59.3)***	1736 (43.5)	28 (43.1)	1759 (52.7)
Coronary artery disease	69 (69.0)	2082 (71.8)	62 (50.4)	2025 (50.7)	31 (47.7)	1962 (58.8)
Myocardial infarction	40 (40.0)	1285 (44.3)	33 (26.8)	930 (23.3)	10 (15.4)	863 (25.9)
Angina	54 (54.0)	1753 (60.4)	52 (42.3)	1721 (43.1)	24 (36.9)	1574 (47.2)
CABG or PCI	28 (28.0)	966 (33.3)	19 (15.4)	523 (13.1)	16 (24.6)	775 (23.3)
Hypertension	54 (54.0)*	1878 (64.8)	100 (81.3)*	3545 (88.8)	55 (84.6)*	3054 (91.6)
Diabetes	37 (37.0)	814 (28.1)	52 (42.3)***	1076 (26.9)	28 (43.1)	1068 (32.0)
Atrial fibrillation	41 (41.0)**	833 (28.7)	62 (50.4)***	1137 (28.5)	39 (60.0)***	1153 (34.6)
Stroke	13 (13.0)	254 (8.8)	16 (13.0)	378 (9.5)	7 (10.8)	253 (7.6)
Pacemaker	14 (14.0)**	200 (6.9)	15 (12.2)**	230 (5.8)	12 (18.5)***	235 (7.1)
COPD or asthma	-	-	18 (14.6)*	368 (9.2)	51 (78.5)**	1988 (59.6)
Dyslipidaemia	-	-	36 (29.3)**	1765 (44.2)	14 (21.5)	529 (15.9)
Treatment (%)						
Digitalis	41 (41.0)**	790 (27.2)	38 (30.9)***	518 (13.0)	13 (20.0)**	324 (9.7)
Diuretics	90 (90.0)**	2150 (74.1)	115 (93.5)**	3292 (82.5)	63 (96.9)**	2715 (81.6)
Loop	86 (86.0)***	1774 (61.2)	103 (83.7)***	2037 (51.1)	59 (90.8)***	1705 (51.2)
Thiazide	12 (12.0)	398 (13.7)	22 (17.9)***	1530 (38.3)	20 (30.8)	1374 (41.3)
ACEI or ARB	54 (54.0)	1721 (59.3)	88 (71.5)*	2484 (62.2)	53 (81.5)	2810 (84.2)
ACEI	17 (17.0)	546 (18.8)	39 (31.7)	1009 (25.3)	35 (53.8)*	2196 (66.0)
ARB	47 (47.0)	1456 (50.2)	69 (56.1)	1993 (49.9)	20 (30.8)*	660 (19.8)
Beta-blocker	36 (36.0)***	1632 (56.3)	61 (49.6)*	2362 (59.2)	57 (87.7)	2580 (77.5)
MRA	22 (22.0)**	328 (11.3)	33 (26.8)***	598 (15.0)	26 (40.0)	1672 (50.1)
Calcium channel blocker	31 (31.0)	907 (31.3)	45 (36.6)	1589 (39.8)	18 (27.7)	1266 (38.0)
Antiarrhythmic agent	15 (15.0)	276 (9.5)	18 (14.6)*	337 (8.4)	3 (4.6)	286 (8.6)
Antiplatelet	50 (50.0)*	1799 (62.0)	54 (43.9)***	2358 (59.1)	41 (63.1)	2251 (67.6)
Aspirin	48 (48.0)*	1704 (58.8)	51 (41.5)**	2198 (55.1)	38 (58.5)	2182 (65.6)
Oral anticoagulant	32 (32.0)	703 (24.2)	42 (34.1)***	741 (18.6)	27 (41.5)***	747 (22.4)
Lipid lowering agent	22 (22.0)***	1226 (42.3)	30 (24.4)	1242 (31.1)	44 (67.7)*	1772 (53.2)
Anti-diabetic agent	-	-	41 (33.3)**	881 (22.1)	24 (36.9)	919 (27.6)
Laboratory tests						
Creatinine -mg/dl	1.43±0.66***a	1.11±0.40b	1.18±0.36***c	0.99±0.32d	1.22±0.34***	1.09±0.30
eGFR -ml/min/1.73m^2	54.7±23.5***a	72.9±26.8b	62.1±21.9***c	72.9±22.4d	58.8±18.1***	67.9±20.2
eGFR <60 ml/min/1.73m^2	23 (62.2)***a	347 (33.5)b	66 (55.0)***c	1173 (30.0)d	38 (58.5)***	1269 (38.1)
NT-proBNP -pg/ml	-	-	1231e [408-2790]***	327f [131-924]	2932g [1455-6455]***	826h [460-1677]

*P<0.05, **p<0.01, *** p<0.001.

PFD denotes pump failure death, “-“ denotes data having not been collected.

The letters denote the number of patients available: a=37 (37%), b=1037 (36%), c=120 (98%), d=3907 (98%), e=100 (81%), f=3370 (84%), g=12 (18%), h=603 (18%).

6.2.4 Sudden death rates in each trial and in each arm of each trial

The annual rate for sudden death was 1.5 per 100 patient-years in the earliest CHARM-Preserved, 1.4 per 100 patient-years in I-PRESERVE and 1.0 per 100 patient-years in the latest TOPCAT (Table 6-4 and Figure 6-1). There was a declining trend in the rate of sudden death across these trials over time (p =0.021) (Figure 6-2), and the trend was attenuated but remained significant in a sensitivity analysis after excluding patients with LVEF below 45% in CHARM-Preserved (p=0.045) (Figure 6-3). A decrease in the rate was accompanied by a falling proportion of sudden death relative to total mortality across trials (Figure 6-4). The rate of death from any cause also decreased across these trials over time (p=0.025), but the rate of non-CV death did not change over time (p=0.24), leading to an increase in proportion of death from non-CV causes in the later trial (Figure 6-4, Figure 6-5 and Figure 6-6).

Table 6-4 Annual rates and cumulative incidences of sudden death at different time points in the included trials in HF-PEF (treatment arms combined)

	CHARM-Preserved (N=3000)	**I-PRESERVE (N=4116)**	**TOPCAT (N=3401)**
Sudden death events	134	230	110
Annual rate (95% CI)	1.5 (1.3-1.8)	1.4 (1.2-1.6)	1.0 (0.8-1.2)
Cumulative incidence (95% CI)			
30 days	0.1 (0.0-0.2)	0.2 (0.0-0.3)	0.1 (0.0-0.2)
60 days	0.1 (0.0-0.2)	0.2 (0.1-0.4)	0.1 (0.0-0.2)
90 days	0.1 (0.0-0.3)	0.3 (0.1-0.5)	0.2 (0.0-0.3)
180 days	0.5 (0.3-0.8)	0.6 (0.4-0.9)	0.5 (0.2-0.7)
1 year	1.2 (0.8-1.6)	1.3 (1.0-1.7)	1.0 (0.6-1.3)
2 years	2.9 (2.3-3.5)	2.5 (2.0-2.9)	1.7 (1.3-2.2)
3 years	4.4 (3.6-5.1)	3.7 (3.1-4.2)	2.4 (1.8-2.9)

Annual rates are shown as per 100 patient-years. Cumulative incidences are presented as percent.

Figure 6-1 Cumulative incidence curves for sudden death by trials in HF-PEF

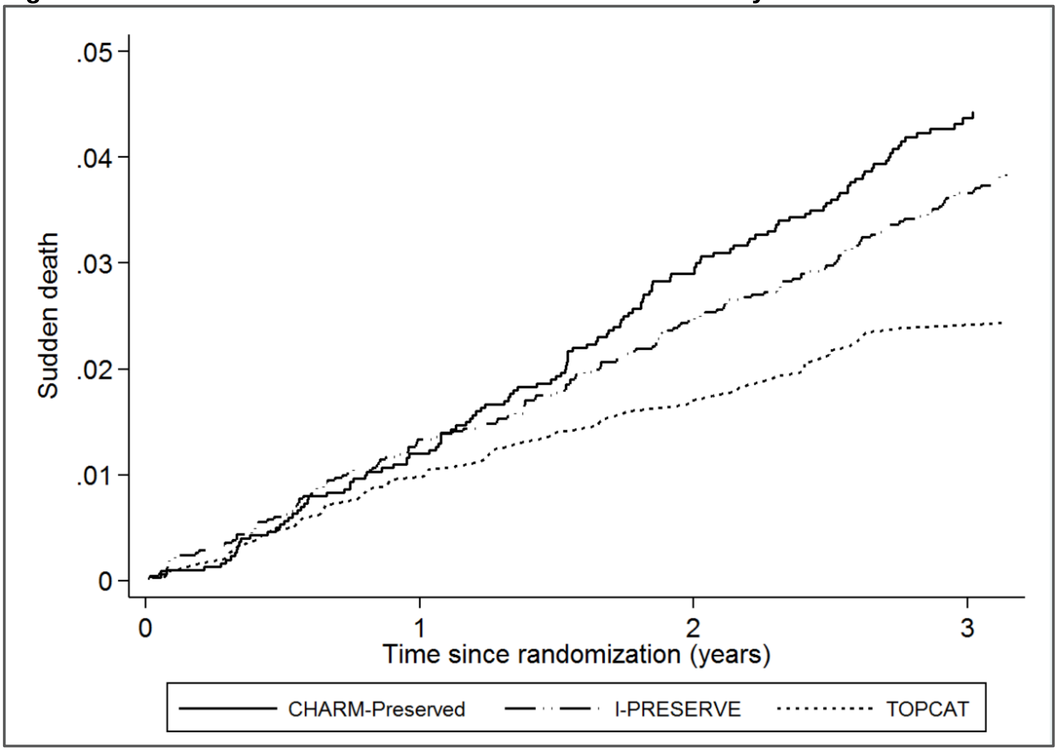
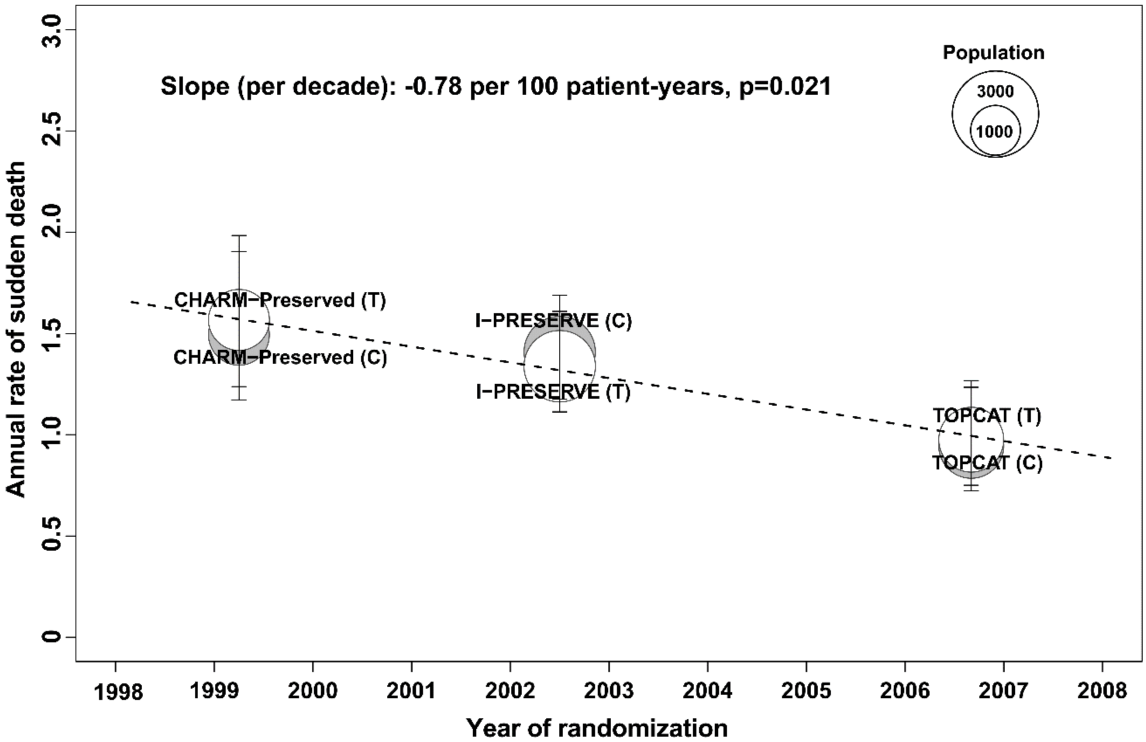
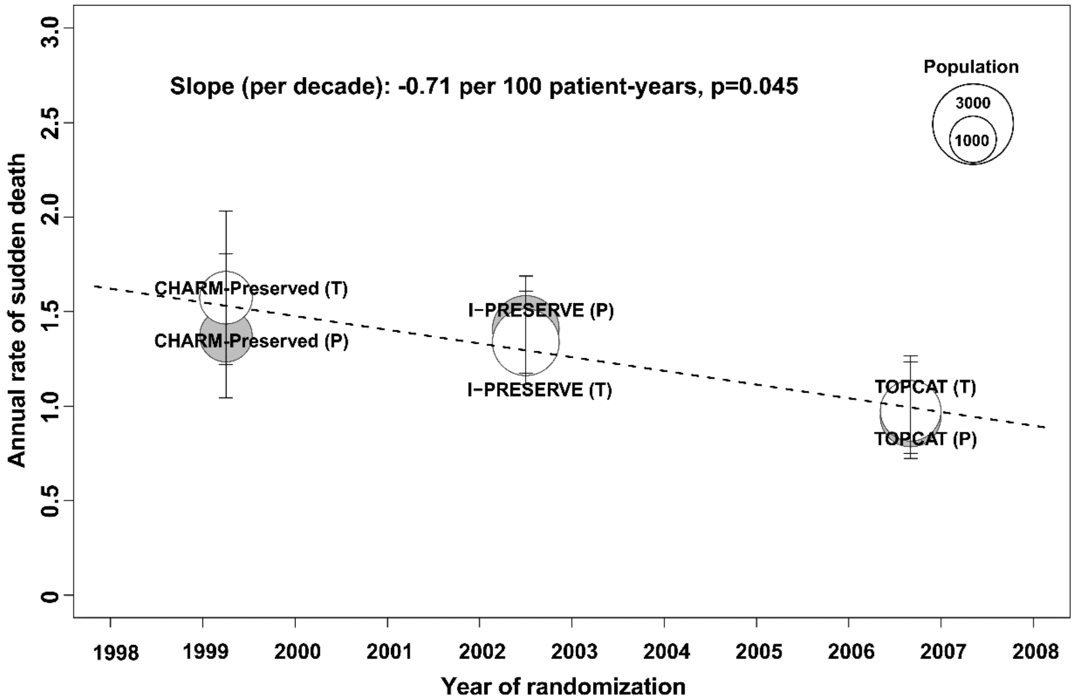


Figure 6-2 Trends in the sudden death rate across trial arms over time in HF-PEF



Annual rates are shown as sudden death per 100 patient-years. The black dotted line is based on the multiple linear regression of the annual rate in each trial arm with the randomisation year and randomisation arm as covariates, weighted by its inverse-variance and with trial as a random effect. P for slope represents the p value for randomisation year based on the linear model. Each circle represents each trial arm as labelled, with the control arm in each trial illustrated in gray and the experimental arm in white. The centre of each circle corresponds to randomisation year (x axis) and the annual rate (y axis) in each arm, the error bars in each circle correspond to the 95% confidence interval of the annual rate. The area of each circle represents the sample size in each arm (reference size shown in the upper right corner). C denotes control arm; T, experimental treatment arm.

Figure 6-3 Trends in the sudden death rate across trial arms over time in HF-PEF with the exclusion of patients with a LVEF below 45% in CHARM-Preserved



Annual rates are shown as sudden death per 100 patient-years. Other notes and abbreviations are same as those in Figure 6-2.

Figure 6-4 Proportions of sudden death and pump failure death relative to overall mortality across the trials in HF-PEF

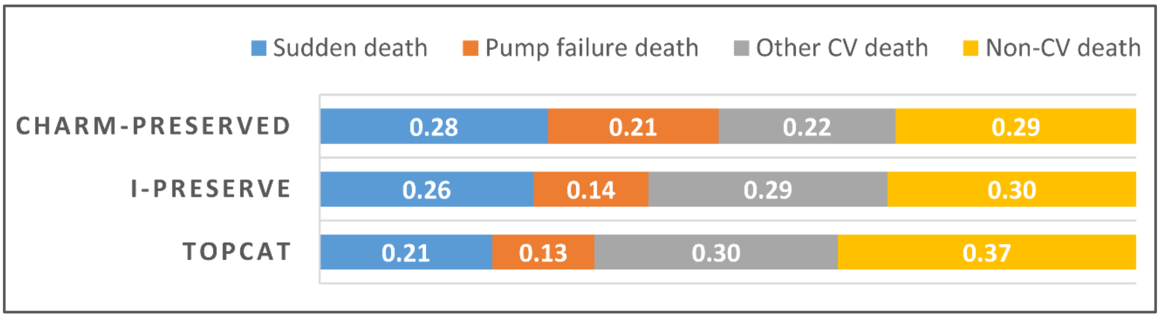
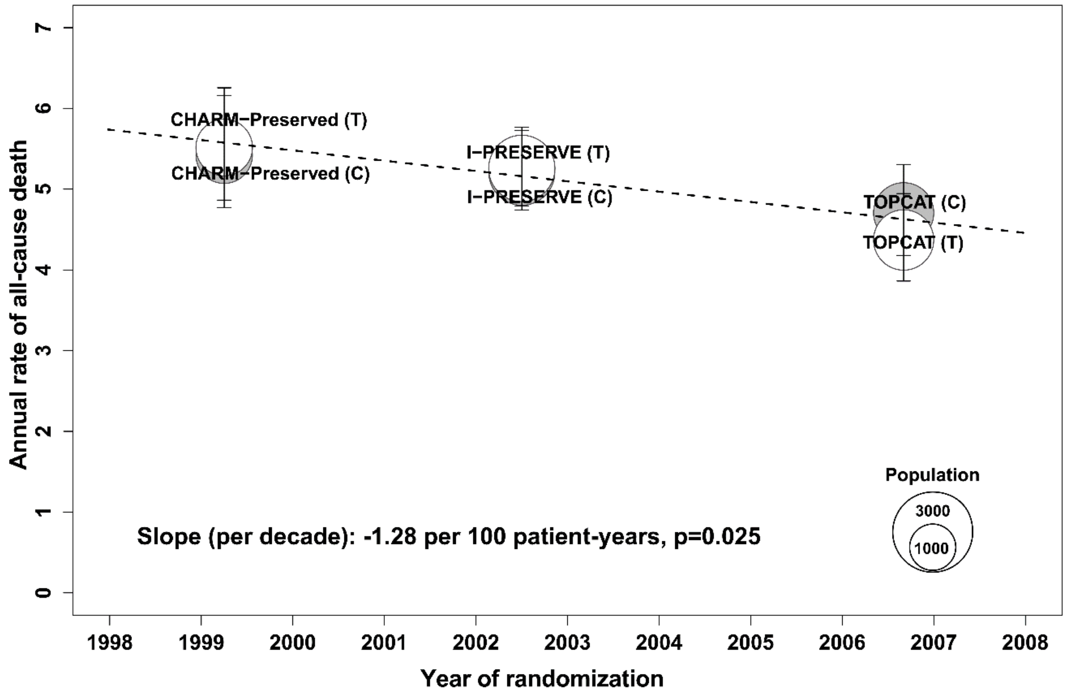
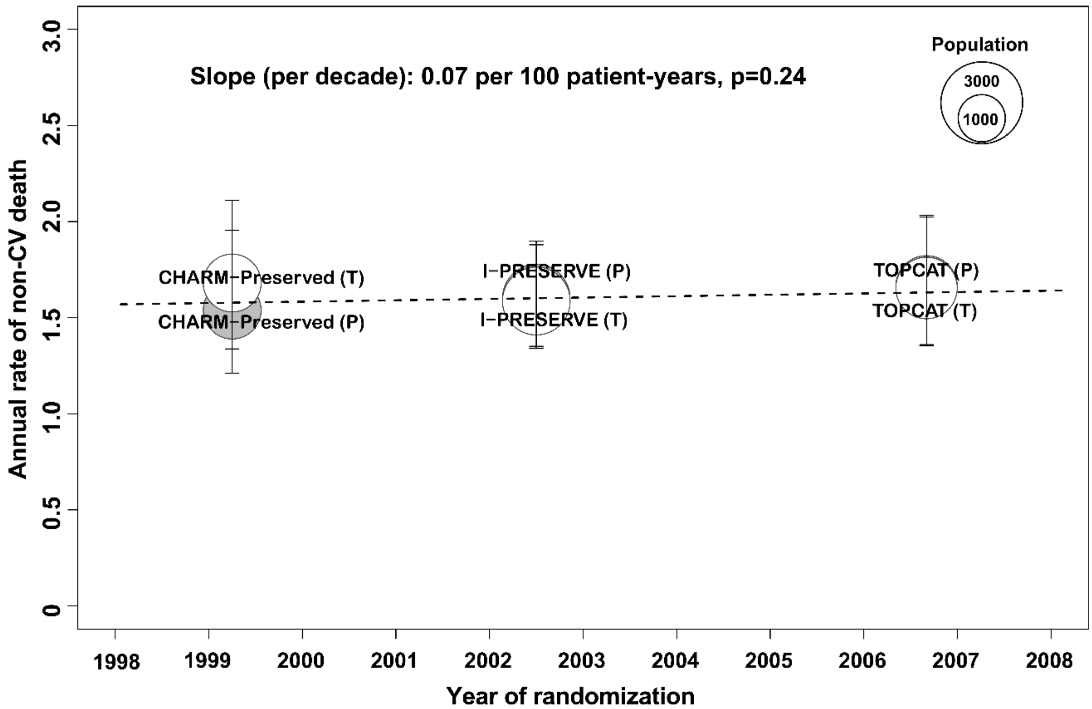


Figure 6-5 Trends in the all-cause death rate across trial arms over time in HF-PEF



Annual rates are shown as all-cause death per 100 patient-years. The black dotted line is based on the multiple linear regression of the annual rate in each trial arm with the randomisation year and randomisation arm as covariates, weighted by its inverse-variance and with trial as a random effect. P for slope represents the p value for randomisation year based on the linear model. Each circle represents each trial arm as labelled, with the control arm in each trial illustrated in gray and the experimental arm in white. The centre of each circle corresponds to randomisation year (x axis) and the annual rate (y axis) in each arm, the error bars in each circle correspond to the 95% confidence interval of the annual rate. The area of each circle represents the sample size in each arm (reference size shown in the upper right corner). C denotes control arm; T, experimental treatment arm.

Figure 6-6 Trends in the non-CV death rate across trial arms over time in HF-PEF



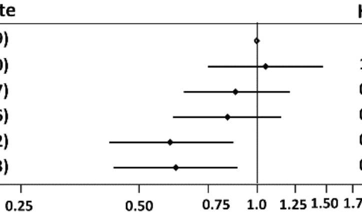
Annual rates are shown as non-CV death per 100 patient-years. Other notes and abbreviations are same as those in Figure 6-5.

The rate of sudden death was quite similar between treatment arms in each trial (Figure 6-2). This was in line with the finding from a Cox regression analysis with randomisation treatment and randomisation year as covariates, in which the risk for sudden death was not significantly associated with randomisation treatment (HR 0.99, 95% CI 0.83-1.19, p=0.954) but with randomisation year (HR per decade 0.48, 95% CI 0.33-0.69, p<0.001). A nearly identical result was observed with adjustment for conventional confounding variables (HR for randomisation treatment 0.98, 95% CI 0.83-1.19, p=0.954; HR for randomisation year per decade 0.48, 95% CI 0.32-0.71, p<0.001).

When examining the risk of sudden death across trial arms, generally, there was no difference in the risk of sudden death between treatment arms within a trial, and the risk was about 40% lower in either arm of TOPCAT than that in the placebo arm of CHARM-Preserved (HR 0.62, 95% CI 0.43-0.89, p=0.010) (Figure 6-7). A similar result was observed with adjustment for conventional confounding covariates (Figure 6-8). The difference was attenuated and marginally significant after further adjustment for eGFR (HR 0.67, 95% CI 0.41-1.11, p=0.118), and the imputation of missing values gave similar results (Figure 6-9). When further adjusting for NT-proBNP, compared with the placebo arm of I-PRESERVE, the risk of sudden death in the treatment arm of TOPCAT was marginally lower using complete case analysis (HR 0.60, 95% CI 0.30-1.19, p=0.141), but was significantly lower with the imputation approach including all patients in I-PRESERVE and TOPCAT (HR 0.65, 95% CI 0.44-0.97, p=0.033) (Figure 6-10).

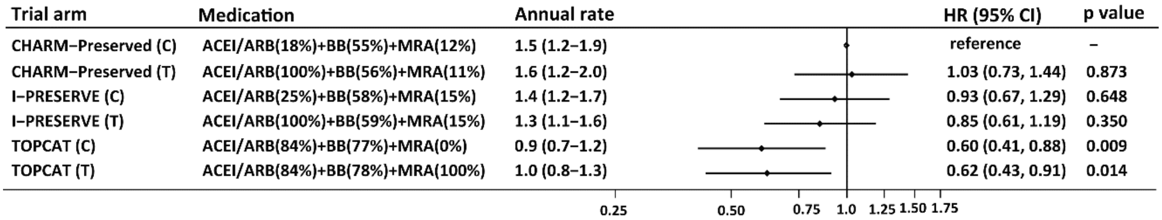
Figure 6-7 Hazard ratio for sudden death across the trial arms in HF-PEF

Trial arm	Medication	Annual rate	HR (95% CI)	p value
CHARM–Preserved (C)	ACEI/ARB(18%)+BB(55%)+MRA(12%)	1.5 (1.2–1.9)	reference	–
CHARM–Preserved (T)	ACEI/ARB(100%)+BB(56%)+MRA(11%)	1.6 (1.2–2.0)	1.05 (0.75, 1.47)	0.784
I–PRESERVE (C)	ACEI/ARB(25%)+BB(58%)+MRA(15%)	1.4 (1.2–1.7)	0.88 (0.65, 1.21)	0.436
I–PRESERVE (T)	ACEI/ARB(100%)+BB(59%)+MRA(15%)	1.3 (1.1–1.6)	0.84 (0.61, 1.15)	0.267
TOPCAT (C)	ACEI/ARB(84%)+BB(77%)+MRA(0%)	0.9 (0.7–1.2)	0.60 (0.42, 0.87)	0.007
TOPCAT (T)	ACEI/ARB(84%)+BB(78%)+MRA(100%)	1.0 (0.8–1.3)	0.62 (0.43, 0.89)	0.010



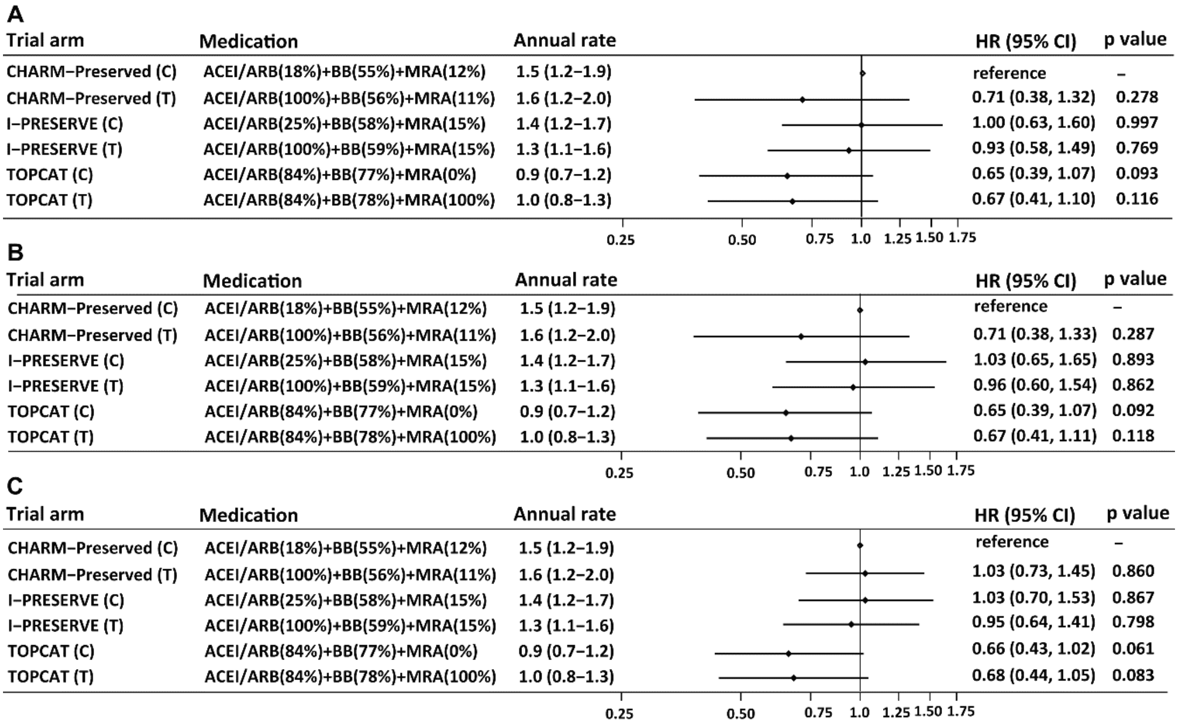
Annual rates are shown as sudden death per 100 patient-years. Hazard ratios shown were compared to the placebo arm of CHARM-Preserved (N=10,515). C denotes control arm; T, experimental treatment arm.

Figure 6-8 Hazard ratio for sudden death across the trial arms in HF-PEF with adjustment for 8 conventional covariates



Annual rates are shown as sudden death per 100 patient-years. Hazard ratios were adjusted for conventional covariates including age, sex, NYHA class, LVEF, systolic blood pressure, HF hospitalisation within the last 6 months, and a history of myocardial infarction, hypertension and diabetes (N=10,506). Hazard ratios shown were compared to the placebo arm of CHARM-Preserved. C denotes control arm; T, experimental treatment arm.

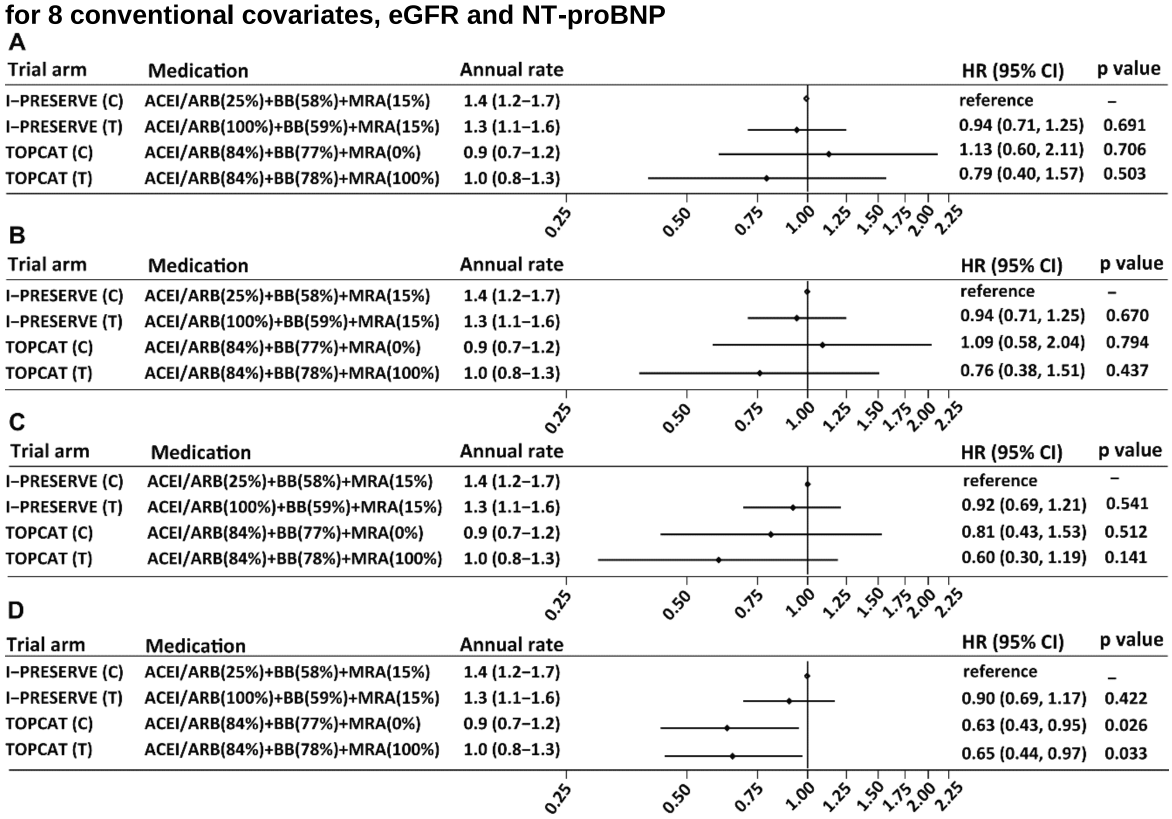
Figure 6-9 Hazard ratio for sudden death across the trial arms in HF-PEF with adjustment for 8 conventional covariates and eGFR



Annual rates are shown as sudden death per 100 patient-years.

Panel A, HRs were adjusted for conventional confounding variables in the subset of patients with eGFR measurements available (N=8492); Panel B, adjustment for conventional covariates and eGFR in the subset of patients with eGFR measurements available (N=8492); Panel C, adjustment for conventional covariates and eGFR with simple imputation of eGFR levels (N=10,506). HRs shown were compared to the placebo arm of CHARM-Preserved. C denotes control arm; T, experimental treatment arm.

Figure 6-10 Hazard ratio for sudden death across the trial arms in HF-PEF with adjustment for 8 conventional covariates, eGFR and NT-proBNP



Annual rates are shown as sudden death per 100 patient-years.

Panel A, adjustment for conventional confounding variables in the subset of patients with NT-proBNP available [N=4059]; Panel B, adjustment for conventional covariates and eGFR in the subset of patients with NT-proBNP available [N=4059]; Panel C, adjustment for conventional covariates, eGFR and log transformed NT-proBNP in the subset of patients with NT-proBNP available [N=4059]; Panel D, adjustment for conventional covariates, eGFR and log transformed NT-proBNP with simple imputation of eGFR and NT-proBNP in the trials with NT-proBNP collected (i.e. not complete missing) [N=7507]. HRs shown were compared to the placebo arm of I-PRESERVE. C denotes control arm; T, experimental treatment arm.

6.2.5 Pump failure death rates in each trial and in each arm of each trial

The annual rate of pump failure death was lower in the more recent trials: 1.1 per 100 patient-years in CHARM-Preserved, 0.7 per 100 patient-years in I-PRESERVE and 0.6 per 100 patient-years in TOPCAT (Table 6-5 and Figure 6-11). There was a borderline downward trend in the annual rate of pump failure death over time (p=0.05) (Figure 6-12), and a similar trend was observed in the sensitivity analysis after excluding patients with a LVEF below 45% in CHARM-Preserved (Figure 6-13). There was a smaller proportion of pump failure death relative to total mortality in TOPCAT (13% of total mortality) and I-PRESERVE (14%) than in CHARM-Preserved (21%) (Figure 6-4).

Table 6-5 Annual rates and cumulative incidences of pump failure death at different time points in the included trials in HF-PEF (treatment arms combined)

	CHARM-Preserved (N=3000)	**I-PRESERVE (N=4116)**	**TOPCAT (N=3401)**
Pump failure death events	100	123	65
Annual rate (95% CI)	1.1 (0.9-1.4)	0.7 (0.6-0.9)	0.6 (0.4-0.7)
Cumulative incidence (95% CI)			
30 days	0.0 (0.0-0.1)	0.0 (0.0-0.1)	0.1 (0.0-0.1)
60 days	0.1 (0.0-0.2)	0.1 (0.0-0.2)	0.1 (0.0-0.2)
90 days	0.2 (0.0-0.4)	0.1 (0.0-0.2)	0.1 (0.0-0.3)
180 days	0.5 (0.2-0.8)	0.2 (0.1-0.4)	0.2 (0.0-0.3)
1 year	1.0 (0.6-1.4)	0.7 (0.5-1.0)	0.4 (0.2-0.6)
2 years	2.0 (1.5-2.5)	1.2 (0.9-1.5)	1.1 (0.7-1.4)
3 years	3.0 (2.4-3.7)	2.1 (1.6-2.5)	1.4 (0.9-1.8)

Annual rates are shown as per 100 patient-years. Cumulative incidences are presented as percent.

Figure 6-11 Cumulative incidence curves for pump failure death by trials in HF-PEF

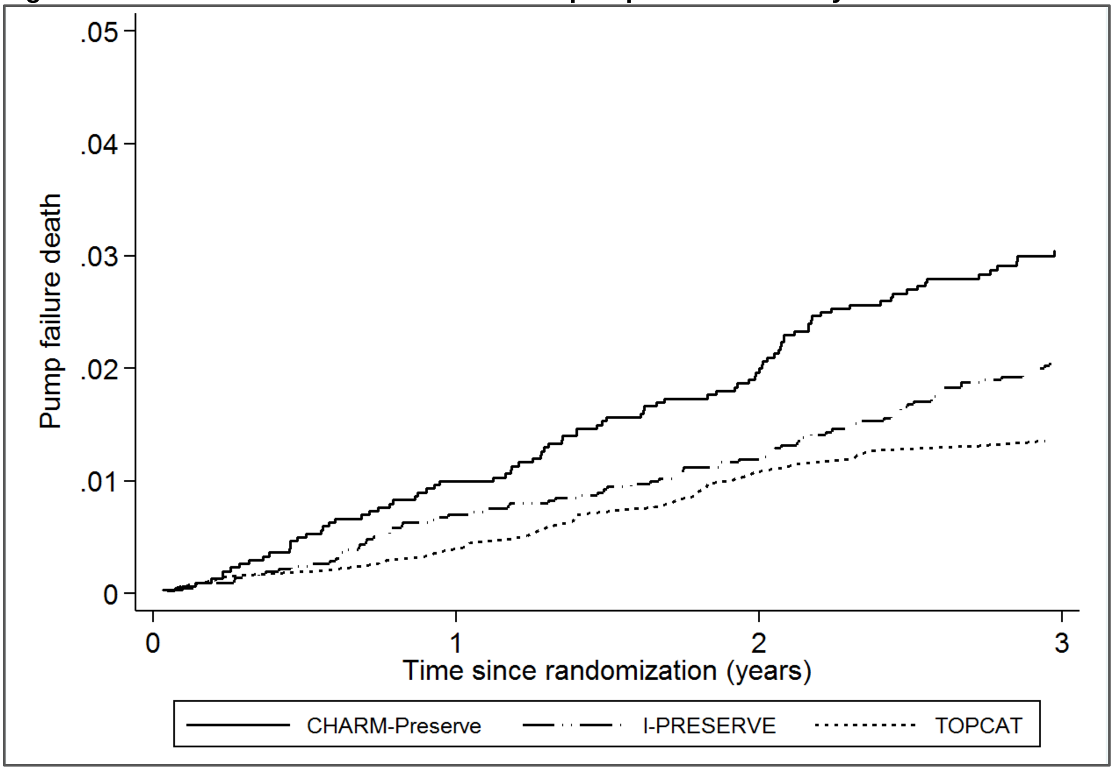
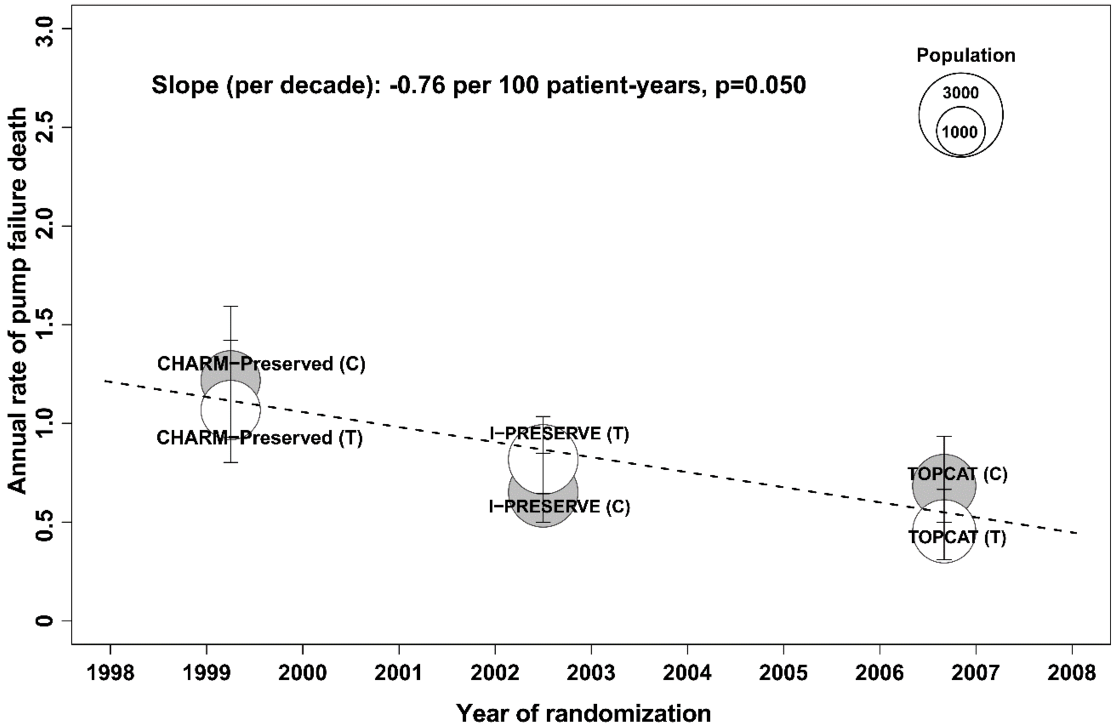
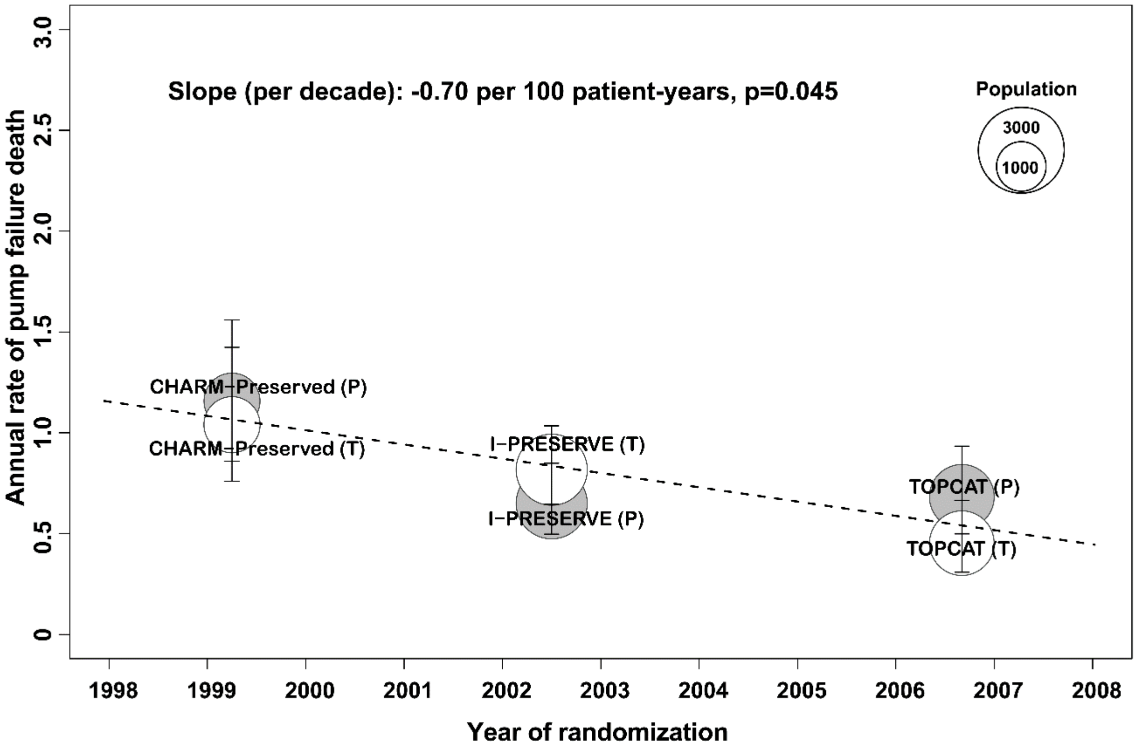


Figure 6-12 Trends in the pump failure death rate across trial arms over time in HF-PEF



Annual rates are shown as pump failure death per 100 patient-years. The black dotted line is based on the multiple linear regression of the annual rate in each trial arm with the randomisation year and randomisation arm as covariates, weighted by its inverse-variance and with trial as a random effect. P for slope represents the p value for randomisation year based on the linear model. Each circle represents each trial arm as labelled, with the control arm in each trial illustrated in gray and the experimental arm in white. The centre of each circle corresponds to randomisation year (x axis) and the annual rate (y axis) in each arm, the error bars in each circle correspond to the 95% confidence interval of the annual rate. The area of each circle represents the sample size in each arm (reference size shown in the upper right corner). C denotes control arm; T, experimental treatment arm.

Figure 6-13 Trends in the pump failure death rate across trial arms over time in HF-PEF with the exclusion of patients with a LVEF below 45% in CHARM-Preserved



Annual rates are shown as pump failure death per 100 patient-years. Other notes and abbreviations are same as those in Figure 6-12.

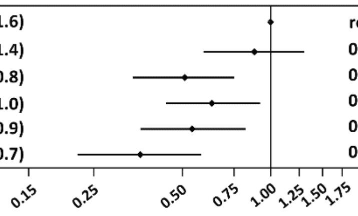
Similar to that of sudden death, the rate of pump failure death was quite similar between treatment arms within each single trial (Figure 6-12). This observation was in concert with the finding from Cox regression analysis with randomisation treatment and randomisation year as covariates, in which the risk for pump failure death had no significant relationship with randomisation treatment (HR 0.96, 95% CI 0.76-1.21, p=0.73), but significant with randomisation year (HR per decade 0.35, 95% CI 0.22-0.56, p<0.001). Adjusting for conventional confounding covariates made little difference (HR for randomisation treatment 0.94, 95% CI 0.75-1.19, p=0.622; HR for randomisation year per decade 0.33, 95% CI 0.20-0.57, p<0.001).

When examining the risk of pump failure death across trial arms, overall, a decrease was observed with about 37% lower in treatment arm of I-PRESERVE and 64% lower in the treatment arm of TOPCAT, compared to the placebo arm of CHARM-Preserved (HR 0.63, 95% CI 0.44-0.92, p=0.015; HR 0.36, 95% CI 0.22-0.58, p<0.001) (Figure 6-14). A similar result was observed with adjustment for conventional confounding variables and with additionally adjusting for eGFR

(Figure 6-15 and Figure 6-16). In the subset of patients with both eGFR and NT-proBNP available, compared with the placebo arm of I-PRESERVE, the risk of pump failure death was marginally higher in placebo arm of TOPCAT (HR 1.73, 95% CI 0.78-3.82, p=0.177), and the difference was attenuated with more covariates being adjusted for (HR 1.14, 95% CI 0.50-2.56, p=0.756 with adjustment for conventional covariates, eGFR and NT-proBNP); nevertheless, the risk was marginally lower in the treatment arm of TOPCAT irrespective of adjusted covariates (crude HR 0.69, 95% CI 0.24-1.98, p=0.489; HR 0.49, 95% CI 0.17-1.44, p=0.196 with adjustment for conventional covariates, eGFR and NT-proBNP) (Figure 6-17). Imputation of missing values made little change to these findings (Figure 6-16 and Figure 6-17).

Figure 6-14 Hazard ratio for pump failure death across the trial arms in HF-PEF

Trial arm	Medication	Annual rate	HR (95% CI)	p value
CHARM−Preserved (C)	ACEI/ARB(18%)+BB(55%)+MRA(12%)	1.2 (0.9−1.6)	reference	−
CHARM−Preserved (T)	ACEI/ARB(100%)+BB(56%)+MRA(11%)	1.1 (0.8−1.4)	0.88 (0.59, 1.30)	0.507
I−PRESERVE (C)	ACEI/ARB(25%)+BB(58%)+MRA(15%)	0.7 (0.5−0.8)	0.51 (0.34, 0.75)	0.001
I−PRESERVE (T)	ACEI/ARB(100%)+BB(59%)+MRA(15%)	0.8 (0.6−1.0)	0.63 (0.44, 0.92)	0.015
TOPCAT (C)	ACEI/ARB(84%)+BB(77%)+MRA(0%)	0.7 (0.5−0.9)	0.54 (0.36, 0.82)	0.004
TOPCAT (T)	ACEI/ARB(84%)+BB(78%)+MRA(100%)	0.5 (0.3−0.7)	0.36 (0.22, 0.58)	<0.001



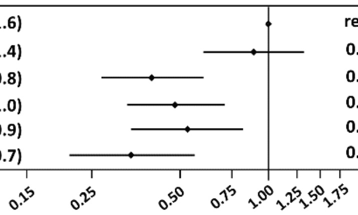
Annual rates are shown as pump failure death per 100 patient-years.

Hazard ratios shown were compared to the placebo arm of CHARM-Preserved (N=10,515).

C denotes control arm; T, experimental treatment arm.

Figure 6-15 Hazard ratio for pump failure death across the trial arms in HF-PEF with adjustment for 8 conventional covariates

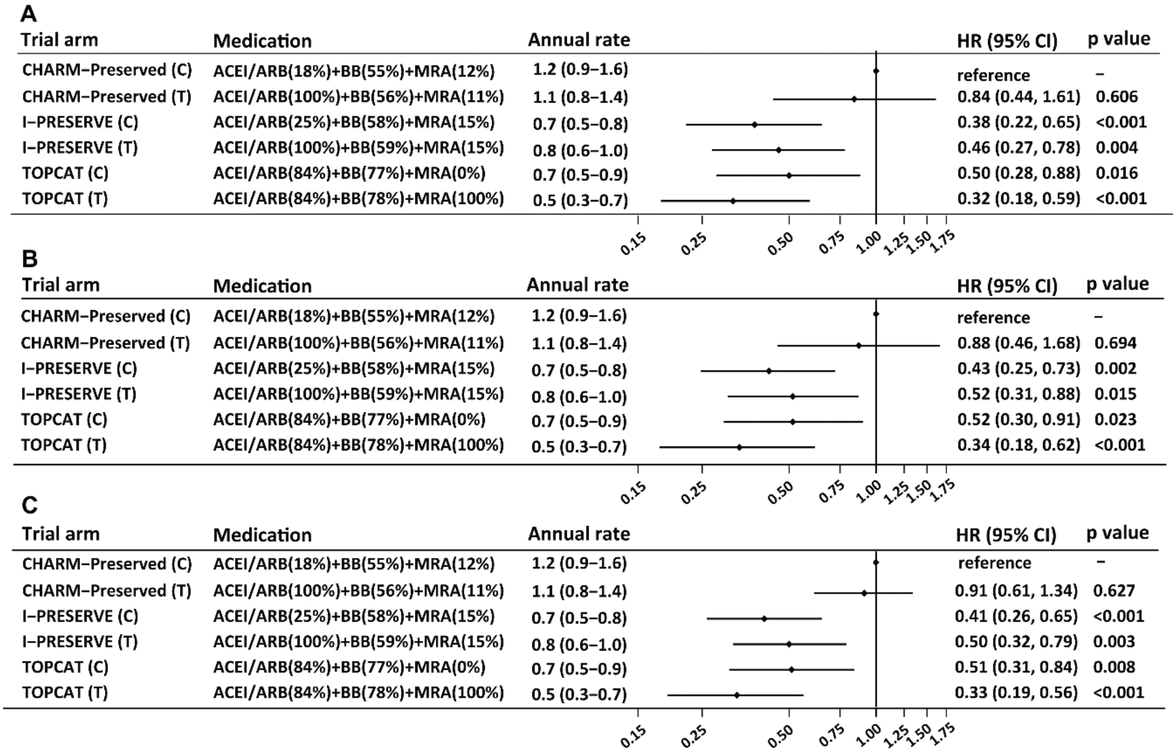
Trial arm	Medication	Annual rate	HR (95% CI)	p value
CHARM−Preserved (C)	ACEI/ARB(18%)+BB(55%)+MRA(12%)	1.2 (0.9−1.6)	reference	−
CHARM−Preserved (T)	ACEI/ARB(100%)+BB(56%)+MRA(11%)	1.1 (0.8−1.4)	0.89 (0.60, 1.32)	0.573
I−PRESERVE (C)	ACEI/ARB(25%)+BB(58%)+MRA(15%)	0.7 (0.5−0.8)	0.40 (0.27, 0.60)	<0.001
I−PRESERVE (T)	ACEI/ARB(100%)+BB(59%)+MRA(15%)	0.8 (0.6−1.0)	0.48 (0.33, 0.71)	<0.001
TOPCAT (C)	ACEI/ARB(84%)+BB(77%)+MRA(0%)	0.7 (0.5−0.9)	0.53 (0.34, 0.82)	0.005
TOPCAT (T)	ACEI/ARB(84%)+BB(78%)+MRA(100%)	0.5 (0.3−0.7)	0.34 (0.21, 0.56)	<0.001



Annual rates are shown as pump failure death per 100 patient-years.

Hazard ratios were adjusted for conventional covariates including age, sex, NYHA class, LVEF, systolic blood pressure, HF hospitalisation within the last 6 months, and a history of myocardial infarction, hypertension and diabetes (N=10,506). Hazard ratios shown were compared to the placebo arm of CHARM-Preserved. C denotes control arm; T, experimental treatment arm.

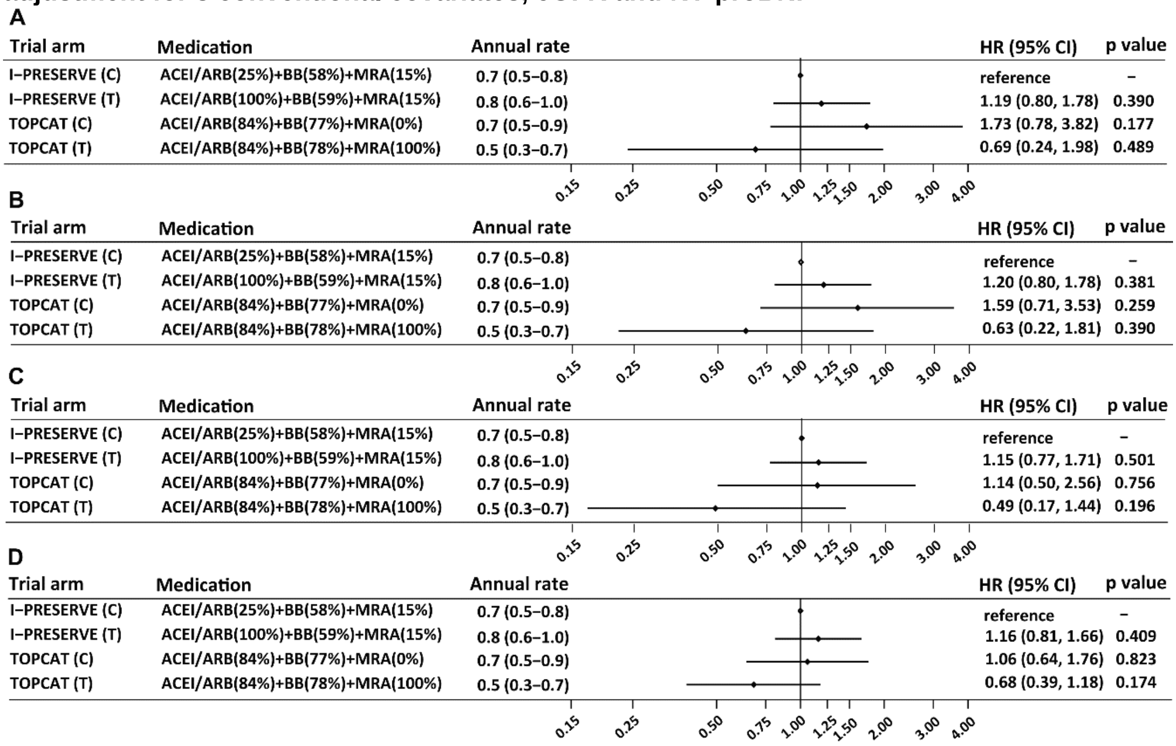
Figure 6-16 Hazard ratio for pump failure death across the trial arms in HF-PEF with adjustment for 8 conventional covariates and eGFR



Annual rates are shown as pump failure death per 100 patient-years.

Panel A, HRs were adjusted for conventional confounding variables in the subset of patients with eGFR measurements available (N=8492); Panel B, adjustment for conventional covariates and eGFR in the subset of patients with eGFR measurements available (N=8492); Panel C, adjustment for conventional covariates and eGFR with simple imputation of eGFR levels (N=10,506). HRs shown were compared to the placebo arm of CHARM-Preserved. C denotes control arm; T, experimental treatment arm.

Figure 6-17 Hazard ratio for pump failure death across the trial arms in HF-PEF with adjustment for 8 conventional covariates, eGFR and NT-proBNP



Annual rates are shown as pump failure death per 100 patient-years.

Panel A, adjustment for conventional confounding variables in the subset of patients with NT-proBNP available [N=4059]; Panel B, adjustment for conventional covariates and eGFR in the subset of patients with NT-proBNP available [N=4059]; Panel C, adjustment for conventional covariates, eGFR and log transformed NT-proBNP in the subset of patients with NT-proBNP available [N=4059]; Panel D, adjustment for conventional covariates, eGFR and log transformed NT-proBNP with simple imputation of eGFR and NT-proBNP in the trials with NT-proBNP collected (i.e. not complete missing) [N=7507]. HRs shown were compared to the placebo arm of I-PRESERVE. C denotes control arm; T, experimental treatment arm.

6.2.6 Sudden death and pump failure death at different time points during follow-up

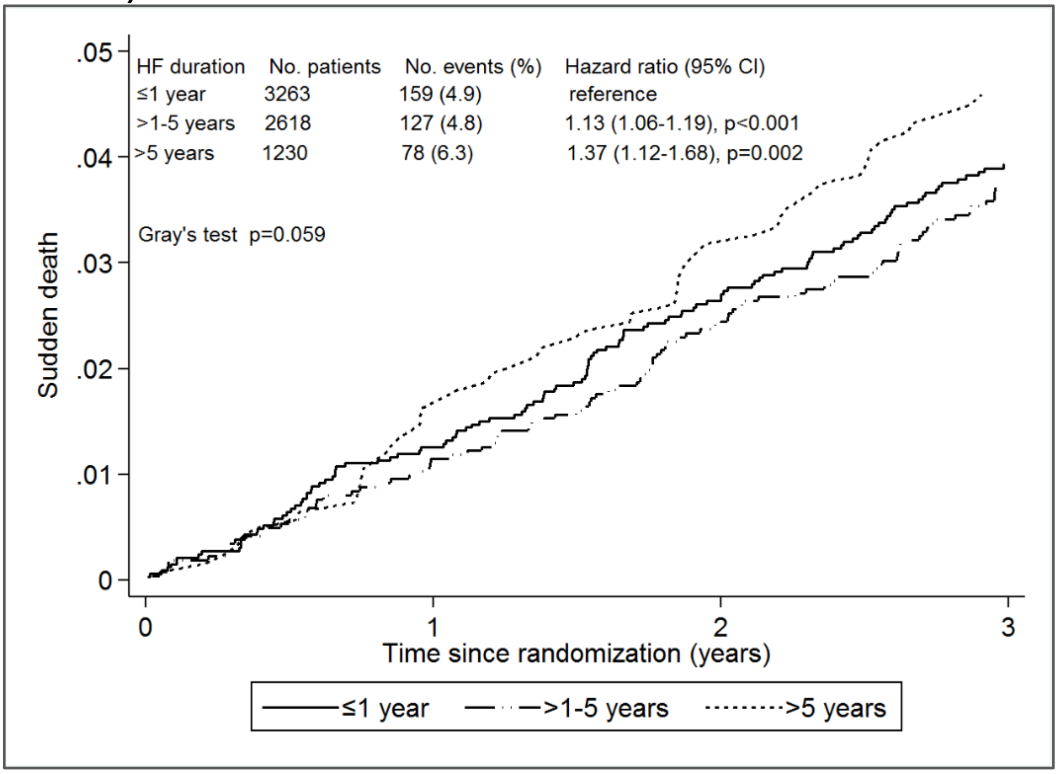
As can be seen from Table 6-4 and Figure 6-1, the cumulative incidences of sudden death at 180 days were consistently low at around 0.5% across these trials. At 1 year, the cumulative incidence was almost double that at 180 days, but remained low in absolute terms at about 1.0-1.3%. At 3 years, the cumulative sudden death rate reached at 4.4% (95% CI 3.6-5.1%) in CHARM-Preserved, 3.7% (95% CI 3.1-4.2%) in I-PRESERVE and remained low at 2.4% (95% CI 1.8-2.9%) in TOPCAT.

The cumulative incidence for pump failure death at 180 days was 0.5% in CHARM-Preserved or lower at 0.2% in I-PRESERVE and TOPCAT (Table 6-5 and Figure 6-11). Similarly, a one-fold increase of the cumulative rates from 180 days to 1 year was observed. Overall, the cumulative incidence of pump failure death at 3 years was quite low, at 3.0% (95% CI 2.4-3.7%) in CHARM-Preserved, 2.1% (95% CI 1.6-2.5%) in I-PRESERVE and 1.4% (95% CI 0.9-1.8%) in TOPCAT.

6.2.7 Sudden death and pump failure death according to HF duration

Figure 6-18 outlines the cumulative incidences of sudden death during follow-up according to the length of time between diagnosis of HF and randomisation based on the merged data from CHARM-Preserved and I-PRESERVE. Overall, there was no significant difference in the cumulative incidence for sudden death among patients with different HF durations (Gray's test p >0.05). After adjusting for confounding variables, there was a trend that longer-standing HF carried a modest higher risk of sudden death: compared to patients diagnosed with HF within 1 year, patients having HF for >1-5 years and over 5 years had a 13% and 37% higher risk for sudden death, respectively (HR 1.13, 95% CI 1.06-1.19, p<0.001; HR 1.37, 95% CI 1.12-1.68, p=0.002, respectively).

Figure 6-18 Cumulative incidence curves for sudden death over time in HF-PEF according to the length of time between diagnosis of HF and randomisation (trials with data available combined)

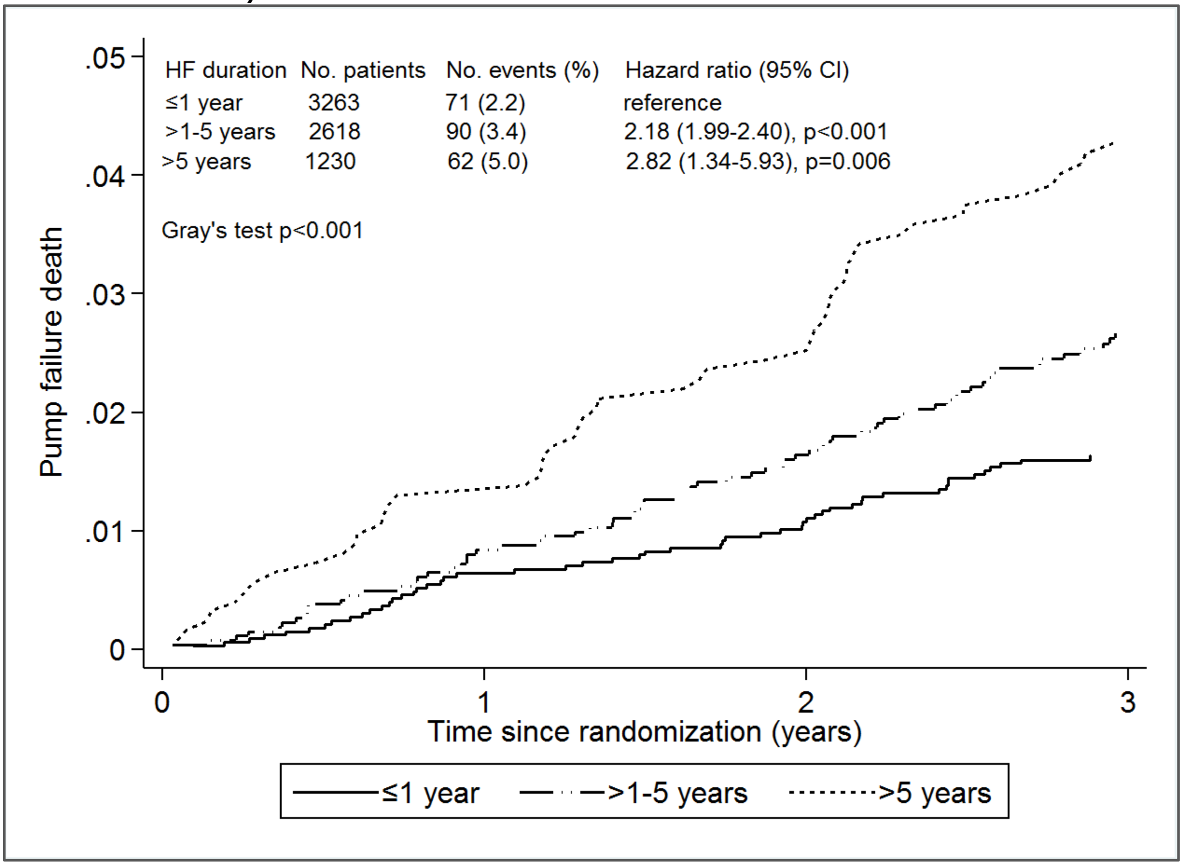


Data were available in CHARM-Preserved and I-PRESERVE (N=7107).

Hazard ratios for sudden death are shown for patients diagnosed within 1 year compared to those diagnosed for >1-5 years and >5 years respectively. These hazard ratios were adjusted for age, sex, NYHA class, LVEF, systolic blood pressure, HF hospitalization with the last 6 months, a history of myocardial infarction, diabetes and hypertension and were counted for within-trial clustering.

The cumulative incidence curves for pump failure death during follow-up by HF duration are presented in Figure 6-19. In general, there was a significant difference in the risk of pump failure death in patients with different HF durations (Gray's test p<0.001), where patients with a longer history of HF carried a much higher risk for pump failure death. Compared to patients diagnosed with HF within 1 year, the risk for pump failure death was around 120% and 180% higher in those diagnosed with HF for >1-5 years and over 5 years respectively (HR 2.18, 95% CI 1.99-2.40, p<0.001; HR 2.82, 95% CI 1.34-5.93, p=0.006).

Figure 6-19 Cumulative incidence curves for pump failure death over time in HF-PEF according to the length of time between diagnosis of HF and randomisation (trials with data available combined)



Data were available in CHARM-Preserved and I-PRESERVE (N=7107).

Hazard ratios for pump failure death are shown for patients diagnosed within 1 year compared to those diagnosed for >1-5 years and >5 years respectively. These hazard ratios were adjusted for age, sex, NYHA class, LVEF, systolic blood pressure, HF hospitalization with the last 6 months, a history of myocardial infarction, diabetes and hypertension and were counted for within-trial clustering.

6.3 Discussion

This analysis including the three largest clinical trials in patients with HF-PEF showed that the rates of sudden death and pump failure death were low across these trials especially in the most recent TOPCAT, and the rate of mode-specific death had negligible difference by treatment group within a trial. There was a temporal downward trend in the rates of sudden death and pump failure death across these trials, and both together led to a falling rate of all-cause death across these trials, whereas the rate of non-CV death remained constant over time. Accordingly, there was an increasing proportional contribution of non-CV death to total mortality across these trials; nevertheless, sudden death remained the most common mode of death, followed by pump failure death, both constituting the majority of CV death. The cumulative incidence was very low at around 0.5% for sudden death and 0.2-0.5% for pump failure death by 6 months. A longer history of HF was associated with a modest higher risk of sudden death but a substantial higher risk of pump failure death.

Despite broad similarities, some notable differences existed in baseline characteristics across these trials. For example, patients in the CHARM-Preserved were more like “HF-REF” patients: more often male and less obese, and more of ischaemic cause and less hypertensive. This discrepancy may be attributable to the heterogenous inclusion criteria used in these trials. In I-PRESERVE and TOPCAT, patients were required to have a higher entry threshold of LVEF (both ≥45%) and other evidence including previous hospital admission for HF, or at least NYHA class III symptoms with evidence of structural heart disease in I-PRESERVE and an elevated natriuretic peptide level (BNP ≥100 pg/ml or NT-proBNP ≥360 pg/ml) in TOPCAT.[11, 12] By contrast, for eligibility in CHARM-Preserved, there was a lower entry threshold of LVEF (>40%) and less stringent requirements for demonstrating the presence of diastolic dysfunction, i.e. symptomatic HF or hospitalisation for, less specific, cardiac reasons if NYHA class II.[9] It is possible that CHARM-Preserved had included a fraction of patients with left ventricular systolic dysfunction.[167]

The average level of NT-proBNP was much higher in TOPCAT than in I-PRESERVE. The reason for this is probably the natriuretic peptide concentration for trial eligibility. Patients in TOPCAT with NT-proBNP available had met the inclusion criteria of NT-proBNP ≥360 pg/ml,[12] and a similar average level of NT-proBNP was reported in the Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) trial in which a similar NT-proBNP inclusion threshold (>400 pg/ml) was applied.[37] On the other hand, I-PRESERVE set no threshold of natriuretic peptides for inclusion,[11] which was also the case for the PEP-CHF study,[166] and these two trials had a similar average level of NT-proBNP. It is worth to mention that natriuretic peptides were highly affected by the comorbidities including obesity, atrial fibrillation and renal dysfunction: obesity was related to a lower level while the presence of atrial fibrillation and renal dysfunction were related to a higher level of natriuretic peptides.[168-171] Compared to I-PRESERVE, patients in TOPCAT tended to be more obese, but were more likely to have a history of atrial fibrillation and renal dysfunction. I cannot rule out the possibility that the comorbidities and their interaction somehow contributed to the observed difference in the NT-proBNP level between I-PRESERVE and TOPCAT.

Of note, the NT-proBNP level was slightly lower in patients with sudden death than those without sudden death in TOPCAT, standing in contrast to the observation in I-PRESERVE and the established fact that NT-proBNP was a powerful prognostic factor for sudden death in HF-PEF.[76, 172] The reason for this inconsistency is unknown, but one possible explanation is that patients with NT-proBNP available was only a small subset of TOPCAT (18%), who were older, more likely to be enrolled from America (than eastern Europe), and had worse renal function and prognosis than patients with NT-proBNP missing.[12] This non-random cohort may not capture the whole picture of the association between NT-proBNP and the risk of sudden death in TOPCAT.

There was a falling trend in the rates of sudden death and pump failure death across these trials over time. This observation was not attributable to the effect of experimental treatments, in agreement with the reality that no therapy has established overall survival benefit in patients with HF-PEF.[9, 11, 12] One possible explanation is that the shifting mode of death was driven by the increasing proportional contribution of non-CV death across trials over time, given that patients in the later trials were older and were more likely to have non-CV comorbid conditions. This, in a way, reflected the background that the understanding of HF-PEF as a disease syndrome has evolved and matured over time, and HF-PEF has been increasingly sophisticatedly defined, and better distinguished from HF-REF,[164] as reflected by the discrepancy in trial inclusion criteria and accordingly the patient characteristics at baseline. On the other hand, the more stringent criteria for trial entry in the later trials may also reflect a desire to establish efficacy of therapy in HF-PEF population by minimising patient variability, given the repeated therapeutic failure in previous trials.

Despite the falling risk, sudden death remained the most common mode of death in the HF-PEF population; besides, findings from observational studies showed that the majority of patients experiencing a sudden death did not have severe left ventricular dysfunction.[173, 174] Therefore, sudden death is still an attractive target for intervention prevention in the HF-PEF population and there has been a recent call for definitive trials of ICD in patients with HF-PEF.[175] Given the lower rate of sudden death and a relatively higher competing risk of death from other causes in HF-PEF than in HF-REF, it is of fundamental importance to identify an enriched subset of patients at high risk for sudden death in designing defibrillator trials in HF-PEF. There is only one prognostic model for sudden death in HF-PEF which did not take into account the prognostic influence of the competing risk of death from other causes and has not yet been validated in an independent cohort.[76] Consequently, there is still an unmet need to develop validated models for sudden death accounting for the competing risk of death from other causes.

Despite the low rate, pump failure death remains the second most common mode of death in HF-PEF. Besides, despite similar definitions used in HF-PEF as in HF-REF,[12, 27] pump failure death may have different mechanisms in HF-PEF and HF-REF, given advanced cardiogenic shock and low cardiac output states are less frequently observed in HF-PEF; instead, patients in HF-PEF more often have terminal events related to progressive right ventricular failure, pulmonary hypertension, end-stage renal disease and multi-organ failure.[44] It is possible that the rates of pump failure death may have been over-estimated, and the actual rates may be even lower than these reported here. On the other hand, it is of great interest and importance to develop prognostic models for pump failure death in HF-PEF which have not been documented, to better understand the mechanism of pump failure death in this population, to aid in nuancing a specific definition tailored to this population, and to identify a high-risk subgroup for decision making in heart transplantation and ventricular assist device and for planning palliative and end-of-life care.

Longer standing HF was associated with higher risks of sudden death and pump failure death alike, but a wider separation by HF duration was observed in the risk of pump failure death than sudden death, especially at the later period of follow-up, which was echoed with the association between HF duration and the risk for mode-specific death in patients with HF-REF in Chapter 3. The HF duration is presumably related to the severity of HF, and, accordingly, the prognosis of HF. There was evidence that the severity of HF better discriminated the risk of pump failure death than sudden death in patients with HF-REF,[84] and the same mechanism may also underlie the observation in patients with HF-PEF, which is yet to be examined in the development of models for both modes of death in this population in the next Chapter. Besides, it is possible that the higher risk of pump failure death during follow-up, especially in the later periods, was mediated by a greater reduction of left ventricular function in patients with longer standing HF over time. However, this assumption cannot be examined here given repeated measurements of LVEF were not available during follow-up.

There were some limitations in this analysis. First, the study was a post-hoc analysis based on clinical trial cohorts, which may be not well representative of "real-world" unselected patients. However, compared to the "real-world" cohorts, cohorts from clinical trials have detailed characterisation and follow-up, which allows more complete multivariable adjustment. It is in patients similar to those in this analysis that device therapies are likely to be investigated. Secondly, in TOPCAT there was a substantial variation in the baseline characteristics and clinical outcomes between regions of enrolment (Americas vs. Russia and Georgia).[176] Although the event rates such as CV death in the Americans were reflective of other clinical trial patients in HF-PEF,[9, 11] much lower event rates were observed in patients enrolled in Russia and Georgia which accounted for 49% of total enrolment.[12] The exclusion of less HF-PEF like patients from Russia and Georgia may lead to a difference in the rates of mode-specific death. Thirdly, the definitions for mode-specific death were not consistent despite broadly similar across these trials. This is not surprising given that there are no standardised definitions for mode-specific death until very recently a consensus was made on the definitions of CV endpoint events used in clinical trials.[46] Use of clinical trials has another strength that cause of death is adjudicated in a careful and standardised way, and this could reduce the bias and variation within a trial. In addition, although the definitions of pump failure death used in HF-PEF was similar to those in HF-REF, pump failure death in HF-PEF may be not classic pump failure as in HF-REF which leads to low cardiac output states and advanced cardiogenic shock. Instead, pump failure in HF-PEF, in many cases, involves progressive right ventricular failure, pulmonary hypertension, end-stage renal disease and multi-organ failure. The rates and the corresponding trends in rates may be different if a more tailored definition had been used in HF-PEF. Finally, in this analysis, time since randomisation instead of time since HF diagnosis was used as the underlying time scale, in other words, the patients examined were the “natural survivors” by the time of randomisation. This may be less likely to reflect the risks of sudden death and pump failure death in the time course of HF progression. However, CHARM-Preserved and I-PRESERVE provided information on the length of time between diagnosis of HF and randomisation.

6.4 Summary

The risks of sudden death and pump failure death were consistently low across the three largest clinical trials in patients with HF-PEF, with little difference by experimental treatment in any trial. There was a downward trend in the rates of sudden death and pump failure death across these trials over time, parallel with a changing characteristic of patients enrolled in these trials; nevertheless, sudden death and pump failure death remained the most common modes of death, altogether accounting for the majority of CV deaths. The absolute rates of sudden death and pump failure death were very low in the early follow-up after randomisation. Longer standing HF was associated with a mild higher risk of sudden death and a substantial higher risk of pump failure death.

Chapter 7 Developing and validating models to predict sudden death and pump failure death in HF-PEF

Despite the declining rates in HF-PEF, sudden death and pump failure death remain the most common modes of death in patients with HF-PEF.[177] Risk stratification of both modes of death would aid with designing trials in the enriched high-risk groups who would benefit most from the therapy under investigation. However, there is a paucity of data in the literature on predictive models for sudden death and, in particular, for pump failure death in patients with HF-PEF. Only one model has been developed to predict sudden death with good discriminatory ability with a C statistic of 0.75.[76] Nevertheless, this model has not been validated in an independent cohort, and did not account for the prognostic influence of the competing risk of death from other causes, which is substantial among the HF-PEF population.[112] No model has been developed to predict pump failure death in HF-PEF. Therefore, there is a need to develop and validate prognostic models for both modes of death in this population taking into account the competing risk of death from other causes.

In this chapter I will develop models to predict sudden death and pump failure death separately in patients with HF-PEF who were enrolled in the I-PRESERVE trial with the use of Fine-Gray sub-distribution hazards models and accounting for the competing risk of death from other causes.[11, 118] For each mode of death, a series of models will be built, first based on candidate variables of demographics, clinical features of HF and medical history, then with the addition of ECG parameters, next with the addition of routine biochemical tests, and finally with the addition of NT-proBNP. In each of the derived models, model performance will be examined by assessing calibration, i.e. the agreement between the observed and predicted cumulative incidences, and discrimination, i.e. the separation of patients at higher risk from those at lower risk, respectively. An individual's risk score for each mode of death will be calculated based on the respective model and the corresponding cumulative incidence will be predicted. The derived models will be externally validated in CHARM-Preserved and in TOPCAT.[9, 12] Validation will be performed by fitting a univariate regression analysis on the risk score which is the sum of the products of predictor coefficients from the derivation model and its corresponding predictor values in the validation cohort.

7.1 Methods

7.1.1 The derivation cohort and candidate prediction variables

Patients with HF-PEF enrolled in the I-PRESERVE trial were used for model derivation after excluding patients with an ICD or CRT-D at baseline.[11]

A number of baseline variables (N=45) were assessed to identify predictors for sudden death and pump failure death separately in I-PRESERVE; these variables included demographics, clinical features of HF, medical history, ECG parameters, routine laboratory tests and NT-proBNP. These variables and their data completeness are shown in detail in Appendix Table 9. A full set of baseline variables was collected in most patients in I-PRESERVE (missing observations <5%), except for NT-proBNP which was measured in 84% of the cohort.

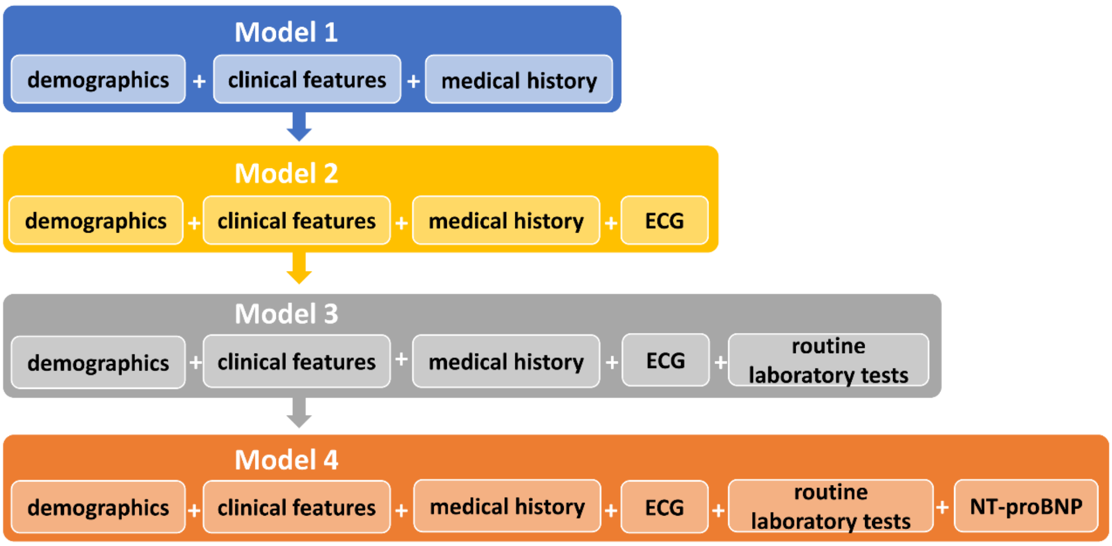
7.1.2 The validation cohorts

The CHARM-Preserved and TOPCAT trials were used for model validation, after excluding patients with an ICD or CRT-D at baseline.[9, 12] Patients with a LVEF <45% in CHARM-Preserved were also excluded to ensure consistency of the LVEF entry threshold across trials.
The clinical variables were available in most patients in both validation cohorts, but laboratory measurements were not recorded in CHARM-Preserved, except eGFR and serum creatinine which were available in the patients from North America (39% of the cohort). In TOPCAT, laboratory measurements were recorded in most patients (missing observations <5%), except blood urea nitrogen (available in 77% of the cohort) and NT-proBNP (available in 18%) (Appendix Table 9).

7.1.3 Statistical analysis

For each mode of death, the prognostic value of each candidate predictor on the cumulative incidence was first examined with the use of a univariate Fine-Gray regression model.[118] For each continuous variable, its linear association with the cumulative incidence of mode-specific death was examined graphically by means of the restricted cubic spline method, and if the response appeared non-linear, certain cut-off values or transformation were used based on the spline curves and clinical relevance. For each categorical variable, appropriate dummy variables were applied based on literature and data availability. For each mode of death, the statistical power for each candidate variable was quantified by X^2 values with one degree of freedom which was positively associated with prediction strength. For each outcome, univariate predictors significant at a p value <0.20 were included in multivariable Fine-Gray regression analyses with a backward stepwise selection at an exclusion p value of 0.05. Each model was developed with the use of the complete-case analysis method. The proportional sub-distribution hazards assumption was examined using time varying terms for the derived models. Specifically, a total of 4 multivariable models were developed for each mode of death: Model 1 was selected from candidate variables of demographics, clinical features and medical history, Model 2 was developed based on candidate variables for Model 1 with the addition of ECG parameters, Model 3 based on routine laboratory tests in addition to variables for Model 2, and Model 4 based on NT-proBNP in addition to variables for Model 3 (Figure 7-1).

Figure 7-1 Model construction steps in HF-PEF



For each derived model, an individual's risk score was calculated as the sum of each predictor value multiplied by its corresponding coefficient from the multivariable model. Model calibration was graphically examined by comparing the predicted cumulative incidence with the observed Aalen-Johansen estimator in each tertile of risk scores (the closer the observed and predicted incidences the better the calibration is). Model discrimination was examined by visually assessing the separation of each set of 3 curves (the wider the separation between the tertiles the better the discrimination is) and by computing the Harrell's C statistic.[71]

External validation was performed in CHARM-Preserved as well as in TOPCAT. In CHARM-Preserved, only Model 1 and Model 2 for mode-specific death were validated, given the laboratory variables were not available in most patients. In TOPCAT the 4 derived models for each mode of death were validated. For each model to be validated, an individual's risk score was calculated as the sum of predictor coefficients from each derivation model multiplied by its corresponding predictor values in the validation cohort. The obtained risk score for each model was then fitted into a univariate Fine-Gray regression analysis. Model performance was examined using the same approach as the derivation procedure. Given the small cohort size of patients with NT-proBNP measurements in TOPCAT, the risk score of Model 4 for each mode of death was categorised into two subgroups by which the observed and predicted cumulative incidences over time were curved and compared.

7.2 Results

7.2.1 Patient characteristics and events in the derivation cohort

The derivation cohort included 4116 patients with HF-PEF enrolled in I-PRESERVE, after excluding 12 patients with an ICD or CRT-D at baseline. The average age was 72 years and 60% were women. The mean LVEF was 59%, the vast majority (97%) were in NYHA class II-III (predominantly in class III [76%]) symptoms, and most had a hypertensive aetiology (64%). The patient characteristics at baseline are shown in Table 7-1.

During a median 52.9 months of follow-up, 877 death events occurred including 230 sudden deaths and 123 pump failure deaths. The corresponding annual rates for sudden death and pump failure death were 1.4 (95% CI 1.2-1.6) and 0.7 (95% CI 0.6-0.9) per 100 patient-years, respectively.

Table 7-1 Baseline characteristics of patients with HF-PEF in the derivation and validation cohorts

	Derivation cohort	Validation cohorts	
	I-PRESERVE (N=4116)	CHARM-Preserved (N=2556)	TOPCAT (N=3401)
Age -years	71.6±6.9	66.9±11.0	68.5±9.6
Female (%)	2485 (60.4)	1077 (42.1)	1760 (51.8)
Race (%)			
White	3847 (93.5)	2337 (91.4)	3028 (89.0)
Black	82 (2.0)	107 (4.2)	294 (8.6)
Asian	35 (0.9)	64 (2.5)	18 (0.5)
Other	152 (3.7)	48 (1.9)	61 (1.8)
Blood pressure -mmHg			
Systolic	136.4±15.0	136.6±18.6	129.3±13.9
Diastolic	78.8±9.1	77.8±10.7	75.9±10.6
Heart rate -beats/min	71.4±10.5	71.4±12.4	69.0±10.6
Body mass index	29.6±5.3	29.3±5.8	32.1±7.1
LVEF -%	59.4±9.2	56.1±8.7	57.1±7.4
NYHA class (%)			
I-II	869 (21.1)	1582 (61.9)	2282 (67.2)
III-IV	3246 (78.9)	974 (38.1)	1116 (32.8)
Aetiology (%)			
Ischaemic	1033 (25.1)	1378 (53.9)	-
Hypertensive	2616 (63.6)	631 (24.7)	-
Other	467 (11.3)	547 (21.4)	-
Medical history (%)			
Current smoking	-	328 (12.8)	357 (10.5)
HF hospitalisation within the previous6 months	1809 (44.0)	935 (36.6)	1787 (52.5)
Myocardial infarction	963 (23.4)	1046 (40.9)	873 (25.7)
Angina	1773 (43.1)	1509 (59.0)	1598 (47.0)
CABG or PCI	542 (13.2)	821 (32.1)	791 (23.3)
Coronary artery disease	2087 (50.7)	1790 (70.0)	1993 (58.6)
Hypertension	3645 (88.6)	1683 (65.8)	3109 (91.5)
Diabetes	1128 (27.4)	727 (28.4)	1096 (32.3)
Atrial fibrillation	1199 (29.1)	762 (29.8)	1192 (35.1)
Stroke	394 (9.6)	222 (8.7)	260 (7.7)
Pacemaker	245 (6.0)	183 (7.2)	247 (7.3)
COPD or asthma	386 (9.4)	-	543 (16.0)
Dyslipidaemia	1801 (43.8)	-	2039 (60.0)
Treatment (%)			
Digitalis	556 (13.5)	680 (26.6)	337 (9.9)
Diuretics	3407 (82.8)	1909 (74.7)	2778 (81.9)
Loop	2140 (52.0)	1576 (61.7)	1764 (52.0)
Thiazide	1552 (37.7)	355 (13.9)	1394 (41.1)
ACEI or ARB	2572 (62.5)	1499 (58.6)	2863 (84.2)
Beta-blocker	2423 (58.9)	1405 (55.0)	2637 (77.7)
MRA	631 (15.3)	302 (11.8)	1698 (49.9)

Calcium channel blocker	1634 (39.7)	833 (32.6)	1284 (37.8)
Antiarrhythmic agent	355 (8.6)	250 (9.8)	289 (8.5)
Antiplatelet	2412 (58.6)	1562 (61.1)	2292 (67.6)
Aspirin	2249 (54.7)	1476 (57.7)	2220 (65.4)
Oral anticoagulant	783 (19.0)	625 (24.5)	774 (22.8)
Lipid lowering agent	1272 (30.9)	1052 (41.2)	1816 (53.5)
Anti-diabetic agent	922 (22.4)	-	943 (27.8)
ECG			
QRS duration -ms	90 (80-106)		92 (82-106)
Atrial fibrillation or flutter (%)	694 (16.9)	421 (16.5)	689 (20.4)
Bundle branch block (%)	613 (14.9)	346 (13.6)	589 (17.4)
Left bundle branch block (%)	336 (8.2)	-	-
Right bundle branch block (%)	283 (6.9)	-	-
Left ventricular hypertrophy (%)	1257 (30.5)	373 (14.7)	738 (21.8)
Laboratory tests			
Albumin -g/L	43.1±3.4	-	41.1±5.4
Aspartate aminotransferase -U/L	23.7±10.5	-	25.4±12.6
Alanine aminotransferase -U/L	23.3±15.2	-	25.1±14.3
Bilirubin -mg/dl	0.65±0.29	-	0.73±0.66
Potassium -mmol/L	4.44±0.47	-	4.25±0.45
Sodium -mmol/L	139.5±3.0	-	141.2±4.2
Haemoglobin -g/L	140.0±15.0	-	133.0±16.8
Haematocrit -%	42.1±4.5	-	41.2±66.3
Leukocyte -10^9/L	7.15±2.0	-	7.07±3.8
Neutrophil -10^9/L	4.53±1.7	-	-
Platelet -10^9/L	233.8±66.8	-	231.6±66.6
Blood urea nitrogen -mg/dl	21.3±9.3	-	21.2±11.3d
Creatinine -mg/dl	1.00±0.32a	1.12±0.41c	1.09±0.30
eGFR -ml/min/1.73m^2	72.6±22.5a	72.2±27.1c	67.7±20.2
eGFR <60 ml/min/1.73m^2	1239 (30.8)a	322 (34.9)c	1307 (38.5)
NT-proBNP -pg/ml	339 (133-960)b	-	843 (463-1727)e

The letters denote the number of patients available: a=4027 (98%), b=3470 (84%), c=922 (39%), d= 2630 (77%), e=615 (18%).

“-” denotes data having not been recorded.

7.2.2 Derivation of the sudden death models

As can be seen from Table 7-2, the 25 strongest prediction variables for sudden death were listed in a descending order of prediction strength from the univariate analysis in I-PRESERVE, and the 5 most powerful prognostic variables were NT-proBNP, LVEF, blood urea nitrogen, male sex and serum creatinine.

Table 7-2 The 25 most powerful predictors for sudden death based on univariate analysis in I-PRESERVE

Prediction variable	sHR (95% CI)	p value	X^2 score
NT-proBNP up to 3000 pg/ml, per 100 pg/ml increase	1.06 (1.05-1.08)	<0.001	96.0
LVEF 45-60%, per 1% decrease	1.08 (1.05-1.10)	<0.001	34.0
Blood urea nitrogen 15-55 mg/dl, per 1 mg/dl increase	1.03 (1.02-1.05)	<0.001	29.6
Male sex	1.92 (1.48-2.49)	<0.001	24.1
Serum creatinine 0.8-2.5 mg/dl, per 0.1 mg/dl increase	1.09 (1.05-1.13)	<0.001	22.9
Ischaemic aetiology	1.89 (1.45-2.47)	<0.001	22.2
Age 60 years or above, per 1 year increase	1.05 (1.03-1.07)	<0.001	22.1
QRS duration 90-130 ms, per 5 ms increase	1.10 (1.05-1.14)	<0.001	20.3
History of myocardial infarction	1.82 (1.39-2.38)	<0.001	18.7
Albumin 35-45 g/L, per 1 g/L decrease	1.10 (1.05-1.15)	<0.001	15.1
Neutrophil -10^9/L, per 10^9/L increase	1.09 (1.04-1.14)	<0.001	14.5
Leukocyte 6-10 10^9/L, per 10^9/L increase	1.18 (1.08-1.29)	<0.001	13.3
History of diabetes	1.64 (1.26-2.14)	<0.001	13.2
History of COPD or asthma	1.91 (1.34-2.72)	<0.001	13.0
HF hospitalisation within the last 6 months	1.60 (1.23-2.07)	<0.001	12.5
Left bundle branch block on ECG	1.84 (1.27-2.68)	0.001	10.2
Bundle branch block on ECG	1.61 (1.18-2.21)	0.003	8.9
BMI 18-45 kg/m^2, per 1 kg/m^2 increase	0.96 (0.93-0.99)	0.004	8.5
eGFR up to 60 ml/min/1.73m^2, per 1 ml/min/1.73m^2 increase	0.98 (0.96-0.99)	0.004	8.5
Heart rate 50-100 beats/min, per 5 beats/min increase	1.09 (1.03-1.16)	0.004	8.1
History of atrial fibrillation	1.46 (1.11-1.90)	0.006	7.6
Potassium 4-6 mmol/L, per 1 mmol/L increase	1.49 (1.11-2.00)	0.008	6.9
Left ventricular hypertrophy on ECG	1.29 (0.99-1.69)	0.061	3.5
Atrial fibrillation or flutter on ECG	1.33 (0.97-1.83)	0.076	3.2
History of dyslipidaemia	0.80 (0.61-1.04)	0.097	2.8

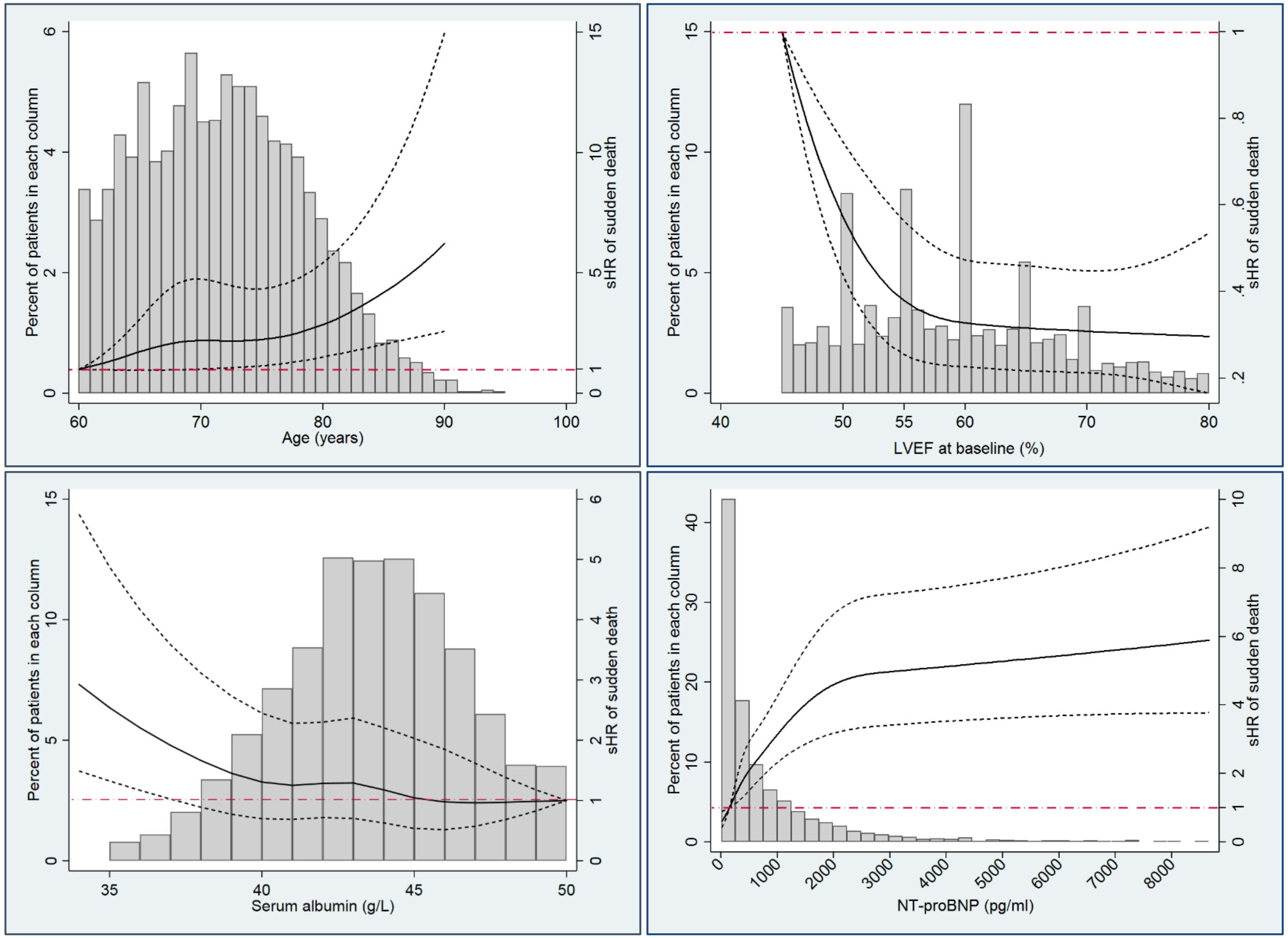
The 4 multivariable models for sudden death derived from 4 sets of candidate variables are summarised in Table 7-3. Model 1 consisted of 7 prediction variables which were independently associated with a higher risk of sudden death including older age, male sex, lower LVEF, higher heart rate, history of diabetes, history of myocardial infarction and HF hospitalisation within the previous 6 months. Model 2 further included LVH and bundle branch block on ECG, and both were associated with a higher risk of sudden death, in addition to the predictive variables in Model 1. In Model 3 serum albumin entered the model and lower albumin were associated with a higher risk of sudden death, but heart rate and bundle branch block on ECG dropped out of the model. In Model 4 albumin and HF hospitalisation in the previous 6 months fell out of the model once NT-proBNP was included with higher levels of NT-proBNP being associated with a higher risk of sudden death.

For the continuous variables, there was no further trend in risk of sudden death for age with values of <60 years, for LVEF with values of >60%, for albumin with values of <35 g/L or >45 g/L, and for NT-proBNP with values of >3000 pg/ml (Figure 7-2).

Table 7-3 Multivariable models for sudden death in I-PRESERVE

	Model 1				Model 2			
Number of patients (number of events)	4109 (230)				4109 (230)			
C statistic	0.71 (95% CI 0.68-0.75)				0.72 (95% CI 0.69-0.75)			
Prediction variable	coefficient	sHR (95% CI)	X^2 score	p value	coefficient	sHR (95% CI)	X^2 score	p value
Age 60 years or above, per 1 year increase	0.049	1.05 (1.03-1.07)	25.5	<0.001	0.050	1.05 (1.03-1.07)	24.8	<0.001
Male sex	0.553	1.74 (1.33-2.27)	16.6	<0.001	0.551	1.74 (1.33-2.27)	16.3	<0.001
LVEF 45-60%, per 1% decrease	0.053	1.05 (1.03-1.08)	15.7	<0.001	0.051	1.05 (1.02-1.08)	14.3	<0.001
Heart rate 50-100 beats/min, per 5 beats/min increase	0.070	1.07 (1.01-1.14)	5.2	0.022	0.067	1.07 (1.01-1.13)	4.8	0.029
History of diabetes	0.519	1.68 (1.28-2.20)	14.3	<0.001	0.531	1.70 (1.30-2.23)	14.7	<0.001
History of myocardial infarction	0.419	1.52 (1.14-2.02)	8.3	0.004	0.435	1.54 (1.16-2.05)	9.0	0.003
HF hospitalisation within the previous 6 months	0.364	1.44 (1.10-1.88)	7.1	0.007	0.373	1.45 (1.11-1.89)	7.5	0.006
Bundle branch block on ECG					0.327	1.39 (1.00-1.92)	3.9	0.049
Left ventricular hypertrophy on ECG					0.376	1.46 (1.11-1.92)	7.3	0.007
	Model 3				**Model 4**			
Number of patients (number of events)	4021 (228)				3467 (195)			
C statistic	0.71 (95% CI 0.68-0.75)				0.75 (95% CI 0.72-0.78)			
Prediction variable	coefficient	sHR (95% CI)	X^2 score	p value	coefficient	sHR (95% CI)	X^2 score	p value
Age 60 years or above, per 1 year increase	0.046	1.05 (1.03-1.07)	21.0	<0.001	0.034	1.03 (1.01-1.06)	9.5	0.002
Male sex	0.529	1.70 (1.30-2.22)	14.8	<0.001	0.506	1.66 (1.23-2.23)	11.3	0.001
LVEF 45-60%, per 1% decrease	0.055	1.06 (1.03-1.08)	16.7	<0.001	0.036	1.04 (1.01-1.07)	5.8	0.017
Heart rate 50-100 beats/min, per 5 beats/min increase								
History of diabetes	0.547	1.73 (1.32-2.27)	15.5	<0.001	0.568	1.76 (1.31-2.37)	14.2	<0.001
History of myocardial infarction	0.415	1.51 (1.14-2.01)	8.2	0.004	0.463	1.59 (1.17-2.15)	9.0	0.003
HF hospitalisation within the previous 6 months	0.336	1.40 (1.07-1.83)	6.0	0.014				
Bundle branch block on ECG								
Left ventricular hypertrophy on ECG	0.395	1.48 (1.13-1.95)	8.0	0.005	0.340	1.40 (1.04-1.90)	4.9	0.027
Albumin 35-45 g/L, per 1 g/L decrease	0.065	1.07 (1.01-1.12)	6.2	0.013				
NT-proBNP up to 3000 pg/ml, per 100 pg/ml increase					0.048	1.05 (1.03-1.06)	42.6	<0.001

Figure 7-2 Histograms of age (A), LVEF (B), serum albumin (C), and NT-proBNP (D) and the corresponding spline curves with the risks of sudden death in I-PRESERVE



The columns are the histogram of a continuous variable, and the left axis shows the percent of patients in each column. The black solid line is the subdistribution hazard ratio (sHR) of sudden death with the corresponding continuous variable and the black dot lines are the 95% confidence intervals. The maroon dash-dot line is the reference line with a sHR of 1.0 (i.e. no association).

7.2.3 Derivation of the pump failure death models

The 25 most powerful prediction variables for pump failure death are shown in Table 7-4 in a descending order of prediction strength based on the univariate analysis, and the 5 strongest prediction variables were NT-proBNP, blood urea nitrogen, serum creatinine, age and eGFR.

Table 7-4 The 25 most powerful predictors for pump failure death based on univariate analysis in I-PRESERVE

Prediction variable	sHR (95% CI)	p value	X^2 score
NT-proBNP up to 3000 pg/ml, per 100 pg/ml increase	1.08 (1.06-1.10)	<0.001	81.7
Blood urea nitrogen 15-55 mg/dl, per 1 mg/dl increase	1.06 (1.04-1.07)	<0.001	62.7
Serum creatinine 0.8-2.5 mg/dl, per 0.1 mg/dl increase	1.15 (1.11-1.19)	<0.001	53.1
Age 60 years or above, per 1 year increase	1.08 (1.06-1.11)	<0.001	41.0
eGFR up to 80 ml/min/1.73m^2, per 1 ml/min/1.73m^2 increase	0.97 (0.96-0.98)	<0.001	39.3
eGFR <60 ml/min/1.73m^2	2.79 (1.95-4.00)	<0.001	31.4
Atrial fibrillation or flutter on ECG	2.74 (1.89-3.97)	<0.001	28.4
Neutrophil 4-10*10^9/L, per 10^9/L increase	1.34 (1.20-1.50)	<0.001	26.3
History of atrial fibrillation	2.52 (1.77-3.59)	<0.001	26.3
Albumin 35-45 g/L, per 1 g/L decrease	1.16 (1.10-1.24)	<0.001	24.1
Diastolic BP up to 80 mmHg, per 1 mmHg decrease	1.05 (1.03-1.07)	<0.001	22.9
Leukocyte 6-13*10^9/L, per 10^9/L increase	1.22 (1.10-1.35)	<0.001	14.5
History of diabetes	2.00 (1.40-2.85)	<0.001	14.4
LVEF 45-60%, per 1% decrease	1.06 (1.03-1.10)	<0.001	12.3
HF hospitalisation within the past 6 months	1.86 (1.29-2.66)	0.001	11.4
QRS duration 90-130 ms, per 1 ms increase	1.02 (1.01-1.03)	0.001	11.0
Potassium 4-5.5 mmol/L, per 1 mmol/L increase	2.01 (1.31-3.07)	0.001	10.4
History of dyslipidaemia	0.54 (0.37-0.80)	0.002	9.5
BMI up to 30 kg/m^2, per 1 kg/m^2 increase	0.91 (0.85-0.97)	0.003	8.9
Pacemaker use	2.21 (1.29-3.79)	0.004	8.4
Heart rate 50-100 beats/min, per 5 beats/min increase	1.13 (1.04-1.23)	0.004	8.1
Ischaemic aetiology	1.69 (1.17-2.45)	0.005	7.8
History of hypertension	0.56 (0.35-0.88)	0.012	6.4
Male sex	1.57 (1.10-2.23)	0.013	6.3
Bundle branch block on ECG	1.70 (1.12-2.60)	0.014	6.1

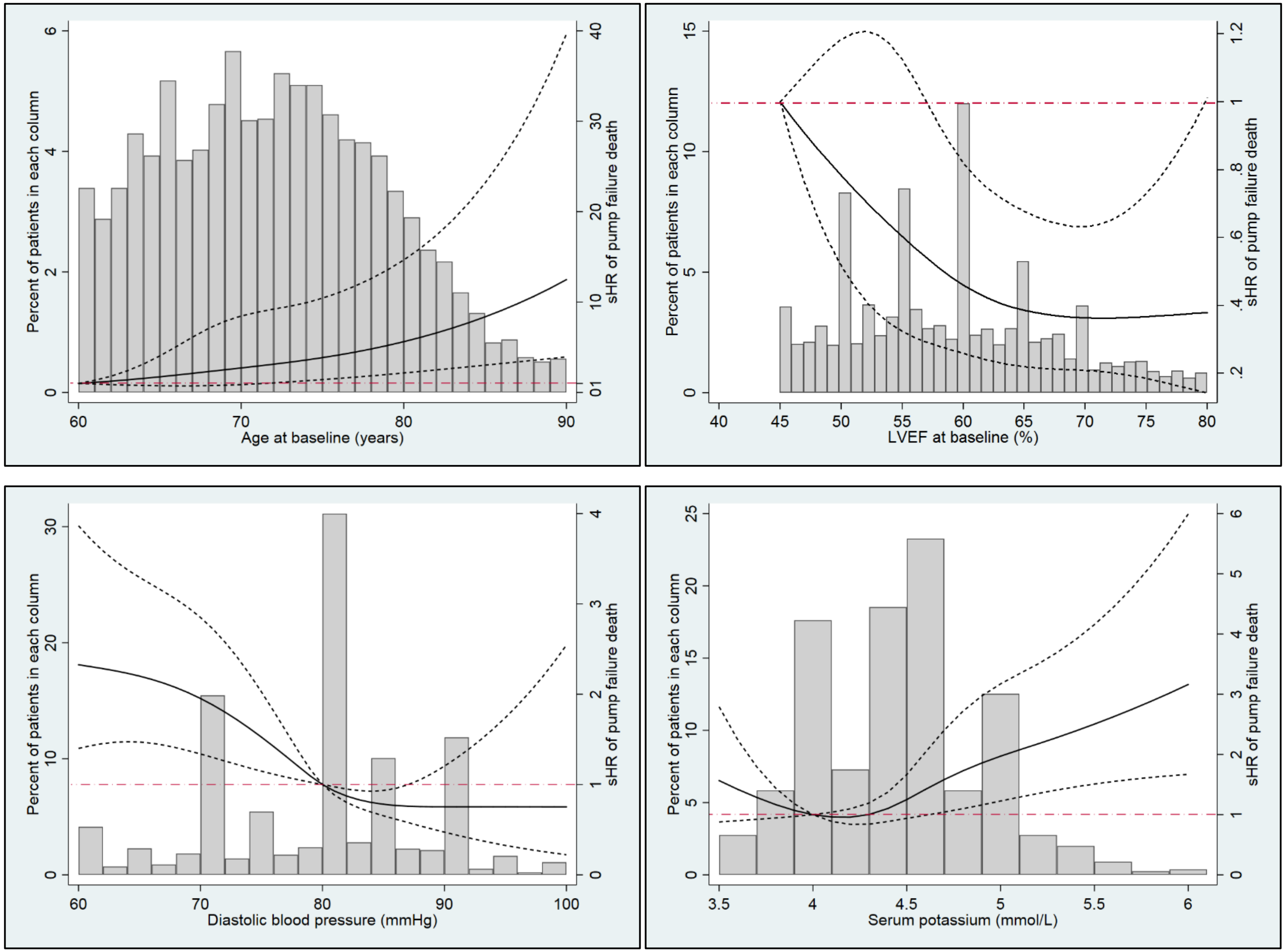
The 4 multivariable models for pump failure death are presented in Table 7-5. Specifically, Model 1 included 8 variables, in which older age, male sex, lower LVEF or diastolic blood pressure, higher heart rate, and history of diabetes or atrial fibrillation were associated with a higher risk of pump failure death, while a history of dyslipidaemia was associated with a lower risk. None of the candidate variables of ECG parameters were further selected, i.e. Model 2 was identical to Model 1. Based on Model 1, Model 3 additionally selected serum albumin, potassium and creatinine, and a lower level of albumin and higher levels of potassium and creatinine were associated with a higher risk of pump failure death. However, with the addition of these variables male sex and heart rate fell out of the model. Model 4 included NT-proBNP, and a higher level of NT-proBNP was associated with a higher risk of pump failure death while LVEF, potassium, albumin and a history of atrial fibrillation fell out of the model.

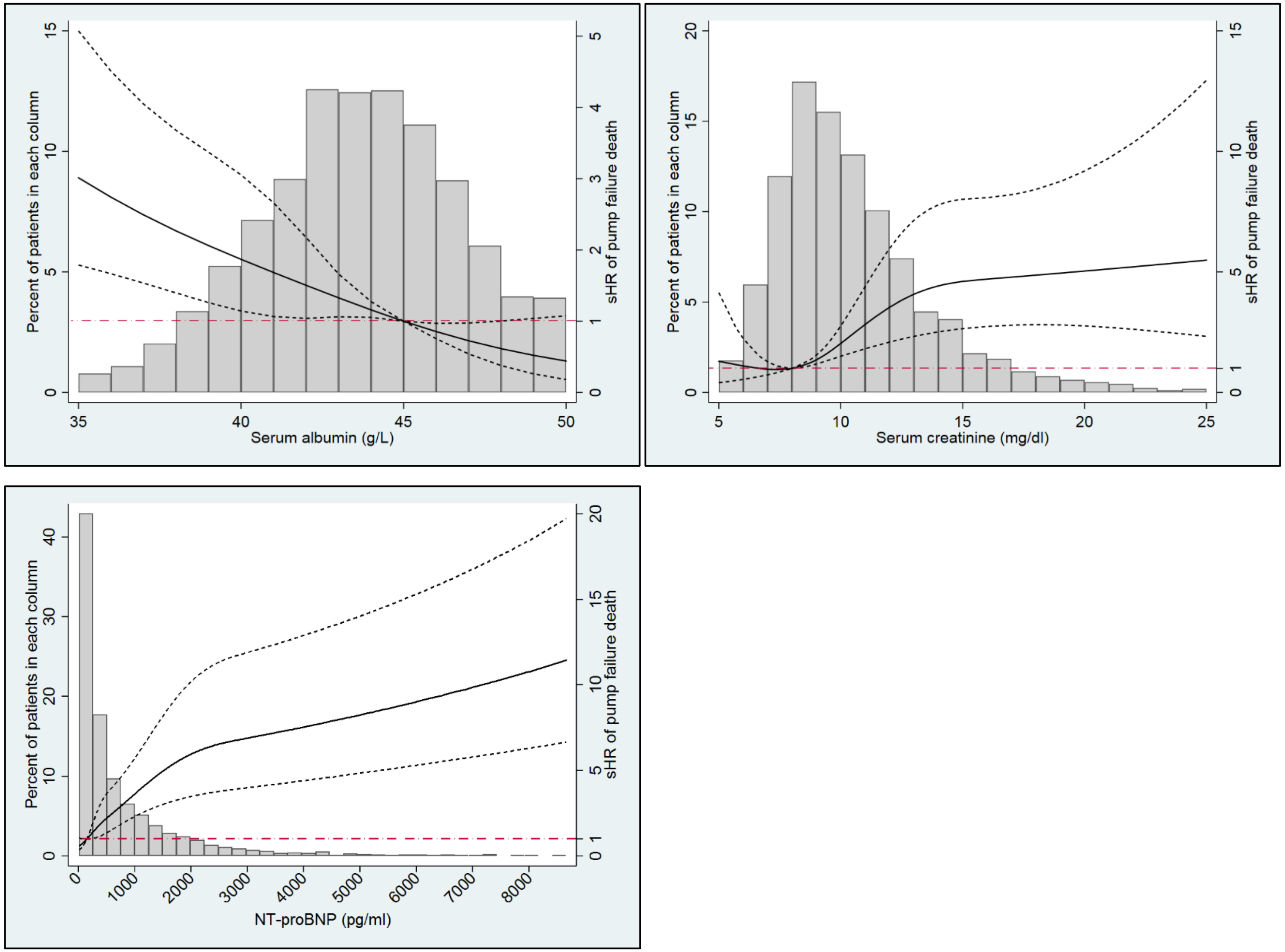
For the continuous variables, there was no further trend in the risk of pump failure death for age with values of <60 years, for LVEF with values of >60%, for diastolic blood pressure with values of >80 mmHg, for potassium with values of <4 mmol/L or >5.5 mmol/L, for albumin with values of <35 g/L or >45 g/L, for creatinine with values of <0.8 mg/dl or >2.5 mg/dl, and for NT-proBNP with values of >3000 pg/ml (Figure 7-3).

Table 7-5 Multivariable models for pump failure death in I-PRESERVE

	Model 1				Model 2			
Number of patients (number of events)	4109 (123)							
C statistic	0.78 (95% CI 0.75-0.82)							
Prediction variable	coefficient	sHR (95% CI)	X^2 score	p value				
Age 60 years or above, per 1 year increase	0.067	1.07 (1.04-1.10)	24.9	<0.001	Same as Model 1			
Male sex	0.395	1.48 (1.03-2.13)	4.6	0.032				
Heart rate 50-100 beats/min, per 5 beats/min increase	0.099	1.10 (1.02-1.20)	5.5	0.019				
LVEF 45-60%, per 1% decrease	0.052	1.05 (1.02-1.09)	8.6	0.003				
Diastolic BP up to 80 mmHg, per 1 mmHg decrease	0.041	1.04 (1.02-1.07)	11.3	0.001				
History of diabetes	0.839	2.31 (1.63-3.29)	21.7	<0.001				
History of dyslipidaemia	-0.646	0.52 (0.36-0.77)	10.6	0.001				
History of atrial fibrillation	0.593	1.81 (1.25-2.62)	9.8	0.002				
	Model 3				**Model 4**			
Number of patients (number of events)	3993 (116)				3448 (98)			
C statistic	0.80 (95% CI 0.76-0.83)				0.80 (95% CI 0.76-0.84)			
Prediction variable	coefficient	sHR (95% CI)	X^2 score	p value	coefficient	sHR (95% CI)	X^2 score	p value
Age 60 years or above, per 1 year increase	0.055	1.06 (1.03-1.09)	14.1	<0.001	0.044	1.05 (1.01-1.08)	8.5	0.004
Male sex								
Heart rate 50-100 beats/min, per 5 beats/min increase								
LVEF 45-60%, per 1% decrease	0.052	1.05 (1.02-1.09)	7.8	0.005				
Diastolic BP up to 80 mmHg, per 1 mmHg decrease	0.028	1.03 (1.00-1.05)	5.2	0.022	0.028	1.03 (1.00-1.06)	4.0	0.044
History of diabetes	0.718	2.05 (1.41-2.98)	14.1	<0.001	0.758	2.13 (1.45-3.15)	14.5	<0.001
History of dyslipidaemia	-0.656	0.52 (0.35-0.78)	10.2	0.001	-0.676	0.51 (0.33-0.79)	9.1	0.003
History of atrial fibrillation	0.588	1.80 (1.23-2.63)	9.3	0.002				
Potassium 4-5.5 mmol/L, per 1 mmol/L increase	0.486	1.63 (1.06-2.50)	4.9	0.027				
Albumin 35-45 g/L, per 1 g/L decrease	0.096	1.10 (1.03-1.18)	7.6	0.006				
Serum creatinine 0.8-2.5 mg/dl, per 0.1 mg/dl increase	0.069	1.07 (1.02-1.12)	8.5	0.004	0.060	1.06 (1.01-1.11)	6.1	0.014
NT-proBNP up to 3000 pg/ml, per 100 pg/ml increase					0.059	1.06 (1.04-1.08)	31.4	<0.001

Figure 7-3 Histograms of age (A), LVEF (B), diastolic BP (C), serum potassium (D), albumin (E), creatinine (F) and NT-proBNP (G) and the corresponding spline curves with the risks of pump failure death in I-PRESERVE


Percent of patients in each column
sHR of pump failure death
Age at baseline (years)
LVEF at baseline (%)
Diastolic blood pressure (mmHg)
Serum potassium (mmol/L)


Percent of patients in each column
sHR of pump failure death
Serum albumin (g/L)
Percent of patients in each column
sHR of pump failure death
Serum creatinine (mg/dl)
Percent of patients in each column
sHR of pump failure death
NT-proBNP (pg/ml)

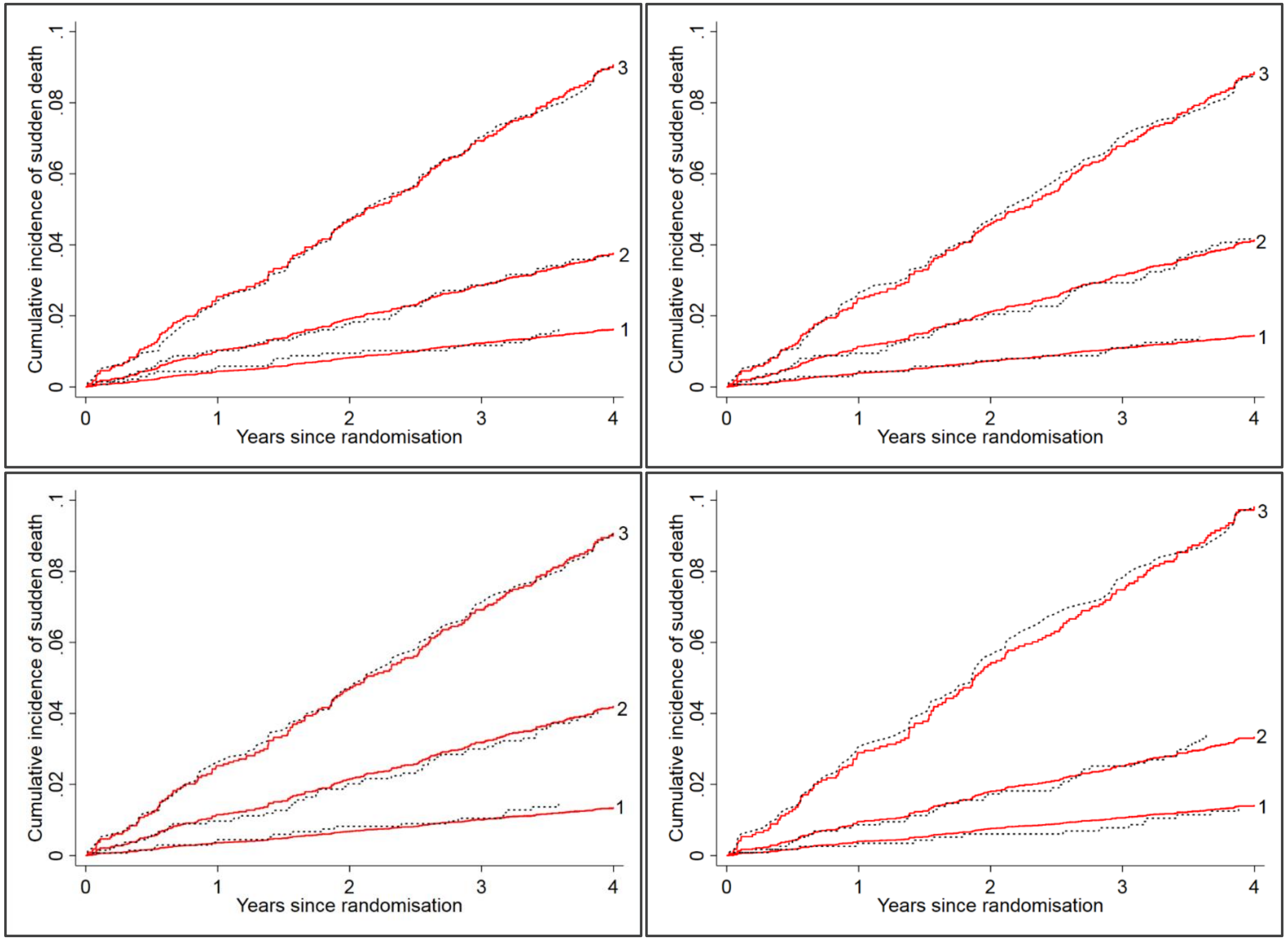
7.2.4 Performance of the derived models

As can be seen from Figure 7-4, each sudden death model demonstrated excellent calibration: the predicted cumulative incidence curve was in good agreement with the corresponding observed one based on the Aalen-Johansen estimator in each tertile of the risk score over time. Both sets of three curves were well separated, suggesting good discrimination; in particular, Model 4 identified the highest tertile with 7 times the risk of the lowest tertile. The discrimination was further quantified by the Harrell's C statistic with values of 0.71 (95% CI 0.68-0.75) in Model 1, 0.72 (95% CI 0.69-0.75) in Model 2, 0.71 (95% CI 0.68-0.75) in Model 3 and 0.75 (95% CI 0.72-0.78) in Model 4.

For each of the pump failure death models, the predicted and observed cumulative incidences were almost identical in each tertile of the risk score over time, indicating good calibration (Figure 7-5). Compared to the lowest tertile, the risk for pump failure death was 12 times higher in the highest tertile in Model 1, and this figure was 13 in Model 3 and 20 in Model 4 respectively. The excellent discrimination was also confirmed by the Harrell's C statistic with values of 0.78 (95% CI 0.75-0.82) in Model 1, 0.80 (95% CI 0.76-0.83) in Model 3 and 0.80 (95% CI 0.76-0.84) in Model 4.

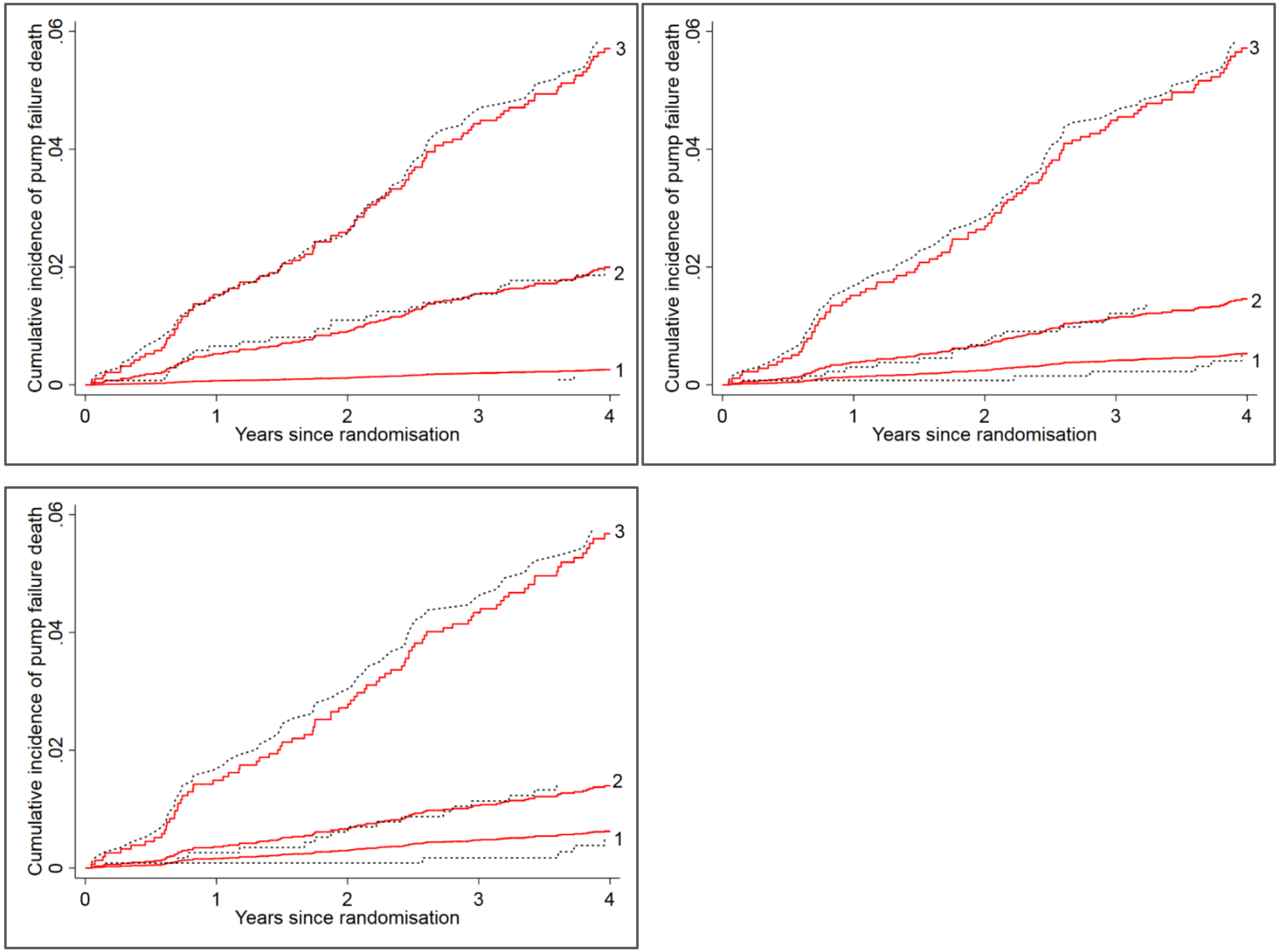
Some violation of proportional sub-distribution hazards assumption was observed for creatinine (p=0.043) in the pump failure death models. When graphically displaying the cumulative incidences of pump failure death by tertiles of creatinine, the curves generally did not cross over time, suggesting this was statistically significant but not relevant to the performance of the model (Figure 7-6).

Figure 7-4 Observed vs. predicted cumulative incidence curves for sudden death by tertiles of the risk scores based on the sudden death models in I-PRESERVE



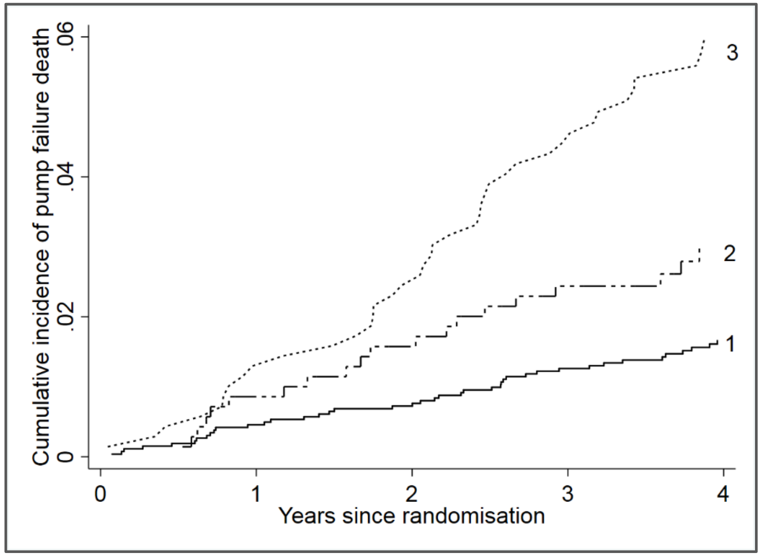
Red solid lines are predicted cumulative incidence curves based the corresponding models, and black dotted lines are the observed cumulative incidence curves based on Aalen-Johansen estimators.

Figure 7-5 Observed vs. predicted cumulative incidence curves for pump failure death by tertiles of the risk scores based on the pump failure death models in I-PRESERVE



Red solid lines are predicted cumulative incidence curves based the corresponding models, and black dotted lines are the observed cumulative incidence curves based on Aalen-Johansen estimators.

Figure 7-6 Cumulative incidence curves for pump failure death by tertiles of serum creatinine level in I-PRESERVE



7.2.5 External validation of the models in CHARM-Preserved

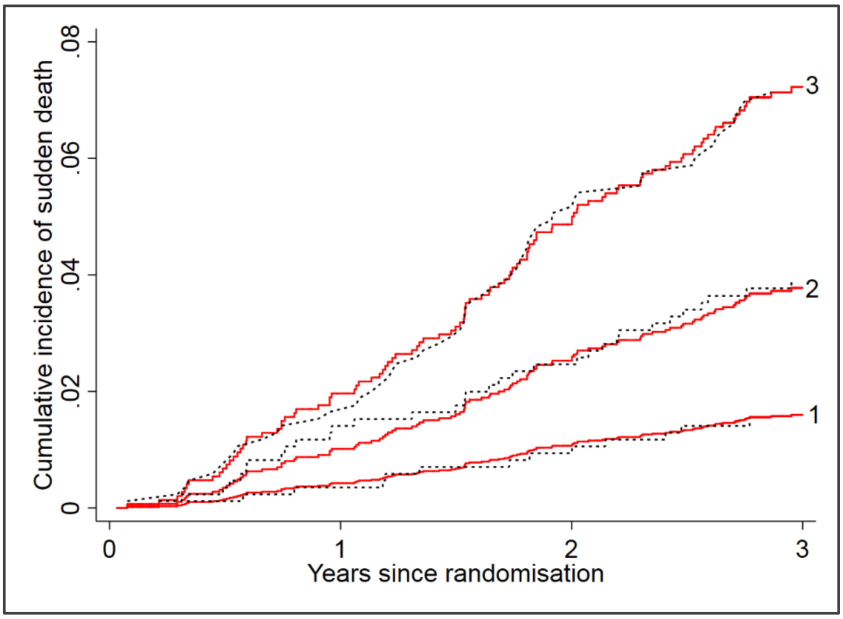
External validation was performed in 2556 patients in CHARM-Preserved after excluding 23 patients with an ICD or CRT-D and 444 patients with a LVEF below 45%. There were some differences in baseline characteristics between CHARM-Preserved and I-PRESERVE. Patients in CHARM-Preserved tended to be younger and more often men with a lower mean LVEF, and were more likely to have an ischaemic aetiology and a history of myocardial infarction, but had a lower prevalence of previous HF hospitalisation and LVH on ECG. Patient characteristics at baseline are summarised in Table 7-1.

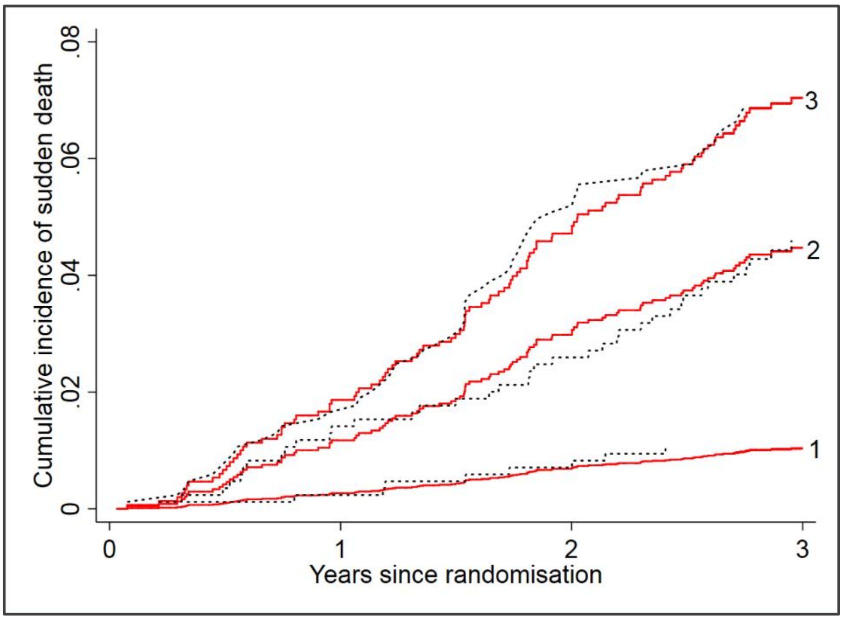
During a median 36.6 months of follow-up, 409 death events were recorded in CHARM-Preserved including 110 sudden deaths and 82 pump failure deaths, with the corresponding annual rates of 1.5 (95% CI 1.2-1.8) and 1.1 (95% CI 0.9-1.4) per 100 patient-years, respectively.

For the sudden death models, there was a marginal decrease in discrimination ability when validated in CHARM-Preserved, with a Harrell's C statistic of 0.68 (95% CI 0.64-0.73) for Model 1 and 0.69 (95% CI 0.65-0.74) for Model 2. For Model 1 the predicted and observed cumulative incidences were broadly similar across tertiles and both set of curves were evenly distributed. However, Model 2 was less able to discriminate the higher two tertiles and slightly under-predicted the highest tertile but over-estimated the middle tertile in the middle period of follow-up (Figure 7-7).

For the pump failure death Model 1 (or Model 2), history of dyslipidaemia was not recorded and treatment with lipid lowering agents was used instead. Discrimination remained excellent in CHARM-Preserved with a Harrell's C statistic of 0.79 (95% CI 0.75-0.83), and calibration was generally reasonable over time (Figure 7-8).

Figure 7-7 Observed vs. predicted cumulative incidence curves for sudden death by tertiles of the risk scores in CHARM-Preserved



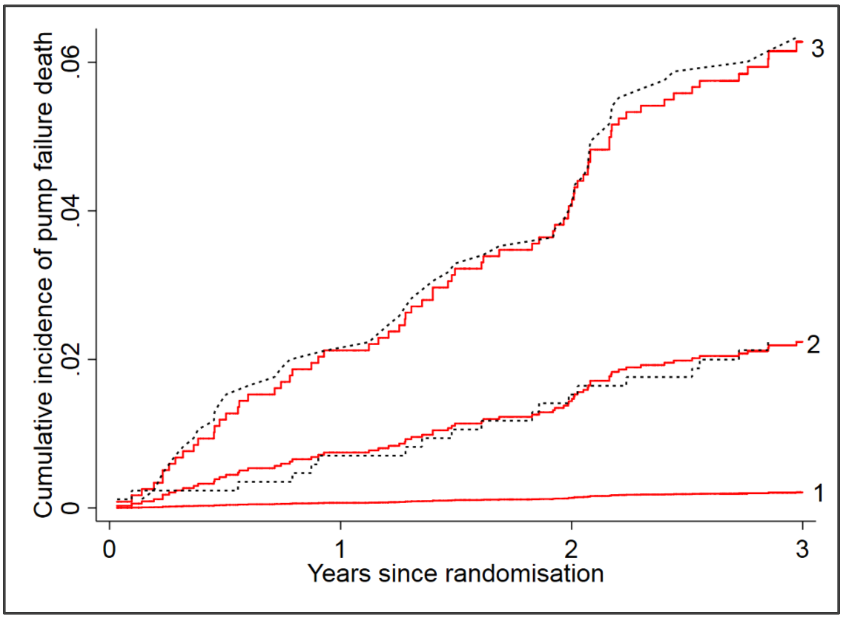


Panel A. Validation of sudden death model 1 from I-PRESERVE in CHARM-Preserved; Panel B. Validation of sudden death model 2 from I-PRESERVE in CHARM-Preserved.

Because laboratory measurements were not examined in the majority of patients in CHARM-Preserved, sudden death model 3 and model 4 from I-PRESERVE were not validated in CHARM-Preserved.

Red solid lines are predicted cumulative incidence curves based the corresponding models, and black dotted lines are the observed cumulative incidence curves based on Aalen-Johansen estimators.

Figure 7-8 Observed vs. predicted cumulative incidence curves for pump failure death by tertiles of the risk scores in CHARM-Preserved



Validation of the pump failure death model 1 (or Model 2) from I-PRESERVE in CHARM-Preserved. Because laboratory measurements were not examined in the majority of patients in CHARM-Preserved, sudden death model 3 and model 4 from I-PRESERVE were not validated in CHARM-Preserved.

Red solid lines are predicted cumulative incidence curves based the corresponding models, and black dotted lines are the observed cumulative incidence curves based on Aalen-Johansen estimators.

7.2.6 External validation of the models in TOPCAT

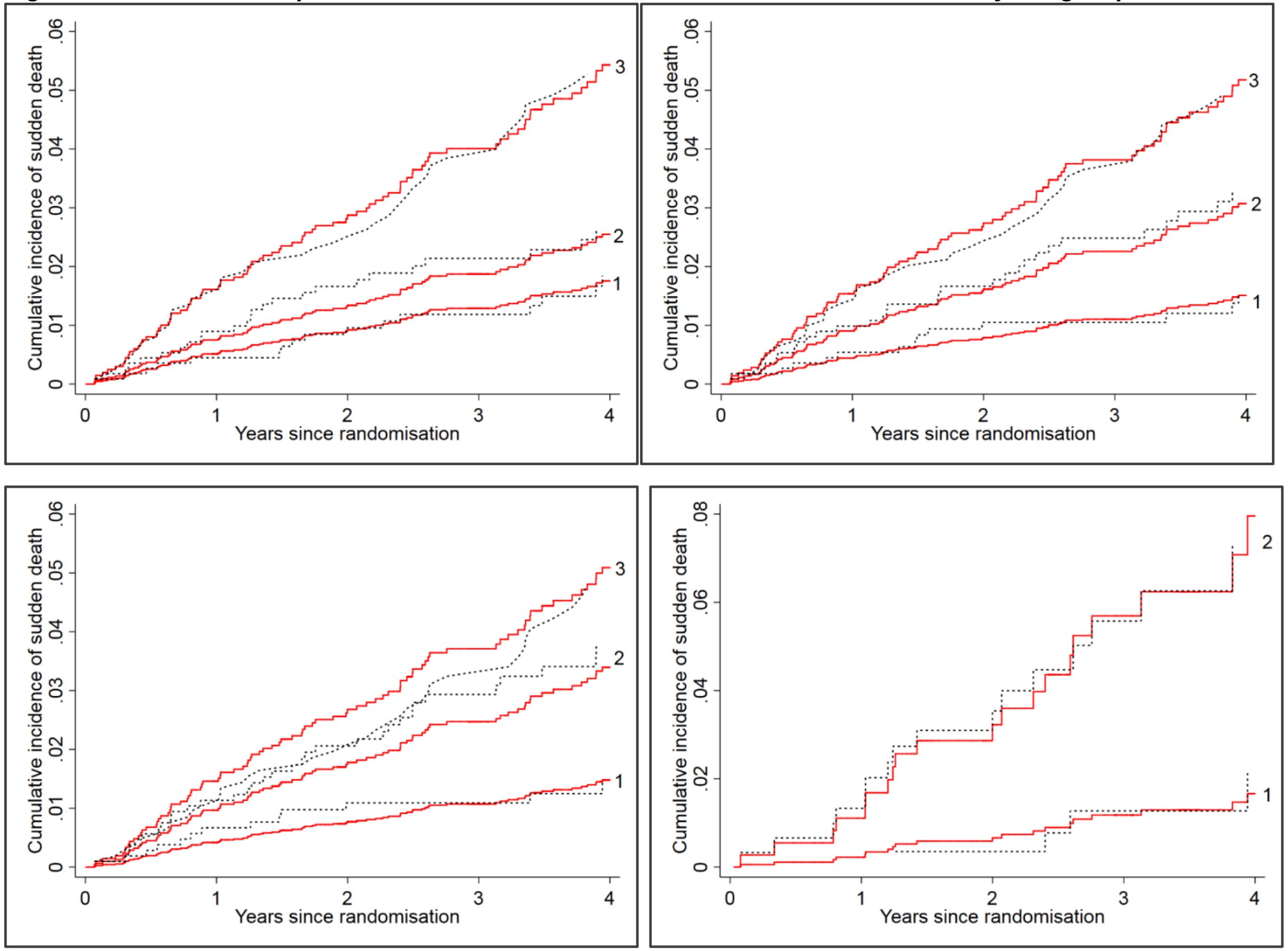
Models developed in I-PRESERVE were also externally validated in 3401 patients in TOPCAT after excluding 44 patients with an ICD or CRT-D. Baseline characteristics were broadly similar between I-PRESERVE and TOPCAT, but some difference was also noted. Patients in TOPCAT were slightly younger and more often men, and had a lower level of mean LVEF, blood pressure and serum albumin, but had a substantially higher level of median NT-proBNP among the 615 patients (18%) with NT-proBNP available. Patients in TOPCAT had a higher average BMI and were more likely to have a history of dyslipidaemia, renal dysfunction or prior HF hospitalisation, but had a lower prevalence of LVH on ECG, compared to I-PRESERVE. Patient characteristics at baseline are shown in Table 7-1.

There were 520 death events in TOPCAT over a median 41.1 months of follow-up, including 110 sudden deaths and 65 pump failure deaths with the corresponding annual rates of 1.0 (95% CI 0.8-1.2) and 0.6 (95% CI 0.4-0.7) per 100 patient-years, respectively.

For the sudden death models, a modest decrease in discrimination ability was observed when validated in TOPCAT, with a Harrell's C of 0.66 (95% CI 0.61-0.71) for Model 1, 0.65 (95% CI 0.60-0.70) for Model 2, 0.64 (95% CI 0.59-0.69) for Model 3, and 0.73 (95% CI 0.64-0.83) for Model 4. Despite some disagreement in the middle period of follow-up, the observed and predicted cumulative incidences were generally similar across subgroups except for Model 3 which failed to separate the higher two tertiles, and largely overestimated the highest tertile and underestimated the middle one (Figure 7-9).

For the pump failure death models, discrimination considerably decreased but remained good in TOPCAT with a Harrell's C of 0.72 (95% CI 0.65-0.79) for Model 1, 0.71 (95% CI 0.63-0.78) for Model 3, and 0.80 (95% CI 0.68-0.92) for Model 4. In general, the calibration was reasonable in these models, except Model 1 which did not separate the lower two tertiles (Figure 7-10).

Figure 7-9 Observed vs. predicted cumulative incidence curves for sudden death by subgroups of the risk scores in TOPCAT

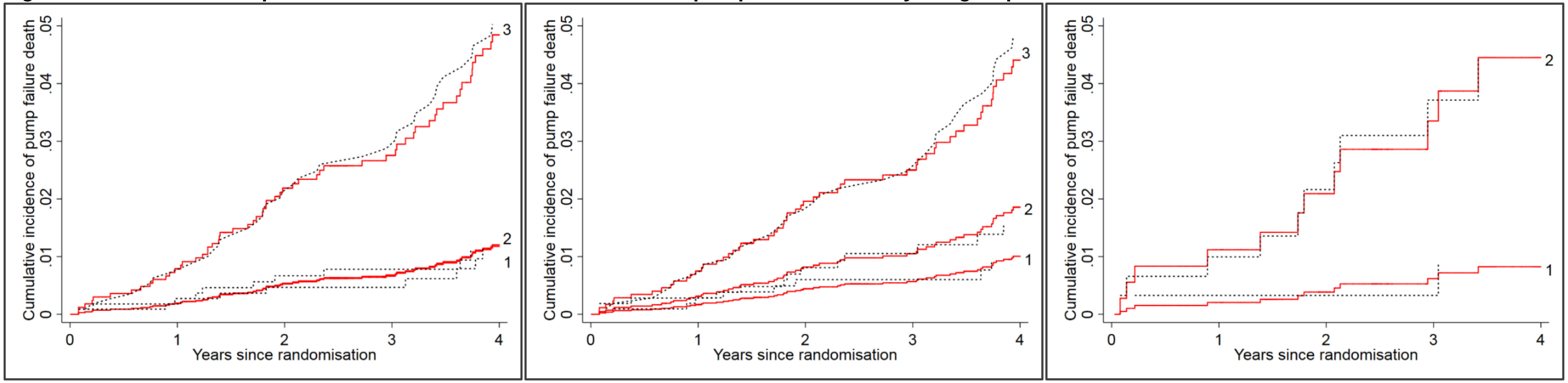


Panel A. Validation of sudden death model 1 from I-PRESERVE in TOPCAT; Panel B. Validation of sudden death model 2 from I-PRESERVE in TOPCAT; Panel C. Validation of sudden death model 3 from I-PRESERVE in TOPCAT; Panel D. Validation of sudden death model 4 from I-PRESERVE in TOPCAT.

*Given the small cohort size of patients with NT-proBNP measurements in TOPCAT (N=615 [18%]), the risk score of Model 4 was categorised into 2 rather than 3 subgroups.

Red solid lines are predicted cumulative incidence curves based the corresponding models, and black dotted lines are the observed cumulative incidence curves based on Aalen-Johansen estimators.

Figure 7-10 Observed vs. predicted cumulative incidence curves for pump failure death by subgroup of the risk scores in TOPCAT



Panel A. Validation of the pump failure death model 1 (or 2) from I-PRESERVE in TOPCAT; Panel B. Validation of the pump failure death model 3 from I-PRESERVE in TOPCAT; Panel C. Validation of the pump failure death model 4 from I-PRESERVE in TOPCAT. *Given the small cohort size of patients with NT-proBNP measurements in TOPCAT (N=615 [18%]), the risk score of Model 4 was categorised into 2 other than 3 subgroups. Red solid lines are predicted cumulative incidence curves based the corresponding models, and black dotted lines are the observed cumulative incidence curves based on Aalen-Johansen estimators.

7.2.7 Predicting an individual's risk

The multivariable models presented in Table 7-3 and Table 7-5 from I-PRESERVE can be used to calculate an individual's risk score for sudden death and pump failure death respectively, by adding up the products of the value and their corresponding coefficient of each prediction variable from each model. Based on the obtained risk score, the corresponding cumulative incidence for each mode of death within 4 years can be estimated using the corresponding curves outlined in Figure 7-11 and Figure 7-12, which showed the distribution of the risk scores for each mode of death, based on the clinical model (Model 1) and the model with NT-proBNP (Model 4), and its association with the corresponding predicted cumulative incidence by 4 years in I-PRESERVE, separately.

Figure 7-11 Distribution of the risk scores for sudden death based on Model 1 (A) and Model 4 (B) and its relation to cumulative incidences within 4 years in I-PRESERVE

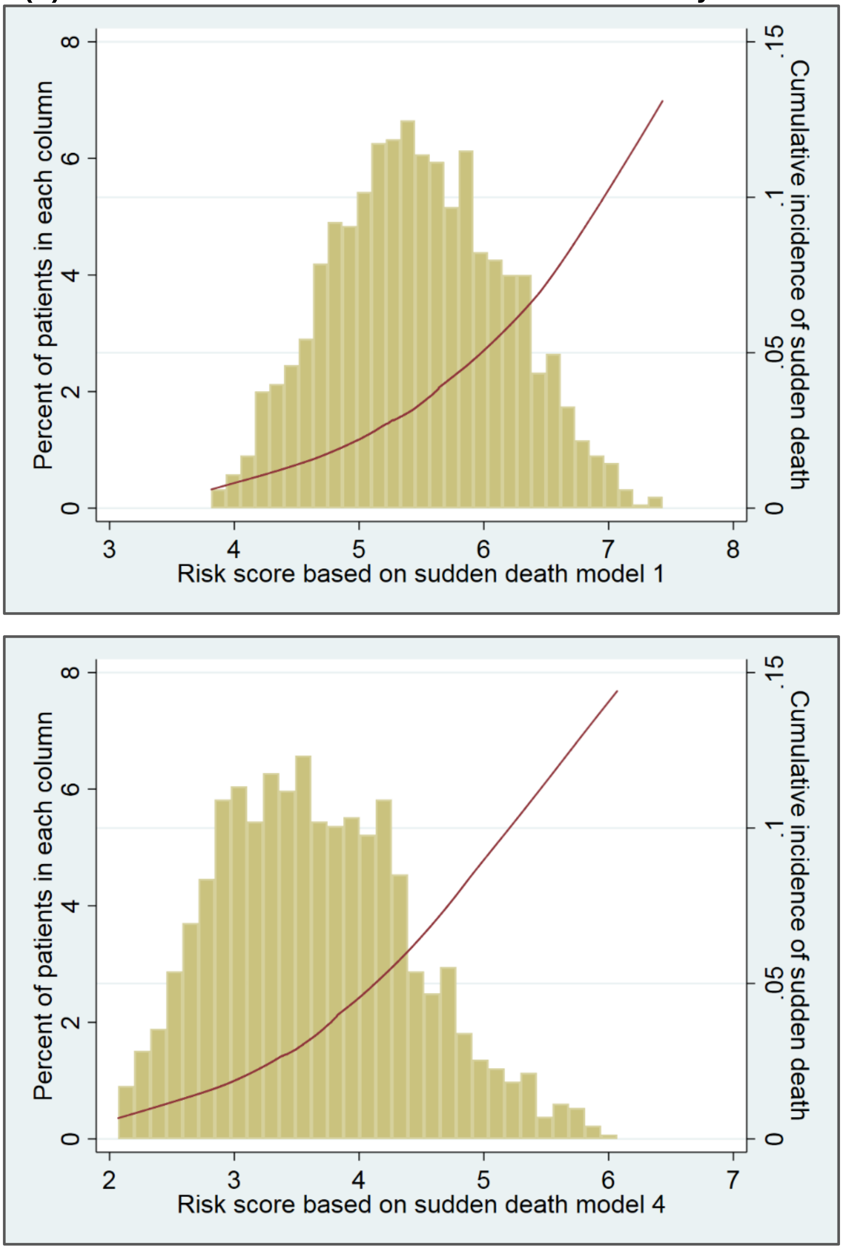
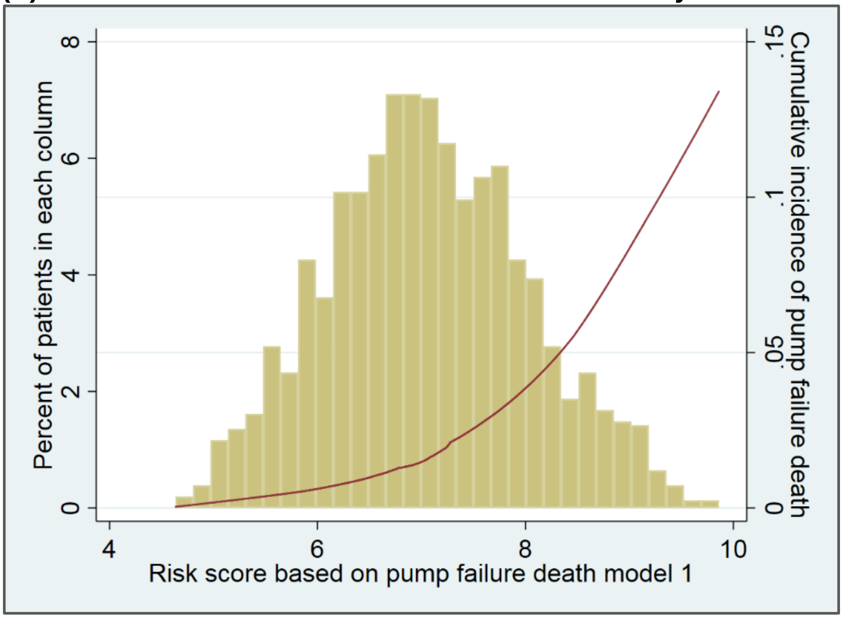
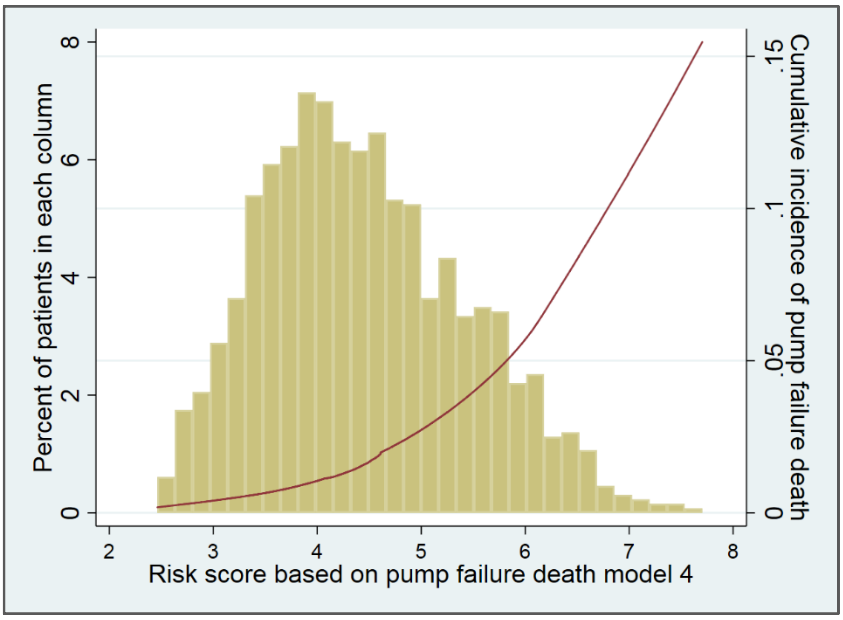


Figure 7-12 Distribution of the risk scores for pump failure death Model 1 (A) and Model 4 (B) and its relation to cumulative incidences within 4 years in I-PRESERVE





7.3 Discussion

In this chapter, I developed a series of prognostic models to predict sudden death and pump failure death separately in the elderly patients with HF-PEF enrolled in I-PRESERVE, and these models were externally validated in CHARM-Preserved and TOPCAT cohorts. The derived models for sudden death and pump failure death using simple demographic and clinical variables showed good discrimination and calibration, and were robust in validation. With the addition of ECG parameters and routine biochemical measurements model performance showed little improvement in the derivation cohort, but decreased in the validation cohorts. Inclusion of the biomarker NT-proBNP substantially increased the discrimination ability of sudden death model, and simplified the model for pump failure death with a marginal increase in discrimination.

Risk stratification for mode-specific death has been studied in patients with HF-REF but remains largely unexplored among HF-PEF population.[78, 79, 84] Identification of prognostic factors for mode-specific death may help with the understanding of the pathophysiological mechanisms underlying this cause of death. It may also allow better classification of risk in patients allowing high-risk subgroups to be enrolled in new trials of interventions or therapies. This in turn will allow adequately powered trials to be conducted with potentially fewer patients and in patients likely to benefit. There is one model published for predicting sudden death in HF-PEF patients, which was also developed in I-PRESERVE.[76] This prior model, using conventional Cox regression analysis, closely resembles the model including NT-proBNP that I developed here using competing risk analysis with equally good discrimination. There were some minor but potentially important differences. In the previously derived model LBBB on ECG was included in the Cox model whereas LVH on ECG was selected by the competing risk model I constructed. There may be a number of explanations for the inconsistency. One possible explanation is the difference in the modelling approaches, i.e. whether or not taking into account death from other causes, which would result in different rates of sudden death, and consequently its associations with prediction variables. Similarly, it was LVH rather than LBBB that was included in the sudden death model in HF-REF using the competing risk analysis in Chapter 3. It is significant that LVH was an independent predictor for sudden death in HF-REF as well as HF-PEF patients.[178] From a pathophysiological perspective, LVH is one of the structural hallmarks of HF-PEF. As it may result from excess collagen deposition and fibrosis which occur in hypertrophy, it may alter regional conduction patterns and serve as islands of re-entry and an arrhythmic substrate, increasing the risk of sudden death.[179] On the other hand, LBBB is a surface marker of multiple underlying cardiac diseases such as ischaemic heart disease. LBBB itself also denotes intra- and inter-ventricular dyssynchrony, abnormal LV diastolic filling patterns and impaired LV systolic function, which may result in worsening cardiac function.[180] It is likely LBBB may correlate with other variables with stronger prognostic effects, such as history of myocardial infarction and LVEF, and in turn LBBB failed to remain in the multivariable models.

There is no prognostic model available specifically to predict pump failure death in HF-PEF patients; existing models focus on death from any cause or a composite of HF hospitalisation (predominantly) or pump failure death.[172] Nevertheless, a series of models for pump failure death developed here have included some variables that have been previously identified to predict death and HF events, such as age, heart rate, LVEF, history of diabetes or atrial fibrillation, creatinine and NT-proBNP.[172] Of note, the presence of prior HF hospitalisation, which has been reported as a strong risk factor of subsequent mortality or HF events,[172, 181] was not included in the models for pump failure death; however, it was included in the sudden death models. The reason for this is unknown, and one explanation could be the inclusion criteria of the trial. All patients in NYHA class II had to have a previous HF hospitalisation within past 6 months to be eligible for enrolment in I-PRESERVE.[11] Consequently, prior HF hospitalisation may be related to mild HF symptoms and less severe disease, in which pump failure death was less likely to occur than sudden death. Intriguingly, dyslipidaemia was independently associated with a *lower* risk of pump failure death. At face value, it possibly reflects the interaction between dyslipidaemia and natriuretic peptides, given the median level of NT-proBNP was much lower in patients with dyslipidaemia than those without (287 versus 386 pg/ml respectively). However, if this was true, dyslipidaemia would have dropped out of the model when including NT-porBNP, but it was maintained. The mechanism underlying requires further exploration.

Overall, a series of models were developed for each mode of death with a broad spectrum of variables being examined and included in a stepwise manner. The derived models with the use of simple demographic and clinical variables (Model 1) showed good calibration and discrimination, in particular for pump failure death, and remained robust despite a modest decrease in discrimination (C statistic decreased by 0.05) when validated in TOPCAT. Interestingly, further addition of ECG parameters alone (Model 2) and even in combination with routine laboratory measurements (Model 3) made little improvement in model performance in the derivation cohort, and led to a decrease in discrimination and poor calibration (particularly Model 3) in validation. By contrast, the inclusion of NT-proBNP (Model 4) increased the discriminative ability for sudden death, while simplifying the model for pump failure death with a marginal increase in discrimination; both models remained robust when validated in the subset of patients with NT-proBNP available in TOPCAT. These observations may reflect two things. First, in line with the findings in HF-REF, NT-proBNP was the most powerful prognostic factor for sudden death as well as pump failure death in HF-PEF. It is plausible from a pathophysiological perspective. The secretion of NT-proBNP increases in response to increased cardiac wall stress, which is related to volume overload, ventricular stretch and hypertrophy during the progression of HF.[182] Aa a result, NT-proBNP serves as a proxy of severity of HF, the higher level the more likely the advanced HF is, in which pump failure death is more frequent.[7] Also, NT-proBNP can be an indirect marker of ventricular stretch and fibrosis which can result in pro-arrhythmic electrophysiological changes that may lead to sudden death, including slowed intraventricular conduction and ventricular ectopic beats.[183] Second, NT-proBNP may correlate to or share some underlying mechanisms with other predictors for mode-specific death. Thus, the inclusion of NT-proBNP may alter the strength of the associations of other predictors with mode-specific death, which in return could lead to the exclusion of these “weakened” predictors, such as LVEF and history of atrial fibrillation for pump failure death.

There are some limitations in this analysis. First, validation of the models that included NT-proBNP was performed in a subset of the TOPCAT cohort (615 patients with 22 sudden death and 12 pump failure death events), together with a substantial difference in the distribution of NT-proBNP levels from the derivation cohort, the robust result in validation should be viewed with some caution. There is a need to re-validate these models in a similar population with more substantial cohort size when available in future. Secondly, in TOPCAT there was a substantial variation in the baseline characteristics and clinical outcomes between regions of enrolment (Americas vs. Russia and Georgia).[176] Although the event rates such as all-cause mortality and HF hospitalisation in the Americans were reflective of other clinical trial patients in HF-PEF,[9, 11] multi-fold lower event rates were observed in patients enrolled in Russia and Georgia which accounted for 49% of total enrolment.[12] The exclusion of less HF-PEF like patients from Russia and Georgia may lead to a difference in model validation. In a sensitivity analysis, I validated the models in the American subgroup, and the sudden death model remained robust, but the pump failure model showed a decrease in discrimination, possibly due to small sample size and number of events (data not shown). Thirdly, these models were developed in a clinical trial cohort. Patients tended to be healthier than “real world” cohorts and the performance of the models in real world cohorts needs to be tested. Nevertheless, it is in patients similar to those in this analysis that device therapies are likely to be investigated and my results would help select patients for any such trial. Moreover, in line with the models in HF-REF, the sudden death model was less discriminative than the pump failure death model.[78, 79] This suggests that there is a need to improve the prediction of sudden death. Recent studies have shown that late gadolinium enhancement (LGE) on cardiovascular magnetic resonance (CMR) is highly predictive of sudden death in patients with dilated cardiomyopathy with relatively preserved ejection fraction,[184] and there is an ongoing trial examining the ICD efficacy in patients with LVEF 36 to 50% and LGE on CMR.[185] However, CMR parameters were not collected in I-PRESERVE, and the prognostic value of LGE alone and its incremental value to the prognostic models are unable to be examined. Finally, the vast majority of trial participants were white in the derivation and validation populations. Therefore, these models need to be re-validated in more ethnically diverse cohorts before using them in clinical practice.

7.4 Summary

The prognostic models developed using simple demographic and clinical variables can predict the risks of sudden death and pump failure death separately with good discrimination and calibration in patients with HF-PEF in I-PRESERVE, and remain robust in external validation. Including NT-proBNP further improved the performance of both models. These models may have important clinical implications for identifying high-risk patients for specific interventions in future trials among HF-PEF population.

Chapter 8 Discussion

8.1 Summary of findings

The aims of the studies were to examine if and how the rates of sudden death and pump failure death have changed over time in patients with HF-REF and in patients with HF-PEF enrolled in clinical trials respectively, and to develop and validate prognostic models to predict mode-specific death in both populations.

8.1.1 Rates of mode-specific death in HF-REF and HF-PEF

The analysis of individual-level data from 46,163 patients randomised in 13 clinical trials has shown that the rates of sudden death and pump failure death have fallen over the last 2 decades between the start of RALES and the completion of ATMOSPHERE, consistent with a cumulative use of evidence based medications known to reduce both modes of death. Based on the analysis of 10,517 patients enrolled in the 3 largest clinical trials in patients with HF-PEF, a downward trend was also observed in the rates of sudden death and pump failure death across these trials over the last 15 years between the start of CHARM-Preserved and the completion of TOPCAT, parallel with a changing characteristic of patients enrolled in the HF-PEF trials.

It would be of interest to understand if there is a similar pattern of change in the rates of sudden death and pump failure death in patients with HF, particularly according to LVEF, from community-based studies. By far, there are two observational studies having examined the change in the rate of mode-specific death in HF-REF over time. One study was based on the prospective UK-HEART 1 and 2 cohorts, which included 281 and 357 ambulatory patients who had HF-REF with a LVEF ≤45% from the same cardiology outpatient clinics of 8 general hospitals in the UK in the therapeutic eras of 1993-1995 and 2006-2009 respectively. It showed that the risk of sudden death was 77% lower in the contemporary cohort (2006-2009) than in the historic cohort (1993-1995), after adjusting for age, sex, ischaemic aetiology and LV end diastolic dimension.[51] The other study examined the mortality rates in 2507 consecutive patients with a mean age of 53 years and severe HF with reduced left ventricular function (LVEF ≤40%) referred to a University hospital in Los Angeles for heart transplantation/VAD evaluation across three 6-year eras between 1993 and 2010. This study showed that the rate of sudden death was 6.9% in the earliest era between 1993 and 1998, and were substantially lower at 3.1% and 2.0% in the latter eras of 1999-2004 and 2005-2010 respectively, while the rate of pump failure death was considerably higher in the latest era (12.6%) compared to the earlier two eras (7.1% and 7.0% respectively).[52] Nevertheless, the UK-HEART study was a comparison of two time-points, and may not capture the true picture of the temporal trend in the rate of mode-specific death.[51] The second study reflected single centre experience and most patients were candidates for heart transplant/VAD, in other words, they were not well representative of the general patients living with HF.[52] Unfortunately, no observational studies have examined the trend in the rates of mode-specific death over time in HF-PEF population.

The paucity of data from the real-world population may be due to a number of factors. First, few observational studies have detailed classification of mode-specific CV death and non-CV death. Unlike clinical trials, in which death events are typically reviewed and adjudicated by an independent event committee using multiple sources of information, observational studies commonly use investigator-reported events or are simply based on death certificates, which are largely inaccurate.[186] Secondly, even if modes of death were carefully classified and adjudicated, observational studies are highly variable in the terms of setting of enrolment (outpatient vs. inpatient), disease stage (newly diagnosed vs. awaiting heart transplantation), HF type (LVEF-category specified vs. unspecified), study design (sample size, duration of follow-up). Moreover, observational studies tend to lack detailed baseline characterisation, which as a result provides limited opportunity for comprehensive covariate adjustment to account for the between-study difference and confounding factors.

If the risks of sudden death and pump failure death had declined over time in HF-REF and HF-PEF populations, what would be the implications on specific device therapies (ICDs and VADs) that aim to prevent mode-specific deaths, such as clinical benefit and cost-effectiveness?

8.1.2 Clinical benefit, side effects and cost-effectiveness of ICD therapy

ICDs are clearly effective in terminating life-threatening ventricular arrhythmias, and the overall survival benefit of ICD demonstrated by two landmark clinical trials, MADIT-II and SCD-HeFT, has translated into clinical guidelines and practice.[31, 32] Prophylactic implantation of ICDs has been recommended in patients with HF who have NYHA class II-III symptoms and a LVEF ≤35%, irrespective of aetiology.[1, 2, 187] It is noteworthy that the evidence of benefit is less robust for patients with non-ischaemic cardiomyopathy. The DEFINITE trial, the single largest trial in non-ischaemic cardiomyopathy before the DANISH trial, included 458 such patients who had a LVEF <36% (mean 21%) and NYHA class I-III (21.6% in class I) symptoms, and only found a trend in reduction in overall mortality by ICD treatment (HR 0.65, 95% CI 0.40-1.06, p=0.08).[33] As a result, the current European guideline recommendations for non-ischaemic cardiomyopathy are additionally based on a meta-analysis of 5 trials as well as the non-ischaemic cardiomyopathy subgroup in SCD-HeFT.[32, 34]

Since the conduction of SCD-HeFT, there has been an increasing use of guideline recommended medications such as beta-blockers and MRAs. The proportion of patients having received a beta-blocker was over 90% in the contemporary trials such as PARADIGM-HF and DANISH compared to 69% in SCD-HeFT; the use of a MRA was much higher in PARADIGM-HF and DANISH (close to 60%) than SCD-HeFT (19%).[27, 32, 35] Besides, there has been an introduction of novel therapies such as CRT and sacubitril/valsartan.[35, 58] In contrast to ICDs which have no effects on ameliorating arrhythmic substrates or improving cardiac function, these HF medications and CRT can target upstream drivers of arrhythmic risk such as adverse left ventricular remodelling, and provide survival benefits for both arrhythmic and non-arrhythmic deaths.[188, 189] Consequently, these advances in HF therapy has translated into falling risks of overall mortality and sudden death alike. As shown in Chapter 3, now the absolute risk of sudden death is relatively low at around 2% at 6 months and 9% by 3 years in patients who have been treated with current guideline-recommended medications.

Doubt may arise that now the benefit of ICD therapy from reducing sudden death may not be large enough to translate into an overall survival benefit. This view is further reinforced by the findings from the very recent DANISH trial,[35] which showed no overall survival benefit of ICD treatment (HR 0.87, 95% CI 0.68-1.12, p=0.28) in patients with non-ischaemic cardiomyopathy with high use rates of evidence-based medications and CRT, although sudden death was reduced by a half (HR 0.50, 95% CI 0.31-0.82, p=0.005). Of note, an interaction between age and the survival benefit was observed, as in patients younger than 68 years there was a significant reduction in all-cause mortality with ICD therapy (HR 0.64, 95% CI 0.45-0.90, p=0.01). The findings reflect two features of the trial. First, the rates of sudden death and overall mortality were low, with annual rates of 1.8 and 5.0 per 100 patient-years respectively in the control group. This is because patients with non-ischaemic cardiomyopathy in nature have lower risks of sudden death and all-cause death than do patients with an ischaemic cause of HF, and the low background risks were further reduced by comprehensive evidence-based treatment in the trial. Second, the competing risk of death from non-sudden causes was high, as 27% of all deaths in the control group were attributed to a non-CV cause, one of the highest proportions ever described in a HF trial.[42] This is likely because the trial enrolled more elderly patients (mean age of 64 years) and had a longer follow-up (median 67.6 months) than did any previous ICD trial (taking SCD-HeFT for example, the figures were 60 years and 45.5 months respectively). The competing risk of non-sudden deaths becomes more frequent with age and with an increasing number of comorbidities, and there is more likely to be a shift towards less sudden death (i.e. more non-sudden CV deaths and non-CV deaths) along with follow-up as HF advances and patients age. This is echoed by the differential response by age as the overall survival benefit was not observed in the older but younger subgroup, and the convergence of the survival curves in the control and ICD arms at 6 years after randomisation.

In patients with ischaemic cardiomyopathy who are treated with modern optimal therapies, will the overall survival benefit remain robust or become non-significant? The answer may lie in the RESET-SCD (REevaluation of optimal treatment Strategies for prEvenTion of Sudden Cardiac Death in patients with ischemic cardiomyopathy) study, a trial similar to DANISH to explore the role of ICD in patients with ischaemic cardiomyopathy and who are treated with modern optimal therapy.[190]

Prophylactic implantation of an ICD is not like an “insurance policy”, as patients who do not benefit from device therapy are still exposed to procedural and device associated complications, such as infection early after insertion, and later adverse outcomes including inappropriate shocks and device malfunction leading, in some patients, to diminished quality of life.[191] Inappropriate ICD activations, commonly caused by supraventricular tachycardia, sinus tachycardia or abnormal sensing, have adverse effects on psychological well-being, worsen quality of life, and even lead to lethal outcomes.[192, 193] In old ICD trials, the reported inappropriate shocks were frequent, occurring in 10% to 24% of patients and accounting for 25% to 35% of all ICD shocks.[194] Although advances in ICD programming have significantly reduced the risk of inappropriate therapy,[195] there were still about 6% of patients having inappropriate shocks after implantation in the contemporary trials.[35, 195] Based on a recent nationwide analysis of complications after primary prevention ICD implantation in ambulatory patients with left ventricular dysfunction in the US,[138] the device-related mortality rate was reported to be 0.73% at 30 days, with a total serious complication rate of 8.4%. These figures are comparable to the sudden death rates in patients with HF-REF who had a high adoption of modern guideline recommended treatment shown in this thesis (about 0.4% at 30 days and around 9% at 3 years). Therefore, there is a need for better risk stratification of sudden death and identify a high-risk subgroup in whom ICDs would confer greater benefit than harm to a patient.

ICD therapies are costly, and the average cost for an ICD (CRT-D) device alone is estimated to be £9692 (£12,293) in the UK, not including other associated medical costs such as implant procedure, hospital admission, device-related complications and device replacement.[196] Primary prevention ICD implantation can pose an immense economic burden on the healthcare systems, owing to the high cost of the device and the large patient population in which it can be applied. Therefore, the cost-effectiveness of this therapy must be considered.

The estimate of cost-effectiveness of a therapy depends on the within-trial efficacy and costs, and the projected effectiveness and costs beyond trial follow-up. Based on the results from 6 clinical trials that showed survival benefit of ICD treatment, the projected life expectancy increment with an ICD ranged from 1.01 quality-adjusted life years (QALY) in SCD-HeFT to 2.99 QALY in MUSTT (Multicenter Unsustained Tachycardia Trial), at a cost between $34,000 per QALY gained in MUSTT to $70,200 per QALY gained in SCD-HeFT.[197] These estimates were based on a fundamental assumption that an ICD had a constant effect on survival after 7 years, which has not been supported by data.[197] The survival curves for the ICD and control arms converged at 6 years in the DANISH trial,[35] and this is conceivable given that with time patients aged and were more likely to be comorbid with other medical conditions and subsequently die from causes other than sudden death, leading to a diminished benefit of an ICD. Indeed, cost-effectiveness is not an inherent property of any particular therapy but depends on the patient population in which the therapy is used, as does the clinical effectiveness of a therapy. In SCD-HeFT, there was a significant interaction between NYHA class and the cost-effectiveness of ICD treatment: cost-effectiveness was only observed in patients in NYHA class II ($29872 per life-year gained), but not in patients in NYHA class III in whom there was no incremental benefit but higher costs.[198] This is conceivable given that in the SCD-HeFT there was also a difference in efficacy of ICD according to NYHA class: use of an ICD was associated with a 46% decreased risk of death in NYHA class II (HR 0.54, 95% CI 0.40-0.74, $p<0.001$), but had no effect on mortality in class III (HR 1.16, 95% CI 0.84-1.61, $p=0.30$).[32] Similarly, in another study CRT-D was only cost-effective (with a threshold of £20,000 per QALY gained) in patients who had NYHA class I/II symptoms with QRS duration ≥150 ms and LBBB,[199] in whom the evidence of survival benefit was most robust.[3]

Collectively, the effect of ICD treatment on reducing sudden death is convincing, but given the declining risk of sudden death, the continuing high costs, the invasive nature and potential complications for the device, and population-dependent cost-effectiveness, it is of clinical and societal importance to target ICDs to patients most likely to benefit (and to avoid unnecessary placement to those unlikely to benefit). Therefore, it is desirable to identify patients who are still at high risk for sudden death but are less likely to die from other causes, despite receiving modern guideline recommended treatment.

8.1.3 Models to predict sudden death

The decision to implant an ICD for primary prevention, currently, is primarily based on LVEF, the dichotomisation of which as a risk stratification tool lacks both specificity and sensitivity.[200] A reduced LVEF is not only a risk factor for sudden death but also for non-sudden death such as pump failure death, and only a small proportion of patients who had implanted a defibrillator received ICD therapy, i.e. a considerable number of patients died from other causes not preventable by an ICD.[32] On the other hand, the majority of patients who experienced sudden death do not have a reduced LVEF.[173] Therefore, either from a therapeutic or health-economic perspective, there is an unmet need for better risk stratification of sudden death in HF-REF and HF-PEF populations. In patients with HF-REF, identification of high-risk subgroups would help target the device therapy to those most likely to benefit and identifying low-risk subgroups would avoid unnecessary implantation, thus improving the cost-effectiveness of the therapy. In patients with HF-PEF, identifying high-risk subgroups would enable further research into the efficacy of ICD therapy and optimise potential for therapeutic success in this population.

A multivariable risk model can provide a more nuanced and reliable risk estimation than a single risk stratifier. There are few models available to predict mode-specific death, and the details of their characteristics have been summarised in the literature review; however, they all have major limitations for the consideration of use in clinical practice. Apart from statistical inadequacy such as having small number of events and no validation, most models were developed in historic cohorts with few patients having received modern guideline recommended therapies and did not consider the competing risk of death from non-sudden causes. Current guidelines recommend ICD implantation only if the LVEF fails to increase to >35% after a sufficient time (≥3 months) of optimal medical therapy.[3] The residual risk of sudden death is lower in patients who have received modern evidence-based medications than those have not. Consequently, the historic models based on cohorts with a few patients having received modern evidence-based therapies may discriminate poorly between high- and low-risk patients in a modern cohort, thus offering little aid in guiding ICD implantation. In keeping with this, the annual rate of sudden death was much lower in the contemporary PARADIGM-HF and

ATMOSPHERE trials than the SHFM cohort (3.4 vs. 6.1 per 100 patient-years), and conceivably, the SHFM had a substantial decrease in discrimination in both modern cohorts.

Moreover, the prognostic influence of death from other causes can no longer be ignored, given that the residual risk of sudden death has declined along with the increasing use of modern evidence-based medications in HF-REF or the changing patient characteristics in HF-PEF, and consequently death from non-sudden causes has been making greater contribution to total mortality. This view was reinforced by the age variation of ICD benefit in the DANISH trial: ICDs were very effective in patients aged <68 years but had no effect on mortality in those aged ≥68 years. This may reflect the higher competing risk of death from other causes in the older subgroup who were more likely to live with multiple comorbidities especially over long-term follow-up. In a sense, the models I developed have a unique strength to account for the competing risk of death from other causes.

The purpose of risk prediction for sudden death is to aid in decision making in ICD use. It is noteworthy that a high absolute risk of sudden death does not necessarily translate into the survival benefit of an ICD, which can be offset by a high competing risk of non-sudden deaths.[188] Accordingly, the concept of proportional risk (instead of absolute risk) of sudden death was proposed, and a bimodal system for risk prediction of sudden death was developed by coupling the proportion of sudden death to total mortality with the absolute risk of total mortality.[74] This bimodal system has been shown to stratify patients with different sizes of benefit from ICDs: patients with lower risk of total mortality and higher proportional risk of sudden death showed the greatest benefit from ICDs, and patients with lower risk of total mortality and lower proportional risk of sudden death showed no benefit from ICDs; however, it is not intuitive to find that patients with higher risk of total mortality but low proportional risk of sudden death (i.e. absolute risk of sudden death remained high) were still predicted to benefit from ICDs.[157] This may be explained by the finding from the same authors which showed that an increase in the risk of total mortality is associated with a decrease in the proportional risk but an increase in the absolute risk of sudden death.[84] Therefore, it may provide greater clarity to directly model the absolute risk than the proportional risk of sudden death.

Although the sudden death model I developed in HF-REF showed good performance and had counted for the competing risks of non-sudden deaths, it needs to be examined if the risk model can stratify patients with different magnitudes of survival benefit from ICDs in existing ICD trials in HF-REF, and if ICDs can demonstrate survival benefit in the high-risk subgroup identified from the sudden death models in both HF-REF and HF-PEF populations in future trials.

Decision making in ICD implantation involves not only estimating the predicted risk of sudden death and therefore the potential benefit from an ICD, but also the device-related harms including side-effects and costs. These estimates may all vary in importance between individual patients, their clinicians, and in different health care systems. Different weights of benefit and harm may be given to these risks by a specific decision maker (e.g. a patient and/or a clinical team, or policy makers).[201] One patient may consider a sudden death to be 50 times worse than the potential harms of an ICD, whereas another patient may rank these risks differently (e.g. 5 time worse). My model offers an alternative to the two extreme choices that can currently be made - a “treat all” strategy (for example in the US) where every patient with the indication is considered for an ICD versus a “treat none” strategy where no patient is treated because the cost of treating every patient with the indication is unaffordable for the health care system. To make an informed choice about ICD therapy, it is important to accurately estimate the predicted risk of sudden death and try and integrate this with the different assessments of benefit and harm. The results from these estimates can then be compared to a “treat all” and a “treat none” strategy. From there is then possible to assess the potential of a more targeted approach to ICD implantation and the benefits and harms versus a “treat none” strategy (no benefit and no harm) and a “treat all’ strategy (maximal benefit but maximal harm). These decisions are complex and difficult to integrate into a single measure. More recently decision curve analysis has been proposed as a method to integrate these different facets of decision making and I aim to assess these aspects of my model in future analyses using the decision curve analysis method.[202, 203]

8.1.4 VADs and heart transplantation, and models to predict pump failure death

For patients with refractory end-stage HF, there is a consensus that heart transplantation is the gold standard treatment, which offers markedly improved long-term survival and increases functional status and quality of life.[204] Nevertheless, heart transplantation is a limited option, given the number of patients on the transplant waiting list far outnumber the heart donors. Besides, this operation is not without complications such as infection early after transplantation, and adverse effects of immunosuppressive therapy in the long term.[2, 3, 204] VAD support was initially used as a short-term bridge to transplant, and recent data suggested that VADs may have improved the prognosis of patients on the transplant waiting list.[205] Given the expanded waiting lists for heart transplant with prolonged waiting time, VADs have increasingly emerged as a permanent therapeutic option and an alternative to heart transplantation.[2, 3] Pump failure death increases with increasing severity of HF, and pump failure death is the predominant mode of death in patients with severe HF.[7, 63] In a sense, assessing the risk for pump failure death is of clinical importance in helping with decision making in VAD therapy, heart transplantation, and planning palliative and end of life care. Besides, as the second most common mode of death, pump failure death can be regarded as the single largest competing risk for sudden death; therefore, understanding the risk of pump failure death may also help make decisions on ICD implantation or when to deactivate implanted ICDs.

The models I developed here to predict the risks of pump failure death in HF-REF and HF-PEF showed excellent discrimination and calibration with robust results in external validation. These models can be considered for use in risk prediction in similar patients with ambulatory HF. If a patient were predicted at high risk for pump failure death, close monitoring of symptoms and signs of congestion and early management of comorbidities that contribute to worsening HF such as renal dysfunction can be implemented, relevant interventions such as VADs and heart transplantation can be considered and consulted, and supportive network and palliative options can be offered. On the other hand, if a patient were predicted at low risk of pump failure death, these specific medical attention and efforts and relevant medical resources may be saved.

8.2 Limitations of the studies

As with all studies, there are limitations. Firstly, the results of these studies are based on clinical trial cohorts, in which patients have met specific eligibility criteria, and consequently tend to be younger, and have less comorbid conditions than the real-world unselected population. Besides, trial participants are more likely to receive optimal (i.e. class and dose) guideline recommended therapies, given that they have greater access to medical care, and undergo more frequent evaluation of medical compliance. Therefore, the results may not truly reflect the real-world scenario. However, few observational studies have sophisticated classification of mode-specific death to make these analyses possible, let alone detailed patient characterisation and follow-up to allow more complete multivariable adjustment. Besides, it is in patients similar to those included in these studies (younger, less comorbid and on optimal therapy) that ICDs are most clearly indicated or most likely to be investigated in trials.

Secondly, the trials included in these analyses did not share a uniform definition of sudden death. This is not surprising given that these trials were conducted before the recent introduction of standardised definitions of endpoints used in clinical trials proposed by the ACCF/AHA in collaboration with the US FDA.[46] Additionally, sudden death is often solely attributed to lethal ventricular tachyarrhythmias but clearly some deaths that occur suddenly are caused by other cardiac and non-cardiac events, e.g. acute myocardial infarction, pulmonary embolism, aortic dissection or stroke. It remains challenging to ascertain cause-specific death in the absence of post-mortem examination and rhythm monitoring. Fortunately, all sudden death events in each included trial were adjudicated by an independent committee according to pre-specified criteria and this should have reduced bias and variation within and between trials.

Thirdly, in my thesis time from randomisation instead of time since HF diagnosis was used as the underlying time scale, in other words, the patients examined were the “natural survivors” by the time of randomisation. This may be less likely to reflect the risks of sudden death and pump failure death in the time course of HF progression. Nevertheless, 12 out of the 16 trials provided information on the length of time between diagnosis of HF and randomisation, by which the risk of mode-specific death from randomisation was further examined.

Fourthly, models to predict sudden death remain less discriminative than models for pump failure death, in line with previous findings,[78, 79] suggesting the risk stratification for sudden death is more difficult. This is plausible given that even when due to a ventricular tachyarrhythmia, sudden death can be the result of a various pathophysiological events, such as an acute ischaemic event caused by plaque rupture or a sudden change in repolarisation caused by electrolyte shifts, and these upstream events may be associated with heterogeneous risk factors, demonstrating the challenge of identifying uniform predictors of sudden death. This highlights an unmet need to further improve the risk stratification for sudden death. Some promising variables have been found predictive of sudden death, but were not collected in the trials included here such as cardiac imaging parameters, 24-h Holter monitoring, and other novel biomarkers. For example, studies have showed that the presence and volume of myocardial scar and fibrosis detected with late gadolinium enhancement on CMR is predictive of sudden death and appropriate ICD therapy in patients with left ventricular dysfunction.[184, 206, 207] Similarly, abnormalities in cardiac sympathetic innervation detected by ^{123}I-MIBG scintigraphy have also shown to be prognostic of sudden death.[208, 209] The addition of these predictors may further improve the model performance. On the other hand, it needs to be examined if the addition would improve the decision making in ICD use to a degree that would justify the additional costs and complexity.

Furthermore, the predictive models are derived and validated in predominantly white populations. Therefore, revalidation and further re-calibration strategies are necessary before it can be applied to other ethnic groups, as well as other cohorts with different characteristics and inherent risks.

Finally, it must be acknowledged that even if mode-specific death were appropriately classified and accurately estimated, a gap may still lie in between the predicted risk and the response to device therapy.

8.3 Future areas of research

The set-up and ongoing prospective, multicentre, international HF registries provide us an important step towards a better understanding of clinical presentation and prognosis of HF in the real-world patients, such as the European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT-R)[210] and the Global Congestive Heart Failure Registry (G-CHF) (ClinicalTrials.gov Identifier: NCT03078166). In order to advance the research in the area of mode-specific death, sophisticated reporting schema for mode-specific death needs to be widely introduced in observational studies and to be standardised across clinical trials. To accrue sufficient information for this purpose, wide-scale systematic autopsy, improved capture and surveillance surrounding death, and long-term rhythm monitoring may better clarify the underlying pathology and mechanisms driving mortal events. The emerging use of post-mortem imaging such as CT scanning and CT angiography may detect non-arrhythmic causes of death that occur suddenly such as myocardial infarction, cerebral events and pulmonary embolism, which may help identify sudden non-arrhythmic death.[211, 212] On the other hand, implantable loop recorders may help characterise the true burden of sudden death in HF that is caused by ventricular tachyarrhythmias amenable to ICD therapy, as is the objective of the ongoing Ventricular Tachyarrhythmia Detection by Implantable Loop Recording in Patients with Heart Failure with Preserved Ejection Fraction (VIP-HF) trial (ClinicalTrials.gov Identifier NCT01989299). It would be of interest to compare the rates of sudden death in the HF-PEF trials I examined here with the incidence of ventricular tachyarrhythmia to be reported in the VIP-HF study.

The prognostic models for sudden death I developed here have shown reasonable discrimination, good calibration, and robustness in external validation. Nevertheless, there is still room for further improvement in risk stratification, given the high costs and potential complications of ICD therapy. There have emerged some promising cardiac imaging parameters in risk classification of sudden death including late gadolinium enhancement on CMR and ^{123}I-MIBG score. There are two ongoing clinical trials to examine their roles in guiding the decision of ICD implantation, i.e. the Cardiovascular magnetic resonance-GUIDEd management of mild to moderate left ventricular systolic dysfunction (CMR GUIDE) trial and the International Study to Determine if AdreView Heart

Function Scan Can be Used to Identify Patients With Mild or Moderate Heart Failure (HF) That Benefit From Implanted Medical Device (ADMIRE-ICD) (Clinical trials.gov identifier NCT01918215 and NCT02656329, respectively). However, these imaging techniques are expensive, especially considering repeated imaging for risk re-evaluation, and not without contraindications. It would be clinically important and economically sensible to examine their incremental prognostic value in addition to the sudden death models using routinely obtained variables.

A high risk of sudden death does not necessarily translate into the survival benefit of ICD treatment. This highlights the need to examine the performance of the sudden death model in stratifying the survival benefit from ICD therapy. In the next step, I will apply the sudden death model to patients with HF-REF randomised in ICD trials, to examine its performance in risk classification of sudden death in the control groups (i.e. external validation) and to evaluate to what extent the correlation (if any) between the risk of sudden death predicted by the model and survival benefit of ICDs. Besides, there is a need for further exploration if ICDs can demonstrate survival benefit in the high-risk subgroup identified from the sudden death model in HF-PEF populations in future trials.

The goal of developing risk models for sudden death in HF-REF is to personalise prophylactic use of ICD therapy for the benefit of patients and society, by targeting the device to those most likely to benefit and avoiding unnecessary placement thereby improving its cost-effectiveness. It is important to examine the likelihood of unnecessary implantation based on the risk estimation from the sudden death model I have developed compared to a “treat none” strategy regardless of the predicted risk, and the chance of missing out on the benefit of an ICD and then comparing this to a “treat all” strategy. I will examine these clinical aspects of the model in future study.

In the digital era, mobile devices have become commonplace in health care settings. Developing software applications of the risk models for a range of platforms (e.g. iOS, Android, Windows Phone and Web) would simplify the use and promote the application of the prognostic models.

8.4 Conclusions

The conclusions and outcomes of the analyses presented in this thesis can be summarised as follows:

The risks of sudden death and pump failure death in patients with HF-REF have fallen across 13 clinical trials conducted over the period 1995-2015, in parallel with a cumulative use of evidence based therapies in this population.

The absolute rates of sudden death and pump failure death were very low in the early follow-up after randomisation in patients with HF-REF receiving modern guideline recommended treatment.

Longer standing HF was associated with greater risks of sudden death and, particularly, pump failure death in patients with HF-REF.

The sudden death and pump failure death models in HF-REF developed in the largest and most contemporary cohort (PARADIGM-HF), included a number of variables collected in routine clinical practice, and accounted for the prognostic impact of the competing risk of death from other causes. Both models showed good calibration and were robust when externally validated in ATMOSPHERE; the discriminating ability was excellent for the pump failure death model but modest for the sudden death model, suggesting further effort is needed to improve the risk stratification of sudden death.

The risks of sudden death and pump failure death were consistently low across the three largest clinical trials in patients with HF-PEF, with little difference by experimental treatment in any trial. There was a downward trend in the rates of sudden death and pump failure death across these trials over time, parallel with a changing characteristic of patients enrolled in these trials; nevertheless, sudden death and pump failure death remained the most common modes of death, altogether accounting for the majority of CV death. The absolute rates of sudden death and pump failure death in patients with HF-PEF were extremely low in the early follow-up after randomisation. Longer standing HF was associated with a slightly higher risk of sudden death and a substantially higher risk of pump failure death in HF-PEF.

The prognostic models in patients with HF-PEF enrolled in I-PRESERVE, using simple demographic and clinical variables showed good discrimination and calibration for both sudden death and pump failure death, and remained robust in external validation in CHARM-Preserved and TOPCAT. Including NT-proBNP further improved the performance of both models.

Appendices

Appendix Table 1 Search strategy and result in MEDLINE

No	Search term	Number of items
1	exp Ambulatory Care/	49727
2	exp Outpatients/	12797
3	(ambulatory or stable or chronic or out-patient or outpatient).mp.	1609708
4	1 or 2 or 3	1614062
5	exp Heart Failure/	104687
6	((heart or cardiac) adj2 failure).ti,ab.	131648
7	5 or 6	164798
8	exp Death/	136807
9	exp Mortality/	333648
10	exp Survival/	4477
11	(death or mortality or survival).ti,ab.	1483216
12	(sudden death or sudden cardiac death or unexpected death or arrhythmi# death).mp.	30715
13	((death or mortality or die) adj3 (heart failure or pump failure)).mp.	5293
14	(mode adj2 (death or mortality)).mp.	780
15	8 or 9 or 10 or 11 or 12 or 13 or 14	1679583
16	((predict* or prognos*) and (scor* or model*)).mp.	519590
17	(risk stratif* or risk classif* or risk scor*).mp.	30117
18	16 or 17	537771
19	4 and 7 and 15 and 18	2424
20	**limit 19 to (english language and humans and "all adult (19 plus years)")**	**2046**

Footnote:

Database: Ovid MEDLINE (R) 1946 to April week 1 2017

Last update date: 17-04-2017

Appendix Table 2 Search strategy and result in Embase

No.	Search term	Number of items
1	exp Ambulatory Care/	47720
2	exp Outpatients/	133284
3	(ambulatory or stable or chronic or out-patient or outpatient).mp.	2520351
4	1 or 2 or 3	2520351
5	exp Heart Failure/	442568
6	((heart or cardiac) adj2 failure).ti,ab.	234676
7	5 or 6	470546
8	exp Death/	833765
9	exp Mortality/	1018689
10	exp Survival/	990656
11	(death or mortality or survival).ti,ab.	2366925
12	(sudden death or sudden cardiac death or unexpected death or arrhythmi# death).mp.	67645
13	((death or mortality or die) adj3 (heart failure or pump failure)).mp.	10081
14	(mode adj2 (death or mortality)).mp.	1215
15	8 or 9 or 10 or 11 or 12 or 13 or 14	3046449
16	((predict* or prognos*) and (scor* or model*)).mp.	781626
17	(risk stratif* or risk classif* or risk scor*).mp.	65813
18	16 or 17	820548
19	4 and 7 and 15 and 18	6642
20	**limit 19 to (human and English language and Embase and (adult <18 to 64 years> or aged <65+ years>))**	**2650**

Footnote:

Database: Ovid Embase 1947-Present, updated daily

Last update date: 17-04-2017

Appendix Table 3 Data extract form

Key aspects	**Description (if needed)**
Study characteristics	
❖ Source of data	
• Patient records (retrospective)	
• Prospective cohort study or registry data	
• Clinical trial database	
❖ Region of study and number of centres	
❖ Data collection period (average follow-up)	
❖ Sample size	
Patient characteristics	
❖ LVEF and NYHA class	LVEF: reduced, preserved, mixed, unspecified
❖ Mean age and proportion of men	
❖ Treatment	ACEI/ARB, beta-blocker, MRA and device
Outcomes	
❖ Number of events	
❖ Definition of outcomes	
❖ Event adjudication	Investigator reported or event committee adjudication
Model construction	
❖ Regression model	
• Cox proportional hazards regression	Dependent variable: time to event, treating death from other causes as independent (i.e. non-informative) censoring.
• Logistic regression	Dependent variable: event (yes/no)
• Competing risk analysis	Dependent variable: time to event, treating death from other causes as informative censoring.
❖ Variable selection	
• Not parsimonious	Inclusion of all variables achieving a cut-off p value at univariate analysis
• Parsimonious	Stepwise selection
❖ Candidate and final variables	
Model validity	
❖ Model over-fitting	The number of events divided by the number of final predictors <10
❖ Model assumption	Proportional hazards for Cox regression
Model performance	
❖ Discrimination	
• Harrell's C statistic	
• ROC AUC	
❖ Calibration	
• Hosmer-Lemeshow test	Goodness of fit test for logistic regression or at a certain time point for Cox regression
• Calibration curve	Graphical display of the observed vs. predicted incidence for specific ranges of risk over time
❖ Validation	
• Internal	Split study samples
• External	Independent populations
Missing data	
❖ Complete case analysis	Drop patients with incomplete data
❖ Simple imputation	Replace missing data with an average value
❖ Multiple imputation	Replace missing data with a plausible value derived from the distribution of the other ones

Appendix Table 4 Design and characteristics of the trials that were eligible but not obtained in HF-REF

	PRAISE 1 (N=1153)	**ATLAS (N=3164)**	**PRAISE 2 (N=1654)**	**COMET (N=3029)**	**ELITE II (N=3152)**	**COPERNICUS (N=2289)**	**AF-CHF (N=1376)**	**HEAAL (N=3846)**	**STICH (N=1212)**	**SHIFT (N=6505)**
Comparison	Amlodipine	Lisinopril high dose	Amlodipine	Carvedilol	Losartan	Carvedilol	Rhythm control	Losartan high dose	CABG + medical therapy	Ivabradine
	Placebo	Lisinopril low dose	Placebo	Metoprolol	Captopril	Placebo	Rate control	Losartan low dose	Medical therapy	Placebo
Study period	1992.03-1994.12	1992.10-1997.09	1995.12-2000.01	1996.12-2002.11	1997.06-1999.07	1997.10-2000.03	2001.05-2007.06	2001.11-2009.03	2002.07-2010.11	2006.10-2010.03
Average follow-up	13.8 months	-	33 months	58 months	1.5 years	10.4 months	37 months	4.7 years	56 months	22.9 months
Site distribution	105 sites	287 sites in 19 countries	-	317 sites in 15 European countries	289 sites in 46 countries	334 sites in 21 countries	123 sites in Canada, the US, Argentina, Brazil, Europe, and Israel	255 sites in 30 countries	127 sites in 26 countries	677 sites in 37 countries
Inclusion criteria										
Age -years	≥18	≥18	≥18	≥18	≥60	≥18	≥18	≥18	≥18	≥18
NYHA class	IIIB-IV	II-IV	III-IV	II-IV	II-IV	III-IV	I-IV	II-IV	I-IV	II-IV
LVEF-%	<30	≤30	<30	≤35	≤40	<25	≤35	≤40	≤35	≤35
HF hospitalisation	-	ER visit or hospitalisation for HF within last 6 months if NYHA class II	-	-	-	-	HF hospitalisation within last 6 months if LVEF not ≤25%	-	-	HF hospitalisation within last 12 months
Others	-	-	non-ischaemic cardiomyopathy	-	-	-	a history of atrial fibrillation	intolerance to ACEIs	CAD suitable for revascularisation	sinus rhythm with resting heart rate ≥70 beats/min
Exclusion criteria										
Creatinine -umol/L	>270	>220	>265	-	>220	>247.5	-	>220	-	-
Systolic BP -mmHg	<85 or >159	-	<85 or >160	<85	<90	<85	-	<90	-	symptomatic hypotension

Potassium -mmol/L	<3.5 or >5.5	-	<3.5 or >5.5	-	-	<3.5 or >5.2	-	<3.5 or >5.7	-	-
Heart rate -beats/min	-	-	-	<60	-	<68	-	-	-	-
Baseline treatment (%)										
ACEI	99	89	100	91	50	NR	86	0	82	79
ARB	NR	NR	NR	7	50	NR	11	100	9	14
ACEI or ARB	NR	NR	NR	NR	NR	97	NR	NR	90	NR
Beta-blocker	NR	11	NR	100	22	50	79	72	85	89
MRA	NR	NR	NR	11	22	19	45	38	46	60
ICD	NR	NR	NR	NR	NR	NR	7	NR	2	3
Mortality events										
No. of all-cause death	413	1383	540	1112	530	425	445	1300	462	1055
No. of sudden death	185	589	NR	479	231	114	159	481	173	451
Proportion of sudden death relative to total mortality (%)	44.8	42.6	-	43.1	43.6	26.8	35.7	37.0	37.4	42.7
No. of pump failure death	165	445	NR	365	99	NR	130	314	82	264
Proportion of pump failure death relative to total mortality (%)	40.0	32.2	-	32.8	18.7	-	29.2	24.2	17.7	25.0

NR denotes “not reported” and ‘-’ denotes data not available.

Appendix Table 5 Candidate variables and missing data in HF-REF

	PARADIGM-HF (N=7156)	**ATMOSPHERE (N=5968)**
Demographics (N=4)		
Age -years	0	0
Sex (male, female)	0	0
Race (white, black, Asian, other)	0	38 (0.6%)
Region (North America, Latin America, Western Europe, Central Europe, Asia or Pacific region)	0	0
Clinical assessment (N=8)		
Body mass index	8 (0.1%)	16 (0.3%)
Systolic BP -mmHg	0	2 (<0.1%)
Diastolic BP -mmHg	0	1 (<0.1%)
Heart rate -beats/min	0	0
LVEF -%	1 (<0.1%)	0
NYHA class (I, II, III, IV)	11 (0.2%)	0
Aetiology (ischaemic, non-ischaemic)	0	0
HF duration (within 1 year, >1-5 years, >5 years)	0	4 (0.1%)
Medical history (N=14)		
Current smoking	0	0
Previous HF hospitalisation	0	0
Myocardial infarction	0	0
Angina	0	0
CABG or PCI	0	0
Hypertension	0	0
Diabetes	0	0
Atrial fibrillation	0	0
Stroke	0	0
Cancer	0	0
Asthma	0	0
COPD	0	0
AAA	0	0
PAD	0	0
Treatment (N=11)		
Digoxin	0	0
Diuretic	0	0
ACEI or ARB	0	0
Beta-blocker	0	0
MRA	0	0
Any antiplatelet agent	0	0
Aspirin	0	0
Anticoagulant	0	0
Statin	0	0
Pacemaker	0	0
CRT-P	0	0
12-lead ECG (N=8)		
QRS duration -ms	103 (1.4%)	160 (2.7%)

Atrial fibrillation	0	61 (1.0%)
Atrial flutter	0	61 (1.0%)
Bundle branch block	0	61 (1.0%)
Left bundle branch block	0	61 (1.0%)
Right bundle branch block	0	61 (1.0%)
Q wave	0	61 (1.0%)
Left ventricular hypertrophy	0	61 (1.0%)
Laboratory measurement (N=14)		
eGFR -ml/min/1.73 m^2	0	1 (<0.1%)
Creatinine -mg/dl	0	1 (<0.1%)
BUN -mmol/L	138 (1.9%)	1 (<0.1%)
Albumin -g/L	147 (2.1%)	7 (0.1%)
Haemoglobin -g/L	229 (3.2%)	40 (0.7%)
Potassium -mmol/L	152 (2.1%)	1 (<0.1%)
Sodium -mmol/L	130 (1.8%)	1 (<0.1%)
Chloride -mmol/L	125 (1.7%)	1 (<0.1%)
Calcium -mmol/L	166 (2.3%)	8 (0.1%)
Total cholesterol -mmol/L	161 (2.2%)	209 (3.5%)
HDL-C -mmol/L	163 (2.3%)	210 (3.5%)
LDL-C -mmol/L	331 (4.6%)	362 (6.1%)
Triglyceride-mmol/L	161 (2.2%)	208 (3.5%)
NT-proBNP -pg/ml	12 (0.2%)	560 (9.4%)

Appendix Table 6 Missing data in prediction variables for sudden death model and pump failure death model from PARADIGM-HF in ATMOSPHERE

Sudden death model from PARADIGM-HF	
Male sex	0
Asian race	38 (0.6%)
Systolic BP -mmHg	2 (<0.1%)
Ischaemic aetiology	0
NYHA class	0
CABG or PCI	0
Cancer history	0
Left ventricular hypertrophy on ECG	61 (1.0%)
QRS duration -ms	160 (2.7%)
NT-proBNP -pg/ml	560 (9.4%)
Pump failure death model from PARADIGM-HF	
Systolic BP -mmHg	2 (<0.1%)
LVEF -%	0
NYHA class	0
Ischaemic aetiology	0
HF duration (>1-5 years, >5 years vs. within 1 year)	4 (0.1%)
Bundle branch block on ECG	61 (1.0%)
Creatinine -mg/dl	1 (<0.1%)
Albumin -g/L	7 (0.1%)
Chloride -mmol/L	1 (<0.1%)
NT-proBNP -pg/ml	560 (9.4%)

Appendix Table 7 Missing data in prediction variables for SHFM and SPRM in PARADIGM-HF and ATMOSPHERE

	PARADIGM-HF (N=7156)	ATMOSPHERE (N=5968)
Seattle Heart Failure Model (SHFM)		
Age -years	0	0
Male sex	0	0
LVEF -%	1 (<0.1%)	0
NYHA class	11 (0.2%)	0
Systolic BP -mmHg	0	2 (<0.1%)
Ischaemic aetiology	0	0
Weight adjusted diuretic dose	1504 (21.1%)	1362 (22.8%)
Allopurinol	0	0
Statins	0	0
Sodium -mmol/L	130 (1.8%)	1 (<0.1%)
Total cholesterol -mmol/L	161 (2.2%)	209 (3.5%)
Haemoglobin -g/L	229 (3.2%)	40 (0.7%)
Lymphocyte -%	356 (5.0%)	48 (0.8%)
Uric acid -g/dl	160 (2.2%)	7 (<0.1%)
ACEI	0	0
ARB	0	0
Beta-blocker	0	0
K-Sparing diuretic	0	0
Seattle Proportional Risk Model (SPRM)		
Age -years	0	0
Male sex	0	0
LVEF -%	1 (<0.1%)	0
NYHA class	11 (0.2%)	0
Systolic BP -mmHg	0	2 (<0.1%)
Body mass index	8 (0.1%)	16 (0.3%)
Diabetes	0	0
Digoxin	0	0
Creatinine -mg/dl	0	1 (<0.1%)
Sodium -mmol/L	130 (1.8%)	1 (<0.1%)

Appendix Table 8 Design and characteristics of the clinical trials that were not eligible in HF-PEF

	DIG-PEF (N=988)	SENOIRS-PEF (N=752)	PEP-CHF (N=850)	J-DHF (N=245)
Comparison	Digoxin Placebo	Nebivolol Placebo	Perindopril Placebo	Carvedilol Placebo
Study period	1991-1995	2000-2003	2000-2003	2004-2011
Duration of follow-up	mean 37 months	NA	mean 2.1 years	mean 3.2 years
Site distribution	302 centres in the US and Canada	11 European countries	53 centres in 8 countries	Multicentre in Japan
Inclusion criteria				
Age -years	≥21	≥70	≥70	≥20
NYHA class	-	-	-	-
LVEF-%	>45	>35	>40	>40
HF hospitalisation	-	HF Hospitalisation within prior 12 months if without a documented LVEF ≤35% within previous 6 months	Hospitalisation for a CV reason within previous 6 months	-
Exclusion criteria				
BP -mmHg	-	systolic BP <90	systolic BP <100	symptomatic hypotension
Renal function	serum creatinine >3.0 mg/dl	significant renal dysfunction	serum creatinine >200 umol/L	serum creatinine >3.0 mg/dl or creatinine clearance ≤30 ml/min
Potassium -mmol/L	<3.2 or >5.5	-	>5.4	>5.5
Others	-	heart rate <60 beats/min	intolerant of ACEIs	-
Baseline treatment (%)				
ACEI	86	86	NA	23
ARB	NR	6	NR	54
ACEI or ARB	NR	NR	NR	71
Beta-blocker	NR	NA	54	NA
MRA	8	6	10	23
CRT	NR	NR	NR	NR
Mortality events				
All-cause death	231	107	109	39
CV death	162	72	78	15
Sudden death	NR	27	NR	NR
Pump failure death	64	NR	NR	NR

Appendix Table 9 Candidate variables and missing data in HF-PEF

	Derivation cohort	Validation cohorts	
	I-PRESERVE (N=4116)	**CHARM-Preserved (N=2556)**	**TOPCAT (N=3401)**
Demographics (N=3)			
Age -years	0	0	0
Sex (male, female)	0	0	0
Race (white, black, Asian, other)	0	0	0
Clinical assessment (N=8)			
Body mass index	19 (0.5%)	8 (0.3%)	10 (0.3%)
Systolic BP -mmHg	0	1 (<0.1%)	4 (0.1%)
Diastolic BP -mmHg	0	1 (<0.1%)	4 (0.1%)
Heart rate -beats/min	4 (0.1%)	1 (<0.1%)	3 (0.1%)
LVEF -%	3 (0.1%)	0	1 (<0.1%)
NYHA class (I-II, III-IV)	0	0	0
Aetiology (ischaemic, hypertensive, other)	0	0	NA
HF duration (≤1 year, >1-5 years, >5 years)	4 (0.1%)	1 (<0.1%)	NA
Medical history (N=13)			
Current smoking	NA	0	4 (0.1%)
Previous HF hospitalization within 6 months	0	0	0
Myocardial infarction	0	0	3 (0.1%)
Angina	0	0	3 (0.1%)
CABG or PCI	0	0	3 (0.1%)
Coronary artery disease	0	0	3 (0.1%)
Hypertension	0	0	3 (0.1%)
Diabetes	0	0	3 (0.1%)
Atrial fibrillation	0	0	3 (0.1%)
Stroke	0	0	3 (0.1%)
Pacemaker	0	0	3 (0.1%)
COPD or asthma	0	NA	3 (0.1%)
Dyslipidaemia	0	NA	3 (0.1%)
Treatment (N=12)			
Digitalis	3 (0.1%)	0	8 (0.2%)
Diuretic	3 (0.1%)	0	8 (0.2%)
Loop diuretic	3 (0.1%)	0	8 (0.2%)
Thiazide diuretic	3 (0.1%)	0	8 (0.2%)
ACEI or ARB	0	0	8 (0.2%)
Beta-blocker	3 (0.1%)	0	8 (0.2%)
MRA	3 (0.1%)	0	8 (0.2%)
Calcium channel blocker	3 (0.1%)	0	8 (0.2%)
Antiarrhythmic agent	3 (0.1%)	0	8 (0.2%)
Antiplatelet	3 (0.1%)	0	8 (0.2%)
Aspirin	3 (0.1%)	0	8 (0.2%)
Lipid lowering agent	3 (0.1%)	0	8 (0.2%)
ECG (N=6)			
QRS duration -ms	143 (3.5%)	NA	93 (2.7%)
Atrial fibrillation or flutter	0	12 (0.5%)	19 (0.6%)
Bundle branch block	0	12 (0.5%)	19 (0.6%)
Left bundle branch block	0	NA	NA
Right bundle branch block	0	NA	NA
Left ventricular hypertrophy	0	12 (0.5%)	19 (0.6%)
Laboratory tests (N=15)			
Albumin -g/L	92 (2.2%)	NA	178 (5.2%)

Aspartate aminotransferase -U/L	92 (2.2%)	NA	46 (1.4%)
Alanine aminotransferase -U/L	92 (2.2%)	NA	41 (1.2%)
Bilirubin -mg/dl	92 (2.2%)	NA	61 (1.8%)
Potassium -mmol/L	117 (2.8%)	NA	4 (0.1%)
Sodium -mmol/L	92 (2.2%)	NA	6 (0.2%)
Haemoglobin -g/L	140 (3.4%)	NA	23 (0.7%)
Haematocrit -%	140 (3.4%)	NA	27 (0.8%)
Leukocyte -10^9/L	140 (3.4%)	NA	24 (0.7%)
Neutrophil -10^9/L	164 (4.0%)	NA	NA
Platelet -10^9/L	147 (3.6%)	NA	35 (1.0%)
Blood urea nitrogen -mg/dl	92 (2.2%)	NA	771 (22.7%)
Creatinine -mg/dl	89 (2.2%)	1634 (63.9%)	2 (0.1%)
eGFR -ml/min/1.73m^2	89 (2.2%)	1634 (63.9%)	2 (0.1%)
NT-proBNP -pg/ml	646 (15.7%)	NA	2786 (81.9%)

NA denotes not available, referring to data being not collected.

List of References

1. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A and Guidelines ESCCfP. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2012;33:1787-1847.

2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL, American College of Cardiology F and American Heart Association Task Force on Practice G. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62:e147-239.

3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P and Authors/Task Force M. 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*. 2016;37:2129-2200.

4. Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC and Vasan RS. Natural history of asymptomatic left ventricular systolic dysfunction in the community. *Circulation*. 2003;108:977-982.

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

6. McMurray JJ, Krum H, Abraham WT, Dickstein K, Kober LV, Desai AS, Solomon SD, Greenlaw N, Ali MA, Chiang Y, Shao Q, Tarnesby G, Massie BM and Investigators AC. Aliskiren, Enalapril, or Aliskiren and Enalapril in Heart Failure. *N Engl J Med*. 2016;374:1521-1532.

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

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

9. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, Michelson EL, Olofsson B and Östergren J. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet*. 2003;362:777-781.

10. Yamamoto K, Origasa H, Hori M and Investigators JD. Effects of carvedilol on heart failure with preserved ejection fraction: the Japanese Diastolic Heart Failure Study (J-DHF). *Eur J Heart Fail*. 2013;15:110-118.

11. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A and Investigators IP. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med*. 2008;359:2456-2467.

12. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM and Investigators T. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370:1383-1392.

13. Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, Love TE, Aronow WS, Adams KF, Jr. and Gheorghiade M. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. *Circulation*. 2006;114:397-403.

14. Ziaeian B and Fonarow GC. Epidemiology and aetiology of heart failure. *Nat Rev Cardiol*. 2016;13:368-378.

15. Mehta PA, Dubrey SW, McIntyre HF, Walker DM, Hardman SM, Sutton GC, McDonagh TA and Cowie MR. Improving survival in the 6 months after diagnosis of heart failure in the past decade: population-based data from the UK. *Heart*. 2009;95:1851-1856.

16. Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, Killian JM and Roger VL. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med*. 2015;175:996-1004.

17. Zarrinkoub R, Wettermark B, Wandell P, Mejhert M, Szulkin R, Ljunggren G and Kahan T. The epidemiology of heart failure, based on data for 2.1 million inhabitants in Sweden. *Eur J Heart Fail*. 2013;15:995-1002.

18. Jiang H and Ge J. Epidemiology and clinical management of cardiomyopathies and heart failure in China. *Heart*. 2009;95:1727-1731.

19. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP and Jacobsen SJ. Trends in heart failure incidence and survival in a community-based population. *JAMA*. 2004;292:344-350.

20. Jhund PS, Macintyre K, Simpson CR, Lewsey JD, Stewart S, Redpath A, Chalmers JW, Capewell S and McMurray JJ. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. *Circulation*. 2009;119:515-523.

21. *Chronic Heart Failure: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care: Partial Update* London; 2010.

22. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jimenez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P, American Heart Association Statistics C and Stroke Statistics S. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation*. 2017;135:e146-e603.

23. Mosterd A, Hoes AW, de Bruyne MC, Deckers JW, Linker DT, Hofman A and Grobbee DE. Prevalence of heart failure and left ventricular dysfunction in the general population; The Rotterdam Study. *Eur Heart J*. 1999;20:447-455.

24. van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA and Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. *Eur J Heart Fail*. 2016;18:242-252.

25. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL and Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006;355:251-259.

26. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, Drazner MH, Filippatos G, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW and Westlake C. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An 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*. 2016;134:e282-293.

27. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, Investigators P-H and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993-1004.

28. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G and Tavazzi L. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010;376:875-885.

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

30. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM and Investigators C. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *New Engl J Med*. 2004;350:2140-2150.

31. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML and Multicenter Automatic Defibrillator Implantation Trial III. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;346:877-883.

32. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH and Sudden Cardiac Death in Heart Failure Trial I. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med*. 2005;352:225-237.

33. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, Calkins H, Hoch D, Goldberger J, Shalaby A, Sanders WE, Schaechter A, Levine JH and Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation I. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med*. 2004;350:2151-2158.

34. Desai AS, Fang JC, Maisel WH and Baughman KL. Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials. *JAMA*. 2004;292:2874-2879.

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

36. Colquitt JL, Mendes D, Clegg AJ, Harris P, Cooper K, Picot J and Bryant J. Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure: systematic review and economic evaluation. *Health Technol Assess*. 2014;18:1-560.

37. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, Shi V, Bransford T, Takeuchi M, Gong J, Lefkowitz M, Packer M and McMurray JJV. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet*. 2012;380:1387-1395.

38. Solomon SD, Rizkala AR, Gong J, Wang W, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, Van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Shi VC, Lefkowitz MP and McMurray JJV. Angiotensin Receptor Neprilysin Inhibition in Heart Failure With Preserved Ejection Fraction: Rationale and Design of the PARAGON-HF Trial. *JACC Heart Fail*. 2017;5:471-482.

39. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, Murabito JM and Vasan RS. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med*. 2002;347:1397-1402.

40. Meta-analysis Global Group in Chronic Heart F. The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J*. 2012;33:1750-1757.

41. Mosterd A and Hoes AW. Clinical epidemiology of heart failure. *Heart*. 2007;93:1137-1146.

42. Rush CJ, Campbell RT, Jhund PS, Connolly EC, Preiss D, Gardner RS, Petrie MC and McMurray JJ. Falling Cardiovascular Mortality in Heart Failure With Reduced Ejection Fraction and Implications for Clinical Trials. *JACC Heart Fail*. 2015;3:603-614.

43. Lam CS, Donal E, Kraigher-Krainer E and Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2011;13:18-28.

44. Vaduganathan M, Patel RB, Michel A, Shah SJ, Senni M, Gheorghiade M and Butler J. Mode of Death in Heart Failure With Preserved Ejection Fraction. *J Am Coll Cardiol*. 2017;69:556-569.

45. Narang R, Cleland JG, Erhardt L, Ball SG, Coats AJ, Cowley AJ, Dargie HJ, Hall AS, Hampton JR and Poole-Wilson PA. Mode of death in chronic heart failure. A request and proposition for more accurate classification. *Eur Heart J*. 1996;17:1390-1403.

46. Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, Fonarow GC, Jacobs JP, Jaff MR, Lichtman JH, Limacher MC, Mahaffey KW, Mehran R, Nissen SE, Smith EE and Targum SL. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *J Am Coll Cardiol*. 2015;66:403-469.

47. Hamaguchi S, Kinugawa S, Sobirin MA, Goto D, Tsuchihashi-Makaya M, Yamada S, Yokoshiki H, Tsutsui H and for the J-CI. Mode of Death in Patients With Heart Failure and Reduced vs. Preserved Ejection Fraction. *Circ J*. 2012;76:1662-1669.

48. Pons F, Lupon J, Urrutia A, Gonzalez B, Crespo E, Diez C, Cano L, Cabanes R, Altimir S, Coll R, Pascual T and Valle V. Mortality and cause of death in patients with heart failure: findings at a specialist multidisciplinary heart failure unit. *Revista Espanola De Cardiologia*. 2010;63:303-314.

49. Zafrir B, Paz H, Wolff R, Salman N, Merhavi D, Lewis BS and Amir O. Mortality rates and modes of death in heart failure patients with reduced versus preserved systolic function. *Eur J Intern Med*. 2011;22:53-56.

50. Zile MR, Gaasch WH, Anand IS, Haass M, Little WC, Miller AB, Lopez-Sendon J, Teerlink JR, White M, McMurray JJ, Komajda M, McKelvie R, Ptaszynska A, Hetzel SJ, Massie BM, Carson PE and Investigators IP. Mode of death in patients with heart failure and a preserved ejection fraction: results from the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-Preserve) trial. *Circulation*. 2010;121:1393-1405.

51. Cubbon RM, Gale CP, Kearney LC, Schechter CB, Brooksby WP, Nolan J, Fox KA, Rajwani A, Baig W, Groves D, Barlow P, Fisher AC, Batin PD, Kahn MB, Zaman AG, Shah AM, Byrne JA, Lindsay SJ, Sapsford RJ, Wheatcroft SB, Witte KK and Kearney MT. 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*. 2011;4:396-403.

52. Loh JC, Creaser J, Rourke DA, Livingston N, Harrison TK, Vandenbogaart E, Moriguchi J, Hamilton MA, Tseng CH, Fonarow GC and Horwich TB. Temporal trends in treatment and outcomes for advanced heart failure with reduced ejection fraction from 1993-2010: findings from a university referral center. *Circ Heart Fail*. 2013;6:411-419.

53. Ushigome R, Sakata Y, Nochioka K, Miyata S, Miura M, Tadaki S, Yamauchi T, Sato K, Onose T, Tsuji K, Abe R, Oikawa T, Kasahara S, Takahashi J, Shimokawa H and Investigators C-. Temporal trends in clinical characteristics, management and prognosis of patients with symptomatic heart failure in Japan -- report from the CHART Studies. *Circ J*. 2015;79:2396-2407.

54. Domanski MJ, Exner DV, Borkowf CB, Geller NL, Rosenberg Y and Pfeffer MA. Effect of angiotensin converting enzyme inhibition on sudden cardiac death in patients following acute myocardial infarction. A meta-analysis of randomized clinical trials. *J Am Coll Cardiol*. 1999;33:598-604.

55. Solomon SD, Wang D, Finn P, Skali H, Zornoff L, McMurray JJ, Swedberg K, Yusuf S, Granger CB, Michelson EL, Pocock S and Pfeffer MA. Effect of candesartan on cause-specific mortality in heart failure patients: the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) program. *Circulation*. 2004;110:2180-2183.

56. Al-Gobari M, El Khatib C, Pillon F and Gueyffier F. beta-Blockers for the prevention of sudden cardiac death in heart failure patients: a meta-analysis of randomized controlled trials. *BMC Cardiovasc Disord*. 2013;13:52.

57. Bapoje SR, Bahia A, Hokanson JE, Peterson PN, Heidenreich PA, Lindenfeld J, Allen LA and Masoudi FA. Effects of mineralocorticoid receptor antagonists on the risk of sudden cardiac death in patients with left ventricular systolic dysfunction: a meta-analysis of randomized controlled trials. *Circ Heart Fail*. 2013;6:166-173.

58. Desai AS, McMurray JJ, Packer M, Swedberg K, Rouleau JL, Chen F, Gong J, Rizkala AR, Brahimi A, Claggett B, Finn PV, Hartley LH, Liu J, Lefkowitz M, Shi V, Zile MR and Solomon SD. Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. *Eur Heart J*. 2015;36:1990-1997.

59. Greenberg H, Case RB, Moss AJ, Brown MW, Carroll ER, Andrews ML and Investigators M-I. Analysis of mortality events in the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II). *J Am Coll Cardiol*. 2004;43:1459-1465.

60. Packer DL, Prutkin JM, Hellkamp AS, Mitchell LB, Bernstein RC, Wood F, Boehmer JP, Carlson MD, Frantz RP, McNulty SE, Rogers JG, Anderson J, Johnson GW, Walsh MN, Poole JE, Mark DB, Lee KL and Bardy GH. Impact of implantable cardioverter-defibrillator, amiodarone, and placebo on the mode of death in stable patients with heart failure: analysis from the sudden cardiac death in heart failure trial. *Circulation*. 2009;120:2170-2176.

61. Rivero-Ayerza M, Theuns DA, Garcia-Garcia HM, Boersma E, Simoons M and Jordaens LJ. Effects of cardiac resynchronization therapy on overall mortality and mode of death: a meta-analysis of randomized controlled trials. *Eur Heart J*. 2006;27:2682-2688.

62. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L and Tavazzi L. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. *Eur Heart J*. 2006;27:1928-1932.

63. Carson P, Anand I, O'Connor C, Jaski B, Steinberg J, Lwin A, Lindenfeld J, Ghali J, Barnet JH, Feldman AM and Bristow MR. Mode of death in advanced heart failure: the Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure (COMPANION) trial. *J Am Coll Cardiol*. 2005;46:2329-2334.

64. Investigators S, Yusuf S, Pitt B, Davis CE, Hood WB and Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991;325:293-302.

65. Domanski M. A comparative analysis of the results from 4 trials of ß-blocker therapy for heart failure: BEST, CIBIS-II, MERIT-HF, and COPERNICUS. *J Card Fail*. 2003;9:354-363.

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

67. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B and Group E-HS. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364:11-21.

68. Alba AC, Agoritsas T, Jankowski M, Courvoisier D, Walter SD, Guyatt GH and Ross HJ. Risk prediction models for mortality in ambulatory patients with heart failure: a systematic review. *Circ Heart Fail*. 2013;6:881-889.

69. Rahimi K, Bennett D, Conrad N, Williams TM, Basu J, Dwight J, Woodward M, Patel A, McMurray J and MacMahon S. Risk prediction in patients with heart failure: a systematic review and analysis. *JACC Heart Fail*. 2014;2:440-446.

70. Ferrero P, Iacovoni A, D'Elia E, Vaduganathan M, Gavazzi A and Senni M. Prognostic scores in heart failure - Critical appraisal and practical use. *Int J Cardiol*. 2015;188:1-9.

71. Harrell FE, Jr., Lee KL and Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996;15:361-387.

72. Royston P and Altman DG. External validation of a Cox prognostic model: principles and methods. *BMC Med Res Methodol*. 2013;13:33.

73. Bleeker SE, Moll HA, Steyerberg EW, Donders ART, Derksen-Lubsen G, Grobbee DE and Moons KGM. External validation is necessary in prediction research. *J Clin Epidemiol*. 2003;56:826-832.

74. Shadman R, Poole JE, Dardas TF, Mozaffarian D, Cleland JG, Swedberg K, Maggioni AP, Anand IS, Carson PE, Miller AB and Levy WC. A novel method to predict the proportional risk of sudden cardiac death in heart failure: Derivation of the Seattle Proportional Risk Model. *Heart Rhythm*. 2015;12:2069-2077.

75. Kawai T, Yamada T, Tamaki S, Morita T, Furukawa Y, Iwasaki Y, Kawasaki M, Kikuchi A, Kondo T, Takahashi S, Ishimi M, Hakui H, Ozaki T, Sato Y, Seo M, Sakata Y and Fukunami M. Usefulness of cardiac meta-iodobenzylguanidine imaging to identify patients with chronic heart failure and left ventricular ejection fraction <35% at low risk for sudden cardiac death. *Am J Cardiol*. 2015;115:1549-1554.

76. Adabag S, Rector TS, Anand IS, McMurray JJ, Zile M, Komajda M, McKelvie RS, Massie B and Carson PE. A prediction model for sudden cardiac death in patients with heart failure and preserved ejection fraction. *Eur J Heart Fail*. 2014;16:1175-1182.

77. Furukawa Y, Yamada T, Morita T, Iwasaki Y, Kawasaki M, Kikuchi A, Naito T, Fujimoto T, Ozu K, Kondo T, Sengoku K, Yamamoto H, Masuyama T and Fukunami M. Early repolarization pattern associated with sudden cardiac death: long-term follow-up in patients with chronic heart failure. *J Cardiovasc Electrophysiol*. 2013;24:632-639.

78. Wedel H, McMurray JJV, Lindberg M, Wikstrand J, Cleland JGF, Cornel JH, Dunselman P, Hjalmarson A, Kjekshus J, Komajda M, Kuusi T, Vanhaecke J and Waagstein F. Predictors of fatal and non-fatal outcomes in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA): Incremental value of apolipoprotein A-1, high-sensitivity C-reactive peptide and N-terminal pro B-type natriuretic peptide. *Eur J Heart Fail*. 2009;11:281-291.

79. Vazquez R, Bayes-Genis A, Cygankiewicz I, Pascual-Figal D, Grigorian-Shamagian L, Pavon R, Gonzalez-Juanatey JR, Cubero JM, Pastor L, Ordonez-Llanos J, Cinca J, de Luna AB and Investigators M. The MUSIC Risk score: a simple method for predicting mortality in ambulatory patients with chronic heart failure. *Eur Heart J*. 2009;30:1088-1096.

80. Tamaki S, Yamada T, Okuyama Y, Morita T, Sanada S, Tsukamoto Y, Masuda M, Okuda K, Iwasaki Y, Yasui T, Hori M and Fukunami M. Cardiac iodine-123 metaiodobenzylguanidine imaging predicts sudden cardiac death independently of left ventricular ejection fraction in patients with chronic heart failure and left ventricular systolic dysfunction: results from a comparative study with signal-averaged electrocardiogram, heart rate variability, and QT dispersion. *J Am Coll Cardiol*. 2009;53:426-435.

81. Smilde TD, van Veldhuisen DJ and van den Berg MP. Prognostic value of heart rate variability and ventricular arrhythmias during 13-year follow-up in patients with mild to moderate heart failure. *Clin Res Cardiol*. 2009;98:233-239.

82. Uretsky BF, Thygesen K, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L and Cleland JG. Predictors of mortality from pump failure and sudden cardiac death in patients with systolic heart failure and left ventricular dyssynchrony: results of the CARE-HF trial. *J Card Fail*. 2008;14:670-675.

83. Mehta PA, Dubrey SW, McIntyre HF, Walker DM, Hardman SM, Sutton GC, McDonagh TA and Cowie MR. Mode of death in patients with newly diagnosed heart failure in the general population. *Eur J Heart Fail*. 2008;10:1108-1116.

84. Mozaffarian D, Anker SD, Anand I, Linker DT, Sullivan MD, Cleland JG, Carson PE, Maggioni AP, Mann DL, Pitt B, Poole-Wilson PA and Levy WC. Prediction of mode of death in heart failure: the Seattle Heart Failure Model. *Circulation*. 2007;116:392-398.

85. Guazzi M, Raimondo R, Vicenzi M, Arena R, Proserpio C, Sarzi Braga S and Pedretti R. Exercise oscillatory ventilation may predict sudden cardiac death in heart failure patients. *J Am Coll Cardiol*. 2007;50:299-308.

86. Watanabe J, Shinozaki T, Shiba N, Fukahori K, Koseki Y, Karibe A, Sakuma M, Miura M, Kagaya Y and Shirato K. Accumulation of risk markers predicts the incidence of sudden death in patients with chronic heart failure. *Eur J Heart Fail*. 2006;8:237-242.

87. Berger R, Huelsmann M, Strecker K, Moertl D, Moser P, Bojic A and Pacher R. Neurohormonal risk stratification for sudden death and death owing to progressive heart failure in chronic heart failure. *Eur J Clin Invest*. 2005;35:24-31.

88. Kyuma M, Nakata T, Hashimoto A, Nagao K, Sasao H, Takahashi T, Tsuchihashi K and Shimamoto K. Incremental prognostic implications of brain natriuretic peptide, cardiac sympathetic nerve innervation, and noncardiac disorders in patients with heart failure. *J Nucl Med*. 2004;45:155-163.

89. Kearney MT, Fox KA, Lee AJ, Brooksby WP, Shah AM, Flapan A, Prescott RJ, Andrews R, Batin PD, Eckberg DL, Gall N, Zaman AG, Lindsay HS and Nolan J. Predicting sudden death in patients with mild to moderate chronic heart failure. *Heart*. 2004;90:1137-1143.

90. Vrtovec B, Delgado R, Zewail A, Thomas CD, Richartz BM and Radovancevic B. Prolonged QTc interval and high B-type natriuretic peptide levels together predict mortality in patients with advanced heart failure. *Circulation*. 2003;107:1764-1769.

91. Poole-Wilson PA, Uretsky BF, Thygesen K, Cleland JG, Massie BM, Ryden L, Atlas Study Group. Assessment of treatment with l and survival. Mode of death in heart failure: findings from the ATLAS trial. *Heart*. 2003;89:42-48.

92. La Rovere MT, Pinna GD, Maestri R, Mortara A, Capomolla S, Febo O, Ferrari R, Franchini M, Gnemmi M, Opasich C, Riccardi PG, Traversi E and Cobelli F. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. *Circulation*. 2003;107:565-570.

93. Isnard R, Pousset F, Chafirovskaia O, Carayon A, Hulot JS, Thomas D and Komajda M. Combination of B-type natriuretic peptide and peak oxygen consumption improves risk stratification in outpatients with chronic heart failure. *Am Heart J*. 2003;146:729-735.

94. Kearney MT, Fox KA, Lee AJ, Prescott RJ, Shah AM, Batin PD, Baig W, Lindsay S, Callahan TS, Shell WE, Eckberg DL, Zaman AG, Williams S, Neilson JM

and Nolan J. Predicting death due to progressive heart failure in patients with mild-to-moderate chronic heart failure. *J Am Coll Cardiol*. 2002;40:1801-1808.

95. Berger R, Huelsman M, Strecker K, Bojic A, Moser P, Stanek B and Pacher R. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. *Circulation*. 2002;105:2392-2397.

96. Baldasseroni S, Opasich C, Gorini M, Lucci D, Marchionni N, Marini M, Campana C, Perini G, Deorsola A, Masotti G, Tavazzi L, Maggioni AP and Italian Network on Congestive Heart Failure I. Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure. *Am Heart J*. 2002;143:398-405.

97. Teerlink JR, Jalaluddin M, Anderson S, Kukin ML, Eichhorn EJ, Francis G, Packer M and Massie BM. Ambulatory ventricular arrhythmias in patients with heart failure do not specifically predict an increased risk of sudden death. *Circulation*. 2000;101:40-46.

98. Szabo BM, van Veldhuisen DJ, van der Veer N, Brouwer J, De Graeff PA and Crijns HJ. Prognostic value of heart rate variability in chronic congestive heart failure secondary to idiopathic or ischemic dilated cardiomyopathy. *Am J Cardiol*. 1997;79:978-980.

99. Madsen BK, Rasmussen V and Hansen JF. Predictors of sudden death and death from pump failure in congestive heart failure are different. Analysis of 24 h Holter monitoring, clinical variables, blood chemistry, exercise test and radionuclide angiography. *Int J Cardiol*. 1997;58:151-162.

100. Szabo BM, van Veldhuisen DJ, Crijns HJ, Wiesfeld AC, Hillege HL and Lie KI. Value of ambulatory electrocardiographic monitoring to identify increased risk of sudden death in patients with left ventricular dysfunction and heart failure. *Eur Heart J*. 1994;15:928-933.

101. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, Anand I, Maggioni A, Burton P, Sullivan MD, Pitt B, Poole-Wilson PA, Mann DL and Packer M. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation*. 2006;113:1424-1433.

102. Beta-Blocker Evaluation of Survival Trial I. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med*. 2001;344:1659-1667.

103. Cohn JN, Tognoni G and Valsartan Heart Failure Trial I. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;345:1667-1675.

104. Granger CB, McMurray JJV, Yusuf S, Held P, Michelson EL, Olofsson B, Östergren J, Pfeffer MA and Swedberg K. 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*. 2003;362:772-776.

105. McMurray JJV, Östergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S and Pfeffer MA. 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*. 2003;362:767-771.

106. investigators G-H. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;372:1231-1239.

107. Rubin DB. Inference and missing data. *Biometrika*. 1976;63:581-592.

108. Groenwold RH, White IR, Donders AR, Carpenter JR, Altman DG and Moons KG. Missing covariate data in clinical research: when and when not to use the missing-indicator method for analysis. *CMAJ*. 2012;184:1265-1269.

109. White IR and Carlin JB. Bias and efficiency of multiple imputation compared with complete-case analysis for missing covariate values. *Stat Med*. 2010;29:2920-2931.

110. Clark TG, Bradburn MJ, Love SB and Altman DG. Survival analysis part I: basic concepts and first analyses. *Br J Cancer*. 2003;89:232-238.

111. Leung KM, Elashoff RM and Afifi AA. Censoring issues in survival analysis. *Annu Rev Public Health*. 1997;18:83-104.

112. Wolbers M, Koller MT, Stel VS, Schaer B, Jager KJ, Leffondre K and Heinze G. Competing risks analyses: objectives and approaches. *Eur Heart J*. 2014;35:2936-2941.

113. Austin PC, Lee DS and Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. *Circulation*. 2016;133:601-609.

114. Andersen PK, Geskus RB, de Witte T and Putter H. Competing risks in epidemiology: possibilities and pitfalls. *Int J Epidemiol*. 2012;41:861-870.

115. Bland JM and Altman DG. Survival probabilities (the Kaplan-Meier method). *BMJ*. 1998;317:1572.

116. Putter H, Fiocco M and Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. *Stat Med*. 2007;26:2389-2430.

117. Cox DR. Regression models and life tables. *Journal of the Royal Statistical Society Series B (Methodological)*. 1972;34:187-220.

118. Fine JP and Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *J Am Stat Assoc*. 1999;94:496-509.

119. Harrell FE, Jr., Lee KL and Pollock BG. Regression models in clinical studies: determining relationships between predictors and response. *J Natl Cancer Inst*. 1988;80:1198-1202.

120. Durrleman S and Simon R. Flexible regression models with cubic splines. *Stat Med*. 1989;8:551-561.

121. Grambsch PM and Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994;81:515-526.

122. Scrucca L, Santucci A and Aversa F. Regression modeling of competing risk using R: an in depth guide for clinicians. *Bone Marrow Transplant*. 2010;45:1388-1395.

123. Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, Pencina MJ and Kattan MW. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology*. 2010;21:128-138.

124. Hosmer DW, Hosmer T, Le Cessie S and Lemeshow S. A comparison of goodness-of-fit tests for the logistic regression model. *Stat Med*. 1997;16:965-980.

125. Hanley JA and McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982;143:29-36.

126. Harrell FE, Jr., Califf RM, Pryor DB, Lee KL and Rosati RA. Evaluating the yield of medical tests. *JAMA*. 1982;247:2543-2546.

127. Wolbers M, Blanche P, Koller MT, Witteman JC and Gerds TA. Concordance for prognostic models with competing risks. *Biostatistics*. 2014;15:526-539.

128. Gray RJ. A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. *Ann Stat*. 1988;16:1141-1154.

129. Chung MK, Szymkiewicz SJ, Shao M, Zishiri E, Niebauer MJ, Lindsay BD and Tchou PJ. Aggregate national experience with the wearable cardioverter-defibrillator: event rates, compliance, and survival. *J Am Coll Cardiol*. 2010;56:194-203.

130. Russo AM, Stainback RF, Bailey SR, Epstein AE, Heidenreich PA, Jessup M, Kapa S, Kremers MS, Lindsay BD and Stevenson LW. ACCF/HRS/AHA/ASE/HFSA/SCAI/SCCT/SCMR 2013 appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy: a report of the American College of Cardiology Foundation appropriate use criteria task force, Heart Rhythm Society, American Heart Association, American Society of Echocardiography, Heart Failure Society of America, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. *Heart Rhythm*. 2013;10:e11-58.

131. Colucci WS, Kolias TJ, Adams KF, Armstrong WF, Ghali JK, Gottlieb SS, Greenberg B, Klibaner MI, Kukin ML and Sugg JE. Metoprolol reverses left ventricular remodeling in patients with asymptomatic systolic dysfunction: the REversal of VEntricular Remodeling with Toprol-XL (REVERT) trial. *Circulation*. 2007;116:49-56.

132. Remme WJ, Riegger G, Hildebrandt P, Komajda M, Jaarsma W, Bobbio M, Soler-Soler J, Scherhag A, Lutiger B and Ryden L. The benefits of early combination treatment of carvedilol and an ACE-inhibitor in mild heart failure and left ventricular systolic dysfunction. The carvedilol and ACE-inhibitor

remodelling mild heart failure evaluation trial (CARMEN). *Cardiovasc Drugs Ther*. 2004;18:57-66.

133. Konstam MA, Kronenberg MW, Rousseau MF, Udelson JE, Melin J, Stewart D, Dolan N, Edens TR, Ahn S, Kinan D and et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dilatation in patients with asymptomatic systolic dysfunction. SOLVD (Studies of Left Ventricular Dysfunction) Investigators. *Circulation*. 1993;88:2277-2283.

134. Wong M, Staszewsky L, Latini R, Barlera S, Volpi A, Chiang YT, Benza RL, Gottlieb SO, Kleemann TD, Rosconi F, Vandervoort PM and Cohn JN. Valsartan benefits left ventricular structure and function in heart failure: Val-HeFT echocardiographic study. *J Am Coll Cardiol*. 2002;40:970-975.

135. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, Kubo SH, Narahara KA, Ingersoll H, Krueger S, Young S and Shusterman N. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. *Circulation*. 1996;94:2807-2816.

136. Zecchin M, Merlo M, Pivetta A, Barbati G, Lutman C, Gregori D, Serdoz LV, Bardari S, Magnani S, Di Lenarda A, Proclemer A and Sinagra G. How can optimization of medical treatment avoid unnecessary implantable cardioverter-defibrillator implantations in patients with idiopathic dilated cardiomyopathy presenting with "SCD-HeFT criteria?". *Am J Cardiol*. 2012;109:729-735.

137. Buxton AE. Implantable cardioverter-defibrillators for primary prevention of sudden death: the quest to identify patients most likely to benefit. *J Am Coll Cardiol*. 2012;60:1656-1658.

138. Masoudi FA, Go AS, Magid DJ, Cassidy-Bushrow AE, Gurwitz JH, Liu TI, Reynolds K, Smith DH, Reifler LM, Glenn KA, Fiocchi F, Goldberg R, Gupta N, Peterson PN, Schuger C, Vidaillet H, Hammill SC and Greenlee RT. Age and sex differences in long-term outcomes following implantable cardioverter-defibrillator placement in contemporary clinical practice: findings from the Cardiovascular Research Network. *J Am Heart Assoc*. 2015;4:e002005.

139. Wong CY, Chaudhry SI, Desai MM and Krumholz HM. Trends in comorbidity, disability, and polypharmacy in heart failure. *Am J Med*. 2011;124:136-143.

140. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW and Young JB. Dosing of beta-blocker therapy before, during, and after hospitalization for heart failure (from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure). *Am J Cardiol*. 2008;102:1524-1529.

141. Eschalier R, Chenaf C, Mulliez A, Yalioua A, Clerfond G, Authier N, Vorilhon C, Citron B, Pereira B, Jean F, Souteyrand G, Motreff P, Eschalier A and Lusson JR. Impact of clinical characteristics and management on the prognosis of unselected heart failure patients. *Cardiovasc Drugs Ther*. 2015;29:89-98.

142. O'Connor CM, Whellan DJ, Wojdyla D, Leifer E, Clare RM, Ellis SJ, Fine LJ, Fleg JL, Zannad F, Keteyian SJ, Kitzman DW, Kraus WE, Rendall D, Pina IL,

Cooper LS, Fiuzat M and Lee KL. Factors related to morbidity and mortality in patients with chronic heart failure with systolic dysfunction: the HF-ACTION predictive risk score model. *Circ Heart Fail*. 2012;5:63-71.

143. Ahmad T, Fiuzat M, Neely B, Neely ML, Pencina MJ, Kraus WE, Zannad F, Whellan DJ, Donahue MP, Pina IL, Adams KF, Kitzman DW, O'Connor CM and Felker GM. Biomarkers of myocardial stress and fibrosis as predictors of mode of death in patients with chronic heart failure. *JACC Heart Fail*. 2014;2:260-268.

144. Liu X, Yu H, Pei J, Chu J, Pu J and Zhang S. Clinical characteristics and long-term prognosis in patients with chronic heart failure and reduced ejection fraction in China. *Heart Lung Circ*. 2014;23:818-826.

145. Horwich TB, Kalantar-Zadeh K, MacLellan RW and Fonarow GC. Albumin levels predict survival in patients with systolic heart failure. *Am Heart J*. 2008;155:883-889.

146. Solomon SD, Anavekar N, Skali H, McMurray JJ, Swedberg K, Yusuf S, Granger CB, Michelson EL, Wang D, Pocock S, Pfeffer MA and Candesartan in Heart Failure Reduction in Mortality I. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation*. 2005;112:3738-3744.

147. Murakoshi N and Aonuma K. Epidemiology of arrhythmias and sudden cardiac death in Asia. *Circ J*. 2013;77:2419-2431.

148. Cinca J, Mendez A, Puig T, Ferrero A, Roig E, Vazquez R, Gonzalez-Juanatey JR, Alonso-Pulpon L, Delgado J, Brugada J, Pascual-Figal D and investigators of the Spanish Heart Failure N. Differential clinical characteristics and prognosis of intraventricular conduction defects in patients with chronic heart failure. *Eur J Heart Fail*. 2013;15:877-884.

149. Felker GM, Allen LA, Pocock SJ, Shaw LK, McMurray JJ, Pfeffer MA, Swedberg K, Wang D, Yusuf S, Michelson EL, Granger CB and Investigators C. Red cell distribution width as a novel prognostic marker in heart failure: data from the CHARM Program and the Duke Databank. *J Am Coll Cardiol*. 2007;50:40-47.

150. Grodin JL, Verbrugge FH, Ellis SG, Mullens W, Testani JM and Tang WHW. Importance of Abnormal Chloride Homeostasis in Stable Chronic Heart Failure. *Circ Heart Fail*. 2016;9: e002453.

151. Vaduganathan M, Pallais JC, Fenves AZ, Butler J and Gheorghiade M. Serum chloride in heart failure: a salty prognosis. *Eur J Heart Fail*. 2016;18:669-671.

152. Testani JM, Hanberg JS, Arroyo JP, Brisco MA, Ter Maaten JM, Wilson FP, Bellumkonda L, Jacoby D, Tang WH and Parikh CR. Hypochloraemia is strongly and independently associated with mortality in patients with chronic heart failure. *Eur J Heart Fail*. 2016;18:660-668.

153. Altman DG, Vergouwe Y, Royston P and Moons KG. Prognosis and prognostic research: validating a prognostic model. *BMJ*. 2009;338:b605.

154. Riley RD, Ensor J, Snell KI, Debray TP, Altman DG, Moons KG and Collins GS. External validation of clinical prediction models using big datasets from e-health records or IPD meta-analysis: opportunities and challenges. *BMJ*. 2016;353:i3140.

155. Bleeker SE, Moll HA, Steyerberg EW, Donders AR, Derksen-Lubsen G, Grobbee DE and Moons KG. External validation is necessary in prediction research: a clinical example. *J Clin Epidemiol*. 2003;56:826-832.

156. Levy WC, Li Y, Reed SD, Zile MR, Shadman R, Dardas T, Whellan DJ, Schulman KA, Ellis SJ, Neilson M and O'Connor CM. Does the Implantable Cardioverter-Defibrillator Benefit Vary With the Estimated Proportional Risk of Sudden Death in Heart Failure Patients? JACC Clin Electrophysiol. 2017;3:291-298.

157. Bilchick KC, Wang Y, Cheng A, Curtis JP, Dharmarajan K, Stukenborg GJ, Shadman R, Anand I, Lund LH, Dahlstrom U, Sartipy U, Maggioni A, Swedberg K, O'Conner C and Levy WC. Seattle Heart Failure and Proportional Risk Models Predict Benefit From Implantable Cardioverter-Defibrillators. *J Am Coll Cardiol*. 2017;69:2606-2618.

158. Takeda Y, Fukutomi T, Suzuki S, Yamamoto K, Ogata M, Kondo H, Sugiura M, Shigeyama J and Itoh M. Effects of carvedilol on plasma B-type natriuretic peptide concentration and symptoms in patients with heart failure and preserved ejection fraction. *Am J Cardiol*. 2004;94:448-453.

159. Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, LeWinter MM, Rouleau JL, Bull DA, Mann DL, Deswal A, Stevenson LW, Givertz MM, Ofili EO, O'Connor CM, Felker GM, Goldsmith SR, Bart BA, McNulty SE, Ibarra JC, Lin G, Oh JK, Patel MR, Kim RJ, Tracy RP, Velazquez EJ, Anstrom KJ, Hernandez AF, Mascette AM, Braunwald E and Trial R. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA*. 2013;309:1268-1277.

160. Kosmala W, Holland DJ, Rojek A, Wright L, Przewlocka-Kosmala M and Marwick TH. Effect of If-channel inhibition on hemodynamic status and exercise tolerance in heart failure with preserved ejection fraction: a randomized trial. *J Am Coll Cardiol*. 2013;62:1330-1338.

161. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, Duvinage A, Stahrenberg R, Durstewitz K, Loffler M, Dungen HD, Tschope C, Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Pieske B and Aldo DHFI. 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*. 2013;309:781-791.

162. Redfield MM, Anstrom KJ, Levine JA, Koepp GA, Borlaug BA, Chen HH, LeWinter MM, Joseph SM, Shah SJ, Semigran MJ, Felker GM, Cole RT, Reeves GR, Tedford RJ, Tang WH, McNulty SE, Velazquez EJ, Shah MR, Braunwald E and Network NHFCR. Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction. *N Engl J Med*. 2015;373:2314-2324.

163. Zile MR, Bourge RC, Redfield MM, Zhou D, Baicu CF and Little WC. Randomized, double-blind, placebo-controlled study of sitaxsentan to improve impaired exercise tolerance in patients with heart failure and a preserved ejection fraction. *JACC Heart Fail*. 2014;2:123-130.

164. Zheng SL, Chan FT, Maclean E, Jayakumar S and Nabeebaccus AA. Reporting trends of randomised controlled trials in heart failure with preserved ejection fraction: a systematic review. *Open Heart*. 2016;3:e000449.

165. van Veldhuisen DJ, Cohen-Solal A, Bohm M, Anker SD, Babalis D, Roughton M, Coats AJ, Poole-Wilson PA, Flather MD and Investigators S. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). *J Am Coll Cardiol*. 2009;53:2150-2158.

166. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J and Investigators P-C. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J*. 2006;27:2338-2345.

167. Campbell RT, Jhund PS, Castagno D, Hawkins NM, Petrie MC and McMurray JJ. What have we learned about patients with heart failure and preserved ejection fraction from DIG-PEF, CHARM-preserved, and I-PRESERVE? *J Am Coll Cardiol*. 2012;60:2349-2356.

168. Kelly JP, Mentz RJ, Mebazaa A, Voors AA, Butler J, Roessig L, Fiuzat M, Zannad F, Pitt B, O'Connor CM and Lam CS. Patient selection in heart failure with preserved ejection fraction clinical trials. *J Am Coll Cardiol*. 2015;65:1668-1682.

169. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Wilson PW and Vasan RS. Impact of obesity on plasma natriuretic peptide levels. *Circulation*. 2004;109:594-600.

170. Corell P, Gustafsson F, Kistorp C, Madsen LH, Schou M and Hildebrandt P. Effect of atrial fibrillation on plasma NT-proBNP in chronic heart failure. *Int J Cardiol*. 2007;117:395-402.

171. Takase H and Dohi Y. Kidney function crucially affects B-type natriuretic peptide (BNP), N-terminal proBNP and their relationship. *Eur J Clin Invest*. 2014;44:303-308.

172. Komajda M, Carson PE, Hetzel S, McKelvie R, McMurray J, Ptaszynska A, Zile MR, Demets D and Massie BM. Factors associated with outcome in heart failure with preserved ejection fraction: findings from the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE). *Circ Heart Fail*. 2011;4:27-35.

173. Stecker EC, Vickers C, Waltz J, Socoteanu C, John BT, Mariani R, McAnulty JH, Gunson K, Jui J and Chugh SS. Population-based analysis of sudden cardiac death with and without left ventricular systolic dysfunction: two-year findings from the Oregon Sudden Unexpected Death Study. *J Am Coll Cardiol*. 2006;47:1161-1166.

174. Gorgels AP, Gijsbers C, de Vreede-Swagemakers J, Lousberg A and Wellens HJ. Out-of-hospital cardiac arrest--the relevance of heart failure. The Maastricht Circulatory Arrest Registry. *Eur Heart J*. 2003;24:1204-1209.

175. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C and Van Veldhuisen DJ. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J*. 2015;36:2793-2867.

176. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Heitner JF, Lewis EF, O'Meara E, Rouleau JL, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, McKinlay SM and Pitt B. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation*. 2015;131:34-42.

177. Chan MM and Lam CS. How do patients with heart failure with preserved ejection fraction die? *Eur J Heart Fail*. 2013;15:604-613.

178. Hawkins NM, Wang D, McMurray JJ, Pfeffer MA, Swedberg K, Granger CB, Yusuf S, Pocock SJ, Ostergren J, Michelson EL, Dunn FG, Investigators C and Committees. Prevalence and prognostic implications of electrocardiographic left ventricular hypertrophy in heart failure: evidence from the CHARM programme. *Heart*. 2007;93:59-64.

179. Tamarappoo BK, John BT, Reinier K, Teodorescu C, Uy-Evanado A, Gunson K, Jui J and Chugh SS. Vulnerable myocardial interstitium in patients with isolated left ventricular hypertrophy and sudden cardiac death: a postmortem histological evaluation. *J Am Heart Assoc*. 2012;1:e001511.

180. Francia P, Balla C, Paneni F and Volpe M. Left bundle-branch block--pathophysiology, prognosis, and clinical management. *Clin Cardiol*. 2007;30:110-115.

181. Carson PE, Anand IS, Win S, Rector T, Haass M, Lopez-Sendon J, Miller A, Teerlink JR, White M, McKelvie RS, Komajda M, Zile MR, McMurray JJ and Massie B. The Hospitalization Burden and Post-Hospitalization Mortality Risk in Heart Failure With Preserved Ejection Fraction: Results From the I-PRESERVE Trial (Irbesartan in Heart Failure and Preserved Ejection Fraction). *JACC Heart Fail*. 2015;3:429-441.

182. Hall C. Essential biochemistry and physiology of (NT-pro)BNP. *Eur J Heart Fail*. 2004;6:257-260.

183. Reiter MJ. Effects of mechano-electrical feedback: potential arrhythmogenic influence in patients with congestive heart failure. *Cardiovasc Res*. 1996;32:44-51.

184. Halliday B, Gulati A, Ali A, Guha K, Newsome SJ, Arzanauskaite M, Vassiliou VS, Lota AS, Izgi C, Tayal U, Khalique Z, Stirrat C, Auger D, Pareek N, Ismail TF, Rosen SD, Vazir A, Alpendurada F, Gregson J, Frenneaux MP, Cowie MR, Cleland JG, Cook SA, Pennell DJ and Prasad SK. Association Between Mid-Wall Late Gadolinium Enhancement and Sudden Cardiac Death in Patients with Dilated Cardiomyopathy and Mild and Moderate Left Ventricular Systolic Dysfunction. *Circulation*. 2017;135:2106-2115.

185. Selvanayagam JB, Hartshorne T, Billot L, Grover S, Hillis GS, Jung W, Krum H, Prasad S and McGavigan AD. Cardiovascular magnetic resonance-GUIDEd management of mild to moderate left ventricular systolic dysfunction (CMR GUIDE): Study protocol for a randomized controlled trial. *Ann Noninvasive Electrocardiol*. 2017;22. doi: 10.1111/anec.12420.

186. Every NR, Parsons L, Hlatky MA, McDonald KM, Thom D, Hallstrom AP, Martin JS and Weaver WD. Use and accuracy of state death certificates for classification of sudden cardiac deaths in high-risk populations. *Am Heart J*. 1997;134:1129-1132.

187. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C, Blanc JJ, Budaj A, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL, Smith SC, Jr., Jacobs AK, Adams CD, Antman EM, Anderson JL, Hunt SA, Halperin JL, Nishimura R, Ornato JP, Page RL, Riegel B, American College of Cardiology/American Heart Association Task F, European Society of Cardiology Committee for Practice G, European Heart Rhythm A and the Heart Rhythm S. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death--executive summary: A report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death) Developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Eur Heart J*. 2006;27:2099-2140.

188. Solomon SD and Chatterjee NA. Who Benefits From Implantable Cardioverter-Defibrillators?: Integrating Absolute, Proportional, and Competing Risk. *J Am Coll Cardiol*. 2017;69:2619-2621.

189. Sutton MG, Plappert T, Hilpisch KE, Abraham WT, Hayes DL and Chinchoy E. Sustained reverse left ventricular structural remodeling with cardiac resynchronization at one year is a function of etiology: quantitative Doppler echocardiographic evidence from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). *Circulation*. 2006;113:266-272.

190. Dagres N and Hindricks G. Devices for management of sudden cardiac death: Successes, challenges and perspectives. *Int J Cardiol*. 2017;237:34-37.

191. Tung R, Zimetbaum P and Josephson ME. A critical appraisal of implantable cardioverter-defibrillator therapy for the prevention of sudden cardiac death. *J Am Coll Cardiol*. 2008;52:1111-1121.

192. van Rees JB, Borleffs CJ, de Bie MK, Stijnen T, van Erven L, Bax JJ and Schalij MJ. Inappropriate implantable cardioverter-defibrillator shocks: incidence, predictors, and impact on mortality. *J Am Coll Cardiol*. 2011;57:556-562.

193. Daubert JP, Zareba W, Cannom DS, McNitt S, Rosero SZ, Wang P, Schuger C, Steinberg JS, Higgins SL, Wilber DJ, Klein H, Andrews ML, Hall WJ, Moss AJ and Investigators MI. Inappropriate implantable cardioverter-defibrillator shocks in MADIT II: frequency, mechanisms, predictors, and survival impact. *J Am Coll Cardiol*. 2008;51:1357-1365.

194. Germano JJ, Reynolds M, Essebag V and Josephson ME. Frequency and causes of implantable cardioverter-defibrillator therapies: is device therapy proarrhythmic? *Am J Cardiol*. 2006;97:1255-1261.

195. Moss AJ, Schuger C, Beck CA, Brown MW, Cannom DS, Daubert JP, Estes NA, 3rd, Greenberg H, Hall WJ, Huang DT, Kautzner J, Klein H, McNitt S, Olshansky B, Shoda M, Wilber D, Zareba W and Investigators M-RT. Reduction in inappropriate therapy and mortality through ICD programming. *N Engl J Med*. 2012;367:2275-2283.

196. https://www.nice.org.uk/guidance/ta314/documents/arrythmias-icds-heart-failure-cardiac-resynchronisation-fad-document2.

197. Sanders GD, Hlatky MA and Owens DK. Cost-effectiveness of implantable cardioverter-defibrillators. *New Engl J Med*. 2005;353:1471-1480.

198. Mark DB, Nelson CL, Anstrom KJ, Al-Khatib SM, Tsiatis AA, Cowper PA, Clapp-Channing NE, Davidson-Ray L, Poole JE, Johnson G, Anderson J, Lee KL, Bardy GH and Investigators SC-H. Cost-effectiveness of defibrillator therapy or amiodarone in chronic stable heart failure: results from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *Circulation*. 2006;114:135-142.

199. Mealing S, Woods B, Hawkins N, Cowie MR, Plummer CJ, Abraham WT, Beshai JF, Klein H and Sculpher M. Cost-effectiveness of implantable cardiac devices in patients with systolic heart failure. *Heart*. 2016;102:1742-1749.

200. Dagres N and Hindricks G. Risk stratification after myocardial infarction: is left ventricular ejection fraction enough to prevent sudden cardiac death? *Eur Heart J*. 2013;34:1964-1971.

201. Vickers AJ, Kattan MW and Daniel S. Method for evaluating prediction models that apply the results of randomized trials to individual patients. *Trials*. 2007;8:14.

202. Vickers AJ and Cronin AM. Traditional statistical methods for evaluating prediction models are uninformative as to clinical value: towards a decision analytic framework. *Semin Oncol*. 2010;37:31-38.

203. Vickers AJ and Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Making*. 2006;26:565-574.

204. Mancini D and Lietz K. Selection of cardiac transplantation candidates in 2010. *Circulation*. 2010;122:173-183.

205. Trivedi JR, Cheng A, Singh R, Williams ML and Slaughter MS. Survival on the heart transplant waiting list: impact of continuous flow left ventricular assist device as bridge to transplant. *Ann Thorac Surg*. 2014;98:830-834.

206. Mordi I, Jhund PS, Gardner RS, Payne J, Carrick D, Berry C and Tzemos N. LGE and NT-proBNP identify low risk of death or arrhythmic events in patients with primary prevention ICDs. *JACC Cardiovasc Imaging*. 2014;7:561-569.

207. Disertori M, Rigoni M, Pace N, Casolo G, Mase M, Gonzini L, Lucci D, Nollo G and Ravelli F. Myocardial Fibrosis Assessment by LGE Is a Powerful Predictor of Ventricular Tachyarrhythmias in Ischemic and Nonischemic LV Dysfunction: A Meta-Analysis. *JACC Cardiovasc Imaging*. 2016;9:1046-1055.

208. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA, Agostini D, Weiland F, Chandna H, Narula J and Investigators A-H. Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. Results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. *J Am Coll Cardiol*. 2010;55:2212-2221.

209. Al Badarin FJ, Wimmer AP, Kennedy KF, Jacobson AF and Bateman TM. The utility of ADMIRE-HF risk score in predicting serious arrhythmic events in heart failure patients: incremental prognostic benefit of cardiac 123I-mIBG scintigraphy. *J Nucl Cardiol*. 2014;21:756-762; quiz 753-755, 763-755.

210. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, Ferrari R, Piepoli MF, Delgado Jimenez JF, Metra M, Fonseca C, Hradec J, Amir O, Logeart D, Dahlstrom U, Merkely B, Drozdz J, Goncalvesova E, Hassanein M, Chioncel O, Lainscak M, Seferovic PM, Tousoulis D, Kavoliuniene A, Fruhwald F, Fazlibegovic E, Temizhan A, Gatzov P, Erglis A, Laroche C, Mebazaa A and Heart Failure Association of the European Society of C. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail*. 2016;18:613-625.

211. Roberts IS, Benamore RE, Benbow EW, Lee SH, Harris JN, Jackson A, Mallett S, Patankar T, Peebles C, Roobottom C and Traill ZC. Post-mortem imaging as an alternative to autopsy in the diagnosis of adult deaths: a validation study. *Lancet*. 2012;379:136-142.

212. Ross SG, Bolliger SA, Ampanozi G, Oesterhelweg L, Thali MJ and Flach PM. Postmortem CT angiography: capabilities and limitations in traumatic and natural causes of death. *Radiographics*. 2014;34:830-846.