Prevalence of coronary artery disease and coronary microvascular dysfunction in heart failure with preserved ejection fraction

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Abstract

Background

Heart failure (HF) is a major cause of morbidity and mortality worldwide. HF with preserved ejection fraction (HFpEF) now accounts for around half of the HF population. To date, no treatments for HFpEF have proven effect and outcomes have not improved in recent decades. The heterogeneity of the HFpEF population and the failure of randomised controlled trials (RCTs) to demonstrate effective therapies has led to attempts to identify sub-phenotypes of HFpEF which may respond to targeted therapies.

Recent studies suggest that epicardial coronary artery disease (CAD) and coronary microvascular dysfunction (CMD) may play an important role in a substantial group of patients with HFpEF. A novel paradigm has been proposed suggesting that endothelium-dependent CMD may play a key role in the unifying pathophysiology of HFpEF.

I performed a systematic review of the literature describing the prevalence of epicardial CAD and CMD in HFpEF populations. Most studies were retrospective observational and population-based studies with inconsistent definitions of HF, preserved left ventricular ejection fraction (LVEF) and CAD. Studies which documented CAD angiographically were almost exclusively performed in highly-selected convenience cohorts. Consequently, prevalence estimates of CAD in HFpEF varied considerably between studies. Similarly, studies assessing CMD in HFpEF reported inconsistent results due to variable definitions of CMD and methods of assessing coronary microvascular function. Therefore, the prevalence of epicardial CAD and CMD have not been prospectively and systematically studied in an unselected HFpEF population.

Aims

The main aims of this study were to determine the prevalence of obstructive epicardial CAD, CMD and previous myocardial infarction (MI) in an unselected cohort of patients hospitalised with HFpEF using reference standard invasive investigations.

Methods

This was a prospective, multicentre, observational study of patients hospitalised with HFpEF. All patients recruited had a confirmed diagnosis of HFpEF according to the 2016 European Society of Cardiology (ESC) HF guidelines. Participants underwent invasive coronary angiography with guidewire-based assessment of coronary flow reserve (CFR) and the index of microcirculatory resistance (IMR), followed by vasoreactivity testing with intra-coronary acetylcholine. This allowed the comprehensive assessment of epicardial and microvascular structure and function to determine the prevalence of CAD, CMD and coronary endothelial dysfunction in the cohort. Adenosine perfusion cardiac magnetic resonance (CMR) imaging was also performed to assess the burden of myocardial infarction (MI), diffuse fibrosis and inducible ischaemia in the study population. Patients were followed up by electronic medical record linkage for a minimum of 12 months.

Results

Of 2285 near-consecutive patients hospitalised with suspected HF, 628 were confirmed to have a diagnosis of HFpEF, and 106 HFpEF patients met the inclusion criteria and agreed to participate in the study. A total of 83 participants underwent invasive coronary angiography or CMR. Seventy-five participants underwent invasive coronary angiography, 62 had guidewire-based coronary physiology testing, and 41 underwent vasoreactivity testing. Fifty-two participants underwent CMR and 44 had both invasive coronary angiography and CMR. Twenty-three patients did not proceed to the study investigations, predominantly due to a decline in health, functional status or renal function making proceeding with the study investigations inappropriate or unsafe.

In this unselected hospitalised HFpEF cohort, the prevalence of obstructive epicardial CAD on invasive assessment was 51% (95% confidence interval [CI] 39-62%); half of patients with obstructive epicardial disease had no clinical history of CAD. On invasive coronary physiological testing, 41 patients (66% [95% CI 53-77%]) had endothelium-independent CMD, and 10 (24% [95% CI 13-40%]) had endothelium-dependent CMD. Overall, 91% of participants had evidence of macrovascular and/or microvascular CAD. Of those who underwent CMR, 27%

(95% CI 16-41%) had evidence of previous MI and 32% (95% CI 19-48%) had inducible ischaemia. Over half of patients with CMR-proven MI had no history of clinically apparent MI.

Over a median follow-up period of 18 months, study participants with obstructive epicardial CAD had significantly more hospitalisations (for any cause, a cardiovascular cause or HF) than those without obstructive CAD. There was no significant difference in outcomes between those with or without endothelium-independent or -dependent CMD.

Conclusion

Both epicardial CAD and CMD are common in the HFpEF population, and there is a high prevalence of clinically unrecognised obstructive epicardial CAD and previous MI. Patients with obstructive epicardial CAD had significantly more hospitalisations than those without obstructive disease. Treatments for epicardial CAD (e.g. coronary revascularisation) might improve quality of life and reduce hospitalisations in HFpEF patients with CAD.

Although it has been hypothesised that CMD in HFpEF is the result of endothelial dysfunction, it appears to be predominantly due to endothelium-independent mechanisms. This may have important implications for future treatments directed at CMD in patients with HFpEF.

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Author's Declaration

The work presented in this thesis was performed during my employment as a Clinical Research Fellow in the Institute of Cardiovascular and Medical Sciences at the BHF Glasgow Cardiovascular Research Centre, University of Glasgow. I was supervised by Professor John McMurray and Professor Mark Petrie.

I performed the screening and recruitment, including obtaining informed consent, of all patients who participated in the study. I completed all electronic case report forms from the index admission and subsequent investigation results. I constructed the electronic database for the study and performed all statistical analyses.

I organised and assisted in all cardiac magnetic resonance (CMR) scans and invasive coronary assessments. I analysed all CMR scans, which were also independently assessed by Professor Colin Berry. The invasive coronary assessments were performed by Professor Keith Oldroyd, Dr Paul Rocchiccioli and Dr Mitchell Lindsay. I performed quantitative coronary angiography on the coronary angiograms and 20% of the angiograms were blindly analysed by Dr Thomas Ford. To date, work from this study has been presented at the European Society for Cardiology (ESC) Congress 2019.

I confirm that this thesis has been composed by me solely and that it has not been submitted for any other degree at the University of Glasgow or any other institution. The writing of this thesis is entirely my own work. All sources of information within this thesis are specifically acknowledged.

Christopher J. Rush

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Publications relating to this work

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Abbreviations

ACh	Acetylcholine
ADHERE-I	Acute decompensated heart failure national registry - international
ADHERE-US	Acute decompensated heart failure national registry - US
AF	Atrial fibrillation
AHA	American Heart Association
ACCF	American College of Cardiology Foundation
ACEI	Angiotensin converting enzyme inhibitor
AKI	Acute kidney injury
ALT	Alanine transaminase
AMI	Acute myocardial infarction
APPROACH	Alberta provincial project for outcome assessment in coronary heart disease
AR	Aortic regurgitation
ARB	Angiotensin receptor blocker
ARIC	Atherosclerosis risk in communities registry
ARNI	Angiotensin receptor-neprilysin inhibitor
AS	Aortic stenosis
ASIAN-HF	Asian sudden cardiac death in heart failure
AST	Aspartate transaminase
ATPase	Adenosine triphosphatase
ATTEND	Acute decompensated heart failure syndromes registry
AV	Atrioventricular
BADAPIC	Base de datos de pacientes con insuficiencia cardíaca registry
BARI	Bypass angioplasty revascularization investigation trial
BEAT	Bucindolol evaluation in acute myocardial infarction trial
BMI	Body mass index
BNP	B-type natriuretic peptide
BSA	Body surface area
bSSFP	Balanced steady-state free precession
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease

CASS	Coronary artery surgery study
CBF	Coronary blood flow
CCB	Calcium channel blocker
CCS	Canadian Cardiovascular Society
CCU	Coronary care unit
CFR	Coronary flow reserve
cGMP	Cyclic guanosine monophosphate
CHARM-Preserved	Candesartan in heart failure assessment of reduction in mortality and morbidity-Preserved
CHART-2	Chronic heart failure analysis and registry in the Tohoku district-2 study
CHF	Chronic heart failure
CHQC	Cleveland health quality choice program
CI	Cardiac index
CI	Confidence interval
Cl^-	Chloride
CMD	Coronary microvascular dysfunction
CK	Creatine kinase
CKD	Chronic kidney disease
CK-MB	Creatine kinase myocardial band
CM	Clinical modification
CMR	Cardiac magnetic resonance
CNHF	Competence network heart failure
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPT	Cold pressor testing
CRC	Clinical research center
CREDO-Kyoto CABG-2	Coronary revascularization demonstrating outcome study in Kyoto coronary artery bypass grafting registry cohort-2
CRP	C-reactive protein
CRS	Coronary revascularisation status
CRUSADE	Can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the American College of Cardiology/American Heart Association guidelines

CT	Computed tomography
CTA	Computed tomography angiography
CV	Cardiovascular
CVD	Cerebrovascular disease
CVF	Collagen volume fraction
CVR	Coronary vascular resistance
CVRN	Cardiovascular research network
CXR	Chest x-ray
DBP	Diastolic blood pressure
DHF	Diastolic heart failure
DIAMOND-CHF	Dofetilide-congestive heart failure
DIG	Digitalis investigation group
DIG-PEF	Digitalis intervention group-preserved ejection fraction
DPP-4	Dipeptidyl peptidase-4
DRG	Diagnosis-related group
E_a	Arterial elastance
EAHFE	Epidemiology of acute heart failure in emergency departments
E_{es}	End-systolic elastance
ECG	Electrocardiogram
ECHOS	Echocardiography and heart outcome study
eCRF	Electronic case report form
ECV	Extracellular volume
EFFECT	Enhanced feedback for effective cardiac treatment study
eGFR	Estimated glomerular filtration rate
EHFS-I	Euro heart failure study-I
eNOS	Endothelial nitric oxide synthase
ESC	European Society of Cardiology
ESC-HF-LT	European Society of Cardiology heart failure long-term registry
Ex-DHF-P	Effects of exercise training on different quality of life dimensions in heart failure with preserved ejection fraction
FAME	Fractional flow reserve versus angiography for multivessel evaluation
FFR	Fractional flow reserve

FiO_2	Fraction of inspired oxygen
FLASH	Fast low-angle shot
$F_{passive}$	Cardiomyocyte resting tension
GCP	Good Clinical Practice
GJNH	Golden Jubilee National Hospital
GLP-1	Glucagon-like peptide-1
GP	General practitioner
GRI	Glasgow Royal Infirmary
GTN	Glyceryl trinitrate
GWTG-HF	Get with the guidelines heart failure registry
Hb	Haemoglobin
HbA1c	Glycated haemoglobin
HF	Heart failure
HFH	Heart failure hospitalisation
HLA	Horizontal long-axis
HFmrEF	Heart failure with mid-range ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
HR	Heart rate
hsTnI	High-sensitivity troponin I
ICAM-1	Intercellular adhesion molecule-1
ICD	International Classification of Diseases
IHD	Ischaemic heart disease
IL-6	Interleukin-6
IMR	Index of microcirculatory resistance
INDIE-HFpEF	Inorganic nitrite delivery to improve exercise capacity in heart failure with preserved ejection fraction
INOCA	Ischaemia with no obstructive coronary artery disease
I-PREFER	Identification of patients with heart failure and preserved systolic function: an epidemiological regional study
I-PRESERVE	Irbesartan in patients with heart failure and preserved ejection fraction
ISCHEMIA	International study of comparative health effectiveness with medical and invasive approaches

ISD	Information Services Division
IQR	Interquartile range
ITISHOPE4HF	Implementation of telerehabilitation in support of home-based physical exercise for heart failure
IV	Intravenous
JVD	Jugular venous distention
JVP	Jugular venous pressure
K^+	Potassium
KorAHF	Korean acute heart failure registry
KPMCP	Kaiser Permanente medical care program
KPNW	Kaiser Permanente Northwest
KPSC	Kaiser Permanente Southern California
LAD	Left anterior descending coronary artery
LA	Left atrium
LAE	Left atrial enlargement
LCx	Left circumflex coronary artery
LDL-C	Low-density lipoprotein cholesterol
LGE	Late gadolinium enhancement
LURIC	Ludwigshafen risk and cardiovascular health study
LV	Left ventricle
LVEDD	Left ventricular end-diastolic dimension
LVEDP	Left ventricular end-diastolic pressure
LVEDV	Left ventricular end-diastolic volume
LVEDVI	Indexed left ventricular end-diastolic volume
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end-systolic dimension
LVESV	Left ventricular end-systolic volume
LVH	Left ventricular hypertrophy
LVOT	Left ventricular outflow tract
LVSV	Left ventricular stroke volume
MACCE	Major adverse cardiac and cerebrovascular events
MAP	Mean arterial pressure
MAPSE	Mitral annular plane systolic excursion
MBG	Myocardial blush grade
MCV	Mean corpuscular volume

MetS-CHF	Metabolic syndrome-chronic heart failure study
MFR	Myocardial flow reserve
MI	Myocardial infarction
MOLLI	Modified Look-Locker inversion-recovery
MPRI	Myocardial-perfusion reserve index
MPS	Myocardial perfusion scintigraphy
MR	Mitral regurgitation
MRA	Mineralocorticoid receptor antagonist
MRI	Magnetic resonance imaging
MS	Mitral stenosis
MVA	Microvascular angina
MVD	Microvascular density
Na^+	Sodium
NCDR PINNACLE	National cardiovascular data practice innovation and clinical excellence registry
NEAT-HFpEF	Nitrate's effect on activity tolerance in heart failure with preserved ejection fraction
NHC	National heart care project
NHLBI	National heart, lung and blood institute
NIS	National inpatient sample
NO	Nitric oxide
NOX	Nicotinamide adenine dinucleotide phosphate oxidase
NSAID	Non-steroidal anti-inflammatory drug
NSTEACS	Non-ST-elevation acute coronary syndrome
NSTEMI	Non-ST-elevation myocardial infarction
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
NYHA	New York Heart Association
$ONOO^-$	Peroxynitrite
OPTIMIZE-HF	Organized program to initiate lifesaving treatment in hospitalized patients with heart failure
OR	Odds ratio
Pa	Mean aortic pressure
PA	Pulmonary artery
PAD	Peripheral arterial disease

PARAGON-HF	Prospective comparison of angiotensin receptor-neprilysin inhibitor with angiotensin receptor blocker in heart failure with preserved ejection fraction
PARAMOUNT	Prospective comparison of angiotensin receptor-neprilysin inhibitor with angiotensin receptor blocker on management of heart failure with preserved ejection fraction
PCI	Percutaneous coronary intervention
PCWP	Pulmonary capillary wedge pressure
Pd	Mean distal coronary pressure
PEP-CHF	Perindopril in elderly people with chronic heart failure
PET	Positron emission tomography
PH	Pulmonary hypertension
PKA	Protein kinase A
PKC	Protein kinase C
PKG	Protein kinase G
PND	Paroxysmal nocturnal dyspnoea
PR	Pulmonary regurgitation
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROMIS-HFpEF	Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction
PSIR	Phase-sensitive inversion-recovery
PTCA	Percutaneous transluminal coronary angioplasty
PTP	Pre-test probability
QCA	Quantitative coronary angiography
QEUH	Queen Elizabeth University Hospital
RAAS	Renin-angiotensin-aldosterone system
RAH	Royal Alexandra Hospital
RAP	Right atrial pressure
RAPID-HF	Rate-adaptive atrial pacing in diastolic heart failure
RCA	Right coronary artery
RCT	Randomised controlled trial
REC	Research Ethics Committee
REDUCE LAP-HF II	Reduce elevated left atrial pressure in patients with heart failure-II

RELAX	Phosphodiesterase-5 inhibition to improve clinical status and exercise capacity in diastolic heart failure
REVIVED-BCIS2	Percutaneous revascularisation for ischaemic ventricular dysfunction
RHI	Reactive hyperaemia index
RICA	Registro de Insuficiencia Cardiaca
RIKS-HIA	Register of information and knowledge about Swedish heart intensive care admissions
ROS	Reactive oxygen species
RR	Respiratory rate
RV	Right ventricle
RVEDD	Right ventricular end-diastolic dimension
RVEDV	Right ventricular end-diastolic volume
RVEF	Right ventricular ejection fraction
RVESV	Right ventricular end-systolic volume
RVSP	Right ventricular systolic pressure
RVSV	Right ventricular stroke volume
SA	Short axis
SBP	Systolic blood pressure
SD	Standard deviation
SECRET-II	Study of the effects of caloric restriction and exercise training in patients with heart failure and a normal ejection fraction-II
SENIORS	Study of the effects of nebivolol intervention on outcomes and rehospitalization in seniors with heart failure
SERCA2a	Sarcoplasmic reticulum calcium adenosine triphosphatase
sGC	Soluble guanylate cyclase
SGLT-2	Sodium-glucose co-transporter-2
SHF	Systolic heart failure
SOCRATES-PRESERVED	Soluble guanylate cyclase stimulator in heart failure patients with preserved ejection fraction
SPECT	Single photon emission computed tomography
SpO_2	Oxygen saturation
sST2	Soluble somatostatin receptor type 2
STICH	Surgical treatment for ischemic heart failure

SWEDEHEART	Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies registry
SwedeHF	Swedish heart failure registry
SYNTAX	Synergy between percutaneous coronary intervention with Taxus and cardiac surgery
TAPSE	Tricuspid annular plane systolic excursion
TFC	Thrombolysis in myocardial infarction frame count
TGF-β	Tissue growth factor-β
TIMI	Thrombolysis in myocardial infarction
T_{mn}	Mean transit time
TNF-α	Tissue necrosis factor-α
TOPCAT	Treatment of preserved cardiac function heart failure with an aldosterone antagonist
TR	Tricuspid regurgitation
TTDE	Transthoracic Doppler echocardiography
uACR	Urinary albumin-to-creatinine ratio
ULN	Upper limit of normal
VA	Veterans Affairs
VALIANT	Valsartan in acute myocardial infarction trial
VCAM	Vascular cell adhesion molecule
VLA	Vertical long-axis
WCC	White cell count
WET-HF	West Tokyo heart failure registry
WMI	Wall motion index
WMSI	Wall motion score index

Chapter 1 Introduction

1.1 What is heart failure with preserved ejection fraction?

1.1.1 Definition of heart failure with preserved ejection fraction

Heart failure (HF) is a clinical syndrome resulting from abnormal cardiac structure and/or function. It is characterised by typical symptoms, predominantly dyspnoea and fatigue, which may be associated with clinical signs of fluid overload. HF can be classified based upon the duration of symptoms, symptom severity, and the left ventricular (LV) ejection fraction (LVEF).

HF can present with the rapid onset of symptoms requiring hospital admission, termed "acute HF", or with a more insidious course in ambulatory patients, known as "chronic HF". Acute HF may present "*de novo*" or, more commonly, patients with chronic HF may experience a sudden deterioration in their clinical condition, termed "acute decompensated HF".

The severity of HF symptoms is most commonly described using the New York Heart Association (NYHA) classification (Table 1-1). This system grades patients in relation to their functional limitation due to HF symptoms. NYHA functional class predicts prognosis and is independent of duration of symptoms or LVEF.[1]

NYHA class	Patient symptoms
I	No limitation of physical activity. Ordinary physical activity dose not cause undue fatigue, palpitation or dyspnoea.
II	Slight limitation of physical activity. Comfortable at rest but ordinary physical activity results in fatigue, palpitation or dyspnoea.
III	Marked limitation of physical activity. Comfortable at rest but less than ordinary activity results in fatigue, palpitation or dyspnoea.
IV	Unable to carry out any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

NYHA, New York Heart Association.

Table 1-1: NYHA functional classification of HF.

HF has two broad phenotypes, based upon the LVEF. This is the most widely used estimate of left ventricular systolic function and is typically measured using echocardiography. The classification of HF in relation to LVEF is considered important for several reasons, including differences in patient demographics, prognosis and response to therapies. International guidelines distinguish between two major HF phenotypes in relation to LVEF. There is consensus between guidelines, randomised controlled trials (RCTs) and epidemiological studies that HF with reduced ejection fraction (HFrEF) represents HF in the presence of an LVEF of ≤40%. The definition of HF with preserved ejection fraction (HFpEF), however, is more contentious. The LVEF threshold used to define HFpEF varies between studies, ranging from 40% to 55%. The European Society of Cardiology (ESC) defines HFpEF as HF in the presence of a LVEF ≥50% (Table 1-2),[2] whereas the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) considers patients with an intermediate LVEF in the range of 40% to 50% to have "borderline" HFpEF (Table 1-3).[3] The ESC defines this intermediary group by a new term called "HF with mid-range ejection fraction" (HFmrEF).[2] Patients in this "grey area" appear to have similar characteristics and response to therapies as those with HFrEF, but outcomes more comparable to HFpEF.[4,5]

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms and signs	Symptoms and signs	Symptoms and signs
	2	LVEF <40%	LVEF 40-49%	LVEF ≥50%
	3	-	1. Elevated levels of natriuretic peptides; 2. At least one additional criterion: a. Relevant structural heart disease (LVH and/or LAE), b. Diastolic dysfunction.	1. Elevated levels of natriuretic peptides; 2. At least one additional criterion: a. Relevant structural heart disease (LVH and/or LAE), b. Diastolic dysfunction.

HF, heart failure; HFmrEF, HF with mid-range ejection fraction; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; LAE, left atrial enlargement; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy.

Table 1-2: Definitions of HFpEF, HFmrEF and HFrEF (ESC).

Classification	LVEF	Description
HFrEF	≤40%	Also referred to as systolic HF. Randomised clinical trials have mainly enrolled patients with HFrEF and it is only in these patients that efficacious therapies have been demonstrated to date.
HFpEF	≥50%	Also referred to as diastolic HF. Several different criteria have been used to further define HFpEF. The diagnosis of HFpEF is challenging because it is largely one of excluding other potential non-cardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.
HFpEF, borderline	41-49%	These patients fall into a borderline or intermediate groups. Their characteristics, treatment patterns and outcomes appear similar to those of patients with HFpEF.

HF, heart failure; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; LAE, LVEF, left ventricular ejection fraction.

Table 1-3: Definitions of HFrEF and HFpEF (ACCF/AHA).

1.1.2 Epidemiology of heart failure with preserved ejection fraction

HF is a major public health issue, affecting over 26 million people worldwide.[6] It is a significant cause of morbidity and mortality and a large burden on global healthcare systems. In Europe and North America, HF affects 1-3% of the population and accounts for 1-2% of healthcare expenditure. Although the incidence of HF appears to have fallen over recent years, the prevalence continues to rise.[7] Epidemiological studies suggest that the prevalence of HFpEF in relation to HFrEF has increased over recent years, with some reporting that HFpEF now accounts for over 50% of HF.[8] However, most of these studies rely on clinical diagnostic codes (e.g. International Classification of Diseases [ICD] coding), therefore, there is potential for both under- and over-diagnosis of HFpEF. Furthermore, the LVEF threshold used to define HFpEF in these studies is not consistent and many patients with other cardiac conditions generally not considered to have HFpEF (e.g. acute coronary syndromes, significant primary valve disease) are defined as such in many studies.

The clinical characteristics of patients with HFpEF are distinct from those with HFrEF. Patients with HFpEF are generally older, more frequently female, and have a higher burden of comorbidities.[9] The ageing population is thought to

represent a major reason for the female predisposition, higher rate of associated comorbidities, and the increasing prevalence of HFpEF when compared to HFrEF.[10]

Outcomes relating to HFpEF vary depending on study design, clinical setting and LVEF threshold used to define HFpEF. Patients with HFpEF have significantly poorer outcomes when compared with populations with similar age and comorbidity profiles without HF.[11] Epidemiological studies consistently report high mortality rates in HFpEF cohorts, with a 1-year mortality of 20-29% and 5-year mortality of over 50%.[8,12,13] Conversely, HFpEF RCTs report much lower annualised mortality rates of around 5% per year.[14–16] Although the prognosis in HFpEF and HFrEF were thought to be similar, more recent studies suggest that patients with HFpEF have better outcomes than those with HFrEF.[17] Despite this, hospitalisation and mortality rates in HFpEF remain high and, in contrast to HFrEF, outcomes have not improved over recent decades.[18]

1.1.3 Diagnosis of heart failure with preserved ejection fraction

The diagnosis of HFpEF can be challenging, especially in ambulatory patients. The symptoms of HF are non-specific and patients with HFpEF have a high incidence of comorbidities which can mimic HF symptoms (e.g. atrial fibrillation [AF], anaemia, chronic lung disease, chronic kidney disease [CKD]). Furthermore, incident HFpEF may be characterised by several distinct clinical phenotypes.

Hospitalised patients with HFpEF typically present with dyspnoea and signs of congestion on clinical examination. The diagnosis of HFpEF must be confirmed by typical cardiac imaging findings (e.g. preserved LVEF, left atrial [LA] enlargement, LV hypertrophy [LVH], evidence of increased LV filling pressures and/or pulmonary hypertension [PH]) and elevated natriuretic peptides.[2] However, ambulatory patients frequently experience symptoms only on exertion and often have no overt clinical signs of fluid overload. In these patients, echocardiography at rest may not reveal typical findings consistent with elevated LV filling pressures and natriuretic peptides may be normal due to lower LV wall stress. Invasive and non-invasive studies report that, in HFpEF patients, LV filling pressures may be normal at rest, but increase dramatically

with exercise.[19,20] Diastolic stress testing may, therefore, be required to confirm or exclude the diagnosis of HFpEF in patients presenting with unexplained exertional dyspnoea.

An alternative presentation of HFpEF is that of a breathless patient with preserved LVEF and evidence of significant PH on echocardiography. These patients frequently undergo invasive assessment to identify the cause of PH and around one third are found to have pulmonary venous hypertension due to chronic HF (Group 2 PH).[21] This HFpEF subgroup represents an advanced stage of the condition and these patients appear to have a poor prognosis (see below).

1.1.4 Comorbidities in heart failure with preserved ejection fraction

HFpEF is a heterogeneous condition characterised by advancing age and the presence of multiple cardiovascular (CV) and non-CV comorbidities. Epidemiological studies and RCTs report a greater burden of hypertension, AF, obesity, chronic lung disease, anaemia, and diabetes in patients with HFpEF than those with HFrEF.[18] The high frequency of comorbidities, many of which can cause similar symptoms and signs to HF, has led some to suggest that these patients do not have HF at all.[22] However, a comparison of trial data of patients with HFpEF versus those with CV conditions without HF found that the poor outcomes associated with HFpEF did not appear to be explained by age or comorbidities.[11]

The failure of RCTs in HFpEF to demonstrate effective treatments has led to attempts to identify sub-phenotypes of HFpEF which may respond favourably to specific therapies. Patients with HFpEF can be phenotyped according to associated comorbidities for which treatments exist (e.g. hypertension, AF, coronary artery disease [CAD]).[23] Furthermore, in a prospective study of 397 patients, Shah and colleagues used phenomapping to identify three distinct HFpEF sub-phenotypes: younger patients with lower natriuretic peptide levels (‘early HFpEF’); obese patients with diabetes and obstructive sleep apnoea; and older patients with CKD, high natriuretic peptide levels and PH (‘advanced HFpEF’).[24]

1.1.5 Pathophysiology of heart failure with preserved ejection fraction

HFpEF is a diverse clinical syndrome and cannot be readily attributed to a single aetiological factor. Consequently, its pathophysiology is not well understood. The major underlying pathological mechanism is thought to be LV diastolic dysfunction. However, various other processes have been implicated, including subtle LV systolic dysfunction, ventricular-arterial stiffening, LA dysfunction and AF, right ventricular (RV) dysfunction and pulmonary vascular disease, ventricular interdependence, chronotropic incompetence, peripheral factors and endothelial dysfunction.

LV diastolic dysfunction

Most patients with HFpEF have evidence of diastolic dysfunction at rest.[25,26] However, in HFpEF patients with exertional symptoms, diastolic dysfunction may only become apparent with exercise.[19] Conversely, elderly patients without HF frequently have echocardiographic evidence of diastolic dysfunction at rest.[27] Diastolic dysfunction may, therefore, play a key role in HFpEF, but other mechanisms are evidently involved.

LV diastolic function is determined by both active relaxation and passive filling. Active relaxation is regulated by calcium homeostasis and the phosphorylation state or levels of specific proteins (e.g. phospholamban) that modify the sarcoplasmic reticulum calcium ATPase pump (SERCA2a).[28] Active relaxation requires the removal of cytosolic calcium during diastole by SERCA2a, which is inhibited by phospholamban in its unphosphorylated state. Active relaxation is an energy-dependent process, therefore, it is vulnerable to ischaemia.[29]

Diastolic function is also influenced by the passive elastic properties of the LV. Increased passive stiffness was previously thought to be due to myocardial fibrosis and changes in extracellular matrix composition, however, diastolic stiffness is frequently elevated in patients without fibrosis, and acute changes to diastolic stiffness are seen in the context of ischaemia or changes in the compliance of the large sarcomeric protein, titin.[30,31]

Cardiomyocyte resting tension is highly dependent on the function of titin, which acts as a physiological molecular spring.[32] The properties of titin can be altered by the expression of different isoforms and by post-translational phosphorylation. Titin exists in two isoforms: N2B (shorter, stiffer) and N2BA (longer, more compliant), and there appears to be a shift toward expression of the N2B-isoform in patients with HFpEF.[33] Phosphorylation of titin can occur at various sites. Protein kinase A (PKA), protein kinase G (PKG), calcium/ calmodulin-dependent protein kinase IIδ, and extracellular signal-regulated kinase-2 signalling improve titin compliance and, therefore, decrease cardiomyocyte resting tension.[34–36] Conversely, phosphorylation by protein kinase C (PKC) reduces titin compliance, resulting in increased resting tension.[37] Endomyocardial biopsy studies have revealed low PKA and PKG activity in HFpEF, and their administration has been shown to acutely reduce cardiomyocyte resting tension in vitro.[38,39]

LV systolic dysfunction

Despite having a preserved LVEF, studies using sensitive measures of LV contractility (e.g. strain imaging using speckle tracking echocardiography) demonstrate that HFpEF patients have subtle LV systolic dysfunction.[40] Patients with HFpEF also exhibit an inability to increase their LVEF and cardiac output with physiological stress, which may contribute to exercise intolerance.[41,42]

Ventricular-arterial stiffening

Patients with HFpEF have increased LV systolic stiffness (end-systolic elastance, E_{es}) and arterial stiffness (arterial elastance, E_a) when compared with healthy controls.[43,44] Elevated LV and arterial stiffness result in a steep end-systolic pressure-volume relationship in HFpEF. This leads to an augmented blood pressure response to changes in preload or afterload, predisposing to both hypotensive and hypertensive crises. Normally, there is a decrease in the E_a/E_{es} ratio with exercise, due to a marked increase in E_{es} with only a small increase in E_a. In HFpEF, this decrease is attenuated, resulting in an impaired cardiac output response to exercise.

LA dysfunction and AF

The LA plays an important role in LV diastolic filling, both as a conduit and via atrial contraction. Patients with HFpEF have chronically elevated LA pressure with resulting atrial dilatation, loss of atrial contractile reserve, and electrical remodelling. This predisposes to AF, which affects up to two-thirds of patients with HFpEF.[45] Whether AF is simply a sign of more advanced HFpEF or if it plays a role in the progression of HFpEF is uncertain.

RV dysfunction and pulmonary vascular disease

In a community-based study of 244 HFpEF patients, the prevalence of PH (defined as an echocardiography-derived pulmonary artery [PA] systolic pressure >35mmHg) was 83%.[46] Chronic LA pressure overload results in pulmonary venous hypertension and post-capillary PH. However, the patients with HFpEF frequently have "out-of-proportion" PH, suggesting an element of pre-capillary PH. It is unclear whether this is a result of reactive changes to the pulmonary vasculature due to longstanding pulmonary venous hypertension, or whether other processes (e.g. primary pulmonary arterial disease) are involved. RV dysfunction in HFpEF is associated with male sex, AF and CAD.[47] It can be a consequence of chronic PH, however, there is also evidence of increased RV diastolic stiffness and abnormal RV-PA coupling.[48] Both PH and RV dysfunction are independent predictors of poor outcomes in HFpEF.[49]

Ventricular interdependence

The pericardium contributes around 40% to the LV end-diastolic pressure under resting conditions.[50] As described above, HFpEF is frequently associated with LA and RV dysfunction and dilatation. This leads to an increase in cardiac size, which may augment ventricular interdependence in patients with HFpEF. The role of pericardial constraint and ventricular interdependence in the pathophysiology of HFpEF is currently unknown.

Chronotropic incompetence

Studies suggest that over half of patients with HFpEF have evidence of chronotropic incompetence, suggestive of autonomic dysfunction.[51,52] Beta-blockers and ivabradine have failed to show benefit in HFpEF, possibly due to

exacerbation of chronotropic incompetence.[4,53] The role of rate-responsive pacing in HFpEF patients with chronotropic incompetence has yet to be established.

Peripheral factors

Various studies have suggested that skeletal muscle abnormalities may contribute to exercise intolerance in some patients with HFpEF.[54,55] Patients with HFpEF have lower lean body mass, increased intramuscular fat content, fewer type I (slow-twitch) fibres, and microvascular rarefaction when compared with healthy controls. Interestingly, the benefits of exercise training in HFpEF seem to be mediated via peripheral, rather than central, mechanisms (i.e. improved skeletal muscle and peripheral microvascular function).[56]

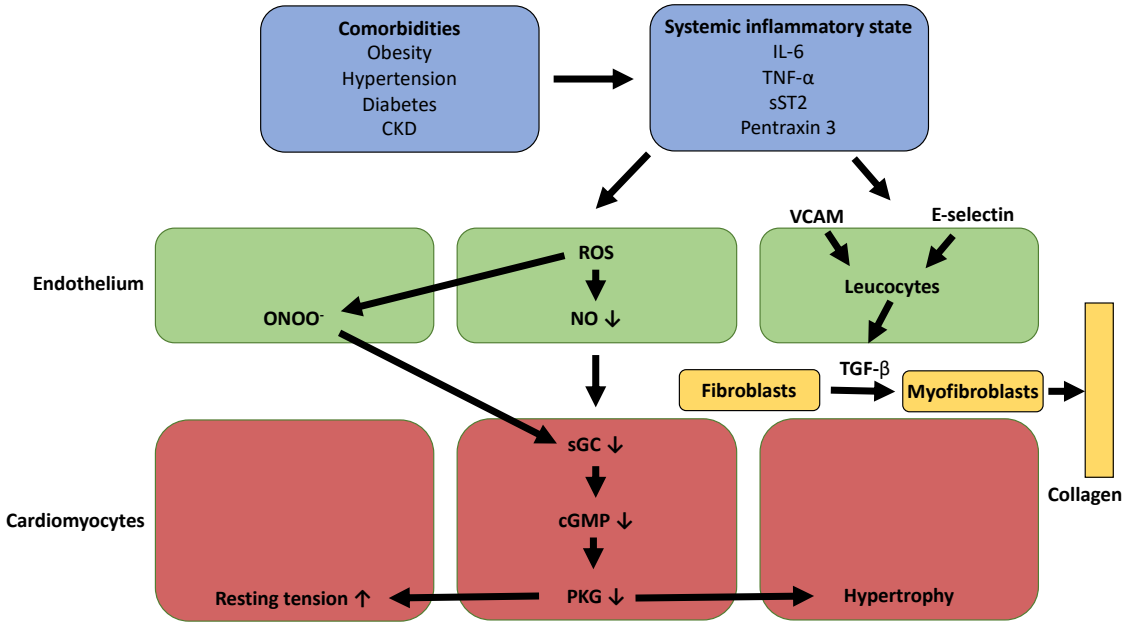
Endothelial dysfunction

That endothelial dysfunction plays a pivotal role in the pathogenesis of HFpEF has attracted a great deal of attention recently. Some studies have reported more peripheral endothelial dysfunction in patients with HFpEF compared to hypertensive and healthy controls.[41,57] However, this finding has not been observed in all HFpEF studies.[58]

Is there a unifying pathophysiological paradigm of HFpEF?

Hypertension is very common in the HFpEF population and, traditionally, it has been thought to be central to the pathogenesis of HFpEF.[59] Longstanding hypertension causes activation of the renin-angiotensin-aldosterone system (RAAS) and afterload excess, with resultant LV remodelling, LVH and diastolic dysfunction. This leads to LA hypertension and dilatation (with or without AF), with pulmonary venous hypertension and, eventually, to right heart dysfunction. However, most patients with HFpEF do not have a history of longstanding poorly-controlled hypertension and over 40% do not have LVH.[60] Furthermore, the neutral outcomes for several trials of RAAS antagonists do not lend support to the hypertensive heart disease hypothesis. Whilst hypertension evidently plays an important role in HFpEF, it does not explain the underlying pathophysiology in the majority of patients.

A novel paradigm has been proposed suggesting that endothelial dysfunction plays a central role in the global pathophysiology of HFpEF.[61] This hypothesises that multimorbidity induces a systemic inflammatory process, with coronary microvascular endothelial inflammation and dysfunction. This results in reduced nitric oxide (NO) bioavailability, cyclic guanosine monophosphate (cGMP) content, and PKG activity in adjacent cardiomyocytes. Low PKG activity favours cardiomyocyte hypertrophy and increase resting tension via hypophosphorylation of titin. Both stiff cardiomyocytes and interstitial fibrosis result in LV diastolic dysfunction and HF (Figure 1-1).



cGMP, cyclic guanosine monophosphate; CKD, chronic kidney disease; IL-6, interleukin-6; $ONOO^-$, peroxynitrite; NO, nitric oxide; PKG, protein kinase G; ROS, reactive oxygen species; sGC, soluble guanylate cyclase; sST2, soluble somatostatin receptor type 2; TGF-ß, tissue growth factor-ß; TNF-α, tissue necrosis factor-α; VCAM, vascular cell adhesion molecule.

Figure 1-1: Microvascular paradigm in HFpEF.

This concept is based on findings from five studies of human endomyocardial biopsies.[30,38,39,62,63] Aside from the small numbers of patients included in the studies, the patients studied represent a highly-selected group. The majority of patients were referred for endomyocardial biopsy because of suspicion of infiltrative cardiomyopathy and, in one study, five out of 12 of the patients included were cardiac transplant recipients.[30] The mean age of patients was considerably younger than the typical HFpEF population and, in all but one of the studies, men comprised a majority. Furthermore, patients with important comorbidities, such as CAD and AF, were frequently excluded. Consequently,

extrapolating the findings of these small highly selected populations to a universal pathophysiological paradigm for HFpEF should be considered carefully.

Given the heterogeneity of the HFpEF population, it is unlikely that an overarching pathophysiological model will be identified. As described above, HFpEF is a complex and diverse condition characterised by multimorbidity and abnormalities in many aspects of CV structure and function. Patients with HFpEF may exhibit a number of functional impairments, and the relative contributions of each factor differ between patients.

1.1.6 Treatment of heart failure with preserved ejection fraction

To date, no treatment has been shown to provide clear prognostic benefit in patients with HFpEF. International guidelines for HFpEF are currently based on expert consensus opinion. These recommend the use of diuretics to improve symptoms and signs of fluid retention and the optimal treatment of associated comorbidities (e.g. hypertension and CAD).[2,3]

Therapies targeting the RAAS system in HFpEF

Randomised trials testing the effect of RAAS antagonists in HFpEF have consistently failed to show benefit. One moderately large randomised trial (PEP-CHF) showed that treatment with the ACE inhibitor perindopril had no effect on the primary composite endpoint of all-cause mortality or HF hospitalisation in elderly patients with HFpEF.[16] Two large RCTs also failed to demonstrate benefit in composite primary endpoints with the angiotensin receptor blockers candesartan (CHARM-Preserved) and irbesartan (I-PRESERVE).[15,64] Similarly, the mineralocorticoid receptor antagonist spironolactone showed a neutral effect on the composite primary outcome of CV death, aborted cardiac arrest, or HF hospitalisation in the TOPCAT trial.[14] *Post hoc* analyses have demonstrated marked regional variations in TOPCAT, with patients enrolled in Russia and Georgia having much lower event rates in the placebo group than those enrolled in the Americas. The majority of patients enrolled in Russia and Georgia were included on the basis of a previous HF hospitalisation, rather than elevated natriuretic peptide levels, raising concerns that a significant proportion of patients in the trial did not have HFpEF.[65] In an analysis restricted to those

enrolled in the Americas, treatment with spironolactone appeared to be beneficial, however, the *post hoc* nature of this analysis means this should be considered with caution.[66]

Therapies targeting NO-cGMP-PKG signalling in HFpEF

Several studies assessing therapies targeting the systemic inflammatory paradigm of HFpEF have failed to show any convincing benefit. In this hypothesis, low cGMP activity is thought to play a central role in the pathophysiology of HFpEF, however, several studies of therapies which (directly or indirectly) increase cGMP levels have failed to meet their primary endpoints. The soluble guanylate cyclase stimulator vericiguat failed to demonstrate benefit in SOCRATES-PRESERVED.[67] When compared with placebo, the phosphodiesterase-5 inhibitor sildenafil did not improve exercise capacity or clinical status in HFpEF patients in the RELAX trial.[68] Treatment with the organic NO donor isosorbide mononitrate reduced activity levels (NEAT-HFpEF)[69], and inhaled inorganic nitrite also failed to improve exercise capacity (INDIE-HFpEF)[70] in patients with HFpEF.

Neprilysin inhibition prevents the breakdown of biologically active natriuretic peptides, leading to increased intracellular cGMP. The neprilysin inhibitor sacubitril in combination with the angiotensin receptor blocker valsartan (sacubitril-valsartan) did not show benefit over valsartan alone in HFpEF in a large multicentre RCT (PARAGON-HF).[71]

Therapies targeting heart rate and exercise intolerance in HFpEF

Lower heart rates increase the duration of diastole and can facilitate greater LV filling. However, this may exacerbate chronotropic incompetence, which is prevalent in HFpEF (discussed above). The beta-blocker nebivolol was assessed in a pre-specified subgroup analysis of a RCT including patients with both HFrEF and HFpEF (SENIORS), showing a neutral effect on a composite of all-cause mortality and CV hospitalisation.[72] The effect of digoxin in HFpEF was assessed in a moderately large RCT (the ancillary DIG trial) with no effect on the primary endpoint of HF mortality or HF hospitalisation.[73] The I_f current blocker ivabradine has also been evaluated in phase II HFpEF trials with mixed results.[53,74,75] A small study is currently underway to assess the effect of rate-

responsive pacing in HFpEF patients with chronotropic incompetence (RAPID-HF, NCT02145351).

One small study demonstrated symptomatic benefit with exercise training in HFpEF (Ex-DHF-P).[76] However, the generalisability of the study has been questioned as it recruited a relatively young cohort of patients (mean age 65 years) and the exercise protocol used is not suitable for many frailer patients with HFpEF. Further studies are ongoing (e.g. SECRET-II [NCT02636439], ITISHOPE4HF [NCT03183323]).

Therapies targeting LA hypertension in HFpEF

Elevated LA pressure is thought to be one of the central pathophysiological findings in HFpEF. Reducing LA pressure by creating an interatrial shunt has been studied in an observational cohort of 64 patients with improved haemodynamics and quality of life.[77] A small, sham-controlled, blinded RCT found reduced exercise PA wedge pressure with this technique[78], and a large RCT is in progress (REDUCE LAP-HF II, NCT02600234).

1.1.7 Summary

Effective treatment strategies for HFpEF represent a large unmet clinical need. Its identification can be challenging and there remains inconsistency and debate regarding which diagnostic criteria should be used. The pathophysiology of HFpEF remains incompletely understood and it is unlikely that there will be a single unifying paradigm.

The “one-size-fits-all” approach to RCTs in HFpEF has so far failed to demonstrate any clinically meaningful benefit. Future trials are likely to focus on assessing targeted therapies in sub-phenotypes of HFpEF.

1.2 What is coronary artery disease?

1.2.1 Functional anatomy of the coronary circulation

The coronary arterial system can be considered to have three compartments with differing functions (Figure 1-2).[79] The proximal compartment comprises the epicardial coronary arteries (diameter 500 μm–5 mm) which, under normal circumstances, offer minimal resistance (~10%) to coronary blood flow (CBF) and function primarily as conduit vessels.[80] The intermediate compartment is represented by the epicardial pre-arterioles (diameter 100-500 μm), which maintain arteriolar pressure in response to changes in wall shear stress and transmural pressure (myogenic response) and contribute ~25% to coronary vascular resistance (CVR).[81] The distal compartment consists of the intramyocardial arterioles (diameter <100 μm), which regulate CBF in response to metabolites (metabolic regulation) and represent the largest proportion (~55%) of total CVR. The capillaries and venules mainly function as capacitance vessels and contribute a further ~10% to CVR. The coronary microcirculation consists of the pre-arterioles and arterioles and, therefore, represents the majority of resistance to CBF.

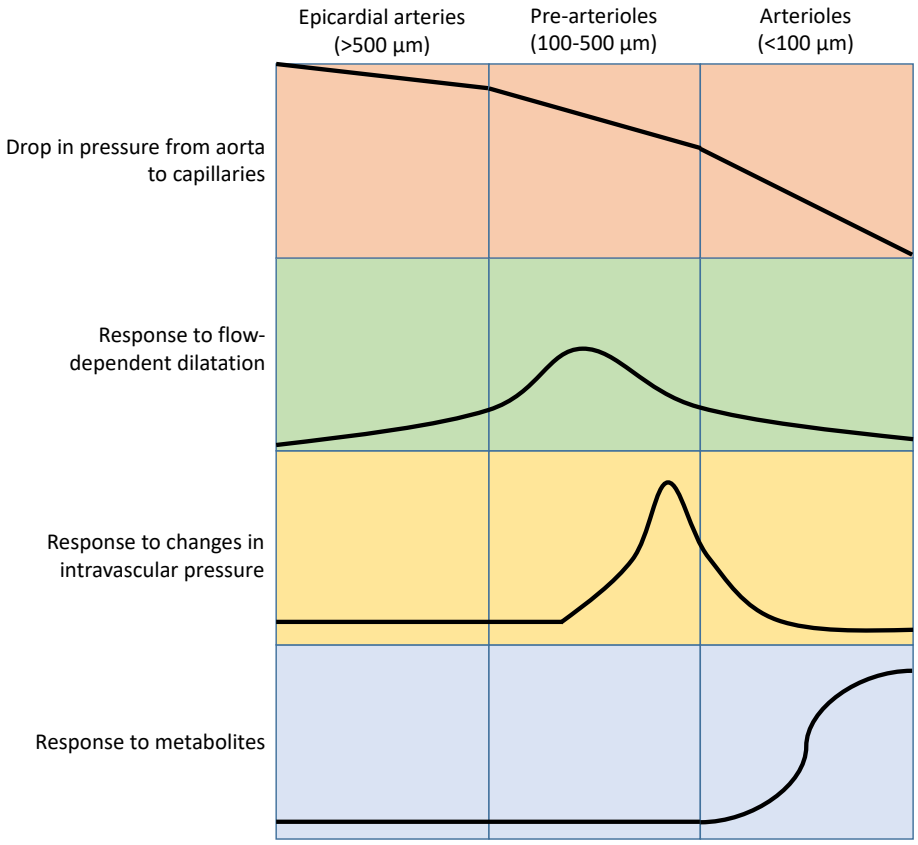


Figure 1-2: Functional anatomy of the coronary arterial system.

1.2.2 Definition of coronary artery disease

Coronary artery disease (CAD) is traditionally defined as obstructive atherosclerotic narrowing of the epicardial coronary arteries that prevents adequate perfusion of the myocardium. Anatomical thresholds for the severity of epicardial CAD vary, however, a widely used cut-off for defining obstructive epicardial disease is a stenosis of ≥70% in a main coronary artery (>2.5 mm diameter) and ≥50% of the left main coronary artery in one angiographic projection.[82] However, frequently patients have a clinical diagnosis of CAD without imaging of their coronary arteries. Therefore, the term "CAD" encompasses a broad range of clinical phenotypes, including: (i) patients with current or previous stable angina or "anginal equivalent" symptoms; (ii) patients with imaging evidence of obstructive or non-obstructive epicardial CAD (with or without symptoms); (iii) patients with current or previous myocardial infarction (MI); and (iv) patients who have previously undergone coronary revascularisation.[83]

1.2.3 Diagnosis of coronary artery disease

Clinical features

CAD can frequently be diagnosed on the basis of clinical history alone. Nevertheless, further investigations are usually required to confirm the diagnosis, exclude alternative diagnoses, and assess the severity of disease.[83,84] The characteristic clinical presentation of CAD is of angina pectoris. This may be typical (i.e. all three of the following: classical retrosternal chest discomfort, provoked by exertion or stress, relieved by rest and/or nitrates) or atypical (two of these criteria). Patients with CAD may present with alternative symptoms, usually exertional dyspnoea, caused by myocardial ischaemia ("anginal equivalents"). This is a particularly common presentation in female patients, older patients, and those with diabetes.[85–87]

Non-invasive diagnostic testing

Current guidelines suggest further investigation of suspected CAD depends on the pre-test probability (PTP) of CAD, based on the patient's presentation, age and sex (Table 1-4).[88] In patients with possible angina but with a low probability of significant epicardial CAD (<5-15%), further diagnostic testing is generally not advocated. Patients with a low-intermediate PTP, coronary computed tomography (CT) angiography (CTA) is the diagnostic test of choice, due to its high negative predictive value. In patients with a high-intermediate probability of obstructive epicardial CAD, non-invasive functional imaging is indicated. The imaging modality used is generally dependent on local expertise and availability. In patients with a high PTP, CAD should be diagnosed clinically, and medical therapy initiated. Further testing is generally not indicated for diagnosis, however, may be used for risk stratification. Frequently, patients in this group with significant symptoms and/or high-risk features should proceed directly to invasive coronary angiography.

	Typical		Atypical		Non-anginal		Dyspnoea	
Age	Men	Women	Men	Women	Men	Women	Men	Women
30-39	3%	5%	4%	3%	1%	1%	0%	3%
40-49	22%	10%	10%	6%	3%	2%	12%	3%
50-59	32%	13%	17%	6%	11%	3%	20%	9%
60-69	44%	16%	26%	11%	22%	6%	27%	14%
70+	52%	27%	34%	19%	24%	10%	32%	12%

Table 1-4: Pre-test probabilities of obstructive CAD.

Coronary computed tomography angiography

Coronary CTA has a high sensitivity and negative predictive value, but lower specificity and positive predictive value for the identification of epicardial CAD.[89] The specificity of coronary CTA is significantly reduced in the presence of severe coronary calcification.[90] The image quality and interpretation are also highly dependent on adequate breath holding, body mass index (BMI), and heart rate and rhythm. Coronary CTA is, therefore, of particular use in patients with a low-intermediate PTP of significant CAD in whom good image quality can be expected.

Exercise electrocardiography

Due to its widespread availability and ease, exercise ECG is routinely used as the initial diagnostic test in patients with suspected CAD. Although non-invasive stress imaging is preferred, exercise ECG can still play a role in patients with an intermediate PTP of CAD, in whom it has high specificity (85-90%).[83,91] However, it has a low sensitivity (45-50%), it is not of diagnostic value in the presence of significant resting ECG abnormalities, and it is frequently inconclusive due to a submaximal test or equivocal ECG changes. Despite its limitations, exercise ECG is frequently used for risk stratification in patients with CAD. The prognosis for patients with a normal exercise ECG and a low clinical risk is excellent, whereas patients with a high-risk test have an annual CV mortality of >3%.[92]

Non-invasive functional imaging

Non-invasive functional imaging techniques have comparable sensitivities and specificities.[83] They are most useful in patients with a high-intermediate PTP of CAD, and include:

- Stress echocardiography – with exercise or pharmacological stress (e.g. dobutamine).

- Myocardial perfusion scintigraphy with single photon emission computed tomography (MPS with SPECT) – ^{99m}Tc with SPECT and exercise or pharmacological stress (e.g. adenosine, dipyridamole).

- Stress cardiac magnetic resonance (CMR) imaging – first-pass contrast-enhanced perfusion CMR (e.g. adenosine) or CMR for stress-induced wall motion abnormalities (e.g. dobutamine).

Invasive coronary angiography

Invasive coronary angiography is the traditional reference standard for the diagnosis of epicardial CAD and the distribution and extent of epicardial CAD on angiography has prognostic importance. In the Coronary Artery Surgery Study (CASS) registry of medically-managed CAD patients with preserved LVEF, the 12-year survival rate was 91% with normal coronary arteries, 74% with one-vessel disease, 59% with two-vessel disease and 50% with three-vessel disease.[93]

Patients with significant stenosis of the left main coronary artery or left anterior descending (LAD) artery have a poor prognosis when treated medically.[94] However, the anatomic assessment of coronary stenoses using coronary angiography has several limitations. Visual assessment of CAD may be inaccurate due to a variety of anatomical (e.g. diffuse disease or multiple stenoses in proximity) or procedural reasons (e.g. lesion foreshortening, angulations, eccentricity). As a result, there is a poor correlation between visually-assessed coronary stenosis severity and the physiological significance of a stenosis.[95,96] In the FAME trial, only 35% of coronary stenoses with an angiographic severity of 50-70% on quantitative coronary angiography were flow-limiting on physiological testing.[97] Even in lesions with a visual severity of 71-90%, 20% were not functionally significant. Therefore, visual assessment of coronary stenosis severity may result in both the under- and over-estimation of the functional significance of epicardial CAD.

Fractional flow reserve

Fractional flow reserve (FFR) is a pressure-derived index of the maximal blood flow in a coronary artery in the presence of a stenosis compared to the maximal flow in the absence of a stenosis. During hyperaemia, coronary resistance is minimised, and blood flow is linearly related to coronary pressure within the physiological range of coronary perfusion pressures.[98] In order to assess the haemodynamic significance of an epicardial coronary stenosis, a pressure-sensitive coronary guidewire is positioned distal to the stenosis and hyperaemia is achieved with the administration of intravenous adenosine. FFR is calculated from the mean distal coronary pressure (Pd) indexed to the mean aortic pressure (Pa) obtained simultaneously during hyperaemia (FFR = hyperaemic Pd/Pa). The theoretical FFR value in a normal coronary artery without obstruction to blood flow is a ratio of 1.0. A threshold of ≤0.80 is used to define a haemodynamically significant lesion.[97] FFR is commonly used to assess stenoses of intermediate severity or where the severity of a stenosis is ambiguous (e.g. diffuse CAD).

1.2.4 Treatment of coronary artery disease

The treatment of CAD patients involves the management of lifestyle factors, control of CV risk factors, pharmacological therapy and revascularisation.

Lifestyle factors

Smoking is a strong independent CV risk factor and patients with CAD who smoke should be encouraged to quit.[99] Observational data suggest that smoking cessation is associated with a one-third reduction in mortality following MI.[100] Patients should be encouraged to maintain a healthy diet and undertake regular physical exercise. Cardiac rehabilitation programmes can be effective in reducing mortality and hospitalisation in patients with CAD.[101]

Management of associated comorbidities

Patients with hypertension and CAD should be adequately treated to achieve a target blood pressure of <140/90 mmHg. CAD patients with diabetes should aim to achieve an HbA1c of <53 mmol/L.[102]

Pharmacological management

Aspirin and statin therapy form the cornerstone of secondary prevention in patients with CAD. Both are recommended for all CAD patients for the prevention of CV events.[83,91] The ESC considers patients with CAD to be a very high CV risk and recommends an LDL-C target of <1.4 mmol/L (or ≥50% reduction if the target level cannot be achieved).[103]

Various medications are used in the symptomatic relief of anginal symptoms. These can be used alone or in combination. International guidelines recommend the use of beta-blockers, calcium channel blockers (CCBs) and short-acting nitrates as first-line therapy, with other agents (e.g. ivabradine, long-acting nitrates) recommended if patients who have contraindications to first-line agents, do not tolerate them or remain symptomatic.[83,91] However, a recent meta-analysis found a lack of data comparing the efficacy of anti-anginal agents but no evidence of superiority of one drug over another in the treatment of angina.[104]

Coronary revascularisation

In patients with stable CAD, coronary revascularisation can be considered for symptomatic improvement and/or prognostic benefit. In patients with ongoing angina (or "anginal equivalent") symptoms despite optimal medical therapy, revascularisation of haemodynamically significant stenosis can provide symptomatic relief.[105,106] Revascularisation has previously been demonstrated to have prognostic benefit over medical therapy alone in the following circumstances:

- Left main stem or proximal LAD stenosis >50% (with an abnormal FFR or documented ischaemia)[107–109]
- >10% ischaemia on non-invasive functional testing or abnormal FFR[110,111]
- Two- or three-vessel disease (>50% stenosis) and an LVEF ≤35% (with abnormal FFR or documented ischaemia)[109,112]
- Single remaining patent coronary artery with a stenosis >50% (with abnormal FFR or documented ischaemia)[113]

The aim of coronary intervention is to achieve complete revascularisation, which is associated with significantly better outcomes when compared with incomplete revascularisation.[114] The decision for percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG) is dependent on various patient and anatomical factors. The presence of significant comorbidities, frailty, less complex CAD (SYNTAX score 0-22), and surgical contraindications (e.g. porcelain aorta) favour a PCI strategy. Conversely, CABG is generally preferred in patients with diabetes, low LVEF (≤35%), complex CAD (SYNTAX score ≥23), severe coronary calcification, or a requirement of concomitant cardiac surgery.[113]

The recently presented ISCHEMIA trial (AHA 2019, Chicago, IL, USA) has challenged the current guideline recommendations for revascularisation in stable CAD. This study randomised 5,179 patients with stable CAD and moderate to severe ischaemia on non-invasive stress testing to routine invasive therapy or medical therapy and failed to show prognostic benefit from a routine invasive

approach over optimal medical therapy. A symptomatic improvement was observed in those with angina; however, the trial was not sham controlled so this finding could be biased by the placebo effect. Patients with left main CAD, NYHA III or IV HF, an LVEF <35%, recent acute coronary syndrome and highly symptomatic patients were excluded so these findings do not apply to these groups.

To date, no RCTs have evaluated the impact of coronary revascularisation in patients with HFpEF. In patients with HFrEF and CAD, the STICH trial failed to demonstrate survival benefit with CABG (versus optimal medical therapy) over a median follow-up of 4.6 years.[115] However, over extended follow-up (median 9.8 years), all-cause mortality, CV mortality and CV hospitalisations were significantly lower in those treated with CABG.[112] A small RCT assessing the role of PCI in patients with HFrEF and CAD is currently underway (REVIVED-BCIS2).[116]

1.2.5 Summary

CAD encompasses a broad range of clinical phenotypes but is generally defined by the presence of obstructive atherosclerotic narrowing of the epicardial coronary arteries. Invasive coronary angiography (with or without FFR) is the reference standard for diagnosis of obstructive epicardial CAD. Various treatment options are available, including management of CV risk factors, pharmacological therapies, PCI and CABG.

There is evidence that coronary revascularisation provides prognostic benefit in selected patients with CAD, including those with HFrEF. To date, no RCTs have investigated the role of revascularisation in HFpEF.

1.3 What is coronary microvascular dysfunction?

Conventionally, myocardial ischaemia is thought to be a consequence of epicardial atherosclerotic CAD. However, it has become increasingly recognised that abnormalities in coronary microvascular function can cause or contribute to ischaemia in various situations. Over one-third of patients undergoing elective coronary angiography for the investigation of angina have no obstructive epicardial CAD.[117] This group includes patients with coronary microvascular and/or endothelial dysfunction.

1.3.1 Definition of coronary microvascular dysfunction

Coronary microvascular dysfunction (CMD) is defined as a mismatch of myocardial blood supply and oxygen consumption due to a dysfunction of the coronary microvessels with a diameter <500 μm.[79] The pathophysiology of CMD is not well understood. It can be the result of several pathophysiological mechanisms, including structural alterations (e.g. vascular remodelling, vascular rarefaction, perivascular fibrosis) and functional abnormalities (e.g. endothelial dysfunction, vascular smooth muscle dysfunction). The relative importance of each of these mechanisms varies depending on the aetiology, but they frequently coexist in the same patient.

CMD is currently subcategorised into four distinct types depending on the clinical setting (Table 1-5).[118] CMD in the absence of myocardial disease or obstructive CAD (type 1 CMD) is usually associated with CV risk factors, such as hypertension and diabetes mellitus. This form of microvascular dysfunction is thought to be due to functional abnormalities and appears to be at least partially reversible. Type 2 CMD occurs in the presence of myocardial diseases (e.g. hypertrophic or dilated cardiomyopathy). This subtype is generally the result of structural alterations, such as vascular remodelling, and it is unclear whether this process is reversible. CMD in the context of obstructive epicardial CAD (type 3 CMD) can occur in chronic CAD or acute coronary syndrome, and various functional and structural factors may be implicated. In certain circumstances, specific interventions can limit or prevent CMD in this context. The fourth subtype represents iatrogenic CMD, typically following coronary revascularisation. The mechanisms involved are coronary vasoconstriction and distal embolisation,

which can result in both functional and structural changes. There is evidence to suggest that vasoconstriction can be corrected with pharmacological therapy and distal embolisation can be prevented or reduced with specific interventions.

	Clinical setting	Main pathogenetic mechanisms
Type 1: in the absence of myocardial diseases and obstructive CAD	Risk factors Microvascular angina	Endothelial dysfunction Smooth muscle cell dysfunction Vascular remodeling
Type 2: in myocardial diseases	Hypertrophic cardiomyopathy Dilated cardiomyopathy Anderson-Fabry's disease Amyloidosis Myocarditis Aortic stenosis	Vascular remodeling Smooth muscle cell dysfunction Extramural compression Luminal obstruction
Type 3: in obstructive CAD	Stable angina Acute coronary syndrome	Endothelial dysfunction Smooth muscle cell dysfunction Luminal obstruction
Type 4: iatrogenic	Percutaneous coronary intervention Coronary artery bypass grafting	Luminal obstruction Autonomic dysfunction

CAD, coronary artery disease.

Table 1-5: Classification of CMD.

1.3.2 Diagnosis of coronary microvascular dysfunction

Clinical features

Coronary microvascular dysfunction (CMD) most frequently presents with symptoms similar to obstructive epicardial CAD. Microvascular angina (MVA) is more prevalent in women and is generally first suspected in patients presenting with typical exertional angina who are found to have no obstructive epicardial CAD at coronary angiography, especially in those patients with evidence of ischaemia on non-invasive stress testing.[119] In contrast to classical angina due to epicardial CAD, MVA may persist or predominate in the post-exercise period and the symptomatic response to nitrates is often less marked than typical angina.[120]

Non-invasive diagnostic testing

Various non-invasive modalities have been utilised in the diagnosis of CMD. Importantly, obstructive epicardial CAD must be excluded before CMD can be diagnosed by any method. Coronary flow reserve (CFR) represents the vasodilator capacity of the coronary circulation and is determined by coronary blood flow during hyperaemia (with vasodilator stress) divided by blood flow at rest. In the absence of epicardial CAD, CFR represents endothelium-independent coronary microvascular function. The normal value of CFR in dependent on the technique used, but most studies consider a CFR <2.0 sufficient to cause ischaemia.[79]

Positron emission tomography (PET) is the non-invasive reference standard modality to assess coronary microvascular function. PET-derived CFR is measured by quantification of absolute myocardial blood flow at rest and during vasodilator stress.[119] While PET is an established method for detection of CMD,[121] its limited availability, cost and exposure to ionising radiation has restricted its use in clinical practice. Quantitative and semi-quantitative CMR techniques have been established to diagnose CMD.[122] However, to date, their use has been limited to small cohorts. Similarly, transthoracic Doppler echocardiography (TTDE) of coronary blood flow (usually the LAD) has been assessed in several small studies. However, this technique can be challenging, lacks precision and requires specialist expertise.[123] Both CMR and TTDE methods require validation in larger populations before they can be considered in routine clinical practice. Novel CT and SPECT techniques are also under evaluation and show potential for the determination of CMD.[124]

Invasive diagnostic testing

Invasive coronary guidewire-based physiological testing is the gold standard for the diagnosis of endothelium-independent CMD.[83,118]

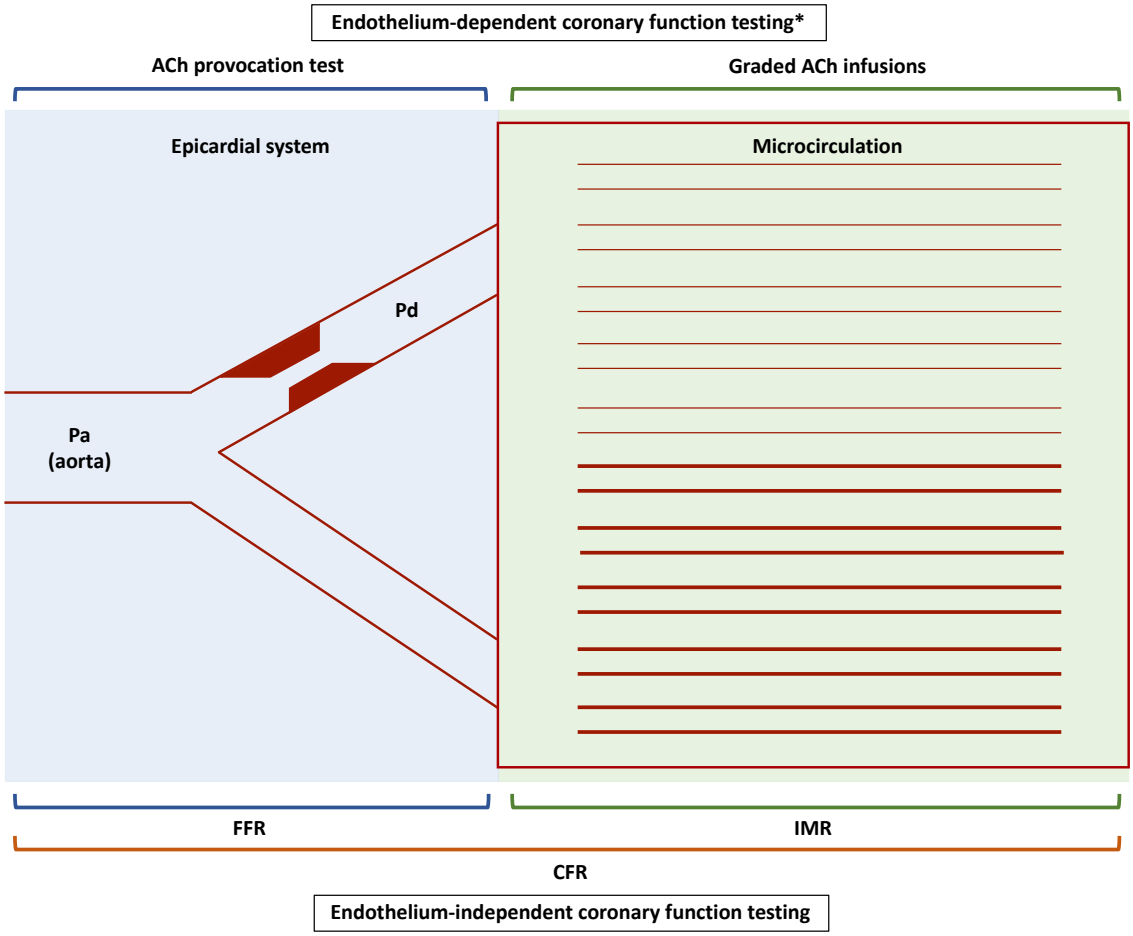
Coronary flow reserve

CFR is measured invasively using a Doppler velocity wire or by a thermodilution-derived method using a coronary pressure wire (Figure 1-3). As described above, CFR reflects the combined vasodilator capacity of the epicardial and microvascular systems. Invasively-measured CFR has limited reproducibility as it

is affected by haemodynamic conditions and it can be difficult to establish resting coronary blood flow during invasive coronary angiography.[125] However, an abnormal CFR has been shown to be associated with microvascular disease and poor prognosis in patients with non-obstructive CAD.[126]

Index of microcirculatory resistance

The index of microvascular resistance (IMR) is a specific measurement of microcirculatory resistance, independent of epicardial CAD. IMR is measured invasively by thermodilution and is calculated from distal coronary pressure (Pd) multiplied by the mean transit time of room temperature saline during hyperaemia (Figure 1-3). As the hyperaemic transit time is inversely correlated with flow, it provides a quantitative measure of coronary microvascular resistance. An IMR ≥25 is consistent with microvascular dysfunction.[127-129] As IMR is measured during hyperaemia, it is independent of haemodynamic variations, therefore, it has better repeatability than CFR.[130]



*Response to ACh is a function of endothelium and vascular smooth muscle cell responses.

ACh, acetylcholine; CFR, coronary flow reserve; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; Pa, aortic pressure; Pd, distal coronary pressure.

Figure 1-3: Overview of coronary physiology testing.

1.3.3 Treatment of coronary microvascular dysfunction

Evidence, in terms of RCTs, to support the use of specific treatments for CMD is very limited, therefore, treatment is empirical.[84] Management of patients with CMD is focused on optimal control of CV risk factors. Patients with MVA are generally treated with traditional anti-anginal therapy, similar to those with epicardial CAD. Beta-blockers are preferred as first-line therapy, with evidence of symptomatic benefit in small studies.[131] In patients with persisting symptoms, small trials have suggested that ACE inhibitors and statins may improve microvascular function, resulting in improved symptoms and exercise tolerance.[132-134] One single-centre trial found that stratified medical treatment (based on the results of CFR, IMR and acetylcholine [ACh] testing) improved symptoms and quality of life compared with standard care in patients with ischaemia and no obstructive CAD (INOCA).[135]

1.3.4 Summary

CMD is defined as myocardial ischaemia due to dysfunction of the coronary microcirculation. It is a heterogeneous condition which can be the result of various structural and functional abnormalities. Invasive physiological testing is the gold standard for the diagnosis of endothelium-independent CMD. Evidence for specific therapies for CMD is lacking, therefore, treatment is empirical and is generally focused on management of CV risk factors.

1.4 What is coronary endothelial dysfunction?

1.4.1 Definition of coronary endothelial dysfunction

Coronary endothelial dysfunction is defined as pathological endothelium-dependent vasoconstriction of a vessel or vascular bed.[136] This vasoconstriction can be focal or diffuse and may affect one or more epicardial coronary arteries and/or the microvasculature.

The vascular endothelium regulates local vascular tone via smooth muscle relaxation and vasodilation through release of NO, prostacyclin and endothelium-derived hyperpolarising factor, or via vasoconstriction through release of thromboxane A_2, endothelin-1 and free radicals.[137] In endothelial dysfunction, there is an imbalance of these factors, with the vasoconstricting factors predominating. Flow-mediated vasodilation is dependent on the presence of an intact endothelium. Under normal circumstances, ACh dilates arteries via NO, however, in the presence of endothelial dysfunction, it causes muscarinic receptor-mediated vascular smooth muscle contraction and vasoconstriction.[138]

Coronary endothelial dysfunction is prevalent in patients with INOCA, affecting almost two-thirds of 124 patients undergoing intracoronary ACh testing in a prospective study.[139] It may also be present in patients with concomitant obstructive or non-obstructive epicardial CAD, where the diagnosis can be more challenging. In patients with and without epicardial CAD, the presence of both epicardial and microvascular coronary endothelial dysfunction independently predicted acute CV events.[140]

1.4.2 Diagnosis of coronary endothelial dysfunction

Clinical features

Coronary endothelial dysfunction typically presents with vasospastic angina, characterised by typical ischaemic chest pain, usually at rest, with ST-segment deviation on ECG. Symptoms typically occur at night and there is usually rapid symptomatic relief with nitrates.

Non-invasive diagnostic testing

Assessment of coronary endothelial function can be performed with cold pressor testing (CPT) in combination with non-invasive flow quantification. This involves immersing the patient's hand or foot in ice-cold water, which induces flow-mediated pre-arteriolar coronary vasodilation.[141] Impaired CPT response has been demonstrated in conditions associated with CMD,[142,143] however, it did not correlate with coronary blood flow response to intra-coronary ACh in women with INOCA.[144]

Intracoronary acetylcholine testing

FFR, CFR and IMR are typically derived using intravenous adenosine, an endothelium-independent vasodilator. Assessment of coronary endothelial function can be assessed with intracoronary administration of ACh, an endothelium agonist (Figure 1-3). An abnormal vasomotor response (representing coronary endothelial dysfunction) is considered to be present if there is: 20-90% luminal constriction and/or ischaemic ECG changes in response to ACh.[135,145] In patients with chest pain syndromes, reproduction of typical ischaemic symptoms are also required to confirm a diagnosis of MVA. High-dose ACh can be administered in a provocation test to detect epicardial vasospasm (>90% luminal constriction) secondary to abnormal coronary vasoreactivity.[146]

1.4.3 Treatment of coronary endothelial dysfunction

Management of patients with coronary endothelial dysfunction is directed at optimal control of CV risk factors. Aspirin and smoking cessation are recommended in all patients.[84] Chronic preventative treatment of vasospastic angina is mainly based on the use of CCBs, which prevent spasm in 90% of patients.[147] Long-acting nitrates can be useful as adjuvant therapy, but beta-blockers are generally avoided due to the theoretical risk of mediating unopposed α-mediated vasoconstriction.

1.4.4 Summary

Coronary endothelial dysfunction represents pathological vasoconstriction of the coronary circulation. It generally presents with vasospastic angina and the reference standard diagnostic investigation is vasoreactivity testing with intra-coronary administration of ACh. Treatment involves optimal control of CV risk factors in addition to CCBs and long-acting nitrates.

1.5 How might coronary artery disease and coronary microvascular dysfunction play a role in heart failure with preserved ejection fraction?

Recent studies suggest that CAD and its consequences may play an important role in the pathophysiology of HFpEF, and (as discussed above) a recent paradigm was proposed suggesting that CMD may play a central role in the overarching pathophysiology of HFpEF.[61,148]

The dyspnoea typical of HFpEF may be caused by myocardial ischaemia, representing an "anginal equivalent" in some patients. This hypothesis is plausible as HFpEF predominantly affects women and the elderly, where CAD commonly presents with atypical symptoms.[85,86]

The diastolic dysfunction that is pathognomonic of HFpEF could be a manifestation of myocardial ischaemia resulting from epicardial CAD and/or CMD.[149] Diastolic dysfunction occurs early in the ischaemic cascade, before the development of chest pain, ECG changes or systolic dysfunction (Figure 1-4).[150] Ischaemia impairs active LV relaxation and increases myocardial stiffness and LV end-diastolic pressure, causing an upward and leftward shift in the LV pressure-volume relationship.[151] Changes in the diastolic properties of the LV have been observed during balloon inflation at coronary angiography,[152,153] and abnormal diastolic filling has been reported by radionuclide angiography with patients with CAD and a preserved LVEF.[29]

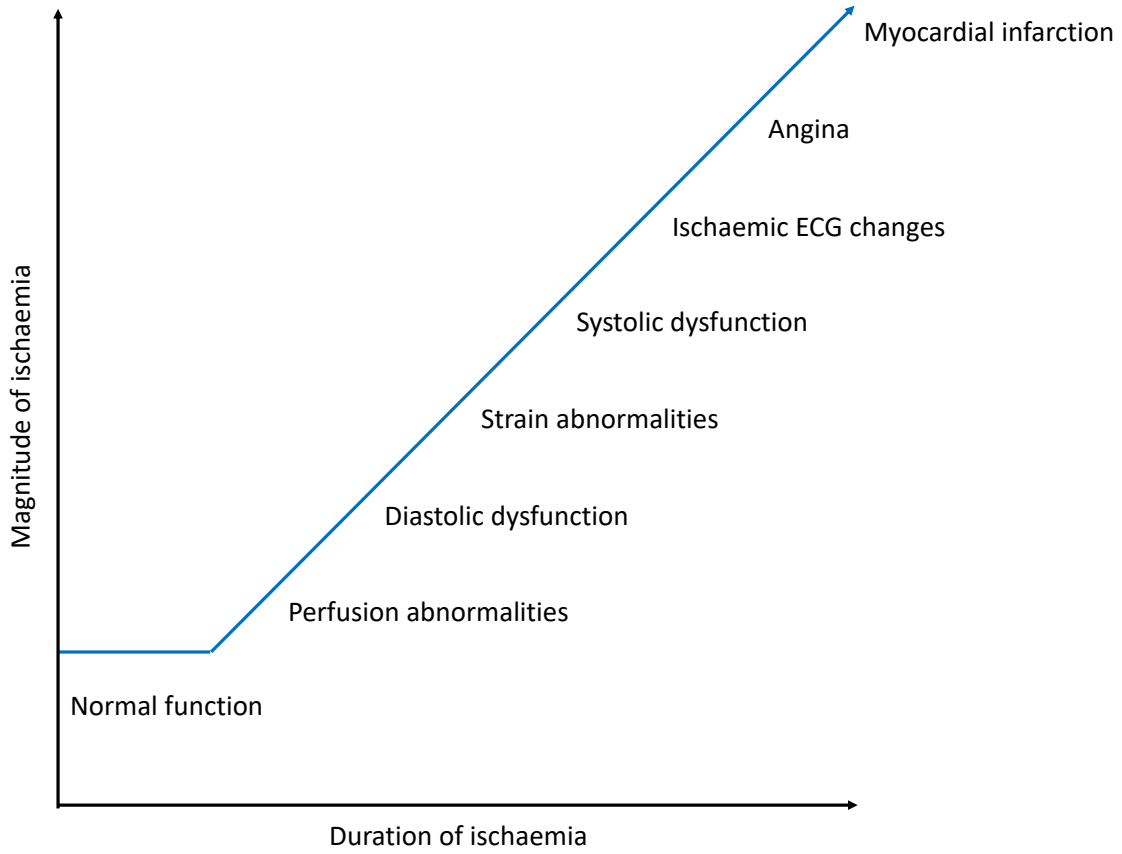


Figure 1-4: The ischaemic cascade.

Longstanding, chronic ischaemia can cause fibrosis which might eventually alter LV compliance permanently.[154] Additionally, or alternatively, dysfunctional but viable ("hibernating") myocardium, or limited areas of MI, could cause subtle LV systolic dysfunction that, in turn, causes HF symptoms in patients with HFpEF.[149,155] A number of studies using sensitive myocardial strain imaging have shown that, compared with both healthy and hypertensive controls, many patients with HFpEF have mild systolic dysfunction.[156-159] In a recent echocardiographic sub-study of the PARAMOUNT trial, longitudinal and circumferential strain were significantly lower in the HFpEF group compared with both normal controls and age- and sex-matched patients with hypertensive heart disease.[40] Patients with HFpEF and a history of CAD had lower strain compared to HFpEF patients without CAD. Therefore, it is possible that CAD may be the cause of HFpEF in some patients, and contributory in others.

1.6 Conclusion

HFpEF is a major public health issue associated with a high burden of morbidity and mortality. The pathophysiology of HFpEF is characterised by a complex interplay of various pathophysiological mechanisms, which is likely to vary significantly between patients. To date, clinical trials have failed to identify any effective treatments, in large part due to the heterogeneity of the population.

Establishing the sub-phenotype of HFpEF (e.g. those with a specific CV abnormality or comorbidity) might identify more homogeneous groups that benefit from specific treatments. Recent studies suggest that CAD, CMD and coronary endothelial dysfunction may play important roles in HFpEF, and each may be a therapeutic target.

Chapter 2 Systematic review of coronary artery disease and coronary microvascular dysfunction in heart failure with preserved ejection fraction

2.1 Introduction

The prevalence of CAD in patients with HFpEF have been studied primarily in retrospective observational and population-based studies with heterogeneous definitions of both CAD and HFpEF. Similarly, the prevalence and potential role of CMD in HFpEF has been inconsistently reported in several small studies using various different diagnostic techniques and definitions of CMD. The epidemiological and clinical data regarding CAD and CMD in HFpEF vary according to study design and setting and, to date, there has been no systematic review of the published literature relating to the burden of CAD and CMD in HFpEF.

2.2 Methods

2.2.1 Search strategy and eligibility criteria

I performed a comprehensive systematic search (updated to 9 November 2019) of the electronic databases Medline and Embase to identify studies that describe CAD or CMD in patients with HFpEF. Various terms relating to HFpEF, CAD and CMD were searched in title or abstract to retrieve all potentially relevant articles (Table 2-1). The search was limited to studies in adult human participants published in the English language. Bibliographies of guidelines, reviews, and articles identified through the search strategy were also searched for additional eligible studies. The review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[160]

HFpEF search terms	"heart failure" AND ("preserved ejection fraction" OR "normal ejection fraction" OR "preserved left ventricular ejection fraction" OR "normal left ventricular ejection fraction" OR "preserved EF" OR "normal EF" OR "preserved LVEF" OR "normal LVEF" OR "preserved systolic function" OR "normal systolic function" OR "preserved left ventricular systolic function" OR "preserved LV systolic function" OR "normal left ventricular systolic function" OR "normal LV systolic function" OR "HFpEF" OR "HFnEF" OR "HF-PEF" OR "HF-NEF" OR "diastolic" OR "DHF" OR "nonsystolic" or "non-systolic")
CAD/CMD search terms	"coronar*" OR "CAD" OR "CHD" OR "CMD" OR "ischaemi*" OR "ischemi*" OR "IHD" OR "infarct*" OR "MI" OR "ACS" OR "STEMI" OR "NSTEMI" OR "revasculari*" OR "coronary artery bypass graft*" OR "CABG" OR "percutaneous coronary intervention" or "PCI" or "angioplasty" OR "stent*" OR "PTCA" OR "angina*" OR "microcirculat*" OR "microvascula*" OR "MVD" OR "flow reserve" OR "flow velocity reserve" OR "FFR" OR "CFR" OR "CFVR" OR "MFR" OR "IMR" OR "rarefaction"

CAD, coronary artery disease; CMD, coronary microvascular dysfunction; HFpEF, heart failure with preserved ejection fraction.

Table 2-1: Search terms used in systematic review.

Population thresholds were applied to studies with a clinical definition of CAD (or those where CAD was not defined) to ensure the inclusion of only large studies – observational studies with greater than 1,000 HFpEF patients and randomised controlled trials (RCTs) with greater than 500 HFpEF patients were included. Studies of HFpEF subgroups (e.g. populations with a specific comorbid condition) were excluded to avoid bias. For multiple studies based on the same population, the study that presented information for the greatest number of patients with HFpEF was selected for inclusion.

2.2.2 Data extraction, synthesis and statistical analysis

All titles and abstracts were screened for their potential eligibility. Data from the manuscripts identified through the search criteria were abstracted and tabulated. The articles retrieved were divided into the following categories for analysis: 1. Studies which report the prevalence of CAD and/or previous MI in a HFpEF population; 2. Studies which report the prevalence of HFpEF complicating incident MI; 3. Studies which evaluate the treatment of CAD in a HFpEF population; 4. Studies which describe CMD in a HFpEF population.

Random effects meta-analyses were performed to estimate the prevalence of CAD and previous MI in HFpEF populations. Heterogeneity was assessed and interpreted using the I^2 statistic and forest plots. All statistical analyses were performed using Stata v.14.2 (StataCorp, College Station, TX, USA).

2.3 Results

2.3.1 Description of included studies

This search strategy retrieved 3,454 eligible studies. Five additional studies were identified through bibliographies of articles identified through the search strategy. After removal of duplicates and limiting the search to studies of humans, English language articles and excluding conference abstracts, 525 titles and abstracts were reviewed, and 197 articles were identified for potential inclusion (Figure 2-1). After full text review, 86 studies met the criteria for inclusion in the systematic review. The studies were divided into the four categories below:

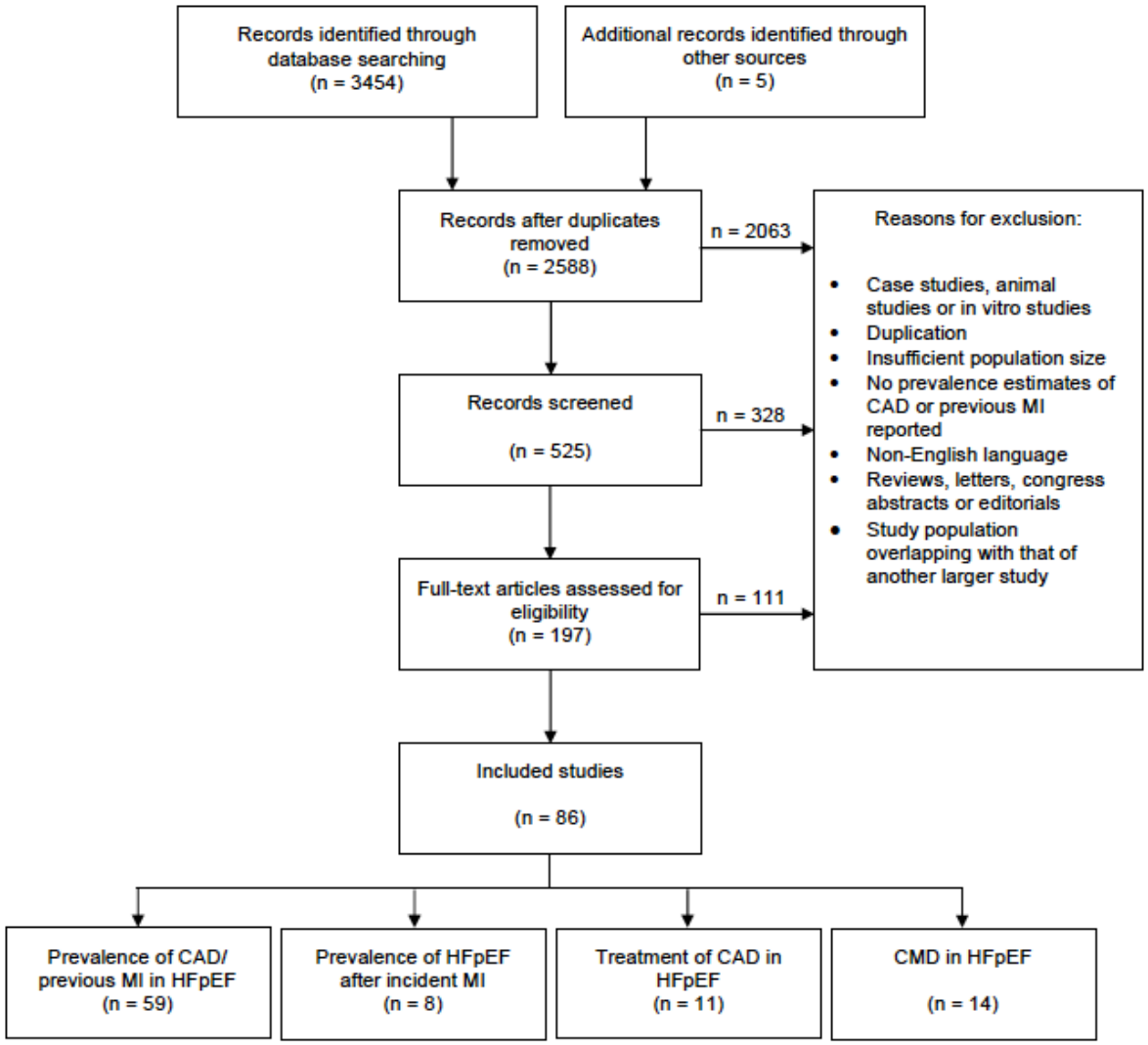
1. Studies which report the prevalence of CAD and/or previous MI in a HFpEF population: 59 studies

2. Studies which report the prevalence of HFpEF after incident MI: eight studies

3. Studies which evaluate the treatment of CAD in a HFpEF population: 11 studies

4. Studies which describe CMD in a HFpEF population: 14 studies

Five studies reported the prevalence and evaluated treatment of CAD in a HFpEF population. One study reported the prevalence of CAD and described CMD in a HFpEF population.



CAD, coronary artery disease; CMD, coronary microvascular dysfunction; HFpEF, heart failure with preserved ejection fraction; MI, myocardial infarction.

Figure 2-1: Systematic review and study selection.

2.3.2 CAD in HFpEF

Of the 59 studies that reported the prevalence of CAD or previous MI in HFpEF populations, 48 (including 494,767 patients with HFpEF) reported prevalence estimates of CAD in HFpEF populations. A further three studies reported data on 2,360,889 hospitalisations for HFpEF (Table 2-2). The mean age was 73 years and 53% of patients were female. Thirty-four studies, including 447,528 HFpEF patients, reported the prevalence of previous MI in HFpEF cohorts. The mean age was 71 years and 51% of patients were female. A further two studies reported data on 30,528 hospitalisations for HFpEF.

Definition of CAD

CAD was reported but not defined in 30 of the 51 studies that reported prevalence estimates of CAD in HFpEF cohorts. The majority of the remaining studies defined CAD based on clinical history or "ischaemic aetiology" of HF. Angiographic CAD was documented in one prospective study and nine retrospective observational studies of convenience cohorts that underwent clinically indicated coronary angiography.

Definition of HFpEF

HF was defined by the International Classification of Diseases (ICD) coding alone in over one-third of observational studies. Of the 59 studies that reported the prevalence of CAD or previous MI, the LVEF cut-off used for preserved LVEF was defined as 50% (or equivalent) in 32 studies, 45% in 10 studies, 40% in 15 studies, and 35% in one study. The largest study in this review included data on 2,330,361 hospitalisations for HFpEF included in the Nationwide Inpatient Sample (NIS) of non-federal US hospitals.[161] In this study, HFpEF was defined as the presence of the ICD-9 code representing acute diastolic HF, and no data on LVEF was reported.

First author, country, year of publication	Study period	Region	Definition of preserved LVEF	Definition of HF	Definition of CAD	HFpEF patients (n)	CAD (%)	MI (%)	PCI/ CABG (%)	Angina (%)	Mean age (y)	Female sex (%)	NYHA class
Hospital based cohorts													
Cheng, Taiwan, 2019[162]	2003-2012	Taiwan	LVEF ≥50%	HFH	-	1836	28	-	-	-	78	37	-
Greenberg, USA, 2019[163]	2009-2016	USA	LVEF ≥50%	Primary or secondary diagnosis with ICD-9-CM code 428 or ICD-10-CM code I50	-	4288	-	4	-	-	74	55	-
Matsushita, Japan, 2019 (Tokyo CCU Network)[164]	2013-2015	Japan	LVEF ≥50%	Clinical features of HF	Medical history of CAD	2238	24	-	-	-	80	50	-
Miró, Spain, 2019 (EAHFE)[165]	2007, 2009, 2011, 2016	Spain	LVEF >49%	HFH (Framingham criteria)	Ischaemic aetiology of HF	4393	28	-	-	-	80	61	-
Takei, Japan, 2019 (WET-HF)[166]	2006-2017	Japan	LVEF ≥50%	HFH (Framingham criteria)	-	1480	16	-	-	-	78	53	-
Guisado-Espartero, Spain, 2018 (age >50 only) (RICA)[167]	2008-2016	Spain	LVEF ≥50%	HFH (ESC criteria)	Ischaemic aetiology of HF	1664	16	-	-	-	81	63	-
Kang, Korea, 2018 (KorAHF)[168]	2011-2014	Korea	LVEF ≥50%	HFH (signs and/or symptoms of HF and lung congestion or evidence of	Ischaemic aetiology of HF	1295	22	9	12 / 3	-	72	62	-

				structural heart disease)									
Zhang, China, 2017 (China-HF)[169]	2012-2015	China	LVEF ≥45% and LVEDD ≤55mm	HFH (Chinese HF guidelines)	-	4062	68	18	-	-	69	47	I-IV
Goyal, USA, 2016 (NIS)[161]	2003-2012	USA	-	ICD-9-CM code for acute diastolic HF (428.31 or 428.33)	-	2330361 *	41	-	7 / 10	-	76	64	-
Zacharias, USA, 2016 (Worcester)[170]	1995, 2000, 2002, 2004, 2006	USA	LVEF ≥50%	HFH (ICD-9 coding, Framingham criteria)	-	2398	46	-	-	-	77	66	-
Nichols, USA, 2015 (KPSC, KPNW)[171]	2008-2011	USA	LVEF ≥50%	HFH (ICD-9 coding) with no previous HFH in the preceding 12 months	ICD-9-CM codes 410-414	3631	36	-	-	-	76	55	-
Kajimoto, Japan, 2015 (ATTEND)[172]	2007-2011	Japan	LVEF >40% or qualitative normal LVSF or mild LVSD	HFH (modified Framingham criteria)	Ischaemic aetiology of HF	2135	21	-	-	-	77	54	-
Caughey, USA, 2014 (age ≥55 only) (ARIC)[173]	2005-2010	USA	LVEF ≥40%	HFH (ICD-9 coding)	-	6414	43	20	-	-	77	61	-
Clarke, USA, 2013 (KPMCP)[174]	2001-2008	USA	LVEF >40% or qualitative normal LVSF or mild LVSD	HFH (ICD-9 coding)	-	1613	-	33	-	-	73	57	-
Steinberg, USA, 2012 (GWTG-HF)[175]	2005-2010	USA	LVEF ≥50%	HFH (ICD-9 coding)	-	40354	44	-	-	-	78	63	-

West, USA, 2011 (ADHERE-I)[176]	2005-2009	10 countries: SE Asia, Australia, Latin America	LVEF ≥40%	HFH (ICD-9/10 coding)	-	4206*	42	21	-	-	71	55	-
Mogensen, Denmark, 2011 (DIAMOND-CHF/ECHOS)[177]	1993-1996, 2001-2002	Denmark, Norway, Sweden	WMI ≥1.5 (LVEF ≥45%)	NYHA III/IV symptoms in the preceding month and treated with diuretic	-	3638	44	23	-	-	72	49	III-IV
Rossi, USA, 2008 (OPTIMIZE-HF)[178]	2003-2004	USA	LVEF ≥40%	HFH (ICD-9 coding)	Medical history of CAD, MI or coronary revascularisation	21149	54	18	25	-	75	62	-
Ezekowitz, Canada, 2008 (EFFECT)[179]	1999-2001	Canada	LVEF >50%	First HFH (ICD-9 coding, Framingham criteria)	-	1026	-	19	8	24	76	64	-
Shah, USA, 2008 (age ≥65 only) (Medicare / NHC)[180]	1998-1999, 2000-2001	USA	LVEF >50%	HFH (ICD-9 coding)	-	13533	48	21	9 / 17	-	80	70	-
Yancy, USA, 2006 (ADHERE-US)[181]	2001-2004	USA	LVEF ≥40%	HFH (ICD-9 coding)	History of clinical or angiographic CAD	26322*	50	24	-	-	74	62	-
Owan, USA, 2006 (Olmsted County)[8]	1987-2001	USA	LVEF ≥50%	HFH (ICD-9 and DRG coding, modified Framingham criteria)	-	2167	53	-	-	-	74	56	-

Lenzen, Netherlands, 2004 (EHFS-I)[182]	2000, 2001	24 ESC countries	LVEF ≥40%	≥1 of: clinical diagnosis of HF during hospital admission or in the last 3 years, administration of loop diuretic (except for renal failure) or pharmacological treatment of HF within 24 hours of death or discharge	-	3148	59	-	12	-	71	55	I-IV
Ibrahim, USA, 2003 (age ≥65 only) (CHQC)[183]	1992-1994	USA	LVEF ≥50%	HFH (ICD-9 coding)	-	1058	46	-	-	6	79	70	-
Community based cohorts													
Fröhlich, Norway, 2019[5]	1995-2015	Norway, Germany, UK	LVEF ≥50% and evidence of structural heart disease	Outpatient clinical diagnosis of HF	Primary ischaemic aetiology of HF	1146	29	-	-	-	66	40	I-IV
Ibrahim, USA, 2019 (NCDR PINNACLE)[184]	2008-2016	USA	LVEF ≥50%	First HF patient visit	-	324387	56	15	22 / 12	-	70	52	-
Tromp, Singapore, 2019 (ASIAN-HF)[185]	2013-2017	Asia	LVEF ≥50%	≥1 HFH or treatment for HF in outpatient clinic	Angiographically documented presence of significant coronary obstruction,	1204	29	-	-	-	68	50	I-IV

					history of MI or revascularisation								
Iorio, Italy, 2018[186]	2009-2013	Italy	LVEF ≥50%	Outpatient clinical diagnosis of HF (ESC 2012 criteria)	-	1373	40	-	-	-	79	51	I-IV
Ather, USA, 2012 (VA)[187]	2000-2002	USA	LVEF ≥50%	Outpatient clinical diagnosis of HF (ICD-9 coding)	-	2843	-	27	-	-	71	9	-
Magaña-Serrano, Mexico, 2011 (I-PREFER)[188]	-	10 countries: Latin America, Middle East, North Africa	LVEF ≥45%	New or previously documented diagnosis of CHF (Framingham criteria)	-	1291	46	21	-	-	65	50	I-IV
Mixed/unspecified cohorts													
Huusko, Finland, 2019 (Turku CRC)[189]	2004-2013	Finland	LVEF ≥40%	Clinical diagnosis of HF (ICD-10 code I50) and NT-proBNP ≥125 ng/L	-	1449	-	27	-	-	74	51	-
Vedin, Sweden, 2017 (SwedeHF)[190]	2000-2012	Sweden	LVEF ≥50%	Clinician-judged HF	Documented IHD or ICD-10 diagnosis corresponding to IHD or revascularisation	9957	52	29	28	32	80	54	I-IV
Chioncel, Romania, 2017 (ESC-HF-LT)[191]	2011-2015	Europe, Turkey, Israel, Egypt	LVEF >50%	Outpatients: clinical-judged chronic HF Inpatients: acute HF requiring IV inotropes, vasodilators or diuretics	Primary ischaemic aetiology of HF	1462	24	-	14 / 9	-	69	39	-

Gerber, USA, 2015 (Olmsted County)[13]	2000-2010	USA	LVEF ≥50%	Incident HF (ICD-9 coding, Framingham criteria)	-	1089	28	17	-	-	78	64	-
Nochioka, Japan, 2015 (CHART-2)[192]	2006-2010	Japan	LVEF ≥50%	ACC/AHA stage B-D HF, Framingham criteria	-	3124	46	30	32 / 9	-	69	35	I-IV
Allen, USA, 2013 (CVRN)[193]	2005-2008	USA	LVEF ≥50%	HFH or ≥3 ambulatory visits with a diagnosis of HF (ICD-9 coding)	-	14907	-	11	9 / 6	-	76	58	-
Kaneko, Japan, 2013 (Shinken)[194]	2004-2011	Japan	LVEF >50%	NYHA II-IV	-	1121	-	10	-	-	66	34	II-IV
Edelmann, Germany, 2011 (CNHF)[195]	2003-2010	Germany	LVEF ≥50%	Clinician-judged HF	-	1294	31	-	-	-	67	54	I-IV
Gomez-Soto, Spain, 2010 (Puerto Real)[196]	2001-2005	Spain	LVEF ≥50%	First diagnosis of HF (Framingham criteria, and ICD-9 coding for hospitalised patients)	Angina or AMI	1120	36	19	14	17	72	58	I-IV
Miura, Japan, 2010 (MetS-CHF)[197]	2006-2008	Japan	LVEF ≥50%	ACC/AHA stage C/D CHF	-	2179	41	-	-	-	70	36	I-IV
Castillo, Spain, 2009 (BADAPIC)[198]	1999-2003	Spain	LVEF ≥45% and echo evidence of diastolic dysfunction	Framingham criteria	-	1416	32	18	12	-	71	53	II-IV

Randomised controlled trials

Solomon, USA, 2019 (age ≥50 only) (PARAGON-HF)[71]	2014-2018	25 countries: Europe, North America, South America, Europe, South Africa, Asia, Australia	LVEF ≥45% and evidence of structural heart disease on echo	Current HF symptoms or HF symptoms requiring treatment with diuretic ≥30 days prior to enrolment, NT-proBNP ≥300 pg/mL (≥900 pg/mL if AF)	-	4822	43	23	-	-	73	52	II-IV
Pitt, USA, 2014 (age ≥50 only) (TOPCAT)[14]	2006-2012	6 countries: North America, South America, Europe, Russia	LVEF ≥45%	≥1 sign and ≥1 symptom of HF and HFH or BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL within the previous 60 days	History of previous MI, coronary revascularisation, or angina	3445	59	26	24	47	69	52	I-IV
van Veldhuisen, Netherlands, 2009 (age ≥70 only) (SENIORS)[72]	2000-2003	10 countries: Europe	LVEF >35%	Clinical history of chronic HF and HFH within the previous 12 months	Prior history of CAD	752	77	34	2 / 4	-	76	50	I-IV
Massie, USA, 2008 (age ≥60 only) (I-PRESERVE)[15]	2002-2005	25 countries: Europe, North America, South America, South Africa, Australia	LVEF ≥45%	Current NYHA III-IV symptoms with corroborative evidence, or current NYHA II-IV symptoms and HFH within 6 months	History of previous MI, revascularisation or primary ischaemic aetiology of HF	4128	36	23	13	40	72	60	II-IV

Cleland, UK, 2006 (age ≥70 only) (PEP-CHF)[16]	2000-2003	8 countries: Europe, Russia	WMI ≥1.4 (LVEF ≥40%) and evidence of diastolic dysfunction on echo	3 out of 9 clinical HF criteria and a CV hospitalisation within the previous 6 months	-	850	-	27	8 / 5	-	75	56	I-IV
Ahmed, USA, 2006 (sinus rhythm only) (DIG-PEF)[73]	1991-1993	USA, Canada	LVEF >45%	Current or past HF symptoms, signs, or radiological evidence of pulmonary congestion	Principal ischaemic aetiology of HF	988	56	49	-	30	67	41	I-IV
Yusuf, Canada, 2003 (CHARM-Preserved)[64]	1999-2000	26 countries: Australia, Europe, Russia, SE Asia, North America	LVEF >40%	NYHA II-IV ≥4 weeks (NYHA III-IV in prior 6 months if taking an ACEI) and previous cardiac hospitalisation	Ischaemic aetiology of HF	3023	56	44	17 / 22	28	67	40	II-IV
Angiographic cohorts													
Trevisan, France, 2018[199]	2015-2016	France	LVEF ≥40%	Hospitalisation with symptoms and signs of acute HF and BNP ≥100pg/mL	>70% stenosis (or 50-70% stenosis with FFR ≤0.80) of ≥1 epicardial coronary artery	108	64	-	-	-	79	54	-
Hwang, USA, 2014[148]	2004-2012	USA	LVEF ≥50%	HFH (ICD-9 coding and Framingham criteria or elevated invasive left heart pressures)	>50% stenosis of ≥1 epicardial coronary artery, prior MI or coronary revascularisation	376	68	14	19 / 21	33	72	53	-
Koller, Austria, 2014 (LURIC)[200]	1997-2000	Germany	LVEF >45% and evidence of	Symptoms and signs of HF	>20% stenosis of ≥1 epicardial coronary artery	459	76	32	-	-	68	37	-

			diastolic dysfunction (on invasive assessment or NT-proBNP >220 pg/mL and ECG evidence of AF)										
Schmaltz, Canada, 2008 (APPROACH)[201]	1999-2004	Canada	LVEF >50%	Clinician-judged HF	≥50% stenosis of ≥1 epicardial coronary artery	2159	59	44	5 / 5	-	68	46	-
Arques, Italy, 2008 (hypertensive and in sinus rhythm only, history of CAD/angina excluded)[202]	2002-2008	Italy	LVEF >50%, LVEDV <76ml/m^2 and LVEDP ≥16mmHg	Clinical and radiographic signs of acute HF with a complete, favourable response to IV diuretics and/or nitrates	>50% stenosis of ≥1 epicardial coronary artery	23	35	-	-	-	74	61	IV
Felker, USA, 2006 (Duke)[203]	1995-2003	USA	LVEF >40%	History of symptomatic HF (NYHA II-IV symptoms)	≥75% stenosis of ≥1 epicardial coronary artery	3093	52	23	14 / 17	-	64	56	II-IV
East, USA, 2004 (Duke)[204]	1984-1996	USA	LVEF >40%	History of symptomatic HF (NYHA II-IV symptoms)	≥75% stenosis of ≥1 epicardial coronary artery	3303	54	26	12 / 12	-	64	55	II-IV
Arques, Italy, 2004 (sinus rhythm only,	2001-2003	Italy	LVEF ≥50% with pseudo-	Dyspnoea at rest, pulmonary rales, radiological	>50% stenosis of ≥1 epicardial coronary artery	18	39	-	-	-	73	61	IV

history of CAD/angina excluded)[205]			normal or restrictive mitral filling on echo	pulmonary oedema with favourable response to loop diuretics and nitrates									
Kramer, USA, 2000[206]	1995-1998	USA	LVEF ≥40%	Hospitalisation with acute respiratory distress with onset ≤6 hours prior to seeking medical attention, and alveolar or interstitial pulmonary oedema on CXR	>50% stenosis of ≥1 epicardial coronary artery	27	74	-	-	-	67	56	IV
Judge, USA, 1991 (CASS)[207]	1975-1979	USA	LVEF ≥45%	Moderate to severe CHF symptoms (NYHA III-IV)	≥70% stenosis of ≥1 epicardial coronary artery	284	67	53	-	70 (CCS III/IV)	56	44	III-IV
Autopsy series													
Mohammed, USA, 2015[208]	1986-2001, 2003-2010	USA	LVEF ≥40%	Previous HFH or outpatient diagnosis of HF (ICD-9 coding)	>50% stenosis of ≥1 epicardial coronary artery (at post-mortem)	119	65	20	-	-	78	56	-

*Hospitalisations (not patients). ACEI, angiotensin converting enzyme inhibitor; ACC/AHA, American College of Cardiology/American Heart Association; ADHERE-I, Acute decompensated heart failure national registry - international; ADHERE-US, Acute decompensated heart failure national registry - US; AF, atrial fibrillation; AMI, acute myocardial infarction; APPROACH, Alberta provincial project for outcome assessment in coronary heart disease; ARIC, Atherosclerosis risk in communities registry; ASIAN-HF, Asian sudden cardiac death in heart failure; ATTEND, Acute decompensated heart failure syndromes registry; BADAPIC, Base de datos de pacientes con insuficiencia cardíaca registry; BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CASS; Coronary artery surgery study; CCS, Canadian Cardiovascular Society; CCU, Coronary care unit; CHARM-Preserved, Candesartan in heart failure assessment of reduction in mortality and morbidity-Preserved; CHART-2, Chronic heart failure analysis and registry in the Tohoku district-2 study; CHF; congestive heart failure; CHQC, Cleveland health quality choice program; CM, clinical modification; CNHF, Competence network heart failure; CRC, Clinical research center; CV, cardiovascular; CVRN, Cardiovascular research network; CXR, chest x-ray; DIAMOND-CHF, Dofetilide-congestive heart failure; DIG-PEF, Digitalis intervention group-preserved ejection fraction; DRG, Diagnosis-related group; EAHFE, Epidemiology of acute heart failure in emergency departments; ECG, electrocardiogram; ECHOS, Echocardiography and heart outcome study; EFFECT, Enhanced feedback for effective cardiac treatment study; EHFS-I, Euro heart failure study-I; ESC, European Society of

Cardiology; ESC-HF-LT, European Society of Cardiology heart failure long-term registry; FFR, fractional flow reserve; GWTG-HF, Get with the guidelines heart failure registry; HF, heart failure; HFH; HF hospitalisation; HFpEF, HF with preserved ejection fraction; ICD, International Classification of Diseases; IHD, ischaemic heart disease; I-PREFER, Identification of patients with heart failure and preserved systolic function: an epidemiological regional study; I-PRESERVE, Irbesartan in patients with heart failure and preserved ejection fraction; IV, intravenous; KorAHF, Korean acute heart failure registry; KPMCP, Kaiser Permanente medical care program; KPNW, Kaiser Permanente Northwest; KPSC, Kaiser Permanente Southern California; LURIC, Ludwigshafen risk and cardiovascular health study; LVEDD, left ventricular end-diastolic dimension; LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVSF, left ventricular systolic function; MetS-CHF, Metabolic syndrome-chronic heart failure study; MI, myocardial infarction; NCDR PINNACLE, National cardiovascular data practice innovation and clinical excellence registry; NHC, National heart care project; NIS, National inpatient sample; NT-proBNP, N-terminal prohormone BNP; NYHA, New York Heart Association; OPTIMIZE-HF, Organized program to initiate lifesaving treatment in hospitalized patients with heart failure; PARAGON-HF, Prospective comparison of angiotensin receptor-neprilysin inhibitor with angiotensin receptor blocker in heart failure with preserved ejection fraction; PCI, percutaneous coronary intervention; PEP-CHF, Perindopril in elderly people with chronic heart failure; RICA, Registro de Insuficiencia Cardiaca; SE, South East; SENIORS, Study of the effects of nebivolol intervention on outcomes and rehospitalization in seniors with heart failure; SwedeHF, Swedish heart failure registry; TOPCAT, Treatment of preserved cardiac function heart failure with an aldosterone antagonist; VA, Veterans Affairs; WET-HF, West Tokyo heart failure registry; WMI, wall motion index.

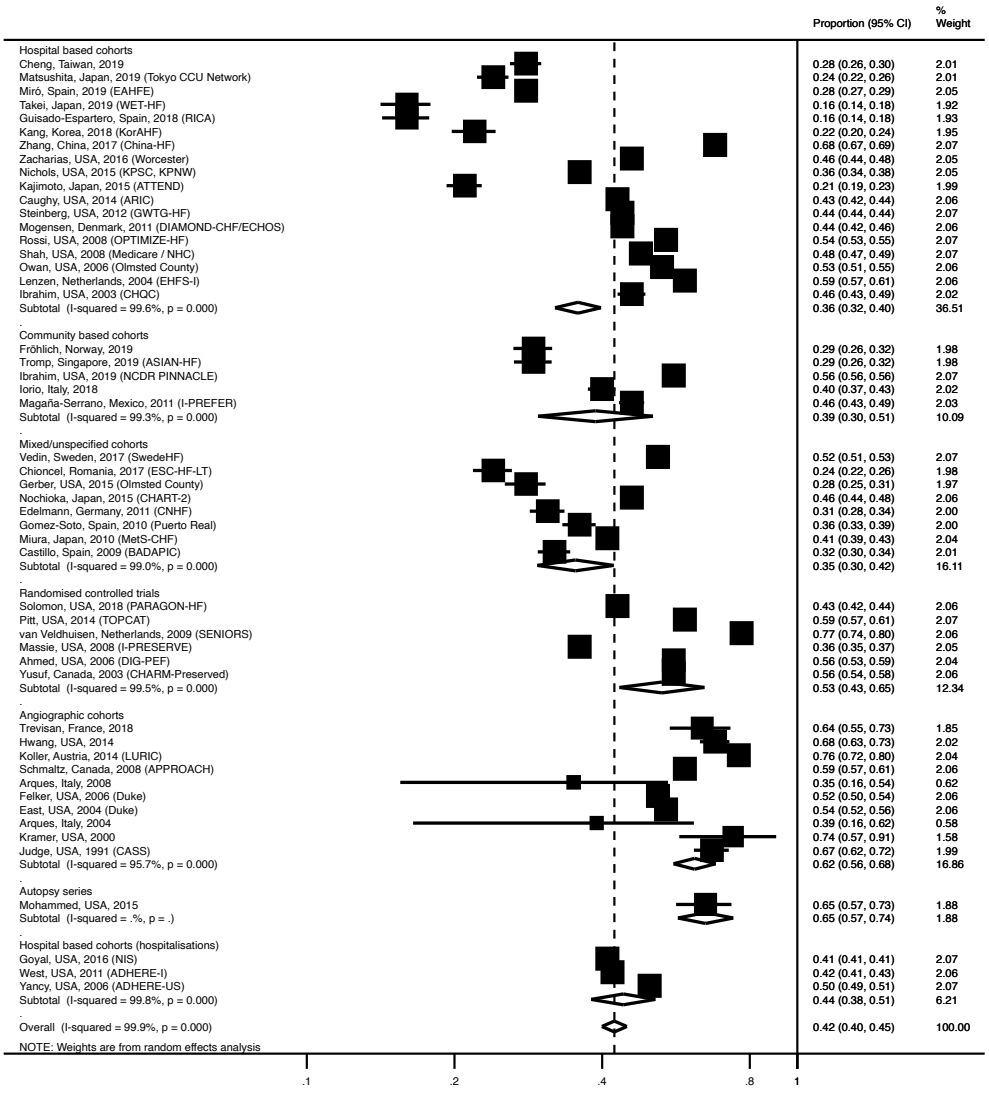
Table 2-2: Prevalence of CAD and previous MI in HFpEF cohorts.

Prevalence of CAD and previous MI in HFpEF

The prevalence of CAD varied widely between the studies, from 16% to 77% (Table 2-2). Previous MI was reported in 36 studies (range 4% to 53%) and a history of angina was reported in 10 studies (range 6% to 70%). CAD, previous MI and angina were more prevalent in studies of patients undergoing coronary angiography and RCTs than in population-based observational studies. The prevalence of CAD, previous MI and coronary revascularisation in the three large hospital-based population registries that reported data on HFpEF hospitalisations were similar to that observed in the HFpEF cohorts that reported data for individual patients. When analysed by random effects meta-analysis, the mean prevalence of CAD in HFpEF populations was 42% (95% confidence interval [CI] 40-45%) (Figure 2-2), and the prevalence of previous MI was 22% (95% CI 19-25%) (Figure 2-3).

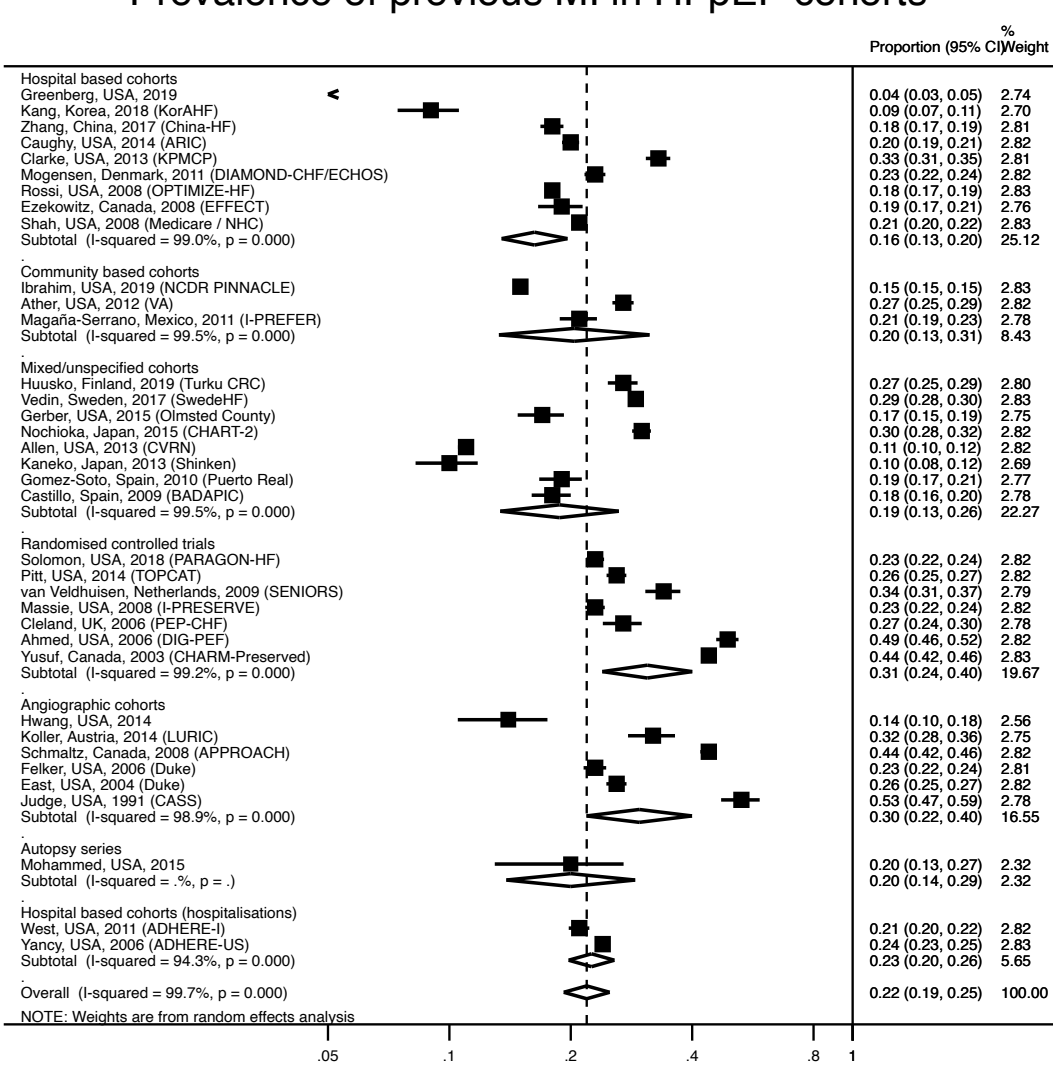
Prognostic impact of CAD in HFpEF

The effect of CAD on outcomes in HFpEF populations was reported in 14 studies. In population-based observational studies and RCTs, the prognostic impact of CAD in HFpEF cohorts was inconsistent. However, in studies of patients with angiographically-proven CAD, the presence and extent of CAD was associated with increased all-cause mortality (Table 2-3).



ADHERE-I, Acute decompensated heart failure national registry - international; ADHERE-US, Acute decompensated heart failure national registry - US; APPROACH, Alberta provincial project for outcome assessment in coronary heart disease; ARIC, Atherosclerosis risk in communities registry; ASIAN-HF, Asian sudden cardiac death in heart failure; ATTEND, Acute decompensated heart failure syndromes registry; BADAPIC, Base de datos de pacientes con insuficiencia cardíaca registry; CAD, coronary artery disease; CASS; Coronary artery surgery study; CCU, Coronary care unit; CHARM-Preserved, Candesartan in heart failure assessment of reduction in mortality and morbidity-Preserved; CHART-2, Chronic heart failure analysis and registry in the Tohoku district-2 study; CHQC, Cleveland health quality choice program; CI, confidence interval; CNHF, Competence network heart failure; DIAMOND-CHF, Dofetilide-congestive heart failure; DIG-PEF, Digitalis intervention group-preserved ejection fraction; EAHFE, Epidemiology of acute heart failure in emergency departments; ECHOS, Echocardiography and heart outcome study; EHFS-I, Euro heart failure study-I; ESC-HF-LT, European Society of Cardiology heart failure long-term registry; GWTG-HF, Get with the guidelines heart failure registry; HFpEF, heart failure with preserved ejection fraction; I-PREFER, Identification of patients with heart failure and preserved systolic function: an epidemiological regional study; I-PRESERVE, Irbesartan in patients with heart failure and preserved ejection fraction; KorAHF, Korean acute heart failure registry; KPNW, Kaiser Permanente Northwest; KPSC, Kaiser Permanente Southern California; LURIC, Ludwigshafen risk and cardiovascular health study; MetS-CHF, Metabolic syndrome-chronic heart failure study; NCDR PINNACLE, National cardiovascular data practice innovation and clinical excellence registry; NHC, National heart care project; NIS, National inpatient sample; OPTIMIZE-HF, Organized program to initiate lifesaving treatment in hospitalized patients with heart failure; PARAGON-HF, Prospective comparison of angiotensin receptor-neprilysin inhibitor with angiotensin receptor blocker in heart failure with preserved ejection fraction; RICA, Registro de Insuficiencia Cardiaca; SENIORS, Study of the effects of nebivolol intervention on outcomes and rehospitalization in seniors with heart failure; SwedeHF, Swedish heart failure registry; TOPCAT, Treatment of preserved cardiac function heart failure with an aldosterone antagonist; WET-HF, West Tokyo heart failure registry.

Figure 2-2: Meta-analysis – prevalence of CAD in HFpEF cohorts.



ADHERE-I, Acute decompensated heart failure national registry - international; ADHERE-US, Acute decompensated heart failure national registry - US; APPROACH, Alberta provincial project for outcome assessment in coronary heart disease; ARIC, Atherosclerosis risk in communities registry; BADAPIC, Base de datos de pacientes con insuficiencia cardíaca registry; CAD, coronary artery disease; CASS; Coronary artery surgery study; CHARM-Preserved, Candesartan in heart failure assessment of reduction in mortality and morbidity-Preserved; CHART-2, Chronic heart failure analysis and registry in the Tohoku district-2 study; CI, confidence interval; CRC, Clinical research center; CVRN, Cardiovascular research network; DIAMOND-CHF, Dofetilide-congestive heart failure; DIG-PEF, Digitalis intervention group-preserved ejection fraction; ECHOS, Echocardiography and heart outcome study; EFFECT, Enhanced feedback for effective cardiac treatment study; HFpEF, heart failure with preserved ejection fraction; I-PREFER, Identification of patients with heart failure and preserved systolic function: an epidemiological regional study; I-PRESERVE, Irbesartan in patients with heart failure and preserved ejection fraction; KorAHF, Korean acute heart failure registry; KPMCP, Kaiser Permanente medical care program; LURIC, Ludwigshafen risk and cardiovascular health study; NCDR PINNACLE, National cardiovascular data practice innovation and clinical excellence registry; NHC, National heart care project; OPTIMIZE-HF, Organized program to initiate lifesaving treatment in hospitalized patients with heart failure; PARAGON-HF, Prospective comparison of angiotensin receptor-neprilysin inhibitor with angiotensin receptor blocker in heart failure with preserved ejection fraction; PEP-CHF, Perindopril in elderly people with chronic heart failure; SENIORS, Study of the effects of nebivolol intervention on outcomes and rehospitalization in seniors with heart failure; SwedeHF, Swedish heart failure registry; TOPCAT, Treatment of preserved cardiac function heart failure with an aldosterone antagonist; VA, Veterans Affairs.

Figure 2-3: Meta-analysis – prevalence of previous MI in HFpEF cohorts.

First author, country, year of publication	HFpEF patients (n)	Follow-up	All-cause mortality	CV mortality	All-cause hospitalisation	HF hospitalisation
Hospital based cohorts						
Goyal, USA, 2016 (NIS)[161]	2330361*	In-hospital	Adjusted HR: History of CAD vs. no history of CAD: 0.79 (0.78-0.80) History of CABG vs. no history of CABG: 0.75 (0.73-0.77) History of PCI vs. no history of PCI: 0.64 (0.62-0.67)	-	-	-
Clarke, USA, 2013 (KPMCP)[174]	1613	4.1 years	Estimated HR for predictors of state changes: History of MI vs. no history of MI: 0.87 (0.70-1.10)	-	-	-
Rossi, USA, 2008 (OPTIMIZE-HF)[178]	21149	In-hospital and post-discharge (60-90 days)	Adjusted OR: History of CAD vs. no history of CAD: In-hospital: 1.13 (0.94-1.36) Post-discharge: 1.39 (0.95-2.03)	-	-	-
Ezekowitz, Canada, 2008 (EFFECT)[179]	1026	1 year	Adjusted HR (death or HFH): History of MI vs. no history of MI: 1.57 (1.23-2.02)	-	-	-
Owan, USA, 2006 (Olmsted County)[8]	2167	10 years	Adjusted HR: History of CAD vs. no history of CAD: 1.03 (0.98-1.09)	-	-	-
Mixed/unspecified cohorts						
Allen, USA, 2013 (CVRN)[193]	14907	1.8 years	Adjusted HR: History of MI vs. no history of MI: 1.61 (1.46-1.78) History of CABG vs. no history of CABG: 0.76 (0.66-0.87) History of PCI vs. no history of PCI: 0.87 (0.77-0.97)	-	Adjusted HR: History of MI vs. no history of MI: 1.40 (1.32-1.48) History of PCI vs. no history of PCI: 1.10 (1.03-1.17)	Adjusted HR: History of MI vs. no history of MI: 1.31 (1.19-1.44) History of CABG vs. no history of CABG: 0.90 (0.78-1.03)
Kaneko, Japan, 2013	1121	1135 days	Unadjusted HR:	-	-	-

(Shinken)[194]			History of MI vs. no history of MI: 0.68 (0.24-1.88)			
Randomised controlled trials						
Badar, UK, 2015 (CHARM-Preserved)[209]	1553	36.6. months (median)	Adjusted HR: Current angina vs. no history of angina: 0.72 (0.52-1.01)	Adjusted HR: Current angina vs. no history of angina: 0.72 (0.52-1.01)	-	Adjusted HR: Current angina vs. no history of angina: 0.80 (0.57-1.12)
Badar, UK, 2015 (age ≥60 only) (I-PRESERVE)[210]	4128	49.5 months	Adjusted HR: CAD/no angina vs. no CAD/no angina: 1.58 (1.22-2.04) CAD/angina vs. no CAD/no angina: 1.29 (1.05-1.59)	Adjusted HR: CAD/no angina vs. no CAD/no angina: 1.50 (1.10-2.06) CAD/angina vs. no CAD/no angina: 1.46 (1.14-1.86)	-	Adjusted HR: CAD/no angina vs. no CAD/no angina: 1.03 (0.75-1.40) CAD/angina vs. no CAD/no angina: 1.12 (0.89-1.41)
Pitt, USA, 2014 (age ≥50 only) (TOPCAT)[14]	3445	3.3 years	Adjusted HR (CV death, aborted cardiac arrest or HFH): History of MI vs. no history of MI: 0.84 (0.64-1.12)	-	-	-
Cleland, UK, 2006 (age ≥70 only) (PEP-CHF)[16]	850	2.1 years (median)	All-cause mortality or unplanned HFH: 17% (history of MI) vs. 12% (no history of MI)	-	-	-
Angiographic cohorts						
Hwang, USA, 2014[148]	376	1457 days (median)	Adjusted HR: History of CAD vs. no history of CAD: 1.71 (1.03-2.98)	-	-	-
Felker, USA, 2006 (Duke)[203]	3093	3.5 years (median)	Adjusted HR: Number of diseased vessels: 1.15 (1.10-1.20)	-	-	-
Judge, USA, 1991 (CASS)[207]	284	6 years	Survival: 92% without CAD, 83% (1- or 2-vessel disease), 68% (3-vessel disease), p 0.0001)	-	-	-

*Hospitalisations (not patients). CABG, coronary artery bypass grafting; CAD, coronary artery disease; CASS; Coronary artery surgery study; CHARM-Preserved, Candesartan in heart failure assessment of reduction in mortality and morbidity-Preserved; CV, cardiovascular; CVRN, Cardiovascular research network; EFFECT, Enhanced feedback for effective cardiac treatment study; HF, heart failure; HFH; HF hospitalisation; HFpEF, HF with preserved ejection fraction; HR, hazard ratio; I-PRESERVE, Irbesartan in patients with heart failure and preserved ejection fraction; KPMCP, Kaiser Permanente medical care program; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NIS, National inpatient sample; OPTIMIZE-HF, Organized program to initiate lifesaving treatment in hospitalized patients with heart failure; OR, odds ratio; PCI, percutaneous coronary intervention; PEP-CHF, Perindopril in elderly people with chronic heart failure; TOPCAT, Treatment of preserved cardiac function heart failure with an aldosterone antagonist.

Table 2-3: Prognostic impact of CAD in HFpEF cohorts.

Prevalence of HFpEF after incident MI

Eight studies reported rates of HFpEF after incident MI; seven studies reported early (in-hospital) HF and one reported late HF following MI. HF in the presence of preserved LV systolic function occurred following MI in a median of 8% (interquartile range [IQR] 7-15%) and accounted for 43% (31-51%) of early HF post-MI. In the one study reporting late-onset HF following MI, HFpEF developed in 8% of patients from three days to a mean follow-up of eight years after MI and accounted for 42% of HF in this cohort.[211] One study described contemporary temporal trends in patients who experienced HF following incident MI.[212] From the 1990s to 2010, a significant reduction in post-MI HF was observed. The incidence of HFrEF declined but there was no change in the rate of HFpEF, resulting in an increase in the proportion of patients with both early- and late-onset post-MI HF with preserved LVEF. HFpEF complicating MI was consistently associated with worse short- and long-term outcomes compared with MI patients with preserved LVEF and no HF (Table 2-5).

First author, country, year of publication	Study period	Region	Definition of preserved LVEF	Definition of HF	Definition of MI	HFpEF patients (n)	Follow-up for development of HF post-MI	Incidence of post-MI HF	Incidence of post-MI HFpEF (proportion of HF / overall)
Gerber, USA, 2016 (Olmsted County)[211]	1990-2010	USA	LVEF ≥50%	Incident diagnosis of HF (ICD-9 coding and Framingham criteria)	Incident MI (ICD-9 coding and 2 of the following: cardiac pain, elevated biomarkers (CK, CK-MB or troponin), and ECG changes)	339	Early: <3 days Late: >3 days to mean 8 years' follow-up	35% (47% early, 53% late)	Early: 32%* / 5% Late: 42%* / 8%
Desta, Sweden, 2015 (SWEDEHEART/ RIKS-HIA)[213]	1998-2010	Sweden	LVEF >49%	In-hospital diagnosis of HF (presence of pulmonary rales or use of IV diuretics or inotropic drugs during admission)	Typical clinical symptoms and/or ECG signs of AMI, and a documented elevation of cardiac enzymes (CK, CK-MB or troponin)	7707	In-hospital	42% (decrease from 55% to 34% 1998-2010)	20% (increase from 18% to 31% 1998-2010) / 8% (static 1998-2010)
Antonelli, Brazil, 2015 (Einstein AMI)[214]	2005-2012	Brazil	LVEF ≥50%	Clinical diagnosis of HF at presentation (Killip class >I)	Typical clinical symptoms and/or ECG signs of AMI, and a documented elevation of cardiac enzymes (CK, CK-MB or troponin)	78	At presentation	15%	36% / 5%
van Diepen, Canada, 2014 (age ≥65 only) (CRUSADE)[215]	2003-2006	USA	LVEF ≥40%	Clinical diagnosis of HF at presentation or during hospital admission (PND, orthopnoea, dyspnoea, or lower extremity oedema and ≥1 of: rales, S3, JVD, elevated BNP or NT-proBNP, or documented pulmonary oedema on CXR)	NSTEMI – ≥10 minutes of ischaemic chest pain at rest and elevated cardiac enzymes (CK-MB or troponin levels above the ULN) or ECG changes (ST depression or transient ST elevation)	4913	In-hospital	33%	57% / 19%

Bennett, USA, 2007 (CRUSADE)[216]	2001-2004	USA	LVEF ≥40%	Clinical diagnosis of HF at presentation (symptoms of HF on initial history: dyspnoea, orthopnoea, laboured breathing, fatigue at rest or on exertion; signs of HF on initial physical examination: rales, S3 gallop, JVD, or pulmonary oedema on initial CXR)	NSTEACS – ≥10 minutes of ischaemic chest pain at rest and elevated cardiac enzymes (CK-MB or troponin levels above the ULN) or ECG changes (ST depression or transient ST elevation)	11860	In-hospital	23%	55% / 13%
Hellermann, USA, 2005 (Olmsted County)[217]	1979-1998	USA	LVEF ≥50%	Incident diagnosis of HF (ICD-9 coding and Framingham criteria)	Incident MI (ICD-9 coding and 2 of the following: cardiac pain, elevated biomarkers (CK, CK-MB), and ECG changes)	143	Early: ≤30 days Mid: 30 days – 1 year Late: 1 year to mean 7 years' follow-up	41% (59% early, 9% mid, 32% late)	29%** / 7%
Velazquez, USA, 2004 (VALIANT)[218]	1999-2001	9 countries: North America, Europe, Australasia	LVEF ≥40%	≥1 of: radiological pulmonary oedema (pulmonary venous congestion with interstitial or alveolar oedema on CXR) or clinical diagnosis of HF (pulmonary oedema, bilateral rales and/or S3 gallop)	Physician-determined clinical diagnosis of MI	377	In-hospital	23%	50%** / 7%
Møller, Denmark, 2003 (BEAT)[219]	1998-1999	Denmark	WMI ≥1.3 (LVEF ≥40%)	Killip class ≥II during hospitalisation or a history of CHF treated with a diuretic on admission	Typical clinical symptoms and/or ECG signs of AMI, and a documented elevation of cardiac enzymes (CK and CK-MB) to at least twice the ULN	717	In-hospital	46%	49% / 23%

*19% of patients with no LVEF data – multiple imputations used; **excluding patients with no LVEF data. AMI, acute myocardial infarction; BEAT, Bucindolol evaluation in acute myocardial infarction trial; BNP, B-type natriuretic peptide; CHF, chronic heart failure; CK, creatine kinase; CK-MB, creatine kinase myocardial band; CRUSADE, Can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the American College of Cardiology/American Heart Association guidelines; CXR, chest x-ray; ECG, electrocardiogram; HF, heart failure; HFpEF, HF with preserved ejection fraction; ICD, International Classification of Diseases; IV, intravenous; JVD, jugular venous distention; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEACS, non-ST-elevation acute coronary syndrome; NT-proBNP, N-terminal prohormone BNP; PND, paroxysmal nocturnal dyspnoea; RIKS-HIA, Register of information and knowledge about Swedish heart intensive care admissions; SWEDEHEART, Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies registry; ULN, upper limit of normal; VALIANT, Valsartan in acute myocardial infarction trial; WMI, wall motion index.

Table 2-4: Rates of HFpEF after incident MI.

First author, country, year of publication	HFpEF patients (n)	Follow-up	All-cause mortality	CV mortality	Non-CV mortality
Gerber, USA, 2016 (Olmsted County)[211]	339	8 years	Adjusted HR: 2.37 (1.96-2.87)	Adjusted HR: 2.65 (2.02-3.49)	Adjusted HR: 2.12 (1.64-2.74)
Desta, Sweden, 2015 (SWEDEHEART/ RIKS-HIA)[213]	7707	1 year	Adjusted HR: 1.9 (1.8-2.0)	-	-
Antonelli, Brazil, 2015 (Einstein AMI)[214]	78	In-hospital	Adjusted OR: 2.91 (1.35-6.27)	-	-
van Diepen, Canada, 2014 (age ≥65 only) (CRUSADE)[215]	4913	30 days / 1 year	Adjusted HR (30 days): 1.99 (1.64-2.41) Adjusted HR (1 year): 1.79 (1.61-1.98)	-	-
Bennett, USA, 2007 (CRUSADE)[216]	11860	In-hospital	Adjusted OR: 2.30 (2.05-2.59)	-	-
Velazquez, USA, 2004 (VALIANT)[218]	377	In-hospital	7.7% (vs. 2.3% for preserved LVEF and no HF)	-	-
Møller, Denmark, 2003 (BEAT)[219]	717	In-hospital	Adjusted HR: 2.10 (1.74-2.55)	-	-

AMI, acute myocardial infarction; BEAT, Bucindolol evaluation in acute myocardial infarction trial; CRUSADE, Can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the American College of Cardiology/American Heart Association guidelines; CV, cardiovascular; HF, heart failure; HFpEF, HF with preserved ejection fraction; HR, hazard ratio; LVEF, left ventricular ejection fraction; OR, odds ratio; RIKS-HIA, Register of information and knowledge about Swedish heart intensive care admissions; SWEDEHEART, Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies registry; VALIANT, Valsartan in acute myocardial infarction trial.

Table 2-5: Prognostic impact of HFpEF after incident MI.

Treatment of CAD in HFpEF

A total of 11 studies reported outcomes based on CAD treatments in HFpEF cohorts – one subgroup analysis of an RCT and 10 observational studies. There were no RCTs which assessed the impact of treatment of CAD in a HFpEF population. In a *post hoc* subgroup analysis of the PEP-CHF trial, the primary endpoint (composite of all-cause mortality and hospitalisation for HF) was reduced in HFpEF patients with a history of MI treated with perindopril, while no such benefit was observed in patients without a history of MI.[16] In four studies, patients with HFpEF had poorer outcomes than patients with preserved LVEF and no HF who underwent percutaneous or surgical coronary revascularisation (Table 2-6). One retrospective single-centre observational study compared patients with HFpEF that underwent either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). There was no difference in mortality between the groups, however, PCI was associated with more major adverse cardiac and cerebrovascular events (MACCE) at a median 18 months' follow-up.[220] One large population-based study observed a mortality benefit at 60 to 90 days following hospital discharge in patients with HFpEF and a clinical history of CAD or previous MI who were revascularised, compared to patients with HFpEF and CAD who were not revascularised.[178] A single-centre retrospective study also observed lower all-cause mortality in patients who were completely revascularised compared to those who were either incompletely revascularised or not revascularised.[148] Conversely, in patients with HFpEF and CAD in the CASS registry, surgical revascularisation did not appear to confer a survival benefit.[207] Furthermore, one small prospective study, including 20 patients with hypertensive pulmonary oedema and CAD, found that revascularisation had no significant effect on the recurrence of pulmonary oedema or death.[206]

First author, country, year of publication	Study patient characteristics	Definition of preserved LVEF	Definition of HF	Definition of CAD	HFpEF-CAD patients (n)	Follow-up	All-cause mortality	Cardiac mortality	HF readmission
Sun, Canada, 2018 (CorHealth Ontario)[221]	Patients with HFpEF vs. patients with preserved LVEF and no HF who underwent primary isolated CABG (≥40 years)	LVEF ≥50%	Physician billing for HFH or ≥2 outpatient HF claims within 1 year	Angiographically documented CAD amenable to CABG	2752	All-cause mortality: 30 days / 4 years (mean)	30 days: Adjusted HR 2.57 (1.96-3.36) 4 years (mean): Adjusted HR 2.06 (1.86-2.27)	-	-
Dalén, Sweden, 2016 (SWEDEHEART)[222]	Patients with HFpEF vs. patients with preserved LVEF and no HF who underwent CABG	LVEF ≥50%	Pre-CABG diagnosis of HF (ICD-10 coding)	Angiographically documented CAD amenable to CABG	1216	All-cause mortality: 30 days / 6 years (mean) HFH and HF mortality: 5 years (mean)	30 days: Adjusted HR 1.83 (1.26-2.66) 6 years (mean): Adjusted HR 1.62 (1.46-1.80)	-	Composite all-cause mortality and HFH: Adjusted HR 1.64 (1.47-1.82)
Marui, Japan, 2015 (CREDO-Kyoto CABG-2)[223]	Patients with HFpEF vs. patients with preserved LVEF and no HF who underwent CABG	LVEF >50%	Clinical-judged ACC/AHA stage C/D HF	Angiographically documented CAD amenable to CABG	152	5 years	Adjusted HR 1.42 (1.02-1.97)	Adjusted HR 2.14 (1.32-3.49)	Adjusted HR 1.93 (1.20-3.11)
Hwang, USA, 2014[148]	Patients with HFpEF and angiographic CAD (complete revascularisation vs. no or incomplete revascularisation)	LVEF ≥50%	HFH (ICD-9 coding and Framingham criteria or elevated left heart pressures at catheterisation)	>50% stenosis of ≥1 epicardial coronary artery, prior MI, or any prior coronary revascularisation	255	4-year all-cause mortality	Adjusted HR 0.56 (0.33-0.93)	-	-

Xue, China, 2012[220]	Patients with HFpEF and angiographic CAD who underwent CABG or PTCA	LVEF ≥50%	HF signs and symptoms (NYHA II-IV)	Angiographically documented CAD amenable to revascularisation	920	All-cause mortality and MACCE (median follow-up 18 months)	2.3% PCI vs. 3.5% CABG (adjusted p 0.423)	1.1% PCI vs. 2.6% CABG (adjusted p 0.237)	-
Rossi, USA, 2008 (OPTIMIZE-HF)[178]	Patients with HFpEF with a clinical history of CAD vs. patients with HFpEF with no clinical history of CAD	LVEF ≥40%	HFH (ICD-9 coding)	History of clinical CAD, MI or coronary revascularisation	11405	In-hospital and post-discharge (60-90 day) all-cause mortality	In-hospital: Adjusted OR 1.16 (0.94-1.43) CRS- vs. no CAD / 1.08 (0.86-1.37) CRS+ vs. no CAD Post-discharge: Adjusted OR 1.58 (1.05-2.39) CRS- vs. no CAD / 1.06 (0.62-1.80) CRS+ vs. no CAD	-	-
Holper, USA, 2007 (BARI)[224]	Patients with HFpEF and multivessel CAD vs. patients with no HF and multivessel CAD who underwent revascularisation	LVEF ≥50%	Positive response to the question: “Does the patients have a history of CHF requiring treatment?” on baseline data form	Clinically severe angina or objective evidence of ischaemia requiring revascularisation and angiographically documented CAD involving 2 or 3 vessels amendable to CABG or PTCA	124	10-year cardiac mortality	-	10-year: Adjusted HR 1.55 (1.05-2.31)	-

Holper, USA, 2006 (NHLBI PTCA/Dynamic)[22][5]	Patients with HFpEF vs. patients with preserved LVEF and no HF and angiographic CAD who underwent their first coronary intervention	LVEF ≥50%	History of PND, dyspnoea on exertion, or pulmonary congestion on CXR	Angiographic CAD amendable to PCI	134	In-hospital and 1-year all-cause mortality	-	In-hospital: 0.7% HFpEF vs. 0.4% preserved LVEF with no HF 1-year: 10.0% vs. 3.0%	-
Cleland, UK, 2006 (age ≥70 only) (PEP-CHF)[16]	Patients ≥70 years with HFpEF	WMI ≥1.4 (LVEF ≥40%) and ≥2 echo criteria for diastolic dysfunction	3 out of 9 clinical HF criteria and a CV hospitalisation within the previous 6 months	History of MI	226	All-cause mortality or HFH at 1 year	-	-	Composite all-cause mortality and HFH: 0.38 (0.19-0.75) with MI vs. 0.92 (0.58-1.46) without MI
Kramer, USA, 2000[206]	Patients admitted with flash pulmonary oedema and preserved LVEF	LVEF ≥40%	Hospitalisation with acute respiratory distress with onset ≤6 hours prior to seeking medical attention, and alveolar or interstitial pulmonary oedema on CXR	>50% stenosis of ≥1 epicardial coronary artery	20	HFH and all-cause death at 3 years	6-month recurrence of pulmonary oedema was 50% (no difference between HFpEF/HFrEF or CAD/no CAD, revascularised/ not revascularised)	-	-

Judge, USA, 1991 (CASS)[207]	Patients with NYHA III-IV HF symptoms and preserved LVEF with known or suspected CAD that underwent coronary angiography	LVEF ≥45%	Moderate to severe symptoms of CHF (NYHA III-IV)	≥70% stenosis of ≥1 epicardial coronary artery	284*	All-cause mortality at 6 years	CABG did not confer a statistically significant survival advantage (p = 0.26)	-	-

*154 with treatment data available. ACC/AHA, American College of Cardiology/American Heart Association; BARI, Bypass angioplasty revascularization investigation trial; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CASS, Coronary artery surgery study; CHF, chronic heart failure; CREDO-Kyoto CABG-2, Coronary revascularization demonstrating outcome study in Kyoto coronary artery bypass grafting registry cohort-2; CRS, coronary revascularisation status; CV, cardiovascular; CXR, chest x-ray; HF, heart failure; HFH, HF hospitalisation; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; HR, hazard ratio; ICD, International Classification of Diseases; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NHLBI, National heart, lung and blood institute; NYHA, New York Heart Association; OPTIMIZE-HF, Organized program to initiate lifesaving treatment in hospitalized patients with heart failure; OR, odds ratio; PCI, percutaneous coronary intervention; PEP-CHF, Perindopril in elderly people with chronic heart failure; PND, paroxysmal nocturnal dyspnoea; PTCA, percutaneous transluminal coronary angioplasty; SWEDEHEART, Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies registry; WMI, wall motion index.

Table 2-6: Treatment of CAD in HFpEF cohorts.

2.3.3 CMD in HFpEF

Thirteen studies investigated the prevalence or potential role of CMD in HFpEF (Table 2-7).

Invasive studies

One small prospective study investigated the burden of CMD using pressure wire-derived coronary flow reserve (CFR) and index of microcirculatory resistance (IMR) in a small convenience cohort of HFpEF patients (n = 30) referred for clinically indicated coronary angiography.[226] This study reported "overt CMD" (defined as CFR ≤2.0 and IMR ≥23) in 37% of patients (n = 11), with a further 37% of patients (n = 11) having some abnormality of coronary microvascular function (CFR ≤2.0 or IMR ≥23). A follow-up study reported that those with "overt CMD" had lower survival free of HF hospitalisation at one year than those without overt CMD.[227] In another small prospective study, nine HFpEF patients underwent invasive assessment of rest and stress haemodynamics and transcardiac oxygen gradients.[228] Patients with HFpEF had an impaired transcardiac oxygen gradient with exercise and this inversely correlated with pulmonary capillary wedge pressure, suggesting that the abnormal diastolic reserve observed in HFpEF may be explained by CMD. Two retrospective convenience cohort of patients with a positive non-invasive stress test and no angiographically significant CAD reported greater evidence of CMD (using pressure wire-derived CFR/IMR and angiographic indices of microvascular function [TIMI frame count, myocardial blush grade], respectively) in patients with HFpEF than those without HFpEF.[229,230]

Non-invasive studies

A prospective multicentre study (PROMIS-HFpEF) recruited 202 ambulatory HFpEF patients and assessed CMD using echocardiography-derived CFR of the left anterior descending (LAD) coronary artery.[231] CMD was reported in 75% of patients, using a CFR threshold of <2.5. A small cardiac magnetic resonance (CMR) study (n = 19) reported CMD in 69% of HFpEF patients (defined as myocardial perfusion reserve <2.5).[232] Coronary microvascular function was assessed non-invasively in two further studies, using CMR phase-contrast cine imaging[233] and Rb-82 positron emission tomography (PET),[234] respectively. Both

studies reported evidence of impaired coronary microvascular function in patients with HFpEF relative to hypertensive and healthy controls.

Biopsy series

A series of small human biopsy studies (n = 12 to 36) evaluated coronary microvascular endothelial function in patients with HFpEF.[30,38,39,235,236] These studies reported evidence of coronary microvascular endothelial activation which was associated with increased cardiomyocyte resting tension. Cardiomyocyte tension was higher in patients with HFpEF than those with HFrEF, aortic stenosis, or control samples from cardiac transplant recipients.

Autopsy series

An autopsy series (n = 124) reported lower coronary microvascular density (MVD) in patients with a pre-mortem diagnosis of HFpEF relative to age- and sex-matched controls who died of non-cardiac causes.[208] The differences in microvascular density were independent of the severity of epicardial CAD and myocardial fibrosis was inversely associated with microvascular density, suggesting that microvascular rarefaction may contribute to chronic ischaemia and diastolic dysfunction in HFpEF.

First author, country, year of publication	Study patient characteristics	Definition of preserved LVEF	Definition of HF	Assessment of coronary microvascular function	HFpEF patients (n)	Findings	Conclusion
Invasive studies							
Dryer, USA, 2018[226]	Patients with previous HFpEF with previous HFH and clinical indication for coronary angiography with no significant angiographic CAD (≥50% stenosis of ≥1 epicardial coronary artery)	LVEF ≥50%	HFH, BNP >100pg/mL or administration ≥2 doses of IV diuretics	Coronary pressure wire-derived CFR, (abnormal ≤2.0) and IMR (abnormal ≥23)	30	HFpEF patients had lower CFR and higher IMR (cf. controls with no HF, a clinical indication of coronary angiography and no significant angiographic CAD)	HFpEF patients had more abnormalities of coronary flow and resistance than asymptomatic control patients, suggesting that CMD may play a role in HFpEF
Xu, China, 2018[229]	Patients with HFpEF with a positive stress test that underwent coronary angiography with no significant angiographic CAD (>50% stenosis or FFR ≤0.80 of ≥1 epicardial coronary artery)	LVEF >50%	Signs and symptoms of HF and LVEDP >16 mmHg	Coronary pressure wire-derived CFR and IMR	56	HFpEF patients had higher IMR (cf. controls with no HF, a positive stress test and no significant angiographic CAD) and IMR correlated with LVEDP. Patients aged >65 years had a higher IMR than those ≤65 years.	Older HFpEF patients have more microvascular dysfunction than younger HFpEF patients and controls without HF
Sucato, Italy, 2015[230]	Patients with HFpEF with angina, a positive stress test and no significant angiographic CAD or history of IHD	LVEF >50%	Echo evidence of diastolic dysfunction and LVH	Angiographic indices of coronary microvascular disease - TFC, MBG	155	Patients with HFpEF had a longer TFC and lower MBG of the three major coronary arteries (cf. non-HFpEF patients)	HFpEF patients with stable angina, a positive stress test and no significant epicardial CAD had angiographic evidence of greater CMD than patients without HFpEF

van Empel, Australia, 2014[228]	Outpatients with HFpEF	LVEF >45%	Exertional dyspnoea and E/e' >15 or exercise PCWP >25 mmHg	Peak exercise PCWP, transcardiac oxygen gradient	9	Despite a lower workload, peak exercise PCWP was markedly higher and transcardiac oxygen gradient was significantly lower in HFpEF patients (cf. hypertensive and healthy controls)	The abnormal diastolic reserve observed during exertion in HFpEF patients may be explained by impaired myocardial oxygen delivery due to CMD
Non-invasive studies							
Löffler, USA, 2019[232]	Patients with HFpEF and no clinical history of CAD or MI	LVEF >45%	NYHA ≥II or BNP ≥150 pg/mL and ≥grade 1 diastolic dysfunction on echo or elevated PWCP	Global LV MFR (stress/rest myocardial blood flow) by CMR (abnormal <2.5)	19	69% of patients with HFpEF had CMD	HFpEF patients have a high prevalence of CMD
Shah, USA, 2018 (PROMIS-HFpEF)[231]	Patients with a confirmed diagnosis of chronic HFpEF without suspected IHD or non-revascularised epicardial CAD	LVEF ≥40%	Signs and symptoms of HF (NYHA II-IV class) and ≥1 of: a. elevated NT-proBNP or BNP; b. HFH within 12 months and LAE or LVH on echo; c. PCWP >15 mmHg at rest or >25 mmHg with exercise; d. E/e' ≥15 at rest	Echocardiography pulse wave Doppler-derived CFR (abnormal <2.5)	202	75% of patients with HFpEF have CMD. Low CFR correlated with lower RHI and TAPSE and right ventricular free wall strain, and higher uACR and NT-proBNP.	There is a high prevalence of CMD in HFpEF and it is associated with signs of systemic endothelial dysfunction and HF severity
Srivaratharajah, Canada, 2016[234]	Patients with HFpEF undergoing clinically indicated Rb-82 cardiac PET with data available for MFR, no history of CAD and summed stress score <4	LVEF ≥50%	NYHA I-IV class HF symptoms and confirmed diagnosis of HFpEF from review of medical records	Global and regional LV MFR (stress/rest myocardial blood flow) by Rb-82 PET	78	HFpEF was associated with a significant reduction in global MFR (cf. hypertensive and healthy controls)	HFpEF in the absence of known history of CAD is associated with reduced MFR independent of other risk factors
Kato, USA, 2016[233]	Patients with HFpEF with no significant	LVEF >50%	Patients with HF syndrome and E/e'	CFR (coronary sinus flow during ATP	25	76% of HFpEF patients had abnormal CFR	CMD might be a pathophysiological

	coronary stenosis on coronary CTA		>15, or 8<E/e′<15 and BNP >200 pg/dL	infusion / coronary sinus flow at rest) by phase-contrast cine-CMR (CFR <2.5 abnormal)		CFR was significantly lower in HFpEF patients (cf. hypertensive LVH and healthy controls) CFR independently and significantly correlated with serum BNP level	factor for HFpEF and might be related to HF severity
Biopsy studies							
Franssen, Netherlands, 2016[235]	Patients with HFpEF undergoing clinically indicated LV endomyocardial biopsy with no evidence of infiltrative or inflammatory cardiomyopathy and no significant angiographic CAD (HFpEF compared with HFrEF and AS samples)	LVEF >50%	HFH, LVEDVI <97 ml/m^2, LVEDP >16 mmHg	ICAM-1 and E-selectin concentrations (microvascular inflammation and macrophage activation); H_2O_2 concentration and NOX expression (oxidative stress); myocardial nitrite/nitrate concentrations (NO bioavailability), eNOS (NO synthase uncoupling)	36	In the myocardium of HFpEF patients, E-selectin and ICAM-1 expression levels were upregulated and there was uncoupling of endothelial NO synthase, which was associated with reduced myocardial nitrite/nitrate concentration	HFpEF is associated with coronary microvascular endothelial activation and oxidative stress. These lead to a reduction of NO-dependent signalling from endothelial cells to cardiomyocytes, which can contribute to the high cardiomyocyte stiffness and hypertrophy observed in HFpEF.
van Heerebeek, Netherlands, 2012[39]	Patients with HFpEF undergoing clinically indicated LV endomyocardial biopsy with no evidence of infiltrative or inflammatory cardiomyopathy and no significant angiographic CAD (HFpEF compared	LVEF >50%	HFH, LVEDVI <97 ml/m^2, LVEDP >16 mmHg	Measures of cardiomyocyte resting tension and hypertrophy, and nitrosative/oxidative stress: $F_{passive}$, cardiomyocyte diameter, myocardial PKG activity, cGMP concentration, nitrotyrosine expression	36	Lower PKG activity in HFpEF than in aortic stenosis or HFrEF was associated with higher $F_{passive}$ and related to lower cGMP concentration and higher nitrosative/oxidative stress. Higher $F_{passive}$ in HFpEF was corrected by in vitro PKG administration.	Low myocardial PKG activity in HFpEF was associated with raised cardiomyocyte $F_{passive}$ and was related to increased myocardial nitrosative/oxidative stress. The latter was probably induced by the high prevalence in HFpEF of metabolic comorbidities. Correction of

	with HFrEF and AS samples)						myocardial PKG activity could be a target for specific HFpEF treatment.
van Heerebeek, Netherlands, 2008[236]	Patients with HFpEF undergoing clinically indicated LV endomyocardial biopsy with no evidence of infiltrative or inflammatory cardiomyopathy and no significant angiographic CAD (HFpEF with and without DM compared with HFrEF with and without DM)	LVEF >50%	HFH, LVEDVI <97 ml/m^2, LVEDP >16 mmHg	Measures of cardiomyocyte resting tension, hypertrophy and fibrosis: $F_{passive}$, cardiomyocyte diameter, CVF	28	Diabetic HF patients had increased diastolic LV stiffness irrespective of LVEF. DM increased the myocardial CVF only in patients with HFrEF, and increased $F_{passive}$ only in patients with HFpEF.	Increased cardiomyocyte resting tension is an important mechanism responsible for the diastolic stiffness seen in patients with HFpEF with and without DM
van Heerebeek, Netherlands, 2006[38]	Patients with HFpEF undergoing clinically indicated LV endomyocardial biopsy with no evidence of infiltrative or inflammatory cardiomyopathy and no significant angiographic CAD (HFpEF compared with HFrEF samples)	LVEF >45%	HFH, LVEDP >16 mmHg	Measures of cardiomyocyte resting tension, hypertrophy and fibrosis: $F_{passive}$, cardiomyocyte diameter, CVF, myofibrillar density	22	Cardiomyocyte diameter was higher in DHF, but collagen volume fraction was equally elevated. Myofibrillar density was lower in SHF. Cardiomyocytes of DHF patients had higher $F_{passive}$, but their total force was comparable. After administration of PKA to the cardiomyocytes, the drop in $F_{passive}$ was larger in DHF than in SHF.	LV myocardium in SHF and DHF differ in both cellular architecture and function and suggests SHF and DHF to be associated with phenotypically distinct cardiomyocyte abnormalities. These differences support the clinical discrimination of HF patients into SHF and DHF groups.

Borbély, Netherlands, 2005[30]	Patients with HFpEF undergoing clinically indicated LV endomyocardial biopsy with no evidence of infiltrative or inflammatory cardiomyopathy and no significant angiographic CAD (HFpEF compared with transplant recipient samples)	LVEF >45%	HFH, LVEDP >16 mmHg, HF signs and symptoms	Measures of cardiomyocyte resting tension, hypertrophy and fibrosis: $F_{passive}$, cardiomyocyte diameter, CVF	12	Patients with DHF had higher $F_{passive}$ and CVF than controls. Administration of PKA to DHF cardiomyocytes lowered $F_{passive}$ to control values.	DHF patients have stiffer cardiomyocytes than controls. Correction of high resting tension with PKA suggests that reduced phosphorylation of sarcomeric proteins is involved in DHF.
Autopsy series							
Mohammed, USA, 2015[208]	Subjects with a pre-mortem diagnosis of HFpEF who underwent autopsy	LVEF ≥40%	Previous HFH or outpatient diagnosis of HF (ICD-9 coding)	Myocardial fibrosis, MVD	124	Subjects with HFpEF had more LVH and LV fibrosis, and lower MVD (cf. healthy controls). LVH, fibrosis and MVD were similar in HFpEF patients with and without epicardial CAD. Adjusting for MVD attenuated the group differences in fibrosis.	Microvascular endothelial inflammation is a plausible trigger for the microvascular rarefaction and myocardial fibrosis observed in HFpEF

AS, aortic stenosis; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CFR, coronary flow reserve; cGMP, cyclic guanosine monophosphate; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance; CVF, collagen volume fraction; CTA, computed tomography angiography; DHF, diastolic heart failure; DM, diabetes mellitus; eNOS, endothelial nitric oxide synthase; FFR, fractional flow reserve; $F_{passive}$, cardiomyocyte resting tension; ICD, International Classification of Diseases; IHD, ischaemic heart disease; HF, heart failure; HFH, HF hospitalisation; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; ICAM-1, intercellular adhesion molecule-1; IMR, index of microcirculatory resistance; LAE, left atrial enlargement; LV, left ventricle; LVEDP, LV end-diastolic pressure; LVEDVI, indexed LV end-diastolic volume; LVEF, LV ejection fraction; LVH, LV hypertrophy; MBG, myocardial blush grade; MFR, myocardial flow reserve; MI, myocardial infarction; MVD, microvascular density; NO, nitric oxide; NT-proBNP, N-terminal prohormone BNP; NOX, nicotinamide adenine dinucleotide phosphate oxidase; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PET, positron emission tomography; PKA, protein kinase A; PKG, protein kinase G; RHI, reactive hyperaemia index; SHF, systolic HF; TAPSE, tricuspid annular plane systolic excursion; TFC, Thrombolysis in myocardial infarction frame count; uACR, urinary albumin-to-creatinine ratio.

Table 2-7: CMD in HFpEF cohorts.

2.4 Discussion

2.4.1 CAD in HFpEF

The prevalence of CAD in HFpEF has been studied primarily in retrospective observational and population-based studies with varied definitions of HF, preserved LVEF and CAD. Consequently, this review found that the rates of CAD reported in HFpEF populations varied widely. In studies which documented angiographic CAD, the prevalence of CAD was significantly higher than that reported in population-based studies or RCTs. However, these were highly selected convenience cohorts that had undergone clinically indicated coronary angiography and, therefore, were subject to considerable referral bias. One prospective single-centre study of 108 patients with HFpEF and HFmrEF found obstructive CAD (defined as >70% stenosis or ≥50% stenosis and fractional flow reserve ≤0.80) in 64% of patients.[199] An autopsy series of patients with a premortem diagnosis of HF and LVEF ≥40% reported "anatomically significant" CAD (defined as ≥50% luminal stenosis) in 65% of patients.[208] The relatively high burden of CAD reported in these studies is likely a reflection of the inclusion of patients with HFmrEF, with similar demographics to patients with HFrEF.

The prevalence of previous MI reported in HFpEF cohorts was variably reported. Almost half of patients with HF complicating MI had preserved LVEF, and poorer outcomes were observed in these patients when compared to MI patients with preserved LVEF and no HF. However, transient HF with preserved LV systolic function in the setting of acute MI does not meet standard definitions of HFpEF, and how it is related to the syndrome of HF is unclear.

Clinical trials in HFpEF have tested standard CAD drug therapies, including beta-blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers, with neutral results. In the PEP-CHF trial, the use of perindopril in HFpEF patients did not improve outcomes. However, there was symptomatic improvement and mortality benefit in the subgroup of patients who had a previous MI.[16] Observational data also suggests possible beneficial effects of statins in patients with HFpEF.[237] Data on the impact of coronary revascularisation in patients with HFpEF and CAD are limited and conflicting. One small prospective study, including 20 patients with an LVEF >40%, found

that pulmonary oedema recurred in patients with CAD and acute hypertensive HF despite revascularisation.[206] In the historical CASS registry (1975-1979), CABG in patients with HFpEF did not improve mortality.[207] Conversely, two recent retrospective studies have reported survival benefit in patients with HFpEF and CAD that were revascularised.[148,178] However, to date, no RCTs have evaluated the impact of coronary revascularisation in HFpEF patients.

Better understanding of the prevalence of obstructive CAD is potentially of clinical importance. For example, in studies of patients with angiographic CAD, the presence and extent of epicardial CAD appears to be associated with increased mortality. However, all these data were obtained from registries, RCTs and retrospective studies with heterogeneous definitions of HFpEF and CAD, and none have addressed the importance of microvascular disease.

2.4.2 CMD in HFpEF

Recent studies suggest that CMD and may be implicated in the pathogenesis of HFpEF and a number of non-invasive and small invasive studies have reported evidence of impaired coronary microvascular function in patients with HFpEF. An autopsy series demonstrated microvascular rarefaction and more severe fibrosis in patients with HFpEF compared with controls (non-cardiac death, no pre-mortem HF diagnosis).[208] The differences in microvascular density were independent of the severity of epicardial CAD and myocardial fibrosis was inversely associated with microvascular density, suggesting that CMD may contribute to chronic ischaemia, fibrosis and diastolic dysfunction in HFpEF. These studies suggest that CMD is prevalent in HFpEF, however, the potential mechanisms of CMD in a representative HFpEF cohort have yet to be explored.

2.5 Conclusion

CAD and CMD appear to be common in the HFpEF population. However, the prevalence of CAD and CMD in patients with HFpEF have not been prospectively and systematically studied, so the true burden is unknown. As epicardial CAD is a treatable comorbidity in HFpEF, its identification is of potential clinical significance. Ischaemia due to CMD may also play an important role in the pathogenesis of HFpEF in some patients and may be amenable to treatment.

Chapter 3 Methods

3.1 Introduction

This chapter will outline the methods used in the study. This was a prospective cross-sectional study of unselected patients admitted to hospital with HFpEF. Patients who consented to participation in the study underwent invasive coronary angiography with guidewire-based physiological testing, vasoreactivity (endothelial function) testing, and adenosine stress perfusion cardiac magnetic resonance (CMR) imaging (where possible). These investigations were used to determine the burden of epicardial coronary artery disease (CAD), coronary microvascular dysfunction (CMD), and myocardial ischaemia, infarction and fibrosis in the study population. The study was approved by the West of Scotland Research Ethics Committee (REC) in July 2016, reference 16/WS/0111.

3.2 Study aims

1. To assess the prevalence of obstructive epicardial CAD in patients with HFpEF.

2. To determine the prevalence of endothelium-independent CMD in patients with HFpEF.

3. To determine the prevalence of coronary endothelial dysfunction in patients with HFpEF.

4. To determine the prevalence of previous MI in patients with HFpEF.

3.3 Study population

I prospectively screened unselected patients hospitalised with suspected HF at three centres: the Queen Elizabeth University Hospital (Glasgow), Glasgow Royal Infirmary (Glasgow) and Royal Alexandra Hospital (Paisley). The combined catchment population of these hospitals is over one million people. Patients were recruited over a 19-month period (1st January 2017 to 1st August 2018).

All patients admitted with symptoms and signs of HF were screened for potential inclusion. A diagnosis of HFpEF was confirmed, according to the 2016 ESC guidelines for the diagnosis and treatment of acute and chronic HF recommendations, when all of the following conditions were met:

1. Typical symptoms and signs of HF

2. LVEF ≥50% on echocardiography

3. Evidence of relevant structural heart disease and/or diastolic dysfunction on echocardiography

4. Elevated natriuretic peptides[2]

Relevant structural heart disease was defined as at least one of: left ventricular hypertrophy (LVH) (i.e. maximal diastolic LV septal or posterior wall thickness ≥13 mm), or LA dilatation (indexed LA volume ≥34 ml/m^2). Evidence of diastolic dysfunction was defined as E/e' >13 with a mean e' <9 cm/s on tissue Doppler imaging, as per the ESC guidelines.[2] Natriuretic peptides play a central role in the diagnosis of HFpEF. Rule-out thresholds of less than 100 pg/mL for B-type natriuretic peptide (BNP) and less than 300 pg/mL for N-terminal prohormone BNP (NT-proBNP) have been shown to have excellent diagnostic accuracy to exclude acute HF.[238] Patients with a confirmed diagnosis of HFpEF based on the above criteria were considered for participation in the study, provided no exclusion criteria are present.

3.3.1 Inclusion criteria

- Written informed consent
- Male or non-pregnant female patients ≥18 years of age
- Hospitalisation with symptoms and signs of HF
- LVEF ≥50% on echocardiography
- Presence of relevant structural heart disease (i.e. LVH, LA dilatation) and/or elevated LV filling pressures
- BNP ≥100 pg/mL or NT-proBNP ≥300 pg/mL

3.3.2 Exclusion criteria

- Patients unwilling to participate in the study
- Patients who are unable to provide valid consent for the study
- Patients unable to take part in the study due to geographical or social reasons
- Patients with severe frailty (i.e. Clinical Frailty Scale [CFS] >6)[239] in whom invasive coronary angiography was considered clinically inappropriate and/or to carry excessive risk
- Patients with significant heart valve disease (greater than moderate valve disease)
- Patients with a previous LVEF <40%
- Patients with known or suspected hypertrophic/infiltrative cardiomyopathy or constrictive pericarditis

- Patients with non-CV comorbidity likely to cause death within 12 months (e.g. terminal cancer)

- Patients with severe renal impairment (eGFR <30 ml/min/1.73m^2) to allow safe administration of contrast agents in imaging studies

- Patients <18 years of age

- Female patients who are breastfeeding

- Patients with a history of allergy to contrast, adenosine, acetylcholine (ACh), nitrates or excipients

- Patients with a contraindication to adenosine (sick sinus syndrome, second or third-degree atrioventricular block, chronic obstructive lung disease with evidence of bronchospasm, or long QT syndrome)

- Patients with a severe concurrent medical condition that would prevent participation in study procedures

3.4 Study protocol

This was a prospective observational study of patients admitted to hospital with a primary diagnosis of HFpEF. Patients were extensively characterised during their inpatient stay by collecting demographic, echocardiographic, biomarker and physiological data. Following discharge from hospital, study participants underwent invasive coronary angiography with guidewire-based physiological testing and vasoreactivity testing. Those with no contraindication also underwent adenosine stress perfusion CMR imaging.

3.4.1 Identification of participants

All potential study participants were identified by screening of patients at three hospital sites: the Queen Elizabeth University Hospital (Glasgow), Glasgow Royal Infirmary (Glasgow) and Royal Alexandra Hospital (Paisley). I screened the case notes (electronic medical record and/or paper case notes) of patients admitted through the medical receiving units, cardiology wards and coronary care units at the three sites. Potential participants were first approached by their usual clinical team and were asked if they would be interested in being considered for participation in the study. I then approached patients who wished to learn more about the study. The details of the study were explained, and written information was provided.

3.4.2 Consent

Two-stage consent process

Consent was a two-stage process for 51 patients (48%); the remaining 55 patients underwent a single-stage consent process (discussed below). The first stage involved consenting to a blood test for NT-proBNP to confirm the suspected diagnosis of HF. A blood sample (150 μL) was analysed for NT-proBNP using a validated, point-of-care assay (Roche Cobas h232). The details of the study were discussed, and patients were provided with a patient information sheet (Appendix I). Patients were given at least one hour to decide whether they would like to participate in the first stage. Patients were informed that if their NT-proBNP level was elevated, they would be invited to participate in the second stage of the study. Those with an NT-proBNP <300 pg/mL were

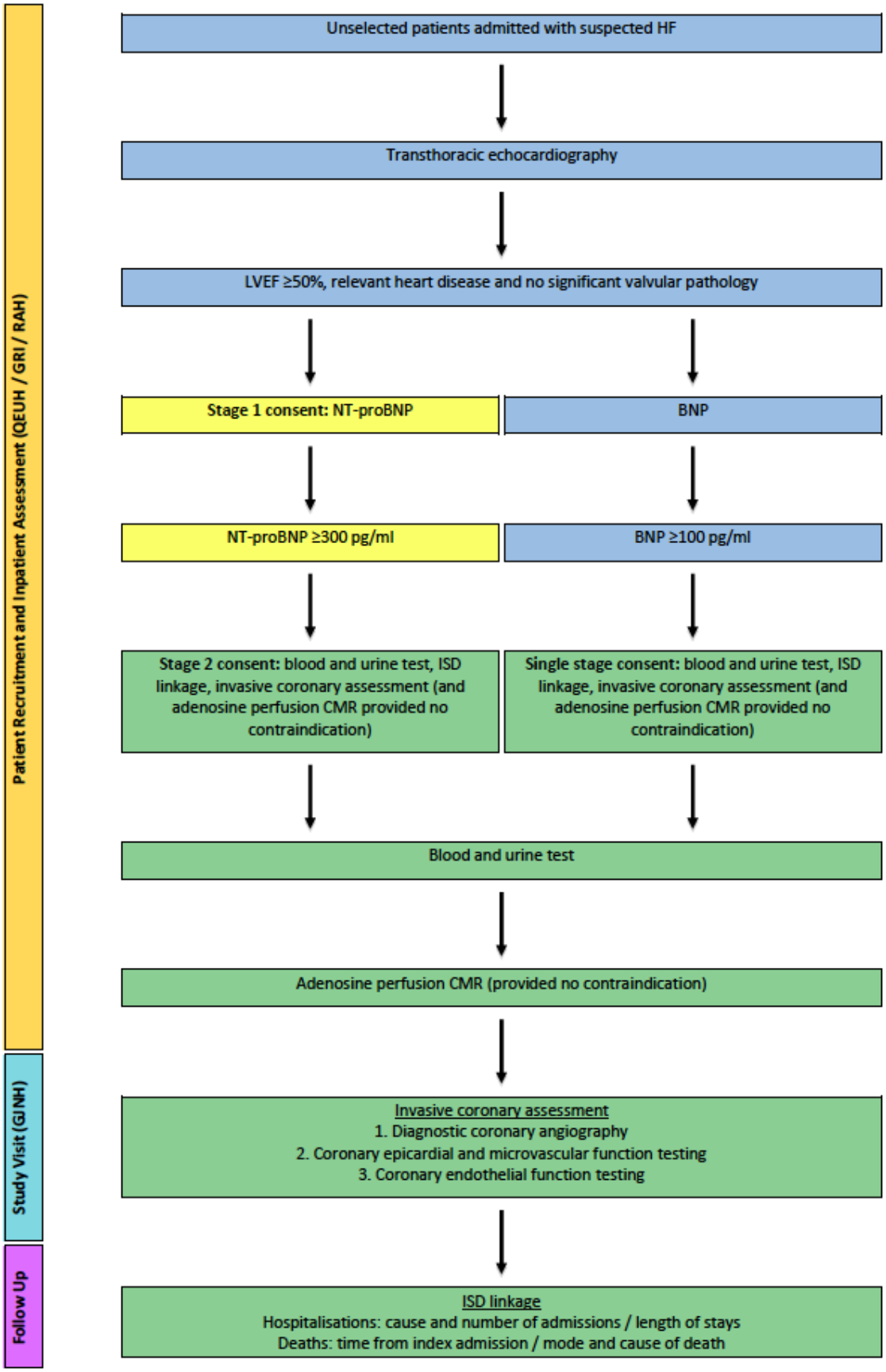
excluded. All patients underwent echocardiography prior to recruitment. LVEF was measured using Simpson's biplane method; if this was not possible due to a poor echocardiographic acoustic window, the LVEF was estimated by the sonographer and independently verified by an independent observer.

The second stage of the study involved consenting to invasive coronary angiography with guidewire-based coronary physiological assessment and vasoreactivity testing, where possible. Patients with no contraindication to magnetic resonance imaging (MRI) also consented to undergo adenosine stress perfusion CMR. In addition, blood (10 mL) and urine samples were collected from each patient. These samples were stored in the Queen Elizabeth University Hospital Clinical Research Biochemistry Laboratory in a locked and secure freezer. Lastly, patients consented to being "flagged" with the Information and Services Division (ISD) of NHS Scotland for follow-up data on hospital readmission or death. All patients were provided with verbal and written information (Appendix II) about the second stage of the study and were given a minimum of 24 hours to decide whether they would like to proceed.

Single-stage consent process

During the course of the recruitment period, BNP was introduced throughout NHS Greater Glasgow and Clyde for routine clinical use. Both BNP and NT-proBNP are recommended by international guidelines for the diagnosis of HF, and both have similar diagnostic performance.[238] Therefore, patients that had plasma BNP measured as part of routine standard of care did not require to have NT-proBNP measured in addition. Consequently, 55 patients (52%) underwent a single-stage consent process, similar to the second stage of the two-stage process (Appendix III).

The consent forms for the two-stage and single-stage processes can be found in Appendices IV-VI. At hospital discharge, a letter was sent to the general practitioner (GP) of each study participant providing information regarding the study and contact information for the research team (Appendix VII). An overview of the consent process and patient flow through the study is shown in Figure 3-1.



BNP, B-type natriuretic peptide; CMR, cardiac magnetic resonance; GJNH, Golden Jubilee National Hospital; HF, heart failure; ISD, Information Services Division; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone BNP; QEUH, Queen Elizabeth University Hospital; RAH, Royal Alexandra Hospital.

Figure 3-1: Overview of patient flow through study.

3.4.3 Inpatient assessment

During the inpatient stay, detailed demographic and clinical data were collected for each patient. Data were obtained through history, clinical examination and review of medical records. Laboratory results, echocardiographic data and radiology results were acquired from various hospital database systems.

Data were recorded on a secure online Good Clinical Practice (GCP)-approved electronic case report form (eCRF) (Castor EDC, Amsterdam, Netherlands). Each study participant was allocated a unique and anonymous study identification number. Baseline data were recorded on the eCRF during the index hospitalisation under the following headings: demographics, HF symptoms, medical history (including HF and CAD history), medications (at hospital admission and discharge), in-hospital treatment, vital signs, cardiovascular (CV) examination findings, and electrocardiography (ECG), chest X-ray (CXR), haematology, biochemistry and echocardiography findings.

3.4.4 Study procedures

Following hospital discharge, participants attended for invasive coronary angiography with guidewire-based coronary physiology testing and coronary vasoreactivity testing (where possible). In the absence of any contraindication to magnetic resonance imaging (MRI) (e.g. pacemaker, severe claustrophobia), participants also underwent adenosine stress perfusion CMR.

Invasive coronary angiography

Invasive coronary assessment was performed at a large regional cardiac centre (Golden Jubilee National Hospital, Clydebank) by three operators with extensive experience in invasive coronary physiology (Professor Keith Oldroyd, Dr Paul Rocchiccioli, Dr Mitchell Lindsay). Coronary angiography was performed as per standard practice with cardiac catheter laboratory equipment (Innova/Centricity, GE Healthcare, Chicago, IL, USA). LV end-diastolic pressure (LVEDP) was routinely measured in all patients. The coronary anatomy of study participants was described based on the interpretation of the attending interventional cardiologist and quantitative coronary angiography (QCA) analysis

performed using computer-assisted angiographic analysis (QAngio XA 7.3, Medis, Leiden, Netherlands) (Figure 3-2).

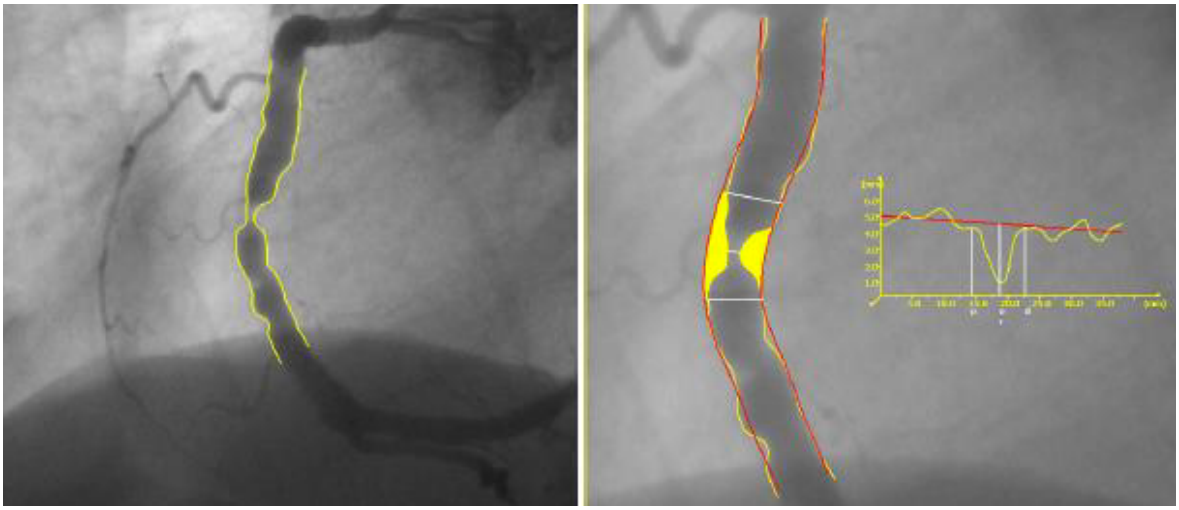


Figure 3-2: Example of QCA.

Guidewire-based coronary physiology testing

Comprehensive coronary guidewire assessment was performed on a single major epicardial coronary artery. The left anterior descending (LAD) artery was preferred as the vessel of choice, however, if technical factors precluded guidewire-based assessment of this vessel (e.g. severe coronary stenosis, tortuosity), the left circumflex (LCx) or right coronary artery (RCA) was selected. A pressure- and temperature-sensitive coronary guidewire (PressureWire Certus, Abbott Vascular, IL, USA) was used with the appropriate software and interface (RadiAnalyzer Xpress, Abbot Vascular, IL, USA) (Figure 3-3). The guidewire was calibrated outside the body and equalised in the guiding catheter before being advanced to the distal portion of the vessel of interest via the catheter. A 6-French coronary guiding catheter was routinely used, and all patients received an initial intra-arterial bolus of 5000 units of unfractionated heparin with additional bolus(es) as required to maintain an activated clotting time of 250 to 300 seconds.

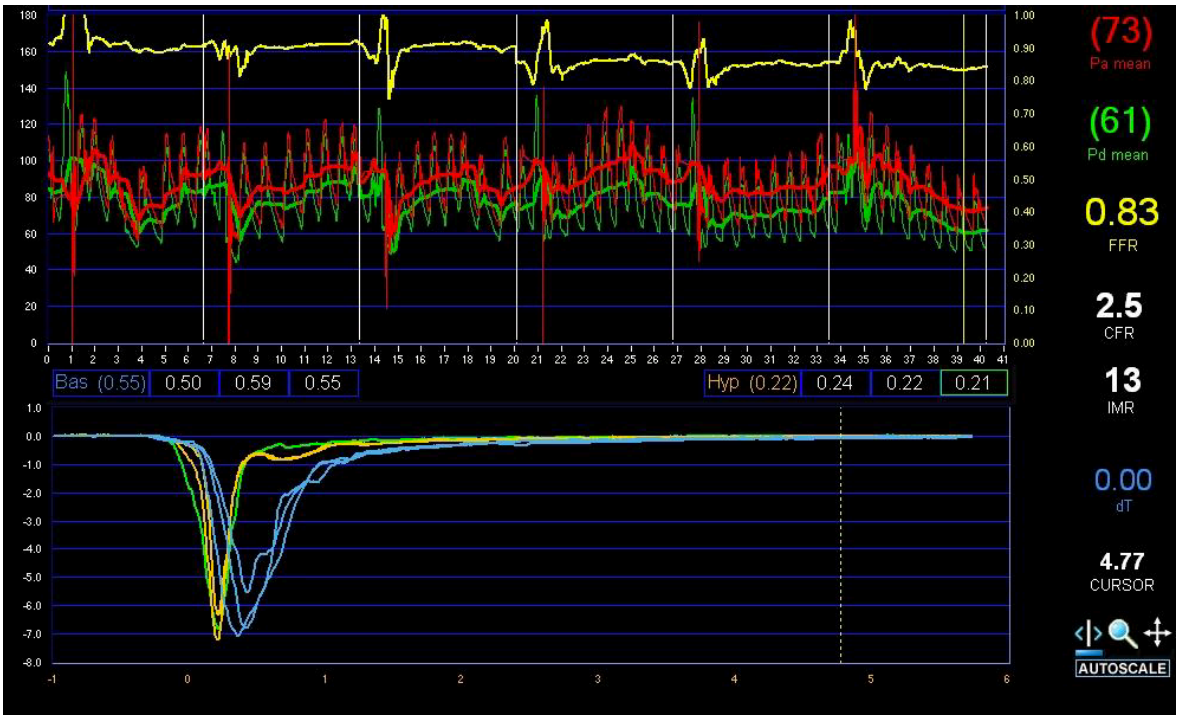


Figure 3-3: Example of output from RadiAnalyzer Xpress.

Hyperaemia

Adenosine was infused by intravenous infusion (140 μg/kg/min) for a minimum of two minutes to induce hyperaemia and the patient was assessed for a symptomatic and physiological response. If there was an inadequate response, the dose was increased to 210 μg/kg/min to achieve maximal hyperaemia. A 200 μg bolus of intra-coronary glyceryl trinitrate (GTN) was administered prior to the adenosine infusion to minimise the potential effects of coronary vasospasm on the readings. The mean aortic (Pa) and distal coronary (Pd) pressures were measured simultaneously under resting and hyperaemic conditions.

Thermodilution

Thermodilution was performed by intra-coronary injection of 3 mL of room temperature saline. The mean resting transit time (T_{mn}) was taken as the average of three transit times measured during resting conditions. Care was taken to obtain consistent and reproducible thermodilution curves. During maximal hyperaemia, these measurements were repeated to give the mean hyperaemic T_{mn} (Figure 3-3).

Using the resting and hyperaemic pressures and transit times, the fractional flow reserve (FFR), coronary flow reserve (CFR), and index of microcirculatory resistance (IMR) were calculated (see Chapter 1: Figure 1-3).

Fractional flow reserve

FFR (abnormal ≤0.80) was used to assess for flow-limiting epicardial CAD and was calculated as the distal coronary to aortic pressure ratio (Pd/Pa) at maximal hyperaemia.[97] All intermediate coronary lesions (50-70% stenosis) were assessed with FFR. In patients with a significant epicardial stenosis (i.e. ≥70% stenosis or 50-70% stenosis with an FFR ≤0.80), CFR and IMR were measured in another (non-obstructed) coronary artery to facilitate accurate assessment of coronary microvascular function.

Coronary flow reserve

CFR (abnormal <2.0) represents the coronary vasodilator capacity (epicardial and microvascular) and was calculated as the resting T_{mn} divided by the hyperaemic T_{mn}.[79,240]

Index of microcirculatory resistance

The IMR (abnormal ≥25) reflects the minimum resistance offered by the coronary microvasculature (independent of epicardial CAD) and was calculated as the product of the mean distal coronary artery pressure and the T_{mn} measured simultaneously at maximal hyperaemia.[127–129]

Coronary vasoreactivity testing

In suitable patients, endothelium-dependent coronary vasomotor function was then assessed using sequential intra-coronary infusions of incremental doses of acetylcholine (ACh) via the guiding catheter. Of note, coronary vasoreactivity testing was contraindicated in the majority of patients with obstructive epicardial CAD due to the risk of acute myocardial ischaemia from the combination of obstructive epicardial stenosis and coronary artery vasospasm.[241] Intra-coronary administration of ACh is an off-label use and is rarely used during standard NHS procedures. For this study, ACh was provided in pre-prepared packs by the Pharmacy Production Unit of NHS Greater Glasgow and Clyde. These packs were issued by the Trials Pharmacy on a named-patient basis on the

day the patient attended for coronary angiography. I prepared the reconstituted solutions in advance of the procedure for immediate administration in the catheter laboratory.

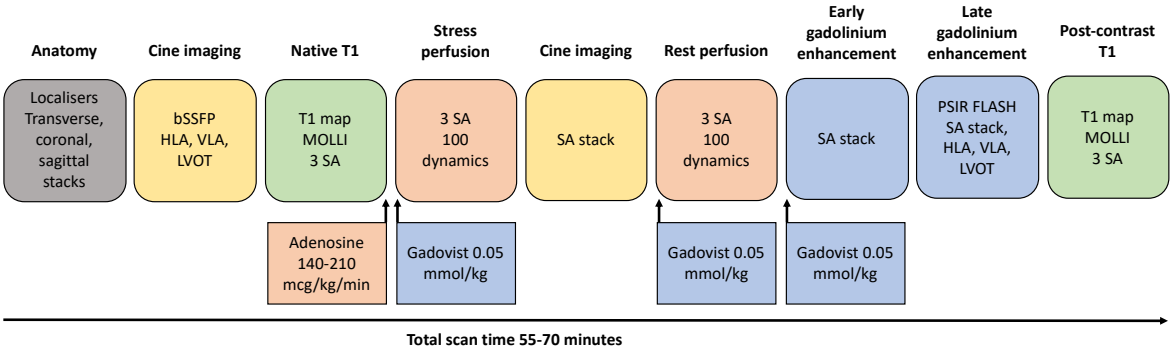
The infused doses of ACh were 0.364 μg, 3.64 μg, and 36.4 μg over 2 minutes followed by coronary vasospasm provocation testing (100 μg ACh bolus for left coronary artery or 50 μg for the right coronary artery over 20 seconds).[242] Finally, non-endothelial vasodilator function was assessed by intra-coronary administration of 300 μg of GTN.

At the end of each ACh infusion, following the ACh bolus and following GTN administration, coronary angiography and a 12-lead ECG were performed, and the patient was asked if they were experiencing any symptoms. I performed QCA of the target coronary artery using computer-assisted angiographic analysis (QAngio XA 7.3, Medis, Leiden, Netherlands). The coronary artery measurements were performed in the region where the greatest change had occurred during coronary reactivity testing. End-diastolic cine frames that best demonstrated the segment were selected, and calibration of the cine images was performed. Coronary artery diameter change (% from baseline) was measured in response to both ACh and GTN.[243] Angiographic evidence of significant endothelial dysfunction was defined by ≥20% luminal constriction during the ACh infusions.[244,245] A second trained observer (Dr Thomas Ford) performed QCA on a consecutive sample of 20% of cases, with high concordance for measurements of percentage lumen diameter change during ACh infusions (intra-class correlation coefficient for average measures 0.95 [95% confidence interval (CI) 0.82-0.99; p <0.001]). Ischaemic ECG changes were defined as ≥1 mm horizontal or down-sloping ST-segment depression or ST-segment elevation, or pathological T-wave inversion.

Adenosine perfusion cardiac magnetic resonance imaging

CMR acquisition

CMR was performed with gadolinium contrast, T1 mapping, and adenosine stress perfusion. All scans were performed on a 3.0 Telsa magnetic resonance imaging (MRI) scanner (MAGNETOM Prisma, Siemens Healthcare, Erlangen, Germany) based at the Glasgow Clinical Research Imaging Facility, Queen Elizabeth University Hospital, Glasgow. Patients were instructed to abstain from caffeine for 24 hours prior to the examination. All patients underwent a standardised protocol summarised in Figure 3-4.



bSSFP, balanced steady-state free precession; FLASH, fast low-angle shot; HLA, horizontal long-axis; LVOT, left ventricular outflow tract; MOLLI, modified Look-Locker inversion-recovery; PSIR, phase-sensitive inversion-recovery; SA, short-axis; VLA, vertical long-axis.

Figure 3-4: Standardised CMR protocol.

I was present throughout all the MRI scans to provide medical cover. Prior to the examination, each patient had a peripheral venous cannula sited in each arm for administration of the gadolinium contrast and adenosine during the scan. A blood pressure cuff, ECG electrodes and a phased-array surface body coil (Siemens Body 60, Erlangen, Germany) were applied. I prepared an infusion of 180 mg adenosine diluted with 0.9% sodium chloride to a volume of 180 mL (1 mg/mL). All patients had ECG monitoring throughout the scan.

The CMR protocol included cine (balanced steady-state free precession [bSSFP]) imaging, rest and stress perfusion imaging, late gadolinium enhancement (LGE) phase-sensitive inversion-recovery (PSIR) acquisitions, and T1 mapping (pre- and post-contrast) sequences.

Balanced steady-state free precession cine imaging

bSSFP cine imaging (using multi-slice single-shot breath-hold true fast imaging) was used for functional assessment and a short-axis (SA) cine stack of the LV from base to apex was acquired, consisting of 7 mm slices with a 3 mm interslice gap. Cine images were also obtained in the horizontal long-axis (HLA), vertical long-axis (VLA) and left ventricular outflow tract (LVOT) planes (Figure 3-5).

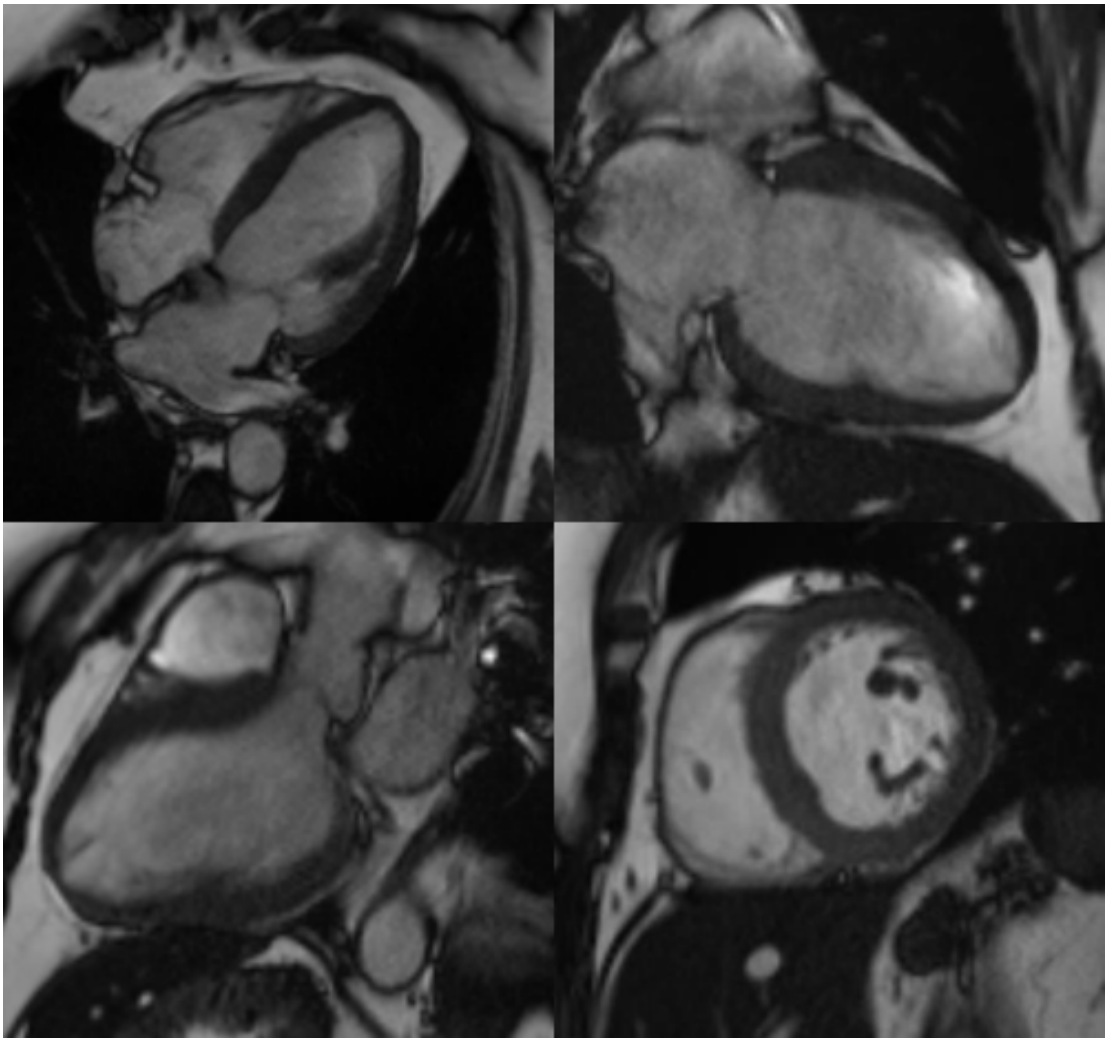


Figure 3-5: Example of HLA, VLA, LVOT and SA bSSFP cine imaging.

Rest and stress perfusion imaging

Perfusion imaging was performed at rest and under stress conditions. Intravenous infusion of adenosine at 140 to 210 μg/kg/min was administered to achieve an adequate haemodynamic stress response with the acquisition of three matched SA stress and rest perfusion images. Hyperaemia was confirmed by a haemodynamic response (i.e. systolic blood pressure drop >10 mmHg, heart rate increase of >10 beats per minute) and/or the onset of typical symptoms (i.e. dyspnoea, chest tightness, flushing) in response to adenosine infusion. A total

dose of 0.15 mmol/kg gadolinium-based contrast (Gadovist) was administered (0.05 mmol/kg bolus for first-pass stress perfusion, 0.05 mmol/kg bolus for first-pass rest perfusion and 0.05 mmol/kg top-up bolus for LGE imaging) (Figure 3-6).

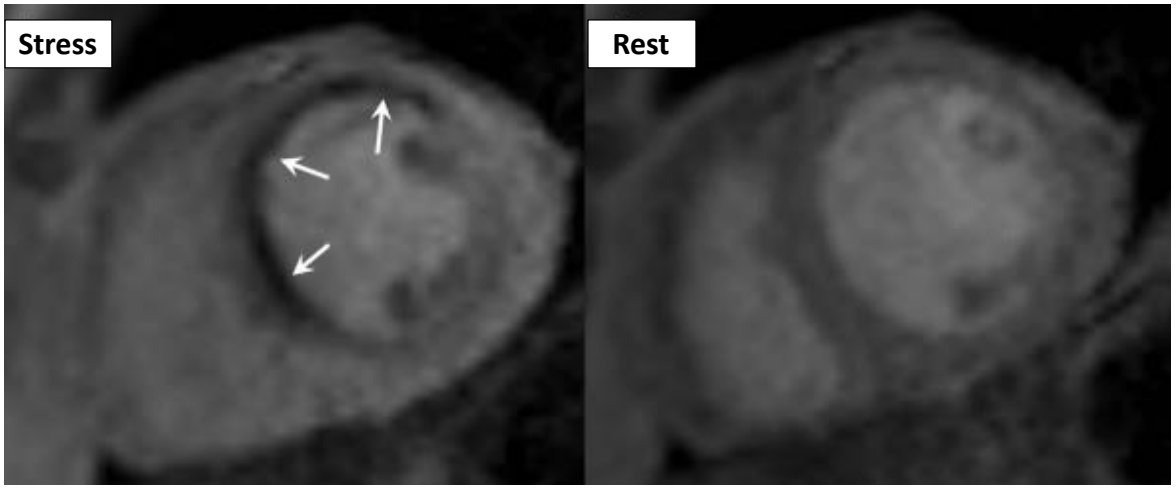


Figure 3-6: Example of inducible anterior/anteroseptal perfusion defect.

Late gadolinium enhancement imaging

Late gadolinium enhancement (LGE) images were acquired 10-15 minutes after intravenous injection of the third 0.05 mmol/kg bolus of Gadovist. A segmented PSIR turbo fast low-angle shot (FLASH) sequence was used to acquire multiple short and long axis images covering the entire LV (Figure 3-7).[246]

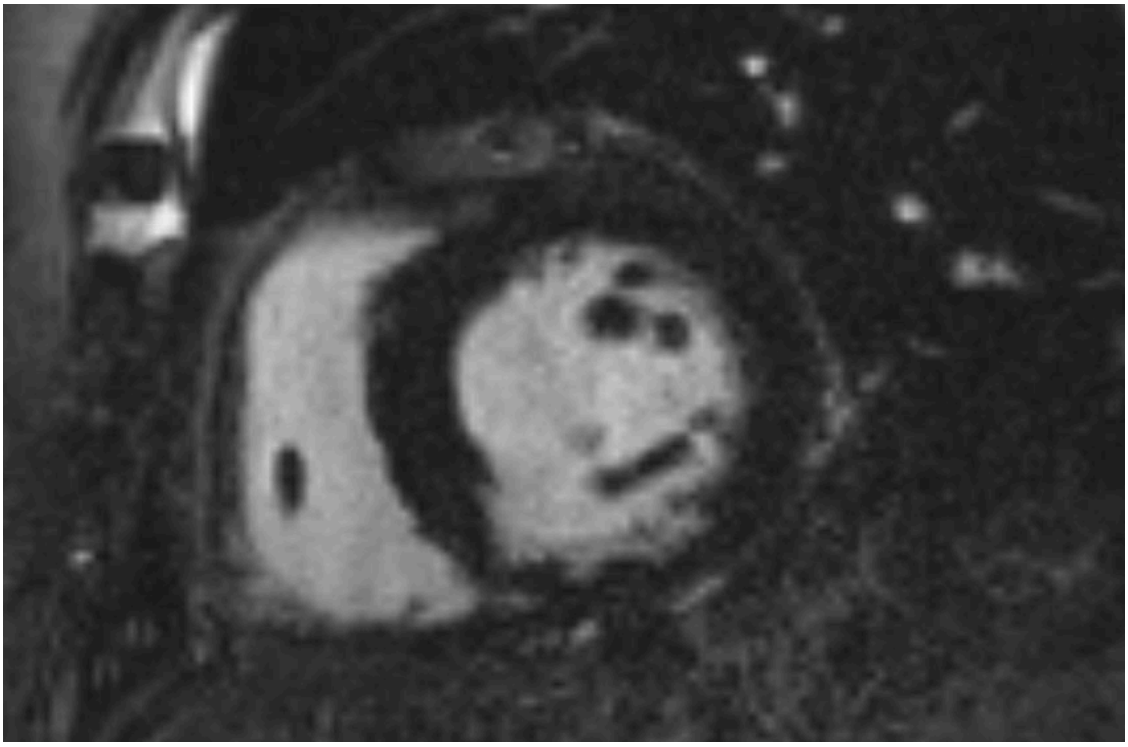


Figure 3-7: Example of subendocardial inferior MI on LGE imaging.

T1 mapping (pre- and post-contrast)

A modified Look-Locker inversion-recovery (MOLLI) sequence was used for T1 mapping and performed in three matched SA slices (basal, mid and apical) in mid-diastole prior to (for native T1) and 20 minutes after contrast (for quantification of extracellular volume [ECV]) (Figure 3-8).

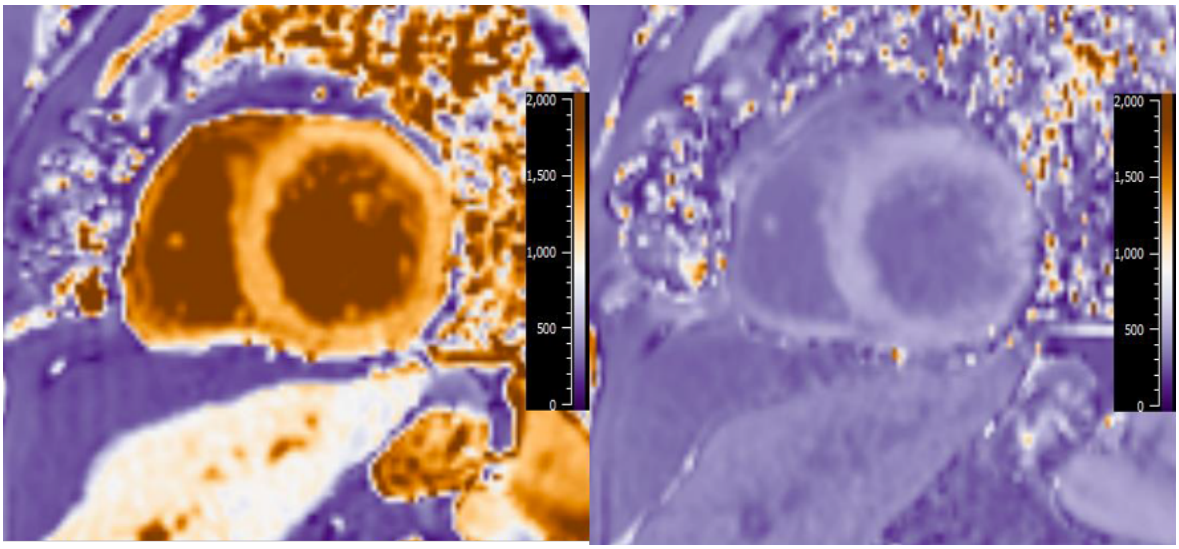


Figure 3-8: Example of pre- and post-contrast T1 mapping.

CMR image analysis

The CMR images were independently analysed on dedicated workstations by two observers with European Association of Cardiovascular Imaging accreditation in CMR analysis (myself [Level 2] and Professor Colin Berry [Level 3]).

Ventricular structure and function

Post-processing was performed using dedicated software (QMass 8.1, Medis, Leiden, Netherlands). End-systole was chosen as the point where the total ventricular blood pool was smallest and end-diastole as the point where it was largest at the mid-ventricular level. The most basal LV slice at both end-diastole and end-systole was defined as that in which the blood pool was surrounded by ≥50% of ventricular myocardium. The endocardial and epicardial borders were outlined using computer-assisted planimetry to obtain LV mass, end-diastolic and end-systolic volumes, and LVEF. The papillary muscles were included as part of the myocardial blood pool. The RV endocardial borders were outlined at end-diastole and end-systole to calculate the RV volumes and

ejection fraction. The normal reference ranges used for cardiac structure and function were derived from the UK Biobank population cohort.[247]

Perfusion imaging and myocardial-perfusion reserve index

Baseline stress and rest perfusion images were analysed using QMass 8.1 (Medis, Leiden, Netherlands). The endocardial and epicardial contours were manually outlined to the myocardial endocardial and epicardial borders with care being taken to avoid encroaching on the LV cavity. These contours were used to obtain the intensity over time curves at rest and stress using the American Heart Association (AHA) coronary arterial 17-segment model[248] (Figure 3-9); the apical segment was not calculated as the perfusion images were only acquired in SA. A blood-pool region of interest was also defined. The myocardial and blood-pool curves were then inspected, and the contours were re-adjusted if required to optimise the segmental time intensity curve slopes. The slope of the first-pass contrast enhancement for each of the myocardial segment was divided by the LV blood-pool slope to correct for changes in the input function caused by the haemodynamic effects of adenosine. The ratio of the myocardial perfusion index during stress to rest was defined as the myocardial-perfusion reserve index (MPRI).[249,250] Inducible ischaemia was defined as a global MPRI of <1.4; this threshold was previously reported to accurately detect obstructive epicardial CAD and CMD in patients with angina.[251]

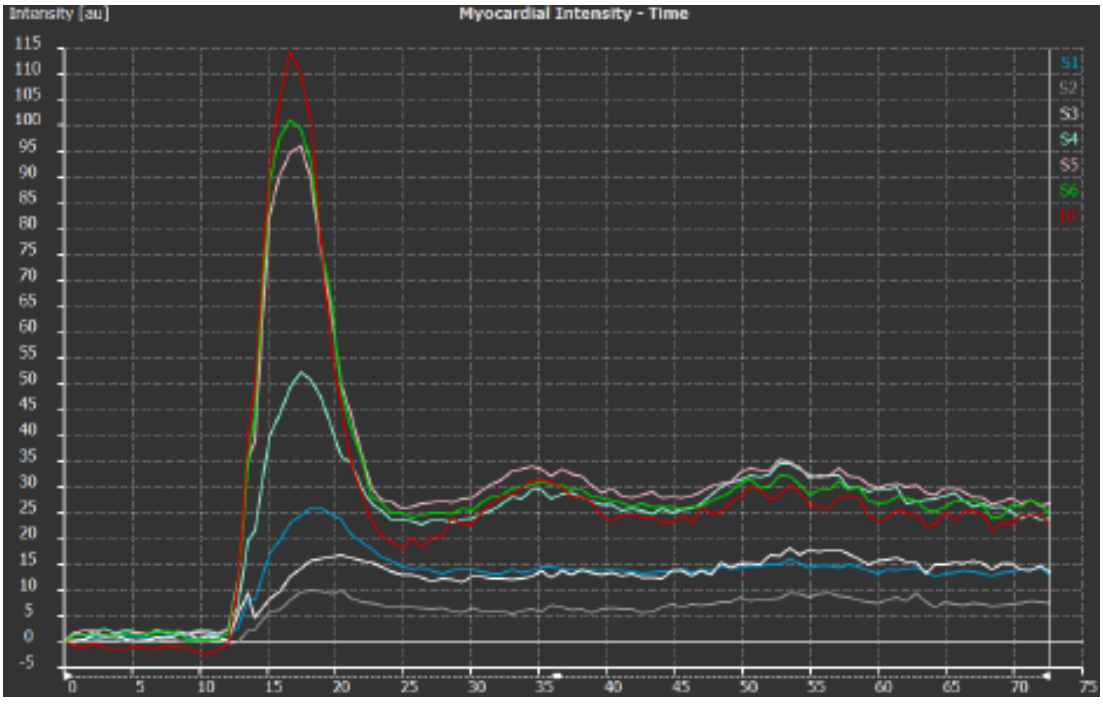


Figure 3-9: Example of myocardial and blood-pool perfusion curves.

LGE imaging

The presence of MI was established based on LGE imaging. MI was considered present if subendocardial or transmural LGE was confirmed in the distribution of a coronary artery territory on both short- and long-axis acquisitions.

T1 mapping and ECV

Gadolinium-based contrast agents distribute throughout the extracellular space and shorten T1 relaxation times of myocardium proportional to the local concentration of gadolinium.[252] Therefore, areas of myocardial fibrosis have shorter T1 relaxation times. The ECV can be estimated from myocardial and blood T1 before and after administration of contrast and the patient's haematocrit (cellular fraction of blood) according to Figure 3-10.[253]

$$ECV = (1 - \text{haematocrit}) \frac{\frac{1}{\text{post-contrast } T1_{myo}} - \frac{1}{\text{native } T1_{myo}}}{\frac{1}{\text{post-contrast } T1_{blood}} - \frac{1}{\text{native } T1_{blood}}}$$

ECV, extracellular volume; $T1_{blood}$, T1 of blood; $T1_{myo}$, T1 of myocardium.

Figure 3-10: ECV formula.

Native T1 and ECV maps were generated based on inline-generated, motion-corrected raw images using QMap 2.2.24 (Medis, Leiden, Netherlands) for quantification of global native T1 and ECV. LV contours were delineated with computer-assisted planimetry on the raw pre- and post-contrast T1 images. The contours were then copied onto the colour-encoded spatially co-registered maps with care being taken to avoid partial volume effects.[254] The patient's haematocrit (obtained at time of the CMR scan) was then entered into the QMap software to produce an ECV map (Figure 3-11). Myocardial segments (AHA model) with focal ischaemic LGE were excluded from native T1 and ECV analysis. Several studies have demonstrated that normal participants scanned at 3.0 Tesla can have an ECV of up to 30%.[255] Therefore, in this study an ECV of >30% was considered abnormal.

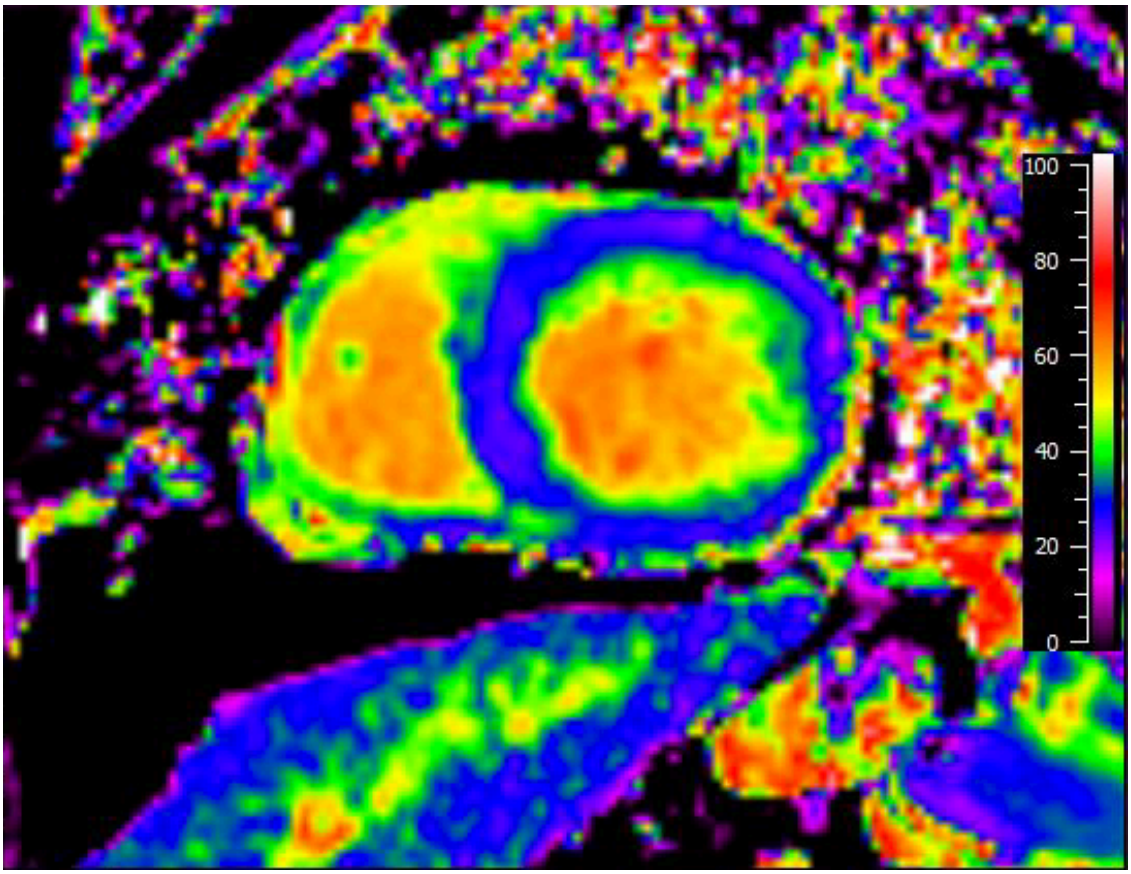


Figure 3-11: Example of ECV map.

3.4.5 Follow-up

All consenting patients were followed-up passively using record linkage through ISD of NHS Scotland. All participants were followed up for a minimum of 12 months. The dates of hospital admissions, reason for hospital admissions, date and cause of death were extracted. The cause of hospital admission and death were determined using the primary discharge diagnosis and cause of death, respectively. Electronic records for each participant were also reviewed to validate hospital discharge diagnoses and ensure that the follow-up data was complete and accurate.

3.5 Outcome measures

1. Obstructive epicardial CAD was defined as:

    - ≥70% stenosis of a major epicardial coronary artery (≥50% stenosis if the left main coronary artery)

    - 50-70% stenosis with an FFR ≤0.80

2. Endothelium-independent CMD was defined as at least one of:

    - CFR <2.0

    - IMR ≥25

3. Coronary endothelial dysfunction was defined as an abnormal response to intra-coronary ACh:

    - Epicardial endothelial dysfunction – epicardial coronary vasospasm (>90% luminal constriction) in association with ischaemic ECG changes in response to intra-coronary ACh infusion or bolus[146]

    - Microvascular endothelial dysfunction (endothelium-dependent CMD) – 20-90% luminal constriction and/or ischaemic ECG changes in response to intra-coronary ACh infusion[135,145]

4. CMR-proven MI was defined as subendocardial or transmural LGE in the distribution of a coronary artery territory

3.6 Sample size calculation

The prior literature suggests that the prevalence of CAD in patients with HFpEF is around 40-50% (see Chapter 2). To detect a prevalence of 50%, with an 8% margin of error at a 95% confidence interval, I estimated that 150 patients would require to be studied, using the following formula for an unlimited population:

$n = z^2*p*(1-p)/\varepsilon^2$

where:

- n is the population size
- z is the critical value of the normal distribution (z = 1.96 for a 95% CI)
- p is the estimated population proportion (p = 0.5 for an estimated population proportion of 50%)
- ε is the margin of error (ε = 0.08 for a margin of error of 8%)

so:

$n = 1.96^2*0.5*(1-0.5)/0.08^2$

n = 150

The sample size required to detect an estimated prevalence of 50% is larger than that required to detect any other estimated proportion, so this sample size was predicted to be more than sufficient to detect the prevalence of the other study endpoints (i.e. prevalence of CMD, coronary endothelial dysfunction and MI) with the same or narrower margin of error.

3.7 Data handling and statistical analysis

3.7.1 Data handling

All participant data were recorded on a secure online GCP-approved data management system (Castor EDC, Amsterdam, Netherlands). I manually entered all data manually into the eCRF. No patient identifying material was entered into the electronic database; patients were anonymised and identified by their unique study identification number. All data were checked manually and also underwent pre-specified electronic data validation checks. All queries were investigated, and data appropriately amended in the eCRF. This robust system ensured quality control of the data.

3.7.2 Statistical analysis

Using the above definitions, I calculated the prevalence and 95% CI of obstructive epicardial CAD, CMD (endothelium-independent), coronary endothelial dysfunction and CMR-proven MI in the study participants. We then divided the participants into those with and those without obstructive epicardial CAD, CMD, coronary endothelial dysfunction and CMR-proven MI, and compared clinical characteristics, laboratory data, and echocardiographic and CMR parameters.

Normally distributed continuous variables are presented as means with standard deviation (SD). Non-parametric continuous variables were presented as median with interquartile range (IQR). Comparison of categorical variables was performed using Chi-square or Fisher's exact tests. Differences in continuous variables between groups were assessed with the t-test or Wilcoxon rank sum test. Pearson tests were used for correlation analyses, where the Pearson correlation coefficient (r) represents the correlation between two continuous variables, the point-biserial correlation coefficient (r_{pb}) represents the correlation between a continuous and categorical variable, and the phi correlation coefficient (φ) represents the correlation between two categorical variables. A random effects model was used to compute the intra-class correlation coefficient for the reliability of QCA assessment of percentage lumen diameter change during ACh vasoreactivity testing measured by two independent observers on a consecutive sample of 20% of cases. Time-to-event analysis for hospitalisations and mortality were analysed using the Kaplan-Meier method. All p-values were two-sided, and a p-value of ≥ 0.05 indicated the absence of a statistically significant effect. All statistical analyses were performed using Stata v.14.2 (StataCorp, College Station, TX, USA).

Chapter 4 Recruitment and baseline characteristics

In this chapter I will describe the screening and recruitment process of the study. I will also describe the baseline characteristics of the cohort recruited, including medical history, physical examination findings, laboratory findings, and results of baseline investigations including echocardiography. I will then compare the recruited cohort to those in other studies and reflect on the generalisability of the study population.

4.1 Recruitment

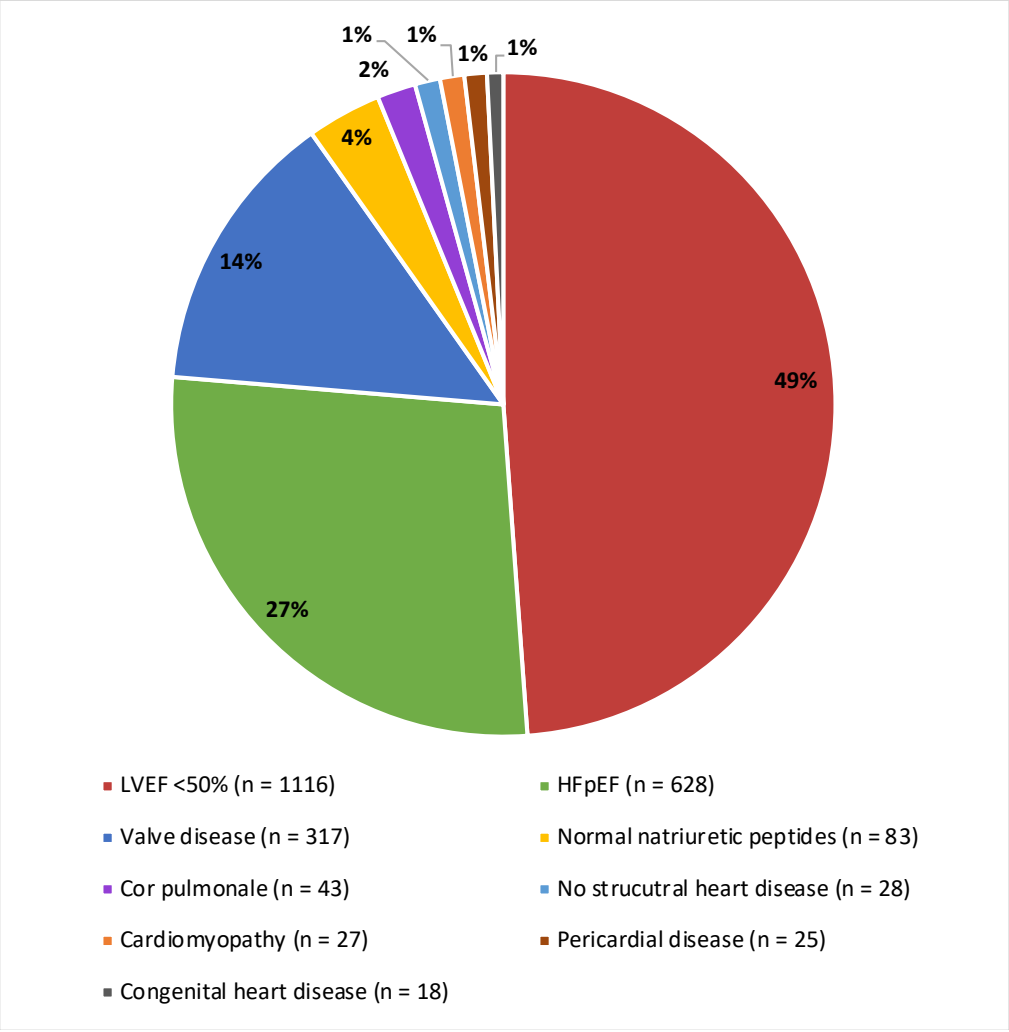
4.1.1 Screening

Patients admitted to the medical receiving units, cardiology wards and coronary care units (CCUs) at the Queen Elizabeth University Hospital (QEUH, Glasgow), Glasgow Royal Infirmary (GRI, Glasgow) and Royal Alexandra Hospital (RAH, Paisley) were screened for eligibility for inclusion. I screened case notes (electronic and/or paper) looking for patients with possible symptoms and signs of HF. I also screened inpatient echocardiography referrals and further investigated requests for suspected HF.

I prospectively screened admissions over a 19-month period between 1st January 2017 and 1st August 2018. I routinely screened all patients admitted to medicine and cardiology with suspected HF on weekdays over the recruitment period. I screened near-consecutive admissions, therefore, I was able to recruit an unselected cohort of 'real world' patients hospitalised with HFpEF. Potential participants who had not had BNP checked as part of standard clinical care were recruited in a two-stage consent process. Firstly, they consented to testing for NT-proBNP to confirm the suspected diagnosis of HF. Those with an elevated NT-proBNP were there then invited to participate in the full study, including invasive coronary angiography, guidewire-based coronary physiology testing, coronary vasoreactivity testing, CMR imaging, and passive follow-up via record linkage with Information Services Division (ISD) of NHS Scotland. Potentially eligible patients that had an elevated BNP as part of their standard clinical care were recruited via a single-stage process to the full study.

4.1.2 Screening log

I screened a total of 2285 patients admitted with suspected HF during the recruitment period. During further screening through history, examination, natriuretic peptides and echocardiography, 1657 patients were excluded as they did not meet the inclusion criteria for a diagnosis of HFpEF. The primary reasons for exclusion were: a left ventricular (LV) ejection fraction (LVEF) <50% (n = 1116); significant (greater than moderate) valvular heart disease (n = 317); normal natriuretic peptides (n = 83); cor pulmonale (n = 43); the absence of structural heart disease or diastolic dysfunction on echocardiography (n = 28); infiltrative or hypertrophic cardiomyopathy (n = 27); pericardial pathology (n = 25); and congenital heart disease (n= 18) (Figure 4-1).



HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction.

Figure 4-1: Diagnoses in unselected patients admitted with suspected HF.

A total of 628 patients were confirmed to have a diagnosis of HFpEF. Of these, 522 were excluded. The most common reasons for exclusion were: patients with severe frailty (i.e. Clinical Frailty Scale [CFS] >6)[239] in whom invasive coronary angiography was considered clinically inappropriate and to carry excessive risk (n = 196); renal impairment (i.e. estimated glomerular filtration rate [eGFR] <30 ml/min/1.73m^2) to allow the safe administration of contrast agents during the study investigations (n = 104); and cognitive impairment (n = 88) (Figure 4-2). A further 80 patients were excluded for miscellaneous reasons, including patients unable to participate due to geographical reasons and those participating in another study.

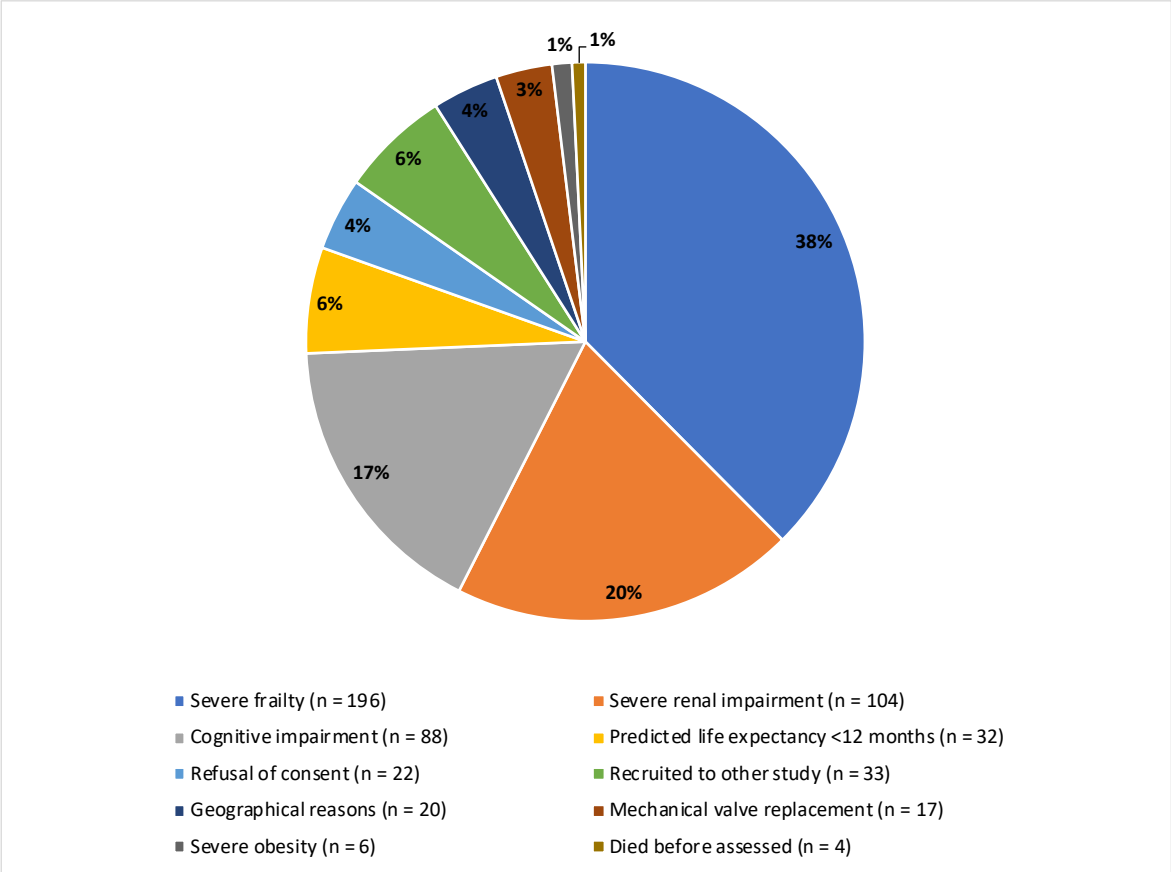


Figure 4-2: Reasons for exclusion of HFpEF patients.

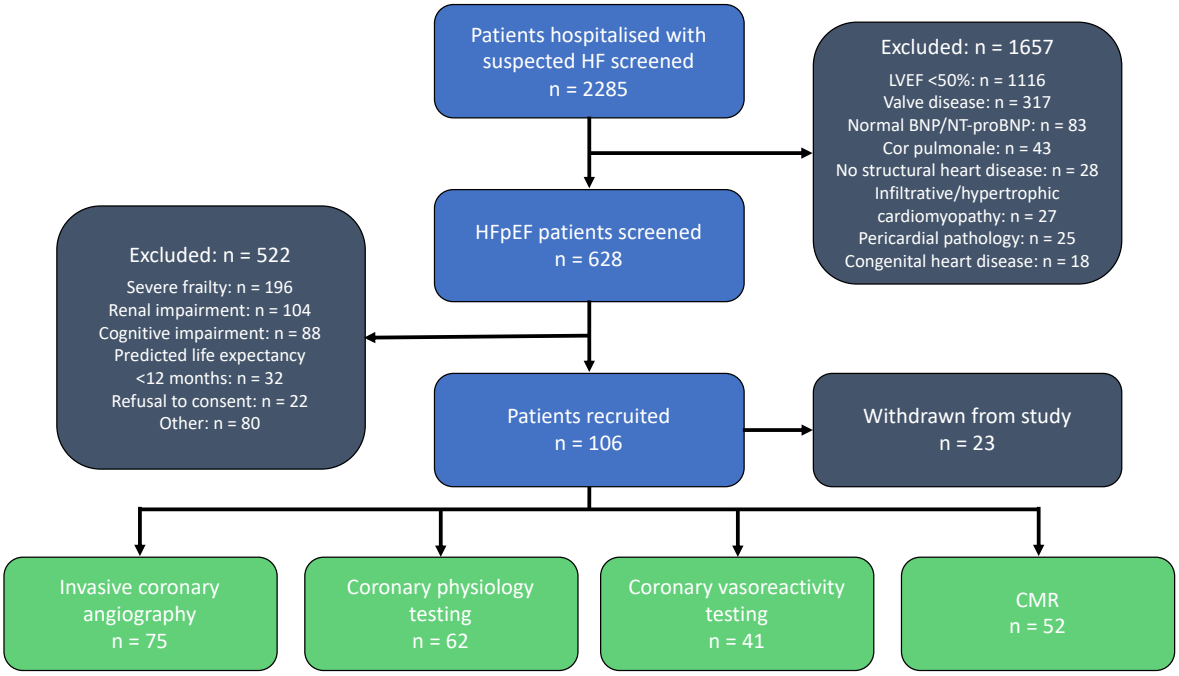
Table 4-1 details selected baseline characteristics of the 522 HFpEF patients who were excluded from the study. The mean age (standard deviation [SD]) of excluded HFpEF patients was 81 (10) years and 66% were female. Cardiovascular (CV) comorbidities were common, natriuretic peptides were significantly elevated and echocardiographic signs of elevated LV filling pressures were highly prevalent in the excluded HFpEF group.

	Excluded HFpEF patients (n = 522)
Demographics	
Age (years)	81 [10]
Female sex	345 (66)
Hospitalisation details	
Length of stay (days)	10 [5-18]
Past medical history	
Any CAD	209 (40)
Hypertension	407 (78)
AF	318 (61)
Biochemistry	
BNP (pg/mL)	712 [377-1127]
NT-proBNP (pg/mL)	2714 [817-4341]
Echocardiography	
LVH	355 (68)
LA dilatation	449 (86)
Diastolic dysfunction	350 (67)

Values are mean [standard deviation], median [Q1-Q3], or n (%). AF, atrial fibrillation; BNP, B-type natriuretic peptide; CAD, coronary artery disease; HFpEF, heart failure with preserved ejection fraction; LA, left atrial; LVH, left ventricular hypertrophy; NT-proBNP, N-terminal prohormone BNP.

Table 4-1: Selected baseline characteristics of excluded HFpEF patients.

A total of 106 HFpEF patients met the inclusion criteria and agreed to participate in the study. Twenty-three participants did not undergo the study investigations after recruitment. This was predominantly due to a decline in participants' health and/or functional status making proceeding with the investigations inappropriate. A total of 83 participants underwent invasive coronary angiography or CMR. Seventy-five participants (71%) underwent invasive coronary angiography. Sixty-two participants (58%) had guidewire-based coronary physiology testing and 41 (39%) underwent vasoreactivity testing. Fifty-two participants (49%) underwent CMR and 44 (42%) had both invasive coronary angiography and CMR (Figure 4-3).



BNP, B-type natriuretic peptide; CMR, cardiac magnetic resonance; HF, heart failure; HFpEF, HF with preserved ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone BNP.

Figure 4-3: Screening and recruitment.

4.2 Baseline characteristics

A total of 106 patients agreed to participate in the study. Of these, 83 underwent study investigations. All 106 patients agreed to long-term follow-up via electronic medical record linkage.

4.2.1 Demographics

The baseline demographics of the recruited patients are shown in Table 4-2. The mean age was 72 (9) years, with a broad overall age range of 45 to 87 years. Half of the entire cohort were female; 97% were Caucasian and the remaining 3% were South Asian.

The mean body mass index (BMI) was 33 (8) kg/m^2; 84% of participants were overweight (i.e. BMI ≥25 kg/m^2) and 62% were obese (i.e. BMI ≥30 kg/m^2). Sixteen percent of patients were current smokers and 44% were ex-smokers; 12% had current or previous excessive alcohol intake and 41% consumed alcohol within recommended limits. Those recruited to the study that did not undertake the study investigations had a longer hospital stay (median 12 vs. 7 days; p <0.01) and were more likely to have a smoking history (83% vs. 53%; p = 0.011) than those that underwent the study investigations.

Sixty-one patients (58%) were recruited from the QEUH, 37 (35%) from GRI and eight (8%) from the RAH. The median duration of hospitalisation was eight (6-13) days. Most patients were referred to hospital by their general practitioner (67%), 28% presented to the emergency department, and 5% were admitted from an outpatient clinic. Ninety-five percent of the cohort recruited were managed on the cardiology wards; the remaining 5% were treated on general medical wards.

	All patients (n = 106)	Had study investigations (n = 83)	Did not have study investigations (n = 23)	p-value
Demographics				
Age (years)	72 [9]	72 [9]	71 [10]	0.69
Female sex	53 (50)	40 (48)	13 (57)	0.48
Ethnicity				
Caucasian	103 (97)	81 (98)	22 (96)	0.62
South Asian	3 (3)	2 (2)	1 (4)	
Height (m)	1.65 [0.10]	1.66 [0.10]	1.65 [0.10]	0.67
Weight (kg)	91 [25]	90 [24]	93 [28]	0.64
BMI (kg/m^2)	33 [8]	33 [7]	34 [10]	0.39
BSA (m^2)	1.96 [0.27]	1.96 [0.27]	1.97 [0.27]	0.88
Obesity	53 (50)	39 (47)	14 (61)	0.24
Clinical Frailty Score				
1 = Very fit	2 (2)	2 (2)	0 (0)	0.96
2 = Well	23 (22)	19 (23)	4 (17)	
3 = Managing well	40 (38)	31 (37)	9 (39)	
4 = Vulnerable	20 (19)	15 (18)	5 (22)	
5 = Mildly frail	17 (16)	13 (16)	4 (17)	
6 = Moderately frail	4 (4)	3 (4)	1 (4)	
Smoking history	63 (59)	44 (53)	19 (83)	0.011
Current smoker	17 (27)	13 (29)	4 (21)	0.81
Ex-smoker (≤12 months)	3 (5)	2 (4)	1 (5)	
Ex-smoker (>12 months)	44 (69)	30 (67)	14 (74)	
Alcohol intake	56 (53)	42 (51)	14 (61)	0.38
Within recommended limits	43 (77)	35 (83)	8 (57)	0.081
Current excess	6 (11)	4 (10)	2 (14)	
Previous excess	7 (12)	3 (7)	4 (29)	
Hospitalisation details				
Length of stay (days)	8 [6-13]	7 [5-11]	12 [7-18]	<0.01
Recruitment site				
QEUH	61 (58)	50 (60)	11 (48)	0.074
GRI	37 (35)	25 (30)	12 (52)	
RAH	8 (8)	8 (10)	0 (0)	
Referral source				
GP referral	71 (67)	57 (69)	14 (61)	0.62
ED via ambulance	18 (17)	12 (14)	6 (26)	
ED self-presentation	12 (11)	10 (12)	2 (9)	
OPC	5 (5)	4 (5)	1 (4)	
Admission ward				
Cardiology ward	82 (77)	61 (73)	21 (91)	0.071
CCU	19 (18)	17 (20)	2 (9)	0.19
General medical ward	3 (3)	3 (4)	0 (0)	0.35

Medical receiving ward	2 (2)	2 (2)	0 (0)	0.45

Values are mean [standard deviation], median [Q1-Q3], or n (%). BMI, body mass index; BSA, body surface area; CCU, coronary care unit; ED, emergency department; GP, general practitioner; GRI, Glasgow Royal Infirmary; OPC, outpatient clinic; QEUH, Queen Elizabeth University Hospital; RAH, Royal Alexandra Hospital.

Table 4-2: Demographics of study participants.

4.2.2 Clinical features

Typical symptoms and signs of HF were very common in the HFpEF cohort (Table 4-3). The most frequently reported symptoms were fatigue (95%) and ankle swelling (92%); 68% experienced orthopnoea and 45% had paroxysmal nocturnal dyspnoea (PND). Most patients were in New York Heart Association (NYHA) functional class III at presentation (56%), with 42% reporting NYHA IV symptoms and only 2% in NYHA class II. No patients were in NYHA class I.

On clinical examination, the most common clinical sign was peripheral oedema (91%). Sixty-two percent of patients had mild to moderate oedema (to below the knee) and 28% had significant oedema to the thigh, sacrum and/or abdomen. Jugular venous distention (JVD) was detected in 72%. Pulmonary crepitations were detected in 77% of patients, and 42% had evidence of pleural effusion(s) (usually bilateral) on clinical examination.

	All patients (n = 106)	**Had study investigations (n = 83)**	**Did not have study investigations (n = 23)**	**p-value**
HF symptoms				
NYHA functional class				
II	2 (2)	2 (2)	0 (0)	0.28
III	59 (56)	43 (52)	16 (70)	
IV	45 (42)	38 (46)	7 (30)	
Orthopnoea	72 (68)	56 (67)	16 (70)	0.85
PND	48 (45)	39 (47)	9 (39)	0.50
Ankle swelling	98 (92)	76 (92)	22 (96)	0.51
Wheeze	18 (17)	13 (16)	5 (22)	0.49
Palpitations	12 (11)	11 (13)	1 (4)	0.23
Fatigue	101 (95)	79 (95)	22 (96)	0.92
Admission vital signs				
HR (bpm)	83 [25]	83 [26]	80 [24]	0.62
SBP (mmHg)	149 [29]	151 [29]	144 [29]	0.31
DBP (mmHg)	78 [19]	80 [19]	72 [16]	0.09
MAP (mmHg)	102 [18]	103 [18]	96 [17]	0.087

HF signs				
JVD	76 (72)	58 (70)	18 (78)	0.43
Murmur	27 (25)	23 (28)	4 (17)	0.31
Crepitations	82 (77)	64 (77)	18 (78)	0.91
Pleural effusion(s)	45 (42)	35 (42)	10 (43)	0.91
Right	4 (9)	4 (11)	0 (0)	0.36
Left	2 (4)	1 (3)	1 (10)	
Bilateral	39 (87)	30 (86)	9 (90)	
Oedema	96 (91)	74 (89)	22 (96)	0.35
Ankle	15 (16)	12 (16)	3 (14)	0.40
Knee	51 (53)	39 (53)	12 (55)	
Thigh	12 (12)	8 (11)	4 (18)	
Sacrum	9 (9)	9 (12)	0 (0)	
Abdomen	9 (9)	6 (8)	3 (14)	
Ascites	6 (6)	4 (5)	2 (9)	0.48

Values are mean [standard deviation] or n (%). DBP, diastolic blood pressure; HF, heart failure; HR, heart rate; JVD, jugular venous distention; MAP, mean arterial pressure; NYHA, New York Heart Association; PND, paroxysmal nocturnal dyspnoea; SBP; systolic blood pressure.

Table 4-3: Clinical features of study participants.

4.2.3 Past medical history

HF history

The majority of the study participants (65%) presented with *de novo* HF (Table 4-4). Of those with a previous diagnosis of HF, 59% had been diagnosed in the preceding two years and 65% were under the care of a cardiologist. Fourteen patients had been admitted to hospital with HF in the preceding six months.

	All patients (n = 106)	**Had study investigations (n = 83)**	**Did not have study investigations (n = 23)**	**p-value**
History of HF				
Previous HF diagnosis	37 (35)	30 (36)	7 (30)	0.61
HF diagnosis >2 years	15 (14)	14 (17)	1 (4)	0.13
Previous HFH	24 (23)	18 (22)	6 (26)	0.66
HFH <6 months	14 (13)	9 (11)	5 (22)	0.17

Values are n (%). HF, heart failure; HFH, HF hospitalisation.

Table 4-4: HF history of study participants.

CAD history

Overall, 36% of the cohort had a previous history of CAD (Table 4-5). A history of CAD was defined as at least one of: a clinical history of CAD (angiographically-

documented CAD or angina requiring treatment); previous myocardial infarction (MI); or coronary revascularisation. Twenty-four patients (23%) had a previous history of MI. Nineteen patients were treated for angina for a median duration of 7 (4-15) years; nine patients had current symptoms of angina. Thirty-three patients had previous undergone coronary angiography; 17 had previously had percutaneous coronary intervention (PCI) and five had previous coronary artery bypass grafting (CABG).

	All patients (n = 106)	**Had study investigations (n = 83)**	**Did not have study investigations (n = 23)**	**p-value**
History of CAD				
Any CAD	38 (36)	28 (34)	10 (43)	0.39
MI	24 (23)	18 (22)	6 (26)	0.65
Angina	19 (18)	13 (16)	6 (26)	0.25
Current angina	9 (8)	6 (7)	3 (13)	0.37
Previous coronary angiography	33 (31)	26 (31)	7 (30)	0.93
Revascularisation	20 (19)	14 (17)	6 (26)	0.32
PCI	17 (16)	12 (14)	5 (22)	0.40
CABG	5 (5)	4 (5)	1 (4)	0.93

Values are n (%). CABG, coronary artery bypass grafting; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 4-5: CAD history of study participants.

Other comorbidities

Table 4-6 demonstrates the burden of comorbid conditions in the cohort. The typical comorbidities associated with HFpEF were highly prevalent, with hypertension and atrial fibrillation (AF) being the most common (75% and 62%, respectively). One patient with AF had a CHA_2DS_2VASc score of <2; the majority had a score of 3 to 5.

Diabetes was present in 51% of the cohort; the majority of whom were managed with oral hypoglycaemic agents. Despite excluding patients with an eGFR <30 mL/min/1.73m^2, 29% of patients had chronic kidney disease (CKD, i.e. baseline eGFR 30-60 mL/min/1.73m^2). Other non-CV comorbidities commonly seen were obstructive airways disease (28%), anaemia (25%), and osteoarthritis (21%). There were no significant differences in the prevalence of comorbidities between those who did and did not undergo the study investigations.

	All patients (n = 106)	Had study investigations (n = 83)	Did not have study investigations (n = 23)	p-value
CV comorbidities				
Hypertension	80 (75)	61 (73)	19 (83)	0.37
Dyslipidaemia	13 (12)	8 (10)	5 (22)	0.12
CVD	17 (16)	15 (18)	2 (9)	0.28
PAD	11 (10)	9 (11)	2 (9)	0.77
AF	66 (62)	55 (66)	11 (48)	0.11
Permanent	31 (29)	27 (33)	4 (17)	0.16
Persistent	17 (16)	15 (18)	2 (9)	0.28
Paroxysmal	11 (10)	6 (7)	5 (22)	0.043
New diagnosis	8 (8)	8 (10)	0 (0)	0.12
$CHA_2DS_2VAS_c$ score				
1	1 (2)	1 (2)	0 (0)	0.49
2	3 (5)	3 (5)	0 (0)	
3	12 (18)	12 (22)	0 (0)	
4	22 (33)	18 (33)	4 (36)	
5	20 (30)	14 (25)	6 (55)	
6	1 (2)	1 (2)	0 (0)	
7	5 (8)	4 (7)	1 (9)	
8	2 (3)	2 (4)	0 (0)	
Valve disease (mild/moderate)	21 (20)	17 (20)	4 (17)	0.74
AS	10 (9)	7 (8)	3 (13)	0.50
AR	5 (5)	5 (6)	0 (0)	0.23
MS	3 (3)	2 (2)	1 (4)	0.62
MR	8 (8)	7 (8)	1 (4)	0.51
TR	3 (3)	3 (4)	0 (0)	0.35
Valve replacement	5 (5)	4 (5)	1 (4)	0.92
Non-CV comorbidities				
Diabetes	54 (51)	44 (53)	10 (43)	0.42
CKD	31 (29)	23 (28)	8 (35)	0.51
Chronic liver disease	2 (2)	1 (1)	1 (4)	0.33
Depression	5 (5)	4 (5)	1 (4)	0.92
Cancer	10 (9)	6 (7)	4 (17)	0.14
COPD	22 (21)	19 (23)	3 (13)	0.30
Asthma	8 (8)	5 (6)	3 (13)	0.26
Anaemia	26 (25)	21 (25)	5 (22)	0.73
Hypothyroidism	14 (13)	12 (14)	2 (9)	0.47
Osteoarthritis	23 (22)	18 (22)	5 (22)	1.0

Values are n (%). AF, atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; CVD, cerebrovascular disease; MR, mitral regurgitation; MS, mitral stenosis; PAD, peripheral arterial disease; TR, tricuspid regurgitation.

Table 4-6: Past medical history of study participants.

4.2.4 Drug history – medication on admission

Table 4-7 shows the frequency of prescription of CV and non-CV medication at the time of hospital admission. The most commonly prescribed medications were statins (68%), for CV risk reduction and hypercholesterolaemia, and beta-blockers (63%), principally for AF and hypertension. Angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) (62%) and calcium channel blockers (CCBs) were also frequently prescribed (42%), predominantly for hypertension. Other medication used for the treatment of angina, such as long-acting nitrates and nicorandil, were not commonly prescribed (11% and 8%, respectively).

Forty-six patients (43%) were treated with loop diuretics on admission. Eighty percent were treated with furosemide and 20% with bumetanide; the median furosemide equivalent dose (i.e. 40 mg furosemide = 1 mg bumetanide) was 80 (40-120) mg. A minority of patients were treated with a thiazide (11%) or mineralocorticoid receptor antagonist (MRA) (5%).

Forty-nine patients (46%) were treated with an anticoagulant (84% of those with AF were anticoagulated) and 34% were on antiplatelet therapy. Eighty-one percent of patients with diabetes were on treatment; 61% were treated with a biguanide, 31% with a sulphonylurea, and 31% with insulin.

In terms of non-CV medication, bronchodilator therapy and antidepressants were commonly prescribed (30% and 26%, respectively).

	All patients (n = 106)	**Had study investigations (n = 83)**	**Did not have study investigations (n = 23)**	**p-value**
CV medication				
Antiplatelet	36 (34)	29 (35)	7 (30)	0.69
Aspirin	24 (23)	19 (23)	5 (22)	0.91
Other antiplatelet	13 (12)	11 (13)	2 (9)	0.56
Anticoagulant	49 (46)	41 (49)	8 (35)	0.21
DOAC	27 (25)	23 (28)	4 (17)	0.31
Warfarin	22 (21)	18 (22)	4 (17)	0.65
Statin	72 (68)	58 (70)	14 (61)	0.41
Loop diuretic	46 (43)	38 (46)	8 (35)	0.35
Furosemide	37 (80)	32 (84)	5 (62)	0.16

Bumetanide	9 (20)	6 (16)	3 (38)	
Furosemide-equivalent dose (mg)	80 [40-120]	80 [40-120]	80 [40-160]	0.87
Thiazide	12 (11)	8 (10)	4 (17)	0.30
MRA	5 (5)	3 (4)	2 (9)	0.31
ACEI/ARB	66 (62)	54 (65)	12 (52)	0.26
ACEI	45 (42)	39 (47)	6 (26)	0.073
ARB	22 (21)	16 (19)	6 (26)	0.48
Beta-blocker	67 (63)	54 (65)	13 (57)	0.45
CCB	45 (42)	34 (41)	11 (48)	0.56
Long-acting nitrate	12 (11)	7 (8)	5 (22)	0.075
Nicorandil	9 (8)	6 (7)	3 (13)	0.38
Amiodarone	5 (5)	3 (4)	2 (9)	0.31
Digoxin	8 (8)	6 (7)	2 (9)	0.81
	(n = 54)	(n = 44)	(n = 10)	
Diabetic medication	44 (81)	37 (84)	7 (70)	0.30
Insulin	17 (31)	16 (36)	1 (10)	0.11
Biguanide	33 (61)	28 (64)	5 (50)	0.42
Sulphonylurea	17 (31)	13 (30)	4 (40)	0.52
Thiazolidinedione	1 (2)	1 (2)	0 (0)	0.63
DPP-4 inhibitor	3 (6)	2 (5)	1 (10)	0.50
GLP-1 receptor antagonist	2 (4)	2 (5)	0 (0)	0.49
SGLT-2 inhibitor	2 (4)	1 (2)	1 (10)	0.24
Non-CV medication				
Inhalers				
Bronchodilator	32 (30)	24 (29)	8 (35)	0.59
Steroid	23 (22)	20 (24)	3 (13)	0.26
Antidepressant	28 (26)	19 (23)	9 (39)	0.12
NSAID	2 (2)	1 (1)	1 (4)	0.33

Values are median [Q1-Q3] or n (%). ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CV, cardiovascular; DOAC, direct oral anticoagulant; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; MRA, mineralocorticoid receptor antagonist; NSAID, non-steroidal anti-inflammatory drug; SGLT-2, sodium-glucose co-transporter-2.

Table 4-7: Admission medication of study participants.

4.2.5 Drug history – medication during admission and at discharge

Table 4-8 summarises the treatment patients received during admission. Almost all patients (98%) were treated with loop diuretics. Ninety-six patients (91%) received intravenous (IV) furosemide; 87 were given more than one IV dose and nine had a single dose followed by oral therapy. Eight patients (8%) were treated with oral diuretics. Five percent of participants were treated with IV nitrate during admission and one patient was treated with dopamine. Forty-

eight patients (45%) required oxygen therapy, two patients were treated with continuous positive airway pressure (CPAP) and no patients required intubation.

	All patients (n = 106)	Had study investigations (n = 83)	Did not have study investigations (n = 23)	p-value
In-hospital treatment				
Furosemide	104 (98)	81 (98)	23 (100)	0.45
IV (>1 dose)	87 (84)	67 (83)	20 (87)	0.79
IV (1 dose)	9 (9)	7 (9)	2 (9)	
Oral	8 (8)	7 (9)	1 (4)	
IV nitrate	5 (5)	4 (5)	1 (4)	0.92
Dopamine	1 (1)	0 (0)	1 (4)	0.056
Oxygen	48 (45)	37 (45)	11 (48)	0.78
FiO_2 (%)	28 [24-35]	28 [24-35]	28 [24-35]	0.79
CPAP	2 (2)	1 (1)	1 (4)	0.33

Values are median [Q1-Q3] or n (%). CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; IV, intravenous.

Table 4-8: In-hospital treatment of study participants.

Table 4-9 details the prescribed drug therapy at hospital discharge. There was no change in ACEI/ARB use at discharge. Beta-blocker and digoxin use increased (63% to 75% and 8% to 29%, respectively), use of CCBs decreased (42% to 25%) and there was no significant change in the use of long-acting nitrates or nicorandil.

The use of diuretic therapy increased markedly, with almost all patients being treated with a loop diuretic at the time of hospital discharge (43% on admission to 98% at discharge). Again, 80% of patients were treated with furosemide and 20% with bumetanide, and the median furosemide-equivalent dose was 80 (80-160) mg. MRA use also increased (5% to 23%) but use of thiazide diuretics decreased (11% to 7%).

The proportion of patients anticoagulated increased from 46% at admission to 67% at discharge; warfarin use declined, and more direct oral anticoagulants were prescribed. A new diagnosis of AF was made in eight patients and a further eight patients with established AF and a high CHA_2DS_2VASc score were not anticoagulated prior to admission.

	All patients (n = 106)	Had study investigations (n = 83)	Did not have study investigations (n = 23)	p-value
CV medication				
Antiplatelet	30 (28)	24 (29)	6 (26)	0.79
Aspirin	18 (17)	14 (17)	4 (17)	0.95
Other antiplatelet	13 (12)	11 (13)	2 (9)	0.56
Anticoagulant	71 (67)	56 (67)	15 (65)	0.84
DOAC	56 (53)	43 (52)	13 (57)	0.69
Warfarin	15 (14)	13 (16)	2 (9)	0.40
Statin	72 (68)	58 (70)	14 (61)	0.41
Loop diuretic	104 (98)	81 (98)	23 (100)	0.45
Furosemide	83 (80)	69 (85)	14 (61)	0.01
Bumetanide	21 (20)	12 (15)	9 (39)	
Furosemide-equivalent dose (mg)	80 [80-160]	80 [80-120]	80 [80-160]	0.14
Thiazide	7 (7)	5 (6)	2 (9)	0.65
ACEI/ARB	62 (58)	53 (64)	9 (39)	0.033
ACEI	45 (42)	37 (45)	8 (35)	0.40
ARB	17 (16)	16 (19)	1 (4)	0.084
MRA	24 (23)	16 (19)	8 (35)	0.12
Beta-blocker	79 (75)	62 (75)	17 (74)	0.94
CCB	27 (25)	21 (25)	6 (26)	0.94
Long-acting nitrate	15 (14)	9 (11)	6 (26)	0.063
Nicorandil	8 (8)	6 (7)	2 (9)	0.81
Amiodarone	4 (4)	2 (2)	2 (9)	0.16
Digoxin	31 (29)	26 (31)	5 (22)	0.37
	(n = 54)	(n = 44)	(n = 10)	
Diabetic medication	45 (83)	37 (84)	8 (80)	0.75
Insulin	18 (33)	17 (39)	1 (10)	0.083
Biguanide	32 (59)	28 (64)	4 (40)	0.17
Sulphonylurea	15 (28)	11 (25)	4 (40)	0.34
Thiazolidinedione	0 (0)	0 (0)	0 (0)	
DPP-4 inhibitor	2 (4)	1 (2)	1 (10)	0.24
GLP-1 receptor antagonist	2 (4)	2 (5)	0 (0)	0.49
SGLT-2 inhibitor	4 (7)	2 (5)	2 (20)	0.092

Values are median [Q1-Q3] or n (%). ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CV, cardiovascular; DOAC, direct oral anticoagulant; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; MRA, mineralocorticoid receptor antagonist; SGLT-2, sodium-glucose co-transporter-2.

Table 4-9: Discharge medication of study participants.

4.2.6 Investigations

Electrocardiography

All patients had an electrocardiogram (ECG) performed on admission to hospital. The ECG findings are presented in Table 4-10. The mean heart rate (HR) was 84 (24) bpm. Fifty-three percent of patients were in AF on the admission ECG, 39% were in sinus rhythm, 6% had a paced rhythm and 3% had first-degree atrioventricular (AV) block. Eleven percent of participants had a bundle branch block pattern, 9% had ECG criteria for left ventricular hypertrophy (LVH) and 9% had Q waves. The mean QRS duration was 98 (27) ms and mean corrected QT interval was 451 (36) ms.

	All patients (n = 106)	**Had study investigations (n = 83)**	**Did not have study investigations (n = 23)**	**p-value**
ECG				
Rate (bpm)	84 [24]	86 [24]	78 [23]	0.19
Rhythm				
Sinus rhythm	41 (39)	30 (36)	11 (48)	0.49
AF	56 (53)	47 (57)	9 (39)	
AV block (first degree)	3 (3)	2 (2)	1 (4)	
Paced rhythm	6 (6)	4 (5)	2 (9)	
Bundle branch block	12 (11)	11 (13)	1 (4)	0.23
Left	7 (58)	6 (55)	1 (100)	0.68
Right	4 (33)	4 (36)	0 (0)	
Indeterminate	1 (8)	1 (9)	0 (0)	
LVH	10 (9)	8 (10)	2 (9)	0.89
Q waves	10 (9)	10 (12)	0 (0)	0.08
Poor R-wave progression	30 (28)	26 (31)	4 (17)	0.19
ST depression	11 (10)	9 (11)	2 (9)	0.77
T-wave inversion	50 (47)	38 (46)	12 (52)	0.59
LA enlargement	4 (4)	2 (2)	2 (9)	0.16
QRS duration (ms)	98 [27]	100 [28]	93 [22]	0.29
QT_c (ms)	451 [36]	450 [35]	457 [40]	0.44

Values are mean [standard deviation] or n (%). AF, atrial fibrillation; AV, atrioventricular; ECG, electrocardiogram; LA, left atrial; LVH, left ventricular hypertrophy.

Table 4-10: ECG findings of study participants.

Chest x-ray

All patients had a chest x-ray (CXR) performed on presentation to hospital and the major findings are detailed in Table 4-11. Radiological signs of HF were frequently seen. The most common findings were cardiomegaly (75%), upper lobe venous diversion (73%) and pleural effusion(s) (55%), which were typically bilateral. Evidence of pulmonary congestion was present in most patients; alveolar oedema was seen in 57% and perihilar oedema in 44%.

	All patients (n = 106)	Had study investigations (n = 83)	Did not have study investigations (n = 23)	p-value
CXR				
Cardiomegaly	79 (75)	63 (76)	16 (70)	0.54
Upper lobe venous diversion	77 (73)	57 (69)	20 (87)	0.082
Interstitial oedema	27 (25)	18 (22)	9 (39)	0.089
Alveolar oedema	60 (57)	48 (58)	12 (52)	0.63
Perihilar oedema	47 (44)	35 (42)	12 (52)	0.39
Pleural effusion(s)	58 (55)	42 (51)	16 (70)	0.11
Right	14 (24)	13 (31)	1 (6)	0.13
Left	2 (3)	1 (2)	1 (6)	
Bilateral	42 (72)	28 (67)	14 (88)	

Values are n (%). CXR, chest x-ray.

Table 4-11: CXR findings of study participants.

Laboratory tests

The laboratory results are summarised in Table 4-12. Urea and electrolytes, liver function tests, C-reactive protein (CRP) and full blood count were routinely measured in all patients on admission to hospital. Plasma glucose was measured in 89% of participants, high-sensitivity troponin I (hsTnI) in 65%, thyroid function tests in 56%, and cholesterol/triglycerides in 29%.

B-type natriuretic peptide (BNP) was measured as part of routine clinical practice in 65% of patients at a median of 1 (1-2) days following admission; N-terminal prohormone BNP (NT-proBNP) was assessed in 51 patients (48%) at a median of 4 (2-6) days. As elevated natriuretic peptides were required for study inclusion, all patients had an elevated BNP or NT-proBNP. The natriuretic levels

were generally markedly elevated (median BNP, 382 pg/mL; median NT-proBNP, 1532 pg/mL).

The median hsTnI in the cohort was 16 (7-27) ng/L. The reference range of this assay is different for men (0-34 ng/L) and women (0-16 ng/L); the median levels for men and women were 19 ng/L and 14 ng/L, respectively. A total of 19 patients (28%) had a hsTnI level above the reference range. Patients presenting with a primary diagnosis of acute coronary syndrome were excluded from the study, however, troponin leaks are frequently observed in patients with HF decompensation, therefore, patients with an elevated troponin were included in the absence of other symptoms and signs suggestive of acute ischaemia.[256]

Urea and electrolytes and liver function tests were measured in all patients on admission. Forty-one patients (39%) had renal impairment (eGFR 30-60 mL/min/1.73m^2); four patients were hyponatraemic (Na^+ <133 mmol/L) on admission. Hypoalbuminaemia was common, with 53% of patients having an albumin below the normal reference range (35-50 g/L).

The median CRP was 12 mg/L and the majority of study participants (57%) had a CRP above the reference range (0-10 mg/L) on admission; one-quarter had a neutrophilia (neutrophils >7.0 x 10^9/L) and 18% had an elevated total white cell count (WCC, >10.0 x 10^9/L).

Anaemia was highly prevalent in the cohort; 49 patients (46%) had a haemoglobin below the normal reference range (130-180 g/L and 115-165 g/L for men and women, respectively) on admission. The majority of patients (71%) had a normal mean corpuscular volume (MCV); 9% had microcytic and 4% had macrocytic anaemia. Haematinics and iron studies were not routinely measured to further investigate the aetiology of anaemia.

	All patients (n = 106)	Had study investigations (n = 83)	Did not have study investigations (n = 23)	p-value
Haematology				
Hb (g/L)	122 [18]	122 [19]	120 [14]	0.61
Anaemia	49 (46)	37 (45)	12 (52)	0.52
MCV (fL)	91 [8]	91 [7]	93 [9]	0.26
Haematocrit (%)	38 [5]	38 [5]	38 [4]	0.98
WCC ($x10^9$/L)	8.2 [2.3]	8.1 [2.3]	8.6 [2.4]	0.35
Neutrophils ($x10^9$/L)	6.0 [2.1]	5.9 [2.1]	6.4 [2.1]	0.30
Lymphocytes ($x10^9$/L)	1.3 [0.6]	1.3 [0.6]	1.3 [0.4]	0.99
Platelets ($x10^9$/L)	241 [103]	235 [106]	262 [91]	0.26
Biochemistry				
NT-proBNP	51 (48)	41 (49)	10 (43)	0.62
NT-proBNP (pg/mL)	1532 [845-3076]	1385 [978-3076]	1579 [384-2799]	0.55
BNP	69 (65)	52 (63)	17 (74)	0.32
BNP (pg/mL)	382 [197-794]	339 [181-829]	459 [332-545]	0.60
hsTnI	69 (65)	55 (66)	14 (61)	0.63
hsTnI (ng/L)	16 [7-27]	16 [7-29]	11 [5-24]	0.58
Elevated hsTnI	19 (28)	16 (29)	3 (21)	0.57
Na^+ (mmol/L)	138 [2]	138 [3]	139 [4]	0.93
Hyponatraemia	4 (4)	3 (4)	1 (4)	0.87
K^+ (mmol/L)	4.4 [0.5]	4.4 [0.6]	4.4 [0.5]	0.60
Cl^- (mmol/L)	104 [5]	104 [5]	103 [4]	0.83
Urea (mmol/L)	7.7 [3.8]	7.9 [4.0]	7.2 [2.7]	0.46
Creatinine (µmol/L)	94 [32]	96 [33]	89 [29]	0.39
eGFR (mL/min/1.73m^2)	66 [20]	65 [20]	68 [22]	0.47
eGFR <60 mL/min/ 1.73m^2	41 (39)	32 (39)	9 (39)	0.96
Bilirubin (µmol/L)	15 [8]	16 [8]	14 [7]	0.31
ALT (U/L)	19 [13-26]	20 [15-36]	13 [12-19]	<0.01
AST (U/L)	21 [18-28]	21 [17-33]	19 [18-22]	0.083
Alkaline phosphatase (U/L)	106 [87-124]	99 [82-120]	118 [101-160]	0.036
Albumin (g/L)	34 [4]	34 [4]	34 [5]	0.95
Hypoalbuminaemia	56 (53)	42 (51)	14 (61)	0.38
CRP (mg/L)	12 [5-25]	12 [5-23]	12 [8-39]	0.43
Elevated CRP	60 (57)	46 (55)	14 (61)	0.64
Glucose (mmol/L)	6.7 [5.4-8.6]	6.6 [5.3-8.6]	7.0 [5.8-7.9]	0.92

Values are mean [standard deviation], median [Q1-Q3], or n (%). ALT, alanine transaminase; AST, aspartate transaminase; BNP, B-type natriuretic peptide; Cl^-, chloride; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; hsTnI, high-sensitivity troponin I; K^+, potassium; MCV, mean corpuscular volume; Na^+, sodium; NT-proBNP, N-terminal prohormone BNP; WCC, white cell count.

Table 4-12: Laboratory results of study participants.

Echocardiography

All patients had an echocardiogram performed as part of the diagnostic work-up for suspected HF. The main echocardiography findings are presented in Table 4-13. LV systolic function was assessed (where possible) by Simpson's biplane method for quantification of LVEF. This technique requires adequate transthoracic imaging to achieve endocardial definition and was possible in 80% of patients. In the other participants, the LVEF was estimated subjectively. Participants were required to have an LVEF of ≥50% for inclusion in the study; the mean LVEF was 59% (6%).

The mean left ventricular (LV) size, as assessed by the LV internal diameter and LV volume in diastole and systole indexed to body surface area (BSA), was within normal limits. The mean LV septal wall thickness in diastole was 13 mm and posterior wall thickness was 12 mm; 58% of participants had echocardiographic evidence of LVH (defined as LV septal and/or posterior wall thickness ≥13 mm). The mean right ventricular (RV) size, as assessed by the mid-RV diameter in diastole, was near the upper limit of normal (34 mm; abnormal >35 mm). The mean RV systolic function, as assessed by the tricuspid annular plane systolic excursion (TAPSE) was preserved (20 mm; abnormal <16 mm).

The majority of patients (84%) had left atrial (LA) dilatation, as defined by the 2016 ESC HF guidelines (i.e. LA volume indexed to BSA >34 mL/m^2).[2] The mean indexed LA volume was 44 (15) mL/m^2. Fifty participants (57% of those with tissue Doppler imaging) had echocardiographic evidence of diastolic dysfunction, as per the ESC HF guidelines (i.e. mean E/e' >13 and e' <9 cm/sec).[2] The mean E/e' was 15.0 (6.6).

Patients with greater than moderate valve disease were excluded from the study, however, mild or moderate valvular heart disease was common in the overall cohort (73%). The most frequently observed valve lesions were mild tricuspid and mitral regurgitation (69% and 63%, respectively).

	All patients (n = 106)	Had study investigations (n = 83)	Did not have study investigations (n = 23)	p-value
LV structure and systolic function				
LVEDD (mm/m^2)	24 [3]	24 [3]	24 [3]	0.87
LVESD (mm/m^2)	16 [4]	15 [5]	16 [3]	0.37
LVEDV (mL/m^2)	45 [15]	44 [15]	47 [18]	0.56
LVESV (mL/m^2)	19 [8]	18 [7]	20 [9]	0.31
LVSV (mL/m^2)	26 [9]	26 [9]	26 [10]	0.77
LVEF measurement				
Biplane	85 (80)	68 (82)	17 (74)	0.39
Estimated	21 (20)	15 (18)	6 (26)	
LVEF (%)	59 [6]	59 [6]	58 [6]	0.41
S' lateral (cm/s)	7.1 [2.3]	6.9 [2.1]	8.2 [2.6]	0.039
Septal wall thickness (mm)	13 [2]	12 [2]	13 [2]	0.48
Posterior wall thickness (mm)	12 [2]	12 [2]	12 [2]	0.57
LVH	62 (59)	49 (59)	13 (57)	0.83
LV diastolic function				
E (m/s)	1.1 [0.3]	1.1 [0.3]	1.1 [0.3]	0.72
A (m/s)	0.9 [0.3]	0.9 [0.3]	0.8 [0.4]	0.38
E/A	1.4 [1.0]	1.2 [0.9]	1.7 [1.1]	0.16
Deceleration time (ms)	217 [78]	218 [85]	215 [46]	0.87
E' average (cm/s)	7.8 [2.6]	7.7 [2.6]	8.1 [2.8]	0.55
E/E' lateral	13.3 [6.5]	13.2 [6.1]	13.9 [8.3]	0.70
E/e' septal	17.8 [8.5]	18.2 [8.9]	16.3 [6.7]	0.44
E/e' average	15.0 [6.6]	15.0 [6.5]	14.7 [7.4]	0.88
Diastolic dysfunction	50 (57)	41 (57)	9 (56)	0.96
LA volume (mL/m^2)	44 [15]	45 [16]	40 [13]	0.17
LA dilatation	88 (84)	71 (87)	17 (74)	0.14
RV structure and function				
RVEDD (mm)	34 [6]	34 [7]	34 [5]	0.99
TAPSE (mm)	20 [5]	20 [5]	20 [5]	0.77
TR max (mmHg)	29 [14]	30 [14]	26 [11]	0.36
Estimated RAP (mmHg)	9 (4)	9 (4)	8 (4)	0.52
Estimated RVSP (mmHg)	38 [15]	40 [15]	30 [11]	0.033
Valve disease				
Mild/moderate valve disease	77 (73)	61 (73)	16 (70)	0.71
AS	12 (16)	10 (16)	2 (12)	0.70
AR	21 (27)	18 (30)	3 (19)	0.39

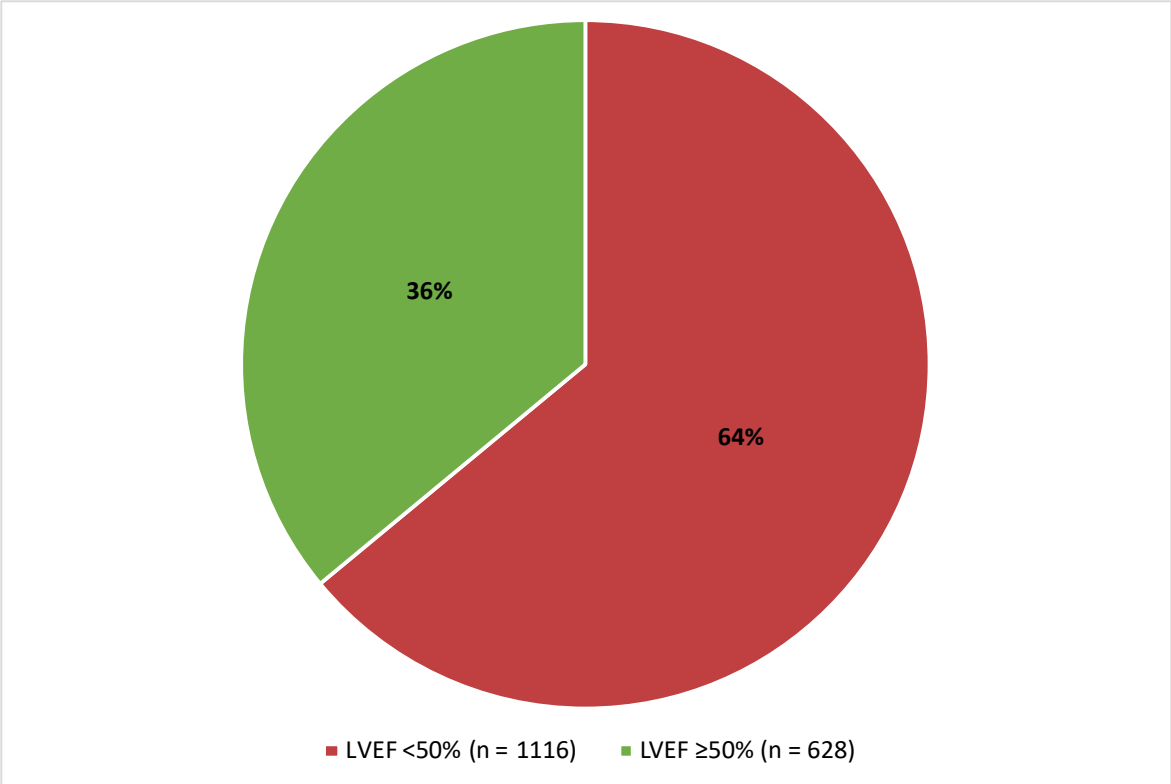
MS	5 (6)	5 (8)	0 (0)	0.24
MR	54 (70)	46 (75)	8 (50)	0.048
TR	51 (66)	39 (64)	12 (75)	0.40
PR	8 (10)	7 (11)	1 (6)	0.54

Values are mean [standard deviation] or n (%). AR, aortic regurgitation; AS, aortic stenosis; LA, left atrial; LV, left ventricular; LVEDD, LV end-diastolic dimension; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESD, LV end-systolic dimension; LVESV, LV end-systolic volume; LVH, LV hypertrophy; LVSV, LV stroke volume; MR, mitral regurgitation; MS, mitral stenosis; PR, pulmonary regurgitation; RAP, right atrial pressure; RV, right ventricular; RVEDD, RV end-diastolic dimension; RVSP, RV systolic pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Table 4-13: Echocardiography findings of study participants.

4.2.7 Summary

This chapter details the study screening and recruitment process in addition to the baseline characteristics of the participants. Contemporary population-based HF studies suggest that HFpEF now accounts for around half of prevalent HF.[18] However, the definition of HF and thresholds used to classify preserved LVEF vary markedly between studies. A recent review of studies using an LVEF threshold of ≥50% reported estimates of HFpEF as a proportion of total prevalent HF ranging from 24% to 55%.[18] In this study, 1116 (49%) of the patients that I screened had a diagnosis of HF with an LVEF <50%. Of the 1169 patients (51%) with preserved LVEF, 541 had an alternative diagnosis (e.g. significant valve disease, primary cardiomyopathy or pericardial disease). Importantly, these patients are often erroneously given a diagnosis of HFpEF in epidemiological studies.[257] A total of 628 patients (27% of all patients screened) had a confirmed diagnosis of HFpEF. Excluding those patients with an alternative diagnosis, 64% of those with confirmed HF had an LVEF <50% and 36% had an LVEF ≥50% (Figure 4-4). I assessed patients hospitalised with HF, therefore, the relative proportions of patients with HFpEF and HF with reduced ejection fraction (HFrEF) are likely to differ in ambulatory cohorts.



LVEF, left ventricular ejection fraction.

Figure 4-4: Screened patients stratified by LVEF.

The inclusion criteria for this study were designed to include as broad a range of hospitalised patients with HFpEF as possible that would be eligible for detailed coronary investigation. By necessity, specific groups of patients were excluded for reasons of safety. Notably, those with an eGFR <30mL/min/1.73m^2 were excluded to facilitate the safe administration of contrast agents during the study investigations. Patients with severe frailty (i.e. CFS >6), in whom invasive coronary angiography was considered to be clinically inappropriate and/or to carry excessive risk, were also excluded. Although these patients accounted for a reasonable number of exclusions, they represent a group that would not otherwise be considered for invasive investigation on the basis of general health and functional status.

Selected baseline characteristics of HFpEF patients that were recruited and those excluded are presented in Table 4-14. The excluded HFpEF patients were older (mean age 81 vs. 72 years; p <0.001) and more frequently female (66% vs. 50%; p = 0.002) than those recruited to the study. Natriuretic peptides were higher in the excluded patients than those recruited (median BNP 712 vs. 382; p = 0.001, respectively), but CV comorbidities and echocardiographic signs of elevated LV filling pressure were not significantly different. Predictably,

therefore, the excluded HFpEF group represent a higher risk group who are likely to have poorer outcomes than the recruited cohort.

	Recruited HFpEF patients (n = 106)	Excluded HFpEF patients (n = 522)	p-value
Demographics			
Age (years)	72 [9]	81 [10]	<0.001
Female sex	53 (50)	345 (66)	0.002
Hospitalisation details			
Length of stay (days)	8 [6-13]	10 [5-18]	0.11
Past medical history			
Any CAD	38 (36)	209 (40)	0.42
Hypertension	80 (75)	407 (78)	0.57
AF	66 (62)	318 (61)	0.80
Biochemistry			
BNP (pg/mL)	382 [197-794]	712 [377-1127]	0.001
NT-proBNP (pg/mL)	1532 [845-3076]	2714 [817-4341]	0.55
Echocardiography			
LVH	62 (59)	355 (68)	0.059
LA dilatation	88 (84)	449 (86)	0.56
Diastolic dysfunction	50 (57)	350 (67)	0.062

Values are mean [standard deviation], median [Q1-Q3], or n (%). AF, atrial fibrillation; BNP, B-type natriuretic peptide; CAD, coronary artery disease; HFpEF, heart failure with preserved ejection fraction; LA, left atrial; LVH, left ventricular hypertrophy; NT-proBNP, N-terminal prohormone BNP.

Table 4-14: Selected baseline characteristics of recruited and excluded HFpEF patients.

Due to the logistics of performing this study within the limits of a busy regional clinical service, there was a significant delay in performing invasive coronary angiography (median 97 days from presentation). The delay in performing the invasive coronary assessment may have affected the results of coronary microvascular testing (see Chapter 6).

Twenty-three patients that were recruited did not undergo the study investigations. For the majority, this was due to a decline in health and functional status prior to the investigations being performed; one patient died prior to investigation. A number of patients developed a decline in their renal function; it was, therefore, not safe to proceed with the imaging studies. Those who subsequently withdrew are likely to represent a higher risk group and might have been expected to have a higher burden of CAD and CMD. However, reassuringly, there were no major differences in the clinical characteristics or

outcomes of those who did and did not undergo the study investigations (Appendix VIII, IX).

As a result of the above issues with recruitment, I did not meet the proposed sample size for recruitment (see Chapter 3). Consequently, the margin of error to detect a prevalence of obstructive epicardial CAD of 50% at a 95% CI increased from 8% to 11%.

I believe that this cohort has a number of strengths. I screened near-consecutive patients prospectively at three large hospitals. All patients enrolled had a clear-cut diagnosis of HFpEF as per the 2016 ESC HF guidelines (necessitating clinical symptoms and signs of HF, preserved LV systolic function, elevated natriuretic peptides, and evidence of structural and/or functional heart disease on echocardiography). Median natriuretic peptides were markedly elevated and the vast majority of patients (92%) had structural heart disease (i.e. LVH or LA dilatation); the remainder had diastolic dysfunction. Furthermore, almost all patients were treated with diuretics during hospital admission and at discharge. The baseline characteristics of this cohort are consistent with contemporary population-based studies in HFpEF.[257,258] One notable exception is regarding the ethnicity of enrolled patients. Almost all participants in this study are Caucasian, with only 3% coming from minority ethnic backgrounds. Although this is relatively representative of the Scottish population (4% of the population was from ethnic minority groups in the 2011 Census[259]), patients from minority ethnic populations are under-represented in clinical research studies.[260]

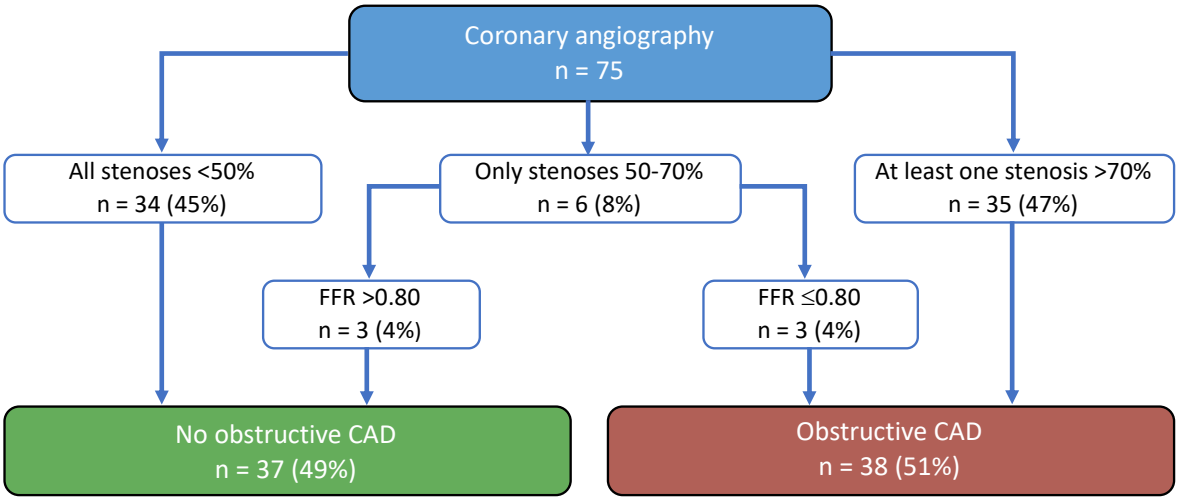
Overall, I feel my study cohort is representative of 'real world' patients hospitalised with HFpEF. In this study, selection bias was minimised due to the prospective and near-consecutive screening process. The recruited patients all had a robust diagnosis of HFpEF in accordance with the contemporary guidelines and the demographics and clinical characteristics of the cohort are comparable to epidemiological HFpEF populations. However, the generalisability of the study is slightly reduced by the design (employing an invasive investigation strategy), limiting the recruitment of elderly and frail patients.

Chapter 5 Results – Coronary artery disease in heart failure with preserved ejection fraction

In this chapter I will report the prevalence of obstructive epicardial coronary artery disease (CAD) in the study population. I will describe the clinical characteristics, investigation results and correlates of the population based on the presence or absence of obstructive CAD. Finally, I will report clinical outcomes (mortality and hospitalisations) based on the presence or absence of epicardial CAD.

5.1 Prevalence of obstructive epicardial coronary artery disease

A total of 75 participants underwent invasive coronary angiography. Invasive coronary angiography revealed obstructive epicardial CAD in 38 participants, giving an estimated prevalence in the HFpEF population of 51% (95% confidence interval [CI] 39-62%) (Figure 5-1).



CAD, coronary artery disease; FFR, fractional flow reserve.

Figure 5-1: Prevalence of obstructive epicardial CAD in study cohort.

As discussed in Chapter 3, obstructive epicardial CAD was defined as: a ≥70% stenosis of a major epicardial coronary artery (>2.5 mm diameter); a ≥50% stenosis of the left main coronary artery; or a 50-70% stenosis of a major coronary artery with an FFR ≤0.80. Thirty-five patients (47%) were diagnosed with obstructive CAD on the basis of at least one epicardial stenosis ≥70% (≥50% if left main coronary artery) on QCA. Six patients (8%) had a maximum stenosis

of 50-70%, all of which were assessed with fractional flow reserve (FFR); three patients (8%) had an FFR ≤0.80 and three (8%) had an FFR >0.80 (Figure 5-1).

Traditionally, "significant" epicardial CAD has been defined as a ≥50% stenosis of a major epicardial artery.[261] However, two-thirds of patients with an intermediate (50-70%) stenosis do not have functionally significant disease when interrogated with FFR.[262] Using the traditional cut-off of a ≥50% epicardial stenosis, the prevalence of epicardial CAD in the cohort is 56% (95% CI 44-67%).

5.2 Clinical characteristics by obstructive epicardial coronary artery disease

5.2.1 Demographics and clinical features

Table 5-1 details the demographics and clinical features of the study participants based on the presence or absence of obstructive epicardial CAD. The groups were similar with regards to age, frailty, smoking history and duration of hospitalisation. Those with obstructive epicardial CAD were more frequently male (63% vs. 38%; p = 0.028) and had a lower mean HR at presentation (76 vs. 90 bpm; p = 0.012) than those without obstructive CAD. The most frequent finding on clinical examination was oedema, which was generally of mild to moderate severity. There were no significant differences in HF symptoms or signs between the groups.

	All angiography (n = 75)	**No obstructive CAD (n = 37)**	**Obstructive CAD (n = 38)**	**p-value**
Demographics				
Age (years)	72 [9]	72 [9]	73 [9]	0.40
Female sex	37 (49)	23 (62)	14 (37)	0.028
BMI (kg/m^2)	33 [8]	34 [8]	31 [7]	0.084
Obesity	35 (47)	20 (54)	15 (39)	0.21
Smoking history	42 (56)	20 (54)	22 (58)	0.74
Hospitalisation details				
Length of stay (days)	7 [5-11]	7 [5-10]	7 [6-12]	0.28
HF symptoms				
NYHA functional class				
II	2 (3)	1 (3)	1 (3)	0.94
III	40 (53)	19 (51)	21 (55)	
IV	33 (44)	17 (46)	16 (42)	

Orthopnoea	51 (68)	26 (70)	25 (66)	0.68
PND	35 (47)	17 (46)	18 (47)	0.90
Ankle swelling	68 (91)	33 (89)	35 (92)	0.66
Admission vital signs				
HR (bpm)	83 [25]	90 [28]	76 [21]	0.012
SBP (mmHg)	150 [29]	152 [31]	148 [29]	0.58
DBP (mmHg)	79 [20]	80 [21]	78 [19]	0.64
MAP (mmHg)	103 [19]	104 [20]	102 [18]	0.54
HF signs				
JVD	52 (69)	26 (70)	26 (68)	0.86
Murmur	22 (29)	11 (30)	11 (29)	0.94
Crepitations	59 (79)	29 (78)	30 (79)	0.95
Pleural effusion(s)	30 (40)	15 (41)	15 (39)	0.92
Oedema	66 (88)	33 (89)	33 (87)	0.75
Ascites	3 (4)	0 (0)	3 (8)	0.081

Values are mean [standard deviation], median [Q1-Q3], or n (%). BMI, body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; HF, heart failure; HR, heart rate; JVD, jugular venous distention; MAP, mean arterial pressure; NYHA, New York Heart Association; PND, paroxysmal nocturnal dyspnoea; SBP; systolic blood pressure.

Table 5-1: Demographics and clinical features stratified by obstructive epicardial CAD.

5.2.2 Past medical history

The past medical history based on the presence or absence of obstructive CAD is presented in Table 5-2. A similar proportion of patients in each group presented with *de novo* HF and had a previous HF hospitalisation. Those with obstructive CAD were more likely to have a previous history of CAD (50% vs. 19%; p <0.01), previous MI (34% vs. 11%; p = 0.016), and previous PCI (24% vs. 5%; p = 0.025) than those without obstructive CAD. Only three patients had previous CABG, all of whom had obstructive epicardial CAD on angiography (i.e. evidence of obstructive disease of both native coronary artery and bypass graft supply to ≥1 epicardial coronary artery territory). A clinical history of angina was not significantly different between those with and without obstructive CAD (8% vs. 21%; p = 0.11, respectively).

The rates of most common comorbidities were similar between those with and without obstructive epicardial disease, including hypertension (71% vs. 76%; p = 0.65, respectively), AF (61% vs. 70%; p = 0.38, respectively), and anaemia (26% vs. 22%; p = 0.63, respectively). Patients with obstructive CAD had a higher prevalence of CKD (42% vs. 16%; p = 0.014) and diabetes (63% vs. 41%; p = 0.05) than those with no obstructive disease.

	All angiography (n = 75)	No obstructive CAD (n = 37)	Obstructive CAD (n = 38)	p-value
History of HF				
Previous HF diagnosis	28 (37)	13 (35)	15 (39)	0.70
Previous HFH	17 (23)	10 (27)	7 (18)	0.37
History of CAD				
Any CAD	26 (35)	7 (19)	19 (50)	<0.01
MI	17 (23)	4 (11)	13 (34)	0.016
Angina	11 (15)	3 (8)	8 (21)	0.11
Current angina	5 (7)	2 (5)	3 (8)	0.67
Revascularisation	12 (16)	2 (5)	10 (26)	0.014
PCI	11 (15)	2 (5)	9 (24)	0.025
CABG	3 (4)	0 (0)	3 (8)	0.081
CV comorbidities				
Hypertension	55 (73)	28 (76)	27 (71)	0.65
Dyslipidaemia	6 (8)	3 (8)	3 (8)	0.97
CVD	15 (20)	5 (14)	10 (26)	0.17
PAD	8 (11)	2 (5)	6 (16)	0.15
AF	49 (65)	26 (70)	23 (61)	0.38
Valve disease (mild/moderate)	17 (23)	8 (22)	9 (24)	0.83
Non-CV comorbidities				
Diabetes	39 (52)	15 (41)	24 (63)	0.05
CKD	22 (29)	6 (16)	16 (42)	0.014
Chronic liver disease	0 (0)	0 (0)	0 (0)	
Depression	4 (5)	1 (3)	3 (8)	0.32
Cancer	5 (7)	3 (8)	2 (5)	0.62
COPD	18 (24)	8 (22)	10 (26)	0.63
Asthma	5 (7)	4 (11)	1 (3)	0.16
Anaemia	18 (24)	8 (22)	10 (26)	0.63
Hypothyroidism	11 (15)	6 (16)	5 (13)	0.71
Osteoarthritis	18 (24)	8 (22)	10 (26)	0.63

Values are n (%). AF, atrial fibrillation; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; CVD, cerebrovascular disease; HF, heart failure; HFH, HF hospitalisation; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention.

Table 5-2: Past medical history stratified by obstructive epicardial CAD.

5.2.3 Drug history – medication on admission

The admission medication of participants based on the presence or absence of obstructive epicardial CAD is described in Table 5-3. Those with obstructive CAD were more likely to be prescribed an antiplatelet than those without (50% vs. 22%; p = 0.01, respectively), but rates of statin prescription were similar (76% vs. 62%; p = 0.18, respectively). Those without obstructive disease were more likely to be treated anticoagulated on admission than those with CAD (59% vs. 34%; p = 0.028, respectively), despite similar rates of AF. Almost half of patients were prescribed a loop diuretic on admission, with no significant difference in the prescription rates (47% vs. 49%; p = 0.91) or furosemide-equivalent dose (median 80 mg vs. 70 mg; p = 0.52) between those with and without obstructive coronary disease. Use of other CV medication, including renin-angiotensin-aldosterone system (RAAS) antagonists and anti-anginal medications, were similar.

	All angiography (n = 75)	**No obstructive CAD (n = 37)**	**Obstructive CAD (n = 38)**	**p-value**
CV medication				
Antiplatelet	27 (36)	8 (22)	19 (50)	0.01
Anticoagulant	35 (47)	22 (59)	13 (34)	0.028
Statin	52 (69)	23 (62)	29 (76)	0.18
Loop diuretic	36 (48)	18 (49)	18 (47)	0.91
Furosemide-equivalent dose (mg)	80 [40-120]	70 [40-120]	80 [40-120]	0.52
Thiazide	5 (7)	4 (11)	1 (3)	0.16
MRA	3 (4)	1 (3)	2 (5)	0.57
ACEI/ARB	50 (67)	22 (59)	28 (74)	0.19
Beta-blocker	48 (64)	22 (59)	26 (68)	0.42
CCB	28 (37)	14 (38)	14 (37)	0.93
Digoxin	6 (8)	4 (11)	2 (5)	0.38
	(n = 39)	(n = 15)	(n = 24)	
Diabetic medication	33 (85)	12 (80)	21 (88)	0.53
Insulin	13 (33)	4 (27)	9 (38)	0.49
Non-CV medication				
Bronchodilator	23 (31)	12 (32)	11 (29)	0.74
Antidepressant	18 (24)	8 (22)	10 (26)	0.63

Values are median [Q1-Q3] or n (%). ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CCB, calcium channel blocker; CV, cardiovascular; MRA, mineralocorticoid receptor antagonist.

Table 5-3: Admission medication stratified by obstructive epicardial CAD.

5.2.4 Drug history – in-hospital treatment and medication at discharge

The in-hospital treatment and discharge medication of participants based on the presence or absence of obstructive epicardial CAD is summarised in Table 5-4. All but one of the participants that underwent invasive coronary angiography were treated with loop diuretics during admission, 90% of whom received intravenous furosemide. Very few patients received IV nitrate (n = 3) and no patients received IV inotropes. Around half of patients required oxygen therapy, with no significant difference between those with and without obstructive CAD. One patient was treated with CPAP and no patients required intubation.

When compared with admission mediation, fewer patients with obstructive CAD were prescribed an antiplatelet (50% vs. 39%) and more were prescribed an anticoagulant (34% vs. 55%) at discharge. There was no significant difference in the rates of antiplatelet or anticoagulant use at discharge between those with and without obstructive CAD.

Loop diuretic use in both groups doubled from admission to discharge, from 49% to 97% in those without obstructive CAD, and 47% to 100% in those with obstructive CAD. The furosemide-equivalent dose at discharge was the same in each group (median 80 mg). The use of MRAs also increased in those with no obstructive CAD (3% to 14%) and those with obstructive disease (5% to 24%).

Beta-blocker and digoxin use increased in both groups, and the use of digoxin in those with no obstructive coronary disease was significantly higher than those with obstructive disease (43% vs. 21%; p = 0.039, respectively).

	All angiography (n = 75)	**No obstructive CAD (n = 37)**	**Obstructive CAD (n = 38)**	**p-value**
In-hospital treatment				
Furosemide	74 (99)	36 (97)	38 (100)	0.31
IV (>1 dose)	61 (82)	27 (75)	34 (89)	0.17
IV (1 dose)	7 (9)	4 (11)	3 (8)	
Oral	6 (8)	5 (14)	1 (3)	
IV nitrate	3 (4)	2 (5)	1 (3)	0.54
Dopamine	0 (0)	0 (0)	0 (0)	
Oxygen	34 (45)	15 (41)	19 (50)	0.41

CPAP	1 (1)	0 (0)	1 (3)	0.32
CV medication				
Antiplatelet	24 (32)	9 (24)	15 (39)	0.16
Anticoagulant	49 (65)	28 (76)	21 (55)	0.063
Statin	52 (69)	23 (62)	29 (76)	0.18
Loop diuretic	74 (99)	36 (97)	38 (100)	0.31
Furosemide-equivalent dose (mg)	80 [80-120]	80 [80-120]	80 [80-160]	0.91
Thiazide	5 (7)	3 (8)	2 (5)	0.62
ACEI/ARB	49 (65)	23 (62)	26 (68)	0.57
MRA	14 (19)	5 (14)	9 (24)	0.26
Beta-blocker	56 (75)	26 (70)	30 (79)	0.39
Calcium channel blocker	17 (23)	9 (24)	8 (21)	0.74
Digoxin	24 (32)	16 (43)	8 (21)	0.039
	(n = 39)	(n = 15)	(n = 24)	
Diabetic medication	33 (85)	12 (80)	21 (88)	0.53
Insulin	14 (36)	4 (27)	10 (42)	0.34

Values are median [Q1-Q3] or n (%). ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CCB, calcium channel blocker; CPAP, continuous positive airway pressure; CV, cardiovascular; IV, intravenous; MRA, mineralocorticoid receptor antagonist.

Table 5-4: In-hospital treatment and discharge medication stratified by obstructive epicardial CAD.

5.2.5 Baseline investigations

Table 5-5 details the ECG, CXR and laboratory results for the participants according to the presence of absence of obstructive CAD. Participants with obstructive CAD had a lower mean HR (79 vs. 94 bpm; p <0.01) and were more likely to have Q waves on ECG (24% vs. 3%; p <0.01) than those without obstructive CAD. The CXR findings was similar in those with and without obstructive coronary disease.

BNP was measured in 61% and NT-proBNP was measured in 51% of patients that underwent coronary angiography. There was no significant difference in natriuretic peptide levels between those with and without obstructive CAD (median 315 vs. 323 pg/mL; p = 0.90 [BNP] and 1132 vs. 1532 pg/mL; p = 0.37 [NT-proBNP], respectively). hsTnI was measured in 65% of patients and there was no difference in peak hsTnI levels between those without and without CAD (median 18 vs. 16 ng/L; p = 0.89, respectively). Twenty-nine percent of participants had an hsTnI above the reference range and there was no difference

between those with and without obstructive CAD (27% vs. 30%; p = 0.86, respectively).

As those with obstructive disease had a higher prevalence of CKD, they had a lower mean estimated glomerular filtration rate (eGFR) than those without obstructive CAD (61 vs. 68 mL/min/1.73m^2; p = 0.17, respectively). Rates of hyponatraemia and hypoalbuminaemia were similar in each group, as was CRP (median 12 vs. 15 mg/L; p = 0.80). Anaemia was significantly more common in those with obstructive CAD than those without (55% vs. 30%; p = 0.025, respectively), however, the mean haemoglobin was similar (121 vs. 125 g/L; p = 0.43, respectively).

	All angiography (n = 75)	**No obstructive CAD (n = 37)**	**Obstructive CAD (n = 38)**	**p-value**
ECG				
Rate (bpm)	86 [25]	94 [28]	79 [18]	<0.01
AF	42 (56)	24 (65)	18 (47)	0.18
Bundle branch block	10 (13)	4 (11)	6 (16)	0.53
LVH	7 (9)	3 (8)	4 (11)	0.72
Q wave	10 (13)	1 (3)	9 (24)	<0.01
T-wave inversion	35 (47)	17 (46)	18 (47)	0.90
QRS duration (ms)	99 [28]	97 [29]	102 [28]	0.48
QT_c (ms)	450 [35]	445 [36]	455 [34]	0.20
CXR				
Cardiomegaly	56 (75)	31 (84)	25 (66)	0.073
Upper lobe venous diversion	53 (71)	28 (76)	25 (66)	0.35
Interstitial oedema	15 (20)	7 (19)	8 (21)	0.82
Alveolar oedema	43 (57)	19 (51)	24 (63)	0.30
Perihilar oedema	31 (41)	15 (41)	16 (42)	0.89
Pleural effusion(s)	35 (47)	18 (49)	17 (45)	0.73
Haematology				
Hb (g/L)	123 [19]	125 [18]	121 [20]	0.43
Anaemia	32 (43)	11 (30)	21 (55)	0.025
WCC (x 10^9/L)	8.2 [2.3]	8.6 [2.0]	7.9 [2.6]	0.21
Biochemistry				
NT-proBNP	38 (51)	17 (46)	21 (55)	0.42
NT-proBNP (pg/mL)	1376 [894-2819]	1532 [1287-2819]	1132 [818-2494]	0.37
BNP	46 (61)	21 (57)	25 (66)	0.42
BNP (pg/mL)	319 [173-856]	323 [185-717]	315 [167-904]	0.90
hsTnI	49 (65)	27 (73)	22 (58)	0.17
hsTnI (ng/L)	16 [9-29]	16 [10-27]	18 [7-34]	0.89

Elevated hsTnI	14 (29)	8 (30)	6 (27)	0.86
Na^+ (mmol/L)	138 [3]	138 [3]	138 [3]	0.95
Hyponatraemia	3 (4)	3 (8)	0 (0)	0.073
K^+ (mmol/L)	4.4 [0.6]	4.3 [0.6]	4.5 [0.5]	0.046
Urea (mmol/L)	8.0 [4.2]	7.5 [4.7]	8.5 [3.5]	0.29
Creatinine (μmol/L)	96 [34]	91 [39]	102 [27]	0.14
eGFR (mL/min/1.73m^2)	64 [20]	68 [21]	61 [19]	0.17
eGFR <60mL/min/ 1.73m^2	31 (41)	12 (32)	19 (50)	0.12
Albumin (g/L)	34 [4]	34 [4]	34 [3]	0.77
Hypoalbuminaemia	38 (51)	17 (46)	21 (55)	0.42
CRP (mg/L)	14 [5-23]	12 [4-24]	15 [5-18]	0.80
Elevated CRP	43 (57)	20 (54)	23 (61)	0.57
Glucose (mmol/L)	6.6 [5.3-8.6]	6.2 [5.3-8.3]	7.0 [5.3-9.6]	0.39

Values are mean [standard deviation], median [Q1-Q3], or n (%). AF, atrial fibrillation; AV, atrioventricular; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CRP, C-reactive protein; CXR, chest x-ray; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; hsTnI, high-sensitivity troponin I; K^+, potassium; LVH, left ventricular hypertrophy; Na^+, sodium; NT-proBNP, N-terminal prohormone BNP; WCC, white cell count.

Table 5-5: ECG, CXR and laboratory results stratified by obstructive epicardial CAD.

The echocardiography findings of the participants based on the presence of absence of obstructive CAD are presented in Table 5-6. The LVEF was similar in those with and without obstructive CAD (mean 58% vs. 60%; p = 0.37, respectively), but the LVESD was slightly larger in those with obstructive disease (mean 17 vs. 15 mm/m^2; p = 0.038). There were no differences in the rates of LVH or LA dilatation between the groups. However, participants with obstructive CAD had a higher mean E/e' and more diastolic dysfunction (defined as E/e' ≥13 and e' <9 cm/s) than those without obstructive CAD (16.4 vs. 12.9; p = 0.027, and 67% vs. 39%; p = 0.029, respectively). Those without obstructive disease had significantly higher rates of mild or moderate valvular heart disease than those without obstructive disease (89% vs. 63%; p <0.01).

	All angiography (n = 75)	**No obstructive CAD (n = 37)**	**Obstructive CAD (n = 38)**	**p-value**
LV structure and systolic function				
LVEDD (mm/m^2)	24 [3]	24 [3]	25 [3]	0.061
LVESD (mm/m^2)	16 [4]	15 [4]	17 [4]	0.038
LVEF (%)	59 [6]	60 [6]	58 [6]	0.37
S' lateral (cm/s)	6.7 [2.0]	7.1 [2.6]	6.4 [1.3]	0.16
Septal wall thickness (mm)	13 [2]	13 [2]	13 [2]	0.51

Posterior wall thickness (mm)	12 [2]	12 [2]	12 [2]	0.90
LVH	46 (61)	23 (62)	23 (61)	0.88
LV diastolic function				
E/A	1.2 [1.0]	1.0 [0.3]	1.3 [1.2]	0.44
Deceleration time (ms)	222 [82]	228 [75]	217 [89]	0.58
E' average (cm/s)	7.7 [2.5]	8.6 [2.8]	7.0 [2.0]	<0.01
E/e' average	14.9 [6.3]	12.9 [4.3]	16.4 [7.3]	0.027
Diastolic dysfunction	35 (55)	11 (39)	24 (67)	0.029
LA volume (mL/m^2)	45 [16]	47 [16]	44 [16]	0.37
LA dilatation	65 (88)	33 (92)	32 (84)	0.33
RV structure and function				
RVEDD (mm)	35 [7]	35 [8]	34 [6]	0.35
TAPSE (mm)	20 [5]	21 [4]	20 [5]	0.75
Estimated RVSP (mmHg)	40 [16]	38 [13]	41 [19]	0.57
Valve disease				
Mild/moderate valve disease	57 (76)	33 (89)	24 (63)	<0.01

Values are mean [standard deviation] or n (%). CAD, coronary artery disease; LA, left atrial; LV, left ventricular; LVEDD, LV end-diastolic dimension; LVEF, LV ejection fraction; LVESD, LV end-systolic dimension; LVH, LV hypertrophy; RV, right ventricular; RVEDD, RV end-diastolic dimension; RVSP, RV systolic pressure; TAPSE, tricuspid annular plane systolic excursion.

Table 5-6: Echocardiography findings stratified by obstructive epicardial CAD.

5.2.6 Cardiac magnetic resonance imaging

Table 5-7 details the cardiac magnetic resonance (CMR) imaging findings based on the presence or absence of obstructive epicardial CAD. Twenty patients with no obstructive CAD and 24 patients with obstructive disease underwent CMR. Similar to the echocardiographic findings, the LVEF was similar in those with and without obstructive CAD (mean 58% vs. 61%; p = 0.17, respectively), but the LVESV was larger in those with obstructive disease (mean 35 vs. 27 mL/m^2; p = 0.047, respectively). The rate of LVH was similar in both groups, but the proportion of patients with LA dilatation were greater in those without obstructive disease than those with epicardial CAD (84% vs. 48%; p = 0.014, respectively).

Ischaemic late gadolinium enhancement (LGE) was more frequent in those with obstructive CAD (46% vs. 10%; p <0.01), whereas non-ischaemic LGE was similar in those with and without epicardial CAD. Native T1 values were similar but the

mean extracellular volume (ECV) and the proportion of patients with a high ECV (>30%) were significantly greater in those with obstructive CAD than those without CAD (29.9% vs. 26.6%; p = 0.011, and 64% vs. 22%; p <0.01, respectively). The median global myocardial-perfusion reserve index (MPRI) and the proportion of patients with CMR evidence of inducible ischaemia (i.e. global MPRI <1.4) were not significantly different between those with and without obstructive epicardial CAD (1.41 vs. 1.65; p = 0.23, and 45% vs. 29%; p = 0.33, respectively).

	All angiography (n = 44)	No obstructive CAD (n = 20)	Obstructive CAD (n = 24)	p-value
LV structure and function				
LVEDV (mL/m^2)	76 [22]	69 [21]	81 [22]	0.061
LVESV (mL/m^2)	31 [13]	27 [11]	35 [13]	0.047
LVSV (mL/m^2)	44 [11]	42 [12]	47 [11]	0.16
CI (L/min/m^2)	3.2 [0.9]	3.2 [0.9]	3.3 [0.9]	0.70
LVEF (%)	59 [7]	61 [6]	58 [7]	0.17
MAPSE (mm)	13 [3]	13 [4]	13 [3]	1.0
WMSI	1.1 [0.2]	1.0 [0.1]	1.1 [0.2]	0.049
LV mass (g/m^2)	67 [16]	65 [19]	69 [13]	0.50
LVH	26 (58)	10 (50)	16 (64)	0.34
LA structure				
LA volume (mL/m^2)	68 [22]	70 [15]	65 [26]	0.44
LA dilatation	27 (64)	16 (84)	11 (48)	0.014
RV structure and function				
RVEDV (mL/m^2)	80 [27]	75 [25]	83 [29]	0.33
RVESV (mL/m^2)	38 [15]	36 [15]	39 [16]	0.65
RVSV (mL/m^2)	42 [16]	39 [14]	44 [18]	0.27
RVEF (%)	53 [9]	52 [9]	54 [8]	0.43
TAPSE (mm)	18 [5]	18 [5]	19 [5]	0.64
LGE				
Any LGE	27 (61)	9 (45)	18 (75)	0.042
Ischaemic LGE	13 (30)	2 (10)	11 (46)	<0.01
Non-ischaemic LGE	16 (36)	7 (35)	9 (38)	0.86
T1 mapping				
Native T1 (ms)	1283 [64]	1268 [74]	1296 [53]	0.17
ECV (%)	28.4 [4.2]	26.6 [3.3]	29.9 [4.3]	0.011
ECV >30%	18 (45)	4 (22)	14 (64)	<0.01
Adenosine stress perfusion imaging				
MPRI	1.49 [1.33-1.85]	1.65 [1.39-1.87]	1.41 [1.26-1.75]	0.23
MPRI <1.4	13 (38)	4 (29)	9 (45)	0.33

Values are mean [standard deviation], median [Q1-Q3], or n (%). CAD, coronary artery disease; CI, cardiac index; ECV, extracellular volume; LA, left atrial; LGE, late gadolinium enhancement; LV, left ventricular; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume; LVH, LV hypertrophy; LVSV, LV stroke volume; MAPSE, mitral annular plane systolic excursion; MPRI, myocardial-

perfusion reserve index; RV, right ventricular; RVEDV, RV end-diastolic volume; RVEF, RV ejection fraction; RVESV, RV end-systolic volume; RVSV, RV stroke volume; TAPSE, tricuspid annular plane systolic excursion; WMSI, wall motion score index.

Table 5-7: CMR findings stratified by obstructive epicardial CAD.

5.2.7 Invasive coronary physiology and haemodynamics

Table 5-8 describes the invasive coronary physiology and haemodynamics of those with and without obstructive CAD. Coronary physiology testing was performed in 36 of those no obstructive CAD and 26 of those with obstructive CAD. The prevalence of endothelium-independent CMD was similar in both those with and without epicardial CAD (62% vs. 69%; p = 0.52, respectively). CFR was not significantly different in those with and without obstructive CAD (median 2.0 vs. 2.4; p = 0.059, respectively), but the median IMR was higher in those without than with obstructive epicardial disease (27 vs. 18; p = 0.015, respectively). Endothelium-dependent CMD was present in 24% of the 36 participants with no obstructive CAD, whereas none of the five patients with obstructive epicardial disease that underwent endothelial function testing had evidence of coronary endothelial dysfunction.

LVEDP was measured invasively in 69 of the 75 patients (92%) that underwent coronary angiography. The median LVEDP was 12 mmHg and 31 patients (45%) had an elevated LVEDP (≥12 mmHg). Of note, coronary angiography was performed at an interval of around three months (median 97 days) from recruitment and all but one (99%) were discharged from hospital on a loop diuretic. Those without obstructive CAD were more likely to have an elevated LVEDP (≥12 mmHg) than those with obstructive disease (60% vs 29%; p = 0.011, respectively).

	All angiography	**No obstructive CAD**	**Obstructive CAD**	**p-value**
	(n = 62)	(n = 36)	(n = 26)	
Endothelium-independent CMD	41 (66)	25 (69)	16 (62)	0.52
CFR	2.1 [1.4-2.7]	2.4 [1.5-3.1]	2.0 [1.2-2.4]	0.059
CFR <2.0	28 (45)	15 (42)	15 (50)	0.52
IMR	23 [15-39]	27 [19-43]	18 [12-26]	0.015
IMR ≥25	32 (52)	21 (58)	11 (42)	0.21
	(n = 41)	(n = 36)	(n = 5)	

Endothelium-dependent CMD	10 (24)	10 (28)	0 (0)	0.18
	(n = 69)	(n = 35)	(n = 34)	
LVEDP (mmHg)	12 [9-15]	13 [10-15]	10 [8-15]	0.25
LVEDP ≥12 mmHg	31 (45)	21 (60)	10 (29)	0.011

Values are median [Q1-Q3] or n (%). CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; IMR, index of microcirculatory resistance; LVEDP, left ventricular end-diastolic pressure.

Table 5-8: Invasive coronary physiology and haemodynamics stratified by obstructive epicardial CAD.

5.3 Correlates of obstructive epicardial coronary artery disease

The correlates of obstructive epicardial CAD on invasive coronary angiography are presented in Table 5-9. Obstructive epicardial CAD was associated with a past history of CAD ($\varphi = 0.33$; $p < 0.01$), MI ($\varphi = 0.28$; $p = 0.015$), revascularisation ($\varphi = 0.29$; $p = 0.013$) and CKD ($\varphi = 0.28$; $p = 0.013$). Epicardial CAD was also correlated with ischaemic LGE ($\varphi = 0.39$; $p < 0.01$), ECV ($r_{pb} = 0.40$; $p = 0.011$) and an elevated ECV ($\varphi = 0.41$; $p < 0.01$) on CMR. It was inversely correlated with female sex ($\varphi = -0.25$; $p = 0.028$), CFR ($r_{pb} = -0.27$; $p = 0.035$) and an elevated LVEDP ($\varphi = -0.31$; $p = 0.01$).

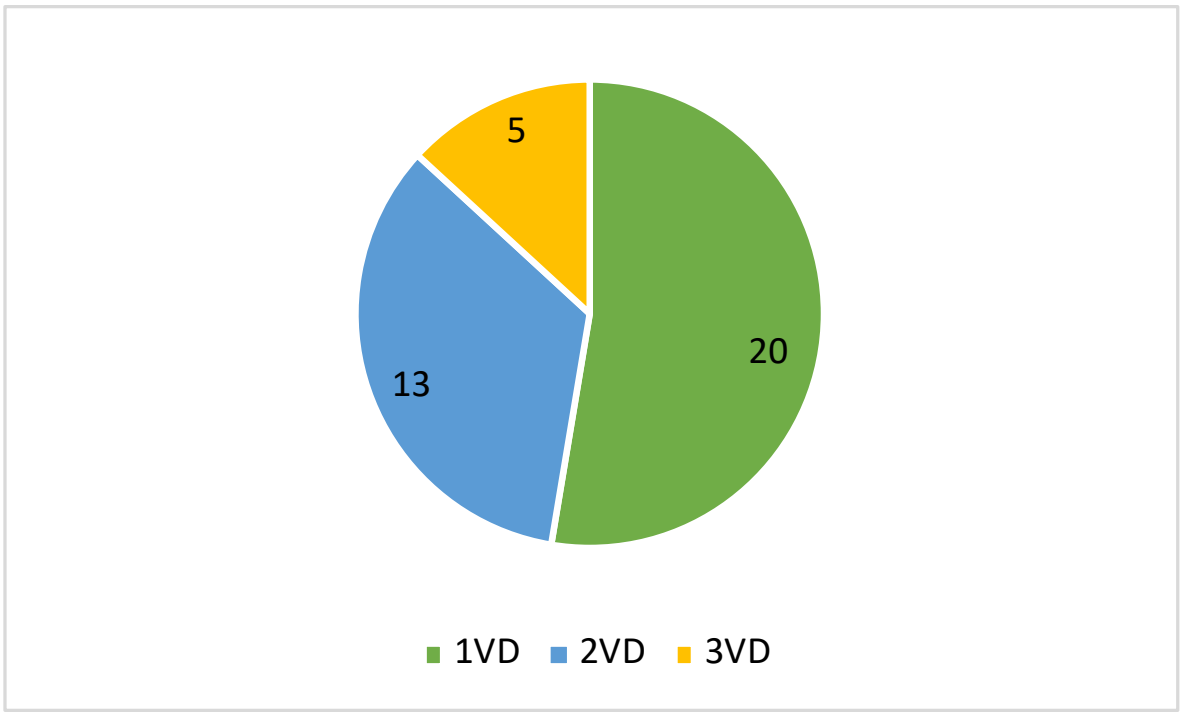
	Obstructive CAD	p-value
Female sex	-0.25	0.028
History of CAD	0.33	<0.01
History of MI	0.28	0.015
History of revascularisation	0.29	0.013
CKD	0.28	0.013
E/e'	0.28	0.027
Ischaemic LGE	0.39	<0.01
ECV (%)	0.40	0.011
ECV >30%	0.41	<0.01
CFR	-0.27	0.035
LVEDP ≥12 mmHg	-0.31	0.01

BMI, body mass index; CAD, coronary artery disease; CFR, coronary flow reserve; CKD, chronic kidney disease; CMR, cardiac magnetic resonance imaging; LGE, late gadolinium enhancement; LVEDP, left ventricular end-diastolic volume; MI, myocardial infarction.

Table 5-9: Correlates of obstructive epicardial CAD.

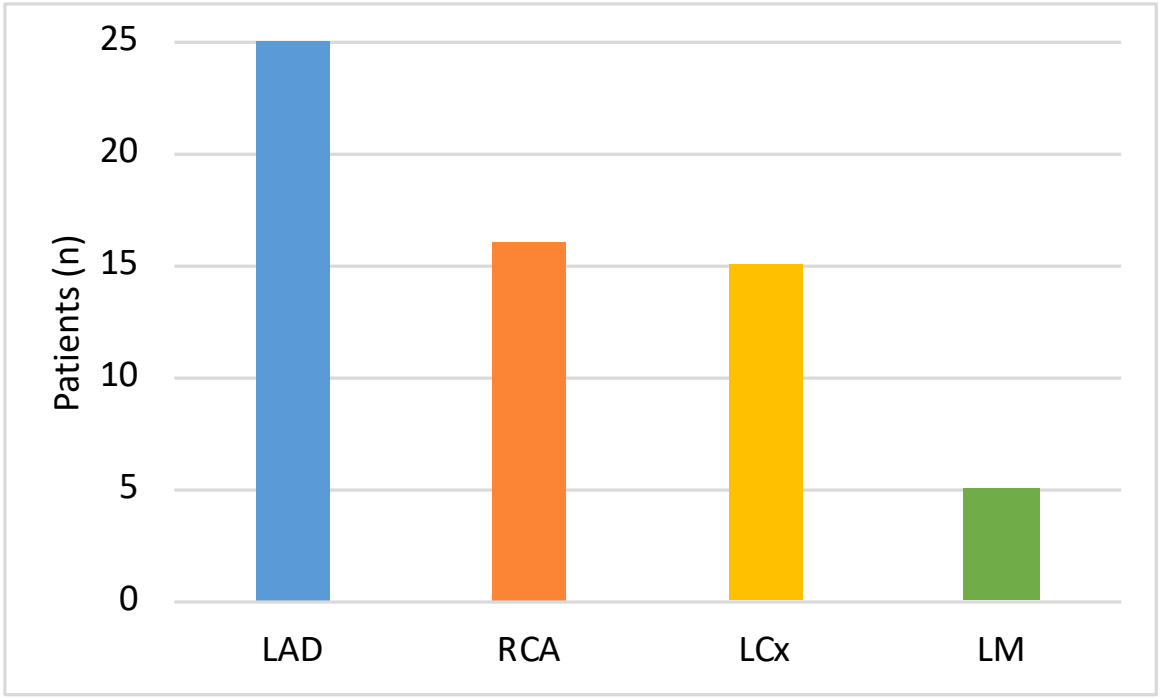
5.4 Pattern and severity of coronary artery disease

Of the 38 participants with obstructive epicardial CAD, 20 (53%) had single-vessel and 18 (47%) had multi-vessel CAD (13 [34%] with two-vessel and five [13%] with three-vessel disease) (Figure 5-2). Five patients (13%) had a ≥50% stenosis of the left main coronary artery; this was considered to represent two-vessel CAD. Twenty-five patients (66%) had obstructive disease in the left anterior descending (LAD) artery, 16 (42%) in the right coronary artery (RCA), and 15 (39%) in the left circumflex (LCx) artery (Figure 5-3). Of those with two-vessel CAD, five (38%) had obstructive LAD and LCx (or left main coronary artery) disease, five (38%) had LAD and RCA lesions, and three (23%) had LCx and RCA disease.



1VD, single-vessel disease; 2VD, two-vessel disease; 3VD, three-vessel disease.

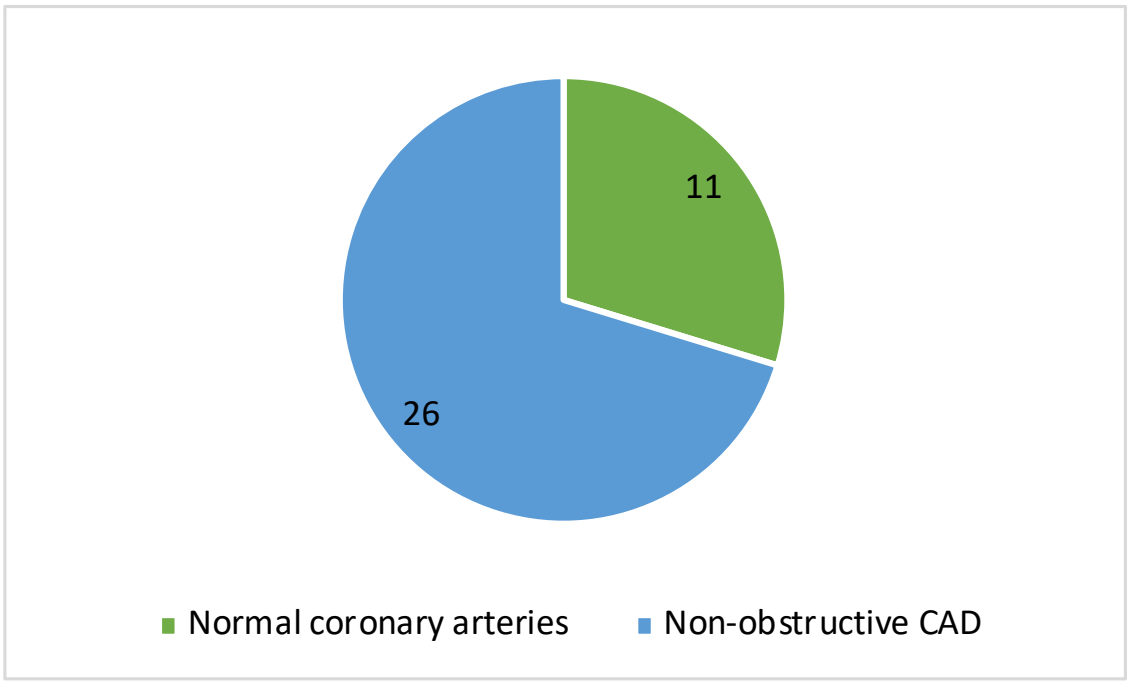
Figure 5-2: Number of diseased epicardial coronary arteries in study participants with obstructive epicardial CAD.



LAD, left anterior descending artery; LCx, left circumflex artery; LM, left main coronary artery; RCA, right coronary artery.

Figure 5-3: Location of obstructive epicardial coronary stenoses in study cohort.

Of the 37 participants with no obstructive epicardial CAD, 11 (30%) had normal coronary arteries and 26 (70%) had minor non-obstructive CAD (Figure 5-4).



CAD, coronary artery disease.

Figure 5-4: Normal coronary arteries and non-obstructive CAD in study participants with no obstructive CAD.

5.5 Outcomes related to obstructive epicardial coronary artery disease

Mortality

Over a median follow-up of 18 months, there were no significant differences in mortality rates between those with and without obstructive epicardial CAD (Figures 5-5, 5-6, 5-7, 5-8). However, there were very few deaths during the follow-up period.

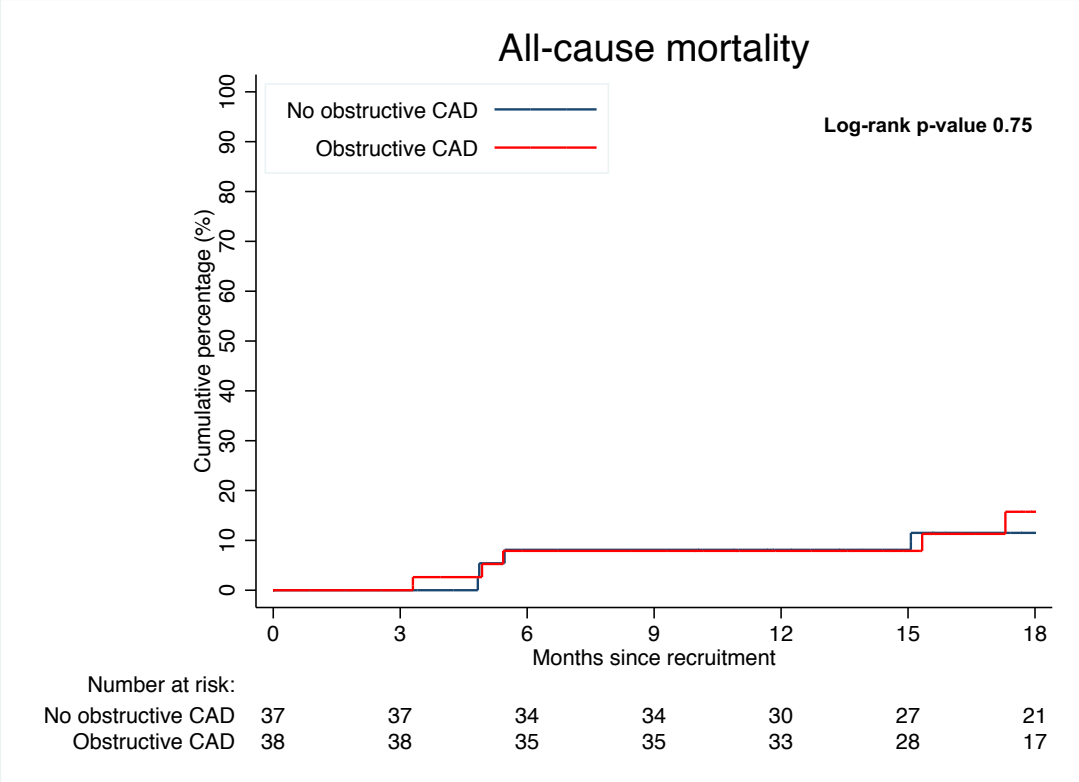


Figure 5-5: Kaplan-Meier curves for all-cause mortality by obstructive CAD.

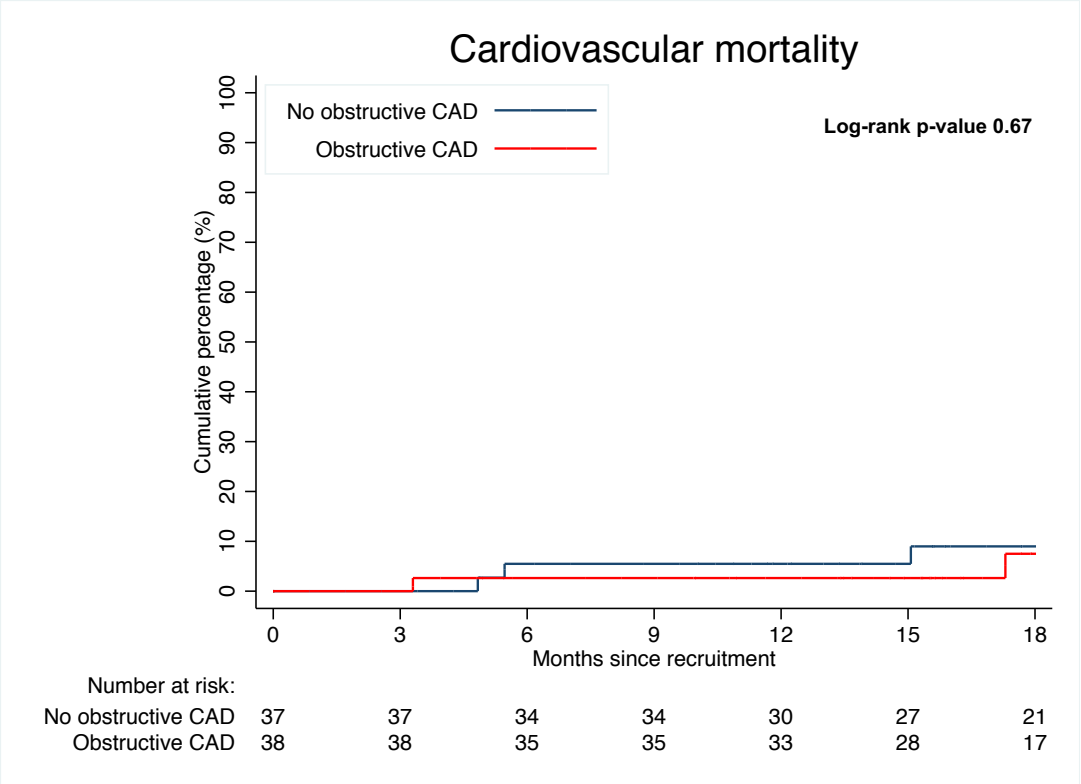


Figure 5-6: Kaplan-Meier curves for CV mortality by obstructive CAD.

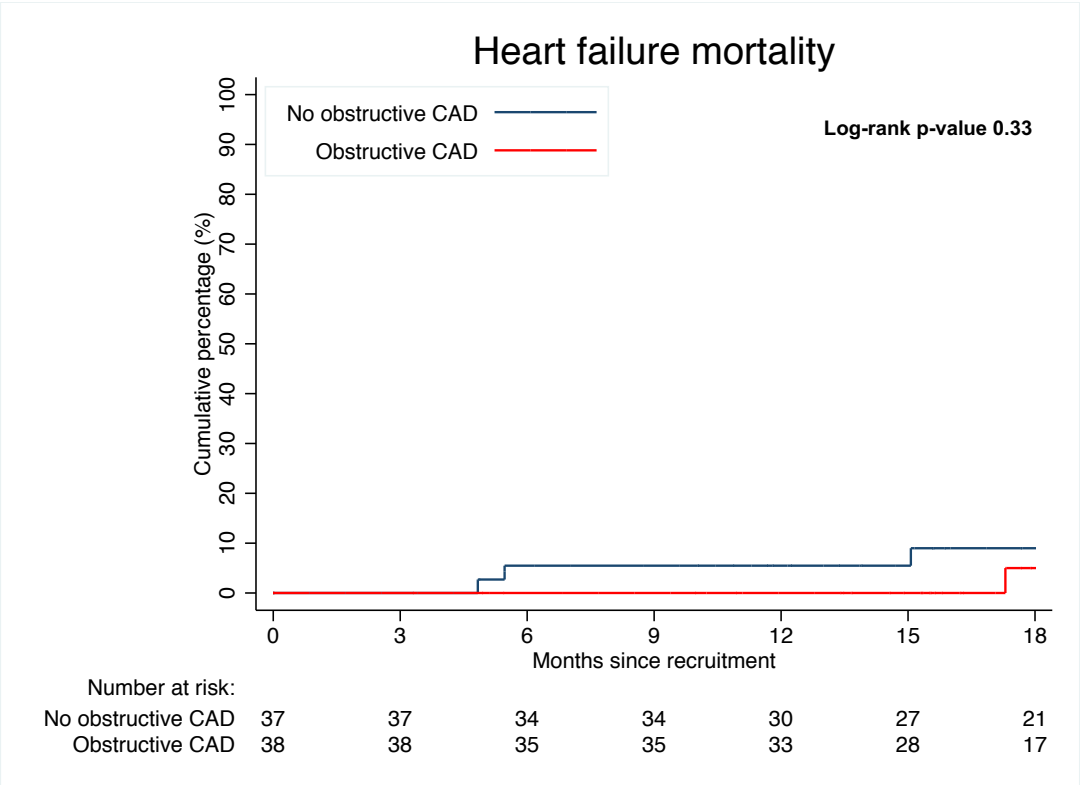


Figure 5-7: Kaplan-Meier curves for HF mortality by obstructive CAD.

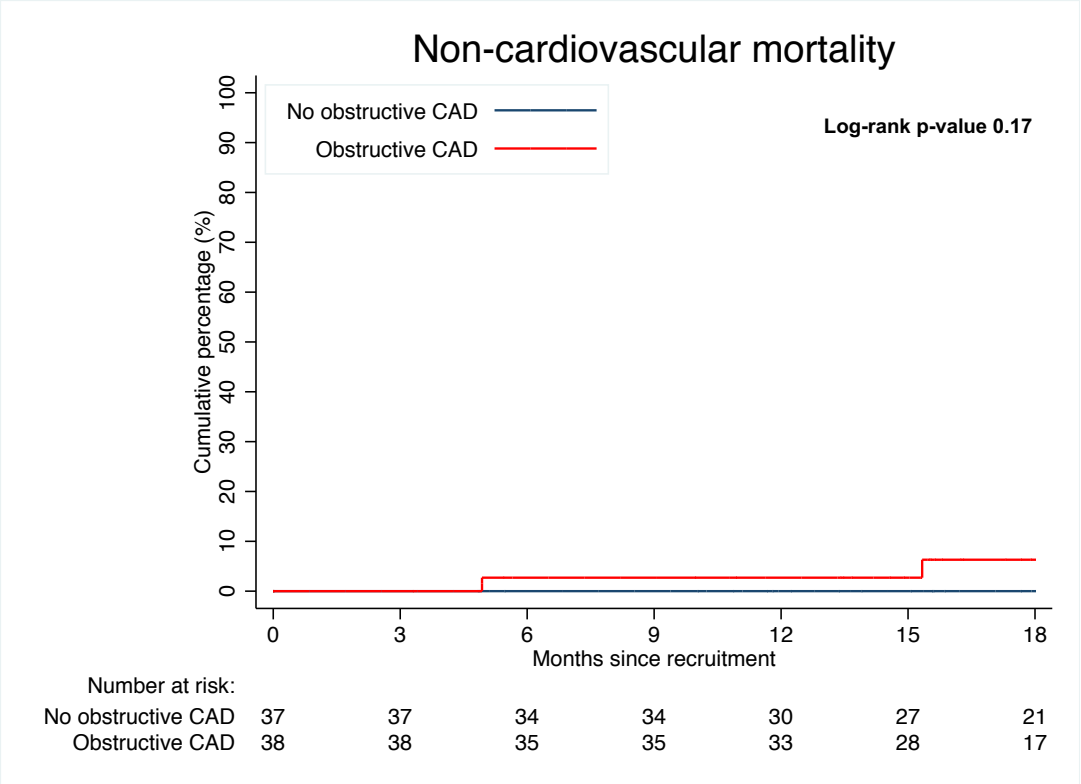


Figure 5-8: Kaplan-Meier curves for non-CV mortality by obstructive CAD.

Hospitalisations

Participants with CAD had significantly more hospitalisations for any reason (Figure 5-9), for a CV cause (Figure 5-10), and for HF (Figure 5-11) than those with no obstructive CAD. Non-CV hospitalisations were similar in both groups (Figure 5-12).

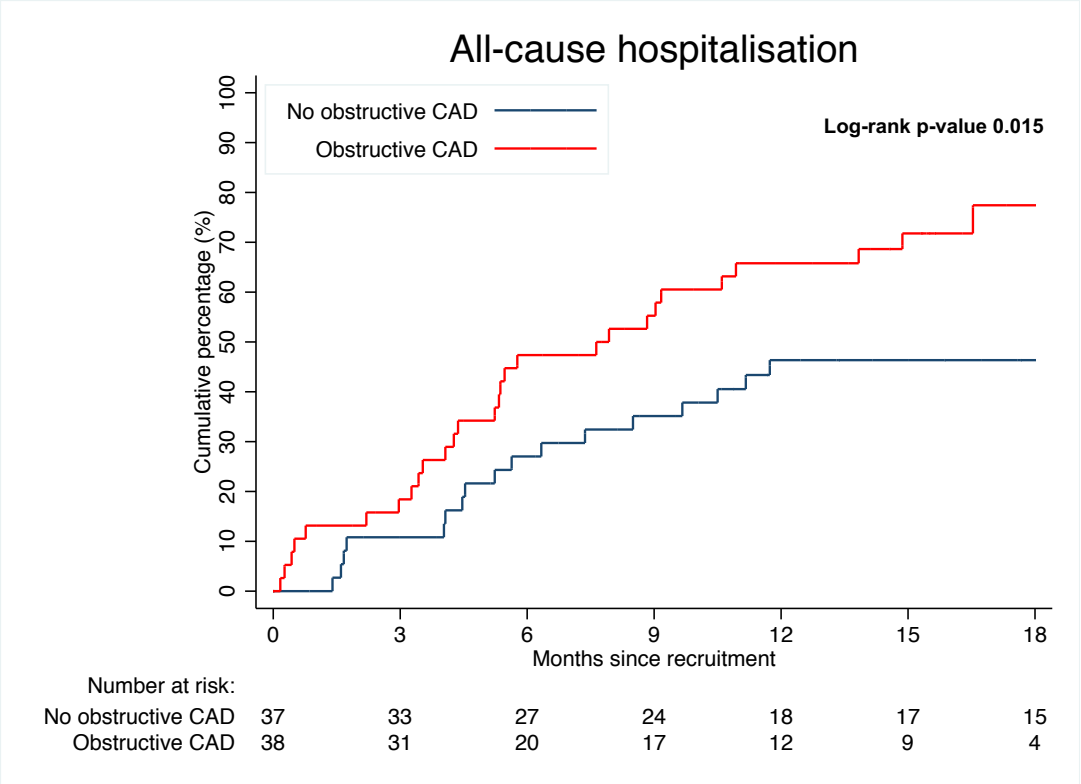


Figure 5-9: Kaplan-Meier curves for all-cause hospitalisation by obstructive CAD.

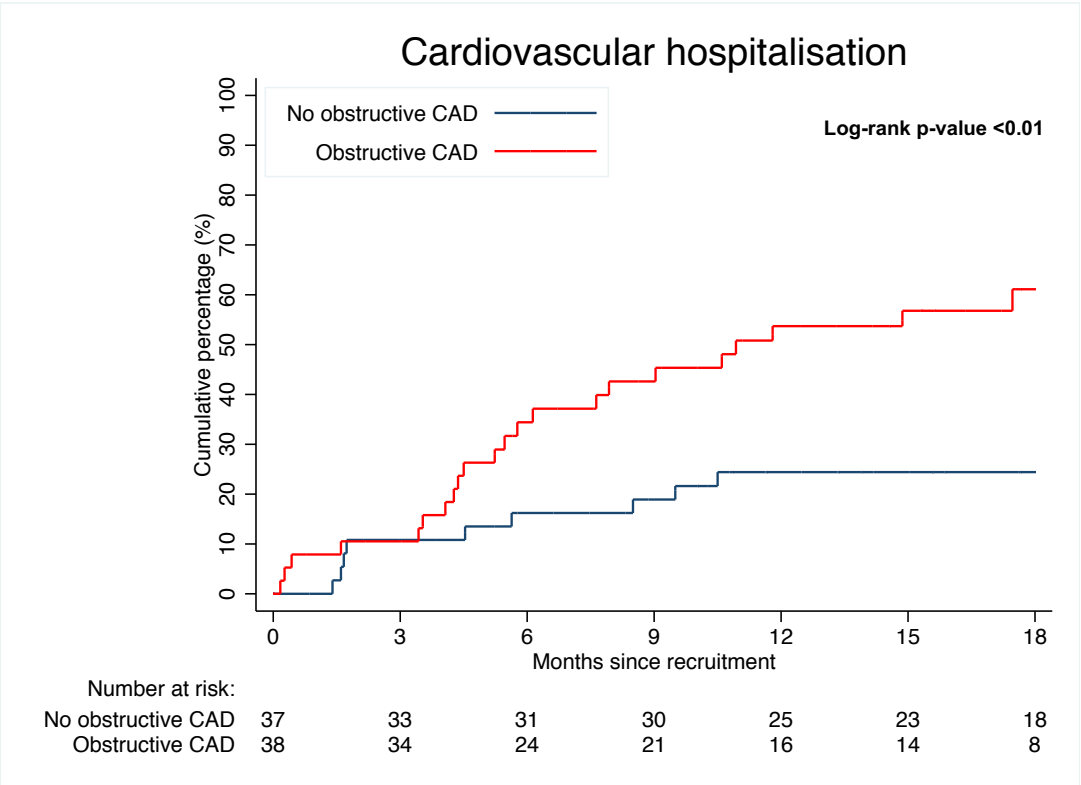


Figure 5-10: Kaplan-Meier curves for CV hospitalisation by obstructive CAD.

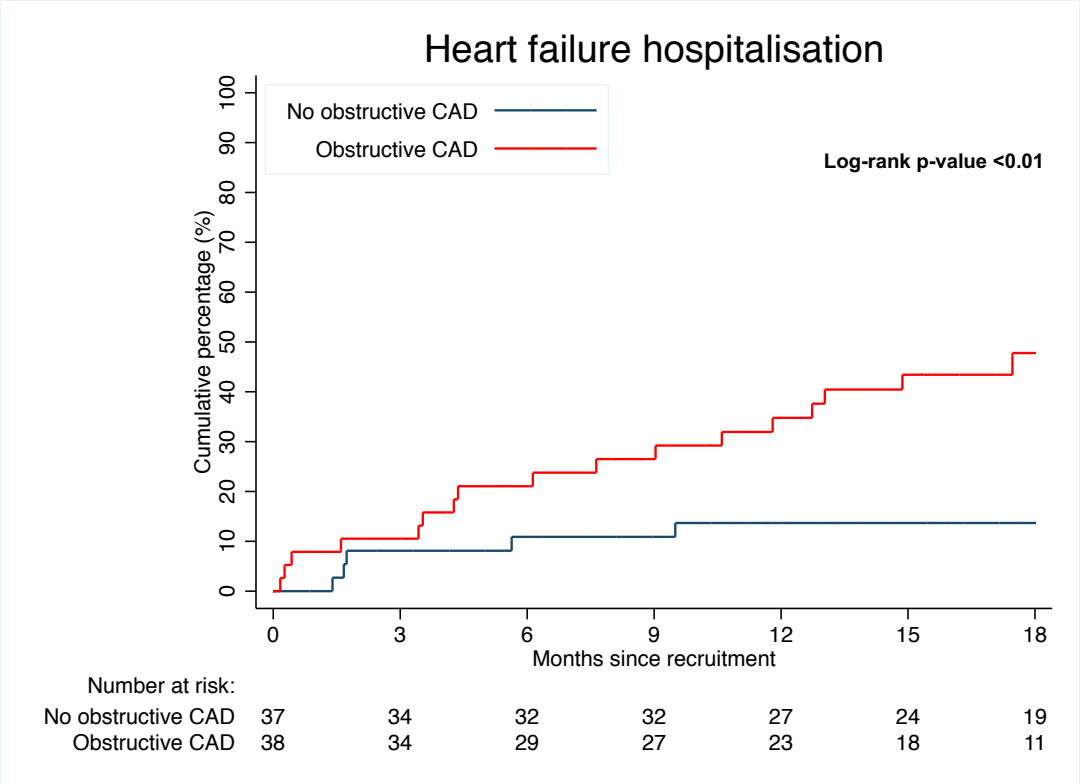


Figure 5-11: Kaplan-Meier curves for HF hospitalisation by obstructive CAD.

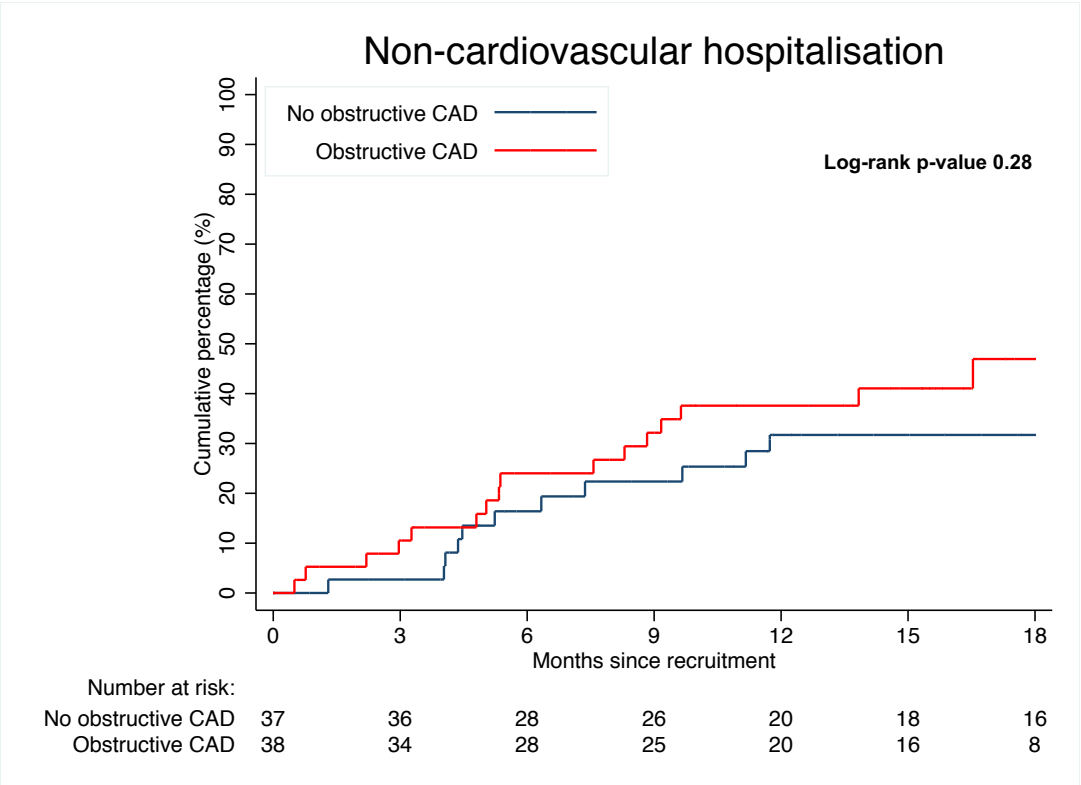


Figure 5-12: Kaplan-Meier curves for non-CV hospitalisation by obstructive CAD.

Following invasive coronary assessment as part of the study, eight participants (21% of those with obstructive CAD) subsequently underwent PCI. The reasons given by clinicians for revascularisation in these subjects were: "prognostically significant disease" or angina/"anginal equivalent" symptoms despite medical therapy. The number of patients revascularised was very small, so I was unable to evaluate the association between revascularisation and outcomes.

5.6 Complications of invasive coronary angiography

There were no procedural complications related to invasive coronary angiography in any of the study participants. Two patients (3%) required hospitalisation for treatment of acute kidney injury (AKI) following coronary angiography. Both patients had established stage 3 CKD before cardiac catheterisation and had a stable eGFR on blood testing in the week prior to angiography.

One patient had significant urological problems which were felt to have contributed to the deterioration in renal function in addition to contrast-induced nephropathy. His AKI was managed with IV fluids and temporary discontinuation of nephrotoxic medication with full renal recovery. The other patient had an arrangement to have his renal function checked by the general practitioner (GP) three days after angiography. This showed a significant decline in his eGFR and the GP advised hospital admission, but the patient declined. He subsequently developed oligoanuria and was hospitalised three days later. He required temporary haemodialysis for four days after which there was full renal recovery.

5.7 Summary

In this hospitalised HFpEF cohort, over half of patients had obstructive CAD on invasive coronary angiography. Those with obstructive disease were more often male and had a high burden of previous CAD, CKD and diabetes. There was no significant difference in natriuretic peptide levels between those with and without obstructive CAD. Interestingly, there was also no difference in troponin levels, suggesting that significant acute myocardial ischaemia was not a major cause of HF decompensation. Patients with obstructive CAD had higher estimated LV filling pressures on echocardiography than those without. Therefore, it is possible that sub-clinical ischaemia might contribute to diastolic dysfunction and decompensation in HFpEF. On CMR, participants with obstructive CAD had more ischaemic LGE and higher ECV than those without significant coronary disease. This suggests that myocardial ischaemia not only results in MI, but also contributes to diffuse myocardial fibrosis, which may play an important role in those with HFpEF and CAD.

Although the prevalence of AF was similar in those with and without obstructive CAD, those with non-obstructive disease had larger LA volumes on CMR and were more frequently prescribed digoxin at hospital discharge, suggesting that atrial remodelling and AF with sub-optimal rate-control may have played a role in HF decompensation in those without obstructive CAD. Those without obstructive disease had higher rates of mild or moderate valve disease than those with significant epicardial CAD. Nonetheless, the majority of patients both with and without obstructive CAD had a degree of valve disease on echocardiography, so it is possible that seemingly non-significant valve disease may play a role in precipitating decompensation in HFpEF patients, regardless of the presence of obstructive CAD. All echocardiograms were performed at rest, therefore, the possibility of worsening of valve dysfunction under stress conditions (e.g. exercise) cannot be excluded. Indeed, previous studies have reported that mild functional mitral regurgitation can become significant during stress and is associated with increased adverse events in HFpEF.[263,264]

In the 2019 Scottish Health Survey, the prevalence of ischaemic heart disease (IHD, defined as a history of MI or angina) in the Scottish population was 5% (7% in men, 4% in women).[265] For comparison with my study population (mean age 72 years), the prevalence of IHD in the Scottish population was 13% (17% in men, 9% in women) in those aged 65-74 years, and 23% (30% in men, 18% in women) in those aged >75 years. However, data on the prevalence of angiographically documented CAD in unselected patients is extremely limited. A pooled analysis assessed the prevalence of obstructive CAD (determined by invasive coronary angiography and FFR) in patients referred for investigation of suspected CAD.[88] In patients presenting with dyspnoea, the prevalence of obstructive CAD in those aged 60-69 years was 27% in men and 14% in women, and in those aged >70 years was 32% in men and 12% in women. Therefore, the prevalence of angiographically documented CAD in my HFpEF cohort (51% overall, 63% in men, 38% in women) is significantly higher than would be expected in patients of the same age in the general population.

Over a median follow-up period of 18 months, there was no significant difference in mortality rates between those with and without obstructive epicardial CAD. However, there were few deaths during the follow-up period. Nonetheless, patients with obstructive CAD had significantly more hospitalisations for any reason, for a CV cause and for HF than those with no obstructive CAD. Of note, HF re-hospitalisation was defined as a primary discharge diagnosis of HF, therefore, it is possible that some re-hospitalisations attributed to HF could have been due to an alternative cause.

These findings suggest that obstructive epicardial CAD may contribute to HF decompensation in many patients with HFpEF and, therefore, coronary revascularisation might result in reduced hospitalisations and improved quality of life. Only eight study participants (21% of those with obstructive CAD) subsequently underwent PCI for clinical indications, therefore, I was unable to assess the association between revascularisation and outcomes in this cohort.

Reported outcomes in HFpEF patients vary depending on study design, clinical setting and LVEF threshold used to define HFpEF. Epidemiological studies report high mortality rates in HFpEF patients, with a 1-year mortality of 20-29%,[8,12,13] whilst randomised controlled trials (RCTs) have much lower annualised mortality

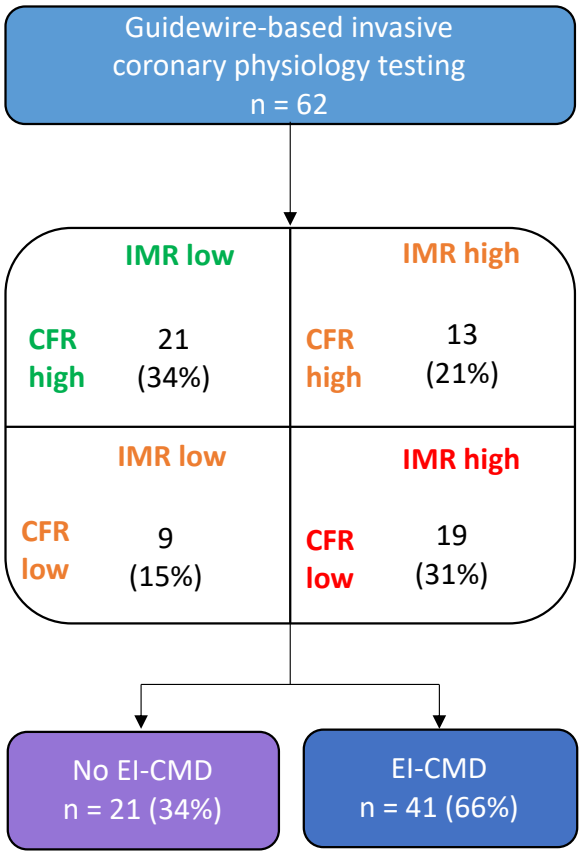
rates of 4-5% per year.[14-16] The annualised mortality rate in my cohort was 9%, suggesting that I recruited a higher risk group than that enrolled in RCTs (generally younger with less comorbidities), but a lower risk group than unselected HFpEF patients in epidemiological studies (generally older with a greater burden of comorbidities and frailty). In terms of hospitalisations, epidemiological studies report a >50% rate of re-hospitalisation within one year of a hospitalisation with HFpEF.[18] In my cohort, the annualised re-hospitalisation rate was 43%, slightly lower than that reported in epidemiological studies, again reflecting the lower risk nature of my study population.

Chapter 6 Results – Endothelium-independent coronary microvascular dysfunction in heart failure with preserved ejection fraction

In this chapter I will report the prevalence of endothelium-independent coronary microvascular dysfunction (CMD) in the study cohort. I will describe the clinical characteristics, investigation results and correlates of the population based on different measures of endothelium-independent coronary microvascular function, based on coronary flow reserve (CFR) and the index of microcirculatory reserve (IMR). Finally, I will report clinical outcomes (mortality and hospitalisations) on the basis of these assessments of coronary microvascular function.

6.1 Prevalence of endothelium-independent coronary microvascular dysfunction

A total of 62 participants underwent guidewire-based invasive coronary physiology testing for quantification of CFR and IMR. Endothelium-independent CMD (defined as CFR <2.0 and/or IMR ≥25) was present in 41 of the 62 participants (66% [95% CI 53-77%]) that underwent guidewire-based coronary physiology testing (Figure 6-1).



CFR, coronary flow reserve; EI-CMD, endothelium-independent coronary microvascular dysfunction; IMR, index of microcirculatory resistance.

Figure 6-1: Prevalence of endothelium-independent CMD in study cohort.

Forty-two patients (68%) had microvascular assessment of the LAD, 11 (18%) had RCA, and nine (15%) had assessment of the LCx. If a patient was found to have a functionally significant epicardial stenosis, coronary microvascular function was performed in another non-obstructed artery; this was the case in three patients.

6.2 Clinical characteristics by endothelium-independent coronary microvascular dysfunction

6.2.1 Demographics and clinical features

The baseline demographics and clinical features of the participants on the basis of endothelium-independent coronary microvascular function are described in Table 6-1. The groups had similar demographics, including age, sex, frailty, BMI and smoking history. There were no major differences in NYHA functional class or HF symptoms and signs at presentation between those with and without CMD.

	All pressure wire studies (n = 62)	No endothelium-independent CMD (n = 21)	Endothelium-independent CMD (n = 41)	p-value
Demographics				
Age (years)	72 [9]	74 [8]	72 [9]	0.41
Female sex	33 (53)	11 (52)	22 (54)	0.92
BMI (kg/m^2)	33 [8]	33 [9]	33 [7]	0.80
Obesity	28 (45)	9 (43)	19 (46)	0.79
Smoking history	34 (55)	11 (52)	23 (56)	0.78
Hospitalisation details				
Length of stay (days)	7 [5-11]	6 [6-9]	7 [5-11]	0.56
HF symptoms				
NYHA functional class				
II	2 (3)	1 (5)	1 (2)	0.68
III	31 (50)	9 (43)	22 (54)	
IV	29 (47)	11 (52)	18 (44)	
Orthopnoea	42 (68)	14 (67)	28 (68)	0.90
PND	30 (48)	11 (52)	19 (46)	0.65
Ankle swelling	56 (90)	20 (95)	36 (88)	0.35
Admission vital signs				
HR (bpm)	85 [26]	89 [22]	82 [20]	0.36
SBP (mmHg)	151 [31]	155 [33]	149 [30]	0.44
DBP (mmHg)	81 [20]	81 [22]	82 [20]	0.89
MAP (mmHg)	105 [20]	106 [20]	104 [20]	0.75
HF signs				
JVD	45 (73)	16 (76)	29 (71)	0.65
Murmur	17 (27)	8 (38)	9 (22)	0.18
Crepitations	48 (77)	15 (71)	33 (80)	0.42
Pleural effusion(s)	25 (40)	10 (48)	15 (37)	0.40
Oedema	56 (90)	20 (95)	36 (88)	0.35
Ascites	1 (2)	0 (0)	1 (2)	0.47

Values are mean [standard deviation], median [Q1-Q3], or n (%). BMI, body mass index; CMD, coronary microvascular dysfunction; DBP, diastolic blood pressure; HF, heart failure; HR, heart rate; JVD, jugular venous distention; MAP, mean arterial pressure; NYHA, New York Heart Association; PND, paroxysmal nocturnal dyspnoea; SBP; systolic blood pressure.

Table 6-1: Demographics and clinical features stratified by endothelium-independent CMD.

6.2.2 Past medical history

Table 6-2 details the past medical history of participants according to the presence or absence of endothelium-independent CMD. Thirty-one percent of those who underwent microvascular function testing had a previous history of CAD. There were no significant differences between the groups in rates of

previous CAD, MI, revascularisation or angina. Comorbidities including hypertension (76%), AF (65%) and diabetes (53%) were frequent. There were no major differences in the comorbidity profile of the two groups.

	All pressure wire studies (n = 62)	No endothelium-independent CMD (n = 21)	Endothelium-independent CMD (n = 41)	p-value
History of HF				
Previous HF diagnosis	23 (37)	5 (24)	18 (44)	0.12
Previous HFH	15 (24)	5 (24)	10 (24)	0.96
History of CAD				
Any CAD	19 (31)	7 (33)	12 (29)	0.74
MI	13 (21)	4 (19)	9 (22)	0.79
Angina	6 (10)	3 (14)	3 (7)	0.38
Current angina	5 (8)	2 (10)	3 (7)	0.76
Revascularisation	8 (13)	2 (10)	6 (15)	0.57
PCI	8 (13)	2 (10)	6 (15)	0.57
CABG	1 (2)	0 (0)	1 (2)	0.47
CV comorbidities				
Hypertension	47 (76)	15 (71)	32 (78)	0.56
Dyslipidaemia	5 (8)	1 (5)	4 (10)	0.49
CVD	13 (21)	6 (29)	7 (17)	0.29
PAD	7 (11)	4 (19)	3 (7)	0.17
AF	40 (65)	11 (52)	29 (71)	0.15
Valve disease (mild/moderate)	12 (19)	6 (29)	6 (15)	0.19
Non-CV comorbidities				
Diabetes	33 (53)	11 (52)	22 (54)	0.92
CKD	19 (31)	9 (43)	10 (24)	0.14
Chronic liver disease	0 (0)	0 (0)	0 (0)	
Depression	4 (6)	1 (5)	3 (7)	0.70
Cancer	5 (8)	2 (10)	3 (7)	0.76
COPD	15 (24)	5 (24)	10 (24)	0.96
Asthma	5 (8)	0 (0)	5 (12)	0.095
Anaemia	14 (23)	3 (14)	11 (27)	0.26
Hypothyroidism	9 (15)	5 (24)	4 (10)	0.14
Osteoarthritis	15 (24)	5 (24)	10 (24)	0.96

Values are n (%). AF, atrial fibrillation; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; CMD, coronary microvascular dysfunction; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; CVD, cerebrovascular disease; HF, heart failure; HFH, HF hospitalisation; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention.

Table 6-2: Past medical history stratified by endothelium-independent CMD.

6.2.3 Drug history – medication on admission, in-hospital treatment and medication at discharge

Table 6-3 summarises the admission medication, in-hospital treatment and discharge medication in those with and without endothelium-independent CMD. There were no significant differences in the rates of prescription of CV or non-CV drugs at either hospital admission or discharge. During hospitalisation, all those without CMD treated with diuretics received regular IV doses, compared with only 73% of those with CMD; 15% with microvascular dysfunction received a single dose of IV diuretic and 12% received oral diuretic therapy (p = 0.038).

	All pressure wire studies (n = 62)	**No endothelium-independent CMD (n = 21)**	**Endothelium-independent CMD (n = 41)**	**p-value**
Admission medication				
CV medication				
Antiplatelet	21 (34)	9 (43)	12 (29)	0.28
Anticoagulant	31 (50)	8 (38)	23 (56)	0.18
Statin	42 (68)	12 (57)	30 (73)	0.20
Loop diuretic	28 (45)	8 (38)	20 (49)	0.42
Furosemide-equivalent dose (mg)	80 [40-140]	80 [40-120]	80 [40-160]	0.62
Thiazide	5 (8)	1 (5)	4 (10)	0.49
MRA	1 (2)	0 (0)	1 (2)	0.47
ACEI/ARB	42 (68)	13 (62)	29 (71)	0.48
Beta-blocker	42 (68)	14 (67)	28 (68)	0.90
CCB	23 (37)	7 (33)	16 (39)	0.66
Digoxin	6 (10)	2 (10)	4 (10)	0.98
	(n = 33)	(n = 11)	(n = 22)	
Diabetic medication	27 (82)	10 (91)	17 (77)	0.34
Insulin	11 (33)	4 (36)	7 (32)	0.79
Non-CV medication				
Bronchodilator	20 (32)	5 (24)	15 (37)	0.31
Antidepressant	14 (23)	6 (29)	8 (20)	0.42
In-hospital treatment				
Furosemide	61 (98)	20 (95)	41 (100)	0.16
IV (>1 dose)	50 (82)	20 (100)	30 (73)	0.038
IV (1 dose)	6 (10)	0 (0)	6 (15)	
Oral	5 (8)	0 (0)	5 (12)	
IV nitrate	3 (5)	1 (5)	2 (5)	0.98
Dopamine	0 (0)	0 (0)	0 (0)	

Oxygen	28 (45)	11 (52)	17 (41)	0.41
CPAP	1 (2)	0 (0)	1 (2)	0.47
Discharge medication				
CV medication				
Antiplatelet	21 (34)	10 (48)	11 (27)	0.10
Anticoagulant	41 (66)	11 (52)	30 (73)	0.10
Statin	42 (68)	12 (57)	30 (73)	0.20
Loop diuretic	61 (98)	20 (95)	41 (100)	0.16
Furosemide-equivalent dose (mg)	80 [80-120]	80 [80-140]	80 [80-120]	0.76
Thiazide	5 (8)	1 (5)	4 (10)	0.49
ACEI/ARB	41 (66)	14 (67)	27 (66)	0.95
MRA	10 (16)	2 (10)	8 (20)	0.31
Beta-blocker	46 (74)	16 (76)	30 (73)	0.80
CCB	15 (24)	6 (29)	9 (22)	0.56
Digoxin	22 (35) (n= 33)	8 (38) (n = 11)	14 (34) (n = 22)	0.76
Diabetic medication	27 (82)	10 (91)	17 (77)	0.34
Insulin	12 (36)	5 (45)	7 (32)	0.44

Values are mean [standard deviation] or n (%). ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CMD, coronary microvascular dysfunction; CPAP, continuous positive airway pressure; CV, cardiovascular; IV, intravenous; MRA, mineralocorticoid receptor antagonist.

Table 6-3: Admission medication, in-hospital treatment and discharge medication stratified by endothelium-independent CMD.

6.2.4 Baseline investigations

The baseline ECG, CXR and laboratory results of those with and without endothelium-independent CMD are presented in Table 6-4. ECG and CXR findings were generally similar in both groups, but those with CMD had more radiological interstitial oedema than those without CMD (27% vs. 5%; p = 0.037, respectively). Most routine haematology and biochemistry results were comparable between the groups. The proportion of those with renal impairment and anaemia was similar in both groups. BNP was measured in 60% of patients and those with CMD had significantly higher levels than those without CMD (median 569 vs. 197 pg/mL; p = 0.036, respectively). However, NT-proBNP was measured in 53% of patients and was only slightly higher in those with CMD than those without (median 1459 vs. 1366; p = 0.37, respectively). hsTnI levels were similar in those with CMD and those with no CMD (median 16 vs. 20 ng/L; p = 0.22, respectively).

	All pressure wire studies (n = 62)	No endothelium-independent CMD (n = 21)	Endothelium-independent CMD (n = 41)	p-value
ECG				
Rate (bpm)	87 [26]	92 [32]	84 [23]	0.25
AF	36 (58)	10 (48)	26 (63)	0.66
Bundle branch block	8 (13)	3 (14)	5 (12)	0.82
LVH	7 (11)	3 (14)	4 (10)	0.59
Q waves	6 (10)	2 (10)	4 (10)	0.98
T-wave inversion	28 (45)	11 (52)	17 (41)	0.41
QRS duration (ms)	98 [26]	100 [22]	97 [29]	0.62
QT_c (ms)	445 [32]	444 [33]	446 [32]	0.82
CXR				
Cardiomegaly	48 (77)	14 (67)	34 (83)	0.15
Upper lobe venous diversion	42 (68)	17 (81)	25 (61)	0.11
Interstitial oedema	12 (19)	1 (5)	11 (27)	0.037
Alveolar oedema	33 (53)	10 (48)	23 (56)	0.53
Perihilar oedema	22 (35)	5 (24)	17 (41)	0.17
Pleural effusion(s)	29 (47)	9 (43)	20 (49)	0.66
Haematology				
Hb (g/L)	123 [19]	119 [20]	125 [19]	0.32
Anaemia	26 (42)	10 (48)	16 (39)	0.52
WCC (x 10^9/L)	8.3 [2.3]	8.4 [2.2]	8.2 [2.4]	0.81
Biochemistry				
NT-proBNP	33 (53)	13 (62)	20 (49)	0.33
NT-proBNP (pg/mL)	1385 [1040-2819]	1366 [414-2494]	1459 [1152-2948]	0.37
BNP	37 (60)	11 (52)	26 (63)	0.40
BNP (pg/mL)	355 [177-904]	197 [123-623]	569 [189-1253]	0.036
hsTnI	41 (66)	14 (67)	27 (66)	0.95
hsTnI (ng/L)	16 [7-29]	20 [14-36]	16 [5-25]	0.22
Elevated hsTnI	12 (29)	4 (29)	8 (30)	0.94
Na^+ (mmol/L)	138 [3]	139 [2]	138 [4]	0.14
Hyponatraemia	3 (5)	0 (0)	3 (7)	0.20
K^+ (mmol/L)	4.4 [0.6]	4.4 [0.5]	4.4 [0.6]	0.81
Urea (mmol/L)	7.9 [4.3]	7.6 [3.1]	8.1 [4.9]	0.65
Creatinine (µmol/L)	96 [36]	95 [25]	97 [41]	0.85
eGFR (mL/min/1.73m^2)	65 [21]	63 [15]	66 [24]	0.58
eGFR <60 mL/min/ 1.73m^2	24 (39)	8 (38)	16 (39)	0.94
Albumin (g/L)	34 [4]	35 [4]	34 [4]	0.47
Hypoalbuminaemia	29 (47)	9 (43)	20 (49)	0.66
CRP (mg/L)	13 [5-21]	9 [4-22]	13 [7-21]	0.61
Elevated CRP	34 (55)	10 (48)	24 (59)	0.41

Glucose (mmol/L)	6.4 [5.3-8.5]	6.2 [5.3-8.2]	6.5 [5.3-8.6]	0.75

Values are mean [standard deviation], median [Q1-Q3], or n (%). AF, atrial fibrillation; AV, atrioventricular; BNP, B-type natriuretic peptide; CMD, coronary microvascular dysfunction; CRP, C-reactive protein; CXR, chest x-ray; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; hsTnI, high-sensitivity troponin I; K^+, potassium; LVH, left ventricular hypertrophy; Na^+, sodium; NT-proBNP, N-terminal prohormone BNP; WCC, white cell count.

Table 6-4: ECG, CXR and laboratory results stratified by endothelium-independent CMD.

Table 6-5 details the echocardiography findings of patients stratified by endothelium-independent CMD; there were no significant differences between the groups.

	All pressure wire studies (n = 62)	No endothelium-independent CMD (n = 21)	Endothelium-independent CMD (n = 41)	p-value
LV structure and systolic function				
LVEDD (mm/m^2)	24 [3]	25 [3]	24 [4]	0.78
LVESD (mm/m^2)	16 [4]	15 [4]	16 [4]	0.42
LVEF (%)	58 [6]	60 [6]	57 [5]	0.06
S' lateral (cm/s)	6.8 [2.2]	6.9 [2.3]	6.7 [2.1]	0.73
Septal wall thickness (mm)	13 [3]	13 [2]	13 [3]	0.42
Posterior wall thickness (mm)	12 [2]	13 [2]	12 [2]	0.31
LVH	36 (58)	14 (67)	22 (54)	0.33
LV diastolic function				
E/A	1.3 [1.1]	1.0 [0.4]	1.4 [1.3]	0.43
Deceleration time (ms)	226 [83]	224 [81]	227 [84]	0.88
E' average (cm/s)	7.8 [2.5]	8.0 [1.6]	7.7 [2.9]	0.62
E/e' average	14.1 [4.9]	13.5 [4.2]	14.4 [5.3]	0.54
Diastolic dysfunction	27 (52)	11 (58)	16 (48)	0.51
LA volume (mL/m^2)	46 [15]	43 [11]	47 [17]	0.26
LA dilatation	56 (92)	19 (90)	37 (92)	0.78
RV structure and function				
RVEDD (mm)	35 [7]	34 [6]	36 [7]	0.34
TAPSE (mm)	21 [4]	20 [3]	21 [5]	0.32
Estimated RVSP (mmHg)	39 [14]	42 [16]	36 [12]	0.25
Valve disease				
Mild/moderate valve disease	50 (81)	17 (81)	33 (80)	0.97

Values are mean [standard deviation] or n (%). CMD, coronary microvascular disease; LA, left atrial; LV, left ventricular; LVEDD, LV end-diastolic dimension; LVEF, LV ejection fraction; LVESD, LV end-systolic dimension; LVH, LV hypertrophy; RV, right ventricular; RVEDD, RV end-diastolic dimension; RVSP, RV systolic pressure; TAPSE, tricuspid annular plane systolic excursion.

Table 6-5: Echocardiography findings stratified by endothelium-independent CMD.

6.2.5 Cardiac magnetic resonance imaging

Table 6-6 details the CMR findings stratified by endothelium-independent coronary microvascular function. Again, there were no statistically significant differences between the groups.

	All pressure wire studies (n = 35)	No endothelium-independent CMD (n = 11)	Endothelium-independent CMD (n = 24)	p-value
LV structure and function				
LVEDV (mL/m^2)	74 [22]	75 [19]	74 [23]	0.91
LVESV (mL/m^2)	31 [13]	32 [12]	31 [14]	0.93
LVSV (mL/m^2)	43 [10]	43 [10]	43 [11]	0.89
CI (L/min/m^2)	3.2 [0.8]	3.2 [0.7]	3.1 [0.9]	0.75
LVEF (%)	59 [7]	58 [7]	59 [7]	0.94
MAPSE (mm)	13 [3]	12 [3]	13 [3]	0.32
WMSI	1.1 [0.2]	1.1 [0.2]	1.1 [0.2]	0.50
LV mass (g/m^2)	67 [15]	70 [18]	65 [12]	0.29
LVH	21 (58)	8 (73)	13 (52)	0.25
LA structure				
LA volume (mL/m^2)	67 [22]	65 [14]	68 [25]	0.69
LA dilatation	21 (64)	7 (70)	14 (61)	0.62
RV structure and function				
RVEDV (mL/m^2)	76 [22]	84 [27]	73 [18]	0.17
RVESV (mL/m^2)	37 [14]	44 [20]	34 [11]	0.065
RVSV (mL/m^2)	39 [11]	40 [10]	39 [12]	0.78
RVEF (%)	52 [9]	49 [8]	53 [9]	0.22
TAPSE (mm)	18 [5]	20 [5]	18 [5]	0.38
LGE				
Any LGE	22 (63)	7 (64)	15 (62)	0.95
Ischaemic LGE	10 (29)	3 (27)	7 (29)	0.91
Non-ischaemic LGE	13 (37)	4 (36)	9 (38)	0.95
T1 mapping				
Native T1 (ms)	1279 [67]	1308 [70]	1266 [63]	0.10
ECV (%)	28.0 [4.2]	29.5 [3.4]	27.4 [4.5]	0.23
ECV >30%	12 (39)	4 (44)	8 (36)	0.68
Adenosine stress perfusion imaging				
MPRI	1.66 [1.39-1.87]	1.55 [1.33-1.85]	1.70 [1.39-1.97]	0.37
MPRI <1.4	7 (28)	3 (30)	4 (27)	0.86

Values are mean [standard deviation], median [Q1-Q3], or n (%). CMD, coronary microvascular dysfunction; CI, cardiac index; ECV, extracellular volume; LA, left atrial; LGE, late gadolinium enhancement; LV, left ventricular; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume; LVH, LV hypertrophy; LVSV, LV stroke volume; MAPSE, mitral annular plane systolic excursion; MPRI, myocardial-perfusion reserve index; RV, right ventricular; RVEDV, RV end-diastolic volume; RVEF, RV ejection fraction; RVESV, RV end-systolic volume; RVSV, RV stroke volume; TAPSE, tricuspid annular plane systolic excursion; WMSI, wall motion score index.

Table 6-6: CMR findings stratified by endothelium-independent CMD.

6.2.6 Invasive coronary angiography, physiology and haemodynamics

Table 6-7 summarises the invasive coronary angiography, physiology and haemodynamics stratified by the presence or absence of endothelium-independent CMD. There were no significant differences in the proportion of patients with epicardial CAD between the groups. Of the 41 participants with endothelium-independent CMD, only six (21%) had evidence of endothelium-dependent CMD, whereas four of the 21 patients (33%) without endothelium-independent CMD had evidence of endothelium-dependent CMD. The median LVEDP and the proportion of those with an LVEDP ≥12 mmHg was similar in those with and without CMD (13 vs. 11 mmHg; p = 0.41, and 53% vs. 33%; p = 0.15, respectively).

	All pressure wire studies	No endothelium-independent CMD	Endothelium-independent CMD	p-value
	(n = 62)	(n = 21)	(n = 41)	
Obstructive epicardial CAD	26 (42)	10 (48)	16 (39)	0.52
	(n = 41)	(n = 12)	(n = 29)	
Endothelium-dependent CMD	10 (24)	4 (33)	6 (21)	0.39
	(n = 59)	(n = 21)	(n = 38)	
LVEDP (mmHg)	12 [9-15]	11 [10-13]	13 [9-15]	0.41
LVEDP ≥12 mmHg	27 (46)	7 (33)	20 (53)	0.15

Values are median [Q1-Q3] or n (%). CAD, coronary artery disease; CMD, coronary microvascular dysfunction; LVEDP, left ventricular end-diastolic pressure.

Table 6-7: Invasive coronary angiography, physiology and haemodynamics stratified by endothelium-independent CMD.

6.3 Correlates of endothelium-independent coronary microvascular dysfunction

There were no statistically significant correlates of endothelium-independent CMD (Table 6-8). Of note, there was no association between endothelium-independent and -dependent CMD (φ = -0.13; p = 0.40).

	Endothelium-independent CMD	p-value
BNP (pg/mL)	0.32	0.057
hsTnI (ng/L)	-0.26	0.097
LVEF (%) - echocardiography	-0.25	0.06
Obstructive CAD	-0.082	0.52
Endothelium-dependent CMD	-0.13	0.40

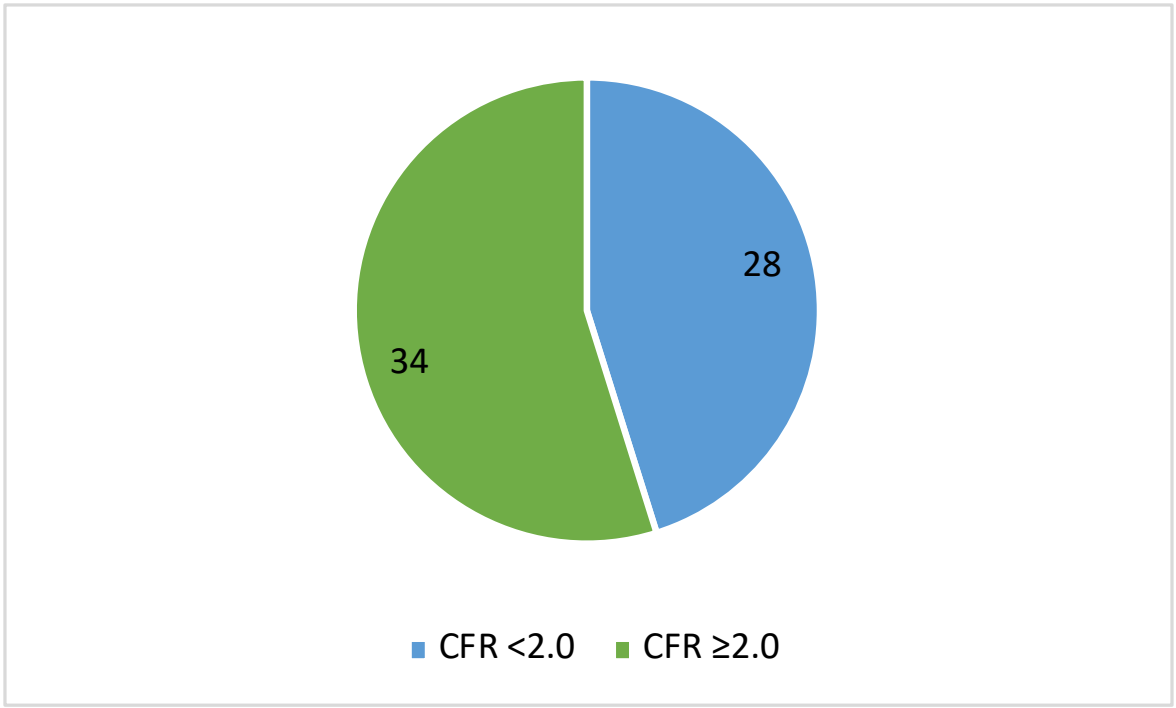
BNP, B-type natriuretic peptide; CAD, coronary artery disease; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance; hsTnI, high-sensitivity troponin I; LVEF, left ventricular ejection fraction.

Table 6-8: Correlates of endothelium-independent CMD.

6.4 Mechanisms of endothelium-independent coronary microvascular dysfunction

6.4.1 Coronary flow reserve

Coronary flow reserve (CFR) represents the vasodilator capacity of the epicardial and microvascular circulation and has been traditionally used to assess coronary microvascular function in the absence of obstructive epicardial CAD. Thresholds to define CMD on the basis of CFR vary between 2.0 and 2.5.[145] Contemporary studies and guidelines use an invasive CFR cut-off of <2.0, however, non-invasive studies continue to use the higher threshold of <2.5. Using a threshold of <2.0, 28 of the 62 participants (45% [95% CI 33-58%]) had an abnormal CFR (Figure 6-2).[231] Using the higher threshold of <2.5, 40 of the 62 patients (65% [95% CI 52-76%]) would be diagnosed with CMD.



CFR, coronary flow reserve.

Figure 6-2: Study participants stratified by CFR.

Baseline characteristics

Table 6-9 details selected baseline characteristics according to a normal or abnormal CFR. Symptoms and signs of HF were similar, and there were no significant differences in the prevalence of major comorbidities (including previous CAD) between the groups. Natriuretic peptide and hsTnI levels were

similar in those with a normal and abnormal CFR, and the echocardiography findings of both groups were comparable.

	Normal CFR (n = 34)	Abnormal CFR (n = 28)	p-value
Demographics			
Age (years)	74 [8]	71 [10]	0.17
Female sex	19 (56)	14 (50)	0.64
BMI (kg/m^2)	33 [8]	33 [8]	0.81
History of CAD			
Any CAD	9 (26)	10 (36)	0.43
MI	5 (15)	8 (29)	0.18
Revascularisation	2 (6)	6 (21)	0.069
Biochemistry			
NT-proBNP (pg/mL)	1376 [845-2819]	1915 [1041-3676]	0.73
BNP (pg/mL)	197 [145-785]	522 [285-1028]	0.12
hsTnI (ng/L)	16 [5-34]	16 [10-25]	0.90
CRP (mg/L)	14 [5-22]	12 [5-21]	0.84
Echocardiography			
LVEF (%)	58 [6]	58 [6]	0.93
LVH	22 (65)	14 (50)	0.24
Diastolic dysfunction	16 (50)	11 (55)	0.73
LA dilatation	32 (94)	24 (89)	0.46

Values are mean [standard deviation], median [Q1-Q3], or n (%). BMI, body mass index; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CFR, coronary flow reserve; CRP, C-reactive protein; hsTnI, high-sensitivity troponin I; LA, left atrial; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MI, myocardial infarction; NT-proBNP, N-terminal prohormone BNP.

Table 6-9: Selected baseline characteristics stratified by CFR.

Study investigations

Table 6-10 details selected findings of CMR and invasive coronary assessment based on CFR. There were no significant differences in cardiac structure and function between the groups. The proportion of patients with epicardial CAD and endothelium-independent CMD was similar in both groups. Those with an abnormal CFR were more likely to have an abnormal IMR than those with a normal CFR (68% vs. 38%; p = 0.02, respectively).

	Normal CFR	Abnormal CFR	p-value
CMR	(n = 20)	(n = 15)	
LVEF (%)	59 [7]	58 [8]	0.71
LVH	12 (60)	9 (56)	0.82
LA dilatation	13 (68)	8 (57)	0.51
Ischaemic LGE	4 (20)	6 (40)	0.19
Non-ischaemic LGE	7 (35)	6 (40)	0.76
Native T1 (ms)	1268 [76]	1295 [52]	0.29
ECV (%)	27.8 [3.7]	28.4 [5.0]	0.72
ECV >30%	7 (39)	5 (38)	0.98
MPRI	1.70 [1.47-1.87]	1.47 [1.24-1.97]	0.68
MPRI <1.4	4 (24)	3 (38)	0.47
Invasive coronary assessment	(n = 34)	(n = 28)	
Obstructive epicardial CAD	13 (38)	13 (46)	0.52
IMR	20 [13-32]	27 [20-44]	0.039
IMR ≥25	13 (38)	19 (68)	0.02
	(n = 22)	(n = 19)	
Endothelium-dependent CMD	5 (23)	5 (26)	0.79
	(n = 24)	(n = 25)	
LVEDP (mmHg)	12 [9-15]	12 [10-15]	0.62

Values are mean [standard deviation], median [Q1-Q3], or n (%). CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance; ECV, extracellular volume; IMR, index of microcirculatory resistance; LA, left atrial; LGE, late gadolinium enhancement; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MPRI, myocardial-perfusion reserve index.

Table 6-10: Selected CMR and invasive coronary assessment findings stratified by CFR.

Correlates of CFR

Tables 6-11 and 6-12 show the correlates of CFR expressed as a binary and continuous variable, respectively. An abnormal CFR was not associated with obstructive epicardial CAD or endothelium-dependent CMD but did correlate with an abnormal IMR ($\varphi = 0.30$; $p = 0.02$) and IMR expressed as a continuous variable ($r_{pb} = 0.26$; $p = 0.042$). When expressed as a continuous variable, CFR was negatively correlated with obstructive epicardial CAD on invasive coronary angiography ($r_{pb} = -0.27$; $p = 0.035$).

	CFR <2.0	p-value
Obstructive CAD	0.083	0.52
IMR	0.26	0.042
IMR ≥25	0.30	0.02
Endothelium-dependent CMD	0.042	0.80

CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; IMR, index of microcirculatory resistance.

Table 6-11: Correlates of CFR <2.0 (binary).

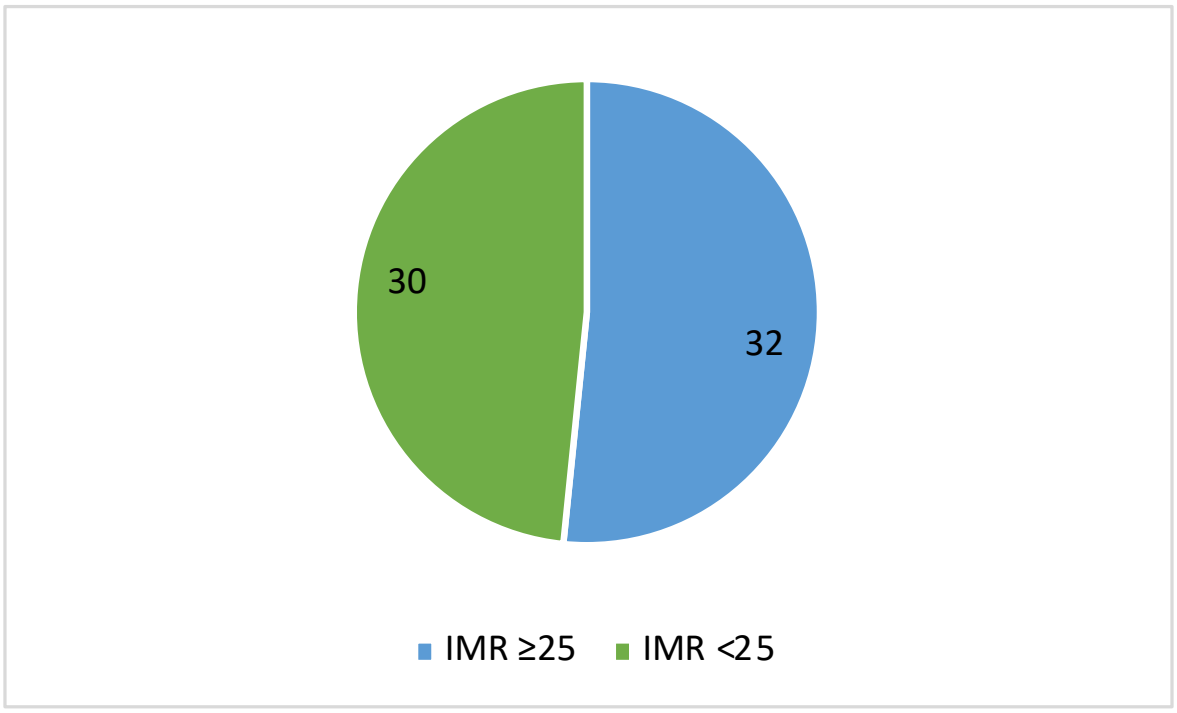
	CFR	p-value
Obstructive CAD	-0.27	0.035
IMR	-0.24	0.066
IMR ≥25	-0.18	0.16
Endothelium-dependent CMD	0.044	0.79

CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance; IMR, index of microcirculatory resistance; LVEDV, left ventricular end-diastolic volume.

Table 6-12: Correlates of CFR (continuous).

6.4.2 Index of microcirculatory resistance

The index of microcirculatory resistance (IMR) represents the minimum resistance offered by the microcirculation. Based on several studies, an abnormal value is defined as an IMR ≥25.[127-129] Using this threshold, 32 of the 62 participants (52% [95% CI 39-64%]) that had invasive physiology testing had an abnormal IMR (Figure 6-3).



IMR, index of microcirculatory resistance.

Figure 6-3: Study participants stratified by IMR.

Baseline characteristics

Table 6-13 summarises selected baseline characteristics of the cohort based on the IMR. The baseline demographics and clinical features of patients with a normal or abnormal IMR were similar. The prevalence of comorbidities, including a previous history of CAD, MI and previous coronary intervention were similar in both groups. ECG and CXR findings were similar in both groups, but those with an abnormal IMR more frequently had radiological evidence of cardiomegaly than those with a normal IMR (91% vs. 63%; p = 0.01, respectively). There were no significantly significant differences in natriuretic peptides, hsTnI or echocardiography findings between the groups.

	Normal IMR (n = 30)	Abnormal IMR (n = 32)	p-value
Demographics			
Age (years)	72 [9]	72 [9]	0.94
Female sex	17 (57)	16 (50)	0.60
BMI (kg/m^2)	34 [8]	32 [7]	0.41
Past medical history			
Previous HF diagnosis	8 (27)	15 (47)	0.10
Any CAD	11 (37)	8 (25)	0.32
MI	8 (27)	5 (16)	0.29
Revascularisation	4 (13)	4 (12)	0.92
CXR			
Cardiomegaly	19 (63)	29 (91)	0.01
Biochemistry			
NT-proBNP (pg/mL)	1204 [414-2494]	1532 [1273-3076]	0.18
BNP (pg/mL)	259 [173-676]	569 [187-1028]	0.33
hsTnI (ng/L)	19 [7-29]	16 [7-25]	0.51
Echocardiography			
LVEF (%)	59 [6]	58 [6]	0.39
LVH	21 (70)	15 (47)	0.065
Diastolic dysfunction	15 (60)	12 (44)	0.26
LA dilatation	26 (90)	30 (94)	0.56

Values are mean [standard deviation], median [Q1-Q3], or n (%). BMI, body mass index; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CRP, C-reactive protein; hsTnI, high-sensitivity troponin I; IMR, index of microcirculatory resistance; LA, left atrial; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MI, myocardial infarction; NT-proBNP, N-terminal prohormone BNP.

Table 6-13: Selected baseline characteristics stratified by IMR.

Study investigations

Table 6-14 summarises selected findings of CMR and invasive coronary assessment on the basis of IMR. Cardiac structure and function were similar in both groups. Those with a low IMR had higher native T1 values (mean 1312 vs. 1250 ms; p <0.01) and ECV (30.0% vs. 26.4%; p = 0.014) than those with a high IMR. The prevalence of obstructive epicardial CAD was similar in those with a normal and abnormal IMR (50% vs. 34%; p = 0.21, respectively).

	Normal IMR	Abnormal IMR	p-value
CMR	(n = 17)	(n = 18)	
LVEF (%)	58 [7]	60 [7]	0.37
LVH	12 (71)	9 (47)	0.16
LA dilatation	10 (67)	11 (61)	0.74
Ischaemic LGE	7 (41)	3 (17)	0.11
Non-ischaemic LGE	6 (35)	7 (39)	0.83
Native T1 (ms)	1312 [66]	1250 [55]	<0.01
ECV (%)	30.0 [3.7]	26.4 [4.0]	0.014
ECV >30%	8 (57)	4 (24)	0.056
MPRI	1.49 [1.33-1.85]	1.71 [1.44-1.95]	0.28
MPRI <1.4	4 (31)	3 (25)	0.75
Invasive coronary assessment	(n = 30)	(n = 32)	
Obstructive epicardial CAD	15 (50)	11 (34)	0.21
CFR	2.4 [1.7-2.9]	1.8 [1.3-2.6]	0.14
CFR <2.0	9 (30)	19 (59)	0.02
	(n = 19)	(n = 4)	
Endothelium-dependent CMD	6 (33)	4 (17)	0.24
	(n = 30)	(n = 29)	
LVEDP (mmHg)	11 [10-15]	13 [9-15]	0.70

Values are mean [standard deviation], median [Q1-Q3], or n (%). CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance; ECV, extracellular volume; IMR, index of microcirculatory resistance; LA, left atrial; LGE, late gadolinium enhancement; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MPRI, myocardial-perfusion reserve index.

Table 6-14: CMR and invasive coronary assessment findings stratified by IMR.

Correlates of IMR

Table 6-15 and 6-16 describe the correlates of IMR expressed as a binary and continuous variable, respectively. An abnormal IMR was correlated with an abnormal CFR (φ = 0.45; p <0.001) and was negatively associated with obstructive epicardial CAD (φ = 0.28; p = 0.015) and ECV (r_{pb} = -0.40; p <0.01). When expressed as a continuous variable, IMR correlated with BNP (r = 0.40; p = 0.021) and was negatively associated with ischaemic LGE (r_{pb} = -0.42; p = 0.012) and ECV (r = -0.41; p = 0.023) on CMR. Figure 6-4 illustrates the association between IMR and ECV.

	IMR ≥25	p-value
ECV (%)	-0.40	<0.01
ECV >30%	-0.27	0.061
Obstructive CAD	-0.28	0.015
CFR	-0.18	0.16
CFR <2.0	0.45	<0.001
Endothelium-dependent CMD	-0.18	0.25

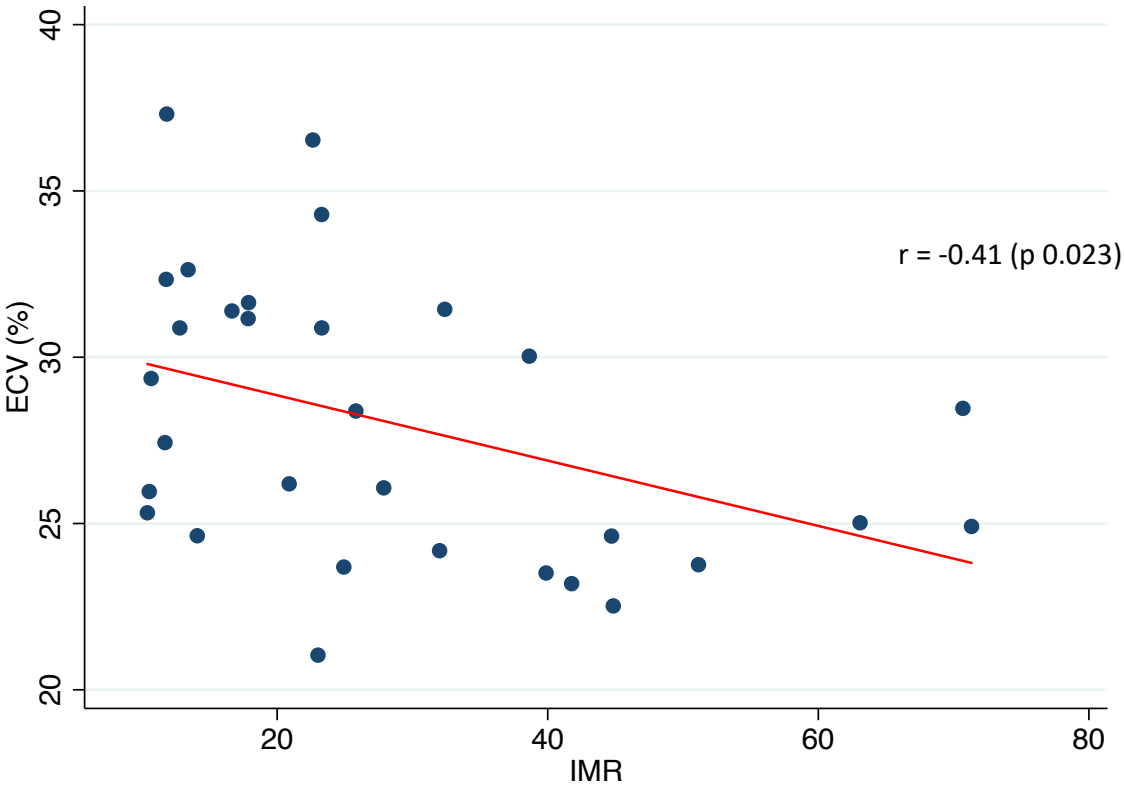
CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; ECV, extracellular volume; IMR, index of microcirculatory resistance.

Table 6-15: Correlates of IMR ≥25 (binary).

	IMR	p-value
BNP (pg/mL)	0.40	0.021
Ischaemic LGE	-0.42	0.012
ECV (%)	-0.41	0.023
ECV >30%	-0.38	0.036
Obstructive CAD	-0.20	0.11
CFR	-0.24	0.066
CFR <2.0	0.20	0.13
Endothelium-dependent CMD	-0.29	0.069

AF, atrial fibrillation; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; ECV, extracellular volume; IMR, index of microcirculatory resistance; LGE, late gadolinium enhancement; MI, myocardial infarction.

Table 6-16: Correlates of IMR (continuous).



ECV, extracellular volume; IMR, index of microcirculatory resistance.

Figure 6-4: Scatterplot of correlation between IMR and ECV.

6.4.3 Microvascular status groups

CFR and IMR were both normal in 21 patients (34%); 13 patients (21%) had normal CFR but high IMR (i.e. preserved flow reserve and high microvascular resistance); nine patients (15%) had low CFR and normal IMR (i.e. impaired flow reserve and normal microvascular resistance), and 19 patients (31%) had low CFR and high IMR (i.e. impaired flow reserve and high microvascular resistance) (Figure 6-5).

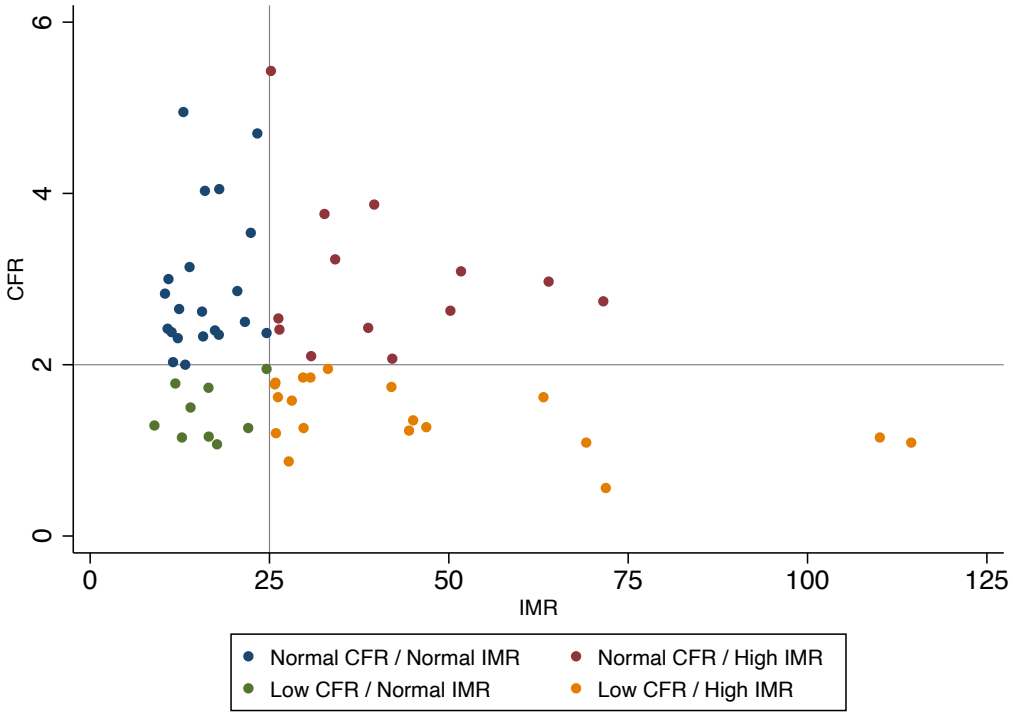


Figure 6-5: Microvascular status groups based on CFR and IMR.

6.5 Outcomes related to endothelium-independent coronary microvascular dysfunction

6.5.1 Endothelium-independent coronary microvascular dysfunction

Mortality

Mortality rates were low during the follow-up period and no significant difference in mortality rates was observed between those with and without endothelium-independent CMD (Figure 6-6, 6-7, 6-8). There were no non-CV deaths during follow-up.

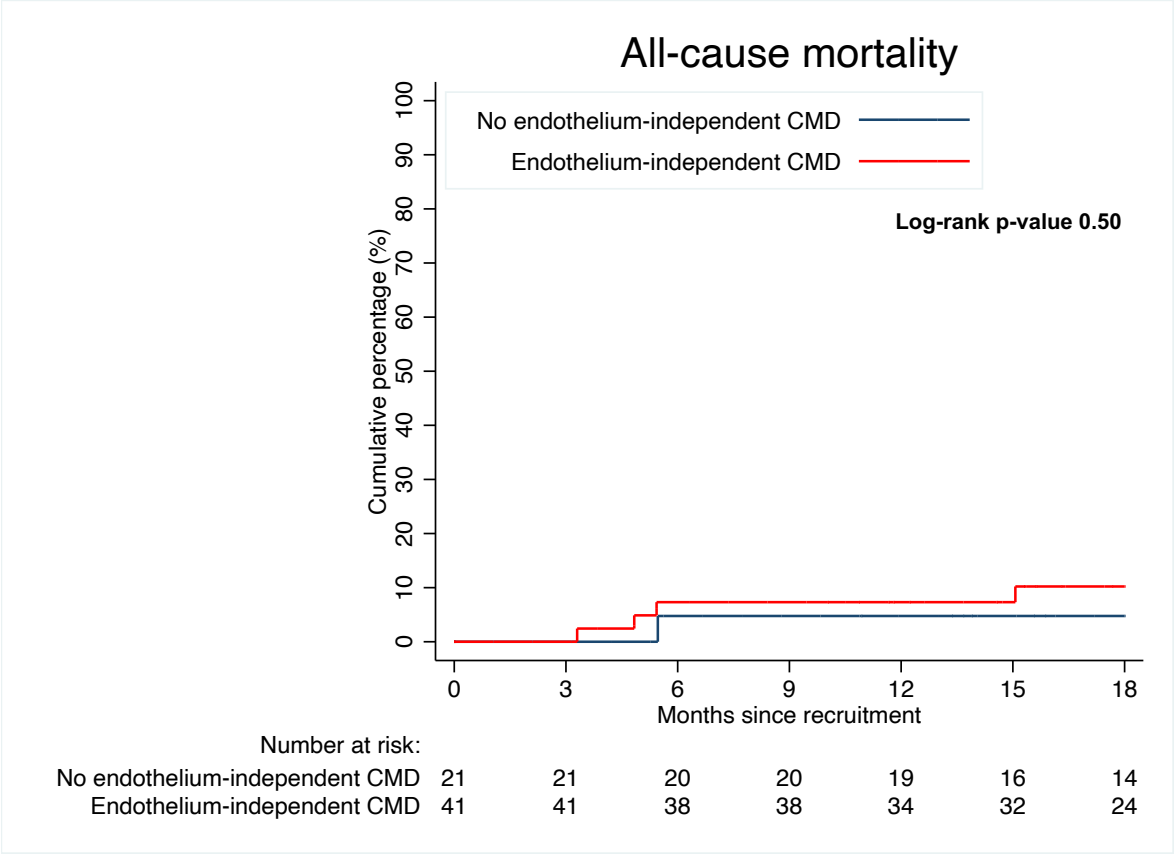


Figure 6-6: Kaplan-Meier curves for all-cause mortality by endothelium-independent CMD.

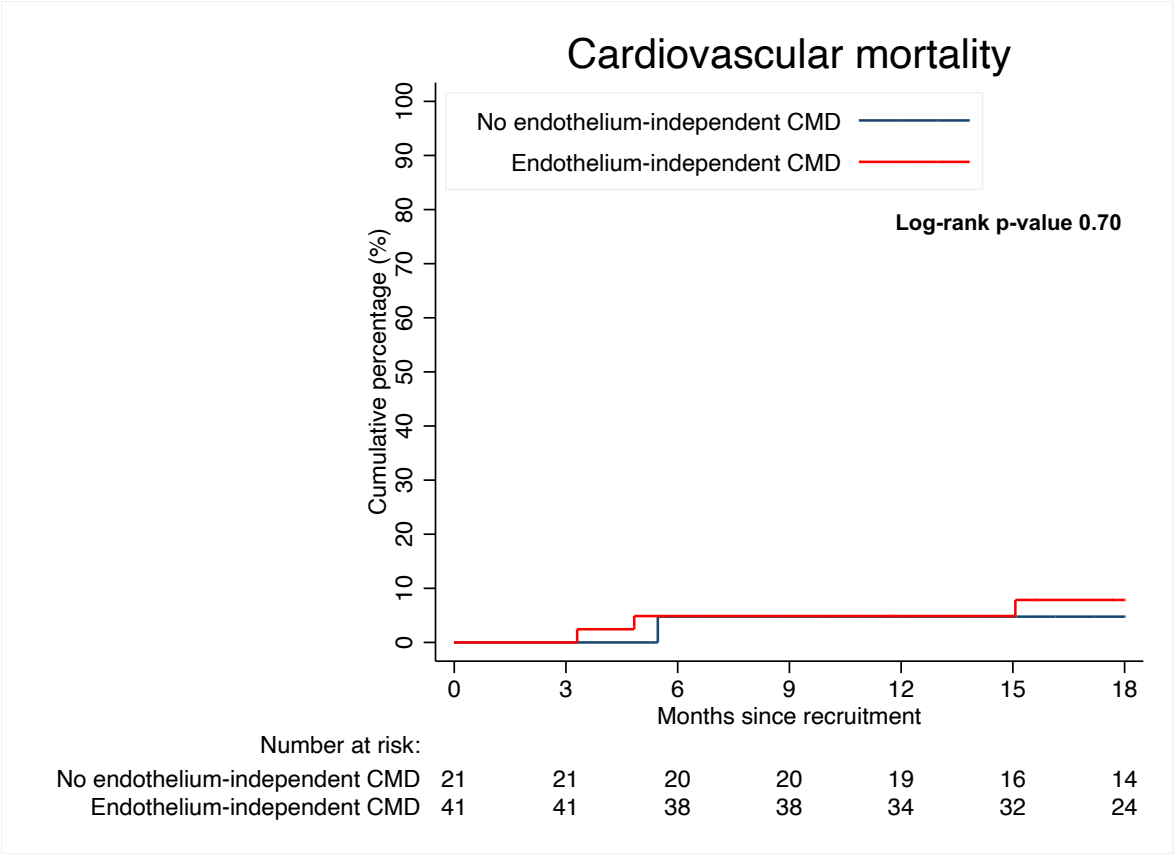


Figure 6-7: Kaplan-Meier curves for CV mortality by endothelium-independent CMD.

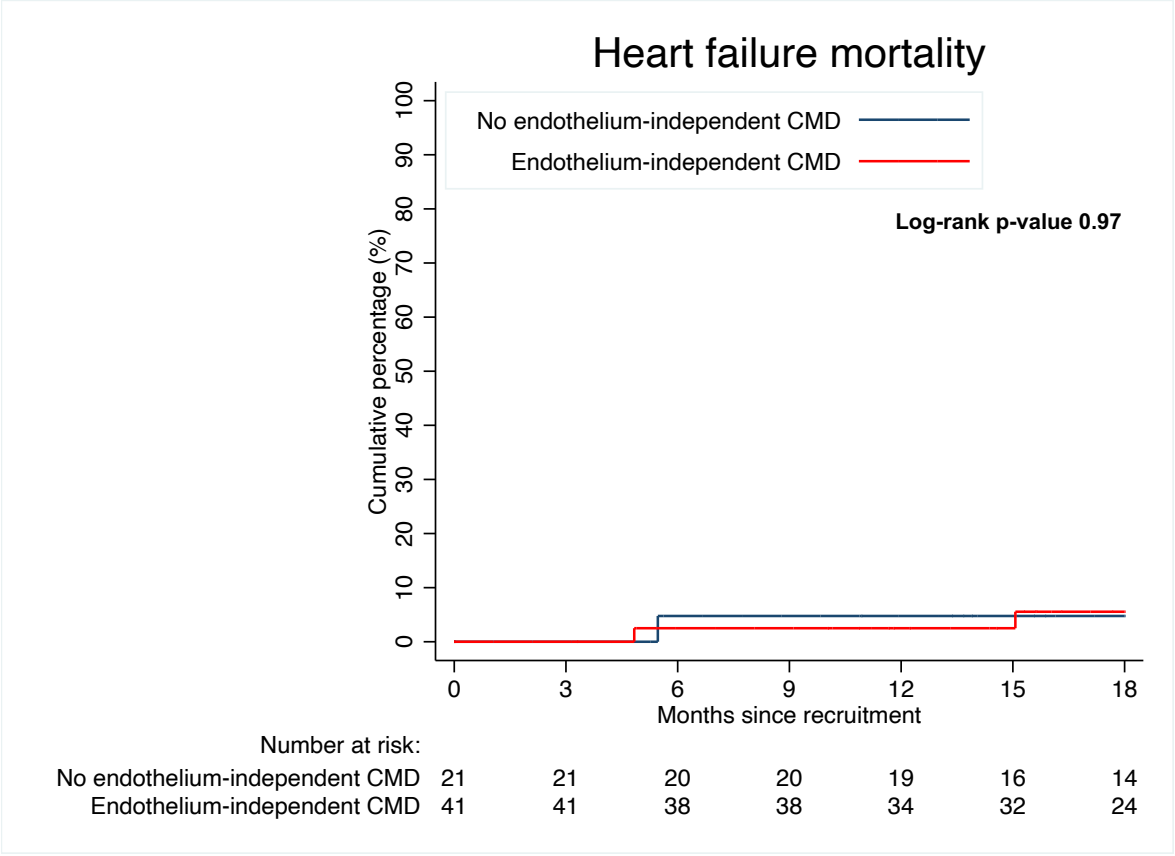


Figure 6-8: Kaplan-Meier curves for HF mortality by endothelium-independent CMD.

Hospitalisations

There were no statistically significant differences in hospitalisations between those and without endothelium-independent CMD (Figures 6-9, 6-10, 6-11, 6-12).

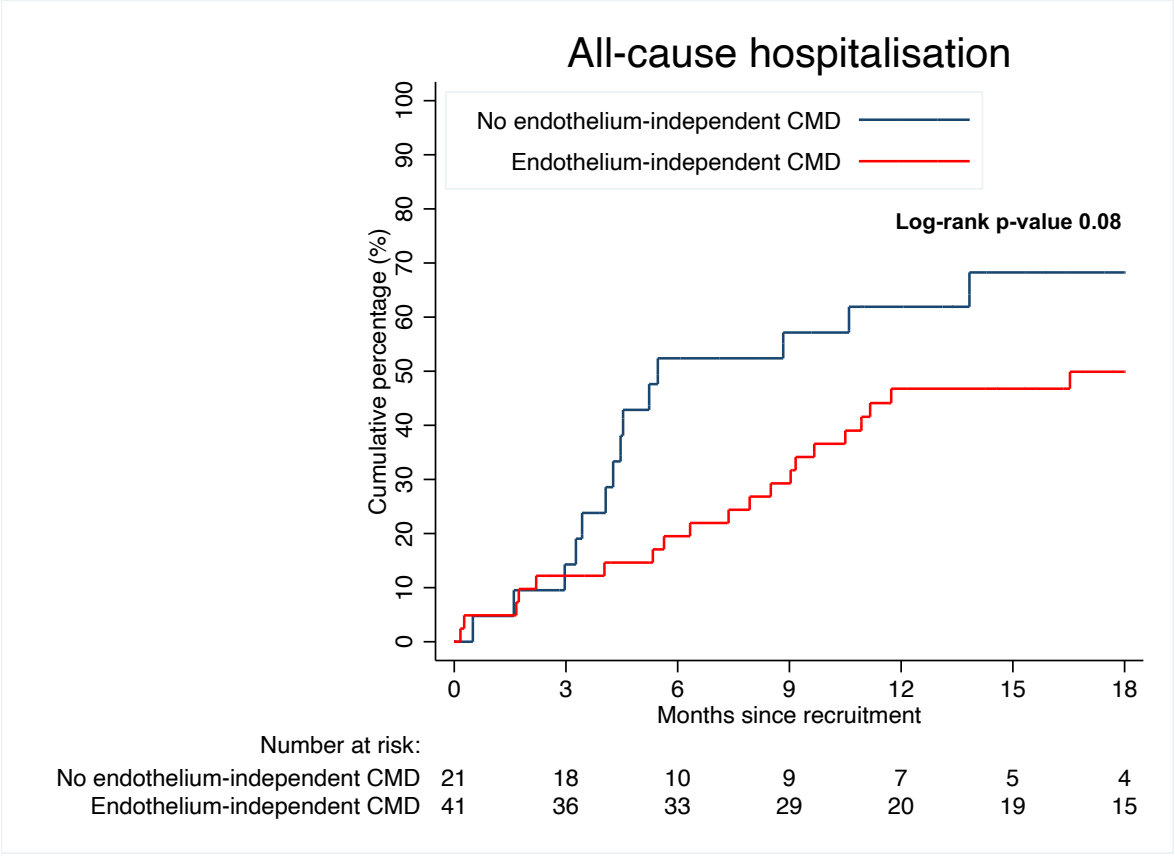


Figure 6-9: Kaplan-Meier curves for all-cause hospitalisation by endothelium-independent CMD.

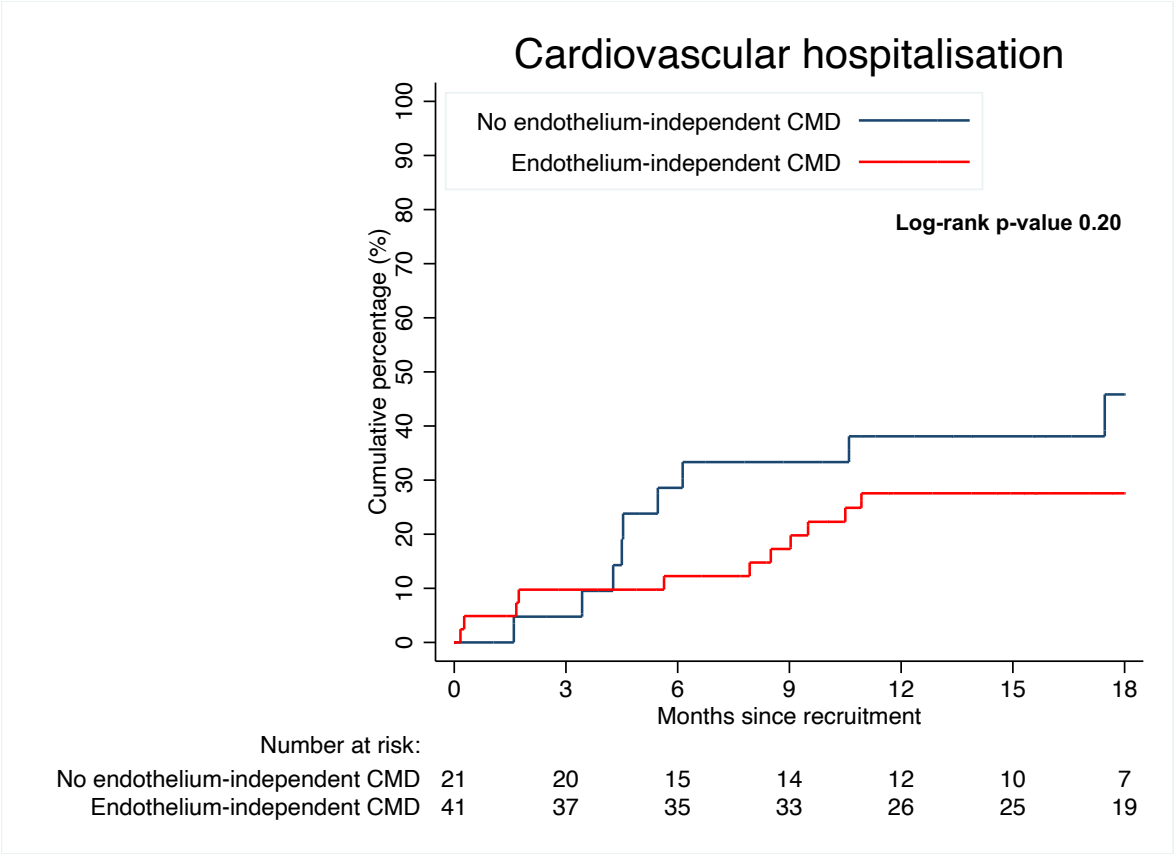


Figure 6-10: Kaplan-Meier curves for CV hospitalisation by endothelium-independent CMD.

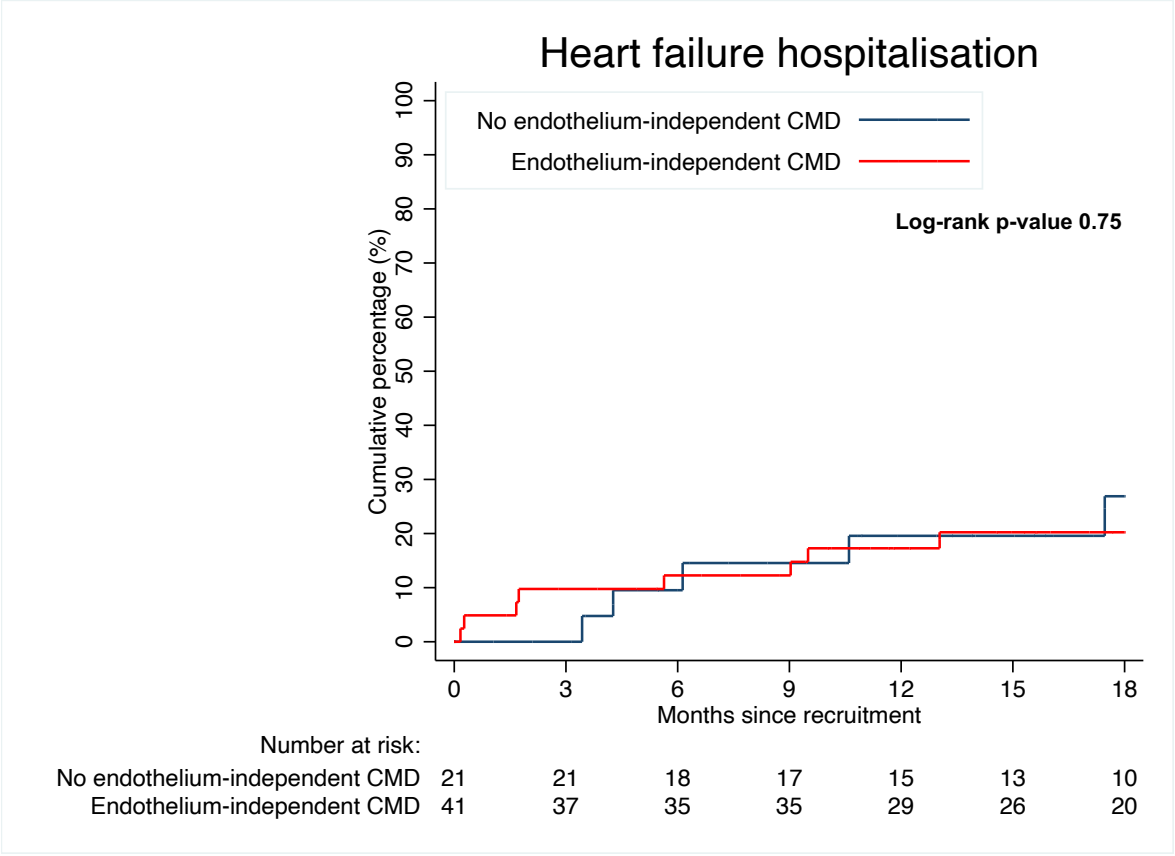


Figure 6-11: Kaplan-Meier curves for HF hospitalisation by endothelium-independent CMD.

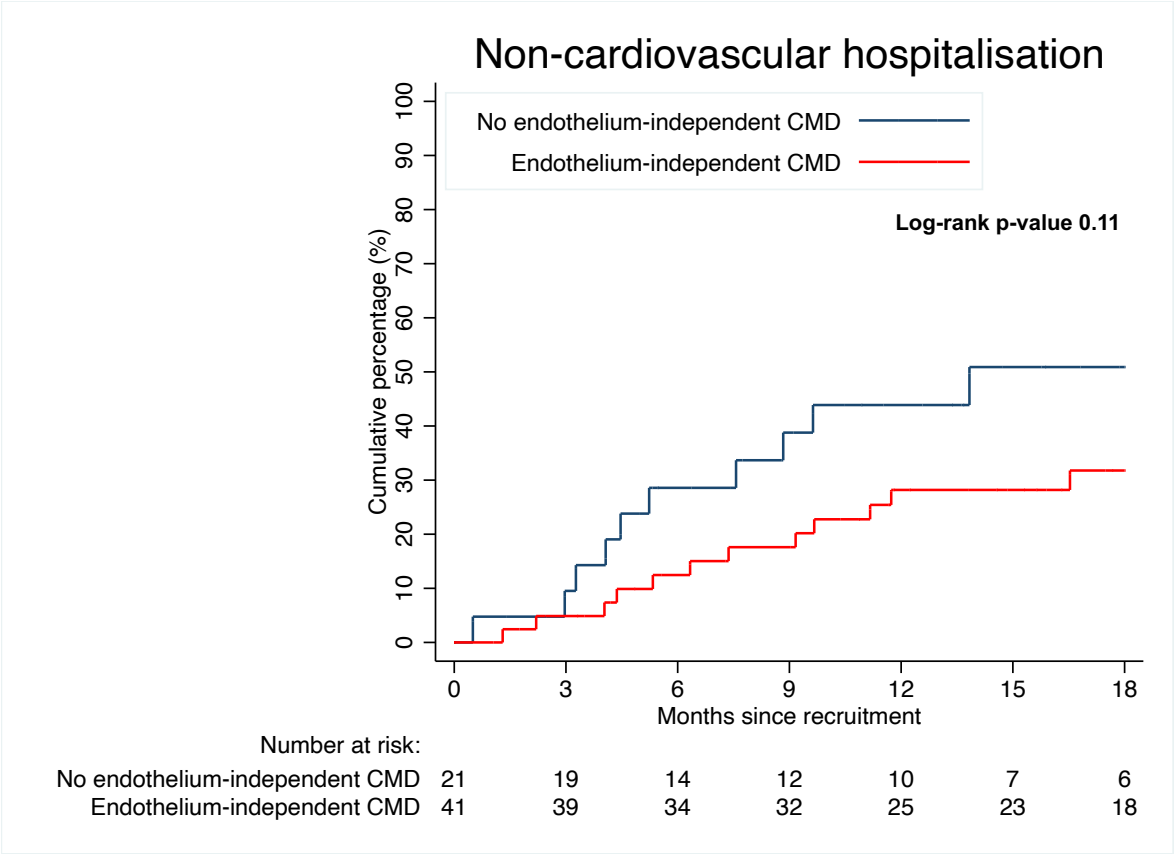


Figure 6-12: Kaplan-Meier curves for non-CV hospitalisation by non-endothelium-independent CMD.

6.5.2 Coronary flow reserve

Mortality and hospitalisations

No differences were observed in mortality or hospitalisations in participants based on CFR (Figures 6-13, 6-14).

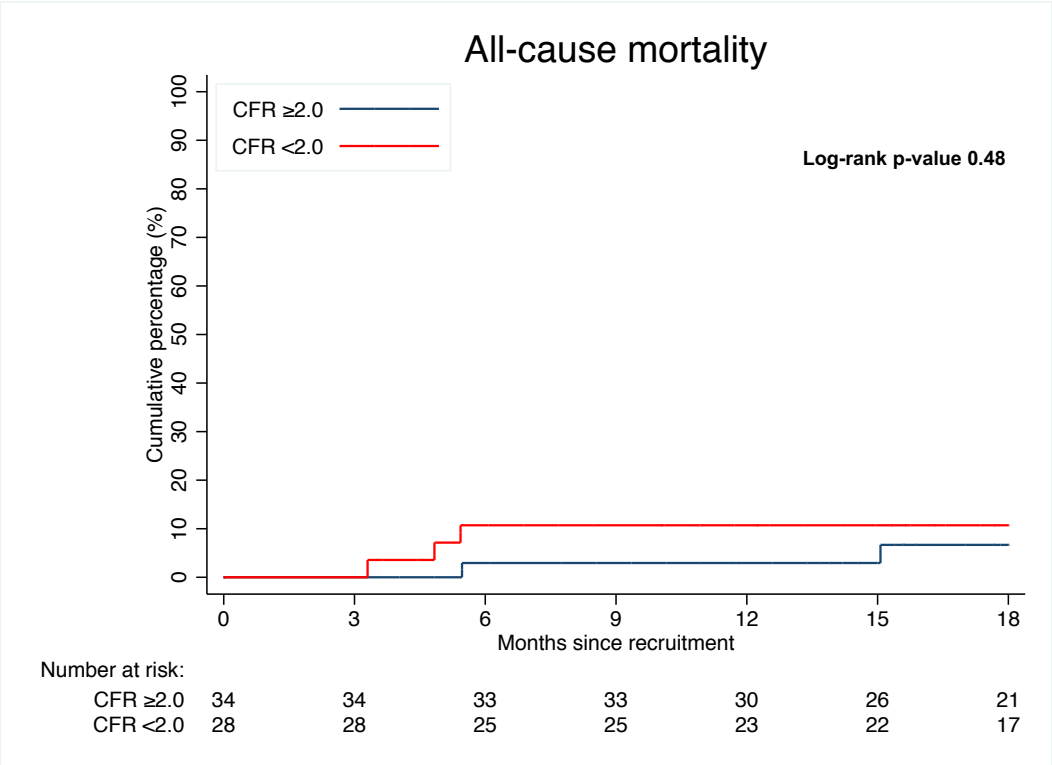


Figure 6-13: Kaplan-Meier curves for all-cause mortality by CFR.

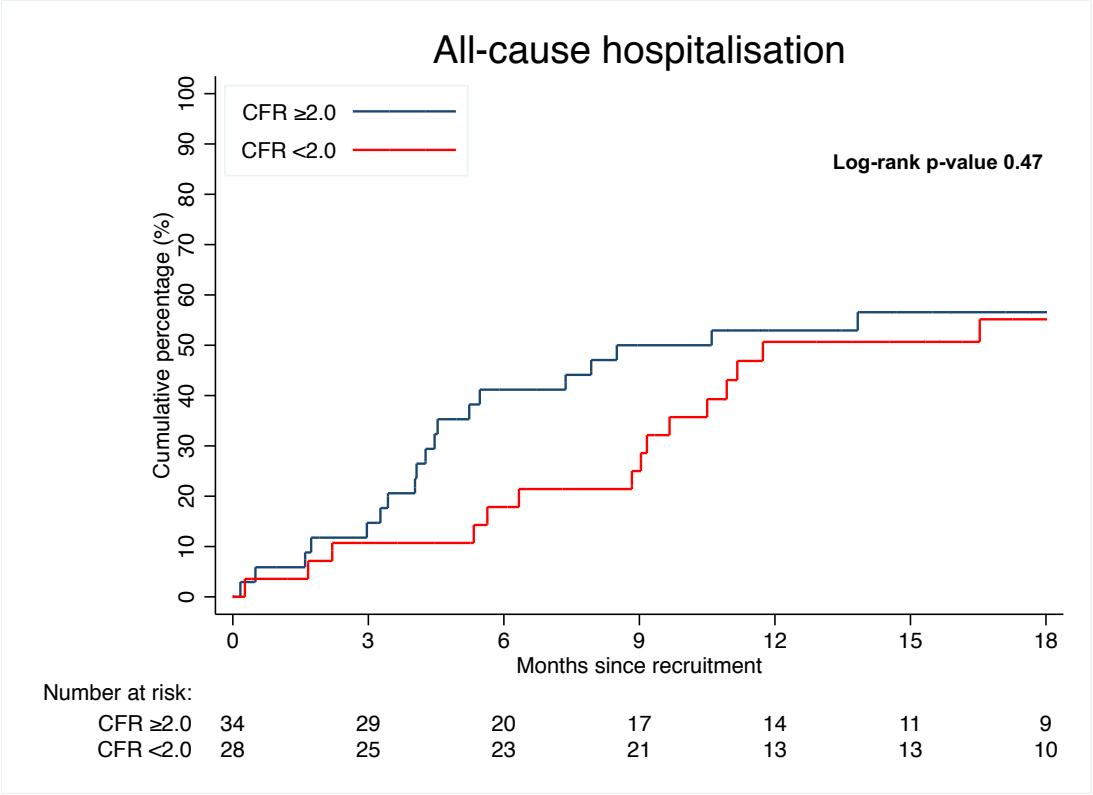


Figure 6-14: Kaplan-Meier curves for all-cause mortality by CFR.

6.5.3 Index of microcirculatory resistance

Mortality and hospitalisations

No significant differences in mortality or hospitalisation rates were observed between the groups based on IMR (Figures 6-15, 6-16).

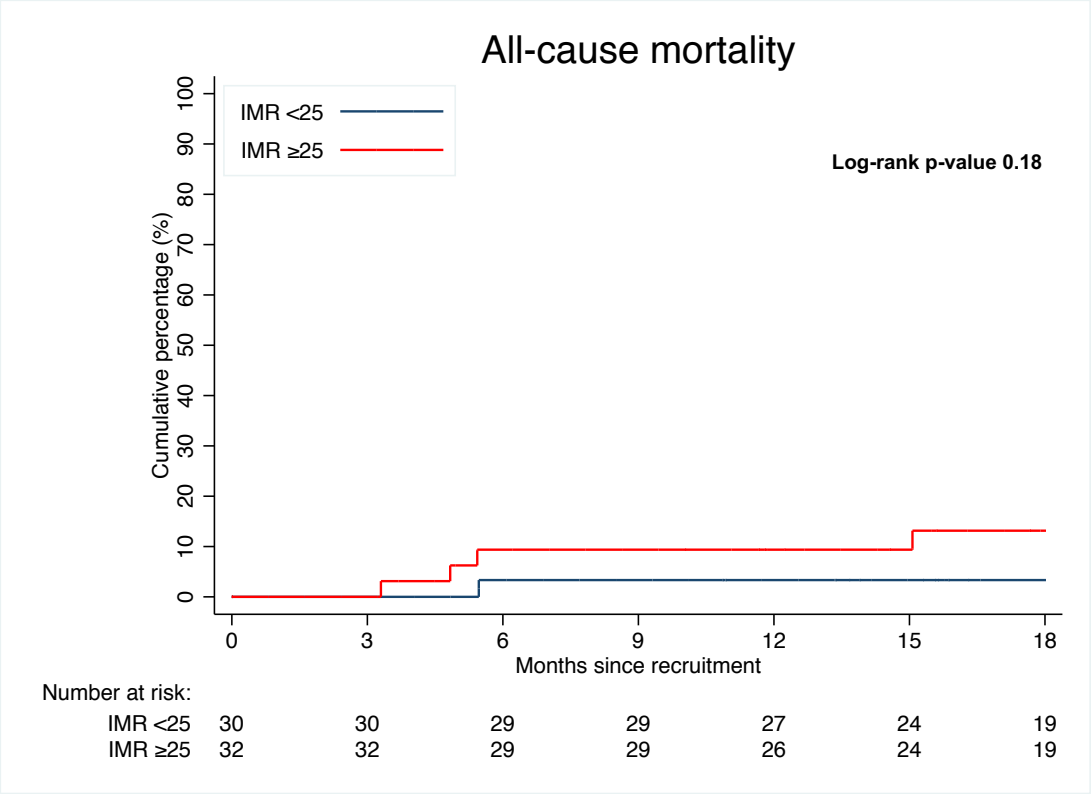


Figure 6-15: Kaplan-Meier curves for all-cause mortality by IMR.

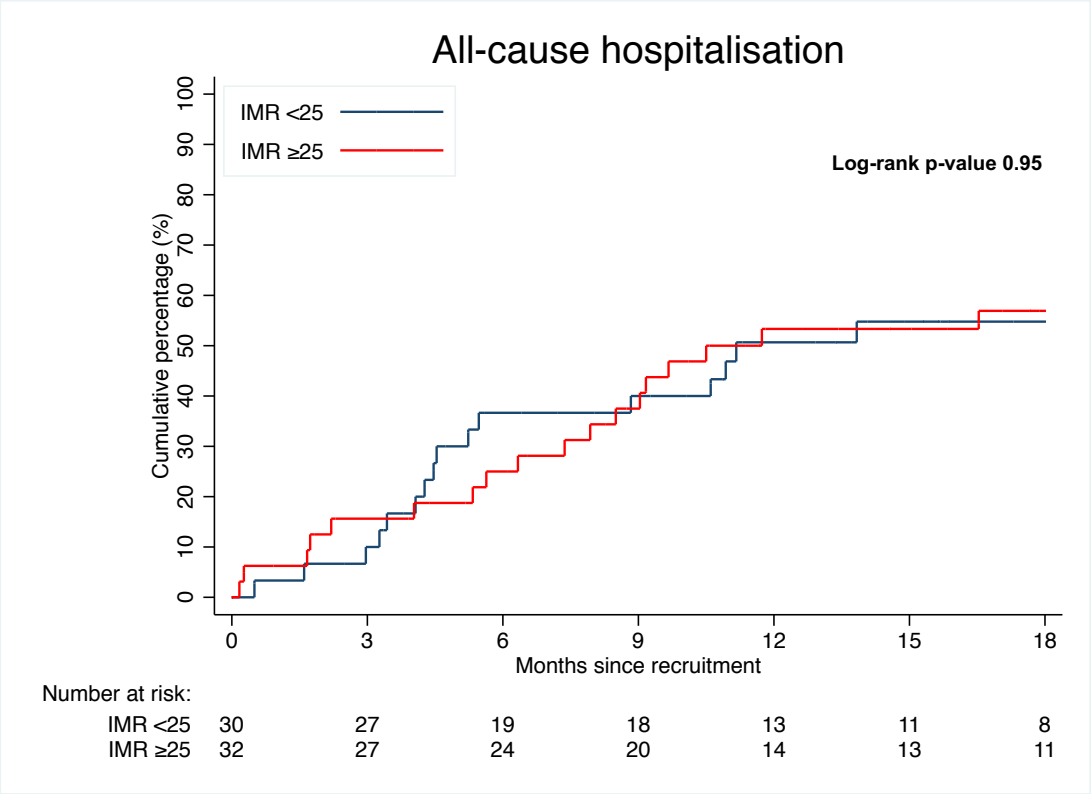


Figure 6-16: Kaplan-Meier curves for all-cause hospitalisation by IMR.

6.6 Complications of coronary guidewire-based coronary physiology testing

There were no procedural complications related to the use of the coronary guidewire. The majority of patients (76%) experienced typical symptoms during the adenosine infusion (i.e. dyspnoea, chest tightness, flushing), all of which subsided with discontinuation of the infusion. No arrhythmia was documented in any patient during the adenosine infusion.

6.7 Summary

Endothelium-independent CMD was present in two-thirds of the 62 participants that underwent guidewire-based coronary physiology testing. Participants with endothelium-independent CMD had a higher burden of AF than those without, but the prevalence of other comorbidities was similar in both groups. There were no significant differences in the echocardiography or CMR findings between those with and without CMD. The burden of myocardial LGE was similar in both groups, and there was no significant difference in ECV or MPRI in participants with and without endothelium-independent CMD.

The prevalence of obstructive epicardial CAD was similar in those with and without endothelium-independent CMD, and no association was observed between endothelium-independent and -dependent CMD.

Of those that underwent coronary microvascular assessment, 45% had an abnormal CFR (<2.0) and 52% had an abnormal IMR (≥25). Of participants with endothelium-independent CMD, 32% had high microvascular resistance (abnormal IMR), 22% had impaired flow reserve (abnormal CFR), and 46% had both high microvascular resistance and impaired flow reserve (abnormal CFR and IMR). There were no major differences in the characteristics of those with a normal or abnormal CFR. The prevalence of obstructive epicardial CAD was similar in those with a normal or abnormal CFR or IMR. Of interest, patients with a normal IMR had significantly higher ECV than those with an abnormal IMR, suggesting that increased microvascular resistance is independent of diffuse myocardial fibrosis in HFpEF patients.

The definition of endothelium-independent CMD used in this study (i.e. CFR <2.0 and/or IMR ≥25) is consistent with the contemporary literature in other populations. However, CFR and IMR are continuous measures and the thresholds used do not accurately represent the spectrum of coronary microvascular function. Furthermore, invasively assessed CFR and (especially) IMR have been performed predominantly in patients presenting with chest pain and have not been validated in the HFpEF population.

The delay between recruitment and performing the invasive coronary assessment (median 97 days) may have impacted on the results of coronary microvascular testing. It is recognised that the elevated LV filling pressures can cause or contribute to CMD as a result of extravascular compression of arterioles.[266] LVEDP was normal in the majority of the study participants, but this likely would not have been the case had the invasive assessment been performed during the index hospitalisation.

Invasive assessment of CFR and IMR are not routinely performed in clinical practice. However, the operators who performed the invasive coronary assessments in this study have extensive experience in performing these measurements in other research studies. Both CFR and IMR incorporate the thermodilution principle (using intra-coronary injection of saline) and an average of three consistent transit times was used to ensure the measurement was reliable and reproducible. Furthermore, in a previous study of patients with ST-elevation MI, repeated IMR measurements obtained by four operators (including two of the operators who performed the invasive assessments in this study) were highly correlated ($r = 0.99$; $p < 0.001$), suggesting minimal inter-observer variability with this technique.[267]

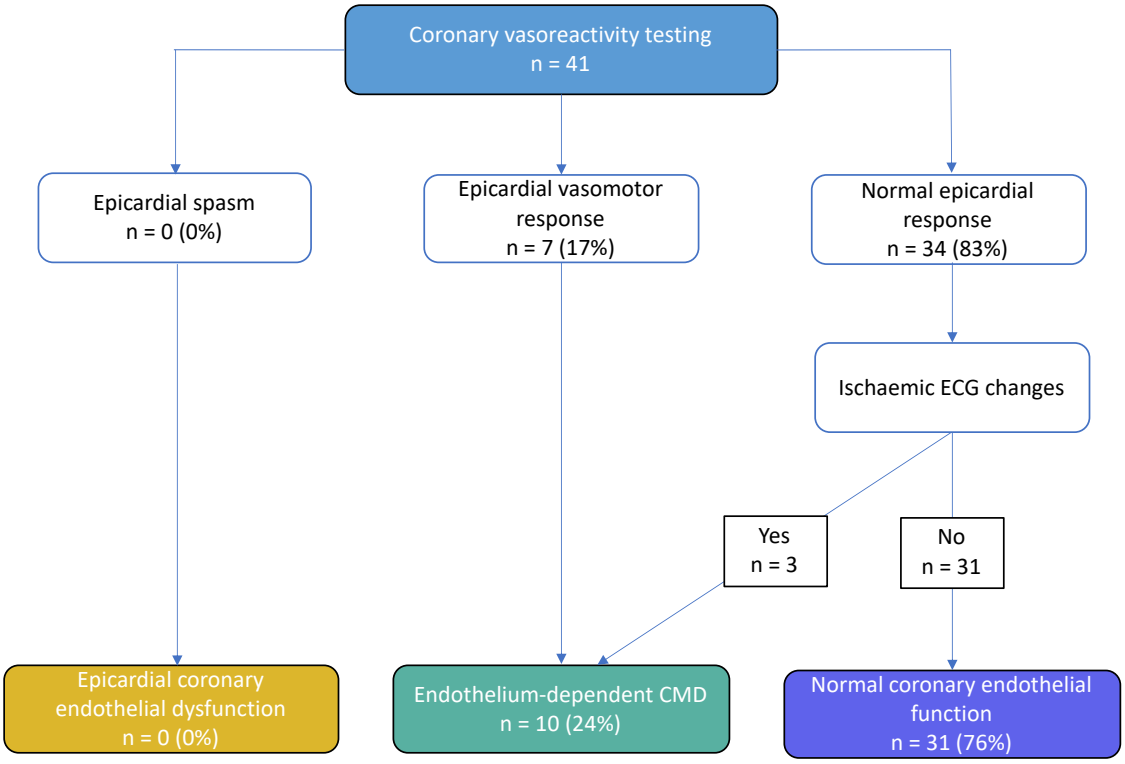
As discussed in Chapter 5, event rates in the study cohort were lower than expected, but no significant differences in mortality or hospitalisation rates were observed based on the presence or absence of abnormal coronary microvascular function, CFR or IMR.

Chapter 7 Results – Endothelium-dependent coronary microvascular dysfunction in heart failure with preserved ejection fraction

In this chapter I will report the prevalence of endothelium-dependent coronary microvascular dysfunction (CMD) in the study cohort. I will describe the clinical characteristics, investigation results and correlates of the population based on the presence or absence of endothelium-dependent CMD. Finally, I will report clinical outcomes (mortality and hospitalisations) stratified by endothelium-dependent CMD.

7.1 Prevalence of endothelium-dependent coronary microvascular dysfunction

A total of 41 participants underwent coronary vasoreactivity testing during intra-coronary acetylcholine (ACh) administration to assess epicardial and microvascular coronary endothelial function. Of these, 10 had evidence of endothelium-dependent CMD, giving an estimated prevalence estimate of 24% (95% CI 13-40%) in the HFpEF population (Figure 7-1). None of the participants had evidence of epicardial coronary vasospasm.



CMD, coronary microvascular dysfunction; ECG, electrocardiogram.

Figure 7-1: Prevalence of endothelium-dependent CMD in study cohort.

7.2 Clinical characteristics by endothelium-dependent coronary microvascular dysfunction

7.2.1 Demographics and clinical features

Table 7-1 describes the baseline demographics and clinical features of the study participants that underwent vasoreactivity testing based on the presence or absence of coronary endothelial microvascular dysfunction. Those with endothelium-dependent CMD were more frequently female (90% vs. 52%; p = 0.03) and were less likely to have a smoking history (20% vs. 68%; p <0.01) than those with no endothelial dysfunction. The groups were similar with regards to age, frailty, BMI, duration of hospitalisation and HF symptoms and signs.

	All endothelial function testing (n = 41)	**No endothelium-dependent CMD (n = 31)**	**Endothelium-dependent CMD (n = 10)**	**p-value**
Demographics				
Age (years)	71 [9]	71 [10]	71 [9]	0.84
Female sex	25 (61)	16 (52)	9 (90)	0.03
BMI (kg/m^2)	34 [8]	34 [8]	34 [10]	0.82
Obesity	20 (49)	15 (48)	5 (50)	0.93
Smoking history	23 (56)	21 (68)	2 (20)	<0.01
Hospitalisation details				
Length of stay (days)	7 [5-10]	8 [4-11]	7 [5-10]	0.69
HF symptoms				
NYHA functional class				
II	2 (5)	2 (6)	0 (0)	0.64
III	21 (51)	15 (48)	6 (60)	
IV	18 (44)	14 (45)	4 (40)	
Orthopnoea	28 (68)	21 (68)	7 (70)	0.89
PND	19 (46)	16 (52)	3 (30)	0.23
Ankle swelling	37 (90)	29 (94)	8 (80)	0.21
Admission vital signs				
HR (bpm)	90 [27]	89 [27]	92 [27]	0.74
SBP (mmHg)	152 [30]	155 [32]	142 [18]	0.22
DBP (mmHg)	82 [20]	82 [20]	83 [24]	0.94
MAP (mmHg)	105 [19]	106 [20]	102 [19]	0.58
HF signs				
JVD	29 (71)	23 (74)	6 (60)	0.39
Murmur	10 (24)	7 (23)	3 (30)	0.63
Crepitations	32 (78)	22 (71)	10 (100)	0.054

Pleural effusion(s)	15 (37)	11 (35)	4 (40)	0.80
Oedema	37 (90)	29 (94)	8 (80)	0.21
Ascites	1 (2)	1 (3)	0 (0)	0.57

Values are mean [standard deviation], median [Q1-Q3], or n (%). BMI, body mass index; DBP, diastolic blood pressure; HF, heart failure; HR, heart rate; JVD, jugular venous distention; MAP, mean arterial pressure; NYHA, New York Heart Association; PND, paroxysmal nocturnal dyspnoea; SBP; systolic blood pressure.

Table 7-1: Demographics and clinical features stratified by endothelium-dependent CMD.

7.2.2 Past medical history

The past medical history of participants stratified by endothelium-dependent coronary microvascular function is detailed in Table 7-2. As vasoreactivity testing was contraindicated in the majority of patients with obstructive epicardial CAD on angiography, the prevalence of previous CAD was low, with no significant difference between those with and without endothelial dysfunction (23% vs. 20%; p = 0.86, respectively). Most comorbidities were similarly prevalent in both groups, but those with endothelium-dependent CMD had a higher prevalence of AF (100% vs. 58%; p = 0.013) and lower rates of COPD (0% vs. 35%; p = 0.028) than those without endothelial dysfunction.

	All endothelial function testing (n = 41)	**No endothelium-dependent CMD (n = 31)**	**Endothelium-dependent CMD (n = 10)**	**p-value**
History of HF				
Previous HF diagnosis	15 (37)	11 (35)	4 (40)	0.80
Previous HFH	12 (29)	9 (29)	3 (30)	0.95
History of CAD				
Any CAD	9 (22)	7 (23)	2 (20)	0.86
MI	6 (15)	5 (16)	1 (10)	0.63
Angina	3 (7)	2 (5)	1 (10)	0.71
Current angina	2 (5)	2 (5)	0 (0)	0.41
Revascularisation	4 (10)	2 (6)	2 (20)	0.21
PCI	4 (10)	2 (5)	2 (20)	0.21
CABG	0 (0)	0 (0)	0 (0)	
CV comorbidities				
Hypertension	31 (76)	24 (77)	7 (70)	0.63
Dyslipidaemia	4 (10)	4 (13)	0 (0)	0.23
CVD	7 (17)	6 (19)	1 (10)	0.49
PAD	3 (7)	3 (10)	0 (0)	0.31
AF	28 (68)	18 (58)	10 (100)	0.013

Valve disease (mild/moderate)	8 (20)	4 (13)	4 (40)	0.06
Non-CV comorbidities				
Diabetes	18 (44)	15 (48)	3 (30)	0.31
CKD	8 (20)	8 (26)	0 (0)	0.073
Chronic liver disease	0 (0)	0 (0)	0 (0)	-
Depression	2 (5)	2 (6)	0 (0)	0.41
Cancer	3 (7)	2 (6)	1 (10)	0.71
COPD	11 (27)	11 (35)	0 (0)	0.028
Asthma	4 (10)	2 (6)	2 (20)	0.21
Anaemia	9 (22)	6 (19)	3 (30)	0.48
Hypothyroidism	6 (15)	4 (13)	2 (20)	0.58
Osteoarthritis	12 (29)	11 (35)	1 (10)	0.12

Values are n (%). AF, atrial fibrillation; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; CVD, cerebrovascular disease; HF, heart failure; HFH, HF hospitalisation; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention.

Table 7-2: Past medical history stratified by endothelium-dependent CMD.

7.2.3 Drug history – medication on admission, in-hospital treatment and medication at discharge

The drug history of patients according to the presence or absence of coronary endothelial dysfunction is presented in Table 7-3. Given the higher prevalence of AF, those with coronary endothelial dysfunction were more often treated with an anticoagulant and digoxin than those with no endothelial dysfunction, both on admission and at discharge. The use of statins, beta-blockers, RAAS antagonists and diuretics were similar in both groups.

	All endothelial function testing (n = 41)	**No endothelium-dependent CMD (n = 31)**	**Endothelium-dependent CMD (n = 10)**	**p-value**
Admission medication				
CV medication				
Antiplatelet	11 (27)	10 (32)	1 (10)	0.17
Anticoagulant	24 (59)	15 (48)	9 (90)	0.02
Statin	28 (68)	22 (71)	6 (60)	0.52
Loop diuretic	20 (49)	14 (45)	6 (60)	0.41
Furosemide-equivalent dose (mg)	80 [40-120]	50 [40-120]	100 [80-120]	0.56
Thiazide	4 (10)	4 (13)	0 (0)	0.23
MRA	1 (2)	1 (3)	0 (0)	0.57
ACEI/ARB	26 (63)	21 (68)	5 (50)	0.31
Beta-blocker	25 (61)	17 (55)	8 (80)	0.16

CCB	16 (39)	14 (45)	2 (20)	0.16
Digoxin	5 (12)	2 (6)	3 (30)	0.048
	(n = 18)	(n = 15)	(n = 3)	
Diabetic medication	14 (78)	12 (80)	2 (67)	0.61
Insulin	5 (28)	3 (20)	2 (67)	0.099
Non-CV medication				
Bronchodilator	14 (34)	12 (39)	2 (20)	0.28
Antidepressant	10 (24)	8 (26)	2 (20)	0.71
In-hospital treatment				
Furosemide	40 (98)	30 (97)	10 (100)	0.57
IV (>1 dose)	31 (78)	24 (80)	7 (70)	0.71
IV (1 dose)	4 (10)	3 (10)	1 (10)	
Oral	5 (12)	3 (10)	2 (20)	
IV nitrate	2 (5)	2 (6)	0 (0)	0.41
Dopamine	0 (0)	0 (0)	0 (0)	
Oxygen	18 (44)	16 (52)	2 (20)	0.08
CPAP	0 (0)	0 (0)	0 (0)	
Discharge medication				
CV medication				
Antiplatelet	12 (29)	11 (35)	1 (10)	0.12
Anticoagulant	30 (73)	20 (65)	10 (100)	0.028
Statin	28 (68)	22 (71)	6 (60)	0.52
Loop diuretic	40 (98)	30 (97)	10 (100)	0.57
Furosemide-equivalent dose (mg)	80 [80-120]	80 [80-120]	100 [80-120]	0.63
Thiazide	4 (10)	4 (13)	0 (0)	0.23
ACEI/ARB	26 (63)	21 (68)	5 (50)	0.31
MRA	6 (15)	5 (16)	1 (10)	0.63
Beta-blocker	29 (71)	20 (65)	9 (90)	0.12
CCB	10 (24)	9 (29)	1 (10)	0.22
Digoxin	18 (44)	10 (32)	8 (80)	<0.01
	(n = 18)	(n = 15)	(n = 3)	
Diabetic medication	14 (78)	12 (80)	2 (67)	0.61
Insulin	5 (28)	3 (20)	2 (67)	0.099

Values are median [Q1-Q3] or n (%). ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CPAP, continuous positive airway pressure; CV, cardiovascular; IV, intravenous; MRA, mineralocorticoid receptor antagonist.

Table 7-3: Admission medication, in-hospital treatment and discharge medication stratified by endothelium-dependent CMD.

7.2.4 Baseline investigations

Table 7-4 details the ECG, CXR and laboratory results of those with and without coronary microvascular endothelial dysfunction. Those with endothelial dysfunction had a higher mean HR (107 vs. 86 bpm; p = 0.036) and shorter mean

QRS duration (82 vs. 105 ms; p = 0.03) than those without. Radiological signs of HF were similar in both groups. There were no statistically significant differences in routine haematology and biochemistry laboratory results.

	All endothelial function testing (n = 41)	No endothelium-dependent CMD (n = 31)	Endothelium-dependent CMD (n = 10)	p-value
ECG				
Rate (bpm)	92 [28]	86 [25]	107 [32]	0.036
AF	26 (63)	16 (52)	10 (100)	0.054
Bundle branch block	6 (15)	6 (19)	0 (0)	0.13
LVH	3 (7)	3 (10)	0 (0)	0.31
Q waves	2 (5)	2 (6)	0 (0)	0.41
T-wave inversion	18 (44)	12 (39)	6 (60)	0.24
QRS duration (ms)	100 [30]	105 [32]	82 [11]	0.03
QT_c (ms)	447 [35]	452 [35]	430 [31]	0.088
CXR				
Cardiomegaly	34 (83)	26 (84)	8 (80)	0.78
Upper lobe venous diversion	29 (71)	21 (68)	8 (80)	0.46
Interstitial oedema	7 (17)	5 (16)	2 (20)	0.78
Alveolar oedema	23 (56)	18 (58)	5 (50)	0.65
Perihilar oedema	17 (41)	14 (45)	3 (30)	0.40
Pleural effusion(s)	18 (44)	15 (48)	3 (30)	0.31
Haematology				
Hb (g/L)	126 [19]	126 [21]	124 [10]	0.68
Anaemia	12 (29)	10 (32)	2 (20)	0.46
WCC (x 10^9/L)	8.6 [1.9]	8.7 [1.6]	8.3 [2.7]	0.55
Biochemistry				
NT-proBNP	21 (51)	15 (48)	6 (60)	0.52
NT-proBNP (pg/mL)	1385 [1132-2819]	1366 [1132-3076]	1562 [540-2108]	0.97
BNP	23 (56)	19 (61)	4 (40)	0.24
BNP (pg/mL)	323 [177-794]	355 [177-1017]	254 [154-559]	0.57
hsTnI	29 (71)	21 (68)	8 (80)	0.46
hsTnI (ng/L)	16 [10-25]	16 [10-29]	16 [9-25]	0.68
Elevated hsTnI	9 (31)	6 (29)	3 (38)	0.64
Na^+ (mmol/L)	138 [3]	138 [4]	139 [2]	0.47
Hyponatraemia	3 (7)	3 (10)	0 (0)	0.31
K^+ (mmol/L)	4.3 [0.5]	4.3 [0.6]	4.1 [0.4]	0.32
Urea (mmol/L)	7.3 [4.6]	7.6 [5.1]	6.3 [2.1]	0.46
Creatinine (µmol/L)	89 [38]	94 [42]	73 [12]	0.13
eGFR (mL/min/1.73m^2)	69 [22]	67 [23]	75 [17]	0.37

eGFR <60 mL/min/ 1.73m^2	12 (29)	11 (35)	1 (10)	0.12
Albumin (g/L)	34 [4]	34 [4]	33 [4]	0.52
Hypoalbuminaemia	19 (46)	13 (42)	6 (60)	0.32
CRP (mg/L)	12 [5-24]	14 [7-35]	5 [4-18]	0.14
Elevated CRP	22 (54)	19 (61)	3 (30)	0.084
Glucose (mmol/L)	6.2 [5.3-8.2]	6.6 [5.5-8.3]	5.3 [5.1-6.8]	0.069

Values are mean [standard deviation], median [Q1-Q3], or n (%). AF, atrial fibrillation; AV, atrioventricular; BNP, B-type natriuretic peptide; CRP, C-reactive protein; CXR, chest x-ray; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; hsTnI, high-sensitivity troponin I; K^+, potassium; LVH, left ventricular hypertrophy; Na^+, sodium; NT-proBNP, N-terminal prohormone BNP; WCC, white cell count.

Table 7-4: ECG, CXR and laboratory results stratified by endothelium-dependent CMD.

The echocardiography findings of patients stratified by endothelium-dependent CMD are detailed in Table 7-5. Those without endothelial dysfunction had greater mean LV wall thickness (13 vs. 11 mm) than those with endothelial dysfunction, but there were similar rates of LVH (65% vs. 50%; p = 0.41, respectively) and no other significant differences between the groups.

	All endothelial function testing (n = 41)	**No endothelium-dependent CMD (n = 31)**	**Endothelium-dependent CMD (n = 10)**	**p-value**
LV structure and systolic function				
LVEDD (mm/m^2)	24 [3]	24 [3]	24 [4]	0.87
LVESD (mm/m^2)	15 [4]	15 [5]	15 [4]	0.71
LVEF (%)	59 [6]	58 [6]	62 [7]	0.11
S' lateral (cm/s)	7.1 [2.5]	6.7 [2.0]	8.7 [4.0]	0.072
Septal wall thickness (mm)	13 [2]	13 [2]	11 [3]	0.013
Posterior wall thickness (mm)	12 [2]	13 [2]	11 [2]	0.024
LVH	25 (61)	20 (65)	5 (50)	0.41
LV diastolic function				
E/A	1.4 [1.4]	1.4 [1.4]	1.5	0.19
Deceleration time (ms)	226 [78]	219 [66]	251 [114]	0.32
E' average (cm/s)	8.3 [2.7]	7.8 [2.3]	10.7 [3.4]	0.016
E/e' average	12.8 [4.0]	13.0 [4.1]	11.9 [3.6]	0.56
Diastolic dysfunction	13 (39)	10 (37)	3 (50)	0.56
LA volume (mL/m^2)	47 [17]	45 [17]	55 [17]	0.15
LA dilatation	37 (92)	28 (90)	9 (100)	0.33
RV structure and function				
RVEDD (mm)	35 [7]	35 [7]	35 [9]	0.84
TAPSE (mm)	21 [4]	21 [4]	20 [3]	0.45
Estimated RVSP (mmHg)	37 [13]	36 [14]	40 [12]	0.45

Valve disease				
Mild/moderate valve disease	35 (85)	26 (84)	9 (90)	0.63

Values are mean [standard deviation] or n (%). LA, left atrial; LV, left ventricular; LVEDD, LV end-diastolic dimension; LVEF, LV ejection fraction; LVESD, LV end-systolic dimension; LVH, LV hypertrophy; RV, right ventricular; RVEDD, RV end-diastolic dimension; RVSP, RV systolic pressure; TAPSE, tricuspid annular plane systolic excursion.

Table 7-5: Echocardiography findings stratified by endothelium-dependent CMD.

7.2.5 Cardiac magnetic resonance imaging

Table 7-6 describes the CMR findings of participants based on the presence or absence of coronary endothelial dysfunction. Those with endothelial dysfunction had less LGE than those with no evidence of coronary endothelial dysfunction (0% vs. 61%; p = 0.027, respectively).

	All endothelial function testing (n = 22)	No endothelium-dependent CMD (n = 18)	Endothelium-dependent CMD (n = 4)	p-value
LV structure and function				
LVEDV (mL/m^2)	71 [21]	74 [21]	58 [17]	0.16
LVESV (mL/m^2)	30 [13]	32 [13]	20 [4]	0.12
LVSV (mL/m^2)	42 [11]	42 [10]	37 [13]	0.39
CI (L/min/m^2)	3.2 [0.9]	3.2 [0.8]	3.4 [1.4]	0.73
LVEF (%)	59 [7]	58 [7]	64 [5]	0.17
MAPSE (mm)	13 [4]	13 [4]	13 [4]	0.86
WMSI	1.1 [0.2]	1.1 [0.2]	1.0 [0]	0.21
LV mass (g/m^2)	64 [16]	67 [17]	52 [9]	0.12
LVH	12 (52)	10 (53)	2 (50)	0.92
LA structure				
LA volume (mL/m^2)	71 [24]	71 [26]	71 [9]	0.98
LA dilatation	16 (73)	12 (67)	4 (100)	0.18
RV structure and function				
RVEDV (mL/m^2)	75 [22]	78 [22]	61 [20]	0.20
RVESV (mL/m^2)	36 [14]	38 [15]	28 [6]	0.23
RVSV (mL/m^2)	39 [13]	40 [12]	33 [15]	0.35
RVEF (%)	52 [9]	52 [10]	53 [6]	0.89
TAPSE (mm)	18 [5]	18 [5]	22 [6]	0.19
LGE				
Any LGE	11 (50)	11 (61)	0 (0)	0.027
Ischaemic LGE	4 (22)	4 (22)	0 (0)	0.30
Non-ischaemic LGE	8 (73)	8 (44)	0 (0)	0.095
T1 mapping				
Native T1 (ms)	1276 [75]	1272 [74]	1295 [90]	0.59

ECV (%)	27.4 [4.1]	27.4 [4.2]	27.7 [4.4]	0.88
ECV >30%	6 (30)	5 (31)	1 (25)	0.81
Adenosine stress perfusion imaging				
MPRI	1.60 [1.39-1.87]	1.60 [1.39-1.87]	1.60 [1.49-1.71]	0.87
MPRI <1.4	4 (27)	4 (31)	0 (0)	0.36

Values are mean [standard deviation], median [Q1-Q3], or n (%). CI, cardiac index; ECV, extracellular volume; LA, left atrial; LGE, late gadolinium enhancement; LV, left ventricular; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume; LVH, LV hypertrophy; LVSV, LV stroke volume; MAPSE, mitral annular plane systolic excursion; MPRI, myocardial-perfusion reserve index; RV, right ventricular; RVEDV, RV end-diastolic volume; RVEF, RV ejection fraction; RVESV, RV end-systolic volume; RVSV, RV stroke volume; TAPSE, tricuspid annular plane systolic excursion; WMSI, wall motion score index.

Table 7-6: CMR findings stratified by endothelium-dependent CMD.

7.2.6 Invasive coronary angiography, physiology and haemodynamics

Table 7-7 summarises the invasive coronary angiography, physiology and haemodynamics stratified by coronary endothelial dysfunction. None of the five patients with obstructive epicardial CAD that underwent vasoreactivity testing had evidence of coronary endothelial dysfunction. There was no significant difference in proportion of patients with endothelium-independent CMD in those with and without endothelium-dependent CMD (60% vs. 74%; p = 0.39, respectively) and no difference in LVEDP between the groups (median 14 vs. 13 mmHg; p = 0.99, respectively).

	All endothelial function testing (n = 41)	**No endothelium-dependent CMD (n = 31)**	**Endothelium-dependent CMD (n = 10)**	**p-value**
Obstructive epicardial CAD	5 (12)	5 (16)	0 (0)	0.18
Endothelium-independent CMD	29 (71)	23 (74)	6 (60)	0.39
CFR	2.3 [1.4-3.0]	2.4 [1.3-3.0]	2.0 [1.5-3.8]	0.99
CFR <2.0	19 (46)	14 (45)	5 (50)	0.79
IMR	26 [18-42]	29 [20-50]	21 [14-28]	0.071
IMR ≥25	23 (56) (n = 40)	19 (61) (n = 30)	4 (40) (n = 10)	0.24
LVEDP (mmHg)	13 [9-15]	13 [9-16]	14 [7-15]	0.99
LVEDP ≥12 mmHg	22 (55)	16 (53)	6 (60)	0.71

Values are median [Q1-Q3] or n (%). CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; IMR, index of microcirculatory resistance; LVEDP, left ventricular end-diastolic pressure.

Table 7-7: Invasive coronary angiography, physiology and haemodynamics stratified by endothelium-dependent CMD.

7.3 Correlates of endothelium-dependent coronary microvascular dysfunction

There was no correlation between endothelium-dependent and endothelium-independent CMD (φ = -0.13; p = 0.40) (Table 7-8). Endothelium-dependent CMD was associated with AF (φ = 0.39; p = 0.012) and had a negative correlation with a smoking history (φ = -0.41; p <0.01) and LGE on CMR (φ = -0.47; p = 0.027).

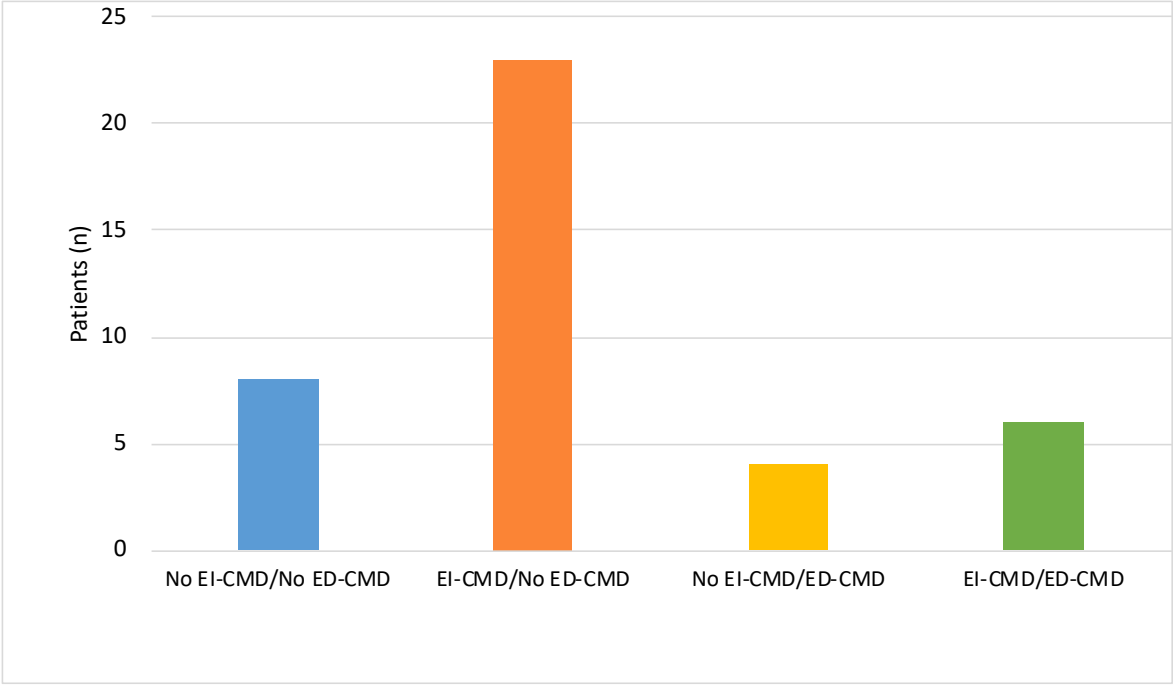
	Endothelium-dependent CMD	p-value
Smoking history	-0.41	<0.01
AF	0.39	0.012
Any LGE	-0.47	0.027
Obstructive CAD	-0.21	0.18
Endothelium-independent CMD	-0.13	0.40

AF, atrial fibrillation; CAD, coronary artery disease; CFR, coronary flow reserve; CKD, chronic kidney disease; CMD, coronary microvascular dysfunction; CRP, C-reactive protein; IMR, index of microcirculatory resistance; LGE, late gadolinium enhancement.

Table 7-8: Correlates of endothelium-dependent CMD.

7.4 Endothelium-independent and endothelium-dependent coronary microvascular dysfunction

Of the 41 participants that underwent coronary vasoreactivity testing, eight (20%) had neither endothelium-independent nor -dependent CMD; 23 (56%) had endothelium-independent CMD but no endothelium-dependent CMD; four (10%) had endothelium-dependent CMD but no endothelium-independent CMD; and six (15%) had both endothelium-independent and -dependent CMD (Figure 7-2).



ED-CMD, endothelium-dependent coronary microvascular dysfunction; EI-CMD, endothelium-independent coronary microvascular dysfunction.

Figure 7-2: Study participants stratified by endothelium-independent and endothelium-dependent CMD.

7.5 Outcomes related to endothelium-dependent coronary microvascular dysfunction

Mortality

Mortality rates were low during the follow-up period and no significant difference in mortality rates was observed between those with and without coronary microvascular endothelial dysfunction (Figures 7-3, 7-4, 7-5).

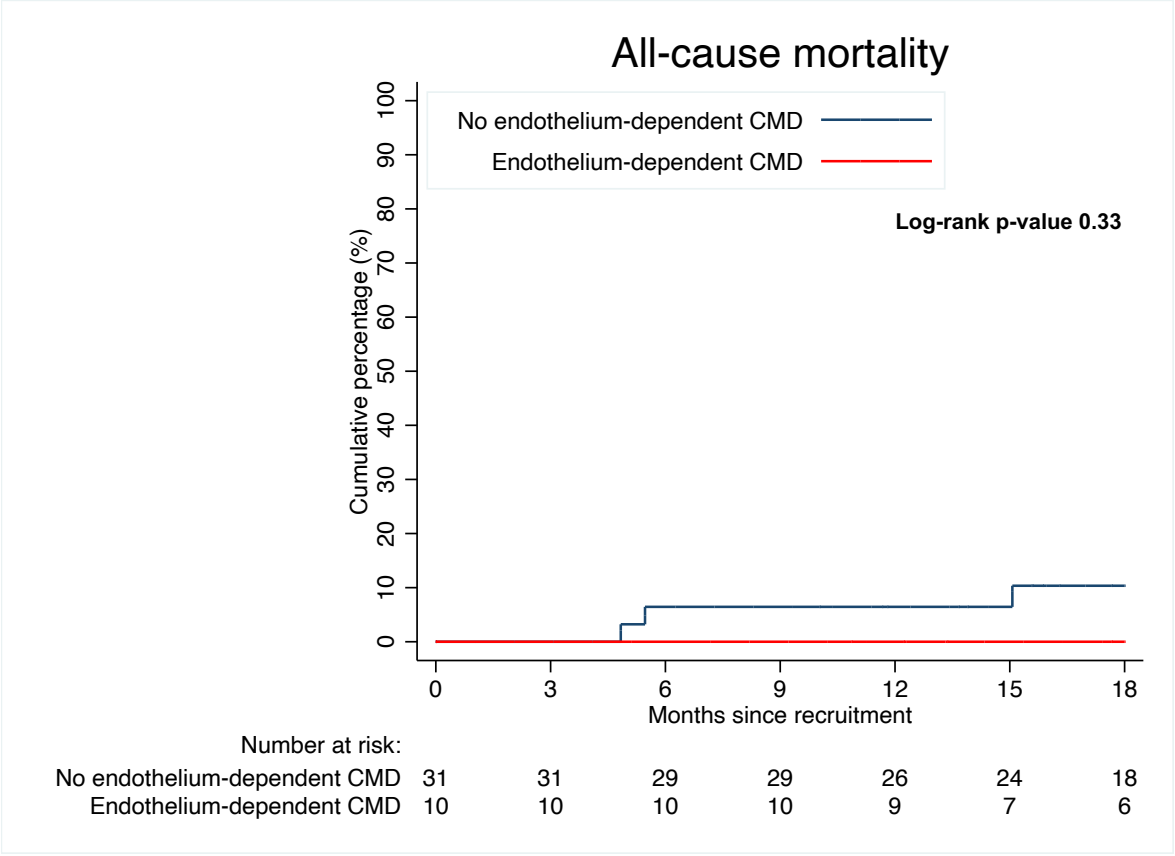


Figure 7-3: Kaplan-Meier curves for all-cause mortality by endothelium-dependent CMD.

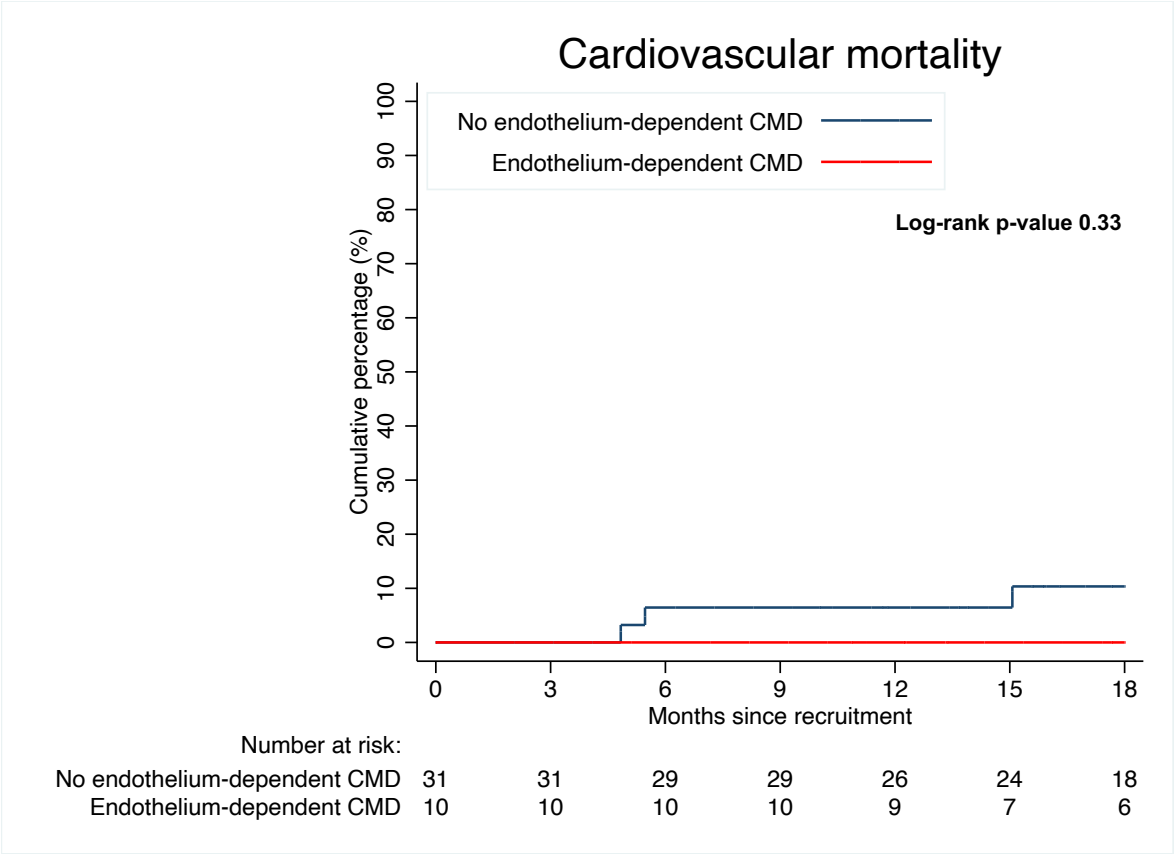


Figure 7-4: Kaplan-Meier curves for CV mortality by endothelium-dependent CMD.

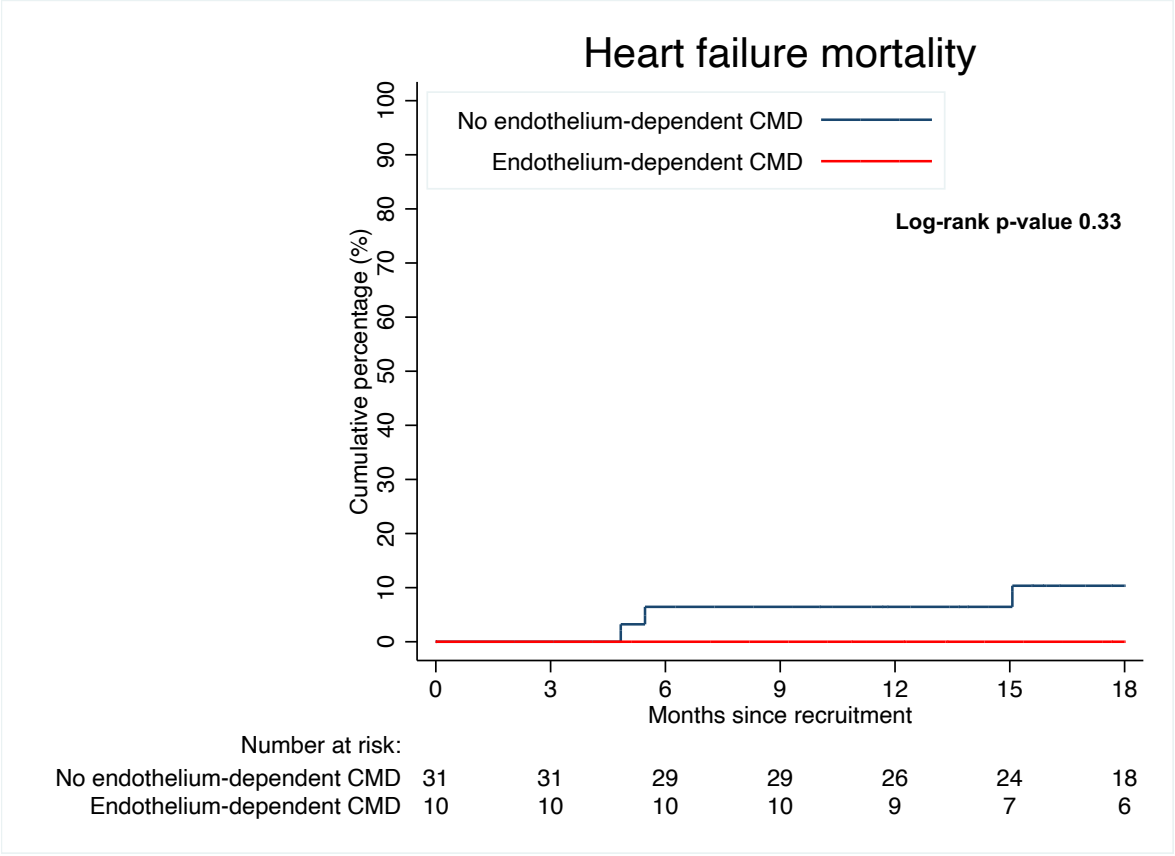


Figure 7-5: Kaplan-Meier curves for HF mortality by endothelium-dependent CMD.

Hospitalisations

There were no significant differences in hospitalisations in those with and without coronary endothelial dysfunction (Figures 7-6, 7-7, 7-8, 7-9).

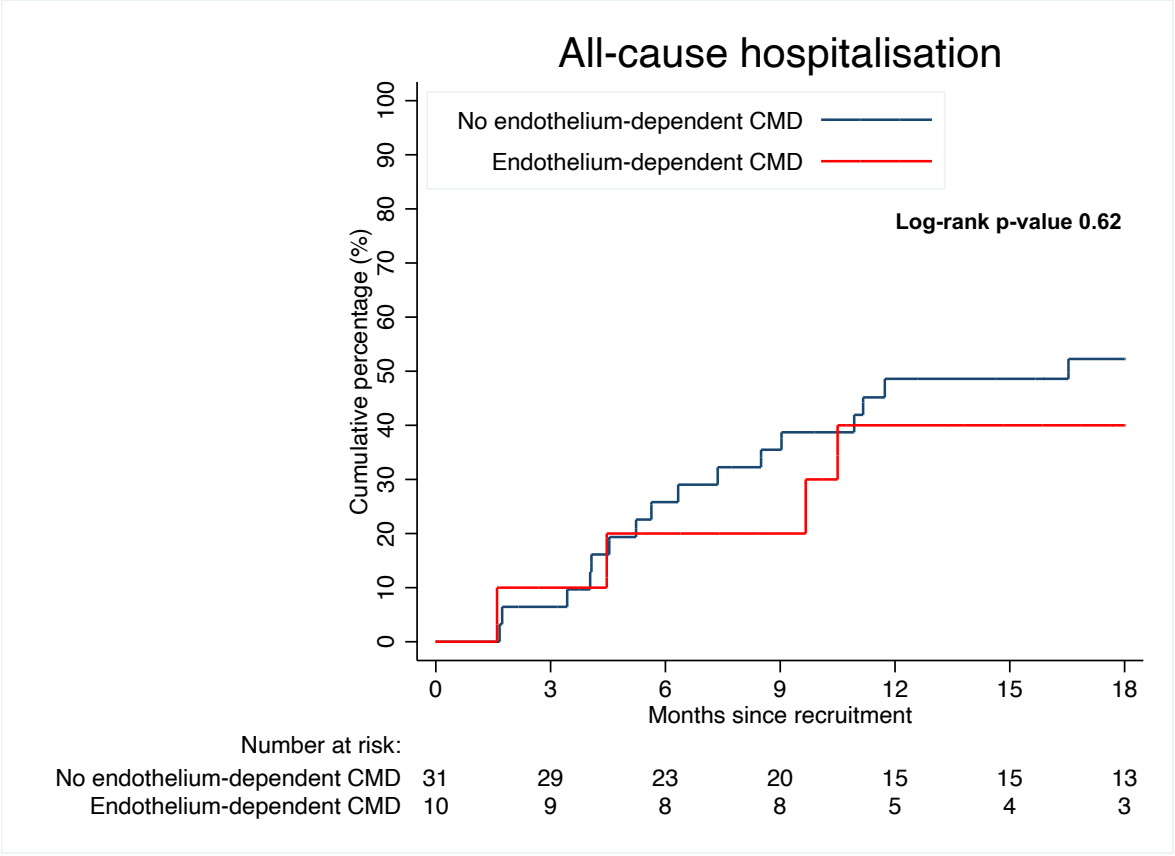


Figure 7-6: Kaplan-Meier curves for all-cause hospitalisation by endothelium-dependent CMD.

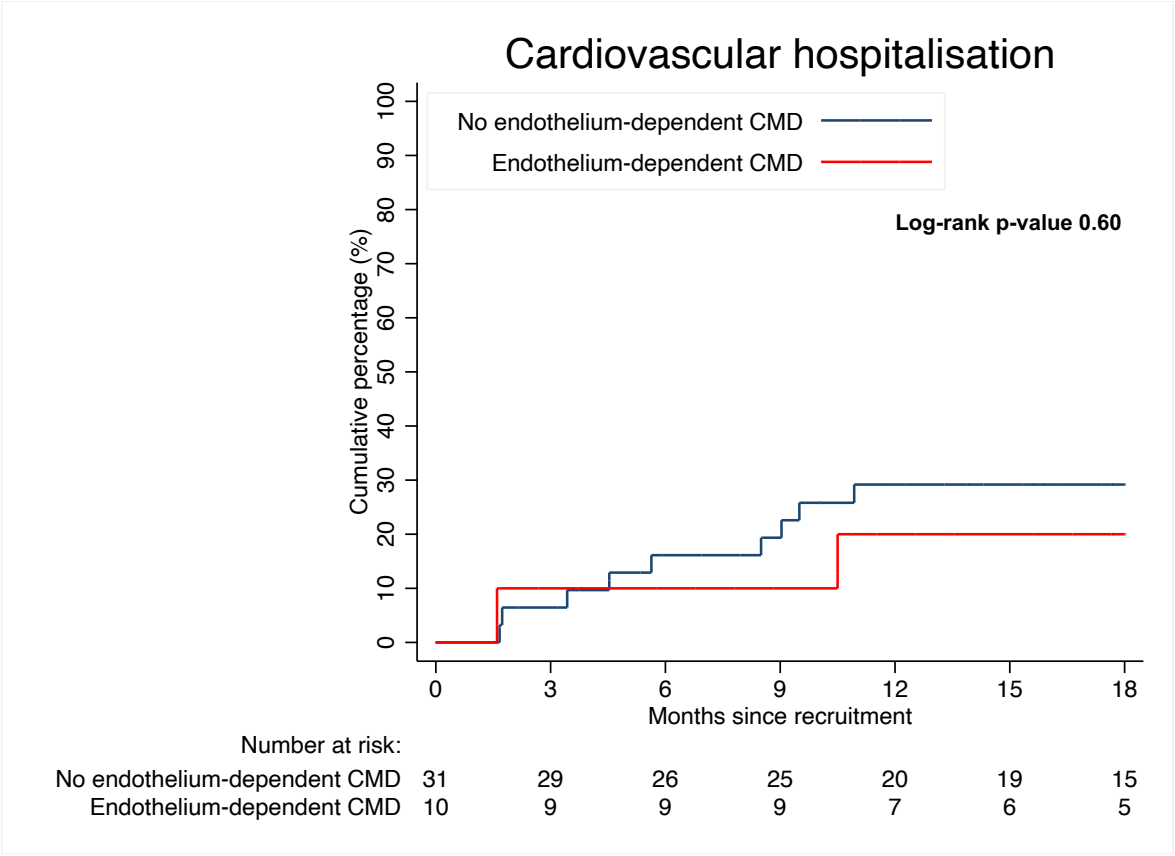


Figure 7-7: Kaplan-Meier curves for CV hospitalisation by endothelium-dependent CMD.

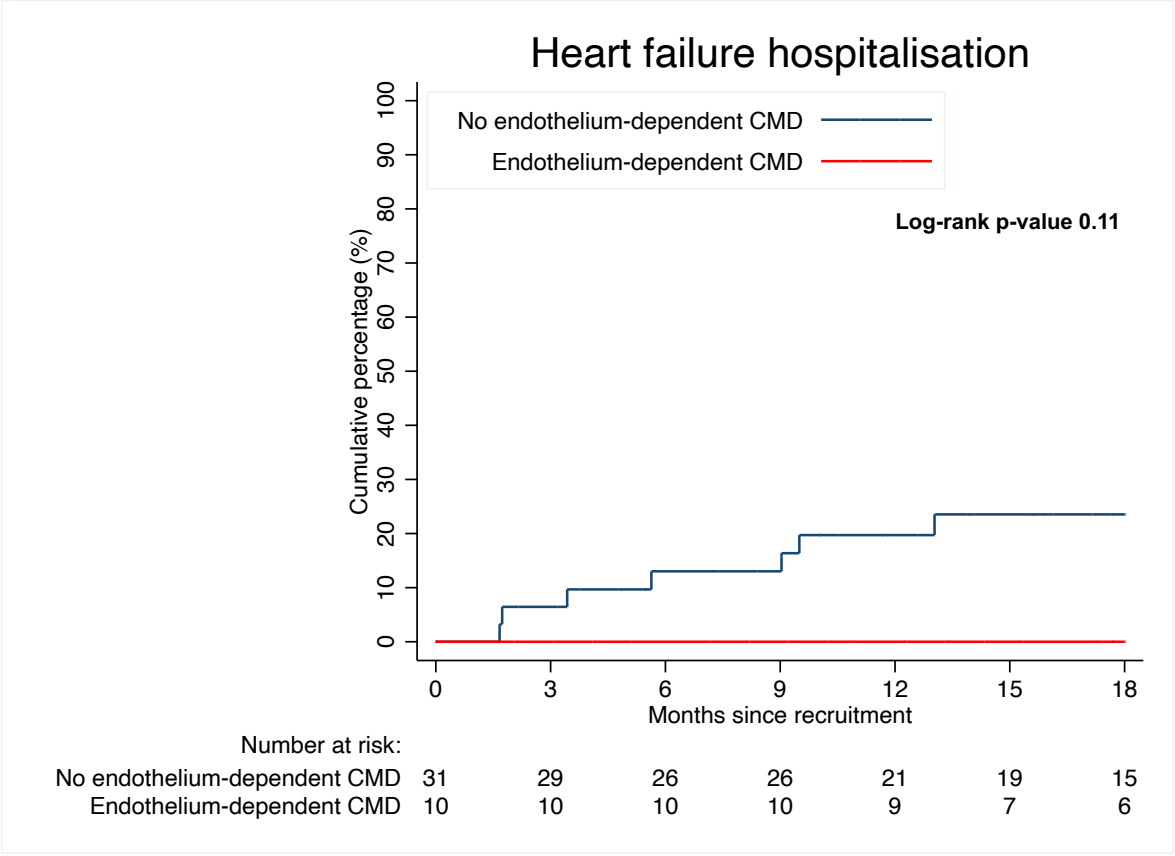


Figure 7-8: Kaplan-Meier curves for HF hospitalisation by endothelium-dependent CMD.

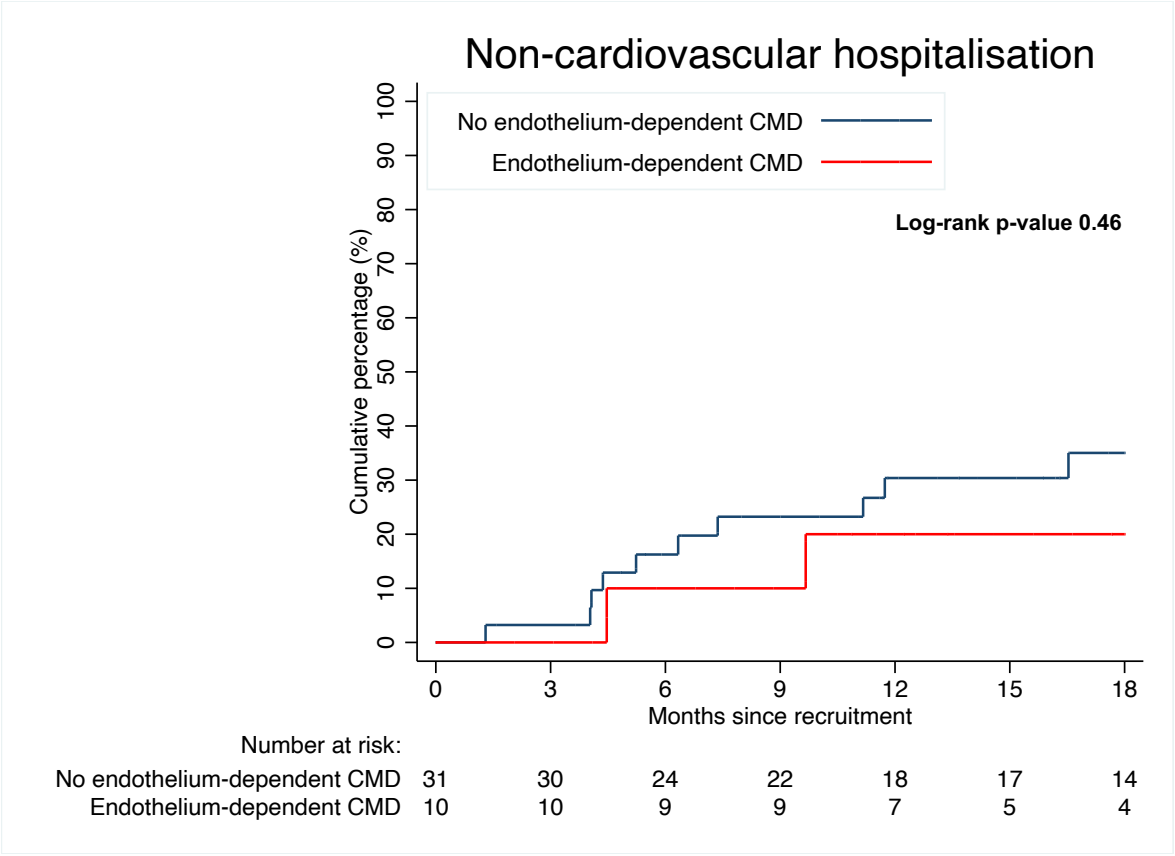


Figure 7-9: Kaplan-Meier curves for non-CV hospitalisation by endothelium-dependent CMD.

7.6 Complications of coronary vasoreactivity testing

There were no serious adverse events related to intracoronary ACh administration. Fourteen patients (34%) experienced chest tightness during vasoreactivity testing, all of which subsided with discontinuation of the infusion. Transient AV block occurred in 12 patients (29%), all of which recovered spontaneously with no treatment.

7.7 Summary

Of the 41 study participants that invasive coronary endothelial function testing, 10 (24%) had evidence of endothelium-dependent CMD. None of the participants had evidence of epicardial coronary vasospasm. Those with endothelium-dependent CMD were more frequently female and were less likely to have a smoking history than those with no endothelial dysfunction. Endothelium-dependent CMD was associated with a higher prevalence of AF but lower rates of COPD than those without endothelial dysfunction. Patients with coronary endothelial dysfunction had less myocardial LGE than those without endothelial dysfunction. There was no difference in MPRI or ECV between those with and without endothelium-dependent CMD. Importantly, there was no correlation between endothelium-dependent and -independent CMD. Recent studies have suggested that measures of endothelium-independent CMD may be a surrogate for coronary microvascular endothelial dysfunction[231], however, these data do not support this claim.

In this study, coronary microvascular endothelial dysfunction appeared to represent a distinct clinical entity characterised by a female preponderance, high prevalence of AF and low burden of focal myocardial fibrosis. Participants with coronary endothelial dysfunction had a higher mean HR on their admission ECG and higher prescription of digoxin at discharge (with a marked increase in prescription rates from pre-admission) than those without endothelial dysfunction, suggesting that AF with sub-optimal rate-control contributed to HF decompensation in a large proportion of this group.

I defined endothelium-dependent CMD based on the contemporary literature and the international standards for the diagnostic criteria of coronary vasomotion

disorders developed by the Coronary Vasomotion Disorders International Study Group (COVADIS).[146] However, the published literature on invasive vasoreactivity testing has been performed almost exclusively in patients presenting with chest pain and this technique has not been validated in the HFpEF population.

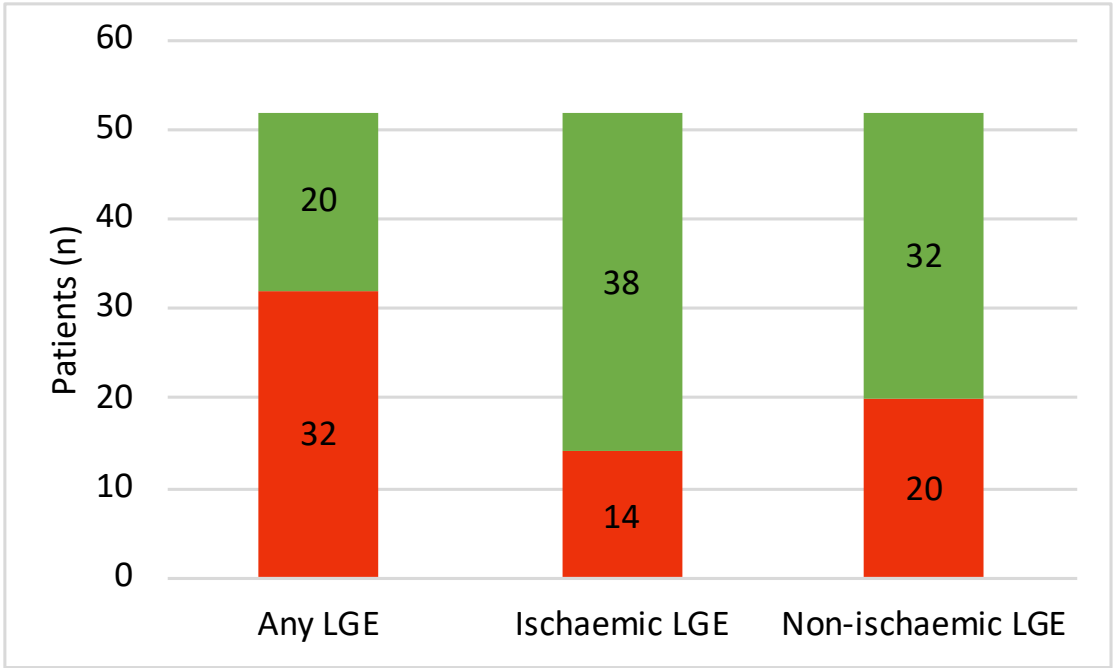
Accepting that patient numbers were small and event rates low (see Chapter 5), no significant differences in outcomes were observed between those with and without coronary endothelial dysfunction.

Chapter 8 Results – Cardiac magnetic resonance imaging in heart failure with preserved ejection fraction

In this chapter I will describe the clinical characteristics of the study participants based on CMR imaging findings. I will report the prevalence of ischaemic myocardial scar (based on late gadolinium enhancement [LGE] imaging) to define the prevalence of previous MI in the study population. I will describe the burden of diffuse myocardial fibrosis (using quantification of extracellular volume [ECV]) and inducible ischaemia (using semi-quantitative assessment of myocardial-perfusion reserve index [MPRI]) in the study participants. Finally, I will report the clinical outcomes (mortality and hospitalisations) on the basis of the CMR findings.

8.1 Prevalence of previous myocardial infarction

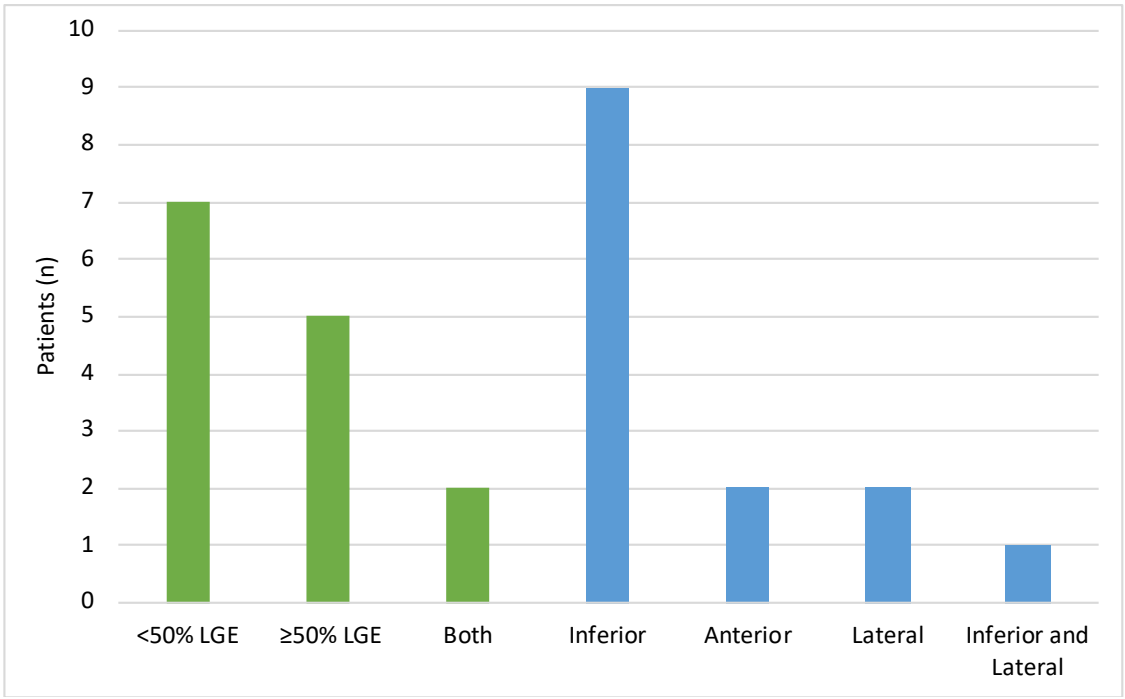
A total of 52 participants underwent contrast enhanced CMR, 48 had pre- and post-contrast T1 mapping, and 46 had rest and adenosine stress perfusion imaging. Of the 52 participants that underwent CMR, 14 had ischaemic LGE consistent with previous MI, giving a prevalence estimate of 27% (95% CI 16-41%) for CMR-proven MI in the HFpEF population. Twenty of the 52 participants (38% [95% CI 26-53%]) had evidence of non-ischaemic (mid-wall or epicardial) LGE on CMR, consistent with focal myocardial fibrosis, and 32 (62% [95% CI 47-74%]) had any LGE (ischaemic or non-ischaemic) (Figure 8-1).



LGE, late gadolinium enhancement.

Figure 8-1: Prevalence of LGE in study cohort.

Of those with ischaemic LGE, seven patients (50%) had <50% subendocardial scar, five (36%) had ≥50% subendocardial (or transmural) scar and two (14%) had areas of both <50% and ≥50% scar. The majority of patients with ischaemic LGE had an inferior MI (nine patients [64%]), two (14%) had an anterior MI and two (14%) had a lateral infarct. One patient (7%) had imaging evidence of two (inferior and lateral) infarcts (Figure 8-2).



LGE, late gadolinium enhancement.

Figure 8-2: Patterns of ischaemic LGE in study cohort.

8.2 Clinical characteristics by previous myocardial infarction

8.2.1 Demographics and clinical features

The demographics and clinical features of the cohort based on the presence and absence of ischaemic LGE are presented in Table 8-1. Patients with CMR-proven previous MI had a longer hospital stay than those with no CMR evidence of MI (median 10 vs. 6 days; p = 0.026, respectively), but here were no significant differences in demographics or HF symptoms and signs between the groups.

	All CMR (n = 52)	No CMR-proven MI (n = 38)	CMR-proven MI (n = 14)	p-value
Demographics				
Age (years)	72 [9]	73 [9]	69 [10]	0.14
Female sex	24 (46)	17 (45)	7 (50)	0.74
BMI (kg/m^2)	32 [6]	31 [6]	33 [4]	0.21
Obesity	22 (42)	15 (39)	7 (50)	0.50
Smoking history	27 (52)	19 (50)	8 (57)	0.65
Hospitalisation details				
Length of stay (days)	7 [5-11]	6 [5-10]	10 [7-15]	0.026
HF symptoms				
NYHA functional class				
II	0 (0)	0 (0)	0 (0)	0.77
III	24 (46)	18 (47)	6 (43)	
IV	28 (54)	20 (53)	8 (57)	
Orthopnoea	39 (75)	26 (68)	13 (93)	0.071
PND	25 (48)	16 (42)	9 (64)	0.16
Ankle swelling	46 (88)	33 (87)	13 (93)	0.55
Admission vital signs				
HR (bpm)	82 [24]	85 [27]	75 [14]	0.21
SBP (mmHg)	152 [29]	154 [29]	146 [28]	0.39
DBP (mmHg)	81 [19]	82 [19]	78 [18]	0.53
MAP (mmHg)	104 [18]	106 [18]	101 [17]	0.37
HF signs				
JVD	37 (71)	27 (71)	10 (71)	0.98
Murmur	15 (29)	11 (29)	4 (29)	0.98
Crepitations	40 (77)	29 (76)	11 (79)	0.86
Pleural effusion(s)	24 (46)	17 (45)	7 (50)	0.74
Oedema	45 (87)	32 (84)	13 (93)	0.42
Ascites	2 (4)	2 (5)	0 (0)	0.38

Values are mean [standard deviation], median [Q1-Q3], or n (%). BMI, body mass index; CMR, cardiac magnetic resonance; DBP, diastolic blood pressure; HF, heart failure; HR, heart rate; JVD, jugular venous distention; MAP, mean arterial pressure; NYHA, New York Heart Association; PND, paroxysmal nocturnal dyspnoea; SBP; systolic blood pressure.

Table 8-1: Demographics and clinical features stratified by CMR-proven MI.

8.2.2 Past medical history

Table 8-2 details the past medical history of those with and without CMR-proven previous MI. Those with ischaemic LGE were more likely to have had a previous hospitalisation for HF than those without (43% vs. 13%; p = 0.02, respectively). Participants with CMR-proven MI more commonly had a previous clinical history of CAD (57% vs. 18%; p <0.01), MI (43% vs. 5%; p <0.001), and coronary revascularisation (43% vs. 11%; p <0.01) than those with no CMR evidence of MI. Eight patients (57% of those with CMR-proven MI) had no clinical history of MI. Of the 44 participants with no clinical history of MI, 18% had evidence of MI on CMR.

The prevalence of diabetes was similar in those with and without imaging evidence of MI (55% vs. 57%; p = 0.90, respectively), however, those with CMR-proven MI were more often treated with insulin than those without (75% vs. 19%; p <0.01, respectively). Those with ischaemic LGE had less AF (36% vs. 76%; p <0.01), but more osteoarthritis (50% vs. 13%; p <0.01) and depression (21% vs. 3%; p = 0.024) than those without ischaemic LGE.

	All CMR (n = 52)	**No CMR-proven MI (n = 38)**	**CMR-proven MI (n = 14)**	**p-value**
History of HF				
Previous HF diagnosis	19 (37)	12 (32)	7 (50)	0.22
Previous HFH	11 (21)	5 (13)	6 (43)	0.02
History of CAD				
Any CAD	15 (29)	7 (18)	8 (57)	<0.01
MI	8 (15)	2 (5)	6 (43)	<0.001
Angina	7 (13)	6 (16)	1 (7)	0.42
Current angina	3 (6)	2 (5)	1 (7)	0.80
Revascularisation	10 (19)	4 (11)	6 (43)	<0.01
PCI	8 (15)	3 (8)	5 (36)	0.014
CABG	3 (6)	1 (3)	2 (14)	0.11
CV comorbidities				
Hypertension	40 (77)	30 (79)	10 (71)	0.57
Dyslipidaemia	6 (12)	3 (8)	3 (21)	0.18

CVD	8 (15)	5 (13)	3 (21)	0.46
PAD	6 (12)	4 (11)	2 (14)	0.71
AF	34 (65)	29 (76)	5 (36)	<0.01
Valve disease (mild/moderate)	13 (25)	10 (26)	3 (21)	0.72
Non-CV comorbidities				
Diabetes	29 (56)	21 (55)	8 (57)	0.90
CKD	17 (33)	11 (29)	6 (43)	0.34
Chronic liver disease	1 (2)	1 (3)	0 (0)	0.54
Depression	4 (8)	1 (3)	3 (21)	0.024
Cancer	4 (8)	3 (8)	1 (7)	0.93
COPD	9 (17)	5 (13)	4 (29)	0.19
Asthma	3 (6)	3 (8)	0 (0)	0.28
Anaemia	11 (21)	8 (21)	3 (21)	0.98
Hypothyroidism	7 (13)	4 (11)	3 (21)	0.31
Osteoarthritis	12 (23)	5 (13)	7 (50)	<0.01

Values are mean [standard deviation], median [Q1-Q3], or n (%). AF, atrial fibrillation; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; CMR, cardiac magnetic resonance; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; CVD, cerebrovascular disease; HF, heart failure; HFH, HF hospitalisation; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention.

Table 8-2: Past medical history stratified by CMR-proven MI.

8.2.3 Drug history – medication on admission, in-hospital treatment and medication at discharge

Table 8-3 summarises the drug history of participants stratified by the presence or absence of evidence of MI on CMR. Those with MI were more often treated with antiplatelets and statins, whereas those with no MI more commonly received anticoagulants, both on admission and at discharge. The in-hospital treatment received by both groups was similar.

	All CMR (n = 52)	**No CMR-proven MI (n = 38)**	**CMR-proven MI (n = 14)**	**p-value**
Admission medication				
CV medication				
Antiplatelet	17 (33)	8 (21)	9 (64)	<0.01
Anticoagulant	25 (48)	22 (58)	3 (21)	0.02
Statin	36 (69)	23 (61)	13 (93)	0.025
Loop diuretic	22 (42)	14 (37)	8 (57)	0.19
Furosemide-equivalent dose (mg)	80 [40-120]	80 [40-120]	80 [50-120]	0.67
Thiazide	7 (13)	6 (16)	1 (7)	0.42
MRA	1 (2)	1 (3)	0 (0)	0.54

ACEI/ARB	34 (65)	22 (58)	12 (86)	0.061
Beta-blocker	36 (69)	25 (66)	11 (79)	0.38
CCB	24 (46)	17 (45)	7 (50)	0.74
Digoxin	3 (6)	2 (5)	1 (7)	0.80
	(n = 29)	(n = 21)	(n = 8)	
Diabetic medication	25 (86)	17 (81)	8 (100)	0.18
Insulin	10 (34)	4 (19)	6 (75)	<0.01
Non-CV medication				
Bronchodilator	19 (37)	13 (34)	6 (43)	0.57
Antidepressant	14 (27)	9 (24)	5 (36)	0.39
In-hospital treatment				
Furosemide	51 (98)	38 (100)	13 (93)	0.096
IV (>1 dose)	40 (78)	28 (74)	12 (92)	0.24
IV (1 dose)	4 (8)	3 (8)	1 (8)	
Oral	7 (14)	7 (18)	0 (0)	
IV nitrate	3 (6)	3 (8)	0 (0)	0.28
Dopamine	0 (0)	0 (0)	0 (0)	
Oxygen	22 (42)	15 (39)	7 (50)	0.50
CPAP	1 (2)	1 (3)	0 (0)	0.54
Discharge medication				
CV medication				
Antiplatelet	13 (25)	4 (11)	9 (64)	<0.001
Anticoagulant	37 (71)	32 (84)	5 (36)	<0.001
Statin	36 (69)	23 (61)	13 (93)	0.025
Loop diuretic	51 (98)	37 (97)	14 (100)	0.54
Furosemide-equivalent dose (mg)	80 [60-120]	80 [80-80]	80 [40-120]	0.76
Thiazide	2 (4)	1 (3)	1 (7)	0.45
ACEI/ARB	34 (65)	23 (61)	11 (79)	0.23
MRA	10 (19)	6 (16)	4 (29)	0.30
Beta-blocker	43 (83)	31 (82)	12 (86)	0.73
CCB	15 (29)	10 (26)	5 (36)	0.51
Digoxin	14 (27)	11 (29)	3 (21)	0.59
	(n = 29)	(n = 21)	(n = 8)	
Diabetic medication	25 (86)	17 (81)	8 (100)	0.18
Insulin	11 (38)	5 (24)	6 (75)	0.011

Values are mean [standard deviation], median [Q1-Q3], or n (%). ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CMR, cardiac magnetic resonance; CPAP, continuous positive airway pressure; CV, cardiovascular; IV, intravenous; MRA, mineralocorticoid receptor antagonist.

Table 8-3: Admission medication, in-hospital treatment and discharge medication stratified by CMR-proven MI.

8.2.4 Investigations

The baseline ECG, CXR and laboratory results of those with and without CMR-proven previous MI are presented in Table 8-4. Those with CMR evidence of MI had less AF on ECG (36% vs. 71%; p = 0.02), but more alveolar oedema on CXR (79% vs. 39%; p = 0.012) than those with no CMR-proven MI. The mean haemoglobin level was lower in those with MI than those without (111 vs. 126; p = 0.018, respectively). There were no other significant differences in haematology and biochemistry results between the groups.

	All CMR (n = 52)	**No CMR-proven MI (n = 38)**	**CMR-proven MI (n = 14)**	**p-value**
ECG				
Rate (bpm)	85 [25]	88 [25]	76 [22]	0.12
AF	32 (62)	27 (71)	5 (36)	0.02
Bundle branch block	8 (15)	7 (18)	1 (7)	0.32
LVH	4 (8)	2 (5)	2 (14)	0.28
Q waves	7 (13)	3 (8)	4 (29)	0.053
T-wave inversion	24 (46)	15 (39)	9 (64)	0.11
QRS duration (ms)	97 [22]	97 [24]	96 [20]	0.91
QT_c (ms)	450 [33]	451 [35]	445 [26]	0.60
CXR				
Cardiomegaly	39 (75)	31 (82)	8 (57)	0.071
Upper lobe venous diversion	36 (69)	26 (68)	10 (71)	0.83
Interstitial oedema	14 (27)	8 (21)	6 (43)	0.12
Alveolar oedema	26 (50)	15 (39)	11 (79)	0.012
Perihilar oedema	22 (42)	15 (39)	7 (50)	0.50
Pleural effusion(s)	27 (52)	21 (55)	6 (43)	0.43
Haematology				
Hb (g/L)	122 [20]	126 [19]	111 [19]	0.018
Anaemia	25 (48)	17 (45)	8 (57)	0.43
WCC (x 10^9/L)	8.3 [2.7]	8.1 [2.3]	8.7 [3.6]	0.45
Biochemistry				
NT-proBNP	27 (52)	20 (53)	7 (50)	0.87
NT-proBNP (pg/mL)	1542 [978-4535]	2175 [1259-4562]	1041 [326-1915]	0.076
BNP	32 (62)	21 (55)	11 (79)	0.13
BNP (pg/mL)	399 [204-829]	421 [229-785]	256 [197-1017]	0.83
hsTnI	37 (71)	27 (71)	10 (71)	0.98
hsTnI (ng/L)	16 [7-34]	19 [5-54]	13 [9-24]	0.34
Elevated hsTnI	12 (32)	11 (41)	1 (10)	0.076
Na^+ (mmol/L)	138 [3]	138 [3]	138 [5]	0.99
Hyponatraemia	3 (6)	2 (5)	1 (7)	0.80

K^+ (mmol/L)	4.4 [0.6]	4.4 [0.5]	4.4 [0.7]	0.78
Urea (mmol/L)	8.1 [4.7]	8.3 [5.2]	7.5 [3.3]	0.59
Creatinine (µmol/L)	99 [37]	101 [40]	93 [26]	0.51
eGFR (mL/min/1.73m^2)	64 [20]	63 [20]	66 [21]	0.56
eGFR <60 mL/min/ 1.73m^2	20 (38)	14 (37)	6 (43)	0.69
Albumin (g/L)	34 [4]	35 [4]	33 [4]	0.37
Hypoalbuminaemia	26 (50)	18 (47)	8 (57)	0.53
CRP (mg/L)	12 [7-21]	11 [7-21]	13 [3-32]	0.96
Elevated CRP	29 (56)	21 (55)	8 (57)	0.90
Glucose (mmol/L)	6.6 [5.3-8.5]	6.5 [5.3-8.6]	7.5 [5.5-8.4]	0.83

Values are mean [standard deviation], median [Q1-Q3], or n (%). AF, atrial fibrillation; AV, atrioventricular; BNP, B-type natriuretic peptide; CMR, cardiac magnetic resonance; CRP, C-reactive protein; CXR, chest x-ray; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; hsTnI, high-sensitivity troponin I; K^+, potassium; LGE, LVH, left ventricular hypertrophy; Na^+, sodium; NT-proBNP, N-terminal prohormone BNP; WCC, white cell count.

Table 8-4: ECG, CXR and laboratory results stratified by CMR-proven MI.

Table 8-5 details the echocardiography findings of patients stratified by CMR-proven previous MI. There were no significant differences in cardiac structure or function on echocardiography between the groups.

	All CMR (n = 52)	**No CMR-proven MI (n = 38)**	**CMR-proven MI (n = 14)**	**p-value**
LV structure and systolic function				
LVEDD (mm/m^2)	24 [3]	24 [3]	25 [3]	0.38
LVESD (mm/m^2)	15 [5]	15 [5]	17 [4]	0.23
LVEF (%)	59 [7]	59 [6]	58 [8]	0.79
S' lateral (cm/s)	7.0 [2.2]	7.0 [2.5]	7.0 [1.3]	0.95
Septal wall thickness (mm)	13 [3]	13 [2]	13 [3]	0.72
Posterior wall thickness (mm)	13 [2]	12 [2]	13 [3]	0.68
LVH	30 (58)	22 (58)	8 (57)	0.96
LV diastolic function				
E/A	1.4 [1.1]	1.1 [0.5]	1.6 [1.5]	0.43
Deceleration time (ms)	210 [73]	212 [75]	205 [71]	0.74
E' average (cm/s)	8.0 [2.9]	8.2 [3.1]	7.3 [2.1]	0.33
E/e' average	15.0 [6.2]	14.7 [6.6]	15.7 [5.5]	0.64
Diastolic dysfunction	28 (60)	18 (55)	10 (71)	0.28
LA volume (mL/m^2)	42 [16]	42 [14]	45 [20]	0.48
LA dilatation	44 (85)	33 (87)	11 (79)	0.46
RV structure and function				
RVEDD (mm)	33 [6]	33 [7]	33 [4]	0.91

TAPSE (mm)	21 [5]	20 [5]	23 [4]	0.098
Estimated RVSP (mmHg)	40 [16]	43 [16]	33 [15]	0.14
Valve disease				
Mild/moderate valve disease	39 (75)	29 (76)	10 (71)	0.72

Values are mean [standard deviation], median [Q1-Q3], or n (%). CMR, cardiac magnetic resonance; LA, left atrial; LV, left ventricular; LVEDD, LV end-diastolic dimension; LVEF, LV ejection fraction; LVESD, LV end-systolic dimension; LVH, LV hypertrophy; RV, right ventricular; RVEDD, RV end-diastolic dimension; RVSP, RV systolic pressure; TAPSE, tricuspid annular plane systolic excursion.

Table 8-5: Echocardiography findings stratified by CMR-proven MI.

8.2.5 Cardiac magnetic resonance imaging

Table 8-6 details the CMR findings stratified by CMR-proven MI. LVEF and ventricular volumes were comparable in those with and without MI. Those with ischaemic LGE had higher mean RVEF (58% vs. 52%; p = 0.036), but less LA dilatation (46% vs. 78%; p = 0.034) than those with no ischaemic LGE. Those with ischaemic LGE were less likely to have non-ischaemic LGE (14% vs. 47%; p = 0.03). Native T1 and ECV were not significantly different between those with and without ischaemic LGE (mean 1315 vs. 1278 ms; p = 0.086, and 30.2% vs. 28.0%; p = 0.096, respectively), as was the global MPRI (median 1.48 vs. 1.57; p = 0.69, respectively).

	All CMR (n = 52)	**No CMR-proven MI (n = 38)**	**CMR-proven MI (n = 14)**	**p-value**
LV structure and function				
LVEDV (mL/m^2)	76 [22]	74 [24]	82 [18]	0.29
LVESV (mL/m^2)	31 [13]	30 [13]	34 [13]	0.32
LVSV (mL/m^2)	45 [11]	44 [12]	48 [8]	0.34
CI (L/min/m^2)	3.2 [0.9]	3.1 [0.9]	3.4 [0.8]	0.40
LVEF (%)	60 [7]	60 [7]	59 [8]	0.59
MAPSE (mm)	13 [3]	12 [3]	14 [4]	0.15
WMSI	1.1 [0.2]	1.1 [0.2]	1.1 [0.2]	0.44
LV mass (g/m^2)	68 [22]	66 [23]	73 [12]	0.25
LVH	28 (54)	17 (45)	11 (79)	0.03
LA structure				
LA volume (mL/m^2)	68 [22]	68 [19]	67 [30]	0.80
LA dilatation	34 (69)	28 (78)	6 (46)	0.034
RV structure and function				
RVEDV (mL/m^2)	81 [28]	82 [32]	78 [13]	0.64
RVESV (mL/m^2)	38 [16]	40 [18]	33 [10]	0.19
RVSV (mL/m^2)	43 [16]	42 [18]	45 [9]	0.58

RVEF (%)	54 [9]	52 [9]	58 [8]	0.036
TAPSE (mm)	19 [5]	18 [5]	20 [5]	0.32
LGE				
Non-ischaemic LGE	20 (38)	18 (47)	2 (14)	0.03
T1 mapping				
Native T1 (ms)	1287 [67]	1278 [69]	1315 [53]	0.086
ECV (%)	28.6 [4.2]	28.0 [3.9]	30.2 [4.4]	0.096
ECV >30%	20 (42)	12 (34)	8 (62)	0.089
Adenosine stress perfusion imaging				
MPRI	1.52 [1.37-1.86]	1.57 [1.39-1.86]	1.48 [1.29-1.89]	0.69
MPRI <1.4	13 (32)	9 (31)	4 (33)	0.89

Values are mean [standard deviation], median [Q1-Q3], or n (%). CMR, cardiac magnetic resonance; CI, cardiac index; ECV, extracellular volume; LA, left atrial; LGE, late gadolinium enhancement; LV, left ventricular; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume; LVH, LV hypertrophy; LVSV, LV stroke volume; MAPSE, mitral annular plane systolic excursion; MPRI, myocardial-perfusion reserve index; RV, right ventricular; RVEDV, RV end-diastolic volume; RVEF, RV ejection fraction; RVESV, RV end-systolic volume; RVSV, RV stroke volume; TAPSE, tricuspid annular plane systolic excursion; WMSI, wall motion score index.

Table 8-6: CMR findings stratified by CMR-proven MI.

8.2.6 Invasive coronary angiography, physiology and haemodynamics

Table 8-7 summarises the invasive coronary angiography, physiology and haemodynamics stratified by the presence or absence of CMR evidence of MI. Those with ischaemic LGE had a greater burden of obstructive epicardial CAD than those without (85% vs. 42%; p <0.01, respectively). There was no difference in the prevalence of endothelium-independent CMD between the those with and without CMR-proven MI (70% vs. 68%; p = 0.91, respectively), but those with imaging evidence of MI had a lower IMR (median 13 vs. 28; p <0.01, respectively). There were no other significant differences in invasive findings between the groups.

	All CMR	**No CMR-proven MI**	**CMR-proven MI**	**p-value**
	(n = 44)	(n = 31)	(n = 13)	
Obstructive epicardial CAD	24 (55)	13 (42)	11 (85)	<0.01
	(n = 35)	(n = 25)	(n = 10)	
Endothelium-independent CMD	24 (69)	17 (68)	7 (70)	0.91
CFR	2.1 [1.3-2.7]	2.4 [1.3-2.8]	1.8 [1.6-2.3]	0.41
CFR <2.0	15 (43)	9 (24)	6 (43)	0.18
IMR	23 [13-39]	28 [18-42]	13 [12-23]	<0.01
IMR ≥25	18 (51)	15 (39)	3 (21)	0.23

	(n = 22)	(n = 18)	(n = 4)	
Endothelium-dependent CMD	4 (18)	4 (22)	0 (0)	0.30
	(n = 39)	(n = 27)	(n =12)	
LVEDP (mmHg)	11 [8-15]	11 [8-15]	11 [9-12]	0.82
LVEDP ≥12 mmHg	15 (38)	13 (48)	2 (17)	0.062

Values are mean [standard deviation], median [Q1-Q3], or n (%). CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance; IMR, index of microcirculatory resistance; LVEDP, left ventricular end-diastolic pressure.

Table 8-7: Invasive coronary angiography, physiology and haemodynamics stratified by CMR-proven MI.

8.3 Correlates of previous myocardial infarction

Table 8-8 describes the correlates of CMR-proven MI. Ischaemic LGE was associated with a past history of CAD (φ = 0.38; p <0.01), MI (φ = 0.46; p <0.001), and revascularisation (φ = 0.36; p <0.01) and was inversely correlated with AF (φ = -0.38; p <0.01). CMR-proven MI was associated with obstructive epicardial CAD on invasive angiography (φ = 0.39; p <0.01) and was negatively correlated with non-ischaemic LGE (φ = -0.30; p = 0.03) and IMR (r_{pb} = 0.42; p = 0.012).

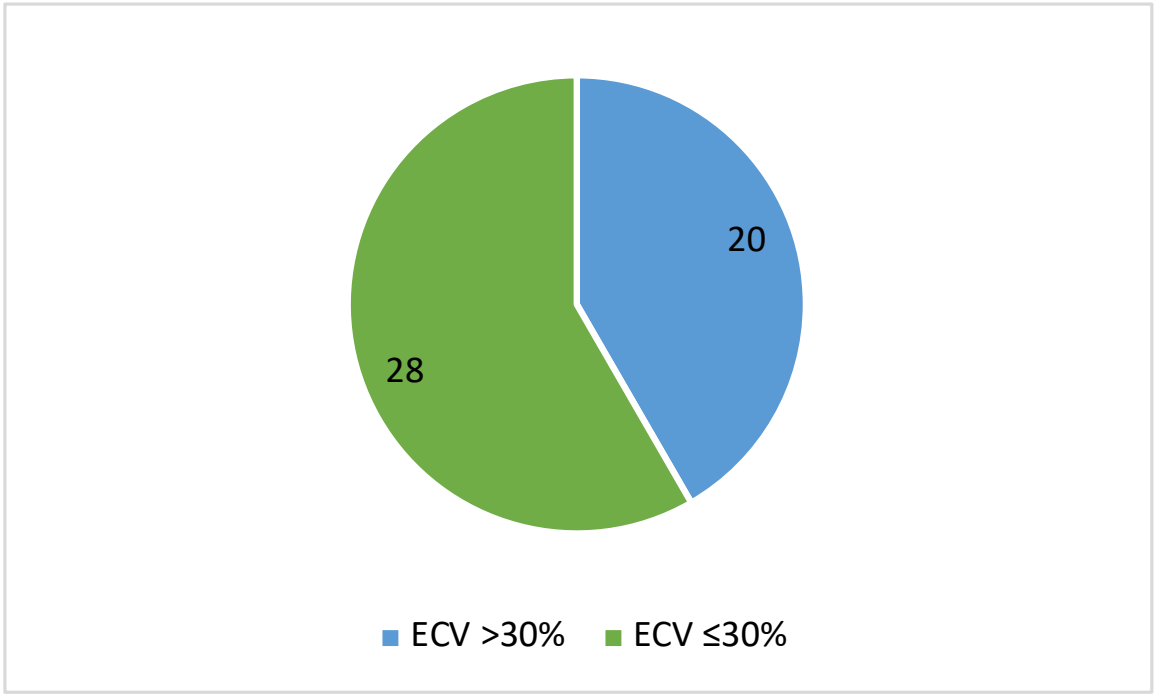
	CMR-proven MI	p-value
History of CAD	0.38	<0.01
History of MI	0.46	<0.001
History of revascularisation	0.36	<0.01
AF	-0.38	<0.01
Non-ischaemic LGE	-0.30	0.03
Obstructive CAD	0.39	<0.01
Endothelium-independent CMD	0.02	0.91
IMR	-0.42	0.012
Endothelium-dependent CMD	-0.22	0.32

AF, atrial fibrillation; CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; ECV, extracellular volume; hsTnI, high-sensitivity troponin I; IMR, index of microcirculatory resistance; LGE, late gadolinium enhancement; LVEDP, left ventricular end-diastolic pressure; MI, myocardial infarction.

Table 8-8: Correlates of CMR-proven MI.

8.4 Extracellular volume

A total of 48 patients had pre- and post-contrast T1 mapping for quantification of extracellular volume (ECV). Of these, 20 (42% [95% CI 28-56%]) had an elevated ECV (defined as an ECV >30%), consistent with diffuse myocardial fibrosis (Figure 8-3).



ECV, extracellular volume.

Figure 8-3: Study participants stratified by ECV.

8.4.1 Baseline characteristics

Table 8-9 details selected baseline characteristics of patients stratified by ECV. The baseline demographics of both groups were similar but those with a high ECV had a lower BMI (mean 29 vs. 33 kg/m^2; p = 0.033) and had a longer hospital stay (median 10 vs. 6 days; p <0.01) than those with a normal ECV. Symptoms and signs of HF were not significantly different between the groups.

Those with a normal and abnormal ECV had similar rates of a pre-existing HF diagnosis, previous HF hospitalisation and previous CAD. Other major comorbidities were not significantly different between those with a normal and high ECV.

Patients with a high ECV more frequently had T-wave inversion on ECG than those with a normal ECV (75% vs. 25%; p <0.001, respectively). Haematology and biochemistry laboratory results were generally fairly similar, and there were no statistically significant differences in echocardiography findings between the groups.

	All ECV (n = 48)	ECV ≤30% (n = 28)	ECV >30% (n = 20)	p-value
Demographics				
Age (years)	72 [9]	72 [8]	73 [11]	0.83
Female sex	22 (46)	15 (54)	7 (35)	0.20
BMI (kg/m^2)	32 [6]	33 [6]	29 [6]	0.033
Hospitalisation details				
Length of stay (days)	7 [5-11]	6 [4-9]	10 [7-14]	<0.01
History of CAD				
Any CAD	15 (31)	8 (29)	7 (35)	0.64
MI	8 (17)	4 (14)	4 (20)	0.60
Revascularisation	7 (15)	6 (21)	1 (5)	0.11
ECG				
T-wave inversion	22 (46)	7 (25)	15 (75)	<0.001
Biochemistry				
NT-proBNP (pg/mL)	1915 [978-4535]	1385 [1171-2819]	3252 [570-9000]	0.51
BNP (pg/mL)	376 [197-856]	301 [200-725]	785 [197-1684]	0.25
hsTnI (ng/L)	16 [7-34]	16 [4-33]	19 [13-34]	0.40
CRP (mg/L)	11 [7-20]	10 [7-17]	16 [5-30]	0.36
Echocardiography				
LVEDV (mL/m^2)	43 [16]	39 [13]	48 [18]	0.069
LVESV (mL/m^2)	18 [8]	16 [7]	20 [9]	0.074
LVEF (%)	59 [7]	60 [7]	58 [7]	0.30
LVH	28 (58)	16 (57)	12 (60)	0.84
Diastolic dysfunction	25 (58)	13 (48)	12 (75)	0.084
LA dilatation	41 (85)	24 (86)	17 (85)	0.94

Values are mean [standard deviation], median [Q1-Q3], or n (%). BMI, body mass index; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CRP, C-reactive protein; ECV, extracellular volume; hsTnI, high-sensitivity troponin I; LA, left atrial; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVH, left ventricular hypertrophy; MI, myocardial infarction; NT-proBNP, N-terminal prohormone BNP.

Table 8-9: Baseline investigation results stratified by ECV.

8.4.2 Study investigations

Table 8-10 details the CMR and invasive coronary assessment findings stratified by ECV. Those with increased ECV had more LVH (75% vs. 43%; p = 0.027) and larger RV volumes (RVEDV 93 vs. 73 mL/m^2; p = 0.018, and RVESV 49 vs. 39

mL/m^2; p = 0.036) than those with a normal ECV. Patients with a high ECV had had a lower MPRI than those with a normal ECV (median 1.37 vs. 1.70; p = 0.012, respectively). Those with a high ECV were much more likely to have obstructive CAD on angiography than those with a normal ECV (78% vs. 36%; p <0.01, respectively). The frequency of endothelium-independent and -dependent CMD were similar in both groups.

	All ECV (n = 48)	**ECV ≤30% (n = 28)**	**ECV >30% (n = 20)**	**p-value**
CMR				
LVEF (%)	61 [7]	61 [7]	60 [7]	0.74
LV mass (g/m^2)	68 [21]	64 [16]	75 [25]	0.061
LVH	27 (56)	12 (43)	15 (75)	0.027
LA dilatation	33 (69)	20 (71)	13 (65)	0.64
RVEDV (mL/m^2)	81 [29]	73 [22]	93 [34]	0.018
RVESV (mL/m^2)	38 [17]	39 [11]	49 [20]	0.036
Ischaemic LGE	13 (27)	5 (18)	8 (40)	0.089
Non-ischaemic LGE	18 (38)	9 (32)	9 (45)	0.36
MPRI	1.52 [1.37-1.86]	1.70 [1.47-1.97]	1.37 [1.26-1.55]	0.012
MPRI <1.4	13 (32)	4 (17)	9 (53)	0.018
Invasive coronary assessment				
	(n = 40)	(n = 22)	(n = 18)	
Obstructive epicardial CAD	22 (55)	8 (36)	14 (78)	<0.01
	(n = 31)	(n = 19)	(n = 12)	
Endothelium-independent CMD	22 (71)	14 (74)	8 (67)	0.68
CFR	2.3 [1.6-2.7]	2.3 [1.5-2.8]	2.2 [1.8-2.5]	0.90
CFR <2.0	13 (42)	8 (42)	5 (42)	0.98
IMR	23 [13-40]	28 [14-45]	18 [13-23]	0.096
IMR ≥25	17 (55)	13 (68)	4 (33)	0.056
	(n = 20)	(n = 14)	(n = 6)	
Endothelium-dependent CMD	4 (20)	3 (21)	1 (17)	0.81
	(n = 35)	(n = 20)	(n = 15)	
LVEDP (mmHg)	10 [8-15]	10 [9-15]	11 [7-15]	0.95

Values are mean [standard deviation], median [Q1-Q3], or n (%). CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance; ECV, extracellular volume; IMR, index of microcirculatory resistance; LA, left atrial; LGE, late gadolinium enhancement; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MPRI, myocardial-perfusion reserve index; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume.

Table 8-10: CMR and invasive coronary assessment findings stratified by ECV.

8.4.3 Correlates of extracellular volume

Tables 8-11 and 8-12 summarise the correlates of ECV expressed as a binary and continuous variable, respectively. An elevated ECV (>30%) was strongly correlated with obstructive CAD (φ = 0.41; p <0.01) and was inversely associated with BMI (r_{pb} = -0.31; p = 0.033), MPRI (r_{pb} = -0.38; p = 0.017) and IMR (r_{pb} = -0.38; p = 0.036).

	ECV >30%	p-value
BMI (kg/m^2)	-0.31	0.033
MPRI	-0.38	0.017
MPRI <1.4	0.38	0.017
Obstructive CAD	0.41	<0.01
Endothelium-independent CMD	-0.075	0.69
IMR	-0.38	0.036
IMR ≥25	-0.27	0.061
Endothelium-dependent CMD	-0.055	0.82

BMI, body mass index; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance; ECV, extracellular volume; IMR, index of microcirculatory resistance; LGE, late gadolinium enhancement; LV, left ventricular; MPRI, myocardial-perfusion reserve index.

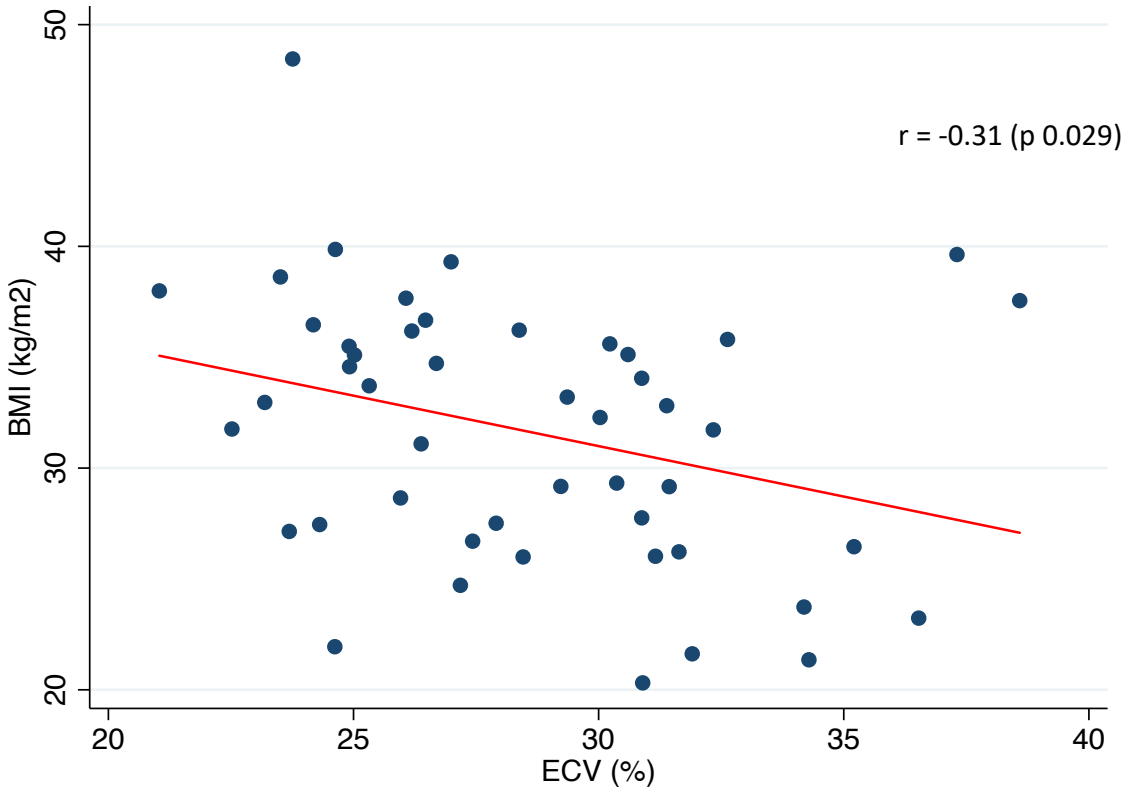
Table 8-11: Correlates of ECV >30% (binary).

When expressed as a continuous variable, ECV was associated with obstructive CAD (r_{pb} = 0.40; p = 0.011) and was inversely correlated with BMI (r = -0.31; p = 0.029) (Figure 8-4), MPRI (r = -0.41; p <0.01), IMR (r = -0.41; p = 0.023) and a high IMR (r_{pb} = -0.40; p <0.01).

	ECV	p-value
BMI (kg/m^2)	-0.31	0.029
MPRI	-0.41	<0.01
MPRI <1.4	0.34	0.032
Obstructive CAD	0.40	0.011
Endothelium-independent CMD	-0.22	0.23
IMR	-0.41	0.023
IMR ≥25	-0.40	<0.01
Endothelium-dependent CMD	0.037	0.88

BMI, body mass index; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance; CRP, C-reactive protein; ECV, extracellular volume; IMR, index of microcirculatory resistance; LGE, late gadolinium enhancement; LVEDV, left ventricular end-diastolic volume; MPRI, myocardial-perfusion reserve index.

Table 8-12: Correlates of ECV (continuous).

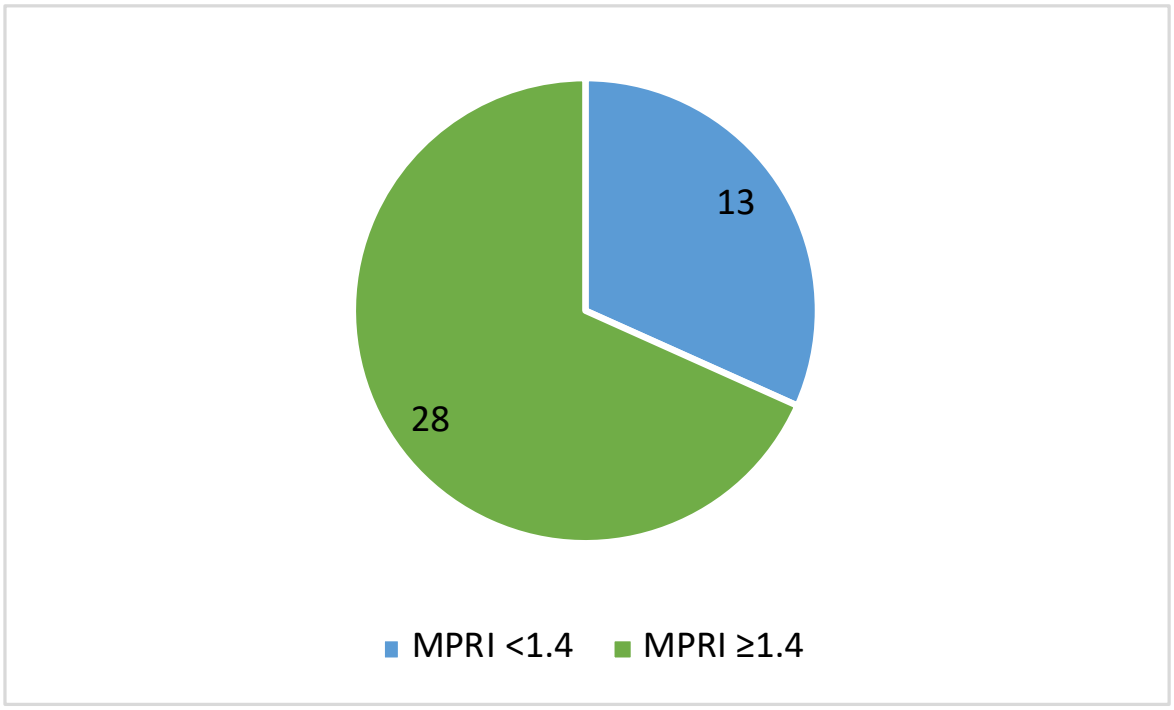


BMI, body mass index; ECV, extracellular volume.

Figure 8-4: Scatterplot of ECV correlation with BMI.

8.5 Myocardial-perfusion reserve index

Forty-six participants had rest and adenosine stress perfusion imaging, of whom 41 had suitable imaging for semi-quantitative assessment of myocardial-perfusion reserve index (MPRI). Thirteen of the 41 participants had a global MPRI <1.4 (32% [95% CI 19-48%]), consistent with inducible myocardial ischaemia (Figure 8-5).



MPRI, myocardial-perfusion reserve index.

Figure 8-5: Study participants stratified by MPRI.

8.5.1 Baseline characteristics

Selected baseline characteristics of participants based on the presence or absence of inducible ischaemia on CMR are presented in Table 8-13. There were no major differences in baseline demographics or past medical history based on MPRI, with the exception of a smoking history which was significantly more prevalent in those with an abnormal compared with a normal MPRI (77% vs. 36%; p = 0.014, respectively).

Natriuretic peptides and hsTnI levels were similar in both groups. The median CRP was lower in those with an abnormal than normal MPRI (7 vs. 13 mg/L; p = 0.041, respectively), but the proportion of patients with an elevated CRP was

not significantly different (46% vs. 54%; p = 0.66, respectively). Echocardiography findings were similar in both groups.

	All MPRI (n = 41)	MPRI <1.4 (n = 28)	MPRI ≥1.4 (n = 13)	p-value
Demographics				
Age (years)	74 [8]	73 [8]	75 [9]	0.44
Female sex	18 (44)	13 (46)	5 (38)	0.63
BMI (kg/m^2)	30 [5]	31 [5]	29 [5]	0.35
Smoking history	20 (49)	10 (36)	10 (77)	0.014
CAD history				
Any CAD	14 (34)	9 (32)	5 (38)	0.69
MI	7 (17)	6 (21)	1 (8)	0.28
Revascularisation	9 (22)	7 (25)	2 (15)	0.49
Biochemistry				
NT-proBNP (pg/mL)	2079 [912-4960]	1915 [978-4535]	2242 [570-5385]	0.97
BNP (pg/mL)	421 [197-856]	465 [233-801]	197 [147-856]	0.37
hsTnI (ng/L)	18 [9-36]	16 [5-38]	24 [14-36]	0.33
Elevated hsTnI (ng/L)	10 (33)	8 (35)	2 (29)	0.76
CRP (mg/L)	11 [6-22]	13 [7-36]	7 [3-16]	0.041
Elevated CRP	21 (51)	15 (54)	6 (46)	0.66
Echocardiography				
LVEF (%)	59 [7]	60 [7]	57 [6]	0.15
LVH	27 (66)	20 (71)	7 (54)	0.27
Diastolic dysfunction	24 (63)	15 (58)	9 (75)	0.30
LA dilatation	36 (88)	25 (89)	11 (85)	0.67

Values are mean [standard deviation], median [Q1-Q3], or n (%). BMI, body mass index; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CRP, C-reactive protein; ECG, electrocardiogram; hsTnI, high-sensitivity troponin I; LA, left atrial; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MI, myocardial infarction; MPRI, myocardial-perfusion reserve index; NT-proBNP, N-terminal prohormone BNP.

Table 8-13: Selected baseline characteristics stratified by MPRI.

8.5.2 Study investigations

Table 8-14 summarises the CMR findings based on the presence or absence of an inducible ischaemia. There was no significant difference in cardiac structure of function on volumetric analysis. Rates of both ischaemic and non-ischaemic LGE were similar in those with and without inducible ischaemia, but ECV was significantly higher in those with abnormal compared with normal global MPRI (30.3% vs. 27.6%; p = 0.031, respectively).

Those with and without inducible ischaemia on CMR did not have significantly different rates of obstructive epicardial CAD on invasive coronary angiography (69% vs. 52%; p = 0.33, respectively). There were also similar rates of endothelium-independent (57% vs. 61%; p = 0.86) and -dependent CMD (0% vs. 18%; p = 0.36) in those with and without imaging evidence of inducible ischaemia.

	All MPRI (n = 41)	**MPRI <1.4 (n = 28)**	**MPRI ≥1.4 (n = 13)**	**p-value**
CMR				
LVEF (%)	61 [7]	60 [7]	62 [7]	0.55
LVH	23 (56)	14 (50)	9 (69)	0.25
LA dilatation	28 (68)	18 (64)	10 (77)	0.42
Any LGE	25 (61)	15 (54)	10 (77)	0.15
Ischaemic LGE	12 (29)	8 (29)	4 (31)	0.89
Non-ischaemic LGE	15 (37)	9 (32)	6 (46)	0.39
Native T1 (ms)	1288 [61]	1276 [51]	1314 [75]	0.06
ECV (%)	28.5 [3.7]	27.6 [3.6]	30.3 [3.3]	0.031
ECV >30%	17 (42)	8 (30)	9 (69)	0.018
Invasive coronary assessment				
	(n = 34)	(n = 21)	(n = 13)	
Obstructive CAD	20 (59)	11 (52)	9 (69)	0.33
	(n = 25)	(n = 18)	(n = 7)	
Endothelium-independent CMD	15 (60)	11 (61)	4 (57)	0.86
CFR	2.4 [1.8-2.7]	2.4 [1.8-2.7]	2.3 [1.1-3.1]	0.55
CFR <2.0	8 (20)	5 (18)	3 (23)	0.69
IMR	23 [13-32]	23 [13-39]	18 [13-32]	0.95
IMR ≥25	12 (29)	9 (32)	3 (23)	0.55
	(n = 15)	(n = 11)	(n = 4)	
Endothelium-dependent CMD	2 (13)	2 (18)	0 (0)	0.36
LVEDP (mmHg)	12 [10-15]	13 [9-15]	11 [10-18]	0.87

Values are mean [standard deviation], median [Q1-Q3], or n (%). CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance; ECV, extracellular volume; IMR, index of microcirculatory resistance; LA, left atrial; LGE, late gadolinium enhancement; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MPRI, myocardial-perfusion reserve index.

Table 8-14: CMR and invasive coronary assessment findings stratified by MPRI.

8.5.3 Correlates of myocardial-perfusion reserve index

Tables 8-15 and 8-16 summarise the correlates of MPRI as binary and continuous variable, respectively. An abnormally low MPRI was associated with a smoking history (φ = -0.38; p = 0.013) and an elevated ECV (φ = 0.38; p = 0.017).

	MPRI <1.4	p-value
Smoking history	0.38	0.013
ECV (%)	0.34	0.032
ECV >30%	0.38	0.017
Obstructive CAD	0.17	0.35
Endothelium-independent CMD	-0.036	0.86
Endothelium-dependent CMD	-0.24	0.40

CAD, coronary artery disease; CMD, coronary microvascular dysfunction; ECV, extracellular volume; MPRI, myocardial-perfusion reserve index.

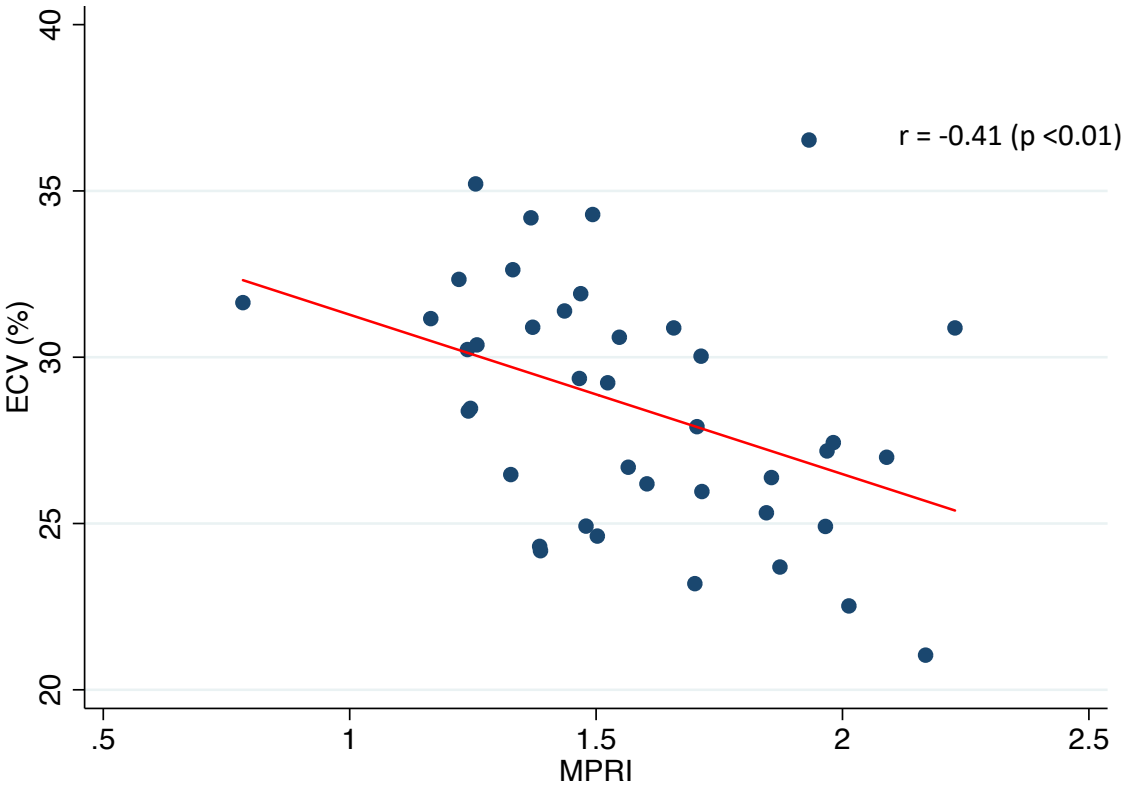
Table 8-15: Correlates of MPRI <1.4 (binary).

When expressed as a continuous variable, MPRI had a strong negative correlation with ECV (r = -0.41; p <0.01) (Figure 8-6) and a strong positive correlation with a previous history of MI (r_{pb} = 0.46; p <0.01).

	MPRI	p-value
History of MI	0.46	<0.01
ECV (%)	-0.41	<0.01
Elevated ECV (>30%)	-0.38	0.017
Obstructive CAD	-0.16	0.31
Endothelium-independent CMD	0.22	0.30
Endothelium-dependent CMD	0.04	0.89

CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance; ECV, extracellular volume; LA, left atrial; LVEDV, left ventricular end-diastolic volume; MI, myocardial infarction; MPRI, myocardial-perfusion reserve index.

Table 8-16: Correlates of MPRI (continuous).



ECV, extracellular volume; MPRI, myocardial-perfusion reserve index.

Figure 8-6: Scatterplot of MPRI correlation with ECV.

8.6 Outcomes related to cardiac magnetic resonance imaging findings

8.6.1 Previous myocardial infarction

Mortality

No differences in mortality were observed in those with or without ischaemic LGE on CMR (Figures 8-7, 8-8, 8-9, 8-10).

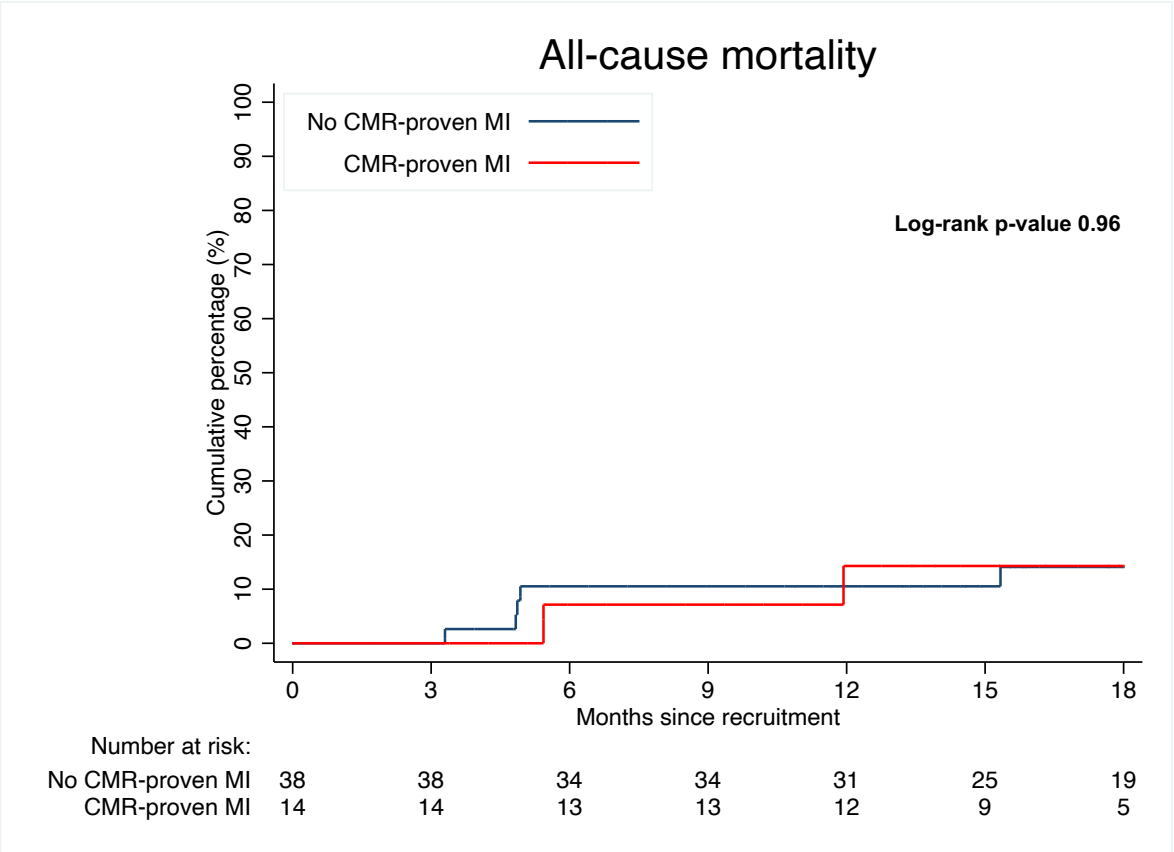


Figure 8-7: Kaplan-Meier curves for all-cause mortality by CMR-proven MI.

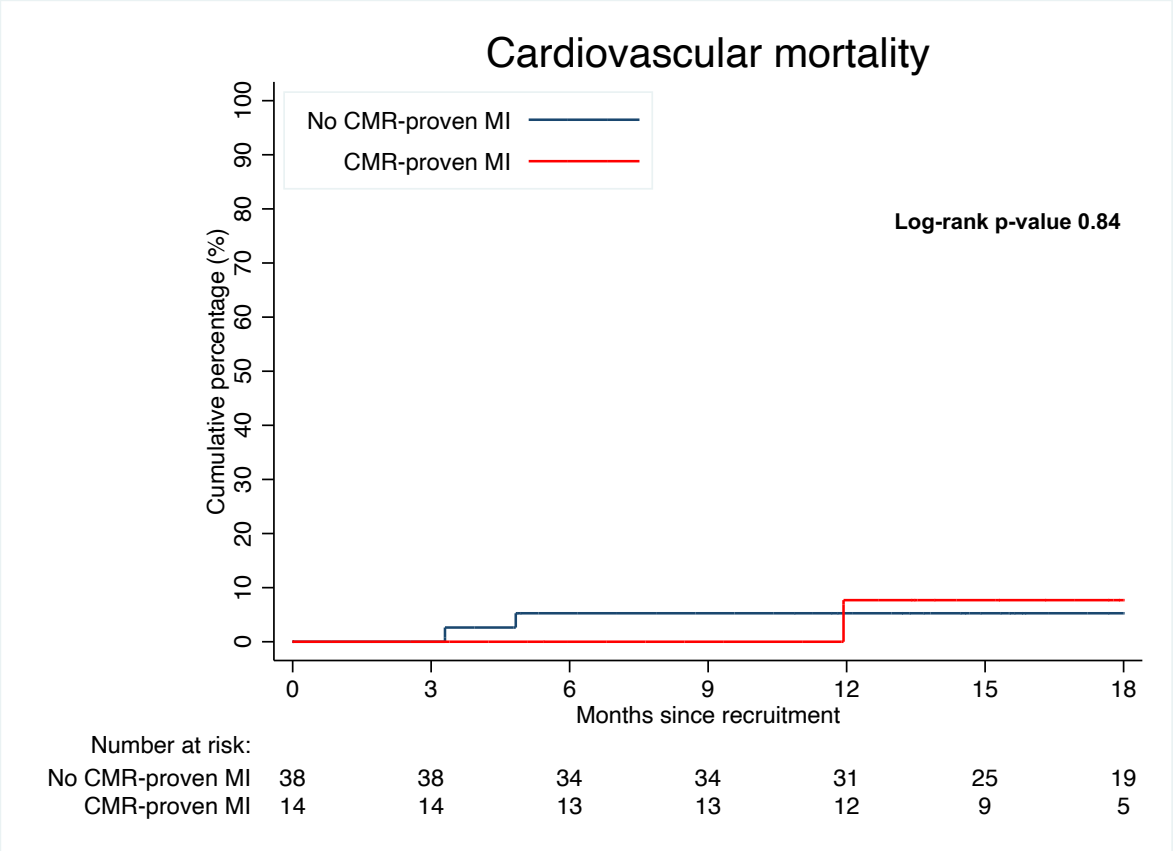


Figure 8-8: Kaplan-Meier curves for CV mortality by CMR-proven MI.

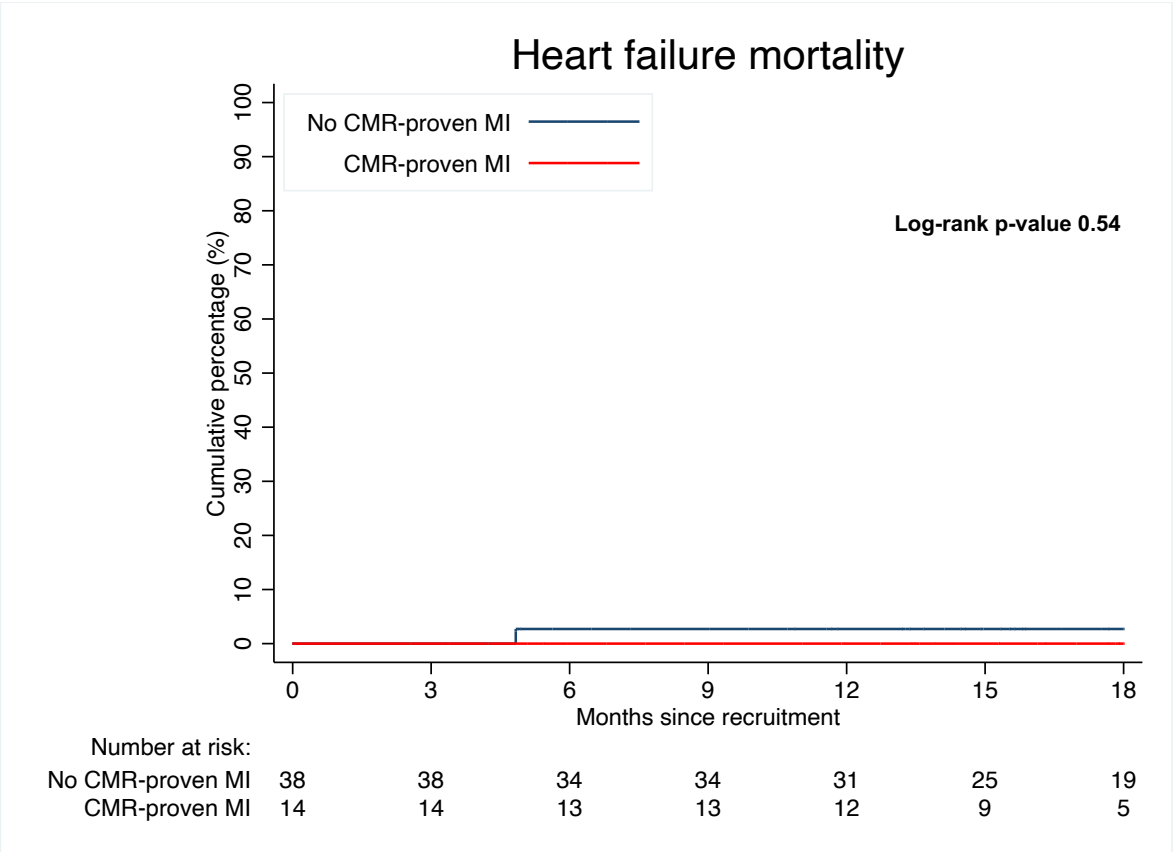


Figure 8-9: Kaplan-Meier curves for HF mortality by CMR-proven MI.

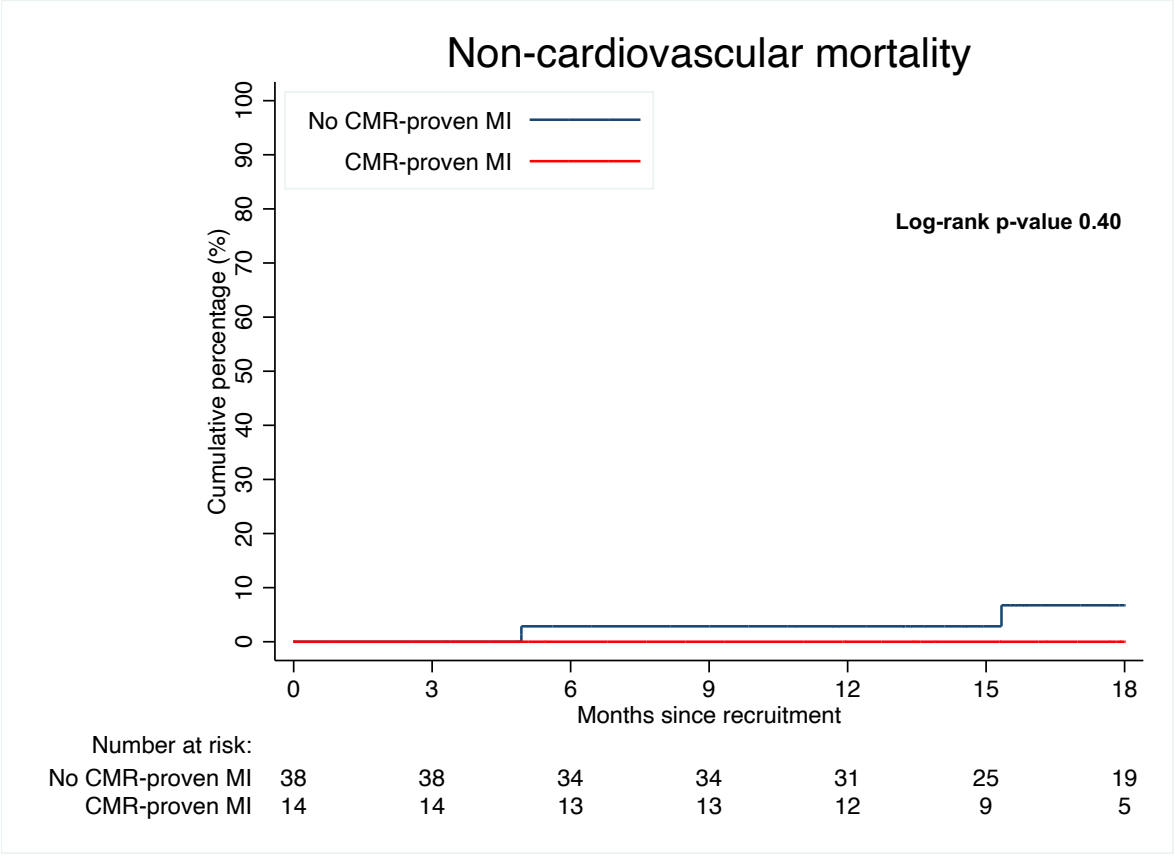


Figure 8-10: Kaplan-Meier curves for non-CV mortality by CMR-proven MI.

Hospitalisations

There were no significant differences in the rates of hospitalisations due to any cause, CV causes or HF between those with and without CMR-proven MI (Figures 8-11, 8-12, 8-13). However, those with CMR-proven MI had more non-CV hospitalisations than those without (Figure 8-14).

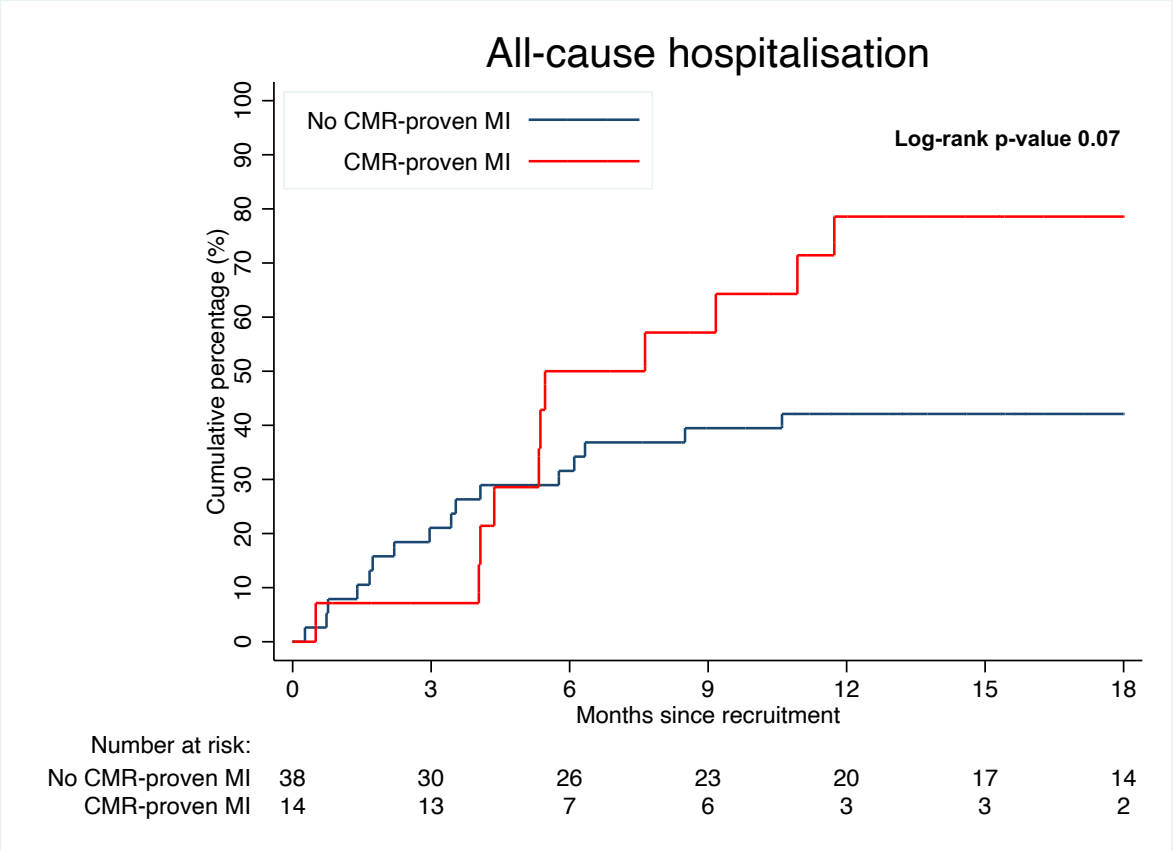


Figure 8-11: Kaplan-Meier curves for all-cause hospitalisation by CMR-proven MI.

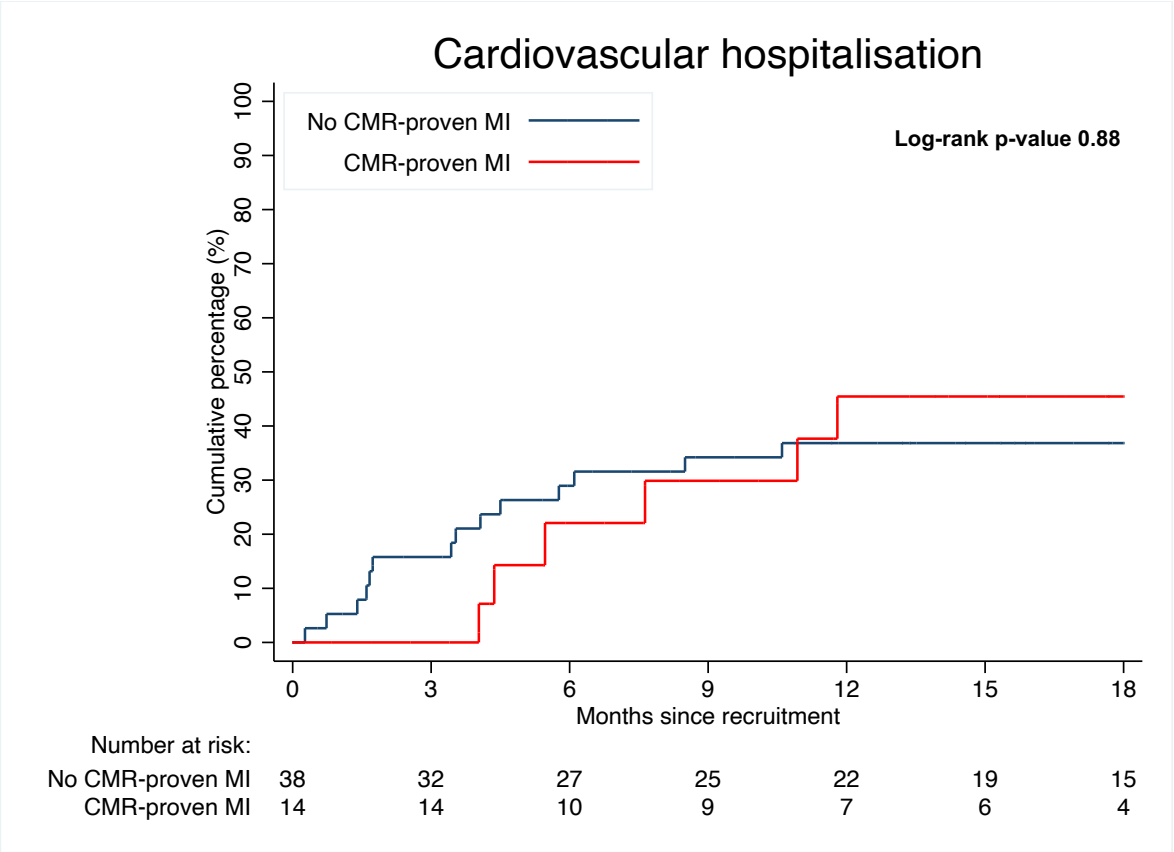


Figure 8-12: Kaplan-Meier curves for CV hospitalisation by CMR-proven MI.

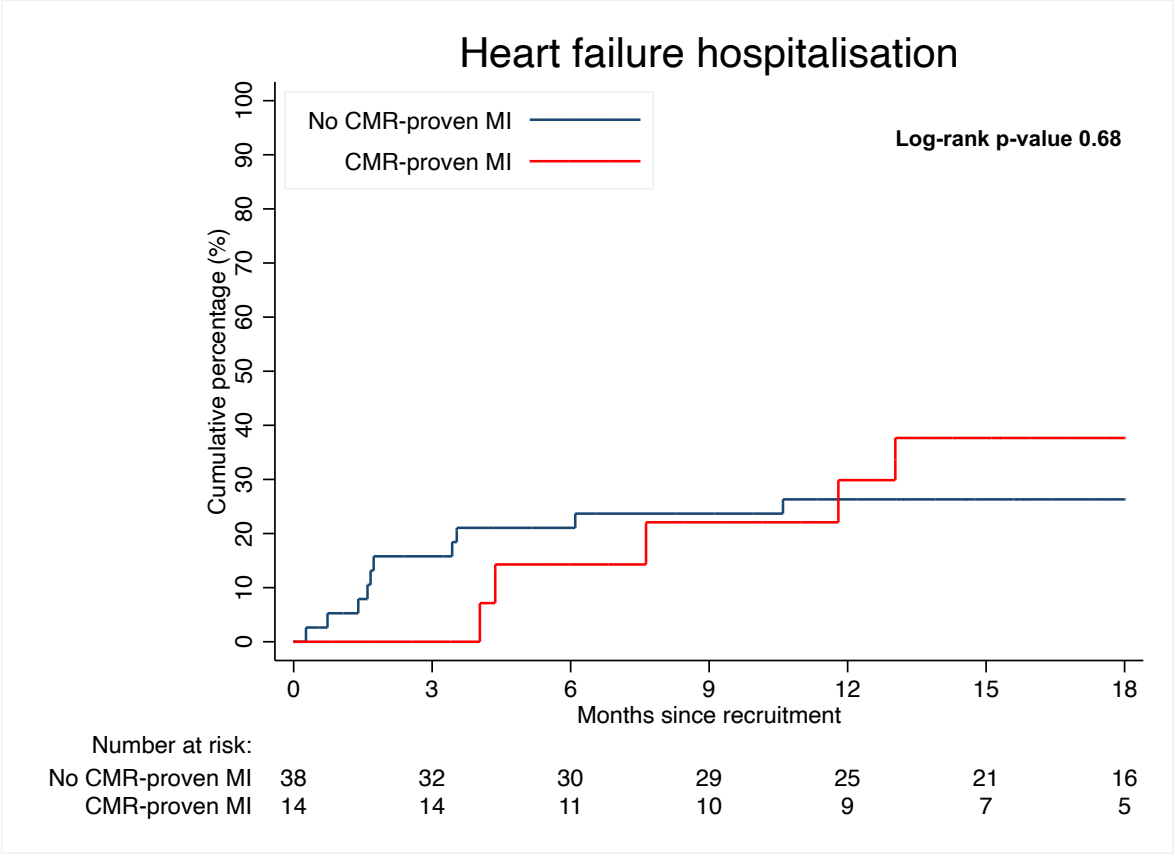


Figure 8-13: Kaplan-Meier curves for HF hospitalisation by CMR-proven MI.

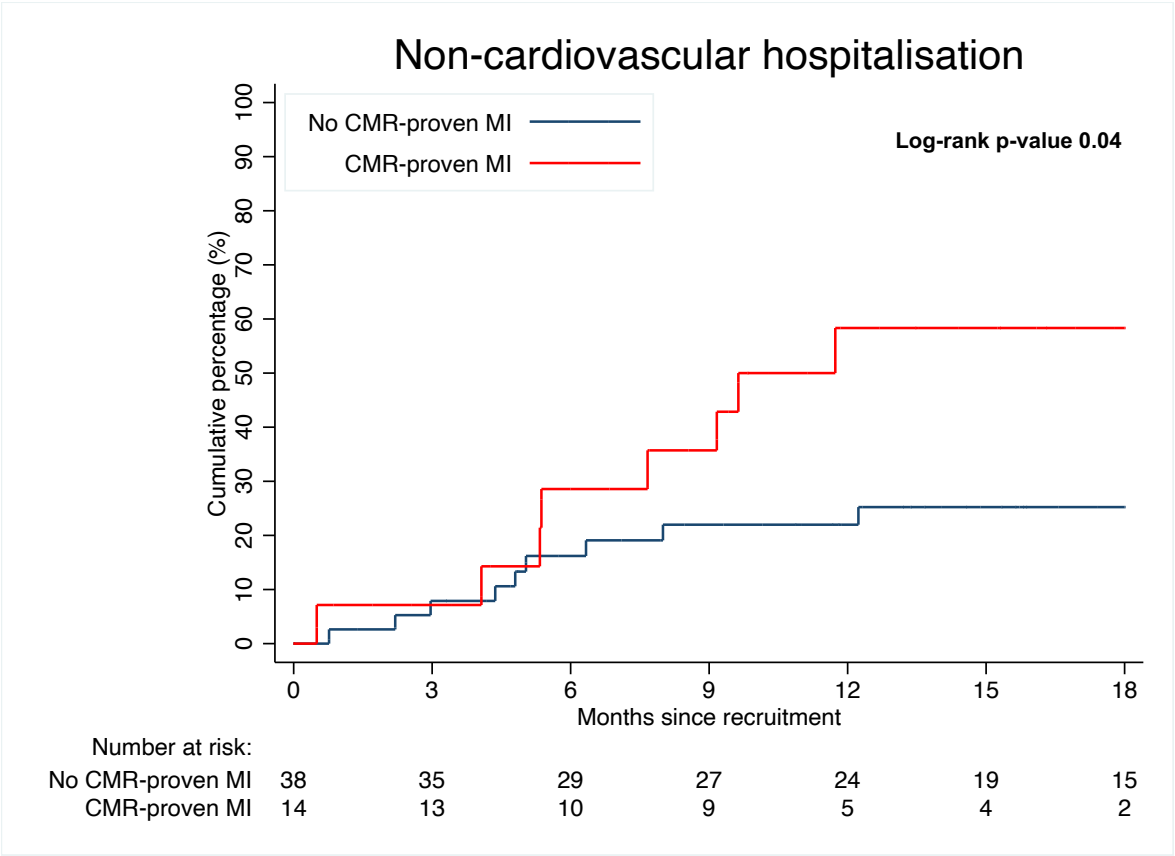


Figure 8-14: Kaplan-Meier curves for non-CV hospitalisation by CMR-proven MI.

8.6.2 Extracellular volume

Mortality and hospitalisations

There was no difference in mortality rates between those with a normal or elevated ECV (Figure 8-15). However, those with an elevated ECV had significantly more hospitalisations than those with a normal ECV (Figure 8-16), due to both CV (Figure 8-17) and non-CV reasons (Figure 8-18).

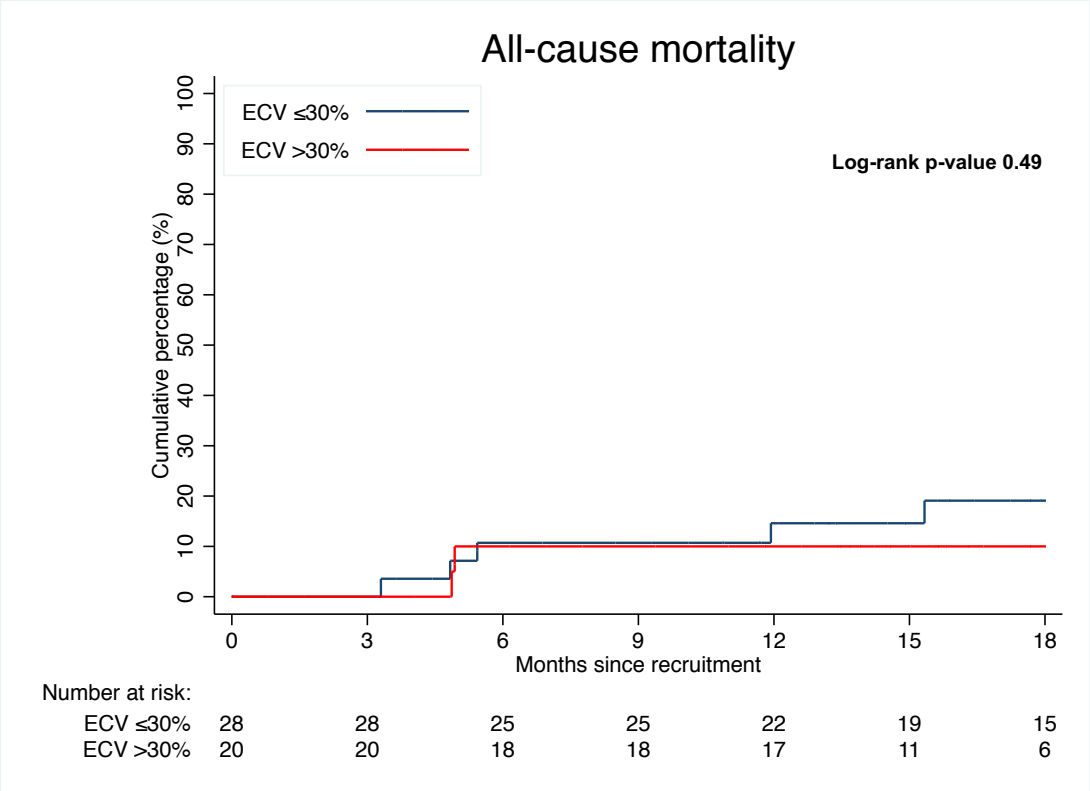


Figure 8-15: Kaplan-Meier curves for all-cause mortality by ECV.

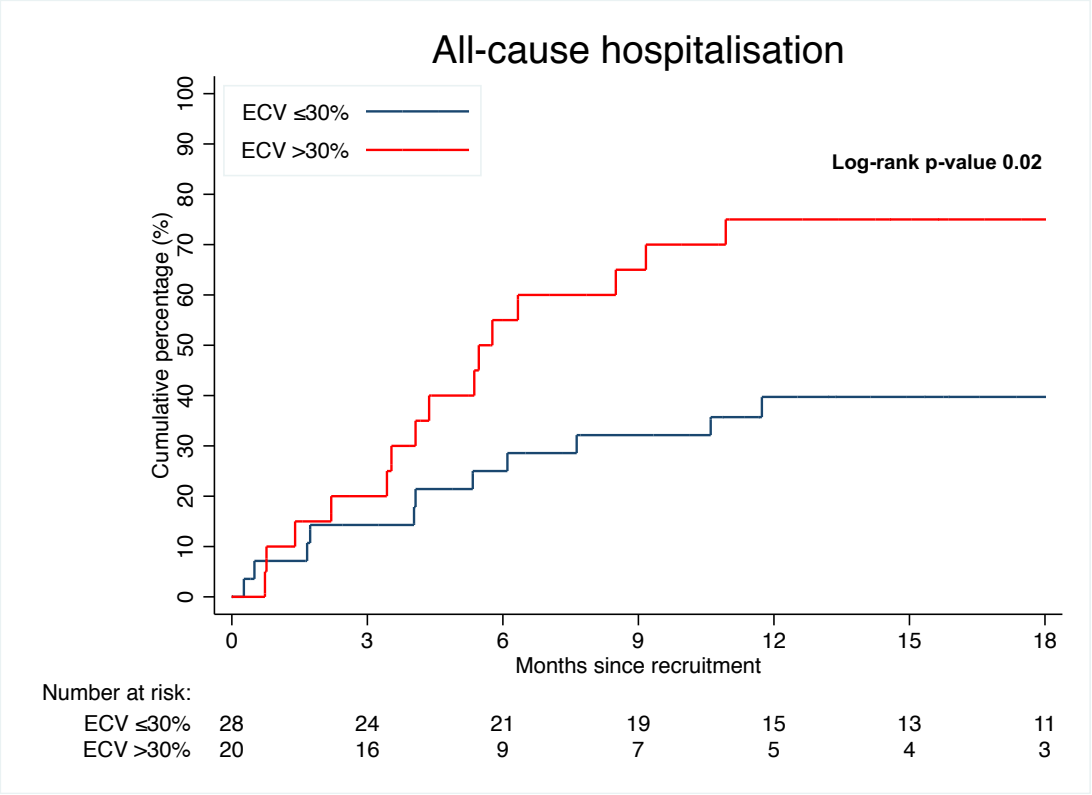


Figure 8-16: Kaplan-Meier curves for all-cause hospitalisation by ECV.

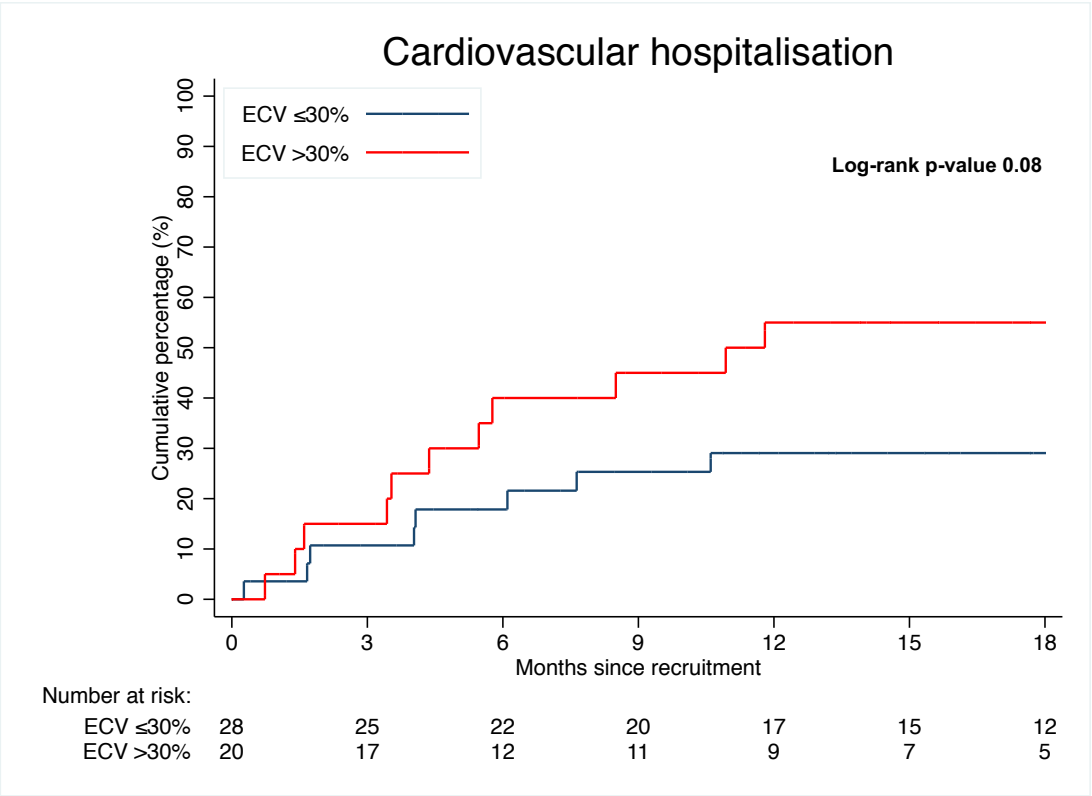


Figure 8-17: Kaplan-Meier curves for CV hospitalisation by ECV.

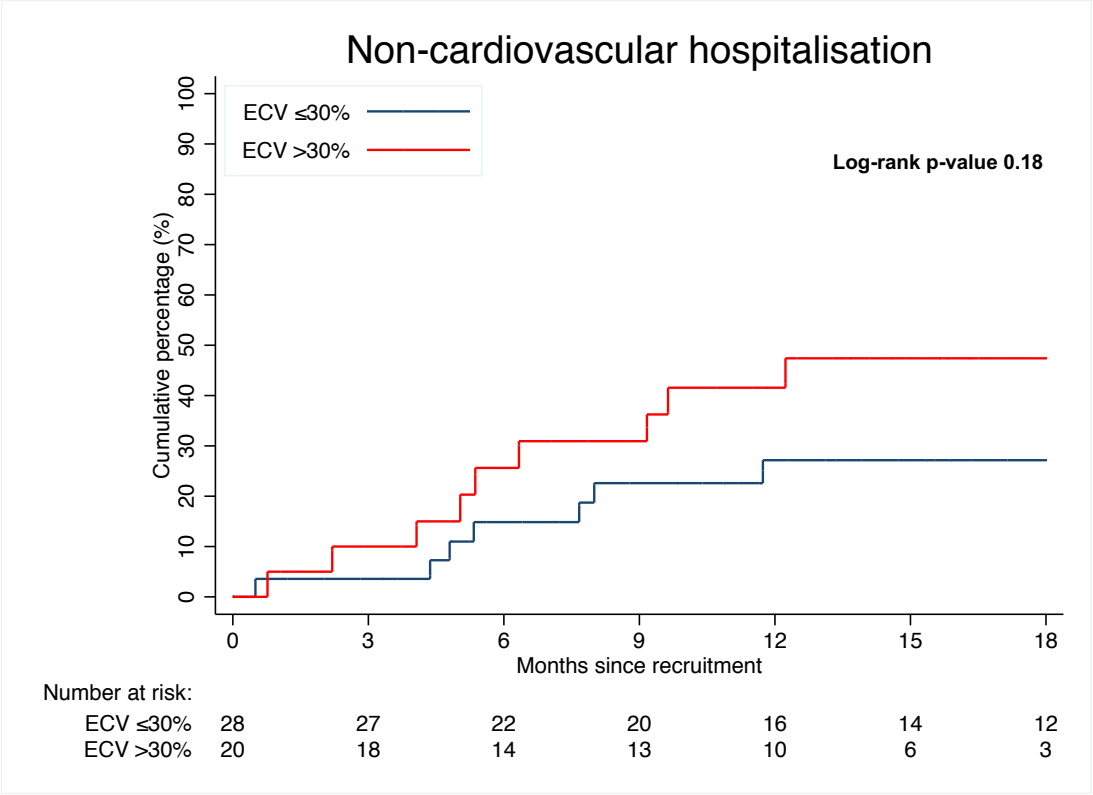


Figure 8-18: Kaplan-Meier curves for non-CV hospitalisation by ECV.

8.6.3 Myocardial-perfusion reserve index

Mortality and hospitalisations

There was no significant difference in mortality or hospitalisations between those with and without an MPRI <1.4 (Figures 8-19, 8-20).

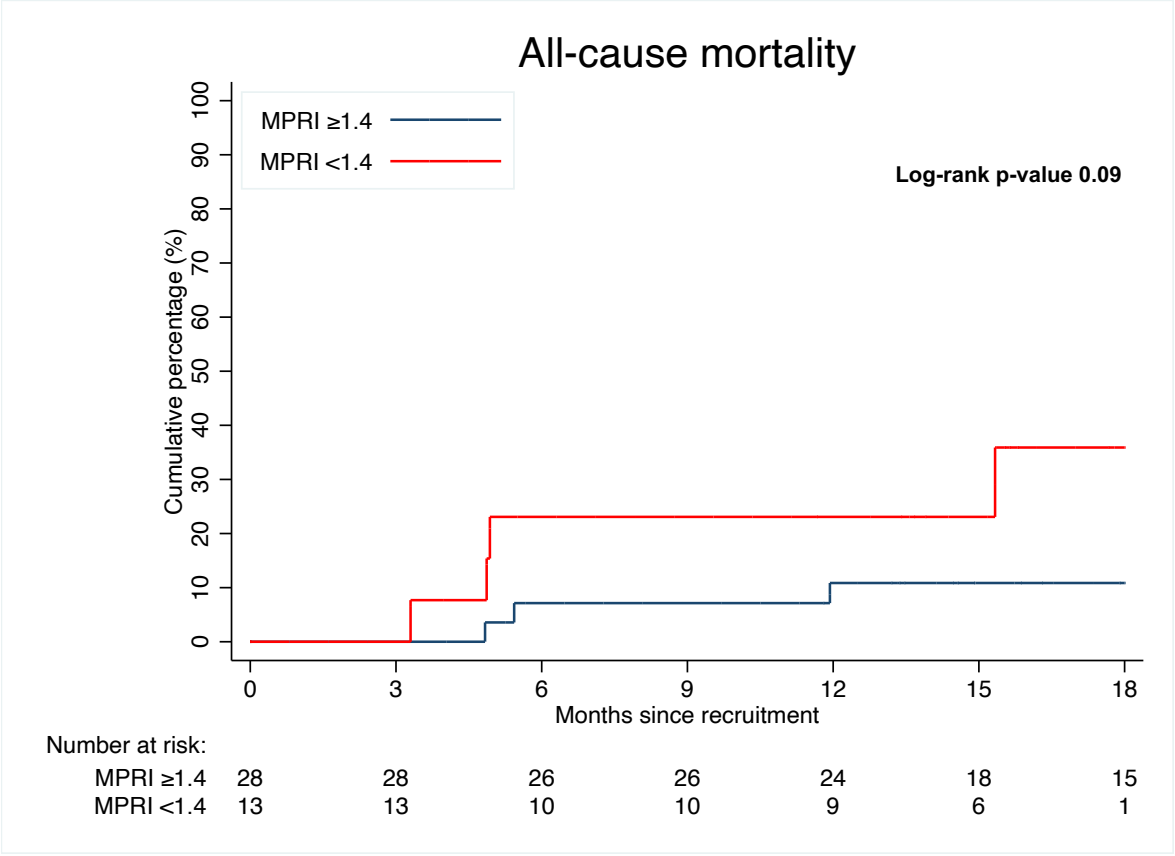


Figure 8-19: Kaplan-Meier curves for all-cause mortality by MPRI.

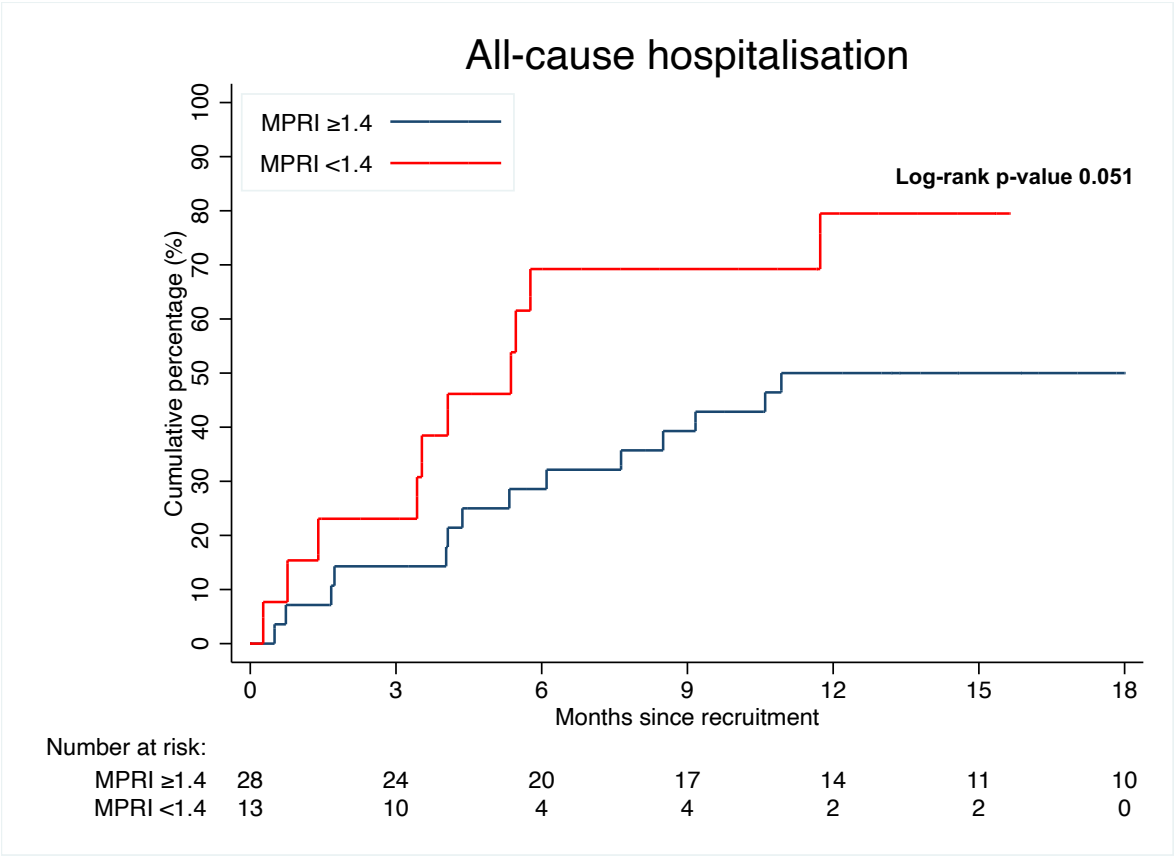


Figure 8-20: Kaplan-Meier curves for all-cause hospitalisation by MPRI.

8.7 Complications of cardiac magnetic resonance imaging

There were no adverse events related to CMR imaging. Five patients attended for CMR but were unable to tolerate the scan due to claustrophobia or back pain. A further four patients were unable to tolerate the entire CMR protocol, and these scans were truncated. Two patients were unable to be scanned due to significant magnetic interference with the surface ECG, making ECG gating impossible. The majority of patients (63%) experienced typical symptoms during the adenosine infusion (i.e. dyspnoea, chest tightness, flushing), all of which subsided with discontinuation of the infusion. No arrhythmia was documented in any patient during the adenosine infusion.

8.8 Summary

Of the 52 patients that underwent CMR, 14 (27%) had ischaemic LGE consistent with previous MI. As expected, those with ischaemic LGE more commonly had a previous clinical history of CAD, MI and coronary revascularisation, but had less AF, than those with no ischaemic LGE. Importantly, 57% of those with CMR-proven MI had no clinical history of MI and 18% of those with no history of MI had CMR-proven MI, suggesting a high burden of clinically unrecognised MI in the HFpEF population. Predictably, ischaemic LGE was associated with obstructive epicardial CAD. However, there was no difference in the prevalence of endothelium-independent or -dependent CMD between the those with and without CMR evidence of MI.

Of the 48 participants that had pre- and post-contrast T1 mapping, 20 (42%) had an elevated ECV (>30%) consistent with diffuse myocardial fibrosis. Those with a high ECV had a lower BMI and longer hospital stay than those with a normal ECV. Patients with an elevated ECV had more T-wave inversion on ECG and LVH on CMR than those with a normal ECV, raising the possibility that some patients with a high ECV had an underlying cardiomyopathy. Indeed, a single-centre study reported that 13% of patients hospitalised with HFpEF had wild-type transthyretin-related amyloidosis (ATTR).[268] This is a particularly relevant in light of recent evidence that tafamidis has prognostic and symptomatic in patients with ATTR.[268] Although it is possible that some study participants could

have had clinically unrecognised ATTR, patients with a strong clinical suspicion of hypertrophic or infiltrative cardiomyopathy were excluded from the study (see Chapter 3). Furthermore, none of the study participants had echocardiographic features of hypertrophic/infiltrative cardiomyopathy or a typical LGE pattern suggestive of cardiac amyloidosis. In two study participants, the CMR LGE/ECV findings prompted further evaluation with ^{99m}Tc-DPD scintigraphy, both of which were negative for ATTR. An elevated ECV was strongly correlated with obstructive epicardial CAD (see Chapter 5). The frequency of endothelium-independent and -dependent CMD was similar in those with a normal and abnormal ECV, however, ECV was inversely associated with IMR (see Chapter 6).

Thirteen of the 41 participants (32%) that had semi-quantitative perfusion imaging had evidence of inducible myocardial ischaemia (i.e. global MPRI <1.4). Those with inducible ischaemia were more likely to have a smoking history than those without. MPRI had a strong negative correlation with ECV, suggesting that chronic ischaemia may contribute to diffuse myocardial fibrosis in HFpEF. Interestingly, those with and without inducible ischaemia on CMR did not have significantly different rates of obstructive epicardial CAD on invasive coronary angiography. Similarly, there was no significant difference in rates of either endothelium-independent or -dependent CMD between those with and without inducible ischaemia. The reason why MPRI did not identify patients with obstructive CAD is uncertain but it may be due to the presence of CMD, the absence of reversible ischaemia in the context of non-viable myocardium, or collateral perfusion of a territory supplied by a stenosed or occluded epicardial coronary artery. There is no general consensus regarding the MPRI threshold used to define ischaemia with variable thresholds used in different studies, therefore, a different cut-point may have had better diagnostic accuracy.[269] Furthermore, I assessed global MPRI which may not be significantly influenced by limited areas of myocardial ischaemia. MPRI assessed on the coronary artery territory level may have better identified those with and without regional ischaemia.

No difference in mortality was observed in those with or without ischaemic LGE on CMR, however, those with CMR-proven MI had more non-CV hospitalisations than those without. The reason for this is unclear, but it may be related to the

higher burden of non-CV comorbidities in the MI group. Those with an elevated ECV had significantly more hospitalisations than those with a normal ECV, suggesting that ECV may represent a non-invasive prognostic biomarker in HFpEF.

Chapter 9 Discussion

9.1 Main findings

Heart failure is a major cause of morbidity and mortality worldwide. Although estimates of the prevalence of HFpEF vary by the study population, study design and LVEF cut-off used, most studies report that HFpEF now accounts for around half of the HF population.[270] While outcomes in HFpEF appear better than in HFrEF, hospitalisation and mortality rates remain high.[8] In contrast to HFrEF, no treatment has so far been shown to provide clear prognostic benefit in patients with HFpEF, and outcomes have not improved in recent decades.[18]

The heterogeneity of the HFpEF population and the consistently neutral results of RCTs has led many to argue that a "one-size-fits-all" treatment is unlikely to demonstrate benefit in unselected patients with HFpEF.[271] Instead, establishing the sub-phenotype of HFpEF (e.g. those with a specific CV abnormality or comorbidity) might identify more homogeneous groups that could gain benefit from specific treatments.

Recent studies suggest that CAD and CMD may play an important role in a substantial group of patients with HFpEF.[148,231] The systematic literature review presented in Chapter 2 found disparate and inconsistent prevalence estimates of CAD in HFpEF cohorts. Similarly, studies assessing CMD in HFpEF have reported variable results due to heterogenous definitions of CMD and methods of assessing coronary microvascular function. Despite the popular hypothesis that coronary endothelial dysfunction plays a central role in the pathophysiology of HFpEF, the evidence for this is currently limited.[61] This prospective, multicentre study is the first to systematically assess the prevalence of CAD, CMD and coronary endothelial dysfunction in an unselected HFpEF cohort using reference standard invasive investigations.

I screened a total of 2285 near-consecutive patients hospitalised with suspected HF. Of these, 628 (27%) were confirmed to have a diagnosis of HFpEF. 106 HFpEF patients (17%) met the inclusion criteria and agreed to participate in the study. The major reasons for exclusion were significant frailty (i.e. CFS [Clinical Frailty Scale] >6; n = 196, 38%), severe renal impairment (i.e. eGFR <30

mL/min/1.73m^2; n = 104, 20%), and lack of capacity to consent (n = 88, 17%). Patients with HFpEF who were excluded from the study were significantly older, more often female, and had higher BNP levels than those who were recruited. Twenty-three patients (22% of those enrolled) did not undergo invasive coronary angiography or CMR, predominantly due to a decline in participants' health, functional status or renal function making proceeding with the study investigations inappropriate or unsafe. Those who did not proceed to the study investigations had a longer hospital stay than those that underwent the study investigations (median 12 vs. 7 days; p = 0.004, respectively). There were no other significant differences in the baseline demographics or investigation results between the groups. Overall, a total of 83 participants (78%) underwent invasive coronary angiography or CMR. Seventy-five participants (71%) underwent invasive coronary angiography, 62 (58%) had guidewire-based coronary physiology testing, and 41 (39%) underwent vasoreactivity testing. Fifty-two participants (49%) underwent CMR and 44 (42%) had both invasive coronary angiography and CMR.

The mean age of the participants was 72 years and 50% were female. Almost all patients were Caucasian, with only 3% coming from minority ethnic backgrounds. Half of patients were obese, with a mean BMI of 33 kg/m^2, and there was a high burden of frailty (39% had a CFS score ≥4). Almost all participants (98%) were in NYHA class III or IV at presentation and two-thirds had a *de novo* diagnosis of HF. Thirty percent of patients had a previous history of CAD, 23% had a previous MI and 19% had previously had coronary revascularisation. The typical comorbidities associated with HFpEF were highly prevalent in the cohort, including hypertension (75%), AF (62%) and diabetes (51%). The mean LVEF on echocardiography was 59% and natriuretic peptides were significantly elevated (median BNP 382 pg/mL and NT-proBNP 1532 pg/mL). The vast majority of patients (92%) had structural heart disease (i.e. LVH or LA dilatation), and the remainder had diastolic dysfunction. Overall, I feel that my study population is representative of 'real world' patients hospitalised with HFpEF.

9.1.1 Obstructive epicardial CAD in HFpEF

In this hospitalised HFpEF cohort, the prevalence of obstructive epicardial CAD on invasive assessment was 51%. In population studies and RCTs, CAD is reported to be present in 40-50% of patients with HFpEF (see Chapter 2). Studies which document CAD angiographically report higher rates, however, these have almost exclusively been carried out on convenience cohorts undergoing clinically indicated coronary angiography. It is unclear whether this higher prevalence represents referral bias or whether there is an underappreciation of the burden of CAD in HFpEF based on clinical criteria alone. A retrospective single-centre convenience cohort of 376 HFpEF patients reported "anatomically significant" CAD (defined as >50% luminal stenosis, previous MI or any previous revascularisation) in 68% of patients[148], and an autopsy series of 124 patients with a premortem diagnosis of HF and LVEF ≥40% reported "anatomically significant" CAD (≥50% luminal stenosis) in 65% of patients[208]. One prospective single-centre study of 108 patients with HFpEF (n = 75) and HFmrEF (n = 33) found obstructive CAD (defined as >70% luminal stenosis or ≥50% stenosis and FFR ≥0.80) in 64% of patients.[199] More patients in each of these latter two studies had a clinical history of CAD (53% and 65%, respectively) when compared with my cohort (35%). This likely reflects the inclusion of patients with HFmrEF, with similar demographics to patients with HFrEF, in these studies. The clinical characteristics of my cohort are reasonably consistent with contemporary epidemiological and RCT HFpEF populations.[18,272,273]

In my study, half of patients with obstructive epicardial coronary disease had no clinical history of CAD. These findings highlight the high burden of clinically unrecognised CAD in the HFpEF population and are supported by other recent studies. Trevisan and colleagues found that 42% of patients with HFpEF and obstructive epicardial CAD had no clinical history of CAD[199], while Mohammed and colleagues reported anatomically significant CAD at post-mortem in 32% of HFpEF patients without known CAD[208]. International guidelines recommend screening patients with HFpEF for CAD[2,3], however, a recent large registry study found that non-invasive and invasive ischaemia testing was performed in only 8% and 6% of HFpEF patients, respectively, within 90 days following first HF hospitalisation.[274]

Interestingly, I found that a semi-quantitative CMR ischaemia testing (using MPRI) did not predict obstructive epicardial CAD on invasive coronary angiography. I defined inducible ischaemia as an MPRI <1.4 which was previously reported to accurately detect obstructive epicardial CAD and CMD in patients with angina[251], however, there is no general consensus regarding the MPRI threshold used to define ischaemia with variable thresholds used in different studies, therefore, a different cut-point may have had better diagnostic accuracy.[269] Furthermore, I assessed global MPRI which may not be significantly influenced by limited areas of myocardial ischaemia. MPRI assessed on the coronary artery territory level may have better identified those with and without regional ischaemia.

The lack of correlation of non-invasive ischaemia testing with angiographic CAD in HFpEF was previously reported by Hwang and colleagues who found an overall accuracy of stress testing to classify CAD of only 66%, with no significant difference between various modalities (i.e. nuclear perfusion imaging, stress echocardiography and exercise ECG).[148] The reason why non-invasive ischaemia testing did not identify patients with obstructive CAD is unclear but it might due to the presence of CMD, the absence of inducible ischaemia in the presence of non-viable myocardium, or collateral perfusion provided by another epicardial coronary artery.

Over a median follow-up period of 18 months, there was no significant difference in mortality between those with and without obstructive CAD. The number of deaths during follow-up was small, therefore, no meaningful conclusion can be reached regarding the association between CAD and mortality in the cohort. Nonetheless, study participants with obstructive epicardial CAD had significantly more hospitalisations (for any cause, CV causes or HF) than those without obstructive CAD, suggesting that obstructive epicardial CAD may precipitate HF decompensation in some patients with HFpEF. These findings align with a recent retrospective observational study and a registry-based study, both of which suggest that HFpEF patients with CAD have poorer outcomes than those without CAD.[148,190] Event rates in this study were lower than those reported in epidemiological HFpEF studies[8,12,13], but higher than in RCTs[14–16]. This reflects the intermediate risk of my study cohort who were younger and less

frail with fewer comorbidities than patients in epidemiological studies, but older, frailer and more comorbid than RCT HFpEF populations.

There are few available data on the impact of revascularisation in patients with CAD in the setting of HFpEF and these are conflicting. The Coronary Artery Surgery Study (CASS) registry found that CABG did not improve mortality in patients with HFpEF[207], and a small study including 27 patients with acute hypertensive HF and an LVEF >40% showed that pulmonary oedema recurred in patients with CAD and HFpEF despite revascularisation[206]. However, two retrospective non-randomised studies reported significantly better survival following revascularisation in HFpEF patients with CAD compared with those who were not revascularised, although these data are difficult to interpret because of selection bias or other confounding.[148,178] Only eight participants (21% of those with obstructive disease) in my cohort underwent percutaneous coronary intervention, therefore, I was unable to evaluate the association between revascularisation and outcomes.

9.1.2 CMD in HFpEF

On invasive guidewire-based coronary physiological testing, 66% of patients had evidence of endothelium-independent CMD; 69% of those with no obstructive epicardial CAD had endothelium-independent CMD. Several studies have been published documenting CMD in HFpEF cohorts, however, these have generally been small and/or convenience cohorts undergoing clinically indicated investigation for evaluation of CAD (see Chapter 2). One small prospective study investigated 30 HFpEF patients and a clinical indication for coronary angiography with invasive coronary physiological testing.[226] The prevalence of CMD in this cohort was 37% (defined as CFR ≤2.0 and IMR ≥23), but 73% if CMD was defined as CFR ≤2.0 or IMR ≥23. These results are limited by referral bias and other factors, such as the inclusion of patients with ischaemia with no obstructive CAD (INOCA) with a high burden of CMD.[135,275] A prospective multicentre study (PROMIS-HFpEF) recruited 202 ambulatory HFpEF patients and assessed CMD using echocardiography-derived CFR of the LAD.[231] CMD was reported in 75% of patients using a CFR threshold of <2.5 (compared with 65% using the same threshold in my study). In PROMIS-HFpEF, LVEF threshold for inclusion was ≥40% and elevated natriuretic peptides were not a requirement for inclusion.

Epicardial CAD was not systematically excluded, therefore, clinically unrecognised obstructive CAD (present in 39% of our cohort) could potentially confound these results. Echocardiography-derived CFR has been validated against PET and invasive CFR in small cohorts.[123,276] Thirty-five percent of the patients in this study were obese and, although this technique appears to be technically feasible in such patients, agreement with myocardial flow reserve on PET was relatively weak.[277]

Both CFR and IMR are commonly used to assess endothelium-independent coronary microvascular function. However, these indices measure different aspects of microvascular function: CFR represents the flow ratio between resting and hyperaemic conditions; IMR represents microvascular resistance during hyperaemia. I was, therefore, able to describe different patterns of CMD in the study population. Thirty-one percent of the cohort had abnormalities of both flow reserve and microvascular resistance and 35% had discordant CFR/IMR results. These findings are comparable to a previous study in INOCA patients and a recent small study of HFpEF patients (n = 30, discussed above).[226,244] The clinical characteristics and outcomes of my patients was similar in those with different mechanisms of CMD.

The concept that the coronary microvasculature may play a central role in the pathophysiology of HFpEF was proposed by Paulus and Tschöpe in 2013.[61] They hypothesised that comorbidities induce a systemic pro-inflammatory state, with coronary microvascular endothelial inflammation and dysfunction. This results in adverse myocardial and vascular remodelling, leading to LV diastolic dysfunction and clinical HF (see Chapter 1). This paradigm was based on a series of small studies of human endomyocardial tissue specimens. However, the patients studied were a highly selected group who were considerably younger and without the usual comorbidity profile of the typical HFpEF patient (see Chapter 2). Despite this, studies reporting evidence of impaired coronary microvascular function and rarefaction in patients with HFpEF have given support to this theory, suggesting that their findings could reflect coronary microvascular endothelial dysfunction.[208,231] In PROMIS-HFpEF, CMD was correlated with a lower reactive hyperaemia index, a measure of peripheral endothelial dysfunction.[231] However, CFR was not associated with comorbidities, such as diabetes and hypertension, suggesting that CMD may be

related to other mechanisms (e.g. myocardial fibrosis, microvascular rarefaction), rather than comorbidity-induced systemic inflammation.

My study is the first to assess endothelium-dependent coronary vasomotor function in vivo in a HFpEF population using the reference standard invasive assessment with intra-coronary ACh administration. During vasoreactivity testing, only 24% of patients assessed had evidence of coronary microvascular endothelial dysfunction (endothelium-dependent CMD). Furthermore, I found no correlation between endothelium-independent and -dependent mechanisms of CMD. These findings suggest that CMD in HFpEF is predominantly due to endothelium-independent structural abnormalities, such as abnormal vascular remodelling, microvascular rarefaction and extrinsic vascular compression, rather than endothelial dysfunction. Although it is possible that these structural abnormalities could be the end-stage result of previous endothelial dysfunction, a minority of hospitalised HFpEF patients appear to have active coronary microvascular endothelial dysfunction. These findings are consistent with the neutral outcomes of several trials of therapies targeting NO-cGMP-PKG signalling, including the soluble guanylate cyclase stimulatory vericiguat[67], the phosphodiesterase-5 inhibitor sildenafil[68], organic nitrates[69] and inorganic nitrites[70], and sacubitril-valsartan[71].

Although several studies have shown CMD to be prevalent in HFpEF, causality has yet to be established. It has been suggested that, rather than primary CMD leading to myocardial remodelling and HFpEF, it may occur as a secondary consequence of the myocardial remodelling and diastolic dysfunction seen in HFpEF.[278] Nevertheless, recent studies report that subclinical CMD and high-sensitivity cardiac troponin elevations predict future HFpEF.[279,280] Early identification of patients with CMD could, therefore, help detect patients at risk for progression to HFpEF who could potentially benefit from targeted therapies.

During follow-up, I found no significant difference in outcomes between those with and without endothelium-independent or -dependent CMD. Only one other study has reported outcomes in HFpEF relating to CMD. Allan and colleagues assessed 32 HFpEF patients with a clinical indication for coronary angiography and reported lower survival free of HF hospitalisation in patients with “overt CMD” (abnormal CFR and IMR) versus those without “overt CMD”.[227] However,

this was a convenience cohort with very few patients and events, so the clinical relevance of this is unclear.

9.1.3 Myocardial infarction and fibrosis in HFpEF

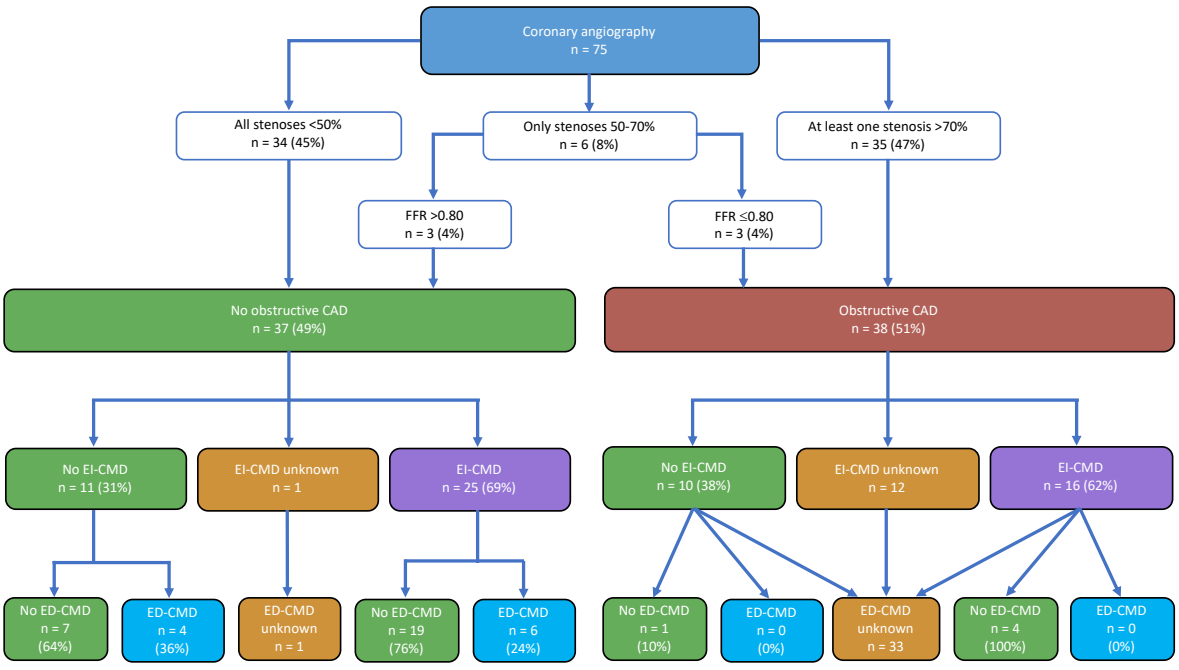
Twenty-seven percent of participants that underwent contrast enhanced CMR had ischaemic LGE consistent with previous MI. Fifty-seven percent of those with CMR-proven MI had no clinical history of MI and 18% of those with no history of MI had CMR-proven MI, suggesting a high burden of clinically unrecognised MI in the HFpEF population. As documented in the systematic review in Chapter 2, the prevalence of previous MI reported in HFpEF cohorts is variably reported. One prospective single-centre observational study of 154 patients with suspected HFpEF found evidence of clinically unrecognised MI in 10% of patients based on LGE imaging.[281] Mohammed and colleagues reported a prevalence of MI at autopsy of 42% and 20% on gross and microscopic pathology, respectively, in 124 patients with a premortem diagnosis of HF and LVEF ≥40%.[208] The prevalence estimate based on this study is consistent with the intermediate risk of my cohort between the former lower risk (predominantly ambulatory patients, lower natriuretic peptides) and latter higher risk (historical cohort, lower LVEF threshold) study populations. The identification of patients with previous MI is important as these patients can gain prognostic benefit from secondary prevention and anti-remodelling drug therapy.[282–285]

Several studies have suggested that myocardial fibrosis may play an important role in causing or contributing to myocardial stiffness and diastolic dysfunction in HFpEF.[44,208] ECV is a non-invasive measure of diffuse myocardial fibrosis and, in this study, 42% of patients had a high ECV (>30%). I found that ECV was inversely correlated with global MPRI, which is consistent with the results of a recent small study of 19 HFpEF patients.[232] These findings suggest that chronic sub-clinical ischaemia may contribute to diffuse myocardial fibrosis in HFpEF. Furthermore, consistent with previous studies which report that diffuse fibrosis is associated with poor outcomes in HFpEF[286,287], I found that patients with a high ECV had significantly more hospitalisations than those with a normal ECV.

9.1.4 Summary

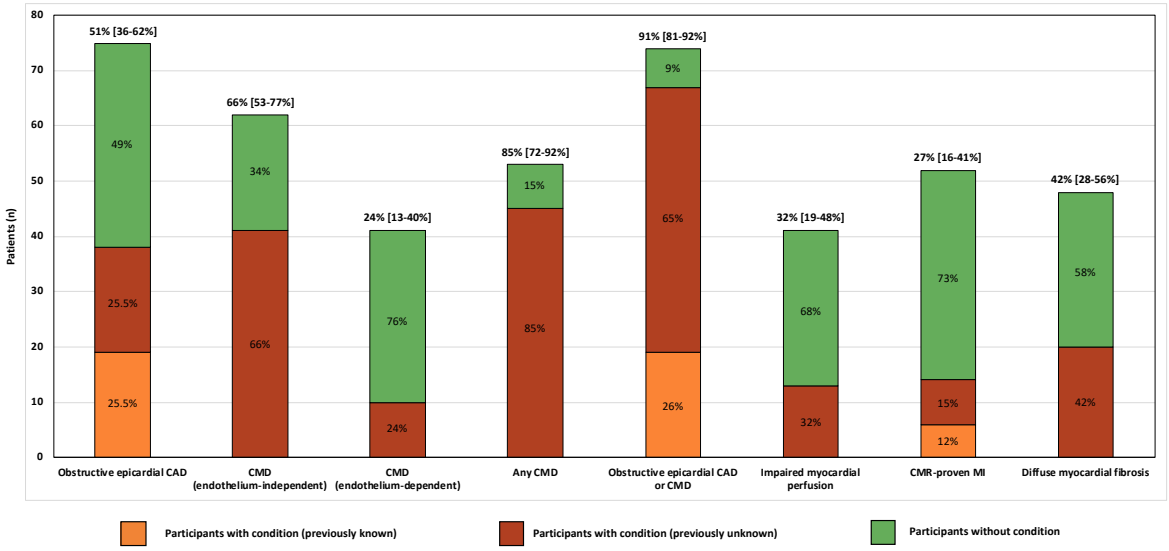
Overall, over 90% of participants in this cohort had evidence of macrovascular and/or microvascular CAD (Figures 9-1 and 9-2). Obstructive epicardial CAD was present in around half of HFpEF patients and those with obstructive CAD had significantly more hospitalisations than those without obstructive disease. Various treatments are available for epicardial CAD which might improve symptoms and/or outcomes in HFpEF.

Of those without obstructive epicardial CAD, over 80% of patients had CMD (endothelium-independent or -dependent). Like HFpEF, CMD is a heterogeneous condition and I have demonstrated a variety of different mechanisms (including impaired flow reserve, high microvascular resistance and endothelial dysfunction) which can occur in isolation or in combination. As such, it is unlikely that therapies targeting a specific process (e.g. coronary microvascular endothelial dysfunction) will be effective in treating most patients with HFpEF. In this cohort, endothelium-independent mechanisms of CMD predominated, with only a minority of patients having evidence of coronary endothelial dysfunction. This has important implications for future treatments directed at CMD in patients with HFpEF.



CAD, coronary artery disease; ED-CMD, endothelium-dependent coronary microvascular dysfunction; EI-CMD, endothelium-independent coronary microvascular dysfunction; FFR, fractional flow reserve.

Figure 9-1: Overview of invasive coronary assessment findings.



Values are % [95% CI].

CAD, coronary artery disease; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance; MI, myocardial infarction.

Figure 9-2: Prevalence of CAD, CMD, and imaging evidence of impaired myocardial perfusion, MI and diffuse myocardial fibrosis.

9.2 Strengths

I believe that this study has many strengths. Firstly, the screening and recruitment processes were systematic. I prospectively screened near-consecutive patients admitted with suspected HF at three large hospitals five days per week for 19 months. I screened all admissions to the coronary care units, cardiology wards and medical receiving units in addition to screening echocardiogram requests at all three sites, therefore, I believe I was able to identify almost all patients admitted with suspected HF.

All patients enrolled had a diagnosis of HFpEF based on the ESC HF guidelines, necessitating clinical symptoms and signs of HF, an LVEF ≥50%, elevated natriuretic peptides, and evidence of structural heart disease and/or diastolic dysfunction on echocardiography. Median natriuretic peptides were markedly elevated and >90% of patients had structural heart disease (i.e. LVH and/or LA dilatation).

The demographics of this cohort are in accordance with contemporary population-based studies in HFpEF, with the exception of ethnicity (discussed below). The typical comorbidities typically associated with HFpEF were highly

prevalent in this cohort, including hypertension, AF, CKD, anaemia, and obstructive airways disease. Interestingly, the proportion of patients with a previous history of CAD in my cohort is identical to the prevalence estimate of hospital-based cohorts in the meta-analysis presented in Chapter 2.

Frailty has been increasingly recognised as an important (but often poorly defined) feature of many patients with HFpEF. Recruitment of frail patients to clinical studies is challenging and, therefore, these patients are frequently excluded from many studies, especially those involving invasive procedures. I assessed the degree of frailty in all patients recruited using the CFS.[239] Although patients with severe frailty were not included, patients with mild or moderate frailty made up a large proportion of the overall study cohort.

Overall, I feel this cohort is representative of 'real world' hospitalised HFpEF patients. Selection bias was minimal due to the prospective and near-consecutive screening process. The recruited patients all had a diagnosis of HFpEF in accordance with the current ESC guidelines.[2] The demographics and clinical characteristics of my cohort are comparable to HFpEF populations in contemporary epidemiological studies.[257,258] Consequently, I believe that the findings of this study are generalisable to 'real world' patients hospitalised with HFpEF.

Another strength of the study is the population size, which was large taking into account the demographics of the study population, the prospective and systematic nature of recruitment, and the invasive investigations involved. This is only the second study to systematically perform invasive coronary angiography in a HFpEF population. Trevisan and colleagues performed coronary angiography on an identical number of patients as this study (n = 75).[199] This is, therefore, the joint largest prospective systematic coronary angiography study in HFpEF.

Possibly the greatest strength of this study was the use of reference standard invasive and non-invasive investigations to comprehensively assess the macrovascular and microvascular coronary structure and function. I was able to assess the burden of obstructive epicardial CAD and examine the different mechanisms of CMD in the study cohort. This is the largest (and only unselected) study to invasively assess endothelium-independent CMD (n = 62), and the first

study (invasive or non-invasive) to assess coronary endothelial function in vivo (n = 41) in a HFpEF population. I was also able to assess the myocardial consequences of CAD and CMD. Using CMR, I assessed the burden of previous MI and diffuse myocardial fibrosis, as well as myocardial ischaemia. I was, therefore, able to compare invasively-assessed CAD and CMD with non-invasive measures of myocardial infarction, fibrosis and ischaemia.

Finally, comprehensive outcome data (death and hospitalisations) was available for all patients over a median follow-up of 18 months. This is the first prospective systematic study to report outcomes based on epicardial CAD on coronary angiography. One small study (n = 32) of selected HFpEF patients recently reported outcomes related to endothelium-independent CMD at 12 months' follow-up. However, this is the first study to report outcomes related to the presence of endothelium-independent and -dependent CMD in a prospectively recruited HFpEF cohort.

9.3 Weaknesses

This study is limited by the high drop-out rate of patients recruited prior to invasive and non-invasive investigation. Due to the logistics of performing this study within the limits of a busy regional clinical service, there was a significant delay in performing invasive coronary angiography (median 97 days from presentation). Twenty-three patients that were recruited did not undergo the study investigations. For the majority, this was due to a decline in health, functional status or renal function prior to the investigations being performed, making it clinically inappropriate or unsafe to proceed with the imaging studies. This reflects the demographics of the unselected HFpEF population I studied, who are predominantly elderly with some degree of frailty and a high burden of comorbidities. I considered that these patients might represent a higher-risk group, however, there was no significant difference in mortality or hospitalisations between those that did and did not undergo the study investigations during follow-up (Appendix VIII, IX).

The inclusion criteria were designed to be as broad as possible in order to accurately represent an unselected 'real world' HFpEF population. However, it was necessary to exclude specific groups of patients for safety reasons. Notably,

those with significant renal dysfunction (eGFR <30 mL/min/1.73m^2) were excluded to facilitate the safe administration of contrast agents during the study investigations. Although many participants had a degree of frailty, those with severe frailty (i.e. CFS >6), in whom invasive coronary angiography was considered clinically inappropriate or an excessive risk, were excluded. The requirement for invasive investigation limited recruitment of elderly and frail patients (who comprise a significant proportion of the HFpEF population), which slightly limits the generalisability of the study results to the HFpEF population at large.

As discussed above, this cohort were almost exclusively Caucasian. Although this is relatively consistent with the Scottish population[259], patients from minority ethnic backgrounds are under-represented in clinical research studies and the study findings may not be applicable in other ethnic groups.[260] I recruited only hospitalised patients who are likely to represent an advanced HFpEF phenotype, therefore, these results may not be representative of the ambulatory HFpEF population. Indeed, patients with hospitalised HF are generally older, have a higher burden of comorbidities and poorer outcomes than ambulatory HF patients.[288] Data on the relative proportions of patients with acute and chronic HFpEF are limited. The percentage of patients with acute HFpEF that develop chronic HF is unclear. Similarly, how many patients with chronic HFpEF will subsequently be hospitalised with acute decompensated HF is unknown. The ESC-HF Long-term Registry recruited unselected HF patients over a two-year period. Acute HF presentations accounted for 47% of the total HFpEF patients recruited, whereas only 38% of patients with HFrEF presented acutely; 28% of acute HF presentations were *de novo* and 72% represented decompensation of chronic HF.[288] Quality of life following hospitalisation for HFpEF is poor and HF re-hospitalisations are high, therefore, the it is likely that a substantial proportion of patients hospitalised with acute HFpEF will go on to develop chronic HF.[18,289]

It was not always possible to perform all investigations in all patients recruited due for various reasons (e.g. coronary vasoreactivity testing was contraindicated in the majority of patients with obstructive epicardial CAD), however, guidewire-based coronary microvascular assessment was performed in all but one of those without obstructive CAD, and the majority of those with obstructive

coronary disease. FFR was used to assess the haemodynamic significance of intermediate (50-70%) epicardial stenoses, however, it was not routinely measured in arteries with a stenosis <50% or ≥70%, therefore, it is possible that a minority of patients with angiographically mild or severe disease might have been incorrectly classified as having non-flow-limiting or flow-limiting CAD, respectively. For practical reasons, it was only possible to perform physiological assessment of one major epicardial coronary artery. Although CMD is commonly thought to be a global myocardial phenomenon, it is possible that we may not have detected regional microvascular dysfunction in other coronary territories.[2]

The definition of endothelium-independent CMD used in my study (i.e. CFR <2.0 and/or IMR ≥25) is consistent with the contemporary literature in other populations. However, CFR and IMR are continuous measures and the thresholds used do not accurately represent the spectrum of coronary microvascular function. I defined coronary endothelial dysfunction based on the contemporary literature and the international standards for the diagnostic criteria of coronary vasomotion disorders developed by the Coronary Vasomotion Disorders International Study Group (COVADIS).[146] However, invasive assessment of both endothelium-independent and -dependent CMD have been assessed predominantly in patients with chest pain syndromes and have not been validated in the HFpEF population. Furthermore, invasive assessment of the coronary microvasculature is not routinely performed in clinical practice and there is likely to be a degree of inter-observer variability in these assessments. However, the operators who performed the invasive coronary assessments in this study have extensive experience in performing these measurements in other research studies with a high degree of repeatability.[267]

The delay between recruitment and performing the invasive coronary assessment may have impacted on the results of coronary microvascular testing. Elevated LV filling pressures can cause or contribute to CMD as a result of extravascular compression.[266] Invasively-assessed LV end-diastolic pressure was normal in over half of the study participants, but this likely would not have been the case had the invasive assessment been performed during the index hospitalisation.

Finally, this study was limited by the lack of an age- and comorbidity-matched control group. It was not possible to recruit a healthy control group due to the

ethical issues regarding invasive assessment in healthy patients. I considered the option of including a control group of patients undergoing clinically indicated coronary angiography (e.g. patients with INOCA or those with aortic stenosis being worked up for intervention). However, no groups were suitable for comparison to the HFpEF cohort. Patients with INOCA are significantly younger than those with HFpEF and a large proportion of these patients have CMD and/or coronary endothelial dysfunction as the underlying cause of their symptoms.[135] In aortic stenosis, the high LV wall stress and haemodynamic load result in significant alterations in coronary microvascular function.[290] Despite the lack of a control group, previous studies have assessed the prevalence of CMD in non-HFpEF populations, and the prevalence is considerably higher in HFpEF when compared with diabetic and hypertensive cohorts.[291-293] In the 2019 Scottish Health Survey, the prevalence of ischaemic heart disease (defined as a history of MI or angina) in the Scottish population was 13% in those aged 65-74 years and 23% in those aged >75 years.[265] However, data on the prevalence of angiographically documented CAD in unselected patients is limited. A pooled analysis assessed the prevalence of obstructive CAD in patients referred for investigation of suspected CAD.[88] In patients presenting with dyspnoea, the prevalence of obstructive CAD in those aged 60-69 years was 27% in men and 14% in women, and in those aged >70 years was 32% in men and 12% in women. Therefore, the prevalence of angiographically documented CAD in my HFpEF cohort (51% overall, 63% in men, 38% in women) is significantly higher than would be expected in age-matched patients in the general population.

9.4 Future research relating to this study

One of the major aims of this study was to determine how prevalent obstructive epicardial CAD is in the HFpEF population. Various treatments, including medications and coronary revascularisation, are available which provide symptomatic and/or prognostic benefit in broad populations with CAD. As none of these trials have included patients with HFpEF, there is currently no knowledge of the efficacy of any of these treatments in the HFpEF population. To date, no therapies have been shown to have any convincing clinical benefit in HFpEF, therefore, identifying a potentially treatable comorbidity (obstructive epicardial CAD) in a large subgroup of the HFpEF population has promising implications.

This study can inform the design of an RCT to answer the question of whether revascularisation of obstructive CAD in HFpEF will result in clinical benefit in HFpEF. I have demonstrated that it is practical to recruit HFpEF patients with a high burden of comorbidities and mild or moderate frailty, and safely perform invasive coronary procedures. I have shown that HFpEF patients with obstructive CAD have a significantly higher rate of hospitalisations, predominantly due to HF, than those without obstructive disease. This suggests that CAD may play an important role in exacerbating symptoms and provoking decompensation in HFpEF. Treatment directed at CAD might, therefore, improve quality of life and outcomes in HFpEF patients.

This study also provides invaluable information regarding the mechanisms of CMD in HFpEF. I have demonstrated that CMD in HFpEF is due to a variety of mechanisms. It is, therefore, unlikely that therapies targeting one specific pathophysiological process will be effective in treating the majority of HFpEF. In this cohort, only a minority of patients had evidence of endothelial dysfunction. This will inform future treatments directed at CMD in patients with HFpEF. Although CMD (as categorised by thresholds derived from other populations) was highly prevalent in this HFpEF population, the clinical significance of this is unclear. In contrast to obstructive epicardial CAD, patients with and without CMD had similar outcomes, therefore, the rationale for trials of treatments directed at CMD in HFpEF appear more limited.

9.5 Conclusions

Both obstructive epicardial CAD and CMD are common in hospitalised patients with HFpEF and each may be a therapeutic target. Patients with HFpEF and obstructive epicardial CAD had significantly more hospitalisations than those without obstructive CAD. This study provides the justification for, and the basis for the design of, an RCT assessing the prognostic impact of treating CAD in HFpEF.

Although it has been hypothesised that CMD may be due to endothelial dysfunction in HFpEF, it appears to be predominantly due to endothelium-independent mechanisms. This may have important implications for future treatments directed at CMD in patients with HFpEF.

Appendices

Appendix I

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Enquiries to: Dr Christopher Rush
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PARTICIPANT INFORMATION SHEET: STAGE 1

STUDY TITLE: Coronary Artery Disease in Heart Failure with Preserved Ejection Fraction

1. Invitation

We would like to invite you to take part in our study. This involves having tests performed to help work out if a lack of blood getting to the heart muscle may be a cause of heart failure in some people. Before you decide whether or not to take part we would like you to understand why the research is being done and what it will involve for you. We can read through the information sheet with you and answer any questions you may have.

2. Why have I been asked to take part?

You have been invited to participate in this study because you have been admitted to hospital with suspected heart failure. This is a condition where the heart does not pump blood around the body as well as it should do. You have also had a heart scan (echocardiogram) showing that your heart muscle appears to be pumping well. This means you may have a type of heart failure called heart failure with preserved ejection fraction, or HF-PEF.

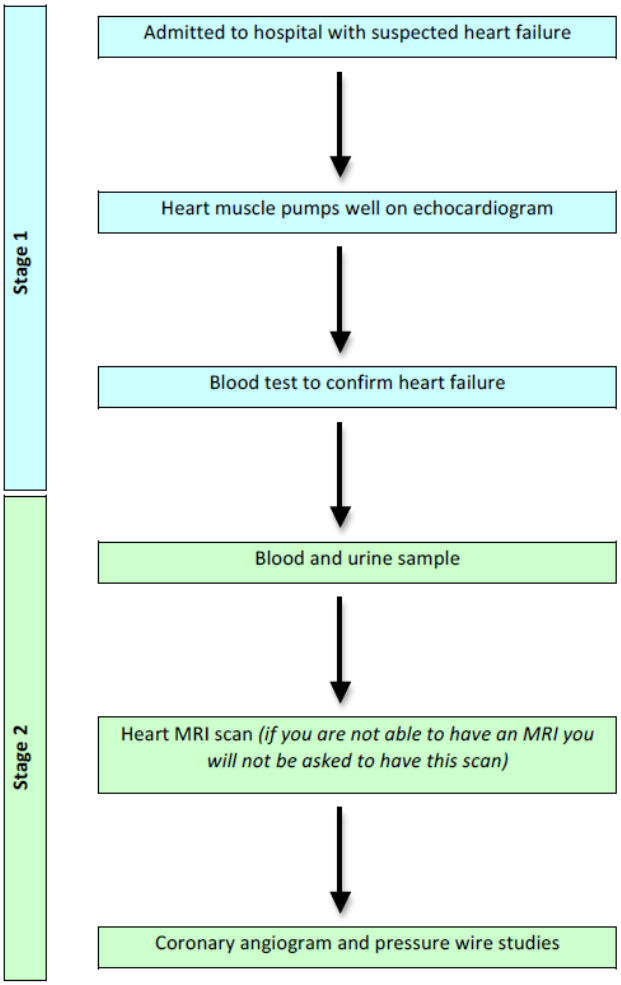
Patients with HF-PEF commonly experience shortness of breath, leg swelling and tiredness. Unfortunately, we do not have a good understanding of the underlying causes and we are currently looking for better treatments for this condition.

3. Why is the study being carried out?

Our aim is to look at whether a lack of blood getting to the heart muscle causes HF-PEF in some people. The most common cause of a lack of blood getting to the heart muscle is due to narrowings of the heart arteries. If there are narrowings of the heart arteries, treatments are available which could potentially improve quality of life. We will perform tests to try and establish what proportion of people admitted to hospital with HF-PEF has narrowings of the heart arteries that could potentially benefit from these treatments.

The next page provides an overview of the tests included in the study.

Flow diagram of study



4. Do I have to take part?

No – participation is entirely voluntary, and if you do decide to take part you can stop at any time. Whatever you decide to do, your medical care will not be affected.

5. What will be involved if I decide to take part?

If you agree to take part, we would first like to take a blood test from you to check for N-terminal prohormone B-type natriuretic peptide (NT-proBNP). This tests how well the heart is pumping. Having blood taken can be uncomfortable and some people feel faint.

- **If the blood test is negative**, this means you do not have heart failure and you will not be asked to participate further in the study**.**

- **If the blood test is positive**, a doctor involved in the study will visit you during your hospital stay to discuss whether or not you would like to take part in stage 2 of the study.

- If you agree to participate in the study, the research doctor will look at your medical records as part of the research.

If you meet the criteria to enter the next stage of the study, you will be invited to participate in stage 2. This involves undergoing further tests to examine the blood supply to the heart muscle and detect any narrowings of the heart arteries (see below). You will also be asked to provide one further blood test and a urine sample.

- **Heart MRI scan –** this is a scan performed when you are lying in a short tunnel which holds a large magnet. It takes 60 minutes to complete. The magnet creates field changes to create a detailed picture of the heart. A contrast agent is given during the scan – this is a colourless liquid used to highlight parts of the heart on the scan. Special medication is also given during the scan to look for evidence of restricted blood flow to the heart muscle. If you are not able to have an MRI (for example, if you have a pacemaker) you will not be asked to have this scan.

- **Coronary angiogram and pressure wire studies –** this test allows the doctors to examine the arteries supplying your heart muscle in detail. A small hollow tube is placed in an artery at the wrist (radial artery) to allow passage of fine catheters and thin wires to your heart. Less commonly, an artery in the groin is used. A contrast agent is injected and moving x-ray pictures are taken to visualise your heart arteries. A pressure wire is a very thin wire that can be passed down the heart arteries. Special medication is given and the wire is used to determine if any narrowings of the heart arteries are restricting blood flow to the heart muscle or not.

6. What are the risks involved in taking part?

There are no risks involved in taking part in stage 1 of the study.

7. Will my taking part in the study be kept confidential?

All the information collected about you in relation to the study will be kept strictly confidential. Your medical notes may be looked at by members of the research team and by representatives of the study Sponsor (NHS Greater Glasgow and Clyde) in relation to your taking part in the study and to ensure the study has been carried out appropriately.

8. What will happen to the results of the research study?

The results of the research study will be stored on a computer database and are likely to be published in medical journals which will be available to the general public. Reports or publications resulting from the study will not contain any personal details. A summary sheet of the research findings will be provided to participants on completion of the study.

9. Who is organising and funding the research?

The University of Glasgow is performing the study and the project is funded by the Chief Scientist Office. NHS Greater Glasgow and Clyde will sponsor the study, i.e. manage and monitor the conduct of the study.

Thank you for taking the time to read this information leaflet.

If you have any questions regarding the study, please contact:

Study doctor

Dr Christopher Rush
Clinical Research Fellow
Telephone: 0141 452 5877
E-mail: Christopher.Rush@glasgow.ac.uk

Supervisors

Professor John McMurray
Telephone: 0141 330 3479

Professor Mark Petrie
Telephone: 0141 330 2000

Independent doctor

Dr Martin Mitchell Lindsay
Telephone: 0141 951 5431

Appendix II

Queen Elizabeth University Hospital
Office Block, Ground Floor, Zone 0.01, Office 0.05
1345 Govan Road
Glasgow G51 4TF

Enquiries to: Dr Christopher Rush
Telephone: 0141 452 5877
E-mail: Christopher.Rush@glasgow.ac.uk

PARTICIPANT INFORMATION SHEET: STAGE 2

STUDY TITLE: Coronary Artery Disease in Heart Failure with Preserved Ejection Fraction

1. Invitation

We would like to invite you to take part in stage 2 of our study. This research involves having tests performed to help work out if a lack of blood getting to the heart muscle may be a cause of heart failure in some people. Before you decide whether or not to take part we would like you to understand why the research is being done and what it will involve for you. We can read through the information sheet with you and answer any questions you may have.

2. What is the purpose of the study and why have I been invited to take part?

You have been invited to participate in this study because you have been admitted to hospital with heart failure. This is a condition where the heart does not pump blood around the body as well as it should do. In stage 1 of the study you had a blood test which confirmed that you have heart failure. You have also had a heart scan (echocardiogram) showing that your heart muscle appears to be pumping well. This means that you have a specific type of heart failure called heart failure with preserved ejection fraction, or HF-PEF.

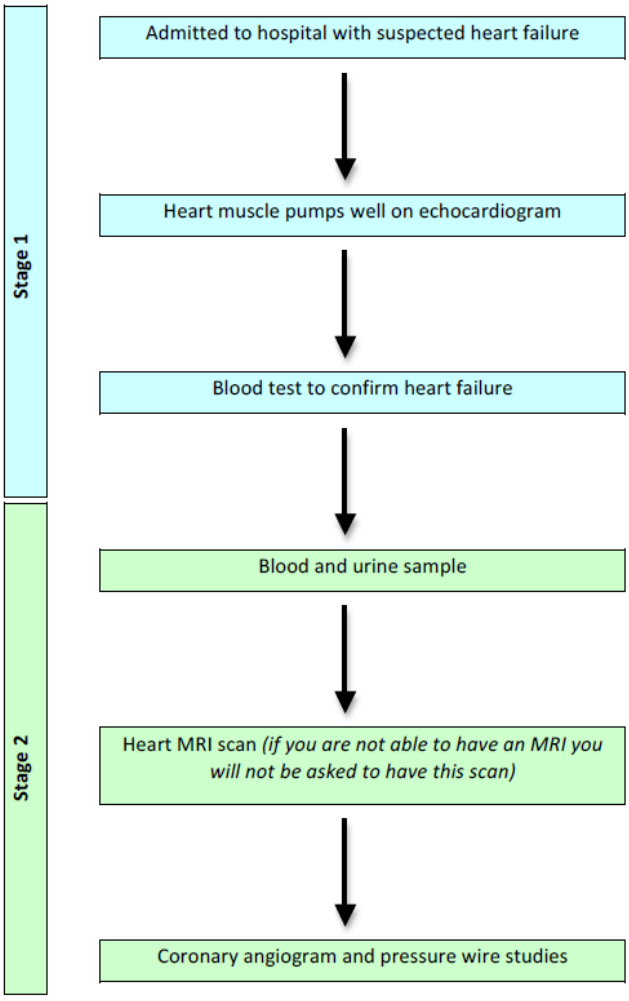
Patients with HF-PEF commonly experience shortness of breath, leg swelling and tiredness. Unfortunately, we do not have a good understanding of the underlying causes and we are currently looking for better treatments for this condition.

Our aim is to look at whether a lack of blood getting to the heart muscle causes HF-PEF in some people. The most common cause of a lack of blood getting to the heart muscle is due to narrowings of the heart arteries. If there are narrowings of the heart arteries, treatments are available which could potentially improve quality of life. These include medications and treatments to open up the heart arteries.

We will perform tests to try and establish what proportion of people admitted to hospital with HF-PEF has narrowings of the heart arteries that could potentially benefit from these treatments.

The next page provides an overview of the tests included in the study.

Flow diagram of study



3. Do I have to take part?

No – taking part in this study is entirely voluntary and your decision. If you take part you will be given this information sheet and asked to sign a consent form. If you decide to take part you are free to withdraw at any time without giving a reason. A decision to withdraw at any time or a decision not to take part will not affect the standard of care you receive.

4. What will happen to me if I would like to take part in stage 2 of the study?

You have already taken the stage 1 of the study which involved having a blood test taken which confirmed that you have heart failure. If you agree to take participate in stage 2 of the study, we will ask you to undergo further tests to examine the blood supply to the heart muscle and detect any narrowings of the heart arteries (see below). You will also be asked to provide one further blood test and a urine sample.

- **Blood test –** you will be asked to provide a blood sample. We will check for substances in the blood that may help identify people with a lack of blood getting to the heart muscle. Approximately 10mls (two teaspoons) of blood will be taken.

- **Urine test –** you will be asked to provide a urine sample. We will check for substances in the urine that may help identify people with a lack of blood getting to the heart muscle. As women who are pregnant are not able to take part in this study, we may require an additional urine sample to perform a pregnancy test.

- **Heart MRI scan –** this is a scan performed when you are lying in a short tunnel which holds a large magnet. It takes 60 minutes to complete. The magnet creates field changes to generate a detailed picture. The scanner does not touch you and you will be unaware of these field changes. The scan is noisy so earphones will be provided with music playing during the test. A contrast agent will be given to you during the scan into a small tube (cannula) in your arm. The contrast agent is a colourless liquid used to highlight parts of the heart on the scan. Special medication called adenosine (which increases the blood flow in the heart arteries) will also be given into the cannula during the scan to look for evidence of restricted blood flow to the heart muscle. If you are not able to have an MRI (for example, if you have a pacemaker) this will be discussed with you and you will not be asked to have this scan.

- **Coronary angiogram and pressure wire studies –** these tests allow the doctors to examine the arteries supplying your heart muscle in detail. You will be awake for the test and can be given medication to help you relax. At the start of the procedure you will feel a needle being passed into the skin in the wrist to inject local anaesthetic. A small hollow tube is placed in an artery at the wrist (radial artery) to allow passage of fine catheters and thin wires to your heart. Less commonly, an artery in the groin is used. A contrast agent is injected and moving x-ray pictures are taken to visualise your heart arteries. These pictures are projected onto a screen and the doctor is able to see any narrowings of the large heart arteries which may be restricting blood flow to the heart muscle. A pressure wire is a very thin wire that is passed down the same catheter used to do the angiogram. The pressure wire is passed down the heart arteries and two special medications (adenosine and acetylcholine) are given to increase the blood flow to the heart muscle. The wire is used to determine whether any narrowings seen on the angiogram are restricting blood flow to the heart muscle or not. If the angiogram does not show any significant narrowings of the large heart arteries, the pressure wire is used to assess blood flow in the small heart arteries which cannot be seen on a standard angiogram.

The heart MRI scan will take place at the Queen Elizabeth University Hospital during your hospital admission or within two weeks of your discharge from hospital. The coronary angiogram and pressure wire

studies will take place at the Golden Jubilee National Hospital in Clydebank within eight weeks of your discharge from hospital. You will receive a letter and phone call with the appointment date and time from the study doctor. A taxi will be organised to and from this appointment free of charge.

The way that we follow a person's progress in a study like this is by entering their details into a national database, which uses hospital notes to record when you come into hospital. This database is run by the NHS and is confidential. Any information gathered is only available to the doctors running this study. It does not require any participation from you, and no one will contact you as part of this process. If you agree to take part in the study at this stage, we will enter you details into this database. The information gathered from this database may be used for future ethically approved research.

5. When will I get the results of the test?

The results of the coronary angiogram and pressure wire studies will be explained to you on the same day as you have the test. If there are narrowed arteries supplying blood to the heart muscle this will be explained to you. If a narrowed artery is identified, and you agree with your specialist doctor, they may proceed to treating the identified problem during the same procedure. A small inflatable balloon on the tip of a narrow tube is passed down the heart artery until its tip reaches the narrowed section. The balloon is gently inflated so that it squashes the fatty tissues responsible for narrowing the artery. A stent (a short tube made of stainless steel mesh) may also be inserted. The stent stays in the artery and often has a special drug coating to prevent the artery re-narrowing.

The heart MRI scan takes more time to interpret so the results will not be available on the day. The scan will be reviewed and the report will be included in your medical records so that your consultant or GP will be able to discuss the results at your next routine visit. Any unexpected findings seen on the scan will be discussed with a specialist x-ray doctor and highlighted to your consultant or GP, who will be able to discuss the findings with you.

6. What are the possible benefits of taking part?

It is hoped that by taking part in this study you will be providing valuable information to help us work out if a lack of blood supply to the heart muscle causes HF-PEF in some patients. These tests may help discover the underlying cause of your heart failure which we might not otherwise find out if you were not participating in the study.

Although this study is designed to provide information that may help patients in the future, rather than the volunteers participating, the tests we carry out may identify people who might benefit from treatment to improve blood flow to the heart muscle. Any treatment you receive is not part of the study and will be carried out following current best practice. You may or may not benefit directly from taking part in the study, however, the information we get from this study may help us give better treatment to patients with HF-PEF in the future.

7. What are the possible disadvantages of taking part?

Heart MRI scan – some patients find the scan claustrophobic. It can be noisy but you will be given earphones so you can listen to music. Some patients find having the needle placed in their arm uncomfortable and may feel faint but the pain does not last long. There is a small risk of bleeding, bruising or infection at the site. Your kidney function will be checked before the scan to ensure it is safe to give you the special dye. The medication given to increase blood flow to the heart (adenosine) is very safe. Adenosine has a very short duration of action, and there are usually no lasting effects. However, this medication can cause a short period of breathlessness, flushing or chest pain which can be unpleasant.

Serious side effects are very rare (less than 1 in 1500) and include: a slow or fast heartbeat (which may require medication or an electric shock), severe chest pain or breathlessness.

Coronary angiogram and pressure wire studies – there are some risks associated with this procedure and it is important that you understand these before deciding whether you would like to take part. The most common side effect is bleeding or bruising in the wrist (or groin area) and there may be some mild discomfort for a few days. There is also a risk of infection where the needle enters the skin. Serious complications (risk of heart attack, stroke or dying) are rare and are estimated to occur in less than 1 in 500 people. There is a small risk of causing damage to a heart artery from the pressure wire (less than 1 in 300 people). You are exposed to x-rays during the procedure to take pictures of the arteries and check the position of the catheters, but this will be kept to a minimum. X-rays are a form of radiation which can be harmful. The dose of radiation you will receive during the study is equivalent to just over 3 years of background radiation. Background radiation is the radiation we are exposed to all the time from natural sources. The dye used can sometimes make patients feel unwell or cause an allergic reaction. This happens in around 1 in 100 people having an angiogram but there are medicines available to treat this. The medications given to increase blood flow to the heart are very safe. The effects of adenosine are described above. Like adenosine, acetylcholine has a very short duration of action and there are usually no lasting effects. However, it can also cause a short period of breathlessness, flushing or chest pain which can be unpleasant. More serious side effects occur in less than 1 in 100 people and include: a slow or fast heartbeat, severe chest pain or breathlessness (which may require treatment with medication).

If a narrowed artery is identified, your doctor may proceed to treating the identified problem with a stent during the same procedure. The risk of serious complications (risk of heart attack, stroke or dying) associated with insertion of a stent are estimated to occur in less than 1 in 100 people. Around 1 in 20 patients that have a stent inserted will develop a re-narrowing (called re-stenosis) of the artery within the stent which can be dealt with by further stenting.

8. What if something goes wrong?

If something goes wrong as a result of a study procedure, we may ask you to remain in hospital for a short time or overnight for close monitoring. In the event of a procedure not going to plan we will explain clearly what has happened and discuss the relevant options available to you. There are no special compensation arrangements if taking part in this research project harms you. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. The normal NHS complaints mechanisms are available if you wish to complain or have any concerns.

9. Will my taking part in this study be kept confidential?

If you consent to take part in the study, the research doctor may view your medical records for purposes of analysing the results. Representatives of the Sponsor, NHS Greater Glasgow and Clyde, may also look at these in relation to checking the study has been carried out appropriately. All information collected about you during the course of the research will be kept strictly confidential. Any information which leaves the hospital will have your name and address removed so that you cannot be recognised.

10. Will my GP be informed that I am taking part?

With your consent, we would like to inform your GP that you are participating in this study. We would like to provide your GP with the results of the tests we perform.

11. What will happen to the results of the research study?

The results of the research study will be stored on a computer database and are likely to be published in medical journals which will be available to the general public. Reports or publications from the study will not contain any personal details. A summary sheet of the research findings will be provided to participants on completion of the study.

12. Who is organising and funding the research?

The University of Glasgow is performing the study and the project is funded by the Chief Scientist Office. NHS Greater Glasgow and Clyde will sponsor the study, i.e. manage and monitor the conduct of the study.

13. Who has reviewed the study?

This study has been approved by one of the West of Scotland Research Ethics Service Committees, which is an independent panel.

Thank you for taking the time to read this information leaflet.

If you have any questions regarding the study, please contact:

Study doctor

Dr Christopher Rush
Clinical Research Fellow
Telephone: 0141 452 5877
E-mail: Christopher.Rush@glasgow.ac.uk

Supervisors

Professor John McMurray
Telephone: 0141 330 3479

Professor Mark Petrie
Telephone: 0141 330 2000

Independent doctor

Dr Martin Mitchell Lindsay
Telephone: 0141 951 5431

Appendix III

Queen Elizabeth University Hospital
Office Block, Ground Floor, Zone 0.01, Office 0.05
1345 Govan Road
Glasgow G51 4TF

Enquiries to: Dr Christopher Rush
Telephone: 0141 452 5877
E-mail: Christopher.Rush@glasgow.ac.uk

PARTICIPANT INFORMATION SHEET

STUDY TITLE: Coronary Artery Disease in Heart Failure with Preserved Ejection Fraction

1. Invitation

We would like to invite you to take part in our study. This research involves having tests performed to help work out if a lack of blood getting to the heart muscle may be a cause of heart failure in some people. Before you decide whether or not to take part we would like you to understand why the research is being done and what it will involve for you. We can read through the information sheet with you and answer any questions you may have.

2. What is the purpose of the study and why have I been invited to take part?

You have been invited to participate in this study because you have been admitted to hospital with heart failure. This is a condition where the heart does not pump blood around the body as well as it should do. You have had a blood test which confirms that you have heart failure. You have also had a heart scan (echocardiogram) showing that your heart muscle appears to be pumping well. This means that you have a specific type of heart failure called heart failure with preserved ejection fraction, or HF-PEF.

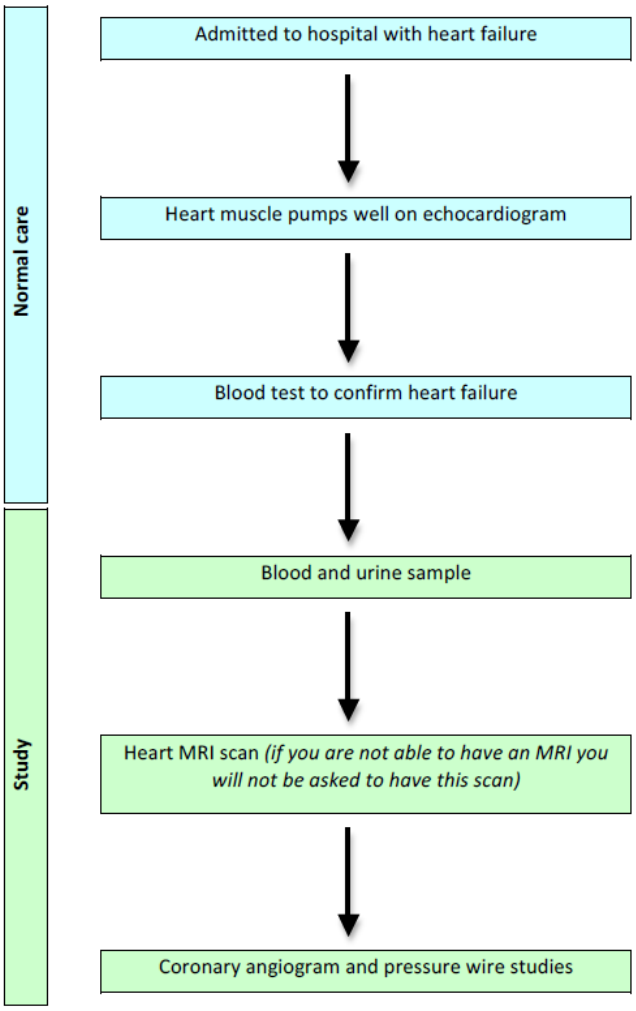
Patients with HF-PEF commonly experience shortness of breath, leg swelling and tiredness. Unfortunately, we do not have a good understanding of the underlying causes and we are currently looking for better treatments for this condition.

Our aim is to look at whether a lack of blood getting to the heart muscle causes HF-PEF in some people. The most common cause of a lack of blood getting to the heart muscle is due to narrowings of the heart arteries. If there are narrowings of the heart arteries, treatments are available which could potentially improve quality of life. These include medications and treatments to open up the heart arteries.

We will perform tests to try and establish what proportion of people admitted to hospital with HF-PEF has narrowings of the heart arteries that could potentially benefit from these treatments.

The next page provides an overview of the tests included in the study.

Flow diagram of study



3. Do I have to take part?

No – taking part in this study is entirely voluntary and your decision. If you take part you will be given this information sheet and asked to sign a consent form. If you decide to take part you are free to withdraw at any time without giving a reason. A decision to withdraw at any time or a decision not to take part will not affect the standard of care you receive.

4. What will happen to me if I would like to take part in the study?

If you agree to take participate in the study, we will ask you to undergo further tests to examine the blood supply to the heart muscle and detect any narrowings of the heart arteries (see below). You will also be asked to provide one further blood test and a urine sample.

- **Blood test –** you will be asked to provide a blood sample. We will check for substances in the blood that may help identify people with a lack of blood getting to the heart muscle. Approximately 10mls (two teaspoons) of blood will be taken.

- **Urine test –** you will be asked to provide a urine sample. We will check for substances in the urine that may help identify people with a lack of blood getting to the heart muscle. As women who are pregnant are not able to take part in this study, we may require an additional urine sample to perform a pregnancy test.

- **Heart MRI scan –** this is a scan performed when you are lying in a short tunnel which holds a large magnet. It takes 60 minutes to complete. The magnet creates field changes to generate a detailed picture. The scanner does not touch you and you will be unaware of these field changes. The scan is noisy so earphones will be provided with music playing during the test. A contrast agent will be given to you during the scan into a small tube (cannula) in your arm. The contrast agent is a colourless liquid used to highlight parts of the heart on the scan. Special medication called adenosine (which increases the blood flow in the heart arteries) will also be given into the cannula during the scan to look for evidence of restricted blood flow to the heart muscle. If you are not able to have an MRI (for example, if you have a pacemaker) this will be discussed with you and you will not be asked to have this scan.

- **Coronary angiogram and pressure wire studies –** these tests allow the doctors to examine the arteries supplying your heart muscle in detail. You will be awake for the test and can be given medication to help you relax. At the start of the procedure you will feel a needle being passed into the skin in the wrist to inject local anaesthetic. A small hollow tube is placed in an artery at the wrist (radial artery) to allow passage of fine catheters and thin wires to your heart. Less commonly, an artery in the groin is used. A contrast agent is injected and moving x-ray pictures are taken to visualise your heart arteries. These pictures are projected onto a screen and the doctor is able to see any narrowings of the large heart arteries which may be restricting blood flow to the heart muscle. A pressure wire is a very thin wire that is passed down the same catheter used to do the angiogram. The pressure wire is passed down the heart arteries and two special medications (adenosine and acetylcholine) are given to increase the blood flow to the heart muscle. The wire is used to determine whether any narrowings seen on the angiogram are restricting blood flow to the heart muscle or not. If the angiogram does not show any significant narrowings of the large heart arteries, the pressure wire is used to assess blood flow in the small heart arteries which cannot be seen on a standard angiogram.

The heart MRI scan will take place at the Queen Elizabeth University Hospital during your hospital admission or within two weeks of your discharge from hospital. The coronary angiogram and pressure wire studies will take place at the Golden Jubilee National Hospital in Clydebank within eight weeks of your discharge from

hospital. You will receive a letter and phone call with the appointment date and time from the study doctor. A taxi will be organised to and from this appointment free of charge.

The way that we follow a person's progress in a study like this is by entering their details into a national database, which uses hospital notes to record when you come into hospital. This database is run by the NHS and is confidential. Any information gathered is only available to the doctors running this study. It does not require any participation from you, and no one will contact you as part of this process. If you agree to take part in the study at this stage, we will enter you details into this database. The information gathered from this database may be used for future ethically approved research.

5. When will I get the results of the test?

The results of the coronary angiogram and pressure wire studies will be explained to you on the same day as you have the test. If there are narrowed arteries supplying blood to the heart muscle this will be explained to you. If a narrowed artery is identified, and you agree with your specialist doctor, they may proceed to treating the identified problem during the same procedure. A small inflatable balloon on the tip of a narrow tube is passed down the heart artery until its tip reaches the narrowed section. The balloon is gently inflated so that it squashes the fatty tissues responsible for narrowing the artery. A stent (a short tube made of stainless steel mesh) may also be inserted. The stent stays in the artery and often has a special drug coating to prevent the artery re-narrowing.

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It is hoped that by taking part in this study you will be providing valuable information to help us work out if a lack of blood supply to the heart muscle causes HF-PEF in some patients. These tests may help discover the underlying cause of your heart failure which we might not otherwise find out if you were not participating in the study.

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Heart MRI scan – some patients find the scan claustrophobic. It can be noisy but you will be given earphones so you can listen to music. Some patients find having the needle placed in their arm uncomfortable and may feel faint but the pain does not last long. There is a small risk of bleeding, bruising or infection at the site. Your kidney function will be checked before the scan to ensure it is safe to give you the special dye. The medication given to increase blood flow to the heart (adenosine) is very safe. Adenosine has a very short duration of action, and there are usually no lasting effects. However, this medication can cause a short period of breathlessness, flushing or chest pain which can be unpleasant. Serious side effects are very rare (less than 1 in 1500) and include: a slow or fast heartbeat (which may require medication or an electric shock), severe chest pain or breathlessness.

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If a narrowed artery is identified, your doctor may proceed to treating the identified problem with a stent during the same procedure. The risk of serious complications (risk of heart attack, stroke or dying) associated with insertion of a stent are estimated to occur in less than 1 in 100 people. Around 1 in 20 patients that have a stent inserted will develop a re-narrowing (called re-stenosis) of the artery within the stent which can be dealt with by further stenting.

8. What if something goes wrong?

If something goes wrong as a result of a study procedure, we may ask you to remain in hospital for a short time or overnight for close monitoring. In the event of a procedure not going to plan we will explain clearly what has happened and discuss the relevant options available to you. There are no special compensation arrangements if taking part in this research project harms you. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. The normal NHS complaints mechanisms are available if you wish to complain or have any concerns.

9. Will my taking part in this study be kept confidential?

If you consent to take part in the study, the research doctor may view your medical records for purposes of analysing the results. Representatives of the Sponsor, NHS Greater Glasgow and Clyde, may also look at these in relation to checking the study has been carried out appropriately. All information collected about you during the course of the research will be kept strictly confidential. Any information which leaves the hospital will have your name and address removed so that you cannot be recognised.

10. Will my GP be informed that I am taking part?

With your consent, we would like to inform your GP that you are participating in this study. We would like to provide your GP with the results of the tests we perform.

11. What will happen to the results of the research study?

The results of the research study will be stored on a computer database and are likely to be published in medical journals which will be available to the general public. Reports or publications from the study will not contain any personal details. A summary sheet of the research findings will be provided to participants on completion of the study.

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13. Who has reviewed the study?

This study has been approved by one of the West of Scotland Research Ethics Service Committees, which is an independent panel.

Thank you for taking the time to read this information leaflet.

If you have any questions regarding the study, please contact:

Study doctor

Dr Christopher Rush
Clinical Research Fellow
Telephone: 0141 452 5877
E-mail: Christopher.Rush@glasgow.ac.uk

Supervisors

Professor John McMurray
Telephone: 0141 330 3479

Professor Mark Petrie
Telephone: 0141 330 2000

Independent doctor

Dr Martin Mitchell Lindsay
Telephone: 0141 951 5431

Appendix IV

Queen Elizabeth University Hospital
Office Block, Ground Floor, Zone 0.01, Office 0.05
1345 Govan Road
Glasgow G51 4TF

Enquiries to: Dr Christopher Rush
Telephone: 0141 452 5877
E-mail: Christopher.Rush@glasgow.ac.uk

PATIENT CONSENT FORM: STAGE 1

STUDY TITLE: Coronary Artery Disease in Heart Failure with Preserved Ejection Fraction

Please initial the box

I confirm that I have read and understand the information sheet dated 23/03/2017 (version 6.0) for stage 1 of the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
I agree to a sample of blood being taken for analysis of N-terminal B-type natriuretic peptide (NT-proBNP).	☐
I understand that sections of my medical notes may be looked at by the research team, and by representatives of the Sponsor, NHS Greater Glasgow and Clyde, where it is relevant to my taking part in the research. I give permission for these people to have access to my records.	☐
I agree to take part in the above study.	☐

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Name of participant	Date	Signature
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Name of researcher	Date	Signature

(3 copies: 1 for patient, 1 for medical notes, 1 for site file)

Version 6.0 23rd March 2017

Appendix V

Queen Elizabeth University Hospital
Office Block, Ground Floor, Zone 0.01, Office 0.05
1345 Govan Road
Glasgow G51 4TF

Enquiries to: Dr Christopher Rush
Telephone: 0141 452 5877
E-mail: Christopher.Rush@glasgow.ac.uk

PATIENT CONSENT FORM: STAGE 2

STUDY TITLE: Coronary Artery Disease in Heart Failure with Preserved Ejection Fraction

Please initial the box

I confirm that I have read and understand the information sheet dated 23/03/2017 (version 6.0) for stage 2 of the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
I agree to undergo a coronary angiogram with pressure wire studies and provide a blood and urine sample.	☐
I agree to undergo a heart MRI scan (if you are unable to have an MRI scan you will not be asked to undergo this test and you should not initial this box).	☐
I understand that sections of my medical notes may be looked at by the research team and by representatives of the Sponsor, NHS Greater Glasgow and Clyde, where it is relevant to my taking part in the research. I give permission for these people to have access to my records.	☐
I agree to my details being entered into the database at Information Services Division of NHS Scotland for use during this study and future ethically approved research.	☐
I agree to my GP being informed of my participation in the study.	☐
I agree to take part in the above study.	☐

----------	----------	----------
Name of participant	Date	Signature
----------	----------	----------
Name of researcher	Date	Signature

(3 copies: 1 for patient, 1 for medical notes, 1 for site file)

Appendix VI

Queen Elizabeth University Hospital
Office Block, Ground Floor, Zone 0.01, Office 0.05
1345 Govan Road
Glasgow G51 4TF

Enquiries to: Dr Christopher Rush
Telephone: 0141 452 5877
E-mail: Christopher.Rush@glasgow.ac.uk

PATIENT CONSENT FORM

STUDY TITLE: Coronary Artery Disease in Heart Failure with Preserved Ejection Fraction

Please initial the box

I confirm that I have read and understand the information sheet dated 23/03/2017 (version 1.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
I agree to undergo a coronary angiogram with pressure wire studies and provide a blood and urine sample.	☐
I agree to undergo a heart MRI scan (if you are unable to have an MRI scan you will not be asked to undergo this test and you should not initial this box).	☐
I understand that sections of my medical notes may be looked at by the research team and by representatives of the Sponsor, NHS Greater Glasgow and Clyde, where it is relevant to my taking part in the research. I give permission for these people to have access to my records.	☐
I agree to my details being entered into the database at Information Services Division of NHS Scotland for use during this study and future ethically approved research.	☐
I agree to my GP being informed of my participation in the study.	☐
I agree to take part in the above study.	☐

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Name of participant	Date	Signature
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Name of researcher	Date	Signature

(3 copies: 1 for patient, 1 for medical notes, 1 for site file)

Appendix VII

Queen Elizabeth University Hospital
Office Block, Ground Floor, Zone 0.01, Office 0.05
1345 Govan Road
Glasgow G51 4TF

Enquiries to: Dr Christopher Rush
Telephone: 0141 452 5877
E-mail: Christopher.Rush@glasgow.ac.uk

GP INFORMATION LETTER

STUDY TITLE: Coronary Artery Disease in Heart Failure with Preserved Ejection Fraction

Dear Doctor,

I am currently carrying out a research project involving patients with heart failure and preserved ejection fraction (HF-PEF) and your patient has kindly agreed to take part in the study.

Patient name:

CHI number:

This study is aiming to investigate the prevalence and role of coronary artery disease in an unselected cohort of patients admitted to hospital with HF-PEF. Patients are recruited on admission to hospital and those who agree to participate in the study are invited to attend the Golden Jubilee National Hospital following discharge for a study visit.

Within eight weeks of discharge, they will attend the Golden Jubilee National Hospital for coronary angiography with pressure wire assessment. Patients with no contraindication will also undergo a cardiac MRI scan at the Queen Elizabeth University Hospital during their hospital admission or within two weeks of discharge from hospital. We will write to you with the results of these investigations. After this study visit your patient has no further commitment to the study. The study does not involve taking any additional medication.

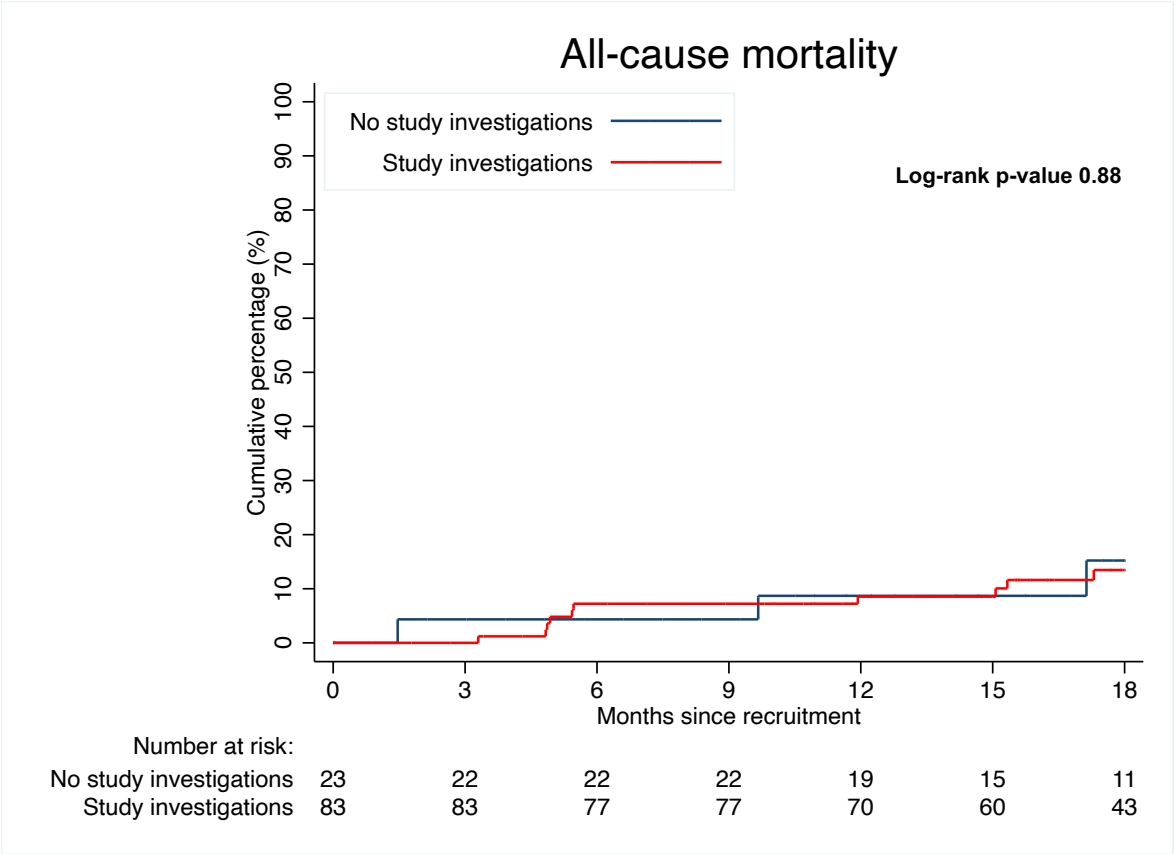
If you require any further information, please do not hesitate to contact me on the above telephone number or e-mail address.

Yours sincerely,

Dr Christopher Rush
Clinical Research Fellow
University of Glasgow

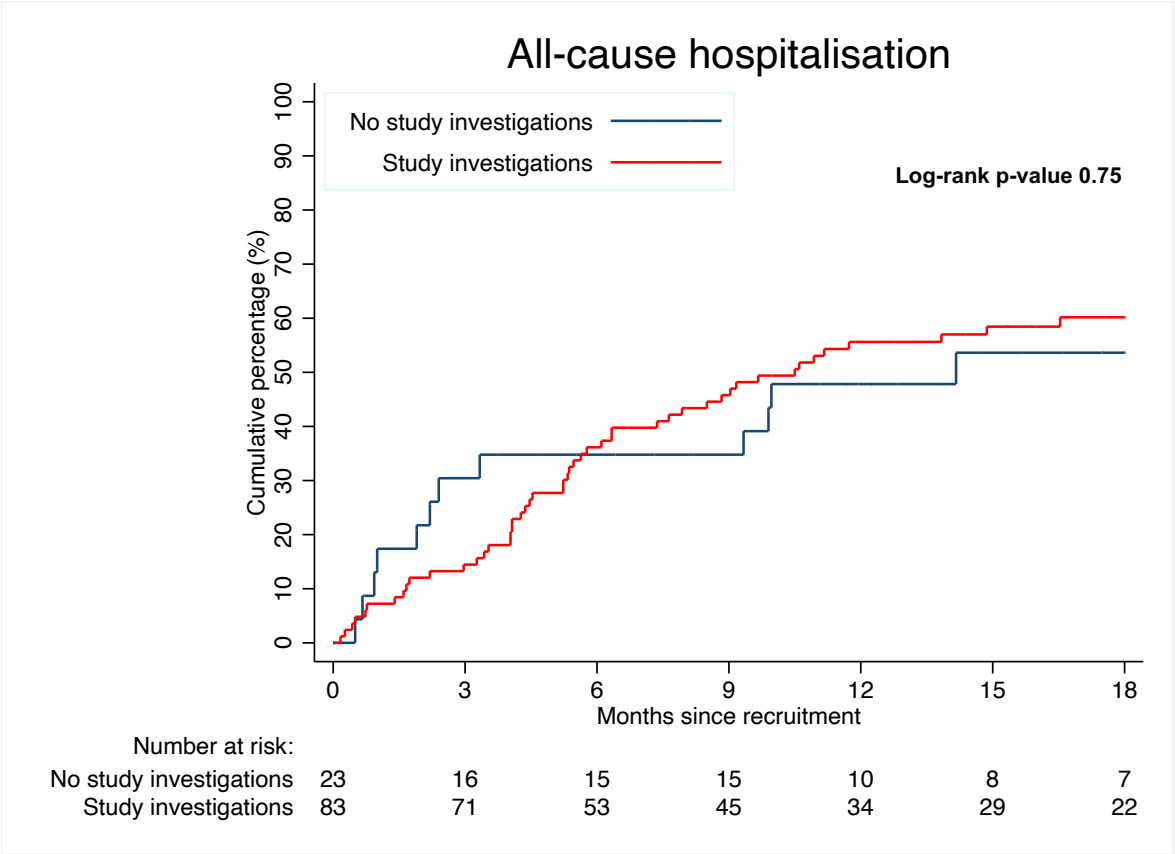
Investigators: Dr Christopher Rush, Professor John McMurray, Professor Mark Petrie, Professor Colin Berry, Professor Keith Oldroyd, Professor Rhian Touyz, Dr Ross Campbell, Dr Clare Murphy

Appendix VIII



Appendix VIII: Kaplan-Meier curves for all-cause mortality in participants who did and did not undergo study investigations.

Appendix IX



Appendix IX: Kaplan-Meier curves for all-cause hospitalisation in participants who did and did not undergo study investigations.

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