Clinical Characteristics and Prognosis of Patients with Angina Pectoris and Heart Failure

Dr Athar A Badar, MBChB, MRCP

University of Glasgow

Ninewells Hospital and Medical School, Dundee

Submitted as part of the requirements for the Degree of Doctor of Medicine

College of Medical, Veterinary & Life Sciences

University of Glasgow

Index

List of tables

List of figures

Acknowledgements

Firstly I would like to offer my thanks to my supervisors Professor Mark Petrie and Professor John McMurray. Professor Petrie's support and encouragement during both my research and my clinical training has been invaluable over a number of years and I will always be very grateful. I also thank Professor McMurray for giving me the opportunity to join his research team and to learn from one of the world's leading academics. A number of colleagues have assisted me during my research but I am particularly grateful to Dr Ana Perez-Moreno, Dr Nathaniel Hawkins and Dr Alan Brunton. Finally, I would like to thank my family for their support and patience whilst completing my thesis.

Author's declarations

The author and his supervisors, Professor Mark Petrie and Professor John McMurray, were responsible for the conception and design of this project. The author performed the analyses with statistical support from Dr Ana Perez-Moreno and Dr Pardeep Jhund. I can confirm this thesis consists of my own work and that this has not previously been submitted or accepted in any other application for a higher degree. All efforts have been made to acknowledge and reference all sources of information appropriately.

Publications arising from this thesis

1. Badar AA, Perez-Moreno AC, Hawkins NM, Jhund P, Brunton AP, Anand IS, McKelvie RS, Komadja M, Zile M, Carson PE, Gardner RS, Petrie MC, McMurray JJV. Clinical characteristics and outcomes of patients with coronary artery disease and angina: an analysis of the irbesartan in patients with heart failure and preserved systolic function (I-Preserve) trial. Circ Heart Fail. 2015;8:717-24.

2. Badar AA, Perez-Moreno AC, Hawkins NM, Brunton AP, Jhund P, Wong CM, Solomon SD, Granger CB, Yusuf S, Pfeffer MA, Swedberg K, Gardner RS, Petrie MC, McMurray JJV. Clinical Characteristics and Outcomes of Patients with Angina and Heart Failure in the CHARM Programme (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity). Eur J Heart Fail. 2015; 17: 196–204.

3. Badar AA, Perez-Moreno AC, Jhund P, Wong CM, Hawkins NM, Cleland JGF, Veldhuisen DJF, Wikstrand J, Kjekshus J, Wedel H, Watkins S, Gardner RS, Petrie MC, McMurray JJV. Relationship between angina pectoris and outcomes in patients with heart failure and reduced ejection fraction: An analysis of the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA). Eur Heart J. 2014; 35: 3426-3433.

Abbreviations

CAD - coronary artery disease

HF - heart failure

CORONA - Controlled Rosuvastatin Multinational Trial in Heart Failure

HF-REF - heart failure with reduced ejection fraction

ACS -acute coronary syndrome

CHARM - Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity

HF-PEF - heart failure with preserved ejection fraction

LVEF - left ventricular ejection fraction

ACEI - angiotensin converting enzyme inhibitor

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

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

ESC - European Society of Cardiology

NICE - National Institute for Health and Care Excellence

ECG - electrocardiogram

ETT - exercise tolerance testing

CT - computed tomography

SAPAT - Swedish Angina Pectoris Aspirin Trial

CV - cardiovascular

PCI - percutaneous coronary intervention

CABG - coronary artery bypass graft surgery

BNP - B-type natriuretic peptide

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

NYHA - New York heart association

MRA - mineralocorticoid receptor antagonists

ARNI - angiotensin receptor neprilysin inhibitor

COMET - Carvedilol Or Metoprolol European Trial

DIG - Digitalis Investigation Group

UA - unstable angina

ICD - implantable cardioverter-defibrillators

CRT - cardiac resynchronisation therapy

STICH - Surgical Treatment for Ischemic Heart Failure Trial

REVIVED-BCIS2 - Study of Efficacy and Safety of Percutaneous Coronary Intervention to Improve Survival in Heart Failure trial

Summary

Although coronary artery disease (CAD) is a leading cause of both angina pectoris and Heart Failure (HF), little is known of the relationship between these two conditions. This is the focus of my thesis (1, 2).

Chapter one gives an overview of these two clinical conditions and presents the findings of a literature review examining the prognostic importance of angina in HF.

Subsequent chapters present the results of a series of retrospective analyses, using data collected from large randomized controlled trials.

In the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) 4878 patients with Heart Failure and Reduced Ejection Fraction (HF-REF) were divided into three groups according to their history of angina. Patients with past and current angina were compared with a reference group of patients with no angina. Current angina was strongly associated with greater functional limitation despite an absence of clinical features of worsening HF. Current angina was also associated with a higher risk of acute coronary syndrome (ACS) but all cause mortality was similar to patients with no angina. Patients with past angina were also at higher risk of ACS but the association was not as strong as in patients with current angina(3, 4).

In CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) I sought to validate the findings of CORONA whilst also investigating the importance of angina in patients with Heart Failure and Preserved Ejection Fraction (HF-PEF). CHARM enrolled 7599 patients with HF into three discrete trials according to left ventricular ejection fraction (LVEF) and angiotensin converting enzyme inhibitor (ACEI) use: CHARM-Preserved (LVEF>40%), CHARM-Added (LVEF ≤40% receiving ACE inhibitor treatment) and CHARM-Alternative (LVEF

≤40% not receiving an ACE inhibitor due to intolerance). As in CORONA, in CHARM patients with current angina and HF-REF were more likely to experience greater function limitation and were at higher risk of ACS than patients with no angina. In CHARM I was also able to demonstrate a similar trend in patients with HF-PEF and current angina(3, 5, 6).

Investigators in the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-Preserve) study did not distinguish between past and current angina. Therefore this analysis examined the prognostic importance of a history of CAD and angina in 4128 patients with HF-PEF. The most important finding from this study was the higher risk of sudden death and all-cause mortality in patients with HF-PEF and a history of CAD. This association was present irrespective of whether or not patients had a history of angina pectoris(7, 8).

In the Prospective comparison of Angiotensin Receptor–Neprilysin Inhibitor with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) 8442 patients with CAD and HF-REF were categorized into four groups according to severity of angina. There was a stepwise increase in functional limitation with worsening severity of angina. When compared with patients with no angina, patients with severe angina were also at significantly higher risk of fatal and non-fatal outcomes including all-cause death (9).

These analyses highlight the importance of angina symptoms on functional class and prognosis in patients with HF. Identification of high-risk groups could guide future treatment strategies. More specifically there may be the potential for coronary revascularization or pharmacotherapy to improve outcomes in these subgroups but such strategies need to be tested in prospective randomised controlled trials.

Chapter 1

Introduction

CAD is a leading cause of both angina and HF but despite this common association, the relationship between these two conditions is incompletely understood(1, 2, 10-13). This is the focus of my thesis.

1.1 Angina Pectoris

1.1.1 Definition of Angina Pectoris

The European Society of Cardiology (ESC) guidelines on the management of stable coronary artery disease define typical angina as 'substernal chest discomfort of characteristic quality and duration, provoked by exertion or emotional stress and relieved by rest and/or nitrates within minutes'(13). Many patients present with atypical angina where only some of these features are present or breathlessness on exertion otherwise referred to as angina equivalent(14-18).

Angina occurs as a consequence of myocardial ischaemia, usually due to atherosclerosis that results in narrowing of the coronary arteries impairing the supply of blood and oxygen to the myocardium. Atherosclerosis can begin in childhood and progresses at a variable rate depending on a patient's genetic predisposition and risk factors. These risk factors include diabetes mellitus, smoking, hypertension and elevated cholesterol (15, 19, 20).

As well as atherosclerosis, numerous factors affecting the demand or supply of oxygen to the myocardium can contribute to angina symptoms. These include microvascular obstruction, left ventricular hypertrophy and anaemia(21-23).

Severity of angina symptoms are graded using the Canadian Cardiovascular Society (CCS) scale:

Class 1: Only occurs with strenuous exertion. Everyday activities do not precipitate angina.

Class 2: Mild limitation of ordinary everyday activity. Angina brought on by walking uphill, emotion, cold weather or meals.

Class 3: Significant limitation of ordinary physical activity (e.g. a single flight of stairs at a normal pace).

Class 4: Inability to carry out basic tasks without bringing on angina. In some cases, angina may even be present at rest(24).

1.1.2 Epidemiology of Angina Pectoris

Epidemiological studies of angina are challenging due to the way in which angina is coded in community databases. In Scotland, general practitioners reported rates of angina of 23.3 per 1000 population in males and 34.3 per 1000 in females aged 65–74. After the age of 75 this increased to 38.5 and 59.7 per 1000 respectively. From 2008 to 2010, a Scottish Health Survey Topic Report on Older People's Health found the overall prevalence of angina was 15% in females and 18% in males over the age of 65(25).

1.1.3 Investigation and Diagnosis of Angina Pectoris

The differential diagnosis of chest discomfort is wide and includes pulmonary, gastrointestinal and musculoskeletal conditions. Clinicians may make a diagnosis of angina from history alone but without objective evidence of ischaemia or obstructive coronary artery disease, patients will often be misdiagnosed. The National Institute for Health and Care Excellence (NICE) recommend confirmatory diagnostic testing in all patients describing typical or atypical angina(26, 27).

The diagnostic yield from the electrocardiogram (ECG) is low and is most likely to be abnormal during an acute angina attack. At rest, it may reveal evidence of prior myocardial infarction or risk factors such as hypertension and should be performed in all patients with suspected angina(15).

Functional tests looking for myocardial ischaemia are often the first line investigation. Exercise tolerance testing (ETT) is a well-established investigation with a number of benefits. It is widely available, has a good safety profile and offers reasonable sensitivity, particularly in patients with multi-vessel disease. The main drawback of ETT is its poor specificity and it performs less well in obese patients, females and those with baseline abnormalities on ECG(28-31). A number of alternative functional tests with improved diagnostic accuracy are now available, e.g. myocardial perfusion imaging, stress echocardiography and cardiac magnetic resonance imaging. Each modality has particular strengths and weaknesses but all generally have less availability and additional expense relative to ETT(15, 28, 30, 32-34).

Multidetector computed tomography (CT) coronary angiography and invasive coronary angiography are anatomical investigations that assess for stenosis of the epicardial coronary arteries. Both NICE and SIGN guidelines recommend CT coronary angiography as the first line diagnostic test. Whilst it has excellent negative predictive value the main drawback is the risk of over diagnosing obstructive CAD, particularly in high-risk patients with calcified arteries(32, 35, 36). Invasive coronary angiography remains the gold standard test and is mandatory in all patients being considered for coronary revascularisation. Recent advances in coronary angiography including intravascular ultrasonography and guidewires with pressure or flow sensors have further enhanced its diagnostic utility(15, 37, 38).

1.1.4 Management of Angina Pectoris

Treatment goals in stable angina are to reduce symptoms and improve prognosis.

Pharmacological therapy

Anti-anginal agents are the mainstay of medical therapy. Whilst there is no convincing evidence any anti-anginal therapy improves prognosis, beta-blockers or rate limiting calcium channel blockers are commonly prescribed in the first instance. A variety of second line agents are available, including oral nitrate preparations, nicorandil and ivabradine(39, 40).

The benefits of antiplatelet therapy in stable angina were confirmed in the Swedish Angina Pectoris Aspirin Trial (SAPAT). This double-blinded, randomised controlled trial compared Aspirin to placebo in 2035 patients. Patients prescribed Aspirin had a reduced risk of the primary endpoint of myocardial infarction and sudden death(41). Clopidogrel may be used as an alternative to Aspirin. In a randomised controlled trial of 19185 patients with stable atherosclerotic disease (22% with stable angina), Clopidogrel was associated with a reduced risk of the composite endpoint of ischaemic stroke, myocardial infarction and vascular death when compared with Aspirin(25, 42).

Patients with stable angina should receive lipid-lowering therapy. In a large meta-analysis of over 90000 patients, including patients with chronic stable angina, statin use was associated with significant reductions in all-cause death and cardiovascular (CV) endpoints(25, 43).

Whilst statins remains the mainstay of lipid lowering therapy, a number of other agents have been shown to improve cardiovascular outcomes in recent years.

Ezetimibe is an agent that reduces LDL cholesterol by preventing cholesterol absorption. In IMPROVE-IT, the combination of ezetimibe and simvastatin was associated with a reduction in the composite endpoint of CV death, non-fatal MI, unstable angina, coronary revascularization or nonfatal stroke, when compared with simvastatin monotherapy(44).

Randomised controlled trials have also demonstrated the efficacy of PCSK9 inhibitors, novel agents that act by preventing destruction of cholesterol receptors in the liver, thereby facilitating the removing of LDL cholesterol from the bloodstream. The ODYSSEY OUTCOMES trial was a large randomized controlled trial that compared alirocumab with placebo in patients on maximally tolerated doses of statins post ACS. Alirocumab use was associated with a significant reduction in the primary composite end point of death from CAD, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization(45).

Studies examining the use of ACE inhibitors in patients with stable angina have produced conflicting results. However, a large meta-analysis concluded ACE inhibitors were associated with significant reductions in all-cause mortality, informing the SIGN guideline recommendation that ACE inhibitors be considered in all patients with stable angina(25, 46-50).

Coronary revascularisation

COURAGE was a randomised controlled trial of 2287 patients with coronary disease and objective evidence of myocardial ischaemia comparing percutaneous coronary intervention (PCI) with optimal medical therapy. Patients with HF were excluded. As an initial management strategy PCI did not reduce the risk of death, myocardial infarction, or other major cardiovascular events(51). Coronary revascularisation with

PCI or coronary artery bypass graft surgery (CABG) is indicated in patients with on-going angina despite optimal medical therapy. In a minority of patients with 'prognostically significant' CAD, revascularisation may be indicated despite adequate symptom control. Whilst there is a lack of consensus over the definition of prognostically significant CAD, the ESC guidelines include patients with significant left main stem or proximal left anterior descending artery disease, multi-vessel disease and patients with large areas of ischaemia on non-invasive testing(15). The role of revascularisation in patients with HF or LVSD is discussed further in section 1.2.4 below.

1.1 Heart Failure

1.2.1 Definition of Heart Failure

The ESC guidelines define heart failure as a 'clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress'(13).

Historically, HF has been divided into two subtypes depending on the left ventricular ejection fraction (LVEF), a specific measure of the hearts function. Heart Failure with reduced ejection fraction (HF-REF) is usually defined as a LVEF <40% whereas Heart Failure with preserved ejection fraction (HF-PEF) has historically been defined as a LVEF >40 or 45%. Since the design and analyses contained in this thesis, a third intermediate category, Heart Failure with mid range ejection fraction (HFmrEF) has been introduced, aiming to identify the optimal treatment strategy in patients with

modest reductions in their LVEF(13, 52). This subgroup is not examined further in this thesis.

The New York Heart Association (NYHA) classification describes the severity of HF according to patient's functional limitations and symptoms:

NYHA class 1: No symptoms during everyday physical activity.

NYHA class 2: Mild limitation of everyday physical activity.

NYHA class 3: Significant limitations with symptoms of HF brought on by less than ordinary everyday activity.

NYHA class 4: Symptoms of HF are present at rest with worsening on exertion(13).

1.2.2 Epidemiology of Heart Failure

HF has been referred to as 'a rising global epidemic' that is estimated to affect almost 40 million people worldwide. Frequency increases with age and in patients over 80, around 10% have a diagnosis of HF(12, 53).

There is no consensus over how best to establish HF aetiology and this has not been evaluated in a systematic fashion. Patients with HF can have multiple potential aetiologies that are not mutually exclusive. The Framingham heart study cited hypertension as the commonest cause of HF, either as a primary or contributory cause. However, Framingham used only clinical criteria to diagnose HF and did not differentiate HF-REF vs. HF-PEF. Subsequent studies have not supported such a central role for hypertension in the development of HF-REF. Moreover, although hypertension is a strong risk factor for development of CAD, the importance of hypertension as a sole cause of LV systolic dysfunction in Western countries remains unclear. More contemporary randomized controlled trials and observational studies frequently identify CAD as the leading cause of HF-REF in the developed world (1, 11, 54, 55). HF epidemiology data in developing nations has not been robustly

collected but infectious causes and nutritional deficiencies are considered important factors. However, as developing countries undergo transition periods with increasingly aged populations disease burden is shifting to more chronic diseases as seen in western populations. As a result CAD has also emerged as a more significant cause of HF in the developing world (26).

Epidemiology studies in HF-PEF are complicated by a lack of consensus over the conditions definition and how it is best diagnosed(56). Allowing for these important limitations it is estimated HF-PEF accounts for 44-72% of all HF cases. Recognised risk factors include ageing, hypertension, diabetes and female sex. CAD is common in patients with HF-PEF but its precise role remains incompletely understood. Whilst it may be central to the development of HF-PEF in some patients, in others it may simply coexist without a direct mechanistic relationship(57, 58).

1.2.3 Investigation and Diagnosis of Heart Failure

Clinical features of HF are non-specific and clinicians should have a low threshold for initiating investigation.

The 12 lead ECG and natriuretic peptide biomarkers are often used as screening tests in patients with clinical features suggestive of HF. Although specificity is poor, a normal ECG makes a HF diagnosis unlikely(59). Similarly, in the acute setting, normal B-type natriuretic peptide (BNP) or N-terminal pro b-type natriuretic peptide (NT-proBNP) essentially exclude HF but diagnostic accuracy falls in patients with stable symptoms. Natriuretic peptides also provide important prognostic information in patients with confirmed diagnoses(60, 61).

Definitive diagnosis requires objective cardiac dysfunction or structural abnormality. This is usually defined by imaging, the cornerstone of which is echocardiography.

This is a widely available test, which provides detailed information including data on systolic and diastolic function, chamber size, valvular heart disease and pulmonary artery pressures(62, 63). In patients where echocardiography is non-diagnostic other tools such as Cardiac MRI may need to be considered(64, 65).

1.2.4 Management of patients with Heart Failure

Pharmacological therapy

Diuretic therapy is used to treat fluid overload and relieve symptoms in HF(66).

Patients with HF-REF should be treated with neuro-hormonal antagonists, which have been shown to improve clinical outcomes in this population. These include beta-blockers, ACE inhibitors, angiotensin receptor blockers and mineralocorticoid receptor antagonists (MRA)(67-71). More recently, Sacubitril Valsartan (formerly LCZ696), a first-in-class angiotensin receptor neprilysin inhibitor (ARNI) was approved for use having demonstrated superiority over ACE inhibitors in the PARADIGM-HF trial. Chapter six of this thesis presents the findings of a retrospective analysis of PARADIGM-HF(9).

Patients with HF-REF, with resting heart rates of more than 70 beats per minute (on beta blockers if tolerated), may also benefit from Ivabradine. This selective sinus node inhibitor reduced the risk of HF death and worsening HF in the SHIFT trial(72).

A number of studies have evaluated pharmacotherapy in HF-PEF but to date no medication has been shown to improve prognosis in these patients(13).

Device therapy

Patients with HF have a higher risk of arrhythmia and sudden cardiac death. Implantable cardioverter defibrillators (ICD) reduce this risk by correcting bradycardia

and treating ventricular arrhythmias(73, 74). Current guidelines recommend implantation in patients with HF-REF, NYHA class II-III symptoms and LVEF <35% following optimal medical therapy(13).

Cardiac resynchronisation therapy (CRT) has also been shown to improve morbidity and mortality in appropriately selected patients(75). CRT is currently recommended in symptomatic patients with HF-REF, prolonged QRS durations and LVEF ≤35% despite optimal medical therapy(13).

Few studies have evaluated the role of device therapy in HF-PEF and at present neither ICD or CRT is recommended in this group of patients(13, 76).

Coronary revascularisation

The role of coronary revascularisation in patients with HF and obstructive CAD is controversial. In the Surgical Treatment for Ischemic Heart Failure (STICH) study, a large randomised controlled trial examining the use of CABG in patients with severe LV systolic dysfunction, patients randomised to CABG were at lower risk of all-cause mortality during long-term follow-up(77). The role of PCI in this population is currently being evaluated in the Study of Efficacy and Safety of Percutaneous Coronary Intervention to Improve Survival in Heart Failure (REVIVED-BCIS2) trial(78).

A common hypothesis focuses on the concept of 'hibernating' and 'viable' myocardium. This proposes that a subset of patients exposed to significant myocardial ischaemia demonstrate reduced contractility that normalises (or improves) when coronary blood flow is restored. This would have the potential to identify patients most likely to benefit from coronary revascularisation. However, questions remain

over how best to identify and define patients with viability and the concept has yet to be proven in the setting of prospective, randomised controlled trials(79, 80). In the aforementioned STICH trial, viability was not shown to be predictive of improved clinical outcomes(77, 81).

1.3 Angina Pectoris in Heart Failure

Given the overlapping aetiologies of HF and angina, it is not surprising angina occurs commonly in this population. The reported prevalence of angina varies widely, ranging from 7-39% in patients with non-differentiated diagnosis of heart failure and 13-59% and 4-46% in patients with HF-REF and HF-PEF respectively(71, 82-99). The reasons for the large differences in reported prevalence are multifactorial. Whilst differences in the populations being studied are likely a significant factor, perhaps more importantly, there is a lack of standardisation and few studies report how angina was diagnosed. In many studies, the diagnosis was based on investigator-determined responses on clinical response forms, without mandating objective supporting evidence from non-invasive imaging tests or coronary angiography.

As detailed in section 1.1.1, obstructive CAD is the commonest cause of angina. However, several studies have demonstrated evidence of myocardial ischaemia or angina in patients with normal coronary arteries on angiography. Myocardial ischaemia in idiopathic dilated cardiomyopathy was assessed in one study of 22 patients with HF-REF and angiographically normal coronary arteries. Compared with a control group, patients with idiopathic dilated cardiomyopathy had significantly more ischaemia on positron emission tomography. The extent of myocardial ischaemia correlated with increased wall stress, which increased oxygen demand and impaired coronary flow reserve (decreasing oxygen supply). This demand supply mismatch was exacerbated during exercise, resulting in worsening ischaemia(100). In

another single-centre study of 376 consecutive patients with HF-PEF referred for coronary angiography, the percentage of patients reporting angina was similar in those with and without obstructive CAD on angiography(58). These findings support the concept that other mechanisms such as microvascular obstruction and left ventricular hypertrophy play an important role in demand and supply of oxygen to the myocardium in HF.

In the following subsection the findings from a literature review of angina in HF are presented.

Angina in HF literature review

Search strategy

Medline, EMBASE and Cochrane electronic databases were searched from 1990 to June 2014. The MESH term, 'Angina pectoris' and the keyword angina were used to define angina pectoris. Heart failure and left ventricular dysfunction were defined using the MESH terms, 'Ventricular Dysfunction, Left' and 'Heart Failure' and keywords including: congestive heart failure, left ventricular systolic dysfunction, systolic heart failure, and cardiac failure. Only English language publications were considered and case reports, letters, editorials and studies with fewer than 250 participants were excluded. The cut-off of 250 patients was agreed by consensus. Similarly, reports in paediatric populations, hypertrophic cardiomyopathy and congenital heart disease were omitted. References of studies selected for inclusion were hand searched, as were risk prediction models from major trials referenced in the European Society of Cardiology and American College of Cardiology HF guidelines.

Study selection

Two authors (Athar Badar and Alan Brunton) independently screened articles by title

and abstract using a hierarchal approach and the full texts of all potentially relevant studies were examined. All studies examining the relationship between angina and clinical outcomes in patients with HF were eligible for inclusion, provided an adjusted analysis was performed. However, the focus of the review was on the association of angina with functional status, mortality, ACS and HF events. Both reviewers independently extracted and recorded data detailing study type, data source, number of patients per study, patient characteristics and outcomes. Data were compared to ensure accuracy. Adjusted outcomes were presented as they appeared in the original studies.

Results

Searches from MEDLINE, EMBASE and the Cochrane Library generated 3706, 10094, and 740 results respectively. An additional 205 potential studies were identified from hand searches of reference lists and other sources. After removal of duplicates, 14171 articles were screened. 443 full-text studies were reviewed and after assessment for eligibility, only 7 studies were included in the final analysis (see figure 1). An overview of the studies characteristics is presented in table 1 and the findings are discussed below(85, 98, 99, 101-104).

Clinical Characteristics and Prognosis of patients with Angina in Heart Failure

Relationship between angina and functional class

Only two studies reported the relationship between angina and functional status in HF. Both single centre, retrospective studies were from the Duke Databank for Cardiovascular Disease. In 2376 patients with HF-REF referred for angiography, those describing recent angina (defined as within the last six weeks) were compared to patients with no recent angina. In this highly selected group, patients with recent

angina were less likely to describe NYHA class III or IV symptoms than patients with no angina (21% vs. 27%; p<0.001)(85). The second study examined 3517 with HF-PEF. This also found patients with recent angina were significantly less likely to have a high functional class when compared with patients with no angina (60% vs. 75%). However, in this study, patients with angina had a number of clinical features suggesting better HF status, namely lower mean resting heart rate, higher mean blood pressure and a reduced frequency of crepitations and third heart sounds on examination(98).

Relationship between angina and all-cause mortality in patients with HF

The three studies to report on the relationship between angina and all-cause mortality in HF are presented in table 2(85, 98, 99).

HF-REF

Retrospective analyses from the Carvedilol Or Metoprolol European Trial (COMET) (n=3029; 53% with ischemic aetiologies) and the Duke Databank for Cardiovascular Disease demonstrated no significant association between the presence of angina and higher all-cause mortality(85, 99).

HF-PEF

In the unadjusted analysis from the Duke Databank for Cardiovascular Disease (n=3517) patients with angina were at lower risk of all-cause mortality when compared with patients with no angina. However, after adjusting for other significant variables, this association was no longer statistically significant(98).

Relationship between angina and acute coronary events in patients with HF

Coronary events were included as part of composite endpoints in several studies but only one study examined the association between angina and an individual coronary endpoint. In a retrospective analysis from the Digitalis Investigation Group (DIG), investigators examined the predictors of unstable angina (UA) hospitalizations in 7716 patients with HF (6800 with HF-REF and 916 with HF-PEF). A risk prediction model identified current angina as a significant predictor of hospitalizations for UA (adjusted HR 2.08 (1.82-2.37); $p<0.0001$)(103).

Relationship between angina and HF outcomes in patients with HF

In COMET there was no significant association between angina and HF endpoints in patients with HF-REF(99).

Relationship between angina and other clinical outcomes in patients with HF

The relationship between angina and a range of other outcomes in patients with HF are detailed in table 3(85, 98, 101, 102, 104).

Limitations

The data presented above has a number of significant limitations.

All the studies identified in this review were retrospective analyses and these therefore share the inherent limitations of such analyses.

The number of studies assessing the relationship between angina and clinical outcomes in HF was very small. Only seven studies were identified in total with only three examining the relationship between angina and all-cause death and only single studies assessing the relationship between angina and HF or coronary outcomes.

The two studies from the Duke Databank for Cardiovascular disease defined angina as 'chest pain within the past six weeks' but investigators included patients with both typical and atypical chest pain. It is not clear how many of these patients truly had angina(85, 98). Please see appendix 1 for assessment of bias in these two studies.

In other studies stable angina was not the focus of the analysis and data was limited to a tabulated hazard ratio assessing the importance of angina on clinical outcomes. In these studies details of how angina was defined or diagnosed was not available. Similarly, although the retrospective analysis of the DIG study reported the prognostic importance of current angina, other studies did not distinguish between patients with past or current symptoms(103).

The quality of multivariate analyses varied significantly across different studies. Greenburg et al did not list the variables used in the multivariate analysis whereas others studies failed to identify for important covariates such as history of revascularisation(102).

Using large datasets from randomised controlled trials, this thesis sets out to examine the prognostic importance of angina in patients with HF. It aims to assess the significance of active symptoms (i.e. current angina) and the severity of angina in patients with HF. Identifying patients at higher risk of adverse outcomes may enable us to test specific treatment strategies in this group with the goal of improving patient outcomes.

Figure 1: Literature search: Study Selection

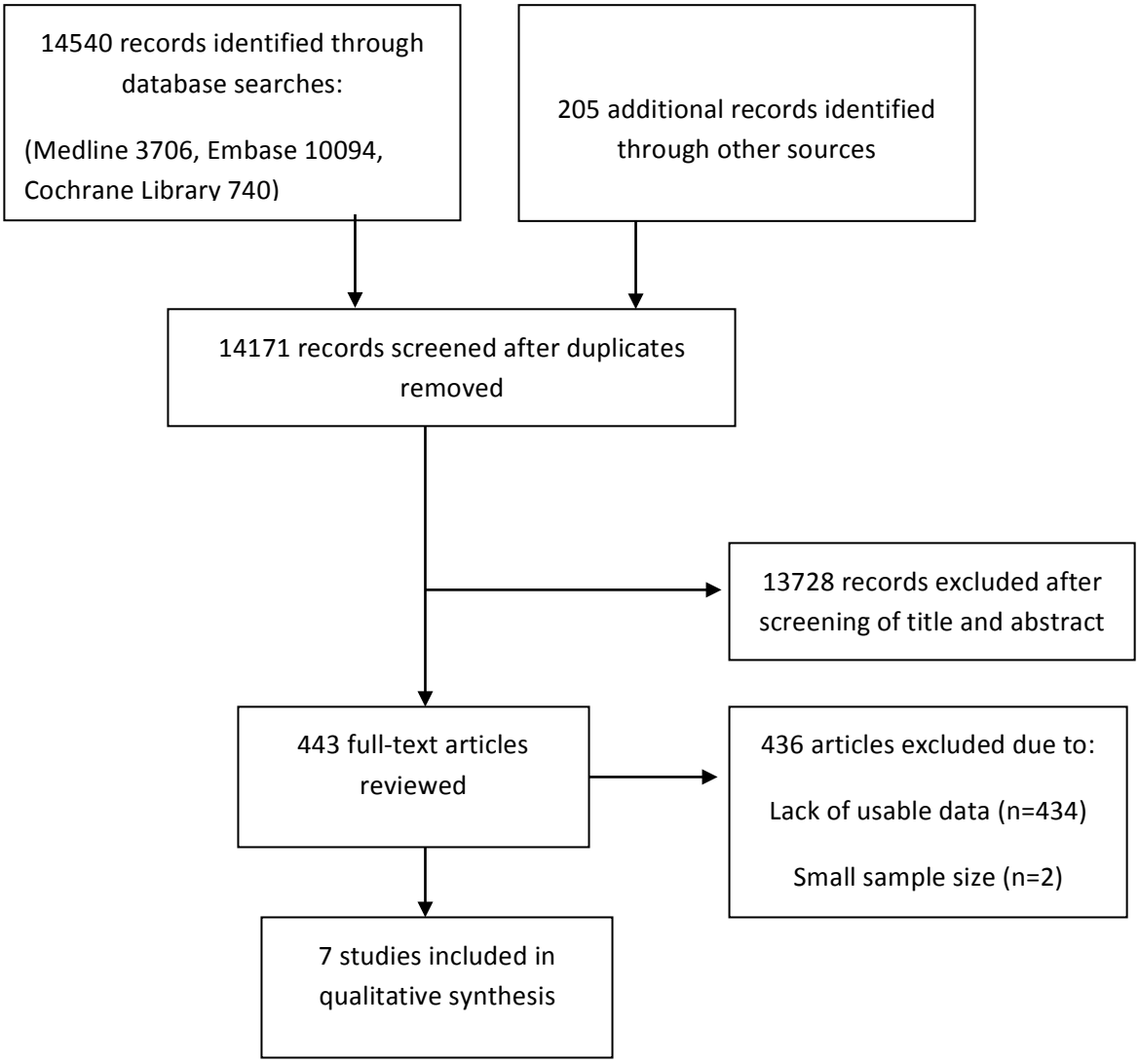


Table 1 Study Characteristics: results of literature search.

Author (Year)	Study/ design	Sample size	HF population	Adjustment
Ahmed(103) (2007)	DIG Retrospective	7788 (HF-REF 6800; HF-PEF 988)	HF-REF and HF-PEF (analysed as single group) 69% ischaemic aetiology	Activity, age, BMI, BP, cardiomegaly, creatinine, diabetes, dyspnoea, heart rate, HF aetiology, HF duration, hypertension, increased JVP, lower limb oedema, medications, NYHA class, potassium, previous MI, pulmonary congestion, rales, race, sex, 3rd heart sound and 6 or more symptoms or signs
Ekman(99) (2005)	COMET Retrospective	3029	HF-REF 53% ischaemic aetiology	Age, antiarrhythmic, ECG findings, Carvedilol use, diabetes, digitalis, FH, HgB, HF duration, lipid-lowering drugs, LVEF, nitrates, NYHA class, prior MI, creatinine, sodium, sex, stroke, BP and weight (mortality analysis)
Greenberg (102) (2006)	COHERE registry Retrospective	4280	Unselected community HF population 56% with CAD	Final list of variables included in multivariable model not presented in manuscript
Lam(101) (2012)	I-PRESERVE Retrospective	4128	HF-PEF 25% ischaemic aetiology	AF, age, COPD/asthma, CVD, diabetes, eGFR, heart rate, HgB, HF cause, recent HF hospitalization, hypertension, log NT-proBNP, LVEF, medications, MI, neutrophil count, NYHA class, obesity, PCI/CABG, smoking, systolic, BP and valve disease
Mentz(85) (2012)	Duke databank Retrospective single-centre	2376	HF-REF 100% with a history of CAD	Age, baseline medications, BMI, CVD, diabetes, heart rate, hypertension, LVEF, number of diseased vessels, NYHA class, previous CABG, previous PCI, PVD, race, serum creatinine/sodium/urea nitrogen/hemoglobin, sex and smoking history
Mentz(98) (2014)	Duke databank Retrospective single-centre	3517	HF-PEF consecutive referrals to large single-centre 100% with a	Age, baseline medications, BMI, Charlson Index, CVD, diabetes, heart rate, hyperlipidaemia, hypertension, LVEF, NYHA class, previous

			history of CAD	coronary revascularization, previous smoking history, prior MI, PVD, serum creatinine/HgB/sodium/ urea, sex, systolic BP, race, ventricular gallop
Richter (2009)(104)	Alberta registry Retrospective	448	Acute HF presentations 39% with a history of CAD	AF, age, asthma, baseline medications, CAD, COPD, diabetes, dyslipidaemia, history of HF, hypertension, previous MI, renal disease, revascularization, sex, smoking status, stroke

ApoA - apolipoprotein A1, ApoB - apolipoprotein B, AF - atrial fibrillation, BBB - bundle branch block, BMI - body mass index, BP - blood pressure, CABG - coronary artery bypass graft surgery, CAD - coronary artery disease, CHARM - Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity, COHERE - the coreg heart failure registry, COMET - Carvedilol Or Metoprolol European Trial, COPD - chronic obstructive pulmonary disease, CORONA - Controlled Rosuvastatin Multinational Trial in Heart failure, CVD - cerebrovascular disease, DIG - Digitalis Investigation Group, ECG - electrocardiogram, eGFR - estimated glomerular filtration rate, FH - family history, HF - heart failure, HF-PEF - heart failure with preserved ejection fraction, HF-REF - heart failure with reduced ejection fraction, HFH - heart failure hospitalization, HgB - haemaglobin, hs-CRP - high sensitivity C-reactive protein, ICD - implantable cardiodefibrillator, I-PRESERVE - Irbesartan in Heart Failure with Preserved Ejection Fraction Study, JVP - jugular venous pressure, log NT-proBNP - N-terminal pro-brain natriuretic peptide, LVEF - left ventricular ejection fraction, MI - myocardial infarction, NYHA - New York Heart Association, PCI - percutaneous coronary intervention, PVD - peripheral vascular disease, TSH - thyroid stimulating hormone

Table 2 Studies reporting the relationship between angina and all-cause death in heart failure

Author (Year)	Comparison	Unadjusted analysis*	Adjusted analysis*
Ekman(99) (2005)	Current angina (vs. no current angina) Unadjusted outcomes presented as relative risk ratios	1.09 (1.00–1.20); 0.05	ns (HR not reported)
Mentz(85) (2012) HF-REF	Angina within the last 6 weeks vs. no angina in the last 6 weeks Outcomes presented as 5 year event rates	43 vs. 41%; 0.07	41 vs. 41%; 0.32
Mentz(98) (2014) HF-PEF	Angina within the last 6 weeks vs. no angina in the last 6 weeks Unadjusted outcomes presented as 5 year event rates	36.2 vs. 30.1; 0.002	0.94 (0.82-1.06); 0.30

***All outcomes presented as HRs unless otherwise stated.**

Parenthesis in the comparison column contain the presumed reference group when not explicitly stated in main manuscript

HF-PEF – heart failure with preserved ejection fraction, HF-REF – heart failure with reduced ejection fraction, ns – non-significant.

Table 3 Studies reporting the relationship between angina and other outcomes in heart failure.

Author **(Year)**	Comparison	Outcome	Unadjusted analysis*	Adjusted analysis*
Ekman(99) (2005)	Current angina (vs. no current angina) *Unadjusted outcomes presented as relative risk ratios	All-Cause Hospitalization	1.23 (1.15–1.31); <0.0001	ns (HR not reported)
Greenberg (102)(2006)	History of angina (vs. no history of angina) *Adjusted outcomes presented as odds ratios	Death, hospitalization for HF, or hospitalization for CV reasons other than HF	-	1.315 (1.117–1.549); 0.0010
Lam(101) (2012)	History of angina (vs. no history of angina)	All-cause events (male)	-	1.117 (0.947–1.317); 0.191
		All-cause events (female)	-	1.020 (0.880–1.182); 0.795
Mentz(85) (2012) **(HF-REF)**	Angina within the last 6 weeks vs. no angina in the last 6 weeks *Outcomes presented as 5 year event rates	Death or MI	48 vs. 46%; 0.10	47 vs. 46%; 0.15
		Death, MI or revascularization	83 vs. 85%; 0.31	87 vs 85%; 0.01
		Death or Hospitalization	85 vs. 87%; 0.29	85 vs. 87%; 0.37
		CV death or CV hospitalization	72 vs. 77%; 0.01	73 vs. 77%; 0.03
Mentz(98) (2014) **(HF-PEF)**	Angina within the last 6 weeks vs. no angina in the last 6	Death or MI	37.7 vs. 32.9; 0.019	0.93 (0.82-1.06); 0.27

	weeks *Unadjusted outcomes presented as 5 year event rates	Death, MI or revascularization	44.5 vs. 57.1; <0.001	1.29 (1.15-1.43); <0.0001
		Death, MI or stroke	40.9 vs. 38.4; 0.33	0.99 (0.87-1.11); 0.81
		Death, MI, revascularization or stroke	47.0 vs. 52.9; <0.001	1.30 (1.17-1.45); <0.0001
		CV death or CV hospitalization	63.7 vs. 61.1; 0.12	0. 95 (0.85-1.05); 0.32
Richter (2009)(104)	Angina (vs. no angina) *Adjusted outcomes presented as odds ratios	Readmission or death at 30 days following acute HF admission	-	0.46 (0.21–0.97)

***All outcomes presented as HRs unless otherwise stated.**

Parenthesis in the comparison column contain presumed reference group when not explicitly stated in main manuscript

HF – heart failure, CV – cardiovascular, HF-PEF – heart failure with preserved ejection fraction, HF-REF – heart failure with reduced ejection fraction, MI – myocardial infarction, ns – non-significant.

My thesis examines the clinical importance of angina in patients with heart failure. More specifically I use a series of retrospective analyses to evaluate the importance of both the presence and severity of angina symptoms on patient outcomes. My hypothesis was that the presence and severity angina pectoris would be associated with more adverse clinical outcomes in patients with heart failure. The hypotheses from the individual analyses are detailed in the relevant chapters.

Chapter 2

Methodology

My thesis investigated the clinical importance of angina pectoris in patients with HF. After completion of the literature search as described above, the main body of the thesis was based on a series of retrospective analyses, using data collected from large randomised controlled trials. Trial funders from the individual studies (namely CORONA, CHARM, I-Preserve and PARADIGM-HF) gave the databases to the academic leaders of the trials interested in pursuing further analyses relevant to better understanding of the disease and its treatment. All analyses were performed using Cox proportional hazards regression analysis. All statistical analyses performed in preparation of this thesis used the STATA software package (version 13, Stata Corp, College Station, Texas, the United States of America). Further details of the methodology of the individual analyses are detailed below.

CORONA

The CORONA trial enrolled 5011 patients who were at least 60 years of age with NYHA class II–IV heart failure, a left ventricular ejection fraction ≤40% (≤35% if NYHA class II) and an ischaemic aetiology (as defined by investigators). Only patients deemed clinically stable, on optimal medical therapy and without an investigator-determined indication for cholesterol-lowering therapy were eligible for inclusion. Exclusion criteria included a history of statin-induced myopathy or hypersensitivity reaction; recent acute coronary syndrome or stroke; coronary revascularization, CRT or ICD implantation within the last three months; cardiac transplantation; pericardial disease; acute myocarditis; hypertrophic cardiomyopathy; significant systemic disease (e.g. amyloidosis); significant (primary) uncorrected valvular heart disease; significant renal or hepatic impairment; or any other condition

expected to markedly impact upon life expectancy or reduce compliance with the study protocol(3, 4, 106).

Ethics committees from participating institutes approved the trial and all patients gave written consent. Randomized patients received either once daily rosuvastatin at a dose of 10mg or placebo. After a median follow-up period of 32.8 months there was no significant reduction in the risk of the primary composite endpoint of CV death, non-fatal MI, or non-fatal stroke in patients receiving rosuvastatin(3, 4, 106).

Investigators documented a history of 'past or current angina' by ticking boxes on the case report form. A history of 'chest pain over the past few days' was also recorded at the time of enrolment. For the purpose of this analysis patients were divided into three groups: group A (those without a history of angina or chest pain at baseline i.e. no angina), group B (those with a history of angina but no chest pain at baseline i.e. past angina) and group C (those with a history of angina and chest pain at baseline i.e. current angina). Patients without a documented history of 'past or current angina' who still reported chest pain at baseline were not considered in the analysis (n = 133)(3).

Clinical outcomes

The endpoints analysed in this retrospective analysis included all-cause mortality, the composite of CV death or HF hospitalization, CV death, HF hospitalization and three coronary endpoints. In CORONA the pre-specified secondary 'coronary event' endpoint was defined as a composite of sudden death, fatal or non-fatal MI, hospitalization for UA, PCI or CABG, ventricular defibrillation by ICD or resuscitation after cardiac arrest. The more restricted composite of non-fatal MI, UA, PCI, or CABG was also examined in order to exclude events such as resuscitation after cardiac arrest or sudden death, which do not always occur as a consequence of

myocardial ischaemia or infarction. Finally, I examined the composite endpoint of non-fatal MI or UA to allow for the fact coronary revascularization may be a reflection of physician preference as much as disease activity(3).

Statistical analysis

Baseline characteristics for the three groups were presented using percentages for categorical variables and means with standard deviations for continuous variables (medians were used when data were not normally distributed). The chi-squared test was used to compare categorical variables and the one-way analysis of variance test was used for continuous variables(3).

Outcomes were compared in patients with group B versus group A (i.e. past versus no angina) and group C versus group A (i.e. current versus no angina) using Cox proportional-hazard models regression analyses. Univariate and multivariate analyses were performed. Previously published predictors of prognosis in CORONA were used in the multivariate analysis; the prognostically significant variables in that model were: age, gender, LVEF, NYHA functional class, heart rate, systolic blood pressure, BMI, coronary revascularization, MI, smoking, stroke, baseline atrial fibrillation/flutter, intermittent claudication, aortic aneurysm, diabetes, hypertension, pacemaker and ICD implantations, (log) NT-proBNP, creatinine, alanine aminotransferase, thyroid stimulating hormone, creatine kinase, C-reactive protein, ApoA-1 and ApoB(107). Adjustment was also made for differences in baseline medications (specifically diuretic use, beta-blockers, ACE inhibitors or ARBs, aldosterone antagonists, digoxin, anti-arrhythmic agents, antiplatelet or anticoagulant medication and randomization to rosuvastatin). The Schoenfeld residuals method was used to assess proportional hazard assumptions. Fatal outcomes (and composite

endpoints containing fatal and non-fatal components) were presented using Kaplan–Meier curves; non-fatal outcomes were analyzed using the cumulative incidence function, taking into account the competing risk of all-cause death. A *p*-value of <0.05 was regarded statistically significant(3).

CHARM

The CHARM program enrolled 7599 patients with NYHA class II-IV HF symptoms into one of three parallel trials according to ACE inhibitor use and LVEF at the time of trial entry: CHARM-Preserved (LVEF>40%, n=3023), CHARM-Added (LVEF ≤40% receiving ACE inhibitor treatment, n=2548) and CHARM-Alternative (LVEF ≤40% not receiving an ACE inhibitor due to prior intolerance, n=2028). All patients received standard medical therapy and were randomized to candesartan, titrated up to a maximally tolerated dose of up to 32mg once daily or matching placebo. Ethics committees from each participating institute approved the trial and patients provided informed written consent. The median follow-up was 38 months(5, 6, 114, 115).

Our analysis focused on the patients in CHARM with a history of ischaemic heart disease; this was defined as a primary or contributing cause of HF, prior coronary revascularization or a history of MI as recorded on the case report form (CRF) (n=5408). A history of 'past' or 'present' angina was also recorded on the CRF and patients were divided into three groups; patients with no history of angina (group A), those with a prior history of angina but no active symptoms (group B) and those with current angina (group C). Outcomes were compared in patients with past and current angina with the reference group of patients with no angina as detailed below. Patients

with HF-REF and HF-PEF were analysed separately (the latter was defined as a LVEF >45%)(5).

Clinical Outcomes

Endpoints examined in this analysis were as follows: all-cause death (the primary endpoint of the overall CHARM program), CV death or HF hospitalization, CV death, HF hospitalization, fatal or nonfatal MI, MI or UA and the composite of MI, UA or coronary revascularization(5).

Statistical analysis

The baseline characteristics for groups were presented using percentages for categorical variables and means with standard deviations for continuous variables. The chi-square test was used to compare categorical variables and the ANOVA to compare continuous variables. The relationship between past or current angina and the endpoints detailed above were examined using Cox proportional-hazard models. Both univariate and multivariate analyses were performed. The multivariate analysis used a previously published risk prediction model from the CHARM program. All-cause death was adjusted for age, sex, body mass index, NYHA class, LVEF, BBB on ECG, previous HF hospitalization, diabetes mellitus, cardiomegaly and smoking history; HF and coronary endpoints were adjusted for age, NYHA class, heart rate, BBB on ECG, LVEF, diastolic blood pressure, duration of heart failure, previous HF hospitalization, diabetes mellitus and cardiomegaly(116). Kaplan-Meier curves were presented by symptom category. All analyses considered a two-tailed p value < 0.05 as statistically significance(5).

I-PRESERVE

The I-PRESERVE trial enrolled 4128 patients aged ≥60 years of age with a LVEF of ≥45%, a recent HF hospitalisation or NYHA class II-IV symptoms and findings consistent with HF-PEF on echocardiography or ECG. To fulfil ECG criteria patients had to have evidence of specific features indicating moderate or severe LVH [e.g. SV1 RV5 or RV6 O3.5 mV (35 mm at normal standard), RaVL O1.1 mV (11 mm at normal standard)]. Patients were randomized to receive irbesartan at a dose of 300mg once daily or matching placebo. After a mean follow-up of 49.5 months, no significant difference was observed in the risk of death from any cause or hospitalization for a CV cause (the primary composite outcome) or in the pre-specified secondary endpoints(7, 8, 121, 122).

Heart failure aetiology and past medical history including prior MI, coronary revascularization and stable angina pectoris were recorded in the CRF. For the purposes of the analysis a history of coronary artery disease was defined as a history of previous MI, PCI, CABG or a primary ischemic aetiology as defined by investigators. Patients were divided into four groups; patients with no history of CAD or angina (group A), those without a history of CAD who were documented as having a history of angina (group B), patients with a history of CAD who had no history of angina (group C) and those with a history of both CAD and angina (group D)(7).

Clinical outcomes

Outcomes were compared in patients from group B versus group A, group C versus group A and group D versus group A. The outcomes assessed were HF death or HF hospitalization (the HF composite endpoint from I-PRESERVE), HF hospitalization, fatal or non-fatal MI, MI or UA, all-cause death, CV death, pump failure death and sudden death(7).

Statistical analysis

Baseline characteristics were presented with means and standard deviations for continuous variables and percentages for categorical variables. The ANOVA test was used to compare continuous variables and the chi-square test to compare categorical variables(7).

The relationship between CAD, angina and the above endpoints was examined using Cox proportional-hazard models analyses. Previously published predictors of outcomes in I-PRESERVE study were used in the multivariate analysis. The variables adjusted were age, heart rate, ejection fraction, recent HF hospitalization, NT-proBNP; log levels, chronic obstructive pulmonary disease or asthma, diabetes mellitus, glomerular filtration rate, neutrophil count (log) and disease-specific quality of life measured using the Minnesota living with HF questionnaire; additionally left bundle branch block was included in the sudden death analysis(7, 123, 124). Kaplan-Meier curves were presented by groups. A two-tailed p value < 0.05 as the statistical level of significance.

PARADIGM-HF

In PARADIGM-HF a total of 8442 patients with NYHA class II-IV symptoms, an ejection fraction of ≤40% and an elevated plasma B-type natriuretic peptide or NT-proBNP level, were randomized to 200mg twice daily of sacubitril/valsartan or 10 mg twice daily of enalapril. Ethics committees from each participating institute approved the trial and all patients provided informed consent. The primary endpoint was a composite of death from CV causes or HF hospitalization, but the trial was powered to identify a difference in the rates of death from CV causes. After a median follow-up period of 27 months, the trial was stopped early, according to pre-specified guidelines

of over-whelming benefit(9, 128, 129).

Investigators recorded details of past medical history and heart failure aetiology at baseline. For the purposes of the present analysis, a history of CAD was defined as an angiographically proven stenosis of ≥50% in at least one major coronary artery, a history of myocardial infarction (MI), prior coronary revascularization, investigator-reported ischaemic aetiology or a history of CAD as defined by investigators. Patients with a history of CAD were further categorized into four mutually exclusive groups according to the severity of angina symptoms at baseline, as defined by the CCS score: no angina, mild (CCS class I symptoms), moderate (class II symptoms) and severe angina (class III or IV symptoms).

Clinical outcomes

Patients with mild, moderate and severe angina were compared to the reference group of patients with CAD but no angina for the following clinical outcomes: the composite of CV death or HF hospitalization (the primary endpoint of PARADIGM-HF) and it components, hospitalization for unstable angina (UA), hospitalization for non-fatal MI and two composite coronary endpoints, UA or non-fatal MI and fatal or non-fatal MI. I also investigated the relationship between angina severity and all-cause death, as well as and the two major modes of CV death (i.e. sudden death and death due to HF)(9).

Statistical analysis

Baseline characteristics for each group were presented using means and standard deviations for continuous variables (or medians if data were not normally distributed) and percentages for categorical variables. The Chi-square test was used to compare

categorical variables and the one-way analysis of variance (ANOVA) test was used to compare continuous variables.

The relationships between severity of angina symptoms and outcomes were assessed using Cox proportional-hazard regression analyses and Kaplan-Meier survival curves. Known predictors of outcome in patients with HF (from the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) prognostic model) were used in the multivariable analyses, namely age, ejection fraction, NYHA class, serum creatinine, diabetes mellitus, chronic obstructive airway disease, beta blocker use, systolic blood pressure, body mass index, time from first diagnosis of HF, smoking status and gender(130). Adjustments were also made for (log) NT-proBNP and randomization to LCZ696. Proportional hazards assumptions were checked using the Schoenfeld residual method. Both the multivariable models and the survival analysis used a two-tailed p value < 0.05 as the statistical level of significance. Finally, an interaction analysis was also performed to examine the effect of LCZ696 versus enalapril according to angina status.

Chapter 3

The relationship between angina pectoris and outcomes in patients with heart failure and reduced ejection fraction: a retrospective analysis of the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA).

3.1 Introduction

As described above, although CAD is the leading cause of HF-REF in the developed world, little is known about the importance of symptomatic myocardial ischaemia (i.e. angina) in this population(11). Whilst a limited number of studies have described past history of angina at baseline few have reported whether patients had *current* angina at the time of enrollment. Similarly, most studies examining the relationship between CAD and prognosis in HF have focused on aetiology without distinguishing between patients with and without angina(3, 11, 105).

Angina symptoms may reflect viable myocardium susceptible to infarction, placing patients with reduced LVEF at risk of further adverse outcomes. The presence of myocardial ischaemia without infarction might also have important prognostic implications. Accordingly, in this retrospective analysis I examined the clinical characteristics and outcomes of patients with past and current angina enrolled in CORONA, where all patients had ischemic aetiologies(3, 4). My hypothesis was that the presence of angina would be predictive of adverse outcomes when compared with patients with no history of angina.

3.2 Methods

The methodology has been described as part of the general methodology section in chapter 2 and has therefore not been replicated here.

3.3 Results

Of the 4878 patients included in this analysis, 25% (n=1240) had no history of angina, 28% (n=1353) had a past history of angina and 47% (n=2285) had current angina. 27% of patients with current angina, reported chest pain on heavy exertion, 49% reported chest pain with moderate exertion and 20% reported chest pain with slight exertion. 4% of the patients with current angina had pain at rest(3).

3.3.1 Baseline characteristics (see table 4)

Comparing patients with past versus no angina (group B vs. group A)

Patients with past angina were more likely to have a history of prior myocardial infarction (70% of patients with past angina vs. 49% with no angina), PCI (17 vs. 9%) and CABG (32 vs. 8%). They were also more likely to have NYHA class III/IV symptoms (58 vs. 54%) and be on anti-platelet therapy (61 vs. 53%) or nitrates (28 vs. 16%) at baseline. They were less likely to have a history of atrial fibrillation or flutter (22 vs. 28%). Other characteristics including age, gender, mean LVEF and treatment with ACE inhibitors and beta-blockers were similar between the two groups(3).

Comparing patients with current versus no angina (group C vs. group A)

When compared with patients with no angina, those with current angina were more likely to be female (27% of patients with current angina vs. 20% with no angina) and have a history of prior MI (60 vs. 49%), CABG (17 vs. 8%) and hypertension (71 vs.

57%). They were also more likely to experience NYHA class III/IV symptoms (71 vs. 54%) despite having a lower LVEF (30 vs. 32%) and NT-proBNP (193 vs. 151 pmol/L). Patients with no angina were more likely to have atrial fibrillation or flutter at baseline(3).

Comparing patients with current versus past angina (group C vs. group B)

Patients with current angina were more likely to be female (27% of patients with current angina vs. 20% with no angina) and have a history of hypertension (71% vs. 57%) compared with patients with past angina. They were also more likely to experience NYHA class III/IV symptoms (71% vs. 58%), despite having a higher mean LVEF (30% vs. 32%) and a lower median NT-proBNP (187 vs. 151 pmol/L). They were less likely to have a history of previous MI (60% vs. 70%), PCI (10% vs. 17%) or CABG (17% vs. 32%)(3).

As well as the above differences, patients with no angina were most likely to be prescribed anti-coagulant agents, anti-arrhythmic medication and digoxin; they had the lowest use of antiplatelet agents and beta-blockers. Patients with current angina were least likely to be taking anti-coagulant and anti-arrhythmic drugs at baseline but had the highest use of nitrates. They were also most likely to have a history of diabetes mellitus and the highest systolic BP and LVEF(3).

3.3.2 Clinical outcomes

CAD outcomes

When compared to patients with no angina, those with current angina were at higher risk of all three coronary composite outcomes (see tables 5 and 6, figure 2). The risk of the composite endpoints of MI, UA or coronary revascularization and MI or UA

was approximately twice as high in the current angina group. This association persisted following multivariate analysis. The risk of the pre-defined 'coronary' composite endpoint from CORONA was also higher in patients with current angina, albeit to a lesser extent(3).

Patients with past angina were also at higher risk of MI, UA or coronary revascularization and MI or UA compared with patients with no angina. The HRs were lower (but not statistically different) to those of the current angina group above. Patients with past angina were, however, not at higher risk of the pre-defined 'coronary' composite outcome(3).

HF outcomes

Patients with current angina were at moderately higher risk of the composite endpoint of CV death or HF hospitalization compared to patients with no angina. They were also at higher risk of HF hospitalization although the risk of CV death was not significantly different to those with no angina. Patients with past angina were not at higher risk of CV death or HF hospitalization (or the components of this endpoint) compared with patients with no angina (see tables 5 and 6, figure 3)(3).

Mortality

The risk of death was not significantly different in patients with past or current angina compared with those with no angina (see tables 5 and 6, figure 3).

3.4 Discussion

In almost 5000 patients with HF-REF and CAD in CORONA, 47% had chest pain at baseline (presumed to be angina). A number of important differences were noted between patients with and without chest pain at baseline. Over 70% of patients with current angina were in NYHA functional class III or IV, compared with only 58% of patients with past angina and 54% of patients with no angina. This worse functional status likely reflected symptomatic myocardial ischaemia rather than severity of HF; patients with current angina had the highest blood pressure and LVEF and the lowest NT-proBNP levels in keeping with better haemodynamic status(3).

When comparing the two groups of patients with a history of angina, those *without* current chest pain (i.e. past angina) were more likely to have a history of MI and prior coronary revascularisation. This was likely a heterogeneous group of patients and the absence of chest pain may have been a reflection of the absence of viable myocardium (due to the extent of infarction) or effective revascularization(3).

Patients with current angina had more than twice as high a risk of ACS, or an ACS plus coronary revascularization, as patients with no angina. Patients with past angina were also more likely to experience an ACS than patients with no angina but their risk was not as high as patients with current angina. These findings suggest anti-ischemic therapy may have the potential to prevent coronary events, as discussed below(3).

The pre-defined composite 'coronary' endpoint from CORONA included defibrillation by an ICD, resuscitated cardiac arrest and sudden death. The risk of this endpoint was not as high as that of an ACS in patients with current angina, compared to those with no angina (and not increased at all in patients with past angina). This suggests that even in patients with HF sudden death is frequently unrelated to

myocardial ischaemia and myocardial scars, rather than active ischaemia, likely caused many of the arrhythmic events(3, 108-111).

In much the same way, the risk of CV and all-cause death was not higher in patients with current angina or past angina, compared to patients with no angina. This was surprising as it suggests the higher risk of ACS in patients with past and current angina was not associated with a higher risk of death due to heart failure or arrhythmia. However, even in patients with HF secondary to CAD and current angina, ACS is a relatively infrequent occurrence. In our retrospective analysis, a first event of this type occurred in approximately 10% of patients, compared with death, which occurred in almost 30%, implying that ACS likely only has a small impact on mortality. In STICH, at 10-year follow-up patients randomised to CABG had a significant reduction in all-cause mortality [HR 0.84 (0.73–0.97); P=0.02](3, 77).

Interestingly, patients with current angina had a modestly increased risk of HF hospitalization compared to patients with no angina. This was despite patients with current angina having a better overall HF risk-profile and suggests myocardial ischaemia may have precipitated some HF hospitalizations. In STICH, although investigators did not report HF hospitalization, CABG did reduce the composite endpoint of all-cause death or HF hospitalization and this persisted at 10-year follow-up [HR 0.81 (0.71–0.93); P=0.002](3, 77, 81).

The potential implications of our study are for therapeutic benefit from reducing myocardial ischaemia, improving functional status and reducing adverse outcomes including coronary events and HF hospitalization. Patients with current angina, with the highest rate of ACS and HF hospitalization, likely have the most to gain but patients with past angina might also benefit. As previously discussed, this is a

heterogeneous group of patients where more than half had undergone coronary revascularization at baseline. The role of CABG in patients with ischaemic cardiomyopathy has been demonstrated but the benefits of PCI are still being investigated. Pharmacological agents should also be considered, including anti-thrombotic therapy and anti-ischaemic agents such as nicorandil, which has been shown to reduce hospitalization for angina in patients without HF(3, 77, 78, 112).

There were a number of limitations to our study. The sub-groups used in our study were not pre-specified and our findings share the fundamental limitations associated with all retrospective analyses. Chest pain at baseline was presumed to be due to angina, which may not always have been the case. On the other hand it is recognised that myocardial ischaemia can occur in patients with HF, even in patients without obstructive coronary artery disease. Finally, the results of coronary angiography were not available and the severity of CAD has been independently linked to prognosis(3, 113).

3.5 Conclusion

Symptoms of angina are very common in patients with HF-REF and CAD. They are associated with worse functional class and a higher risk of both ACS and HF hospitalization. This highlights the potential to improve symptoms and outcomes with anti-ischaemic therapy but such strategies need to be investigated, ideally with randomized controlled-trials(3).

Table 4 CORONA: baseline characteristics of groups stratified by history of angina and chest pain at baseline.

History of angina Current chest pain	All patients (n=4878)	Group A No No (n=1240)	Group B Yes No (n=1353)	Group C Yes Yes (n=2285)	p value for trend
Age yr	72.7 ± 7.1	72.6 ± 7.1	73.1 ± 7.2	72.6 ± 7.0	0.09
Age ≥70 yr %	3190 (65.4)	799 (64.4)	911 (67.3)	1480 (64.8)	0.12
Female %	1148(23.5)	252(20.3)	275(20.3)	621(27.2)	<0.01
NYHA III/IV %	3069 (62.9)	666 (53.7)	784 (58.0)	1619 (70.9)	<0.01
LVEF (%)	30.9 ± 6.5	30.1 ± 6.7	29.9 ± 6.5	31.8 ± 6.1	<0.01
Systolic BP mmHg	129.3±16.5	128.9 ±17.1	128.3 ±17.0	130.1 ±15.8	<0.01
Heart Rate bpm	71.7 ± 11.2	71.9 ± 11.5	71.5 ± 11.5	71.6 ± 10.9	0.64
BMI kg/m^2	27.2 ± 4.5	26.9 ± 4.6	27.0 ± 4.5	27.5 ± 4.5	<0.01
BMI > median %	2467 (50.6)	584 (47.1)	673 (49.7)	1210 (53.0)	<0.01
Current smoker %	422 (8.7)	125 (10.1)	133 (9.8)	164 (7.2)	<0.01
Medical History %					
MI	2922 (59.9)	605 (48.8)	948 (70.1)	1369 (59.9)	<0.01
CABG	835 (18.8)	92 (8.0)	377 (31.8)	366 (17.4)	<0.01
PCI	569 (11.7)	109 (8.8)	225 (16.7)	235 (10.3)	<0.01
Diabetes	1443 (29.6)	353 (28.5)	379 (28.0)	711 (31.1)	0.05
Hypertension	3087 (63.3)	707 (57.0)	769 (56.8)	1611 (70.5)	<0.01
Baseline AF/F	1154 (23.7)	347 (28.0)	297 (22.0)	510 (22.3)	<0.01
Stroke	611 (12.5)	166 (13.4)	174 (12.9)	271 (11.9)	0.19
Pacemaker	544 (11.2)	148 (11.9)	164 (12.1)	232 (10.2)	0.07

ICD	130 (2.7)	34 (2.7)	45 (3.3)	51 (2.2)	0.05
Lab measurements					
Cholesterol, mmol/l	5.4±1.1	5.3±1.1	5.3±1.1	5.4±1.1	0.02
Creatinine, μmol/l	115.3±28.0	116.7±28.6	117.9±28.9	113.0±27.0	<0.01
Median NT-proBNP pmol/L (median)	169.6	193.2	186.6	150.5	<0.01
Median hs-CRP, mg/liter (median)	3.4	3.7	3.3	3.4	0.27
Medication					
Loop diuretic	3674(75.3)	968(76.1)	1021(75.5)	1685(73.7)	<0.01
ACE or ARB	4480(91.8)	1155(93.2)	1240(91.7)	2085(91.3)	0.05
Beta-blocker	3669(75.2)	918 (74.0)	1028(76.0)	1723(75.4)	0.25
Nitrates	1617(33.1)	200(16.1)	384(28.4)	1033(45.2)	<0.01
Antiarrhythmics	604 (12.4)	173 (14.0)	188 (13.9)	243 (10.6)	<0.01
Antiplatelet	2903(59.5)	659 (53.2)	822 (60.8)	1422(62.2)	<0.01
Anticoagulant	1707(35.0)	505 (40.7)	490 (36.2)	712 (31.2)	<0.01

NYHA – New York Heart Association; LVEF – Left Ventricular Ejection Fraction; BMI – body mass index; MI – myocardial infarction; PCI – percutaneous coronary intervention; AF – atrial fibrillation; ICD – implantable cardio defibrillator; ACE – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker.

Table 5 CORONA unadjusted analysis: the association between history of angina, recent chest pain and clinical outcomes.

Angina history Current pain	Group A No No (n=1240)	Group B Yes No (n=1353)	Group C Yes Yes (n=2285)	B vs. A		C vs. A	
	n (%)	n (%)	n (%)	HR (95% CI)	P value	HR (95% CI)	P value
Coronary Outcomes							
Coronary event composite[§]	241 (19.4)	289 (21.4)	580 (25.4)	1.10 (0.92-1.30)	0.287	1.32 (1.14-1.54)	<0.001
Non-fatal MI, UA, PCI or CABG	72 (5.8)	115 (8.5)	292 (12.8)	1.46 (1.09-1.96)	0.011	2.23 (1.72-2.89)	<0.001
Non-fatal MI or UA	52 (4.2)	93 (6.9)	222 (9.7)	1.64 (1.16-2.30)	0.005	2.33 (1.73-3.16)	<0.001
Heart failure Outcomes							
CV death or HFH	468 (37.7)	529 (39.1)	902 (39.5)	1.02 (0.90-1.16)	0.703	1.04 (0.93-1.17)	0.458
CV death	295 (23.8)	332 (24.5)	514 (22.5)	1.02 (0.87-1.19)	0.839	0.92 (0.80-1.06)	0.269
HFH	293 (23.6)	341 (25.2)	621 (27.2)	1.06 (0.90-1.24)	0.482	1.15 (1.00-1.32)	0.050
All-cause death	379 (30.6)	435 (32.2)	634 (27.8)	1.04 (0.90-1.19)	0.611	0.88 (0.78-1.01)	0.060

*MI = myocardial infarction; UA = unstable angina; PCI = percutaneous coronary intervention; CABG =coronary artery bypass graft surgery; CV = cardiovascular; HFH= heart failure hospitalization. [§] Events included sudden death, fatal or non-fatal MI, PCI, CABG, ventricular defibrillation by ICD, resuscitation after cardiac arrest, hospitalization for unstable angina.

Table 6 CORONA adjusted analysis: the association between history of angina, recent chest pain and clinical outcomes.

Angina history Current pain	Group A No No (n=1240)	Group B Yes No (n=1353)	Group C Yes Yes (n=2285)	B vs. A		C vs. A	
	n (%)	n (%)	n (%)	HR (95% CI)	P value	HR (95% CI)	P value
Coronary Outcomes							
Coronary event composite[§]	241 (19.4)	289 (21.4)	580 (25.4)	1.13 (0.90-1.43)	0.290	1.48 (1.20-1.81)	<0.001
Non-fatal MI, UA, PCI or CABG	72 (5.8)	115 (8.5)	292 (12.8)	1.62 (1.07-2.46)	0.023	2.54 (1.76-3.68)	<0.001
Non-fatal MI or UA	52 (4.2)	93 (6.9)	222 (9.7)	1.94 (1.21-3.10)	0.006	2.36 (1.54-3.61)	<0.001
Heart failure Outcomes							
CV death or HFH	468 (37.7)	529 (39.1)	902 (39.5)	1.09 (0.92-1.27)	0.354	1.19 (1.03-1.37)	0.022
CV death	295 (23.8)	332 (24.5)	514 (22.5)	0.98 (0.79-1.20)	0.831	0.98 (0.81-1.19)	0.857
HFH	293 (23.6)	341 (25.2)	621 (27.2)	1.17 (0.95-1.44)	0.137	1.35 (1.13-1.63)	0.001
All-cause death	379 (30.6)	435 (32.2)	634 (27.8)	1.01 (0.84-1.21)	0.951	0.97 (0.82-1.15)	0.713

*See text of Methods for variables adjusted for. MI = myocardial infarction; UA = unstable angina; PCI = percutaneous coronary intervention; CABG =coronary artery bypass graft surgery; CV = cardiovascular; HFH= heart failure hospitalization. [§] Events included sudden death, fatal or non-fatal MI, PCI, CABG, ventricular defibrillation by ICD, resuscitation after cardiac arrest, hospitalization for unstable angina.

Figure 2 CORONA: Kaplan-Meier curves illustrating the relationship between angina history, current chest pain and coronary endpoints.

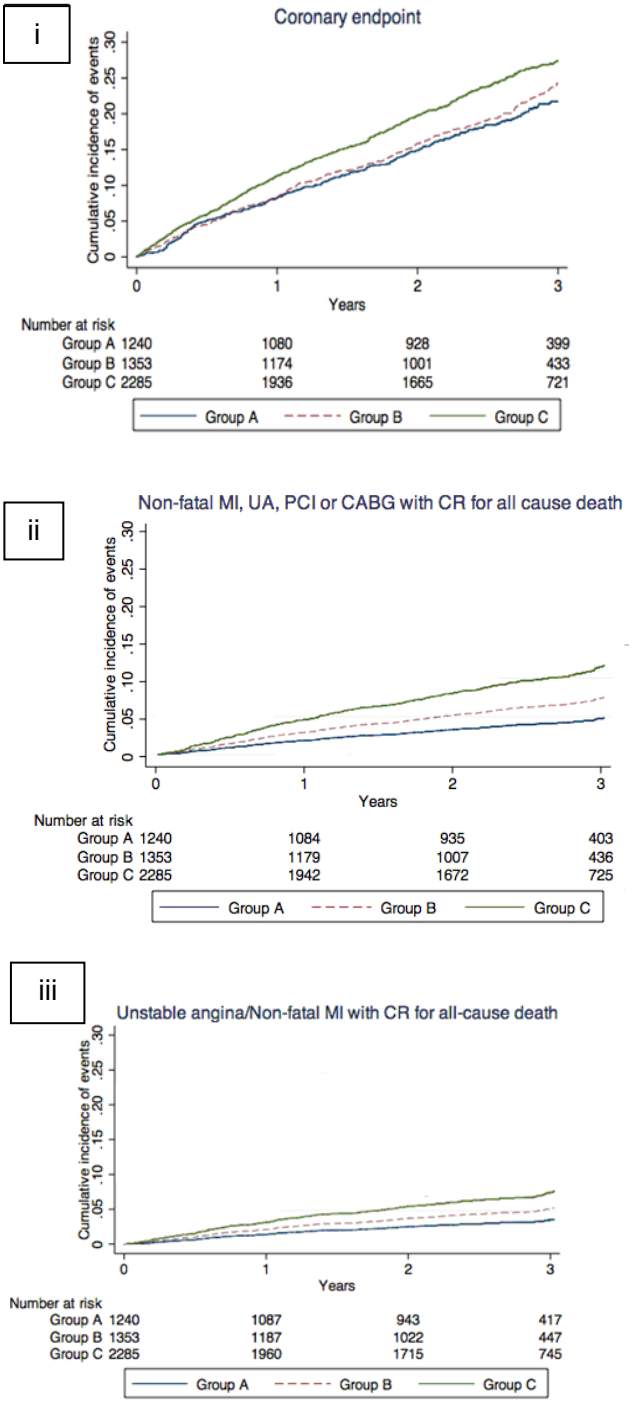
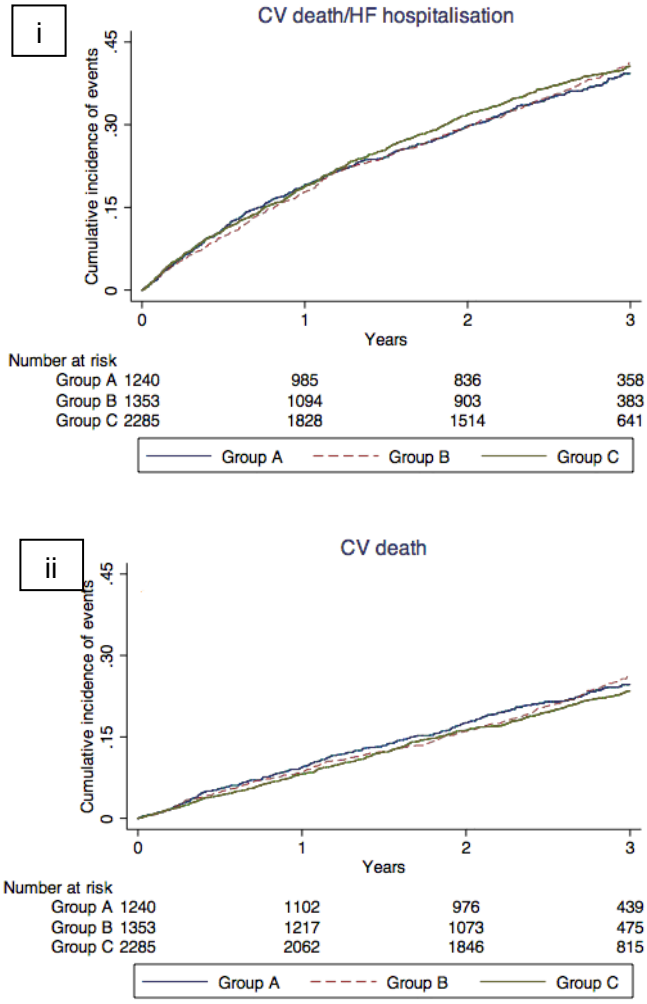
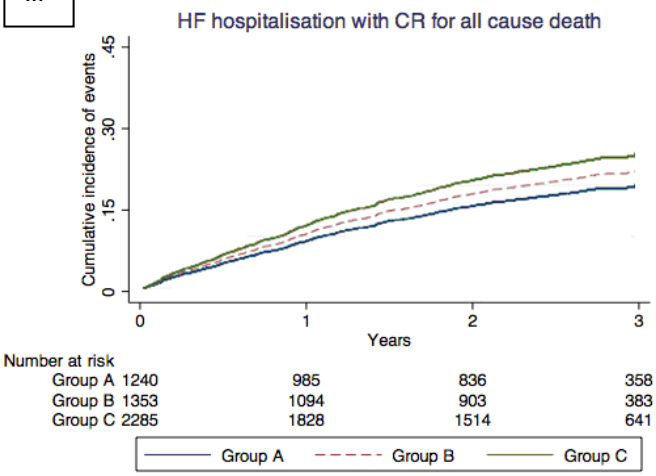


Figure 3 CORONA: Kaplan-Meier curves illustrating the relationship between angina history, current chest pain and heart failure outcomes and all-cause death.



iii

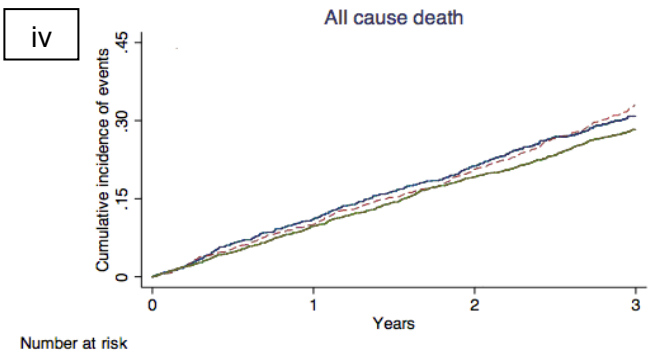


Number at risk

Group A	1240	985	836	358
Group B	1353	1094	903	383
Group C	2285	1828	1514	641

Group A Group B Group C

iv



Number at risk

Group A	1240	1102	976	439
Group B	1353	1217	1073	475
Group C	2285	2062	1846	815

Group A Group B Group C

Figure Legends

Figure 2: CORONA: The relationship between angina history, current chest pain and coronary endpoints. i) Composite coronary outcome of sudden death, hospitalization for UA, fatal/non-fatal MI, coronary revascularization, defibrillation by ICD or resuscitation after cardiac arrest (Kaplan-Meier). ii) Composite of non-fatal MI, UA or coronary revascularization (Cumulative Incidence Function). iii) Composite of non-fatal MI or UA (Cumulative Incidence Function). CR = competing risk.

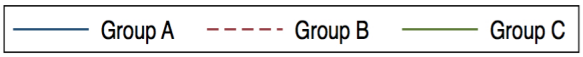
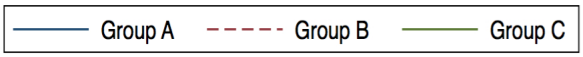


Figure 3: CORONA: The relationship between angina history, current chest pain and heart failure outcomes and all-cause death. i) CV death or HF hospitalization (Kaplan-Meier). ii) CV death iii) HF Hospitalization (Cumulative Incidence Function) iv) All-cause death (Kaplan-Meier). CR = competing risk.



Chapter 4

Clinical Characteristics and Outcomes of Patients with Angina and Heart Failure in the CHARM Programme (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity)

4.1 Introduction

In CORONA patients with HF-REF and current angina had a higher risk of ACS and experienced more functional limitation than patients with no angina. They were also at higher risk of HF hospitalization although the risk of all-cause death was similar to patients with no angina(3). Little is known of the importance of angina symptoms in patients with HF-PEF, which has only previously been investigated in a retrospective analysis of the Duke databank for cardiovascular disease. Patients with angina in the Duke databank for cardiovascular disease had a higher risk of the composite endpoint of death, MI or coronary revascularization, but other outcomes were not significantly different to patients with no angina(98). To further address these issues a further analysis was undertaken examining the outcomes related to angina in patients with both HF-PEF and HF-REF from the CHARM trials database(5). My hypothesis was that patients with angina and both heart failure with reduced and preserved ejection fractions in CHARM would experience more functional limitation and be at higher risk of ACS.

4.2 Methods

The methodology has been described as part of the general methodology section in chapter 2 and has therefore not been replicated here.

4.3 Results

Of the 5408 patients with a history of ischemic heart disease in CHARM, 3855 were categorized as having HF-REF: 28.3% of these had no history of angina (n=1092), 43.2% had past angina (n=1667) and 28.4% had current angina (n=1096). 1553 patients were classified as having HF-PEF: 21.4% with no history of angina (n=332), 42.2% with past angina (n= 655) and 36.4% with current angina (n= 566)(5).

4.3.1 Baseline characteristics

Comparing patients according to baseline LVEF and angina status

Tables 7 and 8 summarise the baseline characteristics of patients included in our study stratified by LVEF and angina status.

HF-REF

When compared with patients with no history of angina, patients with past or current angina were more likely to have a history of prior MI, stroke, diabetes mellitus and hypertension. They were also more likely to have undergone coronary revascularization at baseline; the highest rates of coronary revascularization were in patients with past angina(5).

Those with current angina also had worse NYHA class and were more likely to report symptoms of dyspnea at rest, orthopnea and oedema. However, patients with current angina did not have a lower mean LVEF or systolic BP; they were not at higher risk of HF hospitalization and did not have more clinical or radiologic signs of heart failure

(with the exception of peripheral oedema which may have reflected higher use of vasodilating therapy as detailed below)(5).

Compared with patients with no angina, patients with past and current angina were more likely to be prescribed antiplatelet agents, beta-blockers, lipid-lowering therapy, calcium channel blockers, nitrates and other vasodilators at baseline(5).

HF-PEF

Patients with HF-PEF and past or current angina were also more likely to have a history of hypertension and diabetes and hypertension and to have undergone coronary revascularization than patients with no history of angina although the differences were not as marked as in patients with HF-REF(5).

Similarly, patients with HF-PEF and past or current angina had had evidence of overall worse heart failure status than patients with no angina. Again this was despite the fact that they did not have a lower mean LVEF and were not at higher risk of HF hospitalization than patients with no angina (in actual fact, patients with no angina were most likely to have a history of HF hospitalization)(5).

Another similarity trend with the HF-REF group was in the prescription of cardiovascular medications. Patients with past and current angina had higher use of lipid-lowering agents, antiplatelets, beta-blockers, calcium channel blockers and other vasodilators(5).

4.3.2 Clinical outcomes

HF-REF

All-cause death: There was no difference in the risk of death in patients with past, current or no angina (see tables 9 and 10 and Figure 4).

HF outcomes: There was no significant difference in HF outcomes amongst the three groups. The risk of CV death or HF hospitalization (and the components of this

composite endpoint) did not differ between patients with current and no angina. There was a slightly lower risk of CV death when patients with previous angina were compared to patients with no angina that just reached statistical significance (HR 0.85, 0.73-0.99; p=0.040) (see tables 9 and 10 and Figure 4).

Coronary artery disease outcomes: Patients with current angina were at approximately twice as likely to suffer a fatal or non-fatal MI compared to those with no angina. This association was still evident after adjusting for other prognostically important variables (HR 1.83, 95%CI 1.29-2.60; p=0.001). Similar relationships were seen with regards to MI or UA (adjusted HR 3.13, 2.45-3.98; p<0.001) and the extended composite of MI, UA, PCI or CABG (adjusted HR 2.77, 2.23-3.45; p<0.001).

This higher risk of coronary events was not as marked when patients with past angina were compared to those with no angina but still significant for MI or UA (adjusted HR 1.67, 1.31-2.14; p<0.001) and MI, UA or coronary revascularization (adjusted HR 1.58, 1.27-1.97; p<0.001) (see tables 9 and 10 and Figure 4)(5).

HF-PEF

All-cause death: All-cause death was significantly lower in patients with past and current angina compared to those with no angina in the unadjusted analyses. However, these associations were not significant after adjustment for other prognostic variables (see tables 11 and 12 and Figure 5).

HF outcomes: In unadjusted analyses patients with past or current angina were at lower risk of heart failure outcomes compared with patients with no angina. Although this trend persisted in the adjusted analyses the only statistically significant result observed was for the composite heart failure outcomes comparing patients with past versus no angina (see tables 11 and 12 and Figure 5).

Coronary outcomes: The risk of fatal or non-fatal MI (adjusted HR 1.78, 0.93-3.39; p=0.080), MI or UA (adjusted HR 2.75, 1.88-4.01; p<0.001) and MI, UA or coronary revascularization (adjusted HR 2.74, 1.96-3.84; p<0.001) were all higher in patients with current angina compared with patients with no history of angina. Although no statistically significant differences were seen when comparing patients with past versus no angina, the hazard ratios for each coronary outcome were similar to that seen in patients with HF-REF (see tables 11 and 12 and Figure 5)(5).

4.4 Discussion

In our analysis of more than 5000 patients with HF secondary to ischemic heart disease, 46% of patients with HF-REF had a past history of angina and 28% had current angina; in patients with HF-PEF, 43% of patients had past angina and 36% had current angina(5).

Heart failure status

70% of patients with HF-REF and current angina described NYHA class III or IV symptoms, compared with approximately 60% of patients with past or no angina. These findings are consistent with those in CORONA where patients with current angina were more likely to experience NYHA class III or IV symptoms, despite having lower NT proBNP levels and higher LVEFs. As well as confirming the findings from CORONA, CHARM enables us to describe a more complete clinical profile of this patient group(3, 5).

Current angina was also associated with greater levels of dyspnoea and orthopnea. However, patients with angina did not have a lower LVEF (as was the case in CORONA) or more radiographic or clinical signs of HF (except for peripheral oedema). These consistent findings from both CORONA and CHARM indicate that in some patients with HF-REF, common symptoms such as breathlessness and functional limitation may occur as a consequence of myocardial ischaemia, rather than HF(3, 5).

In CHARM, I demonstrated similar findings in patients with HF-PEF. However, in the only previous study of patients with angina and HF-PEF, a large retrospective single centre analysis from Mentz and colleagues (n=3517), patients with recent angina were much less likely to have a high NYHA class (60 vs. 75%). However, this

study examined a highly selected group of patients who had been referred for coronary angiography and the lower prevalence of NYHA class III/IV symptoms likely reflected better hemodynamic status and less advanced heart failure. Those with angina had lower heart rates, higher blood pressures and were less likely to have crepitations or third heart sounds on clinical examination(5, 98).

Implications of angina on prognosis in HF-REF and HF-PEF

Although a number of studies have demonstrated angina is not associated with higher mortality in patients with HF, little is known of the relationship between angina and other outcomes, including coronary events and HF hospitalization(3, 85, 98, 99). Moreover, only CORONA examined these associations according to whether angina symptoms were past or current. Patients with current angina had a higher risk of MI or UA in CORONA (HR 2.36, 1.54-3.61;p <0.001). These findings were confirmed in CHARM where patients with current angina were approximately twice as likely to experience a MI and three times as likely to experience any ACS. A similar relationship was seen in patients with HF-PEF and an interaction analysis suggested baseline LVEF did not impact upon the association between angina and coronary events(3, 5).

An important difference between this analysis and the previous analysis from CORONA is that in CORONA patients with current angina were at higher risk of HF hospitalization but no such association was evident in the current study. Although this could be due to chance, there were a number of important differences in the two trials. CORONA focused on a much older patient population. The patients were more likely to be prescribed a beta-blocker at baseline (75% of patients in CORONA 75% vs. 56% in CHARM) and had lower rates of CABG (19% vs. 34%) and PCI (12% vs. 21%). Also I was only able to adjust for prior HF hospitalization in CHARM and not in

CORONA; this strong predictor of further HF hospitalization may have influenced our results(3, 5).

One surprising finding in CHARM was that patients with HF-PEF and current angina were at lower risk of HF outcomes. This raises the question as to whether these patients truly had HF-PEF and whether instead, coronary disease was responsible for their symptoms and limitations(5).

This analysis in CHARM confirmed the absence of a relationship between past or current angina and all-cause mortality in HF-REF. Again, this was despite the fact that they were at higher risk of coronary events when compared with patients with no angina(5).

In CHARM another important finding was that in patients with HF-PEF angina was associated with a lower risk of all-cause death, at least in the unadjusted analyses. The possible explanation for HF outcomes detailed above might also account for these findings(5).

Clinical implications

As well as confirming the relationship between current angina with worse functional status and a higher risk of ACS in patients with HF-REF, in CHARM I was able to demonstrate a similar relationship in patients with HF-PEF. This further emphasizes the importance of investigating whether we can improve outcomes in such patients with specific interventions such as target pharmacotherapy or coronary revascularization(5).

Limitations

The sub-groups examined in my study were not pre-specified and caution should be used in interpreting the findings, as is the case with any *post-hoc* analysis. A number of important exclusion criteria in CHARM such as significant renal impairment and

recent coronary events mean the patients in CHARM not fully reflect 'real-life' cohorts. Finally the findings of coronary angiography were unavailable; we know severity of CAD is independently associated with prognosis and it is difficult to know how this information would have impacted upon our findings(5, 117).

Summary

Patients with HF with reduced and preserved ejection fractions and angina report more functional limitation and breathlessness despite there being no evidence of worse HF status.

They are also at higher risk of coronary events and new prospective studies are needed to identify whether specific treatments can improve outcomes in these patients(5).

Table 7 CHARM: baseline characteristics of patients with HF-REF stratified by history of angina pectoris and current chest pain at baseline.

History of angina Current chest pain Variable	Group A No No (n=1092)	Group B Yes No (n=1667)	Group C Yes Yes (n=1096)	P Value for Trend
Age (years)	66.3 (10.1)	66.4 (10.0)	66.6 (9.8)	0.853
Female sex %	255 (23.4)	370 (22.2)	296 (27.0)	0.013
Ejection fraction %	30.8 (8.5)	30.8 (8.4)	31.6 (8.5)	0.019
BMI kg/m^2	27.1 (5.0)	27.6 (4.8)	27.9 (4.9)	<0.001
Medical history %				
MI	787 (72.1)	1387 (83.2)	897 (81.8)	<0.001
PCI	125 (11.5)	449 (26.9)	249 (22.7)	<0.001
CABG	219 (20.1)	720 (43.2)	386 (35.2)	<0.001
Hypertension	470 (43.0)	913 (54.8)	588 (53.7)	<0.001
Diabetes Mellitus	303 (27.8)	573 (34.4)	321 (29.3)	<0.001
AF	279 (25.6)	434 (26.0)	224 (20.4)	0.004
Stroke	89 (8.2)	182 (10.9)	123 (11.2)	0.028
HF hospitalization	776 (71.1)	1235(74.1)	763 (69.6)	0.028
Current smoker	185 (16.9)	243 (14.6)	156 (14.2)	0.145
Symptoms %				
NYHA III/IV	636 (58.2)	1036(62.2)	762 (69.5)	<0.001
Rest dyspnea.	82 (7.5)	191 (11.5)	180 (16.4)	<0.001
Orthopnea.	153 (14.0)	330 (19.8)	299 (27.3)	<0.001
PND	90 (8.2)	215 (12.9)	115 (10.5)	0.001
Examination				
Heart rate bpm	73.5 (12.7)	72.5 (12.2)	71.9(13.1)	0.013
Systolic BP mmHg	128.3(18.7)	127.9(19.1)	128.7(18.5)	0.579
Elevated JVP %	74 (6.8)	154 (9.2)	75 (6.8)	0.021
Oedema %	228 (20.9)	410 (24.6)	347 (31.7)	<0.001
Crackles %	163 (14.9)	304 (18.2)	199 (18.2)	0.053
S3 gallop %	155 (14.2)	269 (16.1)	256 (14.2)	0.254
CXR findings %				
Pulmonary edema	97 (8.9)	180 (10.8)	95 (8.7)	0.107
Cardiomegaly	247 (22.6)	387 (23.2)	256 (23.4)	0.907
Pleural effusions	16 (1.5)	20 (1.5)	13 (1.2)	0.795
Medications %				
Beta Blockers	562 (51.5)	933 (56.0)	671 (61.2)	<0.001
CCBs	125 (11.5)	269 (16.1)	234 (21.4)	<0.001

Other vasodilators	343 (31.4)	712 (42.7)	756 (69.0)	<0.001
ACE inhibitors	552 (50.6)	837 (50.2)	527 (48.1)	0.442
MRA	195 (17.9)	304 (18.2)	182 (16.6)	0.536
Diuretics	927 (84.9)	1412 (84.7)	925 (84.4)	0.949
Anticoagulation	369 (33.8)	532 (31.9)	283 (25.8)	<0.001
Anti-platelet agents	674 (61.7)	1138 (68.3)	797 (72.7)	<0.001
Anti-lipid therapies	462 (42.3)	908 (54.5)	572 (52.2)	<0.001

Table 8 CHARM: baseline characteristics of patients with HF-PEF stratified by history of angina pectoris and current chest pain at baseline.

History of angina Current chest pain Variable	Group A No No (n=332)	Group B Yes No (n=655)	Group C Yes Yes (n=566)	P Value for Trend
Age (years)	68.7 (9.9)	67.2 (10.4)	66.5 (10.3)	0.008
Female sex %	117 (35.2)	253 (38.6)	228 (40.3)	0.324
Ejection fraction %	56.0 (7.8)	56.7 (7.8)	57.1 (8.5)	0.103
BMI kg/m^2	28.4 (5.7)	29.3 (5.7)	28.8 (5.4)	0.033
Medical history %				
MI	204 (61.5)	373 (57.0)	356 (62.9)	0.090
PCI	59 (17.8)	173 (26.4)	173 (30.6)	<0.001
CABG	72 (21.7)	248 (37.9)	146 (25.8)	<0.001
Hypertension	206 (62.1)	429 (65.5)	384 (67.8)	0.210
Diabetes Mellitus	94 (28.3)	208 (31.8)	173 (30.6)	0.541
AF	103 (31.0)	143 (21.8)	97 (17.1)	<0.001
Stroke	33 (9.9)	48 (7.3)	44 (7.8)	0.346
HF hospitalization	222 (66.9)	394 (60.2)	333 (58.8)	0.039
Current smoker	50 (15.1)	86 (13.1)	64 (11.3)	0.260
Symptoms %				
NYHA III/IV	122 (36.8)	236 (36.0)	253 (44.7)	0.005
Rest dyspnea.	19 (5.7)	63 (9.6)	75 (13.3)	0.001
Orthopnea.	41 (12.4)	133 (20.3)	128 (22.6)	0.001
PND	28 (8.4)	41 (6.3)	28 (5.0)	0.114
Examination				
Heart rate bpm	71.1 (12.6)	70.6 (11.9)	69.7 (11.9)	0.237
Systolic BP mmHg	137.3(17.7)	135.7(18.6)	134.7(19.1)	0.116
Elevated JVP %	15 (4.5)	28 (4.3)	23 (4.1)	0.947
Oedema %	81 (24.4)	194 (29.6)	186 (32.9)	0.028
Crackles %	66 (19.9)	95 (14.5)	86 (15.2)	0.078
S3 gallop %	14 (4.2)	32 (4.9)	16 (2.8)	0.182
CXR findings %				
Pulmonary edema	28 (8.4)	48 (7.3)	33 (5.8)	0.310
Cardiomegaly	60 (18.1)	85 (13.0)	71 (12.5)	0.046
Pleural effusions	3 (0.9)	4 (0.6)	3 (0.5)	0.788
Medications %				
Beta Blockers	175 (52.7)	383 (58.5)	367 (64.8)	0.001
CCBs	93 (28.0)	213 (32.5)	216 (38.2)	0.006

Other vasodilators	105 (31.6)	255 (38.9)	376 (66.4)	<0.001
ACE inhibitors	65 (19.6)	133 (20.3)	113 (20.0)	0.963
MRA	40 (12.1)	59 (9.0)	57 (10.1)	0.324
Diuretics	239 (72.0)	472 (72.1)	365 (64.5)	<0.001
Anticoagulation	82 (24.7)	132 (20.2)	77 (13.6)	<0.001
Anti-platelet agents	217 (65.4)	492 (75.1)	452 (79.9)	<0.001
Anti-lipid therapies	143 (43.1)	388 (59.2)	281 (49.7)	<0.001

Table 9 CHARM HF-REF unadjusted analysis: the relationship between history of angina, recent chest pain and clinical outcomes.

Angina history **Current pain**	**Group A** **No** **No** **(n=1092)**	**Group B** **Yes** **No** **(n=1667)**	**Group C** **Yes** **Yes** **(n=1096)**	**Unadjusted** **B vs. A**		**Unadjusted** **C vs. A**	
	Number (Event rate)	Number (Event rate)	Number (Event rate)	HR (95% CI)	P value	HR (95% CI)	P value
Coronary Outcomes							
Fatal or non-fatal MI	50 (1.7)	103 (2.3)	90 (3.1)	1.35 (0.96-1.89)	0.085	1.80 (1.28-2.55)	0.001
MI or UA	90 (3.1)	224 (5.3)	256 (9.8)	1.67 (1.31-2.13)	<0.001	3.09 (2.43-3.92)	<0.001
MI/UA/PCI/ CABG	115 (4.1)	269 (6.4)	286 (11.2)	1.58 (1.27-1.96)	<0.001	2.73 (2.20- 3.39)	<0.001
HF Outcomes							
CV death or HFH	406 (15.0)	653 (16.0)	407 (15.1)	1.07 (0.94-1.21)	0.314	1.01 (0.88-1.15)	0.939
CV death	286 (9.5)	402 (8.7)	262 (8.6)	0.91 (0.79-1.06)	0.249	0.91 (0.77-1.07)	0.244
HF hospitalization	253 (9.4)	447 (11.0)	258 (9.6)	1.17 (1.00-1.36)	0.047	1.02 (0.86-1.22)	0.808
All-cause death	335 (11.2)	506 (11.0)	315 (10.4)	0.98 (0.86-1.13)	0.804	0.93 (0.80-1.08)	0.348

The event rate is the number of events per 100 patient-years of follow-up.

Table 10 CHARM HF-REF adjusted analysis: the relationship between history of angina, recent chest pain and clinical outcomes.

	B vs. A		**C vs. A**	
	HR (95% CI)	P value	HR (95% CI)	P value
Coronary Outcomes				
Fatal or non-fatal MI*	1.32 (0.94-1.85)	0.112	1.83 (1.29-2.60)	0.001
MI or UA*	1.67 (1.31-2.14)	<0.001	3.13 (2.45-3.98)	<0.001
MI/UA/PCI/CABG*	1.58 (1.27-1.97)	<0.001	2.77 (2.23-3.45)	<0.001
Heart failure Outcomes				
CV death or HFH *	1.00 (0.88-1.13)	1.00	1.01 (0.88-1.16)	0.929
CV death*	0.85 (0.73-0.99)	0.040	0.88 (0.74-1.04)	0.145
HF hospitalization*	1.08 (0.93-1.27)	0.313	1.02 (0.86-1.21)	0.837
All-cause death**	0.96 (0.84-1.10)	0.566	0.94 (0.80-1.10)	0.417

*Adjusted for: age, diabetes mellitus, LVEF, prior HF hospitalization, cardiomegaly, duration of heart failure, NYHA class, diastolic blood pressure, BBB on ECG, heart rate

**Adjusted for: age, diabetes mellitus, LVEF, prior HF hospitalization, cardiomegaly, NYHA class, BBB on ECG, sex, BMI, smoking history

Table 11 CHARM HF-PEF unadjusted analysis: the relationship between history of angina, recent chest pain and clinical outcomes.

Angina history **Current pain**	**Group A** **No** **No** **(n=332)**	**Group B** **Yes** **No** **(n=655)**	**Group C** **Yes** **Yes** **(n=566)**	**Unadjusted** **B vs. A**		**Unadjusted** **C vs. A**	
	Number (Event rate)	Number (Event rate)	Number (Event rate)	HR (95% CI)	P value	HR (95% CI)	P value
Coronary Outcomes							
Fatal or non-fatal MI	13 (1.4)	29 (1.5)	36 (2.2)	1.12 (0.58-2.15)	0.734	1.59 (0.84-3.00)	0.151
MI or UA	34 (3.8)	93 (5.2)	146 (10.4)	1.39 (0.94-2.06)	0.101	2.71 (1.86-3.93)	<0.001
MI/UA/PCI/ CABG	43 (4.9)	110 (6.3)	182 (13.6)	1.29 (0.91-1.83)	0.158	2.73 (1.96-3.80)	<0.001
HF Outcomes							
CV death or HFH	91 (10.5)	130 (7.3)	118 (7.7)	0.70 (0.54-0.92)	0.009	0.74 (0.56-0.97)	0.032
CV death	48 (5.1)	63 (3.3)	55 (3.3)	0.65 (0.44-0.94)	0.023	0.64 (0.44-0.95)	0.026
HF hospitalization	65 (7.5)	94 (5.3)	83 (5.4)	0.71 (0.52-0.98)	0.036	0.73 (0.53-1.01)	0.061
All-cause death	70 (7.4)	91 (4.7)	76 (4.5)	0.64 (0.47-0.87)	0.005	0.61 (0.44-0.84)	0.003

Table 12 CHARM HF-PEF adjusted analysis: the relationship between history of angina, recent chest pain and clinical outcomes.

	B vs. A		**C vs. A**	
	HR (95% CI)	P value	HR (95% CI)	P value
Coronary Outcomes				
Fatal or non-fatal MI*	1.15 (0.59-2.23)	0.677	1.78 (0.93-3.39)	0.080
MI or UA*	1.40 (0.94-2.08)	0.096	2.75 (1.88-4.01)	<0.001
MI/UA/PCI/CABG*	1.28 (0.89-1.82)	0.180	2.74 (1.96-3.84)	<0.001
Heart failure Outcomes				
CV death or HFH *	0.75 (0.57-0.98)	0.037	0.81 (0.61-1.07)	0.129
CV death*	0.70 (0.48-1.03)	0.069	0.71 (0.48-1.05)	0.089
HF hospitalization*	0.77 (0.56-1.07)	0.115	0.80 (0.57-1.12)	0.192
All-cause death**	0.77 (0.56-1.05)	0.101	0.72 (0.52-1.01)	0.058

Figure 4 CHARM: The relationship between angina and clinical endpoints (HF-REF)

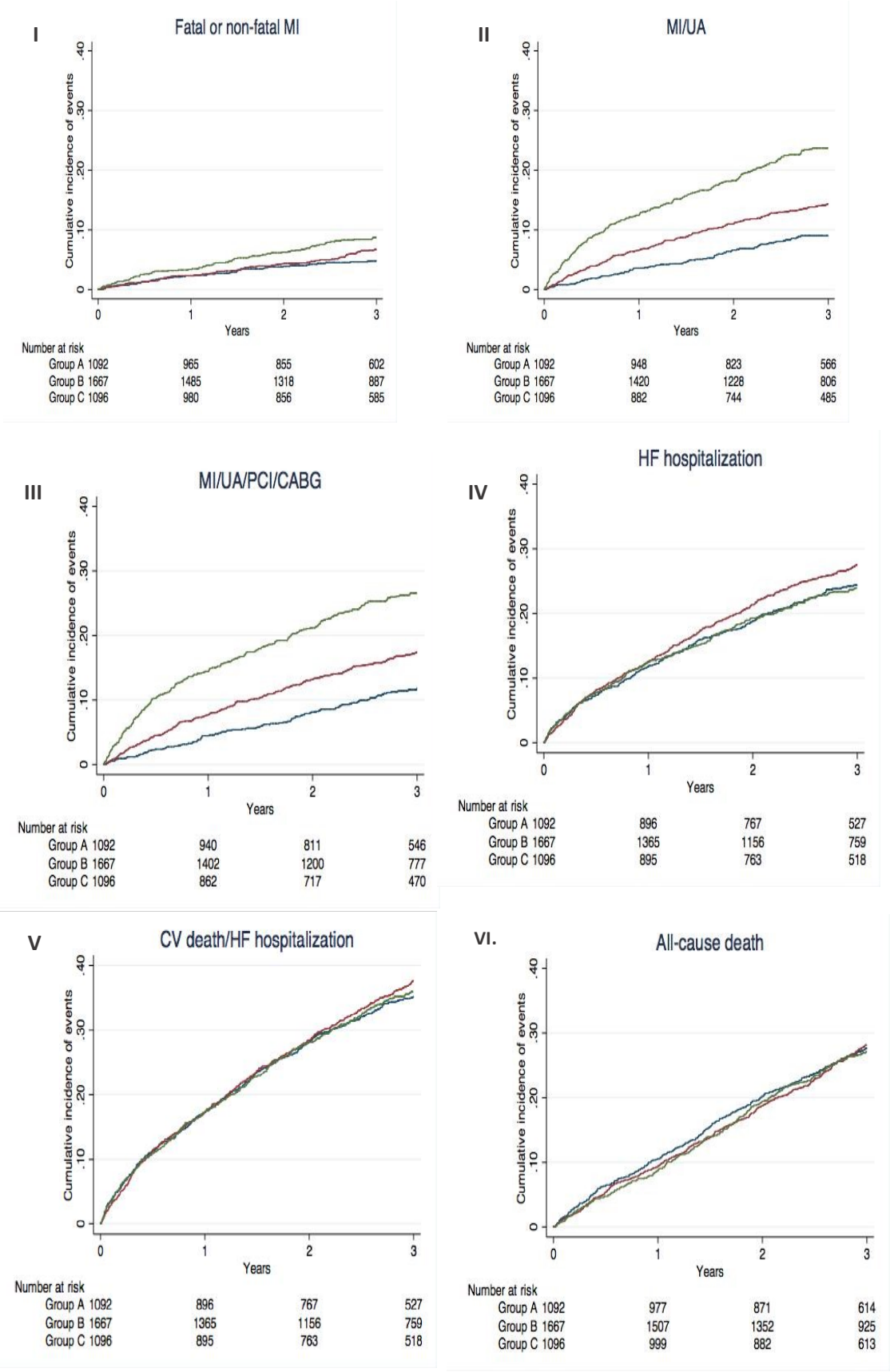


Figure 5 CHARM: The relationship between angina and clinical endpoints (HF-PEF)

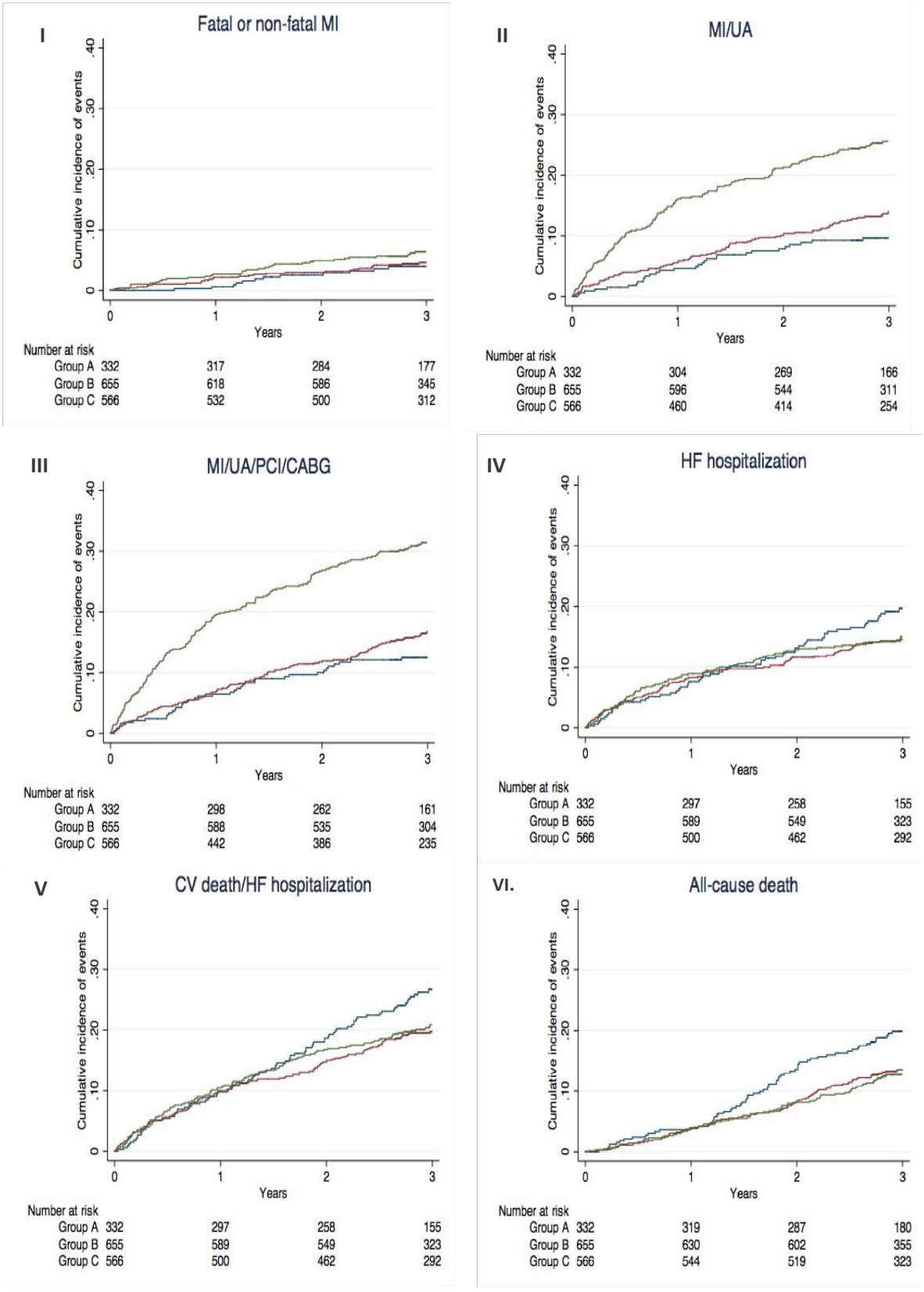


Figure 4: Kaplan-Meier curves illustrating the relationship between angina and clinical endpoints in patients with HF-REF in CHARM. i) Fatal or non-fatal myocardial infarction (MI) ii) Composite of MI or unstable angina (UA) iii) Composite of MI, UA, percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) iv) Heart failure (HF) hospitalization v) Composite of cardiovascular (CV) death or HF hospitalization vi) All-cause death.

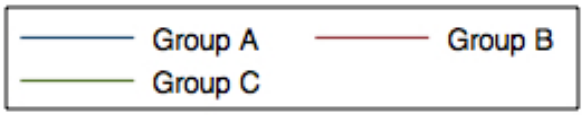
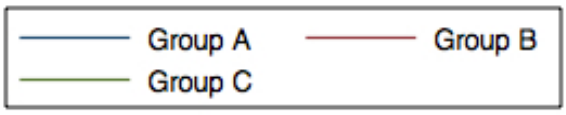


Figure 5: Kaplan-Meier curves illustrating Kaplan-Meier curves illustrating the relationship between angina and clinical endpoints in patients with HF-PEF in CHARM. i) Fatal or non-fatal myocardial infarction (MI) ii) Composite of MI or unstable angina (UA) iii) Composite of MI, UA, percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) iv) Heart failure (HF) hospitalization v) Composite of cardiovascular (CV) death or HF hospitalization vi) All-cause death.



Chapter 5

Clinical Characteristics and Outcomes of Patients with Coronary Artery Disease and Angina: An analysis of the I-PRESERVE trial (Irbesartan in Heart Failure with Preserved Ejection Fraction Study).

5.1 Introduction

Studies examining the relationship between CAD and prognosis in HF-PEF have produced conflicting results(58, 118-120). Even less is known about the importance of angina in these patients, which has only been the focus of two previous analyses(5, 98). In this analysis of the I-PRESERVE trial we looked to expand on the current literature by exploring the relationship between CAD, angina and outcomes in a large HF-PEF population. I also examined the individual components of all-cause mortality to try and further understand the mechanisms by which the presence or absence of CAD angina and CAD might affect prognosis(7). My hypothesis was that the presence of CAD and angina would be associated with a higher risk of adverse clinical outcomes.

5.2 Methods

The methodology has been described as part of the general methodology section in chapter 2 and has therefore not been replicated here.

5.3 Results

Baseline characteristics

Baseline characteristics are presented in table 13.

Comparison of patients with a history of CAD (groups C and D) vs. patients without a history of CAD (groups A and B)

When compared with patients *without* a history of CAD, Patients with a history of CAD had lower mean LVEFs (59/57 vs. 61/60% in groups C and D vs. groups A and B), were more likely to experience NYHA class III or IV symptoms (82/81 vs. 78/76%), and had higher median NT-pro BNP levels (455/454 vs. 298/241). They were more likely to be male (56/51 vs. 34/30%), have a history of stroke (13/10 vs. 9/9%) and diabetes (38/29 vs. 26/22%) and be prescribed anti-platelets (74/81 vs. 42/65%) or ACE inhibitors (30/29 vs. 22/26%) at baseline.

Patients without a history of CAD were more likely to have a history of hypertension (91/96 vs. 81/82%) and be prescribed CCBs at baseline (43/44 vs. 31/36%)(7).

Comparison of patients with no history of CAD or angina vs. patients with no history of CAD but a history of angina

When comparing patients without a history of CAD, a number of important differences were noted in those with and without angina. Despite those with a history of angina having less NYHA class III or IV symptoms (76 vs. 78%) and lower NT-pro BNP levels (241 vs. 298), their quality of life as assessed by the Minnesota living with HF questionnaire was lower (score of 45 vs. 41). Mean LVEFs was similar between

the two groups. Patients with angina were also more likely to be female (70 vs. 66%), Caucasian (98 vs. 91%) and have a history of hypertension (96 vs. 90%). They were less likely to have diabetes (22 vs. 26%) or AF (13 vs. 20%)(7).

Comparison of patients with a history of CAD but no angina vs. patients with a history of CAD and angina

Patients with a history of CAD and angina had lower mean LVEFs (57 vs. 59%), worse quality of life scores (Minnesota living with HF score of 45 vs. 41) and were less likely to have a history of diabetes (29 vs. 38%) or previous coronary revascularization (35 vs. 43%). They were more likely to be prescribed diuretics, BBs, CCBs, nitrates and anti-platelets at baseline. NT-pro BNP levels (445 vs. 455), the proportion of patients with NYHA class III or IV symptoms (82 vs. 81%), and the percentage of patients with previous MIs (66% in both groups) or hypertension (82 vs. 81%) was similar between the two groups(7).

Clinical Outcomes

Mortality outcomes

Cardiovascular death accounted for 70% of all deaths in I-Preserve. Sudden death was the most common cause of cardiovascular death accounting for 38% (n=231) of cases; almost twice as many as the number of deaths due to HF (20% of all cardiovascular deaths, n=125).

When examining patients without a history of CAD, the only significant difference in patients with and without angina was a lower risk of death due to HF in patients with angina in the unadjusted analysis. However this association was no longer significant after adjusting for prognostically important covariates (HR 0.54 (0.24-1.21); p=0.135) (see figure 6 and tables 14-16).

In both adjusted and unadjusted analyses patients with a history of CAD were at higher risk of all-cause death with the highest risk in patients with a history of CAD and no history of angina (adjusted HR 1.58 (1.22-2.04); p<0.001). There was also an association with higher CV death (HR 1.50 (1.10-2.06); p=0.011) and sudden death (HR 2.15 (1.35-3.44); p=0.001) but no significant difference was seen in pump failure deaths (HR 0.66 (0.29-1.49); p=0.315). Patients from group D there were also at higher risk of all-cause mortality (HR 1.29 (1.05-1.59); p=0.016), CV death (HR 1.46 (1.14-1.86); p=0.002) and sudden death (HR 1.83 (1.24-2.69); p=0.002), albeit to a lesser extent than patients in group C(7).

HF outcomes

In patients with no history of CAD, the risk of heart failure outcomes was similar in those with and without angina (see tables 14-16 and Figure 7). Although there was a lower risk of HF hospitalization in patients with a history of angina in the unadjusted analysis, this was not significant after accounting for prognostically important variables in the adjusted analysis (HR 0.94 [0.70–1.25]; P=0.67).

When compared with patients with no history of CAD or angina, patients with a history of CAD (both those with or without angina) had a higher risk of HF hospitalization and the composite end point of HF death or HF hospitalization in the unadjusted analysis. However, in the adjusted analysis the only statistically significant finding was the risk of HF death or HF hospitalization in patients with CAD and angina (HR, 1.26 [1.03–1.54]; P=0.02; Tables 14-16; Figure 7)(7).

Coronary outcomes

In I-Preserve coronary events were relatively infrequent, with only 5% of the study population hospitalized for MI or UA over the follow-up period.

In both adjusted and unadjusted analyses patients with no history of CAD but a history of angina were at elevated risk of UA or MI compared with patients with no history of CAD or angina (adjusted HR, 2.20 [1.10–4.37]; P=0.03). However, their risk of fatal or nonfatal MI was not significantly different to patients with no history of CAD or angina.

Patients with CAD but no history of angina and patients with CAD and angina were both at elevated risk of UA or MI when compared with patients with no history of CAD or angina. Both groups were also at higher risk of fatal or nonfatal MI in the adjusted analyses ([HR, 2.75 ; P=0.01] and [HR, 5.14 ; P<0.01]; Tables 14-16; Figure 7)(7).

5.4 Discussion

In this study, 68% of patients with HF-PEF and CAD had a history of stable angina pectoris compared with 24% of those without CAD. The high frequency of angina symptoms in patients without a known history of CAD is in keeping with the findings of a retrospective study of 376 patients hospitalized with HF-PEF in North America. In that analysis, all patients underwent diagnostic coronary angiography and a similar prevalence of angina was reported regardless of whether or not significant epicardial CAD was identified(58). Other factors such as microvasculature dysfunction may therefore have contributed to angina symptoms in patients without epicardial CAD(125). In our analysis it is also possible that some patients had undiagnosed CAD. I did not have access to coronary angiography data but 3% of patients went on to have an ACS during follow-up(7).

Baseline characteristics

Patients with CAD had evidence of more advanced heart failure with a higher frequency of NYHA class III or IV symptoms, higher NT pro BNP levels and lower LV ejection fractions. However quality of life as assessed by the Minnesota Living with Heart failure questionnaire was not significantly different to those without CAD. A history of angina pectoris, on the other hand, had a significant negative impact on quality of life, irrespective of whether patients had a history of CAD. In I-PRESERVE investigators did not differentiate patients with past or current angina, but these findings suggest there may be potential to improve quality of life in patients with HF-PEF by targeting symptoms of angina pectoris(7).

The relationship between CAD, angina and mortality outcomes.

Few studies have examined the interaction between CAD and all-cause mortality in patients with HF-PEF. CAD was associated with higher all-cause mortality in one

single-centre study of 376 patients with HF hospitalizations due to HF-PEF (adjusted HR, 1.71 [1.03–2.98];p=0.04) and in patients with HF-PEF from the CASS Registry (n=284)(58, 120). However, there was no such association in a prospective multicentre study of patients hospitalized with HF-PEF in France (n=320) and a cohort of 220 patients with HF-PEF from the Framingham Study(118, 119). The reasons for these conflicting findings are not clear but most likely a consequence of the heterogeneity of the populations studied as well as the differences in how CAD was defined. In this analysis of I-Preserve, patients with a history of CAD (with and without angina) were at higher risk of death than patients with no history of CAD or angina(7).

Arguably the most important finding in this analysis was the significantly higher risk of *sudden death* in patients with CAD. This supports the previous findings from two small, retrospective analyses of patients discharged from hospital with a diagnosis of HF-PEF where CAD was also associated with a higher risk of sudden death(118, 126). Presumably, CAD increases the rate of sudden death by precipitating ventricular arrhythmias. Perhaps surprisingly the highest risk was in patients with CAD but *without* a history of angina (HR 2.15 (1.35-3.44); p=0.001). Patients with CAD and angina (HR, 1.83 [1.24–2.69]; P<0.01) were at also at higher risk, albeit to a lesser extent. This was despite patients with CAD and angina having a relatively higher risk of acute coronary syndromes (UA/MI HR 4.44 (2.31-8.54); p<0.001 vs. 5.84 (3.43-9.95); p<0.001). This suggests the majority of sudden death (and presumably arrhythmogenic deaths) were not precipitated by active ischaemia, either in the acute or chronic settings. Silent ischaemia may have been a factor but this is outwith the remit of my thesis and there is no data to confirm or refute its potential impact on our findings. Finally, it is possible the absence of angina was a marker of more 'scarred' myocardium with an increased propensity to promote arrhythmia and sudden death(7).

Whilst patients with CAD and HF-PEF are at higher risk of sudden cardiac death, the absolute rate is still low and the role of implantable cardioverter defibrillators is not clear. A planned study of implantable loop recorders in patients with HF-PEF intended to ascertain the frequency of ventricular arrhythmias in this population will exclude patients with significant CAD or recent MI and is therefore unlikely to fully answer this question (http://clinicaltrials.gov/ct2/show/NCT01989299)(7).

The relationship between CAD, angina and non-fatal outcomes.

In patients with CAD and HF-PEF from CHARM there was a clear relationship between current angina and ACS(5). In I-Preserve, although patients with CAD and a history of angina were at elevated risk of UA/MI (HR 5.84 (3.43-9.95); $p<0.001$), the relative increase when compared to that seen in the group with CAD but no history of angina (HR 4.44 (2.31-8.54); $p<0.001$) was relatively modest. In I-PRESERVE, although investigators detailed a history of stable angina, patients with past and current angina were not differentiated. This may have diluted the association. Nevertheless these results do highlight the importance of investigating whether specific medical therapies or coronary revascularization might have a role to play in reducing adverse outcomes in subgroups of patients with HF-PEF(7).

Again a number of limitations should be considered. Our analysis was not pre-specified and our results have the same limitations of all post hoc analysis. Also, I-PRESERVE only enrolled patients over 60 years of age and our findings cannot be generalized to all patients with HF-PEF. Finally patients did not undergo routine screening for CAD and it is possible that patients with CAD may have been misclassified (or vice versa)(7).

In conclusion, patients with HF-PEF and CAD have evidence of more advanced HF whereas patients with angina and HF-PEF experience poorer quality of life

irrespective of whether they have underlying CAD. Patients underlying CAD are at higher risk of sudden death and our findings highlight the need to investigate whether interventions such as specific medical therapies, coronary revascularization or ICDs might improve outcomes(7).

Table 13 I-Preserve: baseline characteristics of patients with HF-PEF stratified by history of coronary artery disease and angina.

Hx of CAD Hx of Angina Variable	All (n=4128)	Group A No No (n=2008)	Group B No Yes (n=649)	Group C Yes No (n=468)	Group D Yes Yes (n=1003)	p value
Age	71.6 ± 6.9	71.8 ± 7.1	71.0 ± 6.7	72.6 ± 7.0	71.3 ± 6.8	<0.001
Female	2491 (60.3%)	1330 (66.2)	455 (70.1%)	214 (45.7)	492 (49.1)	<0.001
Caucasian race	3859 (93.5%)	1835 (91.4%)	634 (97.7%)	435 (93.0%)	955 (95.2%)	<0.001
NYHA III/IV	3257 (78.9%)	1563 (77.8%)	492 (75.8%)	385 (82.3%)	817 (81.5%)	0.007
Minnesota HF score	42.7 (20.7)	41.2 (21.0)	45.6 (18.5)	41.1 (21.9)	44.5 (20.9)	<0.001
LVEF (%)	59.4 ± 9.2	60.6 ± 9.5	60.1 ± 8.5	58.6 ± 9.4	57.0 ± 8.1	<0.001
Systolic BP (mm/Hg)	136.3 ± 15.0	137.3 ± 15.3	137.2 ±13.4	134.6 ±16.3	134.8 ±14.5	0.004
Heart Rate	71.4 ± 10.4	71.9 ± 10.8	71.3 ± 9.5	70.9 ± 10.6	70.8 ± 10.1	0.017
BMI kg/m^2	29.6 ± 5.3	30.0 ± 5.6	29.4 ± 4.8	29.3 ± 5.1	29.2 ± 4.9	<0.001
Medical Hx						
MI	969 (23.5%)	0 (0%)	0 (0%)	308 (65.8%)	661 (65.9%)	<0.001
PCI or CABG	548 (13.3%)	0 (0%)	0 (0%)	200 (42.7%)	348 (34.7%)	<0.001
Hypertension	3650 (88.4%)	1823 (90.8%)	622 (95.8%)	380 (81.2%)	825 (82.3%)	<0.001
Diabetes Mellitus	1134 (27.5%)	520 (25.9%)	145 (22.3%)	179 (38.3%)	290 (28.9%)	<0.001
AF at baseline	670 (16.2%)	401 (20.0%)	81 (12.5%)	70 (15.0%)	118 (11.8%)	<0.001
Stroke or TIA	399 (9.7%)	178 (8.9%)	56 (8.6%)	61 (13.0%)	104 (10.4%)	0.030
Pacemaker	252	122	35	37	58	0.333

	(6.1%)	(6.1%)	(5.4%)	(7.9%)	(5.8%)	
ICD	12 (0.3%)	3 (0.2%)	1 (0.2%)	3 (0.6%)	5 (0.5%)	0.153
Lab measurements						
Anaemia	514 (12.9%)	239 (12.5%)	60 (9.4%)	72 (16.0%)	143 (14.6%)	0.003
GFR	72.5 ± 22.5	72.5 ± 23.1	72.8 ± 19.8	70.4 ± 21.3	73.4 ± 23.3	0.126
Median NT-pro BNP	339	298	241	455	454.5	0.005
Medication						
Loop diuretic or thiazide	3418 (82.9%)	1639 (81.6%)	576 (88.9%)	357 (76.3%)	846 (84.5%)	<0.001
ACE inhibitor	1033 (25.0%)	438 (21.8%)	167 (25.8%)	139 (29.7%)	289 (28.9%)	<0.001
Beta-blocker	2427 (58.8%)	1016 (50.6%)	434 (67.0%)	296 (63.3%)	681 (68.0%)	<0.001
CCBs	1637 (39.7%)	857 (42.7%)	282 (43.5%)	143 (30.6%)	355 (35.5%)	<0.001
Long-acting Nitrate	1108 (26.9%)	186 (9.3%)	245 (37.8%)	135 (28.9%)	542 (54.2%)	<0.001
Antiplatelet	2416 (58.6%)	843 (42.0%)	422 (65.1%)	344 (73.5%)	807 (80.6%)	<0.001
Statin	1210 (29.3%)	459 (22.9)	150 (23.1)	229 (48.9)	372 (37.1)	<0.001

Table 14 I-PRESERVE: event rates of patients with HF-PEF stratified by history of coronary artery disease and angina.

Group	**A**	**B**	**C**	**D**
History of CAD	**No**	**No**	**Yes**	**Yes**
History of angina	**No**	**Yes**	**No**	**Yes**
	(n=2008)	(n=649)	(n=468)	(n=1003)
Mortality outcomes				
All-cause death	379 (18.9)	110 (16.9)	153 (32.7)	239 (23.8)
CV death	243 (12.1)	83 (12.8)	104 (22.2)	183 (18.2)
Sudden death	83 (4.1)	31 (4.8)	43 (9.2)	74 (7.4)
Pump failure death	61 (3.0)	10 (1.5)	18 (3.8)	36 (3.6)
Heart Failure Outcomes				
HF composite	390 (19.4)	106 (16.3)	126 (26.9)	244 (24.3)
HF hospitalization	312 (15.5)	81 (12.5)	88 (18.8)	180 (17.9)
Coronary Outcomes				
Fatal/non-fatal MI	33 (1.6)	14 (2.2)	25 (5.3)	77 (7.7)
UA/MI	41 (2.0)	20 (3.1)	33 (7.1)	100 (10.0)

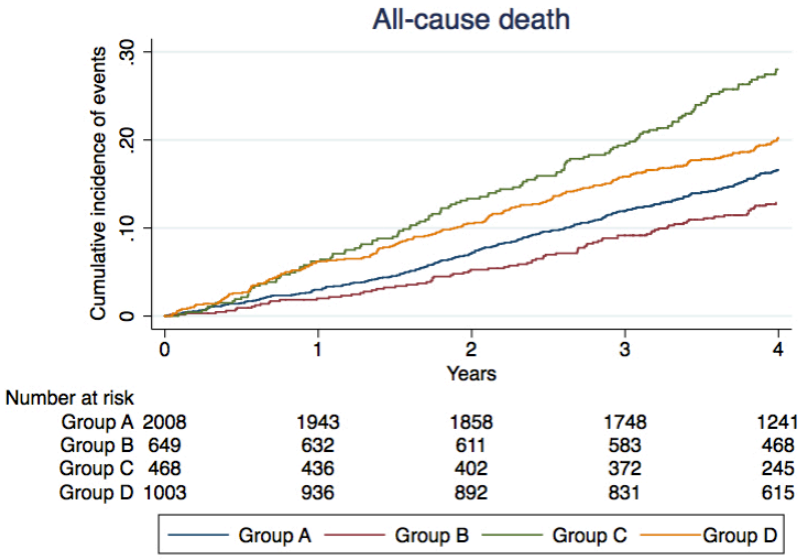
Table 15 I-PRESEVE unadjusted analysis: the relationship between history of coronary artery disease and angina with clinical outcomes.

Group **History of CAD** **History of angina**	**B vs. A**		**C vs. A**		**D vs. A**	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Mortality outcomes						
All-cause death	0.85 (0.69-1.05)	0.135	1.90 (1.57-2.29)	<0.001	1.30 (1.10-1.52)	0.002
CV death	1.00 (0.78-1.29)	0.973	2.00 (1.59-2.52)	<0.001	1.55 (1.28-1.88)	<0.001
Sudden death	1.10 (0.73-1.66)	0.657	2.42 (1.67-3.49)	<0.001	1.83 (1.34-2.50)	<0.001
Pump failure death	0.48 (0.25-0.95)	0.034	1.38 (0.81-2.33)	0.235	1.22 (0.81-1.84)	0.351
Heart Failure Outcomes						
HF composite	0.81 (0.65-1.00)	0.051	1.49 (1.22-1.82)	<0.001	1.31 (1.12-1.54)	0.001
HF hospitalization	0.78 (0.61-0.99)	0.041	1.29 (1.02-1.64)	0.033	1.21 (1.00-1.45)	0.045
Coronary Outcomes						
Fatal/non-fatal MI	1.26 (0.68-2.36)	0.464	3.52 (2.09-5.92)	<0.001	4.89 (3.25-7.35)	<0.001
UA/MI	1.46 (0.86-2.49)	0.166	3.75 (2.37-5.93)	<0.001	5.16 (3.59-7.43)	<0.001

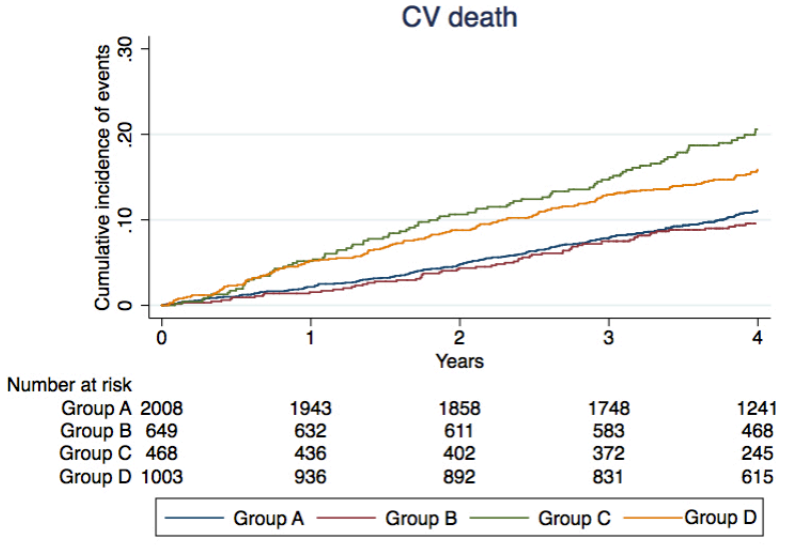
Table 16 I-PRESEVE adjusted analysis: the relationship between history of coronary artery disease and angina with clinical outcomes.

Group **History of CAD** **History of angina**	**B vs. A**		**C vs. A**		**D vs. A**	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Mortality outcomes						
All-cause death	0.95 (0.73-1.25)	0.716	1.58 (1.22-2.04)	<0.001	1.29 (1.05-1.59)	0.016
CV death	1.11 (0.82-1.52)	0.502	1.50 (1.10-2.06)	0.011	1.46 (1.14-1.86)	0.002
Sudden death	1.09 (0.64-1.86)	0.751	2.15 (1.35-3.44)	0.001	1.83 (1.24-2.69)	0.002
Pump failure death	0.54 (0.24-1.21)	0.135	0.66 (0.29-1.49)	0.315	1.08 (0.641.83)	0.775
Heart Failure Outcomes						
HF composite	0.93 (0.72-1.20)	0.557	1.19 (0.91-1.55)	0.196	1.26 (1.03-1.54)	0.023
HF hospitalization	0.94 (0.70-1.25)	0.667	1.03 (0.75-1.40)	0.873	1.12 (0.89-1.41)	0.347
Coronary Outcomes						
Fatal/non-fatal MI	1.51 (0.66-3.43)	0.327	2.75 (1.26-5.97)	0.011	5.14 (2.90-9.13)	<0.001
UA/MI	2.20 (1.10-4.37)	0.025	4.44 (2.31-8.54)	<0.001	5.84 (3.43-9.95)	<0.001

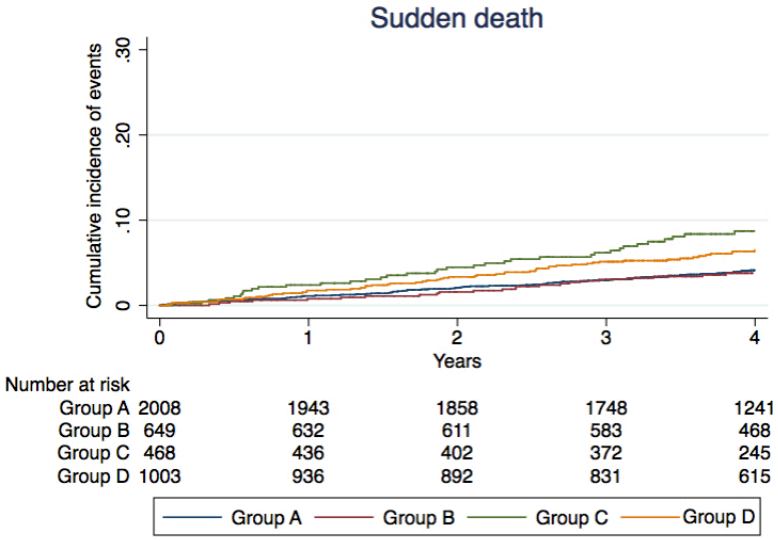
Figure 6: I-Preserve Kaplan-Meier curves illustrating the relationship between angina history, CAD and mortality endpoints



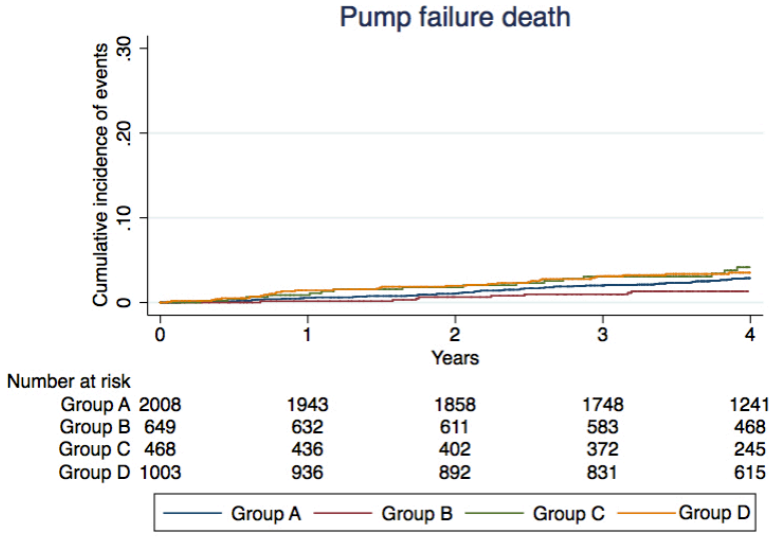
I



II

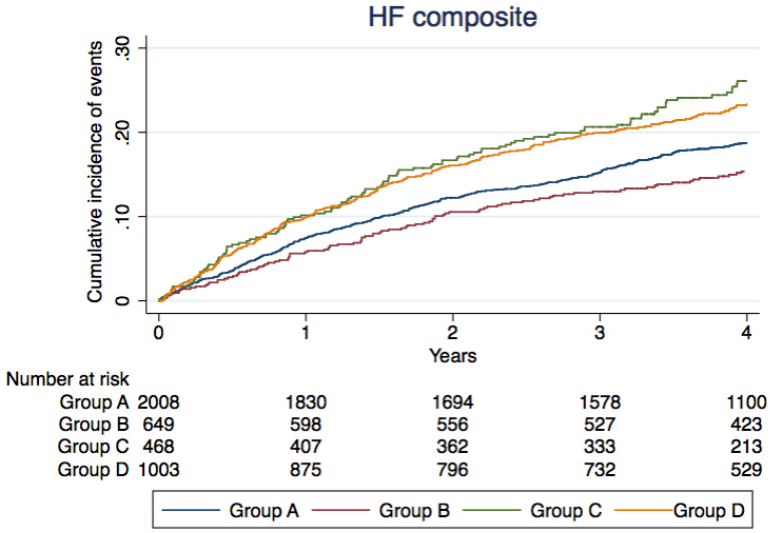

Sudden death
Cumulative incidence of events
0
.10
.20
.30
0
1
2
3
4
Years
Number at risk
Group A 2008 1943 1858 1748 1241
Group B 649 632 611 583 468
Group C 468 436 402 372 245
Group D 1003 936 892 831 615
Group A
Group B
Group C
Group D

III

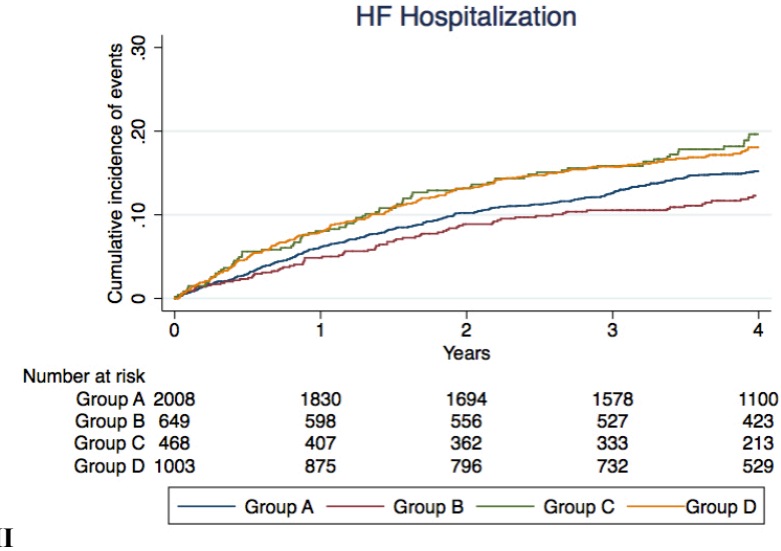

Pump failure death
Cumulative incidence of events
0
.10
.20
.30
0
1
2
3
4
Years
Number at risk
Group A 2008 1943 1858 1748 1241
Group B 649 632 611 583 468
Group C 468 436 402 372 245
Group D 1003 936 892 831 615
Group A
Group B
Group C
Group D

IV

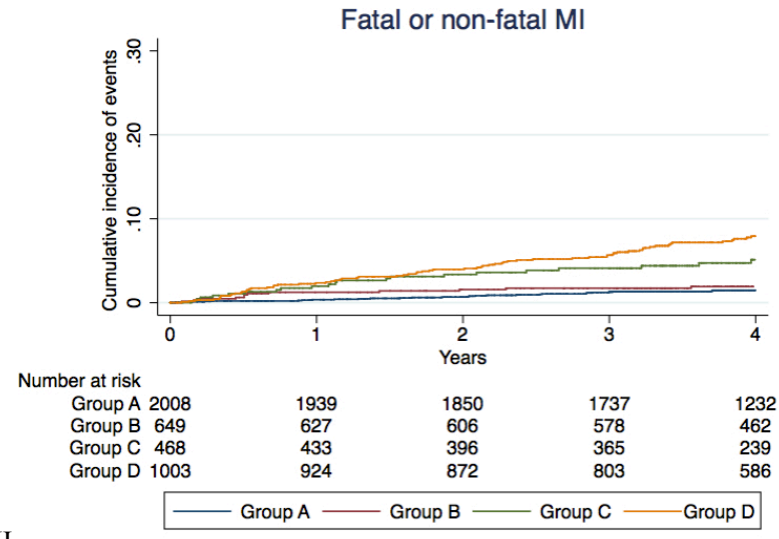
Figure 7:I-Preserve Kaplan-Meier curves illustrating the relationship between angina history, CAD and non-fatal outcomes.



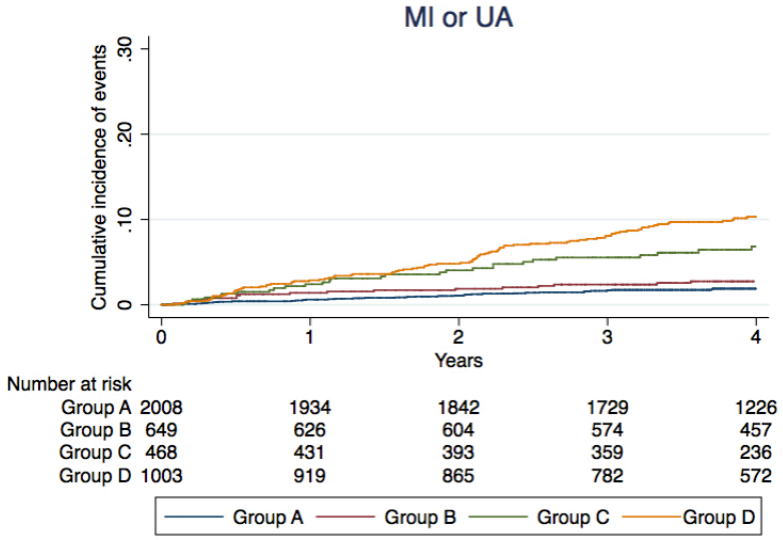
I



II


Fatal or non-fatal MI
Cumulative incidence of events
0
.10
.20
.30
0
1
2
3
4
Years
Number at risk
Group A 2008 1939 1850 1737 1232
Group B 649 627 606 578 462
Group C 468 433 396 365 239
Group D 1003 924 872 803 586
Group A
Group B
Group C
Group D

III


MI or UA
Cumulative incidence of events
0
.10
.20
.30
0
1
2
3
4
Years
Number at risk
Group A 2008 1934 1842 1729 1226
Group B 649 626 604 574 457
Group C 468 431 393 359 236
Group D 1003 919 865 782 572
Group A
Group B
Group C
Group D

IV

Figure 6: I-Preserve Kaplan-Meier curves illustrating the relationship between angina history, CAD and mortality endpoints. i) All-cause death ii) CV death iii) Sudden death iv) Death due to heart failure

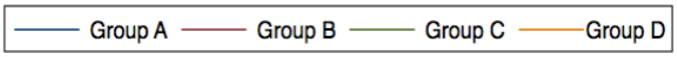
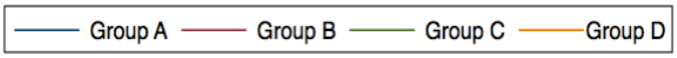


Figure 7: I-Preserve Kaplan-Meier curves illustrating the relationship between angina history, CAD and non-fatal outcomes. i) I-Preserve HF composite ii) HF Hospitalization iii) Fatal or non-fatal myocardial MI iv) MI or unstable angina



Chapter 6

The relationship between severity of angina and outcomes in patients with heart failure and reduced ejection fraction in the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial.

6.1 Introduction

I previously examined the prognostic importance of angina in patients with HF-REF. In retrospective analyses from CORONA and CHARM, patients with HF-REF and current angina experienced greater functional limitation and were at higher risk of coronary events than those with no history of angina. However, current angina was not associated with higher all-cause mortality in these analyses, in a prior analysis of the COMET trial, the STICH trial or a large single centre study from North America (n=2376)(3, 5, 85, 99, 127).

I therefore utilized the Prospective comparison of Angiotensin Receptor-neprilysin inhibitor with Angiotensin-converting–enzyme inhibitor to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF) to examine the relationship between severity of angina and outcomes in patients with HF-REF(9). My hypothesis was that more severe angina would be predictive of mortality, as well as non-fatal outcomes, compared with less severe angina.

6.2 Methods

The methodology has been described as part of the general methodology section in chapter 2 and has therefore not been replicated here.

6.3 Results

Of 8842 patients in PARADIGM-HF, 5594 had a history of CAD. Of the patients with CAD, 1725 (31%) reported angina at baseline; of these, 447 (8% of the patients with CAD) had mild angina, 884 (16%) moderate angina and 394 (7%) severe angina.

Baseline characteristics

Baseline characteristics stratified by severity of angina symptoms are presented in Table 17. Patients with angina of any severity were more likely to be female, Caucasian and older than those with no angina. They also more frequently had a history of prior MI, hypertension and atrial fibrillation, but not diabetes or stroke.

Patients with mild angina had received more interventions, including percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery and a pacemaker, cardiac resynchronization therapy (CRT) or an implantable cardioverter defibrillator (ICD) compared to those with either no angina or moderate or severe angina. They also had the highest use of beta-blockers, statins and anti-platelet agents.

Compared to those with no angina, patients with moderate or severe angina had a higher mean LVEF but worse symptoms and signs of HF, including paroxysmal nocturnal dyspnoea, pulmonary crackles and peripheral oedema and a higher proportion of these patients were in NYHA functional classes III and IV. Their mean KCCQ score was also lower (worse) than in patients with no angina. Patients with moderate or severe angina were less likely to have a pacemaker, ICD or CRT.

Patients with severe angina were most likely to be in NYHA functional class III or IV and experience dyspnoea at rest, paroxysmal nocturnal dyspnoea and fatigue. They had the lowest KCCQ scores and the highest median NT-proBNP levels, despite having the highest mean LVEF. They were also most likely to have experienced a previous MI but least likely to have undergone PCI or ICD implantation.

Clinical Outcomes

CV death or HF hospitalization (the primary endpoint of PARADIGM-HF)

There was no relationship between the presence of mild or moderate angina and the composite endpoint of CV death or HF hospitalization, or with its components (Tables 18-19; Figure 8).

By contrast, patients with severe angina were at significantly higher risk of CV death or HF hospitalization (adjusted HR 1.41, 1.17-1.70; $p<0.01$) and CV death alone (adjusted HR 1.60, 1.27-2.01; $p<0.01$), when compared to those with no angina at baseline. There was also an association between severe angina and a higher risk of HF hospitalization in the univariate analysis but this was no longer significant after adjusting for other covariates (adjusted HR 1.27, 0.98-1.64; $p=0.07$) (Tables 18-19; Figure 8).

Coronary events

The risk of coronary events (hospitalization for UA, hospitalization for non-fatal MI, hospitalization for UA or non-fatal MI and fatal or non-fatal MI) was not significantly different in patients with mild versus no angina at baseline. Patients with moderate angina were at higher risk of UA (adjusted HR 2.02, 1.15-3.53; $p=0.01$) but their risk of MI was not significantly higher than in patients with no angina. Patients with severe angina were at higher risk for all adverse coronary outcomes, having an approximately

six-fold higher risk of hospitalization for UA (adjusted HR 5.81, 3.28-10.28; p<0.01) and being almost twice as likely to experience a fatal or non-fatal MI (adjusted HR 1.90, 1.18-3.06; p=0.01).

Mortality

Compared to those with no angina, patients with severe angina were at significantly higher risk of all-cause mortality (adjusted HR 1.48, 1.20-1.84; p<0.01; Figure 8), CV mortality (see above) and sudden death (adjusted HR 1.86, 1.35-2.57; p<0.01; Figure 8). However their risk of death due to HF was not significantly higher than those with no angina (adjusted HR 1.32, 0.80-2.17; p=0.28; Tables 18-19; Figure 8). Patients with mild or moderate angina were not at higher risk of all-cause or CV mortality (or any of the modes of CV death) compared to those with no angina.

The effect of LCZ696 versus enalapril according to angina status was not significantly different for any of the aforementioned endpoints.

6.4 Discussion

In our analysis of 5594 patients with CAD from PARADIGM-HF, 31% of patients reported angina at baseline; symptoms were mild in 8% of patients, moderate in 16% and severe in 7%. Severe angina symptoms were associated with significantly more functional limitation and a higher risk of the composite outcome of CV death or HF hospitalization, non-fatal MI and CV as well as all-cause death.

Baseline characteristics

There was a strong association between greater severity of angina and worse functional status in PARADIGM-HF. More than two thirds of patients with severe angina were in NYHA functional class III or IV compared with approximately 40% of those with moderate angina and just 20% of patients with mild or no angina. Two of our studies also demonstrated a relationship between the presence of *any* angina and worse functional class but the association in those studies was much weaker (although they did not grade the severity of angina). In CORONA 71% of patients with current angina reported NYHA class III or IV symptoms compared to 54% of patients with no angina; in CHARM 70% of those with current angina were in NYHA functional class III or IV versus 58% of patients with no angina(3, 5). I have extended these observations to include a description of the KCCQ clinical summary score and symptoms and signs according to baseline angina status. The KCCQ clinical summary score showed a gradient of worsening baseline health-related quality of life with increasing severity of angina. In PARADIGM-HF, patients with severe angina were also considerably more likely to report rest and nocturnal dyspnoea and fatigue compared to those without angina. Similarly, patients with severe angina were twice as likely to have peripheral oedema and an elevated jugular venous pressure. Notably, despite this greater functional limitation, and worse symptoms and signs, patients with

more severe angina had a higher average LVEF and higher systolic BP when compared to patients with no angina, consistent with the findings in CORONA and CHARM(3, 5). There was also little gradient in NT pro BNP or estimated glomerular filtration rate according to severity of angina. Therefore, it now seems clear that there is a disconnection between symptoms, signs and functional limitation due to heart failure and measures of haemodynamic and physiological severity in patients with angina. This finding seems to indicate that myocardial ischaemia, rather than worse physiological status, may exacerbate functional status and heart failure symptoms in some patients with HF-REF.

One unexpected finding was that patients with severe angina were least likely to have undergone prior PCI. The results of coronary angiography were not available but patients with severe angina may have had more complex coronary anatomy that was less amenable to revascularization. It is also possible the so-called 'risk treatment paradox' contributed to the underutilization of PCI in this group i.e. patients with more severe heart failure symptoms and functional limitation may have been less likely to be considered for revascularization(131-135). However, a similar gradient in prior coronary artery bypass grafting was not observed, making this explanation less likely.

Patients with moderate and severe angina were also less likely to have an ICD or CRT device implanted when compared to patients with no angina. The higher proportion of patients with NYHA class IV symptoms may (at least partially) account for why fewer patients received ICDs.

The relationship between severity of angina symptoms and clinical outcomes

In CORONA and CHARM *current* angina was associated with a higher risk of acute coronary syndrome but the risk of all-cause and CV death was similar to that of patients with no history of angina(3, 5). There was also a lack of association between

angina and all-cause death in retrospective analyses of COMET and a large single-centre US study (n=2376)(85, 99). The STICH trial has reported the relationship between severity of angina and all-cause death. Patients with moderate or severe angina (defined as a CCS $\geq$ 2) were at higher risk of all-cause death when compared with patients with no angina (adjusted HR 1.27, 1.04-1.57; p=0.02). As only 58 patients in STICH had moderate or severe angina this association required corroboration(127).

Our study builds upon the aforementioned analyses by examining the relationship between *severity* of angina and a range of non-fatal and fatal outcomes in a large population with HF. As in the prior studies, patients in PARADIGM-HF with angina were at higher risk of coronary events but this risk was proportional to the severity of angina. Patients with severe angina had a higher risk of unstable angina and non-fatal MI (the former risk was almost 6-fold higher) when compared to patients with no angina but there was no association between mild angina symptoms and any coronary outcome. However, patients in PARADIGM-HF with angina were also at higher risk of all-cause and CV death compared to patients with no angina – but again this heightened risk was only observed in patients with severe angina symptoms. This difference is probably explained by the earlier studies (except for STICH whose findings were similar to our own) combining all patients with angina when PARADIGM-HF clearly shows that the risk of death is only increased among those with the most severe symptoms and not in those with less severe angina(127). Notably, the increase in CV death was mainly accounted for by an increase in risk of sudden death, rather than in risk of death due to worsening heart failure.

Interestingly, in PARADIGM-HF severe angina was not an independent predictor of heart failure hospitalization in our multivariable analysis, although the p-value for this comparison was of borderline statistical significance (p=0.07). While the strict

interpretation of our analysis showing no association is consistent with the findings from CHARM and COMET, current angina in CORONA was associated with a higher risk of HF hospitalization (adjusted HR 1.35, 1.13-1.63; p=0.001)(3, 5). It remains possible, therefore, that angina may be associated with HF hospitalization.

The potentially important implication of our findings is that while relief of myocardial ischaemia in patients with severe angina might improve functional status and prevent adverse outcomes, such benefits might be harder to show in patients with less severe angina. As patients with severe angina have an indication for revascularization, they have been excluded from previous and ongoing trials (e.g. the STICH trial) comparing CABG and medical therapy in patients with CAD and severe left ventricular dysfunction. In the STICH trial mortality rates in those assigned to medical therapy alone were similar whether angina was present or absent at baseline. Patients with and without angina had a similar benefit from CABG in both the original STICH trial and the 10 year extension study. No conclusions can be drawn from STICH with regard to severity of symptoms as CCS ≥3 was an exclusion criterion(77, 78, 81, 127).

In the on-going Study of Efficacy and Safety of Percutaneous Coronary Intervention to Improve Survival in Heart Failure (REVIVED-BCIS2) trial, designed to investigate the role of PCI in patients with HF, those with significant angina (defined as ≥ CCS class 3 symptoms) are excluded(78). It is notable, however, that while patients with severe angina have been excluded from these trials on the basis of having an existing guideline recommendation for revascularization, the low rate of prior revascularization observed in PARADIGM-HF and earlier studies suggests that clinical practice does not follow the guidelines in this instance.

Limitations

Our study has a number of limitations. The sub-groups in our analysis were not pre-specified and our study therefore has the same limitations associated as all *post-hoc* analyses. The presence and severity of angina used to stratify patients into groups was determined by investigator-reported history. Finally, I did not have the results of coronary angiography and the severity of CAD may be independently related to prognosis(113). It is unclear how our findings would be affected by these results.

Conclusion

In summary, patients with HF-REF, CAD and severe angina experience more functional limitation and are at higher risk of MI, all-cause and CV death. These findings raise the possibility that coronary revascularization and anti-ischaemic pharmacotherapy might improve outcomes in this population but these strategies need to be tested in prospective trials.

Table 17. PARADIGM-HF: baseline characteristics of patients with HF-REF stratified by severity of angina at baseline.

Angina severity Variable	No angina (n=3869)	Mild (n=447)	Moderate (n=884)	Severe (n=394)	p value
Age	65.0 ± 10.7	66.9 ± 9.6	66.1 ± 9.5	67.1 ± 9.2	<0.01
Female	711 (18.4)	92 (20.6)	214 (24.2)	87 (22.1)	<0.01
Race					
Caucasian	2501 (64.6%)	361 (80.8%)	759 (85.9%)	359 (91.1%)	<0.01
Black	134 (3.5%)	13 (2.9%)	13 (1.5%)	2 (0.5%)	<0.01
Asian	822 (21.3%)	45 (10.1%)	74 (8.4%)	22 (5.6%)	<0.01
Other	412 (10.7%)	28 (6.3%)	38 (4.3%)	11 (2.8%)	<0.01
Current smoker	563 (14.6)	67 (15.0)	133 (15.0)	15.7 (14.5)	0.98
LVEF (%)	29.4 ± 6.3	29.8 ±6.0	31.4 ± 5.7	31.7 ± 5.1	<0.01
Systolic BP mm/Hg	121.0 ± 15.4	122.0 ±15.4	124.9 ±14.3	125.4 ±13.4	<0.01
Heart Rate bpm	71.8 ± 12.0	70.6 ± 10.3	72.2 ± 11.6	72.0 ± 11.9	0.12
BMI kg/m^2	28.0 ± 5.4	28.9 ± 5.4	28.8 ± 5.1	28.8 ± 5.1	<0.01
Medical History					
MI	2406 (62.2%)	325 (72.7%)	588 (66.5%)	315 (79.9%)	<0.01
PCI	1251 (32.3%)	191 (42.7%)	267 (30.2%)	92 (23.4%)	<0.01
CABG	852 (22.0)	143 (32.0)	211 (23.9)	97 (24.6)	<0.01
Hypertension	2765 (71.5%)	341 (76.3%)	768 (86.9%)	361 (91.6%)	<0.01
Diabetes Mellitus	1513 (39.1%)	185 (41.4%)	337 (38.1%)	146 (37.1%)	0.57
AF	1283 (33.2%)	176 (39.4%)	373 (42.2%)	164 (41.6%)	<0.01
Stroke	385 (10.0%)	46 (10.3%)	97 (11.0%)	39 (9.9%)	0.84
Pacemaker	538 (13.9%)	87 (19.5%)	82 (9.3%)	36 (9.1%)	<0.01

CRT	282 (7.3)	40 (9.0)	34 (3.9)	22 (5.6)	<0.01
ICD	694 (17.9%)	115 (25.7%)	90 (10.2%)	31 (7.9%)	<0.01
Symptoms					
NYHA class III/IV	849 (22.0%)	84 (18.8%)	337 (38.3%)	266 (67.7%)	<0.01
Rest dyspnoea	125 (3.2%)	22 (4.9%)	48 (5.5%)	39 (9.9%)	<0.01
PND	171 (4.4%)	16 (3.6%)	55 (6.2%)	43 (10.9%)	<0.01
Orthopnea	263 (6.8%)	34 (7.6%)	67 (7.6%)	27 (6.9%)	0.80
Fatigue	1842 (47.7%)	258 (58.0%)	610 (69.2%)	312 (79.4%)	<0.01
KCCQ score	69.5 ± 29.1	68.8 ± 27.2	66.8 ± 23.0	60.9 ± 23.3	<0.01
Signs					
Raised JVP	335 (8.7%)	31 (7.0%)	90 (10.2%)	42 (10.7%)	0.13
Oedema	723 (18.7%)	114 (25.6%)	258 (29.3%)	149 (37.9%)	<0.01
Pulmonary rales	277 (7.2%)	29 (6.5%)	122 (13.8%)	55 (14.0%)	<0.01
Third heart sound	350 (9.1%)	34 (7.6%)	104 (11.8%)	35 (8.9%)	0.04
Lab measurements					
Estimated GFR	66.1 ± 19.4	63.6 ± 19.2	67.0 ± 18.2	64.5 ± 20.9	<0.01
Median NT-proBNP*	1593 (890-3103)	1395 (770-2762)	1411 (766-2612)	1767 (898-3431)	<0.01
Medication					
LCZ696 randomisation	1926 (49.8%)	228 (51.0%)	426 (48.2%)	198 (50.3%)	0.76
Loop or thiazide	3018 (78.0%)	358 (80.1%)	704 (79.6%)	318 (80.7%)	0.39
Beta-blocker	3594 (92.9%)	432 (96.6%)	818 (92.5%)	366 (92.9%)	0.02
MRA	1988 (51.4%)	195 (43.6%)	493 (55.8%)	269 (68.3%)	<0.01
Digoxin	1029 (26.6%)	92 (20.6%)	208 (23.5%)	87 (22.1%)	<0.01
Antiplatelet	2577 (66.6%)	336 (75.2%)	575 (65.1%)	275 (69.8%)	<0.01
Anticoagulant	1136 (29.4%)	145 (32.4%)	298 (33.7%)	111 (28.2%)	0.04
Statins	2639 (68.2)	360 (80.5)	602 (68.1)	265 (67.3)	<0.01

* LVEF – left ventricular ejection fraction; BP – blood pressure; bpm – beats per minute; BMI – body mass index; MI – myocardial infarction; PCI – percutaneous coronary intervention; CABG – coronary artery bypass graft surgery; AF – atrial fibrillation; ICD – implantable

cardioverter defibrillator; CRT – cardiac resynchronization therapy; NYHA – New York Heart Association; PND – paroxysmal nocturnal dyspnea; KCCQ - Kansas City Cardiomyopathy Questionnaire; JVP –jugular venous pressure; GFR – glomerular filtration rate; NT-proBNP - N-terminal proBNP**.**

Table 18. PARADIGM-HF: event rates according to severity of chest pain at baseline.

Severity of chest pain	No angina	Mild angina	Moderate angina	Severe angina
	(n=3869)	(n=447)	(n=884)	(n=394)
CV death or HF hospitalization	954 (24.7)	105 (23.5)	217 (24.6)	137 (34.8)
CV death	577 (14.9)	63 (14.1)	129 (14.6)	95 (24.1)
HF hospitalization	561 (14.5)	65 (14.5)	121 (13.7)	71 (18.0)
Non-fatal MI	114 (2.9)	21 (4.7)	32 (3.6)	19 (4.8)
Fatal or non-fatal MI	123 (3.2)	23 (5.1)	36 (4.1)	22 (5.6)
UA hospitalization	39 (1.0)	7 (1.6)	9 (2.2)	22 (5.6)
UA or non-fatal MI	148 (3.8)	25 (5.6)	47 (5.3)	37 (9.4)
All-cause death	717 (18.5)	82 (18.3)	166 (18.8)	107 (27.2)
Sudden death	270 (7.0)	21 (4.7)	57 (6.4)	50 (12.7)
Death due to HF	144 (3.7)	14 (3.1)	2.1 (2.4)	19 (4.8)

Table 19. PARADIGM-HF unadjusted analysis: the relationship between severity of chest pain and clinical outcomes.

	Mild vs. No angina		Moderate vs. No angina		Severe vs. No angina	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
CV death/ HFH	0.89 (0.72-1.08)	0.24	0.99 (0.85-1.14)	0.87	1.56 (1.31-1.87)	<0.01
CV death	0.88 (0.68-1.14)	0.33	0.97 (0.80-1.17)	0.74	1.77 (1.43-2.20)	<0.01
HFH	0.94 (0.72-1.21)	0.62	0.94 (0.77-1.14)	0.52	1.37 (1.07-1.75)	0.01
Non-fatal MI	1.51 (0.95-2.41)	0.08	1.23 (0.83-1.81)	0.31	1.78 (1.09-2.89)	0.02
Fatal or non-fatal MI	1.53 (0.98-2.39)	0.06	1.28 (0.88-1.85)	0.20	1.92 (1.22-3.02)	0.01
UA	1.46 (0.65-3.27)	0.35	2.13 (1.23-3.68)	<0.01	6.17 (3.65-10.40)	<0.01
UA or non-fatal MI	1.39 (0.91-2.12)	0.13	1.40 (1.01-1.94)	0.05	2.75 (1.92-3.94)	<0.01
All-cause death	0.91 (0.73-1.15)	0.45	1.00 (0.85-1.19)	0.98	1.62 (1.32-1.98)	<0.01
Sudden death	0.63 (0.41-0.98)	0.04	0.92 (0.69-1.22)	0.56	1.97 (1.45-2.66)	<0.01
Death due to HF	0.78 (0.45-1.34)	0.37	0.63 (0.40-1.00)	0.05	1.43 (0.89-2.31)	0.14

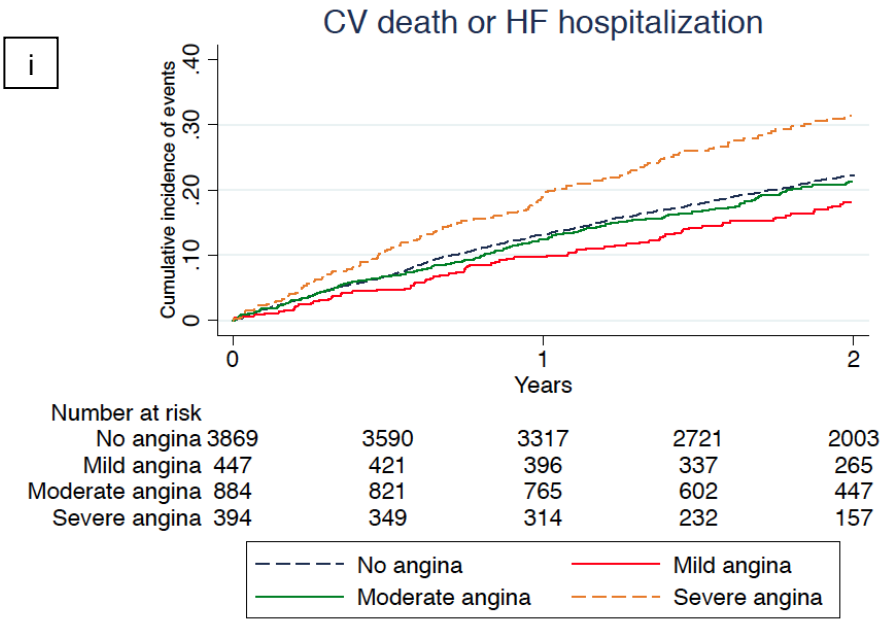
Table 20 PARADIGM-HF adjusted analysis: the relationship between severity of chest pain and clinical outcomes.

	Mild vs. No angina		Moderate vs. No angina		Severe vs. No angina	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
CV death/ HFH	0.89 (0.73-1.09)	0.27	1.06 (0.92-1.24)	0.42	1.41 (1.17-1.70)	<0.01
CV death	0.93 (0.72-1.22)	0.61	1.07 (0.88-1.31)	0.47	1.60 (1.27-2.01)	<0.01
HFH	0.91 (0.69-1.17)	0.43	1.02 (0.83-1.25)	0.84	1.27 (0.98-1.64)	0.07
Non-fatal MI	1.45 (0.91-2.32)	0.12	1.27 (0.86-1.90)	0.23	1.84 (1.11-3.07)	0.02
Fatal or non-fatal MI	1.45 (0.93-2.28)	0.10	1.30 (0.89-1.90)	0.17	1.90 (1.18-3.06)	0.01
UA	1.37 (0.61-3.07)	0.45	2.02 (1.15-3.53)	0.01	5.81 (3.28-10.28)	<0.01
UA or non-fatal MI	1.29 (0.84-1.98)	0.24	1.40 (1.01-1.96)	0.05	2.64 (1.80-3.88)	<0.01
All-cause death	0.95 (0.75-1.19)	0.64	1.10 (0.93-1.31)	0.28	1.48 (1.20-1.84)	<0.01
Sudden death	0.73 (0.46-1.14)	0.16	1.01 (0.76-1.36)	0.93	1.86 (1.35-2.57)	<0.01
Death due to HF	0.77 (0.44-1.33)	0.35	0.78 (0.49-1.25)	0.30	1.32 (0.80-2.17)	0.28

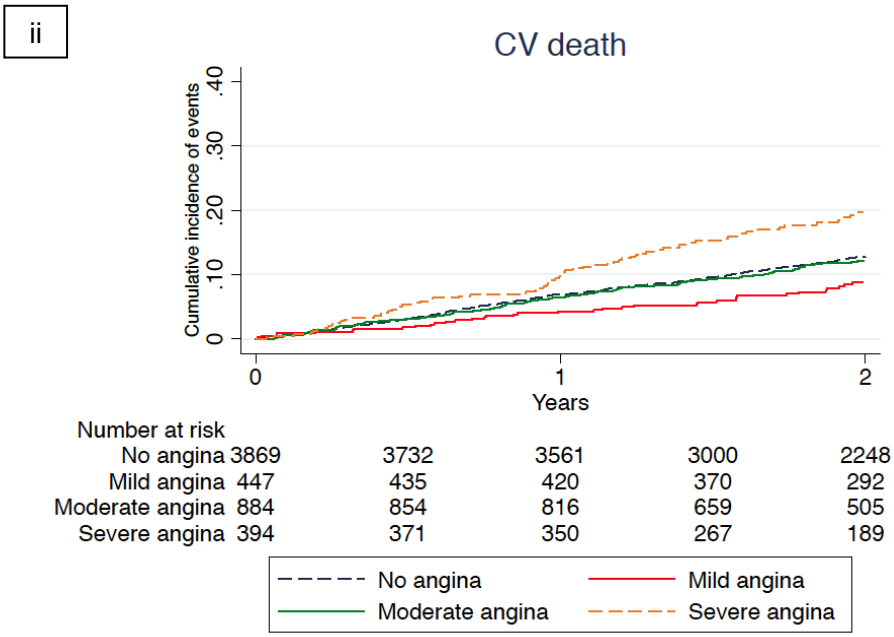
** Adjusted for age, ejection fraction, NYHA class, serum creatinine, diabetes mellitus, COPD, beta blocker use, systolic blood pressure, BMI, time from first diagnosis of HF, smoking status, gender, (log) NT-proBNP levels and randomization to LZC696.

Figure 8: Kaplan-Meier curves of the relationship between severity of angina and clinical outcomes.

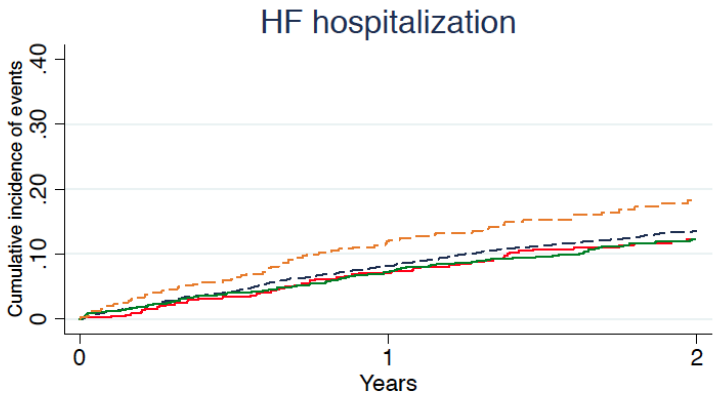
i



ii

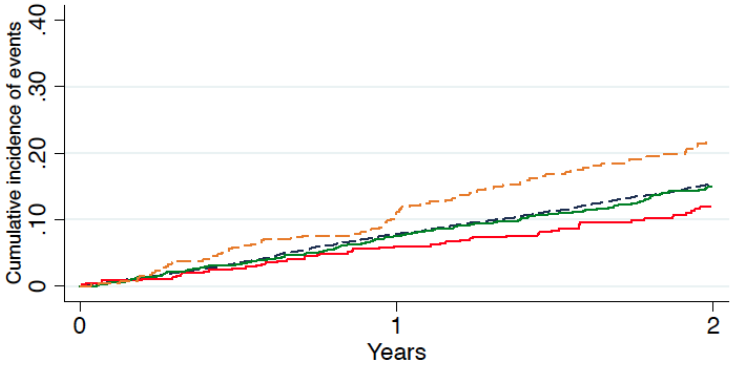


iii

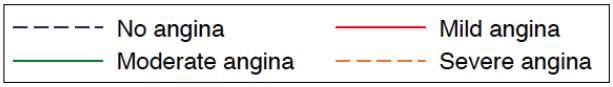


Number at risk					
No angina	3869	3590	3317	2721	2003
Mild angina	447	421	396	337	265
Moderate angina	884	821	765	602	447
Severe angina	394	349	314	232	157

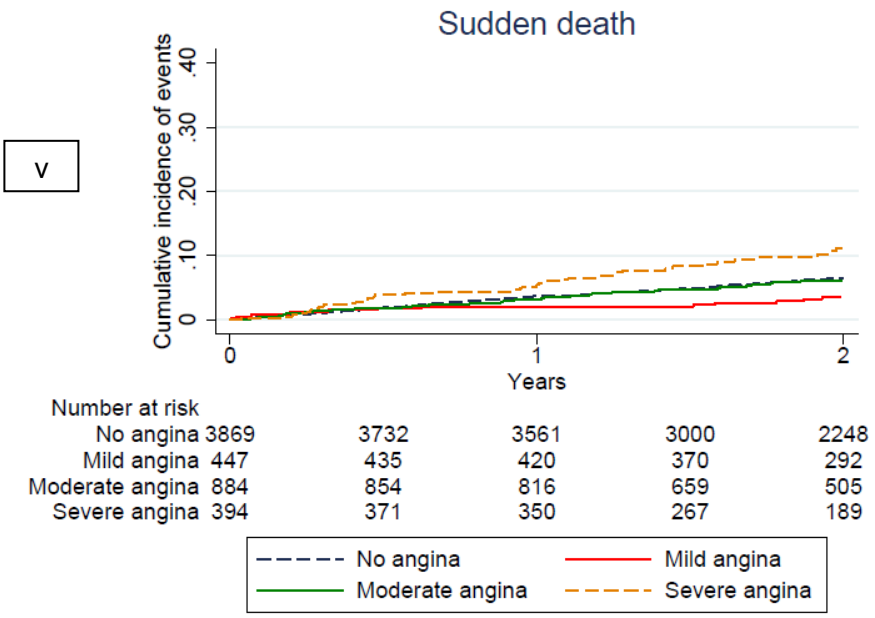
iv



Number at risk					
No angina	3869	3732	3561	3000	2248
Mild angina	447	435	420	370	292
Moderate angina	884	854	816	659	505
Severe angina	394	371	350	267	189

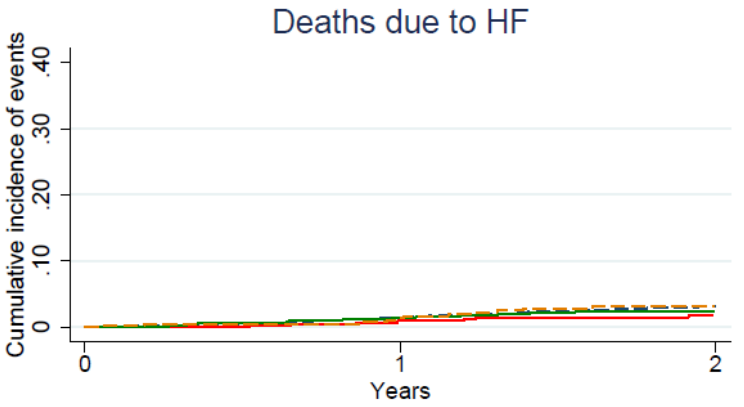


v



Number at risk					
No angina	3869	3732	3561	3000	2248
Mild angina	447	435	420	370	292
Moderate angina	884	854	816	659	505
Severe angina	394	371	350	267	189

vi



Number at risk					
No angina	3869	3732	3561	3000	2248
Mild angina	447	435	420	370	292
Moderate angina	884	854	816	659	505
Severe angina	394	371	350	267	189

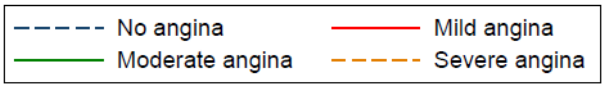


Figure legend

Figure 8: Kaplan-Meier curves of the relationship between severity of angina, all-cause death, HF outcomes

and coronary outcomes. i) Cardiovascular death or HF hospitalization ii) CV death iii) HF hospitalization iv) All-cause death v) Sudden death vi) Death due to HF.

Final Discussion

My thesis examined the clinical characteristics and prognostic importance of angina in patients with HF. Very few studies had examined the association between these two conditions and a number of themes emerged from our analyses.

In patients with HF-REF and HF-PEF, current angina was associated with more functional limitation than in patients with no angina. Worse functional status likely reflected myocardial ischaemia rather than severity of HF. In CORONA, this was evidenced by patients with angina and HF-REF having more NYHA class III or IV symptoms, despite having higher mean LVEF and lower NT-proBNP levels. This suggests their HF was actually less severe than patients with no angina(3). In CHARM I was able to replicate the findings of CORONA whilst also identifying a similar association in patients with heart failure and preserved ejection fraction(5). PARADIGM-HF examined the importance of severity of angina in patients with HF-REF. The relationship between functional limitation and angina became stronger with worsening severity of angina symptoms.

In patients with HF-REF from CORONA and CHARM, current angina was associated with a higher risk of ACS than in patients with no angina. A similar relationship was identified in patients with HF-PEF in CHARM. Patients with past angina in both studies also had a higher risk of ACS but the relationship was not as strong as in patients with current angina(3, 5). In PARADIGM-HF, patients with severe angina were at significantly higher risk of non-fatal MI and angina when compared to patients with angina. Patients with moderate angina were only at higher risk of UA (but not MI) and there was no association

between mild angina symptoms and either UA or MI. The results of the PARADIGM analysis suggest severity of angina rather than simply the presence of angina per se may be a stronger predictor of adverse outcomes.

The importance of angina on HF outcomes is less clear. In CORONA, patients with current angina were at higher risk of HF hospitalization compared to patients with no angina. This suggested chronic myocardial ischaemia (i.e. angina) might be responsible for worsening HF symptoms in some patients(3). However, no association between angina and HF outcomes was evident in CHARM. As discussed previously, this may reflect differences in the two trial populations or that I was only able to adjust for prior HF hospitalization in CHARM but not in CORONA(3, 5). The findings from PARADIGM-HF also highlight a third possibility. In PARADIGM-HF there was a borderline significant increase in HF hospitalization in patients with severe angina (but not mild or moderate angina) compared to patients with no angina. Neither CHARM nor CORONA collected data on severity of angina symptoms and it is possible the differences in severity of angina between the two studies accounted for this difference.

Patients with current angina in CORONA and CHARM and patients with mild or moderate angina in PARADIGM-HF were not at higher risk of CV or all-cause mortality. Only patients with severe angina in PARADIGM-HF were more at higher risk of CV or all-cause mortality.

One major limitation of all the analyses performed in my thesis is that they use data from randomised controlled trials. Selection bias is inevitable and the patient population may not be fully representative of a 'real world' population.

This is particularly true of CORONA, which was limited to patients over the age of 60. Another limitation of our studies was that we were unable to correlate symptoms with coronary angiography or objective tests looking for evidence of myocardial ischaemia. The latter would also have allowed us to examine the potential importance of asymptomatic myocardial ischaemia.

Nevertheless, a common theme that emerges is that symptomatic myocardial ischaemia or angina (particularly if it is severe) is a potentially important therapeutic target. STICH and the on-going REVIVED-BCIS2 trial excluded patients with severe angina (defined as ≥ CCS class 3), the group who could stand to benefit the most(77, 78, 81). As detailed previously, while patients with severe angina have been excluded from these trials on the basis of having an existing guideline recommendation for revascularization, the low rate of prior revascularization observed in PARADIGM-HF and earlier studies suggests that clinical practice does not follow this guideline recommendation. Whether this is indicative of the underlying coronary anatomy in patients with severe angina is not known and requires further research. Most importantly, prospective studies are needed to establish whether patients with angina stand to benefit from a targeted treatment strategy. Randomized controlled trials of medical anti-anginal therapy and coronary revascularisation (in patients with suitable anatomy) in patients with angina and HF might improve functional status and clinical outcomes.

References

1. McMurray JJ, Stewart S. Epidemiology, aetiology, and prognosis of heart failure. Heart. 2000;83(5):596-602.

2. Davies SW. Clinical presentation and diagnosis of coronary artery disease: stable angina. Br Med Bull. 2001;59:17-27.

3. Badar AA, Perez-Moreno AC, Jhund PS, Wong CM, Hawkins NM, Cleland JG, et al. Relationship between angina pectoris and outcomes in patients with heart failure and reduced ejection fraction: an analysis of the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA). Eur Heart J. 2014;35(48):3426-33.

4. Kjekshus J, Apetrei E, Barrios V, Böhm M, Cleland JG, Cornel JH, et al. Rosuvastatin in older patients with systolic heart failure. N Engl J Med. 2007;357(22):2248-61.

5. Badar AA, Perez-Moreno AC, Hawkins NM, Brunton AP, Jhund PS, Wong CM, et al. Clinical characteristics and outcomes of patients with angina and heart failure in the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) Programme. Eur J Heart Fail. 2015;17(2):196-204.

6. Solomon SD, Wang D, Finn P, Skali H, Zornoff L, McMurray JJ, et al. 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(15):2180-3.

7. Badar AA, Perez-Moreno AC, Hawkins NM, Jhund PS, Brunton AP, Anand IS, et al. Clinical Characteristics and Outcomes of Patients With Coronary Artery Disease and Angina: Analysis of the Irbesartan in Patients

With Heart Failure and Preserved Systolic Function Trial. Circ Heart Fail. 2015;8(4):717-24.

8. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008;359(23):2456-67.

9. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993-1004.

10. Lip GY, Gibbs CR, Beevers DG. ABC of heart failure: aetiology. BMJ. 2000;320(7227):104-7.

11. Gheorghiade M, Sopko G, De Luca L, Velazquez EJ, Parker JD, Binkley PF, et al. Navigating the crossroads of coronary artery disease and heart failure. Circulation. 2006;114(11):1202-13.

12. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. Nat Rev Cardiol. 2016;13(6):368-78.

13. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 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(27):2129-200.

14. Diamond GA. A clinically relevant classification of chest discomfort. J Am Coll Cardiol. 1983;1(2 Pt 1):574-5.

15. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable coronary artery

disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013;34(38):2949-3003.

16. Celik A, Karayakali M, Erkorkmaz U, Altunkas F, Karaman K, Koc F, et al. Presence of angina pectoris is related to extensive coronary artery disease in diabetic patients. Clin Cardiol. 2013;36(8):475-9.

17. Zaman MJ, Junghans C, Sekhri N, Chen R, Feder GS, Timmis AD, et al. Presentation of stable angina pectoris among women and South Asian people. CMAJ. 2008;179(7):659-67.

18. Junghans C, Sekhri N, Zaman MJ, Hemingway H, Feder GS, Timmis A. Atypical chest pain in diabetic patients with suspected stable angina: impact on diagnosis and coronary outcomes. Eur Heart J Qual Care Clin Outcomes. 2015;1(1):37-43.

19. McGill HC, McMahan CA, Herderick EE, Malcom GT, Tracy RE, Strong JP. Origin of atherosclerosis in childhood and adolescence. Am J Clin Nutr. 2000;72(5 Suppl):1307S-15S.

20. Wolk MJ, Bailey SR, Doherty JU, Douglas PS, Hendel RC, Kramer CM, et al. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic

Resonance, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2014;63(4):380-406.

21. Brush JE, Cannon RO, Schenke WH, Bonow RO, Leon MB, Maron BJ, et al. Angina due to coronary microvascular disease in hypertensive patients without left ventricular hypertrophy. N Engl J Med. 1988;319(20):1302-7.

22. Iriarte M, Caso R, Murga N, Faus JM, Sagastagoitia D, Molinero E, et al. Microvascular angina pectoris in hypertensive patients with left ventricular hypertrophy and diagnostic value of exercise thallium-201 scintigraphy. Am J Cardiol. 1995;75(5):335-9.

23. Dean J, Cruz SD, Mehta PK, Merz CN. Coronary microvascular dysfunction: sex-specific risk, diagnosis, and therapy. Nat Rev Cardiol. 2015;12(7):406-14.

24. Campeau L. The Canadian Cardiovascular Society grading of angina pectoris revisited 30 years later. Can J Cardiol. 2002;18(4):371-9.

25. https://www.sign.ac.uk/assets/sign151.pdf

26. Alfakih K, Greenwood JP, Plein S. The 2016 update to NICE CG95 guideline for the -investigation of new onset stable chest pain: more - innovation, but at a cost? Clin Med (Lond). 2017;17(3):209-11.

27. Roobottom C. Radical changes to the investigation of stable chest pain following the 2016 NICE update. Br J Radiol. 2018:20170694.

28. Banerjee A, Newman DR, Van den Bruel A, Heneghan C. Diagnostic accuracy of exercise stress testing for coronary artery disease: a systematic review and meta-analysis of prospective studies. Int J Clin Pract. 2012;66(5):477-92.

29. Hill J, Timmis A. Exercise tolerance testing. BMJ. 2002;324(7345):1084-7.

30. Mieres JH, Gulati M, Bairey Merz N, Berman DS, Gerber TC, Hayes SN, et al. Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease: a consensus statement from the American Heart Association. Circulation. 2014;130(4):350-79.

31. Gebker R, Schneeweis C. Stress testing in the obese: are we finally getting the bigger picture? JACC Cardiovasc Imaging. 2014;7(5):473-5.

32. Mordi IR, Badar AA, Irving RJ, Weir-McCall JR, Houston JG, Lang CC. Efficacy of noninvasive cardiac imaging tests in diagnosis and management of stable coronary artery disease. Vasc Health Risk Manag. 2017;13:427-37.

33. Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med. 2000;343(20):1445-53.

34. Marwick TH, Case C, Vasey C, Allen S, Short L, Thomas JD. Prediction of mortality by exercise echocardiography: a strategy for combination with the duke treadmill score. Circulation. 2001;103(21):2566-71.

35. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. J Am Coll Cardiol. 2008;52(21):1724-32.

36. Chen CC, Hsieh IC, Liu YC, Liu CY, Chan T, Wen MS, et al. The effect of calcium score on the diagnostic accuracy of coronary computed tomography angiography. Int J Cardiovasc Imaging. 2011;27 Suppl 1:37-42.

37. Berry C, Corcoran D, Hennigan B, Watkins S, Layland J, Oldroyd KG. Fractional flow reserve-guided management in stable coronary disease and acute myocardial infarction: recent developments. Eur Heart J. 2015;36(45):3155-64.

38. Puri R, Kapadia SR, Nicholls SJ, Harvey JE, Kataoka Y, Tuzcu EM. Optimizing outcomes during left main percutaneous coronary intervention with intravascular ultrasound and fractional flow reserve: the current state of evidence. JACC Cardiovasc Interv. 2012;5(7):697-707.

39. Shu dF, Dong BR, Lin XF, Wu TX, Liu GJ. Long-term beta blockers for stable angina: systematic review and meta-analysis. Eur J Prev Cardiol. 2012;19(3):330-41.

40. Belsey J, Savelieva I, Mugelli A, Camm AJ. Relative efficacy of antianginal drugs used as add-on therapy in patients with stable angina: A systematic review and meta-analysis. Eur J Prev Cardiol. 2015;22(7):837-48.

41. Juul-Möller S, Edvardsson N, Jahnmatz B, Rosén A, Sørensen S, Omblus R. Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. The Swedish Angina Pectoris Aspirin Trial (SAPAT) Group. Lancet. 1992;340(8833):1421-5.

42. Committee CS. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet. 1996;348(9038):1329-39.

43. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366(9493):1267-78.

44. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015;372(25):2387-97.

45. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med. 2018;379(22):2097-107.

46. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med. 2000;342(3):145-53.

47. Fox KM, Investigators EtOrocewPiscAd. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet. 2003;362(9386):782-8.

48. Braunwald E, Domanski MJ, Fowler SE, Geller NL, Gersh BJ, Hsia J, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. N Engl J Med. 2004;351(20):2058-68.

49. Pitt B, O'Neill B, Feldman R, Ferrari R, Schwartz L, Mudra H, et al. The QUinapril Ischemic Event Trial (QUIET): evaluation of chronic ACE inhibitor therapy in patients with ischemic heart disease and preserved left ventricular function. Am J Cardiol. 2001;87(9):1058-63.

50. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. Lancet. 2006;368(9535):581-8.

51. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med. 2007;356(15):1503-16.

52. Lam CS, Solomon SD. The middle child in heart failure: heart failure with mid-range ejection fraction (40-50%). Eur J Heart Fail. 2014;16(10):1049-55.

53. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation. 2016;133(4):e38-360.

54. Drazner MH. The transition from hypertrophy to failure: how certain are we? Circulation. 2005;112(7):936-8.

55. Drazner MH. The progression of hypertensive heart disease. Circulation. 2011;123(3):327-34.

56. Campbell RT, McMurray JJ. Comorbidities and differential diagnosis in heart failure with preserved ejection fraction. Heart Fail Clin. 2014;10(3):481-501.

57. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. J Am Coll Cardiol. 2004;43(3):317-27.

58. Hwang SJ, Melenovsky V, Borlaug BA. Implications of coronary artery disease in heart failure with preserved ejection fraction. J Am Coll Cardiol. 2014;63(25 Pt A):2817-27.

59. Mant J, Doust J, Roalfe A, Barton P, Cowie MR, Glasziou P, et al. Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care. Health Technol Assess. 2009;13(32):1-207, iii.

60. Roberts E, Ludman AJ, Dworzynski K, Al-Mohammad A, Cowie MR, McMurray JJ, et al. The diagnostic accuracy of the natriuretic peptides in heart failure: systematic review and diagnostic meta-analysis in the acute care setting. BMJ. 2015;350:h910.

61. Januzzi JL, Sakhuja R, O'donoghue M, Baggish AL, Anwaruddin S, Chae CU, et al. Utility of amino-terminal pro-brain natriuretic peptide testing for prediction of 1-year mortality in patients with dyspnea treated in the emergency department. Arch Intern Med. 2006;166(3):315-20.

62. Prastaro M, D'Amore C, Paolillo S, Losi M, Marciano C, Perrino C, et al. Prognostic role of transthoracic echocardiography in patients affected by heart failure and reduced ejection fraction. Heart Fail Rev. 2015;20(3):305-16.

63. Gupta DK, Solomon SD. Imaging in heart failure with preserved ejection fraction. Heart Fail Clin. 2014;10(3):419-34.

64. Steeds RP. Multimodality imaging in heart failure patients. Curr Opin Cardiol. 2013;28(2):209-15.

65. Lum YH, McKenzie S, Brown M, Hamilton-Craig C. Impact of Cardiac MRI in Heart Failure Patients referred to a Tertiary Advanced Heart Failure Unit: Improvements in Diagnosis and Management. Intern Med J. 2018.

66. Felker GM, Mentz RJ. Diuretics and ultrafiltration in acute decompensated heart failure. J Am Coll Cardiol. 2012;59(24):2145-53.

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

68. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med. 1996;334(21):1349-55.

69. Group CTS. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987;316(23):1429-35.

70. Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN, Investigators S. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991;325(5):293-302.

71. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011;364(1):11-21.

72. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010;376(9744):875-85.

73. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005;352(3):225-37.

74. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002;346(12):877-83.

75. Cleland JG, Abraham WT, Linde C, Gold MR, Young JB, Claude Daubert J, et al. An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. Eur Heart J. 2013;34(46):3547-56.

76. Chung ES, Katra RP, Ghio S, Bax J, Gerritse B, Hilpisch K, et al. Cardiac resynchronization therapy may benefit patients with left ventricular ejection fraction >35%: a PROSPECT trial substudy. Eur J Heart Fail. 2010;12(6):581-7.

77. Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, et al. Coronary-Artery Bypass Surgery in Patients with Ischemic Cardiomyopathy. N Engl J Med. 2016;374(16):1511-20.

78. Perera D, Clayton T, Petrie MC, Greenwood JP, O'Kane PD, Evans R, et al. Percutaneous Revascularization for Ischemic Ventricular Dysfunction: Rationale and Design of the REVIVED-BCIS2 Trial: Percutaneous Coronary Intervention for Ischemic Cardiomyopathy. JACC Heart Fail. 2018;6(6):517-26.

79. Kim RJ, Shah DJ. Fundamental concepts in myocardial viability assessment revisited: when knowing how much is "alive" is not enough. Heart. 2004;90(2):137-40.

80. Ling LF, Marwick TH, Flores DR, Jaber WA, Brunken RC, Cerqueira MD, et al. Identification of therapeutic benefit from revascularization in

patients with left ventricular systolic dysfunction: inducible ischemia versus hibernating myocardium. Circ Cardiovasc Imaging. 2013;6(3):363-72.

81. Velazquez EJ, Lee KL, Deja MA, Jain A, Sopko G, Marchenko A, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. N Engl J Med. 2011;364(17):1607-16.

82. Brown AM, Cleland JG. Influence of concomitant disease on patterns of hospitalization in patients with heart failure discharged from Scottish hospitals in 1995. Eur Heart J. 1998;19(7):1063-9.

83. Gustafsson F, Torp-Pedersen C, Burchardt H, Buch P, Seibaek M, Kjøller E, et al. Female sex is associated with a better long-term survival in patients hospitalized with congestive heart failure. Eur Heart J. 2004;25(2):129-35.

84. Thomas JT, Kelly RF, Thomas SJ, Stamos TD, Albasha K, Parrillo JE, et al. Utility of history, physical examination, electrocardiogram, and chest radiograph for differentiating normal from decreased systolic function in patients with heart failure. Am J Med. 2002;112(6):437-45.

85. Mentz RJ, Fiuzat M, Shaw LK, Phillips HR, Borges-Neto S, Felker GM, et al. Comparison of Clinical characteristics and long-term outcomes of patients with ischemic cardiomyopathy with versus without angina pectoris (from the Duke Databank for Cardiovascular Disease). Am J Cardiol. 2012;109(9):1272-7.

86. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. J Am Coll Cardiol. 1999;33(7):1948-55.

87. Smith GL, Masoudi FA, Vaccarino V, Radford MJ, Krumholz HM. Outcomes in heart failure patients with preserved ejection fraction: mortality, readmission, and functional decline. J Am Coll Cardiol. 2003;41(9):1510-8.

88. Barker WH, Mullooly JP, Getchell W. Changing incidence and survival for heart failure in a well-defined older population, 1970-1974 and 1990-1994. Circulation. 2006;113(6):799-805.

89. Rathore SS, Foody JM, Wang Y, Herrin J, Masoudi FA, Havranek EP, et al. Sex, quality of care, and outcomes of elderly patients hospitalized with heart failure: findings from the National Heart Failure Project. Am Heart J. 2005;149(1):121-8.

90. Murphy NF, Simpson CR, McAlister FA, Stewart S, MacIntyre K, Kirkpatrick M, et al. National survey of the prevalence, incidence, primary care burden, and treatment of heart failure in Scotland. Heart. 2004;90(10):1129-36.

91. Newton JD, Squire IB. Glucose and haemoglobin in the assessment of prognosis after first hospitalisation for heart failure. Heart. 2006;92(10):1441-6.

92. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med. 2006;355(3):260-9.

93. Bestetti RB, Yoshitake R, Cardoso TA, Freitas PF, Cordeiro JA, Theodoropoulos TA. Clinical characteristics and outcome of chronic ischemic heart failure in angina-free patients. Int J Cardiol. 2008;128(1):145-6.

94. Schellenbaum GD, Rea TD, Heckbert SR, Smith NL, Lumley T, Roger VL, et al. Survival associated with two sets of diagnostic criteria for congestive heart failure. Am J Epidemiol. 2004;160(7):628-35.

95. Carlsen CM, Bay M, Kirk V, Gøtze JP, Køber L, Nielsen OW. Prevalence and prognosis of heart failure with preserved ejection fraction and elevated N-terminal pro brain natriuretic peptide: a 10-year analysis from the Copenhagen Hospital Heart Failure Study. Eur J Heart Fail. 2012;14(3):240-7.

96. Spargias KS, Hall AS, Greenwood DC, Ball SG. beta blocker treatment and other prognostic variables in patients with clinical evidence of heart failure after acute myocardial infarction: evidence from the AIRE study. Heart. 1999;81(1):25-32.

97. Brophy JM, Dagenais GR, McSherry F, Williford W, Yusuf S. A multivariate model for predicting mortality in patients with heart failure and systolic dysfunction. Am J Med. 2004;116(5):300-4.

98. Mentz RJ, Broderick S, Shaw LK, Fiuzat M, O'Connor CM. Heart failure with preserved ejection fraction: comparison of patients with and without angina pectoris (from the Duke Databank for Cardiovascular Disease). J Am Coll Cardiol. 2014;63(3):251-8.

99. Ekman I, Cleland JG, Swedberg K, Charlesworth A, Metra M, Poole-Wilson PA. Symptoms in patients with heart failure are prognostic predictors: insights from COMET. J Card Fail. 2005;11(4):288-92.

100. van den Heuvel AF, van Veldhuisen DJ, van der Wall EE, Blanksma PK, Siebelink HM, Vaalburg WM, et al. Regional myocardial blood flow reserve impairment and metabolic changes suggesting myocardial ischemia in patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol. 2000;35(1):19-28.

101. Lam CS, Carson PE, Anand IS, Rector TS, Kuskowski M, Komajda M, et al. Sex differences in clinical characteristics and outcomes in elderly patients

with heart failure and preserved ejection fraction: the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. Circ Heart Fail. 2012;5(5):571-8.

102. Greenberg B, Lottes SR, Nelson JJ, Lukas MA, Fowler MB, Massie BM, et al. Predictors of clinical outcomes in patients given carvedilol for heart failure. Am J Cardiol. 2006;98(11):1480-4.

103. Ahmed A, Zile MR, Rich MW, Fleg JL, Adams KF, Love TE, et al. Hospitalizations due to unstable angina pectoris in diastolic and systolic heart failure. Am J Cardiol. 2007;99(4):460-4.

104. Richter CA, Kalenga JC, Rowe BH, Bresee LC, Tsuyuki RT. Practice patterns and outcomes in patients presenting to the emergency department with acute heart failure. Can J Cardiol. 2009;25(6):e173-8.

105. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. 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 J Heart Fail. 2012;14(8):803-69.

106. Kjekshus J, Dunselman P, Blideskog M, Eskilson C, Hjalmarson A, McMurray JV, et al. A statin in the treatment of heart failure? Controlled rosuvastatin multinational study in heart failure (CORONA): study design and baseline characteristics. Eur J Heart Fail. 2005;7(6):1059-69.

107. Wedel H, McMurray JJ, Lindberg M, Wikstrand J, Cleland JG, Cornel JH, et al. 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(3):281-91.

108. Chugh SS, Reinier K, Teodorescu C, Evanado A, Kehr E, Al Samara M, et al. Epidemiology of sudden cardiac death: clinical and research implications. Prog Cardiovasc Dis. 2008;51(3):213-28.

109. Fishman GI, Chugh SS, Dimarco JP, Albert CM, Anderson ME, Bonow RO, et al. Sudden cardiac death prediction and prevention: report from a National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop. Circulation. 2010;122(22):2335-48.

110. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 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(41):2793-867.

111. Shen L, Jhund PS, Petrie MC, Claggett BL, Barlera S, Cleland JGF, et al. Declining Risk of Sudden Death in Heart Failure. N Engl J Med. 2017;377(1):41-51.

112. Group IS. Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial. Lancet. 2002;359(9314):1269-75.

113. Bart BA, Shaw LK, McCants CB, Fortin DF, Lee KL, Califf RM, et al. Clinical determinants of mortality in patients with angiographically diagnosed

ischemic or nonischemic cardiomyopathy. J Am Coll Cardiol. 1997;30(4):1002-8.

114. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet. 2003;362(9386):759-66.

115. Swedberg K, Pfeffer M, Granger C, Held P, McMurray J, Ohlin G, et al. Candesartan in heart failure--assessment of reduction in mortality and morbidity (CHARM): rationale and design. Charm-Programme Investigators. J Card Fail. 1999;5(3):276-82.

116. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJ, Swedberg KB, et al. Predictors of mortality and morbidity in patients with chronic heart failure. Eur Heart J. 2006;27(1):65-75.

117. Felker GM, Shaw LK, O'Connor CM. A standardized definition of ischemic cardiomyopathy for use in clinical research. J Am Coll Cardiol. 2002;39(2):210-8.

118. Rusinaru D, Houpe D, Szymanski C, Lévy F, Maréchaux S, Tribouilloy C. Coronary artery disease and 10-year outcome after hospital admission for heart failure with preserved and with reduced ejection fraction. Eur J Heart Fail. 2014;16(9):967-76.

119. Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, et al. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the framingham heart study of the national heart, lung, and blood institute. Circulation. 2009;119(24):3070-7.

120. Judge KW, Pawitan Y, Caldwell J, Gersh BJ, Kennedy JW. Congestive heart failure symptoms in patients with preserved left ventricular systolic function: analysis of the CASS registry. J Am Coll Cardiol. 1991;18(2):377-82.

121. Carson P, Massie BM, McKelvie R, McMurray J, Komajda M, Zile M, et al. The irbesartan in heart failure with preserved systolic function (I-PRESERVE) trial: rationale and design. J Card Fail. 2005;11(8):576-85.

122. McMurray JJ, Carson PE, Komajda M, McKelvie R, Zile MR, Ptaszynska A, et al. Heart failure with preserved ejection fraction: clinical characteristics of 4133 patients enrolled in the I-PRESERVE trial. Eur J Heart Fail. 2008;10(2):149-56.

123. Adabag S, Rector TS, Anand IS, McMurray JJ, Zile M, Komajda M, et al. A prediction model for sudden cardiac death in patients with heart failure and preserved ejection fraction. Eur J Heart Fail. 2014;16(11):1175-82.

124. Komajda M, Carson PE, Hetzel S, McKelvie R, McMurray J, Ptaszynska A, et al. 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(1):27-35.

125. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol. 2013;62(4):263-71.

126. Adabag S, Smith LG, Anand IS, Berger AK, Luepker RV. Sudden cardiac death in heart failure patients with preserved ejection fraction. J Card Fail. 2012;18(10):749-54.

127. Jolicœur EM, Dunning A, Castelvecchio S, Dabrowski R, Waclawiw MA, Petrie MC, et al. Importance of angina in patients with coronary disease, heart failure, and left ventricular systolic dysfunction: insights from STICH. J Am Coll Cardiol. 2015;66(19):2092-100.

128. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz M, Rizkala AR, et al. Baseline characteristics and treatment of patients in prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF). Eur J Heart Fail. 2014;16(7):817-25.

129. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). Eur J Heart Fail. 2013;15(9):1062-73.

130. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Køber L, Squire IB, et al. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. Eur Heart J. 2013;34(19):1404-13.

131. McAlister FA, Oreopoulos A, Norris CM, Graham MM, Tsuyuki RT, Knudtson M, et al. Exploring the treatment-risk paradox in coronary disease. Arch Intern Med. 2007;167(10):1019-25.

132. Yan AT, Yan RT, Tan M, Fung A, Cohen EA, Fitchett DH, et al. Management patterns in relation to risk stratification among patients with non-ST elevation acute coronary syndromes. Arch Intern Med. 2007;167(10):1009-16.

133. Motivala AA, Cannon CP, Srinivas VS, Dai D, Hernandez AF, Peterson ED, et al. Changes in myocardial infarction guideline adherence as a function of patient risk: an end to paradoxical care? J Am Coll Cardiol. 2011;58(17):1760-5.

134. Jedrzkiewicz S, Goodman SG, Yan RT, Welsh RC, Kornder J, DeYoung JP, et al. Temporal trends in the use of invasive cardiac procedures for non-ST segment elevation acute coronary syndromes according to initial risk stratification. Can J Cardiol. 2009;25(11):e370-6.

135. Spertus JA, Furman MI. Translating evidence into practice: are we neglecting the neediest? Arch Intern Med. 2007;167(10):987-8.

Appendix 1: Assessment of bias in prior studies examining prognostic importance of angina in patients with Heart Failure

	Study	
Domain	**Mentz (2012)**	**Mentz (2014)**
Representativeness (expressed cohort)	No	No
Selection (non-exposed cohort)	No	No
Ascertainment of exposures	Yes	Yes
Demonstration outcome of interest not present at start of study	Yes	Yes
Comparability of cohorts on basis of design or analysis	Yes	Yes
Assessment of outcome	Yes	Yes
Follow-up sufficient for outcomes to occur	Yes	Yes
Adequacy of follow-up	Not stated	Not stated