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Heart failure: re-evaluating causes and definitions and the value of routine cardiac magnetic resonance (CMR) imaging

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Heart failure: re-evaluating causes and definitions and the value of routine cardiac magnetic resonance (CMR) imaging

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Abstract

Title

Heart failure: re-evaluating causes and definitions and the value of routine cardiac magnetic resonance (CMR) imaging.

Objective

To differentiate the demographics and imaging characteristics of a heart failure population using a comprehensive echocardiographic protocol and routine CMR imaging, and to assess the clinical value of routine CMR in this population.

Methods

A novel comprehensive diagnostic pathway for heart failure was prospectively applied to 319 new patients attending the Darlington and Bishop Auckland heart failure clinic between May 2013 and July 2014. All had a full clinical assessment and an initial basic clinical transthoracic echo performed. Those patients given a diagnosis of heart failure went on to have routine CMR imaging as well as a more detailed echo scan incorporating a variety of systolic and diastolic measurements.

Retrospectively, a cohort of 116 patients with left ventricular systolic impairment, that had both CMR and invasive coronary angiography, were analysed to determine the ability of late gadolinium enhancement (LGE) CMR to predict prognostic coronary artery disease.

Main results

1. Heart failure with reduced ejection fraction (HFREF) accounted for the cause of heart failure in 73% of cases whereas heart failure with preserved ejection fraction (HFPEF) accounted for only 14% of cases.

2. Incorporating CMR into the routine assessment of newly diagnosed heart failure patients changed the diagnosis in 22% of cases (14% of cases for those who had an echo performed on the same day).

3. CMR left ventricular ejection fraction (LVEF) averages 3.9% units higher than Simpson's Biplane LVEF with echo.

4. Regional wall motion score (RWMS) equations were inferior to a Simpson's Biplane assessment of LVEF by echo and cannot be advocated for routine clinical use.

5. The presence of subendocardial LGE on CMR demonstrated infarcts in 42% of those with HFREF, 20% of those with HFPEF, and 40% of those with heart failure with no major structural disease (HFNMSD).

6. The absence of subendocardial LGE excluded prognostic coronary disease in 100% of cases.

7. LGE in a non subendocardial distribution was prevalent in both the HFREF and HFPEF community with a greater average burden in the HFPEF group.

8. E/e' and left atrial volume index (LAVI) were the most helpful echo measures for a positive diagnosis of HFPEF and could be measured in over 90% of cases.

9. Systolic dysfunction out with reduced ejection fraction is present in 76% of the HFPEF cohort.

Conclusion

Heart failure with preserved ejection fraction (HFPEF) is not the epidemic previous literature would have us believe. It is over-diagnosed in current practice due to lax definitions and inappropriately low left ventricular ejection fraction (LVEF) cut-offs.

CMR has a substantial impact on the diagnostic profile of the heart failure population. It revokes the diagnosis of HFREF to a greater extent than is accounted for by the temporal improvement in LVEF, even when taking into account method specific LVEF thresholds. CMR with LGE has additive value for identifying infarcts in a sizeable number of patients for whom there is no suspicion of ischaemic heart disease (IHD), and raising the novel concept that ischaemia may account for symptoms in many of those with HFNMSD. It also demonstrates an impressive ability to exclude prognostic coronary disease. Additionally, LGE in a non subendocardial distribution establishes aetiology including myocarditis and sarcoidosis that would not be detected with echo alone.

The diagnosis of heart failure with preserved ejection fraction is not standardised and all current protocols are deficient. The cause and mechanism of this condition remains unclear and this study helped clarify the contribution of systolic versus diastolic dysfunction versus simply the presence of atrial fibrillation. Key diagnostic parameters were identified for routine clinical use and CMR LGE imaging demonstrating a greater average burden of non subendocardial LGE may support the postulated fibrotic infiltrative mechanism of pathology in this group.

Declarations

The research contained in this thesis was carried out by the author between 2012 and 2016 whilst a postgraduate student in the School of Medicine and Health at Durham University. None of the work in this thesis has been submitted in candidature for any other degree.

Statement of copyright

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Publications

Thompson ACM, Wilson DW, Duncan RF, Crilley JG, Murphy JJ. Evaluation of a simple regional wall motion score index to predict left ventricular ejection fraction by cardiac MRI. European Journal of Heart Failure 2014; 16 (Suppl. 2): 241-2.

Follows poster presentation at the Heart Failure Congress 2014 and the 1st World Congress on Acute Heart Failure, Athens, May 2014. Poster no 1278.

Thompson ACM, Crilley JG, Wilson DW, Hungin APS, Fuat A, Murphy JJ. Exclusion of prognostic coronary disease in left ventricular dysfunction using late gadolinium enhancement cardiac magnetic resonance. Proceedings of the Association of North of England, Nov 2014.

Associated oral presentation at Darlington Memorial Hospital, Nov 2014.

Thompson ACM, Crilley JG, Wilson DW, Hungin APS, Fuat A, Murphy JJ. Exclusion of prognostic coronary disease in LV dysfunction using late gadolinium enhancement CMR. Journal of Cardiovascular Magnetic Resonance 2015; 17(Suppl 1):P187. http://www.jcmr-online.com/content/17/S1/P187.

Follows poster presentation to the SCMR/EuroCMR 2015 Joint Scientific Sessions, Nice 2015.

Thompson ACM, Crilley JG, Wilson DW, Hungin APS , Fuat A, Murphy JJM. An epidemic of HFPEF? Poster presentation at the British Cardiovascular Society Conference 2016. Also featured in "Young investigators at the British Cardiovascular Society Annual Conference in June 2016", Myat A. *Heart* 2016;102:1509-1510.

Thompson ACM, Crilley JG, Wilson DW, Hungin APS, Fuat A, Murphy JJM. Excluding prognostic coronary disease in left ventricular dysfunction: a retrospective cohort study of late gadolinium enhancement cardiac magnetic resonance. Accepted for publication to the Journal of Clinical Radiology. Citation pending.

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Abbreviations

ACCF = American College of Cardiology Foundation

Ad = Duration of A wave on pulsed wave Doppler through the mitral valve

AHA = American Heart Association

AF = Atrial fibrillation

Ard = Duration of reverse pulmonary vein flow

ARR = Absolute risk reduction

ASE = American Society of Echocardiography

BBB = Bundle branch block

BCS = British Cardiovascular Society

BMI = Body mass index

BNP = Brain natriuretic peptide

BP = Blood pressure

BSA = Body surface area

BSE = British Society of Echocardiography

CABG = Coronary artery bypass graft

CAD = Coronary artery disease

CI = Cardiac Index

CMR = Cardiac Magnetic Resonance

CO = Cardiac output

COPD = Chronic obstructive pulmonary disease

CPEX = Cardiopulmonary exercise testing

CRT-D = Cardiac resynchronisation therapy with defibrillator

CRT-P = Cardiac resynchronisation therapy with pacemaker

CW = Continuous wave

DCM = Dilated cardiomyopathy

DCT = Deceleration time

e' = Early tissue Doppler diastolic velocity of mitral annulus

E/A = Ratio of early to late diastolic mitral inflow waves

E/e' = Peak velocity ratio of mitral inflow E wave to early diastolic mitral annular motion

EAE = European Association of Echocardiography

ECG = Electrocardiogram

EGFR = Estimated glomerular filtration rate

ESC = European Society of Cardiology

FEV1 = Forced expiratory volume at 1 second

FFR = Fractional flow reserve

GCP = Good clinical practice

GLS = Global longitudinal strain

HCM = Hypertrophic cardiomyopathy

HF = Heart failure

HF Alt cause = Heart failure due to an alternative cause

HFNEF = Heart failure with normal ejection fraction

HFNMSD = Heart failure with no major structural disease

HFPEF = Heart failure with preserved ejection fraction

HFREF = Heart failure with reduced ejection fraction

HRA = Health Research Authority

ICD = Internal cardiac defibrillator.

IHD = Ischaemic heart disease

IRAS = Integrated Research Application System

IVRT = Isovolumic relaxation time

IVC = Inferior vena cava

JVP = Jugular venous pressure

LA = Left atrium

LAD = Left anterior descending coronary artery

LAVI = Left atrial volume index

LBBB = Left bundle branch block

LCx = Left circumflex coronary artery

LGE = Late gadolinium enhancement

LMS = Left main stem

LV = Left ventricle

LVEDP = Left ventricle end-diastolic pressure

LVEDV = Left ventricle end-diastolic volume

LVEDVI = Left ventricle end-diastolic volume index

LVEF = Left ventricular ejection fraction

LVESV = Left ventricle end-systolic volume

LVH = Left ventricular hypertrophy

LVMI = Left ventricle mass index

LVOT = Left ventricular outflow tract

LVSD = Left ventricular systolic dysfunction

MAPSE = Mitral annular systolic excursion (by M-mode)

MI = Myocardial infarction

MRCA = Magnetic resonance imaging of the coronary arteries

MRI = Magnetic resonance imaging

NHS = National Health Service

NICE = National Institute for Health and Care Excellence

NNT = Numbers needed to treat

NT-pro BNP = NT-pro Brain natriuretic peptide

NYHA = New York Heart Association

OMT = Optimal medical therapy

OR= Odds ratio

PAP = Pulmonary artery pressure

PASP = Pulmonary artery systolic pressure

PCWP = Pulmonary capillary wedge pressure

PND = Paroxysmal nocturnal dyspnoea

PV = Pulmonary vein

PW = Pulsed wave

RA = Right atrium

RBBB = Right bundle branch block

RCA = Right coronary artery

REC = Research Ethics Committee

RGF = Research Governance Framework

RHF = Right heart failure

RRR = Relative risk reduction

RV = Right ventricle

RWMA = Regional wall motion abnormality

RWMSI = Regional wall motion score index

S' = Mitral annular systolic motion by tissue Doppler

SPECT = Single-photon emission computed tomography

SPSS = Statistical Package for the Social Science

TAPSE = Tricuspid annular plane systolic excursion

TD = Tissue Doppler

TOE = Transoesophageal echo

TTE = Transthoracic echo

VC = vital capacity

VO2 = Oxygen consumption

Vp = Colour Doppler M Mode propagation velocity

Introduction

Heart failure has been studied in western civilisation ever since the works of Hippocrates in ancient Greece and continues to be readily studied worldwide. It is a common diagnosis affecting more than 1% of people in the UK, and one which has a profound impact on National Health Service (NHS) resources. It remains in the top 10 diagnoses for use of hospital bed days in the NHS. Mortality rates are high with 9.4% of patients dying during their admission and over 30% dying within a year of discharge (1, 2).

The differing strategies to identify and classify heart failure through the ages demonstrate the changes in our understanding of heart failure. This ranges from a purely clinical description to abnormal haemodynamics; structural cardiac pathology; biochemical abnormalities; and genetic identification (3). All of the various diagnostic approaches provide useful insights into the syndrome of heart failure but each has its own set of limitations. In the recent past, the emphasis has been to identify simplified, specific measures (that can be easily obtained and reproduced) to act as the overriding component in a diagnosis of heart failure. The introduction of routine transthoracic echocardiography and measurement of left ventricular ejection fraction (LVEF) is a prime example of this. However, such strategies are an oversimplification of the problem.

Although reduced left ventricular ejection fraction (LVEF) has been embraced as the key feature to support a diagnosis of heart failure, over 40% of patients diagnosed with heart failure clinically have normal or near normal ejection fractions (4). Indeed elevated plasma brain natriuretic peptide (BNP) or N-terminal pro-hormone of brain natriuretic peptide (NT-pro BNP) that are secreted in response to cardiac stretch and strain regularly add weight to the suggestion of cardiac dysfunction in such cases (5-7). This means that a substantial number of patients labelled with heart failure either have a cause other than reduced ejection fraction for their symptoms or the echo scan is unable to detect the reduced ejection fraction in a number of cases.

Heart failure with preserved ejection fraction (HFPEF) has been officially recognised over the last decade and is generally thought to be due to diastolic dysfunction of the left ventricle demonstrated by elevated filling pressures, abnormal relaxation and increased chamber stiffness. Formal diagnostic parameters for HFPEF have been suggested by way of various echocardiographic measures in association with symptoms and signs but these are complex and a confirmed diagnostic strategy for HFPEF continues to be debated (8-10). There also continues to be debate surrounding the interplay of HFPEF and heart failure with reduced ejection fraction (HFREF), and whether or not HFPEF represents a distinct entity from that of HFREF (11, 12). Mortality rates in HFPEF are debated and as of yet, there are no evidence based treatments for HFPEF. However,

this is unsurprising for a disease where the name eludes to the lack of a problem (preserved ejection fraction) for its diagnosis rather than establishing a tangible disturbance of cardiac function, and should help to discredit the theory that reduced ejection fraction is of paramount significance when determining cardiac dysfunction.

There is also a sizeable group of patients that present to heart failure services with symptoms suggestive of heart failure but no major structural heart disease on routine imaging. Currently they tend to be reassured and discharged from clinical care, but recent work suggests that this group should be a cause for concern with high rates of early mortality (13). Often these patients have elevated BNP levels (14). Generally they are elderly with multiple co-morbidities and cannot be readily compartmentalised. They form a group that has been poorly studied before and a unifying diagnosis for their symptoms and elevated biomarker remains elusive.

The advent of echocardiography was a major step forward in the understanding of heart failure and allowed an assessment of heart structure and function through the use of ultrasound. It is an ever-expanding and complex field that can offer a wealth of information about cardiac structure and function. The daily practical reality is that scans are limited by time constraints and tend to be used primarily to identify serious valve disease, measure the left ventricle size and ejection fraction as a measure of left ventricular systolic performance, and perform limited measures of left ventricular diastolic function. It also has shortcomings in that various patient factors often result in sub-optimal image quality and poor endocardial definition limits reliable chamber volumes and ejection fractions (15-17). Echo is also unable to provide tissue characterisation to differentiate ischaemic from non-ischaemic cardiomyopathy.

Cardiac Magnetic Resonance (CMR) is the gold standard method for measuring left and right ventricular volumes and myocardial mass and is particularly validated in systolic dysfunction (18). Additional information about myocardial ischaemia, infarction, inflammation and infiltration can be achieved by incorporating the use of gadolinium contrast agent and observing the pattern of myocardial uptake (19). Velocity encoded mapping can determine blood flow velocities through valves and other structures (20-23), and tissue phase mapping or tagging can be used to quantify myocardial movement during the cardiac cycle.

Currently the use of CMR is generally restricted to specialist centres and performed on a case-by-case basis with a specific question in mind. The clinical impact of routine CMR has only been studied in well-defined subgroups. Focused studies suggest that routine CMR has a significant impact on clinical management post myocardial infarction (24), in cases of left bundle branch block (25) or, in a HFREF population to determine the

likelihood of significant coronary artery disease (19, 26-29). Whilst a heart failure clinic CMR service is achievable (30), there is a paucity of observational data, or CMR demographics, for a generic group of heart failure patients that incorporates those with HFPEF and heart failure without major structural heart disease.

Incorporating routine CMR alongside comprehensive echocardiography into the initial screening of patients with heart failure could provide clinically important information to complement echocardiography findings. Epidemiological information provided by CMR may support or refute the current presumed spectrum of pathology in the heart failure population. CMR could alter diagnosis by reclassifying LVEF and left ventricular (LV) size in an individual. It could differentiate the underlying cause of heart failure by way of late enhancement, particularly in the HFREF population. This would also apply to those with heart failure with preserved ejection fraction or no major structural disease, although simply the presence or absence of late enhancement in these groups would be of interest. CMR should help to clarify some already accepted measures of diastolic dysfunction to aid diagnosis in unclear groups. Alternatively, CMR may demonstrate novel imaging findings that help to describe heart failure by way of new defining criteria.

Heart failure is a heterogeneous disorder and much more difficult to characterise than symptoms, isolated echo parameters (such as LVEF), or biomarkers alone would initially lead us to believe. It is time for a paradigm shift in our approach to the diagnosis of heart failure to one that incorporates a multifaceted assessment of cardiac anatomy and function in daily practice. Simply defining the composition of a new heart failure clinic population incorporating CMR would be of interest. Thereafter subgroup analysis will be informative, with perhaps the most novel insight from the HFPEF and non-compartmentalised groups that have been little investigated before.

Research question

What are the demographics and imaging characteristics of a heart failure population using a comprehensive echocardiography protocol and routine CMR imaging? Does routine CMR allow better understanding and differentiation of the heart failure population?

Hypothesis

An enhanced clinical pathway providing detailed assessment and database collection of demographics and imaging characteristics of patients presenting with heart failure will provide better understanding of the causes and definition of heart failure. Incorporating routine CMR imaging will result in a better understanding of the spectrum of pathology in the heart failure population, with a novel insight into those patients currently described as heart failure with a preserved ejection fraction (HFPEF) or heart failure with no major structural heart disease in particular. This will help to differentiate the underlying aetiology of heart failure and compartmentalise heart failure into subgroups that may differ from those currently used.

Rationale for the research: A résumé of the literature

Chapter 1

Heart Failure Epidemiology

Heart failure is a common diagnosis affecting more than 1% of people in the UK, and one which has a profound impact on NHS resources. It remains in the top 10 diagnoses for use of hospital bed days in the NHS with a mean length of stay of 11 days. Mortality rates are high with 9.4% of patients dying during their admission, 14.9% dying either in hospital or in the month following discharge, and over 30% dying within a year of discharge (1, 2). Heart failure is predominantly a disease of old age with the mean age of 77 years at the time of first hospital admission. In an ever aging British population, with increasingly sophisticated and successful percutaneous and medical interventions, allowing people to survive longer with significant coronary artery disease, the impact of this condition on society is set to increase.

Heart Failure: Difficulties defining and diagnosing a multifaceted disease

Heart failure is heavily researched worldwide, and has been studied in western civilisation ever since the works of Hippocrates in ancient Greece. However, because of the heterogeneous nature of this disorder the definition of heart failure remains vague.

The clinical presentation of this condition is varied, ranging from acute pulmonary congestion to chronic peripheral oedema. The underlying causes are also varied, and the same clinical presentation can result from a diverse range of structural and physiological changes, some of which occur in isolation and some of which occur in synchrony. Determining which of these changes is most relevant to precipitating a clinical picture of heart failure is sometimes simple but at other times can be a major challenge. Thereafter, compartmentalising these changes into discrete readily identifiable conditions is fraught with difficulty, and indeed may even be impossible.

Expert synopsis of the differing strategies to identify and classify heart failure through the ages demonstrates the changes in our understanding and interpretation of heart failure ranging from a purely clinical description to abnormal haemodynamics; structural cardiac pathology; biochemical abnormalities; and genetic identification (3).

In current practice, a diagnosis of heart failure generally combines a clinical interpretation of the patient's history and examination, in association with natriuretic biomarkers, an electrocardiogram, chest X-ray and trans-thoracic echocardiogram (TTE). However, differentiation is hampered by varying diagnostic parameters, confounding non-cardiac

pathology, the presence of multiple cardiac abnormalities, and limitations of routine imaging.

The European Society of Cardiology (ESC) 2012 definition is wide reaching and defines heart failure "clinically, as a syndrome in which patients have typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and displaced apex beat) resulting from an abnormality of cardiac structure or function" (31). The specific abnormality of cardiac structure or function is not characterised and the method to identify this abnormality does not form part of the definition. Indeed, they highlight that in view of the difficulty grading the evidence for diagnostic tests all diagnostic investigations represent an evidence level of "C", meaning that the evidence reflects only consensus of opinion of the experts and/or small studies, retrospective studies, or registries.

Heart Failure by this definition could thus incorporate a broad spectrum of abnormalities ranging from intrinsic left ventricular dysfunction to right ventricular dysfunction, primary valve disease, pericardial disease, various congenital heart diseases, and a variety of cardiac conduction abnormalities.

Whilst accepting the same broad range of causes of heart failure above, most clinicians tend to concentrate on impairment of ventricular function as the focus of the definition. Those with specific valvular or conduction abnormality are labelled primarily as such and a diagnosis of heart failure per se may not be given. This may even apply if a ventricle is frankly failing in the context of the severe valve disease. Equally, it is not uncommon for an individual to be labelled as having heart failure following imaging that suggests a degree of left ventricular impairment but in the absence of any clinical symptoms or signs of heart failure (32).

It should always be borne in mind that such diversity in diagnostic frameworks, and clinical interpretation of these diagnostic frameworks, has implications for the meaning and reproducibility of statistics collected and categorized under the heading of "heart failure".

Defining heart failure by left ventricular ejection fraction (LVEF)

Measuring LVEF

LVEF is the percentage of the LV diastolic volume that is ejected through the aortic valve and into the circulation during LV contraction or systole. It is calculated using the equation below, with percent (%) for units.

LVEF = (LVEDV-LVESV)/LVEDV

LVEF = (LV end-diastolic volume – LV end-systolic volume) /LV end-diastolic volume

Until recently LVEF was determined by echo using a single M-Mode cross-section through the base of the heart and extrapolating the fractional shortening into an ejection fraction. However, this extrapolation of a single cross-sectional measurement into a 3D structure made this technique highly inaccurate. Over the last 5-10 years a method called Simpson's Biplane Method of Disks has been labelled as the gold standard for 2 dimensional (2D) echo assessment of LVEF (33, 34). This requires an apical four- and two-chamber view from which the endocardial border is outlined in end-diastole and end-systole. However, accurate measurements are frequently hampered by poor endocardial definition (detailed below). 3 dimensional (3D) echo improves the precision of these measurements (35-37) but is rarely used for routine clinical scans. Cardiac computerised tomography (CT) assessment of LVEF may be more accurate than 2D or 3D transthoracic echo and invasive cine ventriculography (38). In this regard, CMR is generally accepted as the gold standard modality for measurement of LV volumes and LVEF when using the multi slice disk summation method (15, 39). This is because of the ability of CMR to image the LV in multiple planes and provide clear endocardial definition with excellent inter and intra observer variability.

Causes of reduced LVEF and varying underlying aetiology

LVEF is reduced when the ejected stroke volume is reduced relative to the LV end-diastolic volume. This is most commonly due to impaired contractility, be that by either a global reduction in contractility of the LV, or due to regional wall motion abnormalities (RWMAs). The leading cause of RWMAs is coronary artery disease. A global reduction in contractility is generally seen in a dilated cardiomyopathy for which there are many causes including idiopathic, hypertension, alcohol related, infective, various genetic disorders, tachycardia induced, hormone related and vitamin and mineral deficiencies to name a few. LBBB tends to cause a dyssynchrony of septal LV wall motion but often occurs in dilated ventricles where there is also a global disruption to contractile function and so probably spans both groups. Often in patients with contractile dysfunction the LV attempts to maintain stroke volume by dilating and increasing the end-diastolic volume. The heart ejects a smaller fraction of a larger volume. Generally, the more severe the systolic dysfunction the lower the ejection fraction and the larger the end-diastolic and end-systolic volumes.

Whilst dilated ventricles often have reduced ejection fractions, this reduction in ejection fraction may still result in a better cardiac output than a smaller ventricle with the same ejection fraction. It is an increasingly recognised phenomenon that small hypertrophied ventricles may provide sub-optimal stroke volumes and cardiac outputs, particularly on

exertion, despite a reassuringly normal LVEF. As discussed above, a reduced ejection fraction does not help to define the underlying aetiology. A reduced ejection fraction in a globally dilated and impaired ventricle often represents a totally different underlying aetiology and disease process from a reduced ejection fraction in a normal sized or mildly dilated ventricle with RWMAs. This is not apparent by interpreting the ejection fraction alone.

LVEF as trial entry criteria

Despite the limitations of obtaining accurate ejection fractions by echo this measurement was felt to be a readily understandable quantitative representation of LV systolic function and became almost universally reported in echo studies. When the prognostic importance of reduced LVEF was established, the term was embraced as the key imaging feature to support a diagnosis of heart failure (40, 41). This was further enforced by clinical trials insisting upon a reduced ejection fraction as the main entry criterion at a time when randomised clinical trials were becoming established in cardiology (Figure 1) (42-66).

Figure 1. LVEF entry requirements in major cardiology trials

Cardiology Trial	Date	Treatment added	LVEF entry criteria	Trial outcome
SOLVD-T	1991	Enalapril vs placebo for HF	≤35%	Mortality reduction (ARR 4.5%)
ATLAS	1999	High vs low dose lisinopril for HF	≤30%	Reduced death or HF hospitalisation at high dose (RRR 12%)
SAVE	1992	Captopril vs placebo post MI	≤40%	Mortality reduction (RRR 19%)
TRACE	1995	Trandolapril vs placebo post MI	≤35%	Mortality reduction (RRR 22%)
Val-HeFT	2001	Valsartan vs placebo in HF patients taking ace-i	<40%	Reduced HF hospitalisation (RRR 24%)
CHARM-Added	2003	Candesartan added to ace-i +/- BB for HF	≤40%	Reduced HF hospitalisation (RRR 17%)
VALIANT	2003	Valsartan vs captopril post MI	≤35%	Valsartan non-inferior with respect to mortality
MDC	1993	Metoprolol vs placebo for DCM	<40%	Improved symptoms, cardiac function, and need for transplant. No effect on all cause mortality.
CIBIS II	1999	Bisoprolol vs placebo for HF	<35%	Reduced mortality (ARR 5.5%)
MERIT-HF	1999	Metoprolol vs placebo for HF	≤40%	Reduced mortality (ARR 3.8%)
COPERNICUS	2002	Carvedilol vs placebo for HF	<25%	Reduced mortality (ARR 7.1%)
COMET	2003	Carvedilol vs metoprolol for HF	<35%	Reduced mortality with carvedilol (ARR 5.7%)
RALES	1999	Spironolactone vs placebo	≤35%	Reduced mortality (ARR 11.4%)
EPHESUS	2003	Eplerenone vs placebo post MI	≤40%	Reduced mortality (RRR 15%)
EMPHASIS-HF	2011	Eplerenone vs placebo for HF	≤30% ≤35% if QRS >130ms	Reduced mortality (ARR 3%)
DIG	1997	Digoxin vs placebo for HF	≤45%	Reduced HF hospitalisations (ARR 7.9%)
SHIFT	2010	Ivabradine vs placebo for HF	≤35%	Cardiovascular death or HF hospitalization

				(ARR 4.2%)
CORONA	2007	Rosuvastatin vs placebo for HF due to IHD	≤40% or HF admission	No difference in combined endpoint
PARADIGM-HF	2014	LCZ696 vs enalapril for HF	≤35-40%	Reduced mortality (ARR 2.8%)
MADIT II	2002	ICD vs conventional treatment post MI > 40 days	≤30%	Reduced mortality (ARR 5.6%)
COMPANION	2004	CRT-D vs CRT for HF and QRS >120ms	≤35%	Reduced mortality and hospital admission for HF (RRR in death of 24% with a CRT-P, 36% with CRT-D)
CARE-HF	2005	CRT vs OMT for HF and QRS >120ms	≤35%	Reduced mortality (ARR 9.7%)
SCD-HeFT	2005	ICD vs amiodarone or placebo for HF	≤35%	Reduced mortality with ICD (ARR 6.9%)
MADIT-CRT	2009	CRT-D vs ICD for HF and QRS >130ms	≤30%	Reduced HF Hospitalisation (ARR 8.9%)
RAFT	2010	CRT-D vs ICD for HF and QRS >120ms or paced	≤30%	Reduced mortality (ARR 6%)

RRR, Relative risk reduction; ARR, Absolute risk reduction; HF, Heart failure; MI, Myocardial infarction; DCM, Dilated cardiomyopathy; OMT, Optimal medical therapy; CRT-D, cardiac resynchronisation therapy with defibrillator; ICD, Internal cardiac defibrillator.

What is a reduced LVEF?

These trials did not always agree the same LVEF entry criteria, and whilst those that showed treatment benefits tended to have an LVEF <40%, the exact LVEF cut-off varied. As such, the boundaries for a clinically relevant diagnosis of "reduced ejection fraction" became inconsistent in the medical community.

What is a normal LVEF?

Surprisingly, robust data to answer this question only became available in 2014 when the NORRE study, specifically designed to develop normal reference ranges for 2D echo measures, published its findings from measurements on 734 healthy volunteers (Figure 2) (67). This demonstrated a mean Simpson's Biplane LVEF of 63.9% (2SD range of 56.5 to 71.7%). Before this, much of the data supporting the normal Simpson's Biplane LVEF cut-off came from a cross-sectional study of a population where ischaemic heart disease, hypertension and alcohol excess was prevalent as opposed to healthy volunteers, and found a lower mean LVEF of 47.3% (SD 6.5) (32). Boundaries for normal LVEF were set by the British Society of Echocardiography at ≥55% based upon international guidelines that referenced only two studies for their conclusions (34, 68). The first of these studies was conducted in 1983 and observed only 52 normal volunteers (69). The second included 206 healthy individuals (a mixture of New York citizens and American Indians) but the method of LVEF calculation was not clear (70). The BSE guidelines end with a caveat that "where there are differences between published values, or there is a lack of clear evidence, recommended values have been developed on the basis of consensus opinion". Indeed, even the most recent (2012) ESC heart failure guidelines established the normal LVEF as ≥ 50 % according to a raising of hands and a general consensus of opinion from the guideline steering committee, rather than substantive evidence (as confessed by Professor Alan Fraser at the British Cardiovascular Society conference, Manchester 2014).

Importantly, the NORRE study also demonstrates how mean normal LVEF varies significantly with both gender and age so that a single cut-off cannot be universally employed. Consistent with these NORRE study findings, physiological studies have shown that in early aging a reduction in LV longitudinal function, alongside improvement in LV radial movement brings about an improved LVEF, before a deterioration again in very old age when radial function diminishes (71).

Figure 2. Age and gender specific normal ranges for echo Biplane LVEF, adapted from the NORRE study.

Age	Gender	Biplane LVEF% normal range (mean ± 2 SD)
20-40 years (n=262)	Male	53.5-72.3%
	Female	53.9-73.1%
40-60 years (n=341)	Male	53.2-72.4%
	Female	55.1-74.3%
>60 years (n=131)	Male	54.4-75.6%
	Female	55.1-75.1%

Heart Failure with Preserved Ejection Fraction (HFPEF)

The limitations of left ventricular ejection fraction as a way to define heart failure were then highlighted by the realisation that over 40% of patients diagnosed with heart failure clinically have normal or near normal ejection fractions on echo (4). This group was coined as having Heart failure with preserved ejection fraction (HFPEF).

HFPEF has been established as a diagnosis for over a decade yet the definition varies depending upon the differing accepted thresholds for a reduced ejection fraction. There is a subset that has an entirely normal LVEF and the label Heart Failure with Normal Ejection Fraction (HFNEF) is sometimes used to describe the group. However, many people will have a mildly reduced LVEF that is insufficient to establish the diagnosis of HFREF according to previous important prognostic trials yet seems too low to justify a label of normal ejection fraction. This was the scenario in the CHARM-preserved trial, when LVEF >40% was the entry criteria, and led to the coining of the phrase HFPEF (72). In these cases the contribution of reduced LVEF to the patients' symptoms is difficult to ascertain and this population may well represent a diverse range of pathology.

There continues to be debate surrounding the interplay of HFPEF and HFREF, and whether or not they form a continuum of the same condition or represent distinct entities (11, 12, 71, 73).

Some studies suggest that mortality rates in HFPEF are comparable with HFREF (74). Others disagree, demonstrating lower rates of mortality in the HFPEF group compared to the HFREF group (75, 76). Additionally, whereas mortality rates in HFREF have

improved over the last two decades, mortality rates for those with HFPEF have remained static (77).

Many believe HFPEF is due to diastolic dysfunction of the left ventricle demonstrated by elevated filling pressures, abnormal relaxation and increased chamber stiffness. Others feel it is due to subtly reduced LVEF or other aspects of systolic function that are not routinely measured.

LVEF is only a partial representation of LV systolic function. Longitudinal systolic function (the shortening of the left ventricle from base to apex during systole) can often be reduced without any effect on ejection fraction but can result in a clinical consequence. However, longitudinal function is rarely measured or described in echo reports. It is proposed that these markers of longitudinal LV function, specifically S', may be more valid markers of LV systolic function than LVEF (71). These parameters have a more linear relationship with the normal aging ventricle, and they are more sensitive at detecting subtle ischaemia than LVEF because they reflect the function of the subendocardial layer of myocardial fibres which are most susceptible to ischaemia. They are also more reproducible than LVEF by 2D echo.

Whilst the debate goes on about the contribution of systolic versus diastolic dysfunction in HFPEF, one explanation for the differing opinion may be that the variable diagnostic boundaries mean some definitions of HFPEF incorporate more people with subtly reduced LVEF than other definitions. Differences in the physiological response of the LV to vasodilators certainly give some credence to the suggestion that these are two distinct heart failure phenotypes when LVEF <50% defines HFREF (78). In this setting those with HFPEF experience greater blood pressure reduction but with significantly less enhancement in cardiac output, and greater likelihood of stroke volume drop with vasodilators, which would be in keeping with disease specific differences in ventricular-arterial properties.

Prevalence: The epidemic that is or is not HFPEF

Whilst the percentage of people classified as HFPEF may vary depending on the diagnostic criteria for a reduced ejection fraction, even when more encompassing definitions for HFREF are employed (LVEF <50%), studies have reported a substantial proportion (around 50%) of people diagnosed with heart failure and preserved ejection fraction (75). Monitoring trends in prevalence using the same definition also shows how the prevalence of HFPEF has increased over the last two decades, in contrast to reducing rates of HFREF, meaning that this now forms the majority of acute heart failure presentations (77). High rates of heart failure with preserved ejection fraction can be

determined not only by clinical features alone, but also elevated BNP or NT-pro BNP that add weight to the suggestion of cardiac dysfunction in some series (6, 7, 79).

However, many believe that HFPEF is hugely over diagnosed. Certainly, it is difficult to justify that someone has heart failure with a definition that predominantly relies on the absence of pathology, and it is possible that the numbers of people with HFPEF have been widely overestimated as a result of lax definitions. Limitations of a purely clinical diagnosis are widely recognised. Symptoms of exertional breathlessness are common: a third of people over 70 years old and living independently are affected (80). When a similarly aged group of people in the Netherlands who presented to primary care with breathlessness were assessed clinically, with BNP or NT pro BNP, and echocardiography where indicated, a diagnosis of heart failure according to ESC guidelines was established in only 15.7% (2.9% HFREF, 12% HFPEF, and 0.9% isolated right heart failure) (81). It was suggested that the others had symptoms due to a variety of age related deconditioning and sarcopenia (muscle wasting), obesity, airways disease, and anxiety or depression. When a Scottish cohort of 109 patients with normal LVEF were reviewed for suspected heart failure, 40 were obese/morbidly obese, 54 had a reduction in FEV1, and 31 had history of IHD that could also explain their symptoms. Only 7 lacked a recognised explanation for their symptoms other than HFPEF (82).

When strict definitions for HFPEF were applied retrospectively to a cohort of 5883 patients admitted with heart failure (including a clinical diagnosis of heart failure, LVEF ≥50%, alternative cardiac cause or over-riding co-morbidity excluded, a non-dilated ventricle, LV hypertrophy or dilated left atrium, and impaired diastolic function or raised BNP) Patel and colleagues found that only 0.8% of patients met the diagnostic criteria for HFPEF (83).

Time after time epidemiological studies show that the typical characteristics of a HFPEF population include being female, old age, hypertension, diabetes mellitus, atrial fibrillation, obesity and chronic kidney disease. Some individuals suggest a pathophysiological mechanism for diastolic dysfunction as a direct result of these co-morbidities, whereby they induce a systemic pro-inflammatory state that results in stiffening of the cardiomyocytes, interstitial fibrosis, and thus high diastolic LV stiffness (84). This shifts the emphasis from the commonly held belief that LV afterload excess is the predominant cause and would go some way to understanding the high prevalence of these other conditions in the HFPEF community. Others are sceptical of this pathophysiological model and suggest these multiple associations reflect how HFPEF is a single diagnosis given to a heterogeneous group with other co-morbidities that alone could explain the symptoms. A counter argument to this comes from a comparison of

mortality rates in patients from HFPEF trials to an age and co-morbidity matched population without HFPEF. This showed significantly higher rates of mortality in the HFPEF group, suggesting that HFPEF is an independent entity (85).

The recently published Darlington Retrospective Outpatient Study (DROPSY) also suggested high rates of mortality in those diagnosed with HFPEF. The authors investigated the long-term outcomes of patients presenting to local heart failure clinics between 2002 and 2007 (13). They established three groups of patients according to routinely utilised parameters of cardiac dysfunction. The groups comprised left ventricular systolic dysfunction, heart failure with preserved ejection fraction and non-heart failure. Heart failure with preserved ejection fraction was defined as LVEF >40% by Simpson's rule, or "normal" function on "eye balling", hospitalisation for heart failure in the last 6 months or NYHA class II-IV with signs of heart failure and two of the three (chest X-ray, ECG or echo) abnormal; echo abnormalities including LVH, LA enlargement or E/A <0.5. Mortality rates over the study period were highest in the group with LV systolic dysfunction at 60%. Those with HFPEF had lower mortality rates at 50% but these were still higher than the 41% in non-heart failure group (Figure 3).

Figure 3. Long-term outcomes of patients presenting to local heart failure clinics 2002-2007 according to the DROPSY study (13).
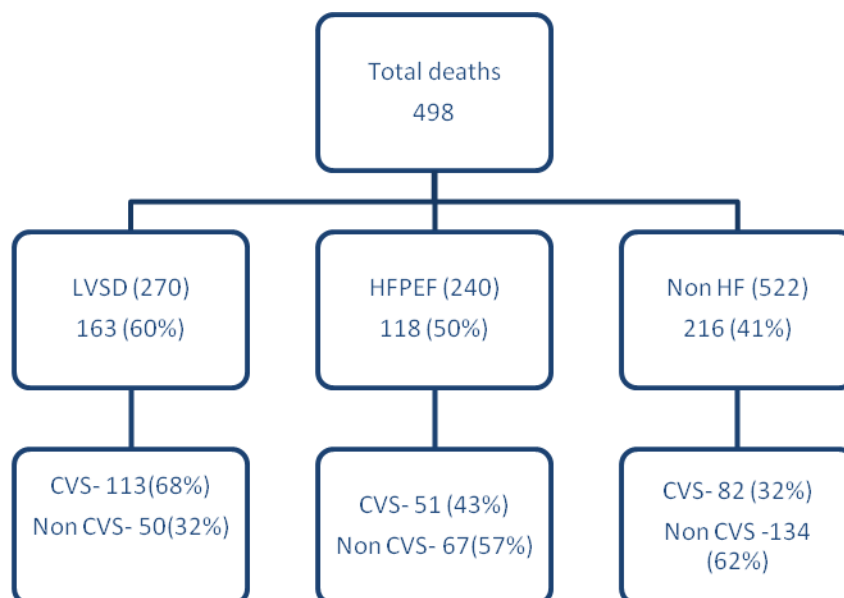
Taken with permission from R Singh's thesis (13). LVSD, group with left ventricular systolic dysfunction; HFPEF, group with heart failure with preserved ejection fraction; Non HF, group with no evidence of heart failure; CVS, death from cardiovascular causes.

Current imaging assessment of diastology by echo has limitations for the diagnosis of HFPEF. Seemingly abnormal echo measures may be normal for aging. Despite

reductions in arterial load with medical therapy, it has been shown that LV systolic and diastolic stiffness increase over time in humans, particularly in women, and in a passive manner as opposed to actively enhanced systolic function that which would occur with hypertension (86). These changes may also be more prominent with increasing body mass index (BMI). The overall prevalence of some form of LV diastolic dysfunction in a random sample of a general population in various European countries ranged from 22.4% to 27.3% according to echo measures (87, 88). There have also been challenges to the diagnosis of diastolic heart failure based on commonly used echo criteria that includes E/A ratios, isovolumic relaxation time (IVRT) and deceleration time (DCT) after finding very poor concordance between measures, with a 16-fold difference in the prevalence of diastolic dysfunction in patients with suspected HFPEF (89).

The echo E/e' ratio relates the peak velocity of early diastolic transmitral flow to the peak velocity of early diastolic mitral annular motion. This measure represents end-diastolic filling pressure but has limitations in that the value increases normally with age, and is not valid in mitral valve disease, annular calcification or septal or lateral wall infarcts. When E/e' is elevated above 15 there is a consensus that this is diagnostic of elevated diastolic filling pressures and can be used to define HFPEF (8-10, 90). However, the underlying pathophysiological cause of the raised LV diastolic filling pressure is not demonstrated by the E/e' measure and a value >15 occurs frequently in HFREF. Also, when this value is between 8 and 15 a variety of parameters are employed to help to confirm the diagnosis and these are not universally defined.

With increasing recognition of the limitations of diagnosing HFPEF by a purely clinical or imaging based approach, the role for biomarkers has gained much support over the last 10 years. Their potential impact was been demonstrated most recently by the results of the TOPCAT trial subgroup analysis. TOPCAT was a trial of spironolactone for HFPEF. Published in 2014, it showed no overall benefit of spironolactone for the composite endpoint of death from cardiovascular causes, aborted cardiac arrest, or hospitalisation for the management of heart failure. However, subgroup analysis seemed to show distinctive differences between the American/South American versus the Russian cohort so that spironolactone was beneficial in the American/South American population but not in the Russian population (91). The rationale proposed for this difference was that BNP may be crucial to identify true HFPEF and that clinical judgement alone is not sufficiently accurate. BNP tended to be used alongside clinical judgement for inclusion in the American/South American population whereas clinical judgement alone tended to be sufficient for inclusion in the Russian subgroup, and it is postulated that a significant number of the Russian cohort did not actually have HFPEF. Other studies have shown

the disconnection between the perceived severity of congestive heart failure by an emergency department physician, and severity as determined by BNP level (92).

Defining heart failure with biomarkers

The advent of biomarkers, particularly brain natriuretic peptide (BNP) or N-terminal prohormone of brain natriuretic peptide (NT-pro BNP) changed the way of thinking about heart failure. Here was a test that had the potential to identify heart failure at an early stage when current imaging modalities of heart function would be reported as normal, or similarly identify those with overt clinical heart failure but a preserved ejection fraction on echo.

Myocardial wall stress results in the release of BNP and NT pro BNP which in turn induce vasodilation, natriuresis and diuresis with a view to reducing the afterload for the heart when in heart failure. The plasma circulating levels can be measured as part of a diagnostic work-up for heart failure. Many agree BNP is a useful tool to exclude heart failure, exemplified in a study that showed how a normal level will exclude this diagnosis with a sensitivity of between 84-93% (93). A BNP guided treatment strategy to encourage up titration of ace inhibitors and beta-blockers can also be used to reduce heart failure related mortality or hospital admissions when compared to standard management in a HFREF (94).

Also, the superior prognostic influence of elevated BNP in comparison with LVEF was convincingly demonstrated recently. A group from the Netherlands and Sweden observed 615 patients with heart failure for 18 months. Although BNP levels were lower in patients with HFPEF than HFREF, for a given BNP level, the prognosis in patients with HFPEF was as poor as those with HFREF. Where BNP was found to be a strong predictor of outcome, LVEF was not (95). Ever accumulating evidence of the prognostic power of the natriuretic peptides (96) has led to some experts advocating the sole use of biomarkers to diagnose heart failure, or at the very least to select a population with high cardiovascular morbidity and mortality where one should target intervention (97). Indeed, many studies have since used an elevated BNP level as part of the diagnostic pathway for diastolic impairment and trial entry criteria (60, 98, 99).

However, an elevated BNP to confirm a diagnosis of heart failure has some limitations. Average specificity has been reported as only 73-74% (93), recognising that the specificity increases the higher the level of BNP (100). There is variation in what is defined as a normal level depending upon the clinical presentation; current recommendations would use a cut-off of 100pg/ml in the emergency setting and 35pg/ml in the outpatient setting (31). Interpretation is confounded by the fact that BNP and NT pro-BNP levels increase with age and lower body mass and numerous studies have

reported how BNP and NT pro-BNP perform poorly to detect asymptomatic or symptomatic systolic or diastolic dysfunction in an elderly population (5, 101-104). BNP levels also increase with renal failure, and reduce with obesity (105). The presence of atrial fibrillation impairs the diagnostic performance of natriuretic peptides in patients with dyspnoea (106) according to a gold standard physician's diagnosis of HFPEF by reducing the specificity. This may be particularly important in a HFPEF population, where atrial fibrillation is commonplace. Alternatively, it could be argued that atrial fibrillation is a form of diastolic dysfunction, as exemplified by the fact that it is included in many diagnostic frameworks for HFPEF, and that a raised BNP in the setting of symptoms of heart failure with atrial fibrillation should be diagnosed as HFPEF in all circumstances.

Whilst the number of deaths or hospitalisations due to heart failure increases with higher levels of NT pro BNP in a HFPEF population (5), (indeed in a more predictive manner than echo parameters) (5-7), it remains unclear as to whether this represents more pronounced diastolic dysfunction, a generally sicker individual with co-morbidities, or indeed systolic dysfunction but with an ejection fraction that is not low enough to meet trial entry criteria. Higher NT pro BNP levels are associated with lower ejection fraction and larger ventricular dimensions (5) but BNP level also seems to be useful in the diagnosis of diastolic dysfunction (79, 107), and indeed may be representative of the degree of diastolic dysfunction (108-110), (taking into account the limitations with older age groups noted above), although this has been disputed by other studies (87).

Some regional heart failure clinics utilising biomarkers have found a substantial number of patients with symptoms of heart failure, elevated BNP but no major structural heart disease on routine imaging (14). Generally these patients are elderly with multiple co-morbidities and cannot be readily compartmentalised. They form a group that has been poorly studied before and a unifying diagnosis for their symptoms and elevated biomarker remains elusive. This begs the question, does the elevated BNP represent undiscovered structural heart disease, or is it simply a marker of adverse prognosis in a co-morbid individual with no specific cardiovascular abnormality?

Those that believe BNP and NT pro BNP biomarkers are the key to a diagnosis of heart failure (be that HFREF or HFPEF), looked at their cohort of outpatient heart failure patients. They found that BNP was significantly higher in the HFREF group compared to a control population, but no difference existed between the controls and those thought to have HFPEF. However, perception of breathlessness and the six min walks were similar between the HFREF and HFPEF groups. They concluded that patients being treated for a clinical diagnosis of HFPEF have a perception of their symptoms that is out

of proportion to their evidence of cardiac pathology (111), and indeed may not have HFPEF. An alternative explanation could be that BNP is not as sensitive at detecting HFPEF as it is HFREF. Obesity may lower levels of BNP giving falsely reassuring levels, particularly in the HFPEF group (112). Perhaps more conceivable is the proposition that HFPEF is sometimes a disease of exercise not rest, and as such resting biomarkers may not be elevated to the same extent; it introduces the concept of differing phenotypes of a HFPEF population, differentiated by biomarker levels and alternatively differentiated by exercise related physiological changes (96).

Of note for the future, biomarker guided management and prognostication may be of limited value. The novel dual angiotensin and neprilysin inhibitor (ARNi) LCZ696 agent to treat heart failure increases the levels of the natriuretic peptides through its actions. Neprilysisn breaksdown endogenous vasoactive peptides, including natriuretic peptides. Inhibition of neprilysin increases the levels of these substances, with the aim of offsetting the neurohormonal overactivation that contributes to the vasoconstriction, sodium retention, and cellular remodelling seen in heart failure. It has been shown to reduce the rates of death from any cause when compared with enalapril (NNT=35) at 27 months in a HFREF population (60) but has the effect of increasing natriuretic peptide levels through its actions. A similar trial is now underway for a HFPEF cohort in the PARAGON-HF study (99).

Exercise Assessment

With this increasing recognition that HFPEF may be a disease that presents only on exertion in some cases, some teams have tried to observe the various haemodynamic responses to exercise in this group of patients. Borlaug and colleagues have shown how euvolemic patients with normal BNP, normal coronary arteries, and normal cardiac filling pressures at rest have markedly abnormal hemodynamic responses during exercise in over half of 55 patients with exertional dyspnoea, to suggest HFPEF (113). These haemodynamic parameters included pulmonary capillary wedge pressure (PCWP) and pulmonary artery systolic pressure (PASP) and were measured invasively. Others have demonstrated various parameters of systolic and diastolic left ventricular dysfunction during exercise in a HFPEF population with proven cardiopulmonary limitation, including mitral annular tissue Doppler parameters, colour flow propagation velocities, speckle tracking and longitudinal and radial strain in particular (114-116). The publication of normal ranges for left ventricular strain help to encourage the application of this imaging technique more widely (117). Recently, specialist centres have also convincingly demonstrated that left atrial dysfunction (by way of strain imaging) is associated with reduced exercise capacity in patients with preserved ejection fraction (118).

Comprehensive diastolic imaging protocols that include exercise assessments are beginning to be established for the diagnosis of HFPEF (119).

Other prognostic markers in heart failure

Recently it has also been appreciated that right-sided heart and inferior vena cava measurements are perhaps more predictive of outcome than left-sided heart measurements, including LVEF, or biomarkers (BNP) (120, 121). The rationale for the superior prognostic importance of right-sided heart measurements remains to be established and has been only minimally studied thus far and it is still to be established whether abnormal right heart measurements reflect left heart disease or intrinsic pulmonary arterial pathology.

Chapter 2

Diagnostic algorithms for HFPEF

Formal diagnostic parameters for HFPEF have been suggested by way of various echocardiographic measures in association with symptoms and signs, plus or minus support from elevated biomarkers, but there are no widely agreed criteria for the diagnosis of HFPEF.

Large trials investigating medical treatment in a HFPEF cohort have used varying inclusion parameters for the diagnosis (Figure 4). The first large study (CHARM-Preserved) enrolled 3025 patients with preserved ejection fraction. This was defined as LVEF >40% and NYHA II-IV but no formal measures of diastolic dysfunction (72). DIG-PEF a few years later redefined HFPEF as current or past symptoms of heart failure with the higher LVEF of ≥ 45%, but once again with no imaging evidence to confirm cardiac dysfunction (122). PEP-CHF was the first large study to use echo derived measures of cardiac dysfunction to confirm a diagnosis of HFPEF for study purposes as shown below. The investigators agreed that at least three out of nine clinical and at least two out of four additional echocardiographic criteria were required for a diagnosis. Atrial fibrillation could be substituted for an echocardiographic criteria recognising that many diastolic measurements above would be unreliable and that atrial fibrillation alone could be considered equivalent to evidence of impaired LV filling by Doppler (123). These entry measures were a mixture of systolic and diastolic dysfunction, or raised diastolic pressures, but excluded those with a LVEF < 40% (equivalent to a RWMSI <1.4). Whilst those with moderate to severely reduced LVEF were excluded, such a varied inclusion criteria would have undoubtedly resulted in a broad mix of pathologies with a variety of underlying aetiologies. In 2008 the I-PRESERVE trial categorised HFPEF as those with heart failure symptoms and left ventricular ejection fraction of at least 45% with some form of corroborative evidence of symptomatic heart failure by way of hospital admission or pulmonary oedema on X-ray, and structural cardiac abnormality by way of left ventricular hypertrophy or left atrial enlargement on echo. LBBB as corroborative evidence was used for the first time in this study (124).

The two most recently published trials used different entry criteria again. The ALDO-DHF trial insisted upon an LVEF ≥ 50%. It was the first study to require evidence of diastolic dysfunction according to recognised diagnostic pathways (or else atrial fibrillation), supporting evidence of impaired exercise capacity by way of a reduced peak VO2 ≤ 25ml/kg/min on cardiopulmonary exercise testing, and exclusion of significant airways disease by spirometry (125). TOPCAT, to evaluate the effects of spironolactone in patients with HFPEF, insisted upon symptoms of heart failure, LVEF ≥ 45%, and for

the presence of a raised BNP or NT-pro BNP in many cases. The inclusion of biomarkers was novel for such a trial and the controversy surrounding the meaning of the trial outcome may be explained, in part, by differences between the countries from which the participants were recruited, or else the use of a biomarker to aid recruitment (91).

PARAGON-HF is currently recruiting. The study aims to look at the effects of the new LCZ696 angiotensin receptor neprilysin inhibitor in patients with HFPEF (99). Similarly to TOPCAT it uses BNP or NT-pro BNP as a possible (but not essential) entry criteria. These latest trials reflect some scientific opinion that biomarkers may be more accurate for diagnosing heart failure than symptoms, clinician opinion, or resting structural changes on echocardiography but to date, no trial has insisted upon an elevated biomarker to ensure inclusion.

Figure 4: The diagnostic criteria for Heart Failure with Preserved Ejection Fraction (HFPEF) used in recent landmark trials.

Study	Diagnostic criteria for Heart Failure with HFPEF: **Compulsory** versus contributory			
	Clinical	Echocardiographic	Other	Exclusion criteria
CHARM-Preserved (72) 2003	**NYHA II-IV; Prior hospitalisation for a cardiac condition; HF symptoms & signs as judged by investigator.**	**LVEF > 40%**		
DIG-PEF (122) 2006	**Current/past symptoms/signs of HF or radiographic pulmonary congestion Normal Sinus Rhythm**	**LVEF > 45%**		Atrial Fibrillation/flutter Cor Pulmonale
PEP-CHF (123) 2006	**≥70yrs 3 out of 9 below:** Exertional breathlessness; Orthopnoea or PND; Ankle swelling; Improved with diuretics; Increased JVP; Previous pulmonary oedema; Prior MI; Cardiothoracic ratio >0.55; Previous radiological pulmonary oedema	**2 out of 4 below:** Some impairment of systolic function: LV WMSI 1.4–1.6 or LVEF fraction 40-50% LA enlargement LA >25 mm/m^2 or >40 mm LVH Posterior or septal wall ≥12 mm Evidence of impaired LV filling by ≥ 1 of list below: Atrial Fibrillation E/A ratio <0.5 Deceleration time >280 ms IVRT >105 ms		Significant valve disease RWMSI <1.4 LVEF <40%
I-PRESERVE (124) 2008	**≥60yrs old NYHA II-IV (and hospitalised for HF in last 6 months) or NYHA III-IV**	**LVEF ≥ 45% 1 of echo or other corroborative evidence** LVH LA enlargement	CxR - pulmonary congestion ECG – LVH or LBBB	Significant valve disease; HCM; Restrictive cardiomyopathy; Pericardial disease; Isolated right heart failure;
ALDO-DHF (125) 2013	**>50 yrs old Current HF symptoms (NYHA II-III)**	**LVEF ≥50% ≥ Grade I Diastolic dysfunction or atrial fibrillation**	**Peak VO2 ≤ 25ml/kg/min**	LVEF ≤40% Significant coronary disease or angina VC or FEV1 < 80% predicted EGFR<30ml/min/1.73m^2
TOPCAT (91) 2014	**≥50yrs old Symptomatic HF**	**≥45%**	**HF hospitalization within prior year OR elevated BNP ≥100pg/mL or NT-proBNP ≥360 pg/mL) within last 60 days**	Uncontrolled Hypertension, Infiltrative cardiomyopathy, HCM
PARAGON-HF (99) Recruiting	**≥55 years old Symptoms of HF requiring diuretic for ≥ 30 days Current HF symptoms (NYHA II-IV)**	**LVEF ≥ 45% Structural heart disease (Left atrial enlargement or LVH)**	**A HF hospitalisation within the last 9 months OR Elevated NT-proBNP (>300pg/ml, or >900pg/ml if AF at baseline)**	Prior documented LVEF<45% Prior IHD event that culd have reduced LVEF < 45%

NYHA, New York Heart Association; HF, Heart failure; PND, Paroxysmal nocturnal dyspnoea; JVP, Jugular venous pressure; MI, Myocardial infarction; LVEF, Left ventricular ejection fraction; LV, Left ventricle; LA, Left atrium; LVH, Left ventricular hypertrophy; LVWMSI, Left ventricular wall motion score index; IVRT, Isovolumic relaxation time; LBBB, left bundle branch block; VO2, Oxygen consumption; BNP, Brain natriuretic peptide; AF, Atrial fibrillation; HCM, Hypertrophic cardiomyopathy; VC, Vital capacity; FEV1, Forced expiratory volume in 1 second; EGFR, Estimated glomerular filtration rate; IHD, Ischaemic heart disease.

Various sets of guidelines and consensus statements have been published over the last decade suggesting a diagnostic framework for the diagnosis of HFPEF/HFNEF and diastolic dysfunction (8, 9, 31, 68, 126-129).

In 2007 the Heart Failure and Echocardiography Associations of the European Society of Cardiology is reproduced in Figure 5. It advocated that the diagnosis of HFNEF requires the following conditions to be satisfied: (i) signs or symptoms of heart failure; (ii) normal or mildly abnormal systolic LV function; (iii) evidence of diastolic LV dysfunction (9). Normal or mildly abnormal LV systolic function implies both an LVEF >50% and an LV end-diastolic volume index (LVEDVI) <97mL/m^2, noting that no upper limit for an abnormal LVEF is defined. In this framework diagnostic evidence of diastolic LV dysfunction by way of elevated diastolic pressures can be obtained invasively (LV end-diastolic pressure >16 mmHg or mean pulmonary capillary wedge pressure >12 mmHg) or non-invasively by tissue Doppler (TD) (E/e'). An E/e' >15 is diagnostic HFPEF by this strategy. When E/e' is between 8 and 15, additional non-invasive investigations are required for diagnostic evidence of diastolic LV dysfunction. These can consist of blood flow Doppler of mitral valve or pulmonary veins, echo measures of LV mass index or left atrial volume index, electrocardiographic evidence of atrial fibrillation, or plasma levels of natriuretic peptides. If plasma levels of natriuretic peptides are elevated, evidence of diastolic LV dysfunction is still required from additional non-invasive investigations such as tissue Doppler, blood flow Doppler of mitral valve or pulmonary veins, echo measures of LV mass index or left atrial volume index, or electrocardiographic evidence of atrial fibrillation (9).

Figure 5: HFNEF diagnostic flowchart according to the 2007 European Heart Failure and Echocardiography Associations of the European Society of Cardiology.

How to diagnose HFNEF

Symptoms or signs of heart failure

Normal or mildly reduced left ventricular systolic function
LVEF > 50%
and
LVEDVI < 97 mL/m^2

Evidence of abnormal LV relaxation, filling, diastolic distensibility, and diastolic stiffness

Invasive Haemodynamic measurements
mPCW > 12 mmHg
or
LVEDP > 16 mmHg
or
τ > 48 ms
or
b > 0.27

TD
E/E' > 15 | 15 > E/E' > 8

Biomarkers
NT-proBNP > 220 pg/ml
or
BNP > 200 pg/mL

Biomarkers
NT-proBNP > 220 pg/mL
or
BNP > 200 pg/mL

Echo – bloodflow Doppler
$E/A_{>50\,yr}$ < 0.5 and $DT_{>50\,yr}$ > 280 ms
or
Ard–Ad > 30 ms
or
LAVI > 40 mL/m^2
or
LVMI > 122 g/m^2 (♀); >149 g/m^2 (♂)
or
Atrial fibrillation

TD
E/E' > 8

HFNEF

Image reproduced from the 2007 European Heart Failure and Echocardiography Associations, ESC guidelines (9). HFNEF, Heart failure with normal ejection fraction; LVEDVI, left ventricular end-diastolic volume index; mPCW, mean pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure; t, time constant of left ventricular relaxation; b, constant of left ventricular chamber stiffness; TD, tissue Doppler; E, early mitral valve flow velocity; e', early TD lengthening velocity; NT-proBNP, N-terminal-pro brain natriuretic peptide; BNP, brain natriuretic peptide; E/A, ratio of early (E) to late (A) mitral valve flow velocity; DT, deceleration time; LVMI, left ventricular mass index; LAVI, left atrial volume index; Ard, duration of reverse pulmonary vein atrial systole flow; Ad, duration of mitral valve atrial wave flow.

In 2009, the joint American Society of Echocardiography (ASE) and European Association of Echocardiography (EAE) defined discrete pathways for the diagnosis of raised filling pressures and diastolic dysfunction, with the guidance that researchers/clinicians "on the basis of a clearly formulated question, should define the needs: to examine changes in relaxation, stiffness, and/or filling pressures" (8). Both

diagnostic algorithms are shown below (Figure 6 and Figure 7). The scheme to estimate LV filling pressures is very similar to the 2007 European model to diagnose HFNEF, albeit with a slightly lower cut-off for LA volume, use of valsalva E/A measurements, pulmonary artery systolic pressure estimations and τ (IVRT/(T_E-$T_{e'}$)) in the 2009 protocol. There is also an absence of biomarker influence given that this is a purely echocardiographic scheme. The scheme to grade diastolic dysfunction uses a direct measure of impaired LV relaxation (reduced e') as the primary influence followed by estimates of LVEDP using E/e' thereafter.

These 2009 guidelines allow the user to determine whether to take a diagnostic approach according to raised filling pressures versus diastolic relaxation or stiffness abnormalities depending upon the specific question. The 2007 European Heart Failure and Echocardiography associations (9) ask the specific question "does this person with normal ejection fraction have heart failure?" and uses elevated LVEDP (by way of the surrogate echocardiographic measure E/e') as the crucial echo abnormality, thus promoting the need for evidence of haemodynamic changes to diagnose HFNEF. Measures of diastolic relaxation or stiffness abnormalities are only required to support indeterminate cases.

However, in both guidelines echocardiographic measurements are taken with the patient at rest. This may have limitations in light of increasing evidence that normal resting E/e' measurements may become pathological and of prognostic significance during exercise (130).

Figure 6. Estimation of LV filling pressures in patients with normal ejection fractions according to the joint American Society of Echocardiography (ASE) and European Association of Echocardiography (EAE), 2009.
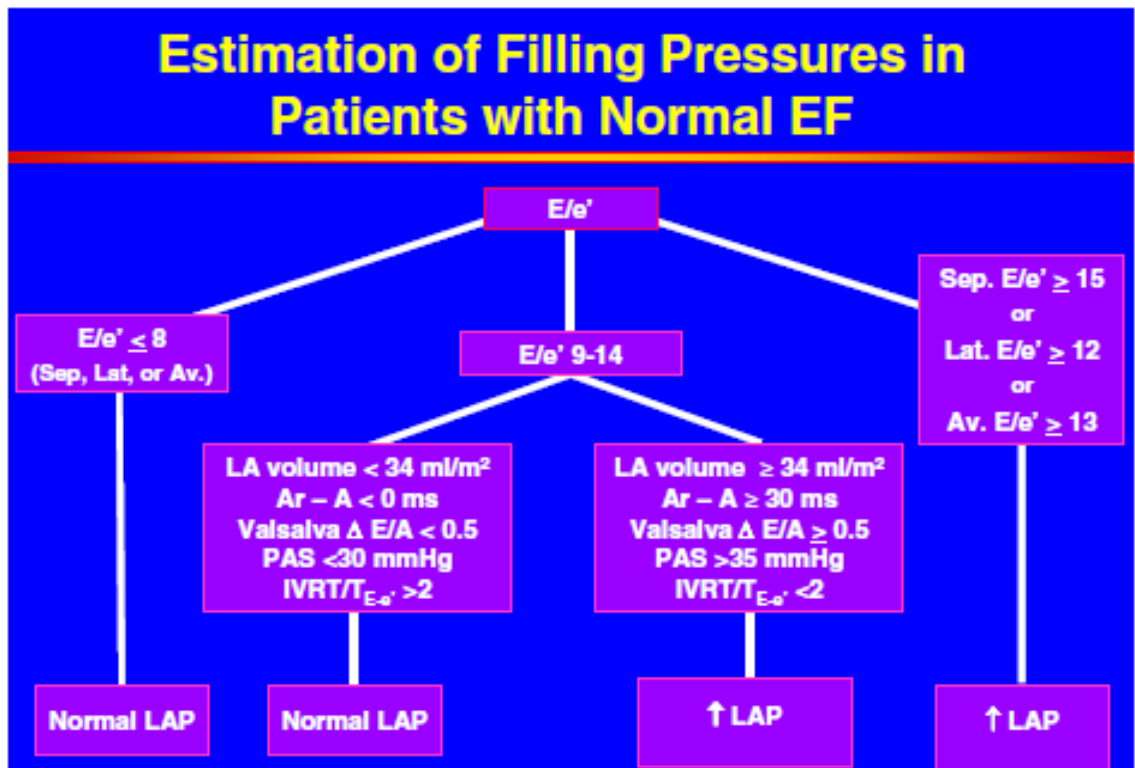
Image reproduced from the Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography the joint American Society of Echocardiography (ASE) and European Association of Echocardiography (EAE) (131). Av., Average; LA, Left atrium; PAS, Pulmonary artery systolic pressure; IVRT, Isovolumic relaxation time; LAP, Left atrial pressure.

Figure 7. Scheme for diagnosing and grading diastolic dysfunction according to the joint American Society of Echocardiography (ASE) and European Association of Echocardiography (EAE), 2009.
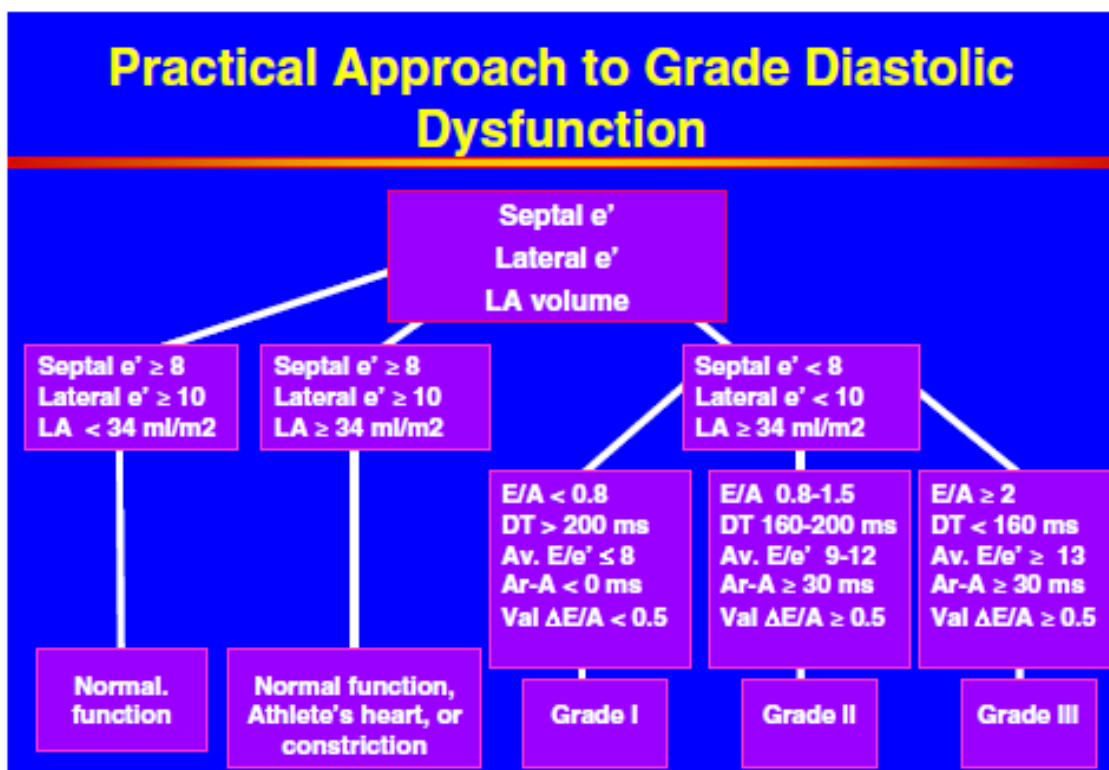
Image reproduced from the Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography the joint American Society of Echocardiography (ASE) and European Association of Echocardiography (EAE) (131). Av., Average; LA, left atrium; Val., Valsalva; DT, deceleration time.

Shuai and colleagues derived a simpler model of abnormal resting echo parameters that would accurately diagnose HFPEF (10). A strategy that consisted of either:

(i) lateral E/e' ≥ 12; or

(ii) lateral E/e' ≥ 8 but <12, with either LAVI ≥ 34 mL/m^2 or Ard–Ad > 30 ms,

provided good diagnostic accuracy for identifying HFPEF, with a sensitivity of 77% and specificity of 81%. These observations were subsequently confirmed in a small validation cohort of 98 subjects. The comparative gold standard diagnosis of HFPEF was by way of a history of hypertension, typical heart failure symptoms or signs evaluated by two cardiologists, and LVEF > 50%, without any invasive measurement to confirm elevated LV filling pressures. This strategy compared favourably with the 2007 European consensus statement pathway which produced a sensitivity of 72% and specificity of 87%. Interestingly the joint ASE and EAE strategy fared poorly with a sensitivity of only

47%, although maintained a good specificity of 87%. The authors also described a low diagnostic accuracy of E/A <0.5 and DT > 280ms for detecting HFPEF most likely due to the U-shaped relation with LV diastolic function, making it difficult to discriminate patients with pseudonormalisation from normal patients.

Emery and colleagues performed a retrospective analysis of 1229 echocardiograms to discern which echocardiographic parameters were most helpful to diagnose diastolic dysfunction (132). Measurements were correlated against the 2007 European guidelines whereby an E/e' > 15 is confirmatory of diastolic dysfunction, and an E/e' < 8 is normal. A LAVI ≥ 40ml/m² provided the greatest sensitivity and specificity of 76% and 77% respectively. Similar to the findings of Shaui et al, the combination of E/A < 0.5 with an E wave deceleration time > 280 ms in patients over the age of 50 years was not a sensitive marker of HFPEF, with only 0.5% of the group fulfilling these three criteria. In contrast to Shaui et al, pulmonary venous inflow measurements also added little to the overall diastolic functional assessment. It should be remembered however that the echocardiograms included for analysis were broad in their indication and the referral reason may not have been heart failure. As such, the population may not be representative of a group with a clinical diagnosis of suspected HFPEF. LVMI criteria according to the 2007 European guidelines were of little use, being highly specific but poorly sensitive. However when the cut-off was changed to the upper limit of the normal (> 116 and > 96 g/m^2 for males and females, respectively) instead of the lower limits of severe this yielded a much greater sensitivity, but with little change in specificity. The application of LVMI and LA volume as a combined marker to differentiate HFPEF from those with asymptomatic LVH or normal controls has been justified previously but this was a small study recruiting predominantly obese African-American women and cannot be extrapolated to the wider population (133).

In a study of 122 patients with high burden of ischaemic and hypertensive heart disease yet preserved ejection fraction (LVEF > 50%), Dokainish and colleagues demonstrated that E/e' had a strong correlation with LVEDP by invasive measures, and that E/e'> 12 had a 75% sensitivity and 78% specificity for LVEDP ≥ 20mmHg (134). The secondary most useful measurements identified were LAVI, E alone, and estimated pulmonary artery pressure (PAP). When these measures were collated into (E + LAVI)/2 and (PAP + LAVI)/2 they were shown to have similar diagnostic accuracy to E/e' for the estimation of LVEDP. (E + LAVI)/2 also provided incremental accuracy to E/e' when E/e' was in the grey zone (10, 127, 128, 130, 132). In addition, E alone <60cm/sec ruled out, and >90cm/sec ruled in elevated LVEDP with high negative and positive predictive values respectively.

The European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012 (31) combine the 2007 European and 2009 joint ASE and EAE recommendations to guide the clinician's decision making process about the presence or absence of diastolic dysfunction (Figure 8). No specific diagnostic strategy is endorsed. Instead, a table of common echocardiographic measures of LV diastolic dysfunction is displayed along with the caveat that "no single echocardiographic parameter is sufficiently accurate and reproducible to be used in isolation to make a diagnosis of LV diastolic dysfunction". They suggest a comprehensive echocardiographic examination including the evaluation of both structural (LV hypertrophy, LA dilation) and functional abnormalities, and conclude that the presence of at least two abnormal measurements and/or AF increases the likelihood of the diagnosis of diastolic dysfunction. These guidelines also define HFREF echocardiographically as an LVEF <50% or LVEDV ≥97ml/m^2. This cut-off value for LVEF was agreed by a show of hands from the guideline committee rather than being based upon any specific trials or evidence as highlighted by Dr Alan Fraser at the British Cardiovascular Society annual conference 2014.

Figure 8: Common echocardiographic measures of left ventricular diastolic dysfunction in patients with heart failure according to the ESC heart failure guidelines 2012.

Measurement	Abnormality	Clinical implication
e'	Decreased (<8cm/s septal, <10cm/s lateral, or <9cm/s average)	Delayed LV relaxation
E/e' ratio	High (>15)	High LV filling pressures
	Low (<8)	Normal LV filling pressures
	Intermediate (8-15)	Indeterminate LV filling pressures (additional measures needed)
Mitral inflow E/A	Restrictive (>2)	Delayed LV relaxation
	Impaired relaxation (<1)	Normal LV filling pressures
	Normal (1-2)	Inconclusive
Mitral inflow E/A during valsalva	Change of the pseudonormal to the impaired relaxation pattern (with a decrease in E/A ratio ≥0.5)	High LV filling pressures unmasked through valsalva
A pulmonary-A mitral duration	>30ms	High LV filling pressures

Adapted from the European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012 (31).

A subsequent large European multi-centre epidemiological study of 734 healthy subjects (mean age 45.8 ± 13.3 years) published in 2014 was the first piece of work to provide a comprehensive assessment of 2D transthoracic echo measurements to produce normal references ranges (67). These data demonstrate that the mean normal LVEF by Simpson's Biplane assessment is 63.9%, (56.5% to 71.7% to include 2 standard deviations).

This lower (2SD) cut-off of 56.5% for a normal LVEF closely mirrors the British Society of Echocardiography (BSE) guidelines (68). These stipulate that an LVEF <55% equates to mild LV impairment, and that a LVEF ≥ 55% can be considered normal. These BSE guidelines provide the references ranges for all echocardiographers in the UK and a diagnosis of "mild LV impairment" will be documented when the echocardiographer feels

the LVEF is below 55% by eyeballing or RWMS, when an accurate Simpson's measurement could not be obtained.

Most recently in 2013 the British Society of Echocardiography published a protocol for the diagnosis and grading of diastolic dysfunction (Figure 9) (129). Similarly to the ASE/EAE 2009 guidelines, this is purely echo based and as such does not include biomarkers in the pathway.

Figure 9. Diagnosis and grading of diastolic dysfunction according to the British Society of Echocardiography
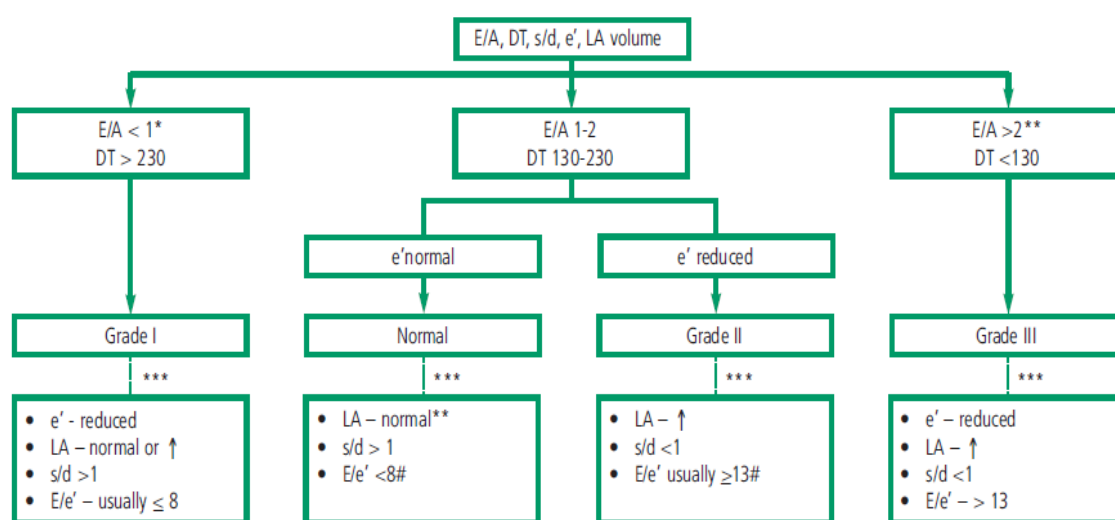
Flow chart

*E/A < 1 without any additional evidence of diastolic dysfunction can be normal above 60 years of age.

**E/A >2 and/or increased LA size without structural heart disease can be seen in young subjects and athletes.

***Combined with one or more parameters from below. Confidence of categorisation increases with increasing number of corroborative parameters.

If E/e' is between 9 and 12, additional measurements should be used (see text).

Reproduced from the British Society of Echocardiography (BSE) protocol for the diagnosis and grading of diastolic dysfunction (129).

The BSE utilises the most commonly measured and understood markers of diastolic function in the initial step of assessment (E/A ratio and DT). Thereafter, the next most readily obtainable measurement (e') contributes to separating apart normal from diastolic dysfunction in controversial cases due to the U-shaped curve pattern of changes with the E/A measurement. The diagnosis is then consolidated by supportive information from other diastolic parameters. This protocol is very user friendly and incorporates features of both haemodynamic changes in LV/LA diastolic pressures through the use of

the E/A ratio, alongside structural changes to suggest LV stiffness or impaired relaxation by way of the DT and e' measures. In controversial cases once again a combined approach of haemodynamic and structural measures are called upon to aid decision making.

Limitations of the E/A measurement are highlighted, including age and athletic status. Clinical scenarios that limit the application of this pathway are also given including left ventricular hypertrophy (LVH), tachycardia, atrial fibrillation, systolic dysfunction, mitral valve disease and constrictive pericarditis, and these should all be observed when using any of the diastolic diagnostic pathways described thus far.

In summary, the current official strategies for diagnosing HFNEF and diastolic dysfunction by echocardiographic parameters are as documented in the 2007 European, 2009 joint ASE and EAE, 2012 ESC, and 2013 BSE guidelines above. The 2007 European guidelines are the only ones that provide a specific pathway to diagnose heart failure due to diastolic dysfunction as opposed to diastolic dysfunction alone and as such in-corporate the use of biomarkers where the others do not. Small clinical studies have tried to validate and improve upon these guidelines. They highlight the limitations of incorporating E/A and Deceleration time (DT) measurements due to difficulty discriminating between pseudonormalisation and normal LV filling patterns. E/e' seems to stand up to validation but the consensus as to the cut-off for accurate prediction of elevated LVEDP > 20mmHg is not clear and probably lies between ≥ 12 to ≥ 15. However E/e' < 8 seems to be universally accepted as reflecting a normal LVEDP. When the E/e' is in the grey zone there is gathering evidence that the most helpful measurements to diagnose diastolic dysfunction and HFPEF are elevated LAVI, e', Ard–Ad, PAP, and LVMI. Out of all of these, elevated LAVI is probably the most consistently helpful, and indeed the only marker of chronic diastolic LV function rather than being affected by the volume status of the patient. However, the cut-off values for each of these measurements varies between studies. Most likely a LAVI ≥ 34ml/m^2 or ≥ 40ml/m^2, Ard–Ad > 30 ms, and LVMI at the upper limit of the normal range (> 116 and > 96 g/m^2 for males and females, respectively) would be most discriminative as to whether diastolic dysfunction exists.

The diagnosis of HFPEF remains challenging and resting echocardiographic measurements have significant limitations. Currently no universal diagnostic pathway has been agreed and convincingly validated. Ruling out HFPEF in individuals with symptoms or signs of heart failure should also be subject to a formalised screening strategy that includes normal ECG (including no atrial fibrillation), normal BNP and normal echocardiogram that includes normal chamber volumes, myocardial mass and

Doppler parameters according to current echocardiography accepted criteria. 3D echo and speckle tracking imaging may provide superior methods of assessment but are still sensitive to the patient's volume status. Exercise derived values of diastology may prove to be necessary and there is on-going research into the utility of novel biomarkers of myocardial fibroinflammation which would reflect chronic myocardial remodelling (135).

This analysis will continue to use the 2007 European diagnostic framework as the discriminator for the presence or absence of HFPEF with the exception of the cut-off LVEF, below which a diagnosis of HFREF would be given. In this regard, and in keeping with the new epidemiological evidence (67) and daily British echocardiographers practice, I will use a LVEF <55% to represent HFREF and ≥ 55% will be necessary to pursue a diagnosis of HFPEF. The LV chamber volume cut-off criteria will remain the same at 97ml/m^2, as dictated by the 2007 European guidelines, and re-enforced by the ESC 2012 guidelines.

This 2007 framework makes more physiological sense for a diagnosis of heart failure as it requires criteria to suggest haemodynamic changes within the heart rather than just structural changes. It is probably least likely to result in false positive diagnoses of HFPEF due to the fact that it uses the higher values of E/e', LAVI, and LVMI.

I have opted not to use the pulmonary artery systolic pressures (PAS) > 30mmHg adopted by the ASE/EAE 2009 guidelines to support a diagnosis of HFPEF. PASP may be elevated as a result of pulmonary disease or pulmonary artery hypertension rather than left-sided cardiac dysfunction and so may result in a falsely positive diagnosis for HFPEF. Neither will I incorporate the ϒ (IVRT/(TE-Te')) or Valsalva manoeuvre into my diagnostic pathway due to inexperience of use within the echo department. Also, cardiopulmonary exercise testing is not available.

I will be able to compare the prevalence of the different diagnostic groups with previously reported data and examine how this more robust diagnostic framework would affect the distribution of the different groups. In those deemed to have HFREF by this pathway I will establish if other markers of systolic dysfunction are also abnormal and whether these other markers correlate with the degree of LV impairment or BNP level. In those deemed to have HFPEF or HFNMSD by this diagnostic pathway I will establish what echo and CMR abnormalities of systolic and diastolic function can be identified, and I will look at the grade of diastolic dysfunction according to BSE or ASE/EAE pathways. The numbers of patients in the HFNMSD diagnostic bracket may be large due to the tight diagnostic constraints on the normal and definitely abnormal groups. This will be an interesting group to differentiate in its own right.

Chapter 3

Echocardiography versus Cardiac Magnetic Resonance

The role of Echocardiography in heart failure

The advent of echocardiography was a major step forward in the understanding of heart failure and allowed an assessment of heart structure and function through the use of ultrasound. It remains the main imaging modality for investigation of people with suspected heart failure in today's practice. It is widely available, non-invasive and can identify chamber volumes, measures of ventricular systolic and diastolic performance, and valve structure and function when image quality is good.

Unfortunately, the limits of echocardiography by way of sub-optimal image quality are frequently apparent. As a cardiology registrar, with 4 years of echocardiography experience, I am still filled with a sense of excitement when I am able to obtain a complete scan with clear images and measurements that I can be confident about. All too often patient related factors mean that it is difficult for the individual to lie in the correct position for scanning or lie still for long enough to obtain good images. Chest wall deformities and obesity or lung disease undoubtedly impair image quality and then sometimes the clearest images completely disappear as the acoustic window vanishes with inspiration or expiration. Even when you believe you have obtained clear images at the time of scanning, trying to perform measurements on the work station is hampered by the clearly defined LV wall disappearing as the cine loop is stopped. Poor endocardial definition limits reliable chamber volumes and ejection fractions, and off axis images can underestimate flow velocities. Echo is also unable to provide tissue characterisation and as such cannot differentiate ischaemic from non-ischaemic cardiomyopathy.

In daily practice with limited scanning time, the most embraced use of this modality is to identify serious valve disease and measure the left ventricle (LV) size and ejection fraction (EF) as a measure of left ventricular systolic performance.

Some measurements of diastolic dysfunction and elevated end-diastolic filling pressures are routinely performed in an echo study however in a number of cases the results are not clear cut enough to establish a firm diagnosis of HFPEF. In these circumstances more complex 2D echo measurements should be performed to help clarify the diagnosis. These measures include blood flow Doppler of the pulmonary veins, LV mass index or left atrial volume index, but they are often difficult to obtain.

The evolving role of Cardiac Magnetic Resonance imaging in heart failure

Cardiac Magnetic Resonance (CMR) is a highly accurate, non-invasive method for more detailed assessment of the heart. It is the gold standard for measuring left and right ventricular volumes, myocardial mass and particularly validated in systolic dysfunction (18). Some pericardial diseases and most congenital defects are also readily identifiable. Additional information about myocardial infarction, inflammation and infiltration can be achieved by incorporating the use of gadolinium contrast agent and assessing the pattern of uptake into the myocardium (19). However, it is not without limitations and patients who have difficulty holding their breath or lying flat, claustrophobia, ferromagnetic contraindications, or very irregular heart rhythms are generally not suitable for scanning.

Cardiac chamber size and systolic function

2D echo Simpson's Biplane LVEF versus CMR LVEF

CMR is the gold standard method of measuring LV volume and LVEF. However, 2D echo continues to be used for the routine assessment of systolic function in most centres and it is important to remember that previous trial inclusion criteria have used 2D echo LVEF measures and as such CMR measures may not be valid when practising the evidence based medicine according to such trials.

The most widely accepted and validated method of demonstrating LV systolic function with 2D echo is via LVEF by way of the Simpson's Biplane methods of disks. This is achieved by planimetry of the LV endocardial borders in end-diastole and end-systole in both a 4 chamber and 2 chamber view to obtain LV end-diastolic and end-systolic volumes from a series of disks created by the imaging software, and thereafter LVEF by way of the equation LVEF= (LVEDV-LVESV)/LVEDV. This measurement is generally done on a single cycle, and should be averaged in irregular rhythms. It can be done by visually guided line drawing of the endocardial edge, or semi-automatic feature tracking imaging (16, 136, 137).

LVEF by CMR uses multiple slices through the LV from a short stack, and images are obtained from a composite of a number of cardiac cycles. One time frame deemed to be smallest and largest volume for all slices and endocardial borders are traced at these end-systolic and end-diastolic phases. The inclusion or exclusion of papillary muscles tends to be operator and centre depended and trabeculations are generally excluded from the analysis. It is sometimes difficult to fully differentiate the most basal slice of the LV from the LA but the slice is generally considered to be within LV if blood volume is surrounded by >50% ventricular myocardium. Cross-referencing packages also help in this regard.

It is not uncommon for LVEF by 2D echo versus CMR to differ in clinical practice. In my experience it is not uncommon that an echo report of moderate or severe LV impairment converts to normal or only mildly impaired LV function following CMR. The reverse can also be true though.

Whether the differences between 2D echo and CMR LVEF are due to true differences in function over time (e.g. medical therapy improving LVEF prior to the CMR being performed) is not clear. However, a small audit within the cardiology department at Darlington Memorial Hospital would suggest the difference is due to more than true temporal discrepancies. The audit compared the consistency of LVEF measurements using 2D echo (via an automated method, traditional Simpson's Biplane method and physiologist "eyeballing" LVEF) with CMR LVEF in 15 patients (5 with LV impairment) who had both scans performed on the same day (138). Image quality with echo was satisfactory in only 56% of cases compared with 100% of CMR studies and the audit demonstrated that all echo methods gave statistically different results to the CMR, whilst being fairly well correlated with other echo techniques. CMR tended to give higher LVEF results than the echo measures. This very small local audit demonstrates significant differences on same day scanning, discounting the theory about differences due to real temporal changes in LVEF. Thus, other causes to be considered include either frequent inaccuracies in one method making it unreliable, or intrinsic differences in the methods of measurement leading to different normal and abnormal reference ranges with the two modalities. Whilst some published literature suggests similarly that 2D echo LVEF tends to universally underestimate CMR LVEF (16, 37, 139), others show statistically similar mean LVEF between the two methods but with wide variation in the level of agreement, making the techniques clinically non-interchangeable (15). Overall the literature on this topic is surprisingly scarce and patient numbers small. Whilst 3D echo has more robust comparison data of LV volumes and LVEF with CMR it is rarely used in routine clinical practice (37, 140).

A normal CMR LVEF is judged to be above 56-60%, whereas a 2D echo LVEF by the Simpson's Biplane method is 54-55%, (sex and age dependent) (67) (141, 142) and so would suggest that CMR would tend to give, albeit small, a higher LVEF than 2D echo in the same patient on the same day. If the same cut-off to define normal LVEF is being used for both imaging modalities then there will invariably be discrepancies in the diagnoses for a number of patients.

Echo volumes tend to be universally smaller than volumes calculated by CMR, which may reflect the different recognition of the trabeculated endocardial borders with the two methods (139). The different methods of identifying end diastole between echo and

CMR may also have a role to play and this may be particularly relevant in those with dyssynchronous left ventricles. The averaging of a number cycles for CMR measurements versus a measurement from a single cycle with echo could also result in differences between the two measurements, particularly in irregular rhythms such as atrial fibrillation.

In day to day practice the 2D echo Simpson's Biplane method of disks method is frequently hampered by poor endocardial definition and off axis imaging preventing its application in a large number of cases (15). Regional wall motion scoring index may be more applicable (137) but the reality is that most commonly a method of visual estimation of LV systolic function is employed despite highly subjective, and often inaccurate results (16, 34).

The recent audit of echo practice of 39 trained physiologists and cardiologists in the north east of England demonstrated that a qualitative assessment of LV function was used frequently in 38 responders. It highlighted substantial variation in individuals' and centres' interpretation of LV function when applying a qualitative assessment, visual ejection fraction, or wall motion scoring (17).

Other methods of assessing systolic function

Other methods of quantifying LV systolic function by 2D echo include M-Mode % fractional shortening, regional wall motion scoring, subaortic velocity time integral measurements and myocardial performance indices, LV dp/dt (change in pressure/change in time of mitral regurgitation signal), M-mode mitral annular systolic excursion (MAPSE), tissue Doppler measures of mitral annular motion (S' waves), and strain imaging, most commonly global longitudinal strain.

Global longitudinal strain measures the deformation of myocardium between two points in multiple areas of the LV. Positive strain represents relaxation or lengthening of a fibre and negative values represent active contraction. A mean normal value of -19.7 was comprehensively established from a meta-analysis of 2,597 subjects from 24 studies recently (117) and there is strong evidence of the prognostic value of GLS, which appears to have superior prognostic value to EF for predicting major adverse cardiac events, and correlates better than LVEF with peak VO2 in both a HFREF and HFPEF populations (143-145). It may be a helpful measure to identify heart failure in someone presenting with dyspnoea but preserved LVEF (146).

Diastolic function

Echocardiography is superior to CMR for diastolic measurements of blood flow and tissue movement due to real time Doppler imaging with excellent time and spatial

resolution when focused on a specific point. The numbers of diastolic measures that can be obtained using echo are vast. Most have been described within the HFPEF diagnostic framework chapter above and include E/A ratio, E/e' ratio, deceleration time (DCT), isolvolumic relaxation time (IVRT), left atrial size, pulmonary vein Dopplers and Ard–Ad, LV mass and colour flow propagation velocity.

All of these have standardised protocols for acquisition and analysis, as well as widely accepted caveats to their use. These are freely available in text books and national and international guidelines and so have not been covered in detail.

The ability of CMR to perform measures of diastolic function by way of mitral flow velocities, mitral annular motion and pulmonary vein flow have been demonstrated in small studies (20-23) but echo remains the superior imaging modality for these (when the image quality is acceptable) and so these CMR measures tend not to be used in daily practice.

CMR might add to the echo assessment of diastolic function by way of more accurate measurements of atria and ventricular sizes and mass, right heart function, myocardial grid tagging, and tissue characterisation with gadolinium contrast enhancement, but these have not yet been adequately investigated or validated in diagnostic framework for HFPEF.

Only one study has compared evidence of fibrosis on CMR with echo derived E/e' Doppler markers of diastolic dysfunction (147) and described a correlation between the degree of fibrosis seen with late enhancement and degree of diastolic dysfunction. However the study comprised only 91 subjects and the population was not clearly defined, and contained patients with congenital heart disease. Similar studies using a general heart failure population and the distinct groups of HFREF and HFPEF patients are needed.

Late gadolinium enhancement (LGE) - A CMR specific tool
CMR has the added benefit over echo that it can incorporate the use of a gadolinium contrast agent, which is taken up into scarred areas of the myocardium, to provide information about the cellular matrix of the myocardium. The pattern of uptake reflects the underlying cause of myocardial scarring, and clearly differentiates between ischaemic and non ischaemic pathology in most cases. This is discussed further in the next chapter with regards to the use of CMR as a gatekeeper to angiography in a heart failure population.

The diagnostic utility of LGE in those with LV systolic dysfunction has been convincingly demonstrated (19). The transmural extent of LGE also predicts viability on revascularisation in ischaemic LV systolic dysfunction (148, 149). The presence and extent of delayed contrast enhancement has also been found to be a prognostic indicator in ischaemic and non ischaemic LV systolic dysfunction as well as those with preserved ejection fraction (150-153). It also helps to predict mortality following cardiac resynchronisation therapy (154). Although the prevalence, diagnostic and prognostic utility of LGE in pre-defined groups above has been demonstrated, the prevalence and extent of delayed enhancement in a generic newly diagnosed heart failure population has not apparently been published and would be of interest.

For the future, there will also be the introduction of T1 mapping in CMR which provides a quantitative assessment of the cellular matrix of the myocardium using the relaxation properties of hydrogen protons. Although very promising, currently this software tends to be restricted to research applications.

Routine use

Currently the use of CMR is generally restricted to specialist centres and performed on a case-by-case basis with a specific question in mind. The clinical impact of routine CMR has been studied in well-defined subgroup analyses but there is a complete lack of CMR demographics for a generic group of heart failure patients, which incorporates HFPEF and heart failure without major structural heart disease.

Focused studies suggest that routine CMR should have a significant impact on clinical management. For instance a study in 100 patients with acute myocardial infarction and ejection fraction <40% demonstrated that routine CMR influenced management in 24% of cases (24). Another study showed how CMR provides additional clinically relevant information compared with transthoracic echo in over 50% of patients by way of a retrospective review of 54 patients with left bundle branch block (LBBB) (25).

In 2000, the National Heart and Lung Institute Unit in London performed a same day CMR on 64 people attending a heart function clinic and concluded that CMR can provide a rapid, reproducible and patient acceptable assessment of cardiac function in heart failure (30). However, this study is now out-dated and used CMR to look at only cardiac volume, mass and function without the use of contrast agents. It was performed in only a small group of patients in a tertiary centre setting and groups were not defined according to presence or absence of systolic dysfunction.

A Canadian study is currently recruiting patients to examine the impact of routine CMR on the aetiological diagnosis in patients with a non-ischaemic heart failure (155). This

will compare the frequency of definitive diagnosis in a cohort receiving routine CMR versus a standard workup that is generally without CMR imaging. However all those patients that are deemed likely to have ischaemic cardiomyopathy due to history of coronary artery disease will be excluded and as such does not examine the impact of routine CMR in this group or indeed all comers to the heart failure services.

Incorporating routine CMR into the initial screening of patients with heart failure could provide clinically important information that could not be obtained with echocardiography. Indeed requests for the validation and cost analysis of routine CMR in this setting are being expressed (156). Epidemiological information provided by CMR may support or refute the current presumed spectrum of pathology in the heart failure population. From a population and individual perspective, CMR could alter diagnosis and reclassify the presence or absence of systolic dysfunction, and better differentiate the cause of cardiomyopathy compared with echo.

Chapter 4

Ischaemic Heart Disease in Heart Failure

The national heart failure audit in England and Wales 2013 demonstrated that almost half of all heart failure admissions had a history of ischaemic heart disease. When subdividing according to the presence of LV systolic dysfunction, 51% those with LV systolic dysfunction had history of ischaemic heart disease, as opposed to 40% of those without LV systolic dysfunction (2). The ESC guidelines for acute and chronic heart failure suggest that two thirds of cases of LV systolic dysfunction are caused by ischaemic heart disease (31). The rationale for this is well established in that infarcted myocardium becomes thinned and non-contractile, and that ischaemic but non infarcted myocardium may hibernate and become hypokinetic.

The rational for ischaemia as a cause of diastolic dysfunction is less well established, but some models do exist to provide a plausible pathophysiological model whereby ischaemia causes diastolic as well as subtle systolic function that may result in HFPEF (157, 158). Ischaemia results in impaired calcium ion sequestration into the sarcoplasmic reticulum during the energy dependent phase of myocyte relaxation. Localised infarcts causing fibrosis interspersed with relative areas of hypertrophy will also affect the passive relaxation properties. However, because CAD and HFPEF have similar risk factors it is entirely possible that CAD merely coexists with HFPEF with greater frequency than a non HFPEF population. Prevalence data comes from inferred CAD in HFPEF populations by way of clinical history and ECG findings and suggests varied prevalence rates of 20 to 75%, and generally around 40% (77, 159-161). However, the only known study that undertook stress testing found no evidence of significant ischaemia in the 20 patients enrolled (162). There have been no studies looking at infarct prevalence by CMR in this group. Some prognostic data is available from the Coronary Artery Surgery Study (CASS) registry for the HFPEF population, and shows that the 6-year survival rate for patients who had three vessel disease was 68% compared with 83% in those with one or two vessel disease and 92% for those without CAD (163). A recent retrospective observational study of the prognostic impact of CAD and revascularisation in a HFPEF cohort showed a high prevalence of CAD, approaching 70% (164). However this was a pre-selected sample of individuals that all underwent X-ray angiogram for clinical reasons and thus will have been subject to referral bias. More interesting was that, despite similar rates of angina and heart failure symptoms, and matched baseline echocardiographic LV function, those with CAD went on to have a greater deterioration in LVEF as well as increased mortality compared to those without CAD. Thereafter, complete revascularisation was associated with a lesser reduction in

LVEF and lower mortality than patients who were not completely revascularised. Whether this survival gain and maintenance of LVEF relates specifically to a HFPEF population as opposed to screening general population with similar characteristics but without heart failure cannot be elucidated.

Cardiac Magnetic Resonance to detect significant coronary artery disease

A gatekeeper to angiography

This topic needs to be divided into those patients with angina and those without.

In patients with angina or suspected coronary heart disease, Greenwood et al established that stress perfusion CMR has a high diagnostic accuracy, and has superiority over single-photon emission computed tomography (SPECT) (165). Klem et al also demonstrated the high sensitivity and specificity of stress perfusion CMR in combination with late gadolinium enhancement in this group. However, the sensitivity was low if using late gadolinium enhancement alone (166).

When patients have systolic heart failure but no symptoms of angina studies have suggested that late gadolinium enhancement alone is a sensitive and specific marker of significant coronary artery disease (19, 26-28). However a recent investigation in HFREF patients with ischaemic heart disease but without angina questioned this by demonstrating that two thirds of abnormal regional wall motion was not associated with scar. Unfortunately this study did not confirm that this was due to ischaemia (167). The most recent and largest trial of CMR as a gatekeeper for angiography in heart failure patients with reduced ejection fraction and without a history of ischaemic heart disease or angina used late gadolinium enhancement alongside magnetic resonance imaging of the coronary arteries (MRCA) and reported a diagnostic accuracy of 96% compared with invasive angiography (29). However, no mention was made about the extent that MRCA added to the accuracy of late gadolinium enhancement alone. This is important because in general CMR in a clinical setting of newly diagnosed heart failure patients would rarely employ routine MRCA. Also the patient selection excluded those with atrial fibrillation and so does not represent a generic district general heart failure population.

No studies have looked at the relationship between the presence and extent of late gadolinium enhancement of the myocardium with angiographic evidence of coronary disease in a HFPEF population.

Defining prognostic coronary disease in general

The ESC guidelines on the management of stable coronary artery disease from 2013 provide a summary of the indications for revascularisation of patients with stable

coronary artery disease in a variety of clinical scenarios (168). They highlight the complexity and nuances of the trial data within this area. "Prognostic coronary disease" is an expression used not infrequently within the cardiology community but the specifics of this term are not clear cut, as demonstrated by the fact that the foremost recommendation by the ESC is that "A Heart Team approach to revascularisation is recommended in patients with unprotected left main, 2-3 vessel disease, diabetes or comorbidities."

Developments in medical, interventional and surgical techniques over the last 10-20 years mean that most of the trials in this field are reduced to historic value. Many of the trials that compared revascularisation with optimal medical therapy occurred at a time when optimal medical therapy did not include beta-blockers, ace inhibitors, statins, or other drugs with proven survival benefit that are used in standard practice today. Many of these trials were also analysed using an intention to treat model with high cross over rates from the medical to revascularisation arm and interpretation of the results could be debated. Also, these previous angiogram-only criteria to justify revascularisation have been superseded by the need to prove functional significance of a coronary artery stenosis either by way of severe angina symptoms, or documented ischaemia on non-invasive or invasive fractional flow reserve (FFR) testing.

The ESC provides a number of recommendations for revascularisation of stable coronary artery disease patients on optimal medical therapy to improve prognosis (Figure 10) (168). The definition of prognostic LMS disease as >50% stenosis mirrors the ESC guidelines on myocardial revascularisation from 2010 (169), yet the accompanying 2013 guideline text refers to LMS CAD as "stenosis 50% or greater". The ACCF/AHA guidelines for the diagnosis and management of patients with stable ischaemic heart disease from 2012, which refer to the same evidence, specify a definition of prognostic LMS as ≥ 50% (170). Whilst the difference appears subtle, in practice the distinction between these definitions could be significant. Many coronary stenosis classifications use set boundaries and exactly 50% stenosis would be one of these boundaries, with 70% or 75% stenosis being the next grading level. Inclusion versus exclusion of the 50% stenosis in this scenario would result in two very different cohorts.

Figure 10. Current ESC recommendations for revascularisation of stable coronary artery disease.

Indication	Class & level of evidence
LMS > 50% stenosis (with ischaemia or FFR <0.8 if stenosis 50-90%)	I, A
Any proximal LAD >50% stenosis (with ischaemia or FFR < 0.8 if stenosis 50-90%)	I, A
2-3 vessel disease with impaired LV function (if asymptomatic the decision should be decided by the extent of ischaemia on stress testing)	I, B
Single vessel >50% diameter stenosis (with ischaemia or FFR < 0.8 if stenosis 50-90%)	I, C
Proven large area of ischaemia (>10% of LV) as assessed by non-invasive imaging (SPECT, MRI, Stress echo)	I, B
Dyspnoea/cardiac failure with > 10% ischaemia/viability supplied by a stenosis >50%	IIb, B

Adapted from the 2013 ESC guidelines on the management of stable coronary artery disease (168). LMS, Left main stem; LAD, Left anterior descending coronary artery; FFR, Fractional flow reserve; LV, Left ventricle.

This confusion is manifest in the wider trial data. Some recent LMS intervention trials have used a definition of >50% for inclusion (171, 172), and some editorials and clinical decision sources specify that >50% is required for a definition of LMS disease (173, 174). Yet other pivotal, both historical and recent, intervention trials use entry criteria of ≥50% stenosis. These include the Veterans Administration Cooperative, Coronary Artery Surgery Study (CASS), and SYNTAX group (175-181). Although interestingly, the subgroup analysis from the Veterans Administration Cooperative data would suggest a significant survival gain with CABG for LMS >75% stenosis but only a non-significant trend towards survival benefit in the 50-75% stenosis groups (bearing in mind the limitations of a small cohort compared at less than two years follow-up to eliminate cross-over confounding) (182).

It is difficult to know if the ESC guidelines have mis-defined LMS disease in error, or as a deliberate reflection of nuances in opinion or trial data. Certainly the addition of the FFR study data would not justify the guidelines' stance (183) and there is sufficient evidence to suggest that the lower cut-off definition of ≥ 50% should be applied. The data should be re-evaluated in light of the studies that assess the functional significance of the LMS disease by FFR and suggest that revascularisation can be safely deferred if

the FFR is >0.8. Yet when functional information is not available, LMS disease ≥ 50% remains a Class 1 indication for revascularisation.

A definition for 2-3 vessel disease is not provided in the ESC guidelines and this may be because the specifics of these terms are assumed. More likely, they were not fully disclosed in some of the earliest trials and also that the definition varied from one study to another with some using a definition of 70% stenosis (176, 179) and others using a definition of 75% (184, 185). Certainly angiographer opinion as to what constitutes two or three vessel disease remains inconsistent (186). When functional information is not available, the ACCF/AHA guidelines affirm that CABG to improve survival is beneficial in patients with significant (≥70%) stenosis in 3 major coronary arteries (with or without involvement of the proximal LAD) or in the proximal LAD artery and one other major coronary artery with class I, level B evidence (170). CABG to improve survival is also deemed reasonable for ≥70% stenoses in two major coronary arteries (without proximal LAD involvement) in the presence of significant ischaemia or viable myocardium in that territory (level IIa class B evidence). What constitutes a major or main epicardial artery is also debatable although the consensus is probably the main LAD or large secondary branch (generally the 1st diagonal), the main LCx or large secondary branch (generally the first obtuse marginal) or the main right coronary artery alone (175, 187).

In practice, those people with convincing angina despite optimal medical therapy may be revascularised according to the visual assessment of a stenosis at angiogram, without functional testing. If the reason for revascularisation is heart failure without angina then functional testing would generally be obtained to identify ischaemia or viability. However, many clinicians would prefer an angiogram assessment prior to functional tests in this group. If there is only minor disease at angiography functional testing would not be pursued. Alternatively, knowing about severe stenoses on angiogram will allow functional testing to be performed with a higher degree of caution, acknowledging an individual at higher risk of complications. The angiogram features thought to be of prognostic value for revascularisation in heart failure are debatable and out-dated but the appraisal below reflects on previous trials in this area to create a clinically workable definition.

Prognostic coronary disease in a heart failure (HFREF) population
The guidance for prognostic revascularisation discussed above also applies to a heart failure population. However, LV dysfunction, with reduced ejection fraction, portends a worse prognosis in ischaemic cardiomyopathy (176) and represents a group whereby revascularisation can offer greater survival gains for similar, or even lesser, degrees of coronary disease than matched cohorts with preserved LV function.

Whilst overall, the Veterans Administration Cooperative Study confirmed a significant improvement in survival with CABG for LMS ≥50%, subgroup analysis would later show that this was limited to those with abnormal LV function (182).

The original CASS randomised trial of CABG versus medical therapy showed a distinction between normal and impaired LV function with a survival benefit of CABG for three-vessel disease (stenosis ≥ 70%) only when LV dysfunction was present (LVEF 35% to 49%) (188). Subsequent observational studies from the CASS registry have confirmed this (189), but also shown survival benefit in only those individuals with LV impairment for left main stem equivalent disease (combined stenoses of ≥70% in the proximal LAD and proximal LCx coronary artery) (190).

The contemporary STITCH trial investigated survival differences between CABG and optimal medical therapy in those with LVEF ≤35% and less severe forms of coronary disease (191). Inclusion coronary disease was that deemed to be "amenable to revascularisation by their treating clinicians". The exception was those with LMS disease ≥ 50% for whom it was deemed unethical to receive medical treatment alone. Over a third of the population had no symptoms of angina. Most patients had two vessel (31%) or three vessel (60%) coronary disease, and 68% had severe proximal LAD stenosis. The trial results both refute and support the added benefit of CABG depending upon whether one takes an "intention to treat" versus an "as treated" approach to analysis, but some argue a prognostic benefit of CABG in "STICH like" patients with two vessel disease, including an LAD stenosis.

In an attempt to promote a standardised definition of ischaemic cardiomyopathy for use in clinical research one group looked at survival rates of those with LVEF ≤40% to create a prognostically powerful clinical definition according to the degree of coronary artery disease (184). More extensive disease was associated with shorter survival, and all traditional definitions of ischaemic cardiomyopathy had reduced survival rates compared with a non-ischaemic cardiomyopathy except in those patients with single vessel disease (non LMS/proximal LAD) disease ≥75% stenosis. Those with ≥75% stenosis of two epicardial vessels (regardless of LMS or proximal LAD involvement) had survival rates similar to three vessel disease, and certainly reduced compared with zero or one vessel disease. In addition, those with ≥75% isolated proximal LAD disease had significantly reduced survival rates compared with non-ischaemic cardiomyopathy. The authors concluded that these additional groups should be incorporated into the definition of ischaemic cardiomyopathy on prognostic grounds. Interestingly the definition for LMS disease was set at ≥ 75% stenosis and those with 50-74% stenosis were not studied.

Significant coronary artery disease as defined by LGE trials in heart failure

A number of studies have observed the predictive value of late enhancement with gadolinium on CMR to detect significant coronary artery disease in the setting of systolic heart failure. In all studies the presence of any subendocardial LGE was used as the marker of significant coronary disease however "significant coronary disease" was defined differently for all. The earliest study used >50% stenosis in ≥1 coronary artery in the context of a previously documented myocardial infarction to differentiate ischaemic cardiomyopathy from dilated cardiomyopathy (19). Later, Soriano et al defined ischaemic LVSD by the requirement of ≥70% stenosis of a major epicardial vessel (26). Another group described ischaemic heart failure as LVEF <40% associated with ≥75% stenosis of one or more major proximal epicardial vessels or "LMS disease" which was not defined (27).

One unifying feature of all these definitions is that one stenotic epicardial artery is sufficient to justify a diagnosis of ischaemic cardiomyopathy. Whilst this is entirely plausible at a physiological level, the data above suggest that the prognostic impact of single vessel disease is minimal, even in heart failure. The exceptions are proximal LAD disease or when significant ischaemia can be proven. As such, the implications for LGE to alter management of these patients would be simply by way of the addition of an antiplatelet or lipid lowering therapy for IHD, rather than consideration of revascularisation for prognostic purposes.

Most recently, Assomull and colleagues explored the predictive value of the combined presence of LGE with proximal magnetic resonance coronary angiography to detect the basis of cardiac dysfunction in new presentations of heart failure (29). Significant coronary disease at X-ray angiogram was defined as LMS >50% stenosis or >75% stenosis in either the proximal LAD or ≥ 2 epicardial vessels. The gold standard consensus panel definition of ischaemic heart failure without infarction on CMR was slightly different "severe proximal 3 vessel or left main stem disease". What constituted severe was not defined and the rational for the difference in definitions isn't fully explained. Single vessel disease not in the proximal LAD was not considered to be a cause of LVSD. This definition is much more in keeping with a prognostic pattern of coronary disease, and so of superior clinical value in a heart failure population.

A workable definition of significant coronary artery disease

Revascularisation in heart failure could be justified for prognostic reasons for all the ESC indications for stable CAD as described above but on the basis of ACCF/AHA and the other evidence reviewed the following list is a more accurate reflection of prognostic disease in a heart failure population based upon the visual interpretation of angiographic findings alone:

- LMS disease (≥ 50% alone) (170)

- LMS equivalent disease (proximal LAD ≥ 70% and proximal LCx ≥ 70%) (190)

- Three vessel disease (≥ 70% stenosis in each main epicardial vessel) (178, 180)

- Two vessel disease excluding LAD stenosis if ≥75% stenosis (184)

- Single vessel disease only if proximal LAD ≥75% stenosis (184)

- Two vessel disease (≥70% stenosis, and without proximal LAD involvement) in the presence of significant ischaemia or viable myocardium in that territory (170)

A simplification of these indications to incorporate all of the above scenarios yet allow practical application within a trial setting is described below:

- LMS ≥ 50% stenosis

- Proximal LAD ≥ 75% stenosis

- Two or three vessel disease with ≥ 70% stenosis of a main epicardial vessel (defined as main LAD or large secondary branch, main LCx or large secondary branch or main right coronary artery excluding branches)

This definition will be used when assessing for prognostic disease during this analysis.

Chapter 5

Heart Failure nationally compared with Darlington Hospital

The National Heart Failure Audit monitors the care and treatment of patients in England and Wales with acute heart failure. It summarises individual trust and hospital data alongside national averages and is a good marker of individual and collective performance at one point in time but also over a trend of a number of years. The latest data collated from April 2013-April 2014 is summarised in Figure 11 below and demonstrates Darlington hospital in the national picture (192).

Figure 11. National versus local heart failure population statistics.

Point of interest	Darlington figures	National Average (England and Wales)	Lowest value (England)	Highest value (England)
Heart failure admissions	240	n/s	15	697 (LGI)
Received echo (%)	97%	91%	57%	100%
Cardiology inpatient ward (%)	49%	49-51% (1st vs readmission)	0%	100%
Input from Consultant Cardiologist (%)	64%	60-63% (1st vs readmission)	0%	100%
Input from specialist (%)	100%	78-80% (1st vs readmission)	2%	100%
ACE on discharge (%)	62%	73%	33%	100%
ACE/ARB on discharge (%)	75%	85%	33%	100%
Beta blocker on discharge (%)	85%	85%	0%	100%
MRA on discharge (%)	43%	51%	20%	100%
Received discharge planning (%)	79%	n/s	7%	100%
Referral to HF nurse follow-up (%)	82%	58%	0%	100%
Referral to HF nurse follow-up (LVSD only) (%)	81%	69%	0%	100%
Referral to cardiology follow-up (%)	44%	54%	11%	97%
Referral to cardiac rehab (%)	5%	10%	0%	100%

*LGI, Leeds General Infirmary; n/s, not specified; ACE, Angiotensin converting enzyme inhibitor; ARB, Angiotensin receptor blocker; MRA, Mineralocorticoid receptor antagonist; HF, Heart failure; LVSD, Left ventricular systolic dysfunction.

The Durham and Darlington Locality and heart failure services

The County Durham and Darlington NHS Foundation Trust is the largest trust in the region in terms of patient population size. It employs a dedicated team of cardiology specialists over a number of sites and at Darlington Memorial Hospital there is a predominance of Consultants that specialise in heart failure or imaging. This includes an Honorary Professor of Cardiovascular Medicine with expertise in heart failure and clinical research, two Consultant cardiologists with expertise in CMR who run an on-site CMR clinical service, and a Consultant cardiologist with expertise in complex echocardiography and previous research in diastolic dysfunction. They are supported by a dedicated team of cardiac physiologists and echocardiographers, many of whom have conducted their own research within the trust and with links to Durham University. There has been a dedicated post for a trust cardiology research fellow for a number of years, resulting in MD and PhD research. Two dedicated cardiac research nurses help to co-ordinate the local, national and international research activity within the unit. There is a strong desire within the cardiology department to develop the heart failure and imaging activity in both clinical and research domains and recently the trust was granted funding for a dedicated clinical research centre to be based at Darlington Memorial Hospital.

As a leader in the field for heart failure services, a dedicated heart failure clinic was set up at Darlington in 2002 and was probably the first GP specialist led diagnostic and management clinic. This clinic is now well established and run by a GP with a specialist interest in heart failure and national profile in heart failure research, alongside a Consultant cardiologist with expertise in heart failure and clinical research, and heart failure nurse specialists. It runs as a one-stop diagnostic heart failure clinic and reviews around 10 new patients with a presumed diagnosis of heart failure every week. Diagnosis and management is according to National and European guidelines and local protocols. As such, it is perfectly suited to recruit patients with heart failure for research.

Since December 2012, an enhanced clinical pathway has been instigated for the investigation of patients with heart failure or presumed heart failure. It incorporates the routine measurement of:

- BNP and other validated prognostic blood tests
- Quality of life questionnaire
- Detailed echocardiogram attempting to measure Simpson's Biplane LVEF, other measures of longitudinal systolic function, LV strain, and all parameters of diastolic function
- Cardiac magnetic resonance scan with gadolinium and myocardial tagging.

The hope is that this service will improve diagnostic certainty and better guide management for patients on an individual basis. At the same time, this enhanced clinical pathway has the potential to provide a wealth of information that would improve our understanding of heart failure as a whole.

Hypothesis Development

Heart failure is a heterogeneous disorder and much more difficult to characterise than symptoms, isolated echo parameters (such as LVEF), or biomarkers alone would initially lead us to believe. It is time for a paradigm shift in our approach to the diagnosis of heart failure to one that incorporates a multifaceted assessment of cardiac anatomy and function in daily practice.

Incorporating routine CMR, alongside comprehensive echocardiography, into the initial screening of patients with heart failure could provide clinically important information to complement basic echocardiographic findings. Epidemiological information provided by CMR may support or refute the current presumed spectrum of pathology in the heart failure population. CMR could alter diagnosis by reclassifying LVEF and LV size in an individual. It could differentiate the underlying cause of heart failure by way of late enhancement, particularly in the HFREF population. This would also apply to those with heart failure with preserved ejection fraction or no major structural disease, although simply the presence or absence of late enhancement in these groups would be of interest. CMR could help to clarify some already accepted measures of diastolic dysfunction to aid diagnosis in unclear groups. Alternatively, CMR may demonstrate novel imaging findings that help to describe heart failure by way of new defining criteria.

There is sufficient suspicion that Simpson's Biplane 2D echocardiographic measurement of LVEF is at odds with the CMR derived LVEF to warrant further comparison of this in our cohort. If this proves to be the case, and in light of the difficulties obtaining a Simpson's Biplane measurement with 2D echo, it would be worth exploring whether assessment of LVEF using a regional wall motion scoring index (RWMSI) is valid and reproducible.

Comprehensive echocardiography with detailed systolic and diastolic assessments will be an important element in the diagnostic profiling of those without a preserved ejection fraction. It will be interesting to see how the application of a comprehensive HFPEF diastolic framework affects the profile of the heart failure community compared with currently held beliefs and may help to better clarify the heart failure population's true characteristics.

The likelihood is that the population attending the outpatient heart failure clinic would consist of a group with systolic dysfunction by way of reduced ejection fraction, another group with preserved ejection fraction and evidence of formal diastolic dysfunction or subtle systolic dysfunction (e.g. longitudinal impairment), a third group with presumed heart failure (generally with elevated heart failure biomarker) but normal ejection fraction

and no major structural heart disease on routine imaging, and a group without heart failure. This third group is by no means small as demonstrated by Rajender Singh's Darlington Retrospective OutPatient Study (DROPSY), Durham University 2009 (13). Simply defining the composition of a new heart failure clinic population incorporating the routine use of CMR would be of interest. Thereafter subgroup analysis with both CMR and detailed echo measurements will be informative, with perhaps the most novel insight from the HFPEF group and those thought to have heart failure but with no major structural disease that have been little investigated before.

Coronary artery disease (CAD) is the underlying aetiology for heart failure with reduced ejection fraction (HFREF) in the majority of cases (193-195). Establishing an ischaemic basis to the left ventricular (LV) dysfunction has important prognostic implications, with higher mortality rates than compared with idiopathic dilated cardiomyopathy (184, 185). Revascularisation improves survival in ischaemic cardiomyopathy in certain settings including prognostic coronary disease, particularly with demonstrable ischaemia (31, 168, 170, 196), but there may also be a rationale for revascularisation in those without angina or ischaemia (182, 188-191).

Invasive X-ray coronary angiography is frequently performed as an initial investigation to identify CAD in a heart failure population. Whilst complication rates are low, they can be serious. Guidelines recommend invasive X-ray angiography only in the presence of angina or evidence of ischaemia (31) but stress testing in LV dysfunction with potentially significant CAD is not without risk. A non-invasive, non-stress assessment would be preferable. CMR is increasingly used in this setting and incorporates gadolinium contrast to reveal infarcted myocardium by subendocardial or transmural late enhancement (19). CMR using late gadolinium enhancement imaging (LGE CMR) with proximal coronary artery imaging (MRCA) has been shown to accurately categorise the aetiology of heart failure as ascribed by a consensus panel, and in no case was significant left main stem (LMS), proximal left anterior descending (LAD) or 3 vessel disease missed (29). However, MRCA is not routinely practiced in many centres. LGE CMR without MRCA is a sensitive and specific marker of single vessel CAD in heart failure for those with a previously diagnosed myocardial infarction (19). The sensitivity of LGE CMR is lower for those without a history of myocardial infarction (80-95%) (26-28) and whilst these false negative rates may be acceptable for non-prognostic single vessel disease, they may not good enough for the routine exclusion of prognostic CAD. The evidence for the predictive value of LGE CMR alone to detect prognostic CAD in a heart failure population is lacking, and understanding local performance is important.

Specific sub-questions to be addressed

1) What is the diagnostic profile of a newly diagnosed heart failure population in the County Durham and Darlington NHS Foundation Trust?
    a. How would the group divisions differ using different LVEF thresholds to diagnose HFREF?
2) What is the diagnostic profile of this newly diagnosed heart failure population when incorporating routine CMR and comprehensive 2D echocardiography according to a contemporary diagnostic framework?
    a. Does this differ from the diagnostic profile of the heart failure population using routine echocardiography alone?
    b. Do echo and CMR measurements of LVEF correlate?
3) What are the most useful diastolic criteria to confirm a diagnosis of HFPEF?
4) How many of those given a diagnosis of not having heart failure by a clinician would have met the HFREF or HFPEF diagnostic criteria?
5) Is there systolic dysfunction other than reduced LVEF in those with HFPEF?
6) Is there systolic or diastolic dysfunction in those diagnosed as HFNMSD?
7) If current CMR and echo measurements of LVEF do not correlate can this be improved upon using a regional wall motion score index (RWMSI) equation?
8) How does routine CMR affect the understanding about the underlying aetiology for the heart failure?
    a. Consider the frequency of ischaemic versus non-ischaemic aetiology pre versus post CMR.
        i. Can the presence and degree of subendocardial LGE reliably predict CAD on angiography in a retrospective cohort?
    b. Consider the presence and degree of non-subendocardial LGE in the heart failure cohort.

Methodology

There were two phases to the study; retrospective and prospective. Both were important to help answer the questions above. The prospective arm allowed a real time assessment of the local heart failure population using up to date echo and CMR imaging techniques and analysis according to a pre-defined protocol. The retrospective arm provided a larger cohort of patients from which to obtain a subset with specific features to investigate in more detail, when a prospective cohort would not be able to offer sufficient sample sizes. Specifically the retrospective cohort would provide a sample of patients to investigate whether the presence and degree of subendocardial LGE reliably predict CAD on angiography and also allow the development a new RWMSI equation which could then be subsequently tested and validated on a different prospective group.

Prospective cohort

A prospective cross sectional observational study for all new referrals to the heart failure clinics in the County Durham and Darlington NHS Foundation Trust (principally Darlington Memorial and Bishop Auckland Hospitals) was undertaken.

A protocol for selection, recruitment, consent, data storage, analysis and ethical considerations was undertaken. This protocol was formally peer reviewed by various health professionals locally, including cardiology Consultants not involved in the study, cardiac research nurses, clinical cardiac specialist heart failure nurses, echocardiographers, and cardiac physiologists. As a result of this meeting the design of the study was altered to delay the time of consent beyond the initial diagnostic clinic due to concerns that asking for consent immediately following the news of a serious diagnosis may not be appropriate. There was also encouragement to delay the timing of CMR to around 6 weeks after diagnosis and treatment to allow better stabilisation of heart failure symptoms. Following local peer review, a meeting with a heart failure patient representative and heart failure patient support group was undertaken with prototypes of the patient literature and forms. From this meeting came useful suggestions for improvements to the patient information leaflet and consent form, including defining memory loss more clearly.

Thereafter the research proposal was discussed by the ethics review panel at Durham University. The panel felt the wide breadth of data gathering necessitated ethical approval for a large database and recommended seeking ethical approval from a NHS research ethics committee with expertise in databases. Thereafter, specific questions that would utilise this data for University related research would go through the University ethical approval process. As such the research proposal was submitted via the online

Integrated Research Application System (IRAS) to a database specific committee and subsequently considered and approved by the National Research Ethics Service (NRES) Committee South Central-Oxford C. A few months later, amendments had to be made to the protocol in light of some difficulties with patient recruitment. An IRAS amendment form was completed and approved by the Oxford REC and the local Research and Development unit.   Following guidance from Durham University, a substantial amendment was approved prior to submission of the final thesis to allow extended approval for the use of anonymised non-identifiable basic demographic data from the entire group of patients attending the heart failure clinic, including those without heart failure that were discharged from follow-up at the first clinic.

Patient selection and recruitment

Potential participants were generally GP/community referrals with elevated BNP and symptoms of heart failure or recent inpatients given a new diagnosis of heart failure, referred to the Bishop Auckland or Darlington Memorial Hospital weekly heart failure clinic. The expectation was for a total of approximately 10 new referrals per week to the clinics based on a retrospective review of the previous 3 months of clinic attendances.

A database of all attendees and the physician's diagnosis for each was kept for all new referrals as part of the hospital Trust's own data collection for audit purposes and consent was not be required for this.

Each new patient attending the heart failure clinic has a set of observations performed, ECG, basic echo (if not previously done) and a quality of life questionnaire. They are then reviewed by a clinician who takes a medical history and performs an examination according to a standard template. At the end of this clinic a provisional diagnosis is made according to the standard diagnostic pathway (Figure 13), and treatment commenced.

It was estimated that approximately 50% would be diagnosed as HFREF, HFPEF or possible HFREF/HFPEF and that this would equate to 250 individuals with a new diagnosis of heart failure over 12 months assuming 100% were agreeable to participate. These individuals would be diagnosed according to the predefined diagnostic pathway described below and inclusion and exclusion criteria were adhered to as shown in the Figure 12.

Figure 12. Inclusion and Exclusion criteria for prospective database entry.

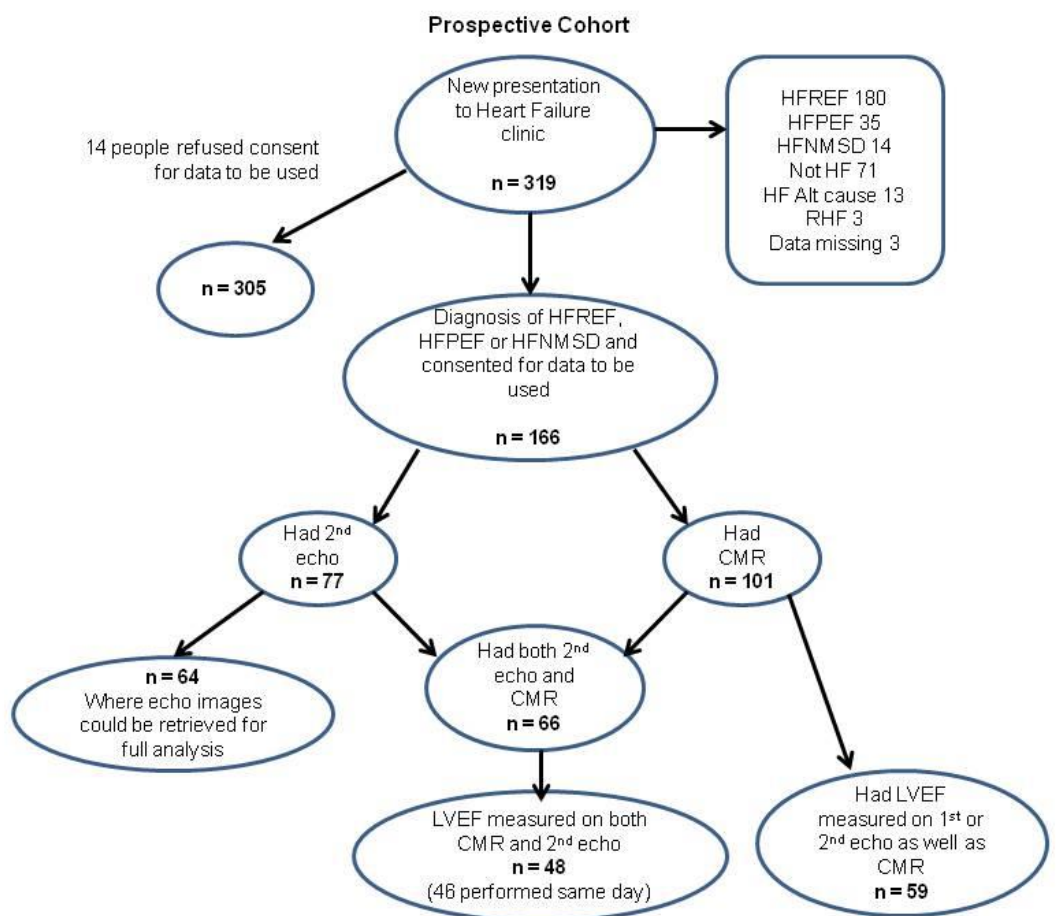| Inclusion Criteria	Exclusion Criteria
New diagnosis of heart failure or possible heart failure due to HFREF and HFPEF according to standardised template.	Diagnosis of heart failure due to another cause or non-heart failure according to standardised template.
Over 18	Under 18
Capacity to consent to the study	Lacking capacity to provide consent
Attending County Durham and Darlington NHS Foundation Trust heart failure clinic	Patients previously seen in the heart failure clinic

Figure 13. Diagnostic protocol for new patients presenting to the heart failure clinic.
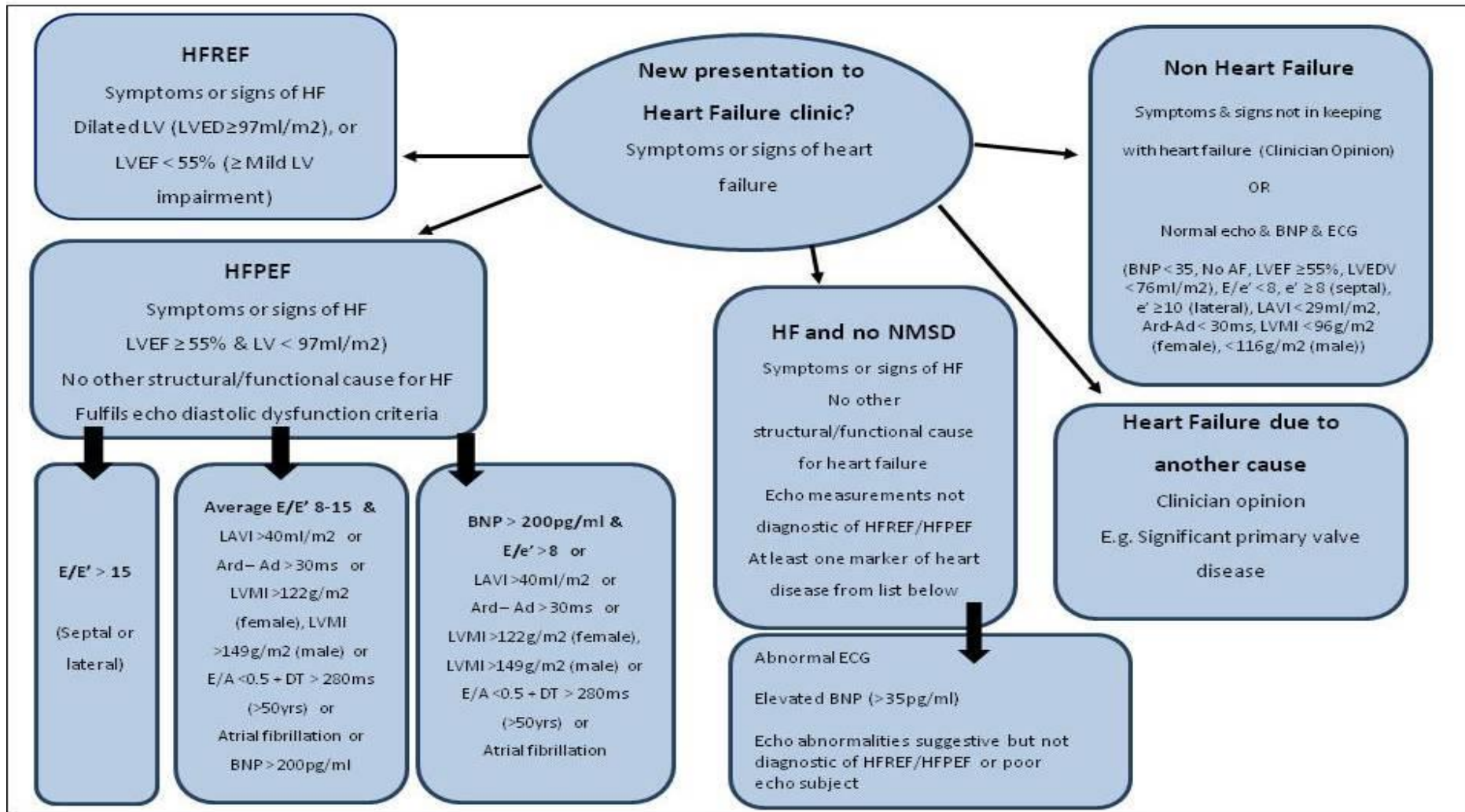
HFREF, Heart failure with reduced ejection fraction; HFPEF, Heart failure with preserved ejection fraction; HFNMSD, Heart failure with no major structural disease; LVEF, Left ventricular ejection fraction.

Those patients given a diagnosis of HFREF, HFPEF or HFNMSD went on to have an outpatient CMR scan and further detailed echo approximately 6 weeks after the clinic as standard practice barring any contra-indications. Those given a diagnosis of Heart Failure due to another cause or Non Heart Failure did not undergo routine CMR or repeat echo, and instead further investigations was tailored to their specific requirements. The numbers of individuals that went on to have these various investigations, and thus the cohorts available for analysis are described in the consort diagram (Figure 14) below. This will be referred to in its various components throughout the prospective results sections for clarification of the patient cohort being examined in each section.

Figure 14. Consort diagram of prospective patient cohort.

Cardiac magnetic resonance acquisition and reporting

The CMR scans were performed according to standard heart failure protocols and exclusion criteria. CMR images were obtained using a 1.5 Tesla GE Signa Excite scanner. Following scout images, ECG-gated, steady-state, free precession breath-hold sequences (typical echo time/repetition time 1.3/3.1 ms, flip angle 45°) were performed to produce three long-axis cines and sequential short axis cines (8mm slices with 2mm gaps) from the atrioventricular ring to the apex of the heart. Phase contrast velocity encoding sequences through the mitral and aortic valve, LV tagging sequences and late gadolinium enhancement (LGE) sequences were all obtained. The LGE images were acquired 10 minutes after intravenous gadolinium-DOTA (Dotarem 0.2 mmol/kg) into a peripheral vein using an inversion recovery gradient-echo sequence. Inversion times were individualised to null normal myocardium (typically 180 to 260ms; pixel size 1.4 x 1.3 mm) and identical views were obtained as for cine imaging except for the removal of basal short axis slices in the LV outflow tract.

The scan was reported by a consultant cardiologist with level 3 accreditation in CMR, and images stored in a format that allowed further post-processing. LVEF and LVEDVI were measured using the standard techniques but with the inclusion of papillary muscles in LV volumes (197). The latter was automatically indexed to body surface area in the report. Regional wall function was described in a pictorial representation of the 17 segment American Heart Association (AHA) model, and differentiating normokinesis, hypokinesis, akinesis and dyskinesis using differing colours.

LGE was deemed to be present only when signal enhancement could be seen in two planes. It was described as subendocardial, epicardial, transmural or midwall and then reported according to the AHA 17 segment model in terms of the myocardial segments affected when subendocardial. Subendocardial and transmural LGE was assumed to represent a myocardial infarction due to CAD. The degree of wall thickness affected was graded using differing colours, generally according to a <50% versus >50% differentiation.

Some individuals had CMR stress imaging sequences performed using a standardised adenosine stress protocol. These were also reported according to the AHA 17 segment model and labelled and being normal or having a stress perfusion defect.

Transthoracic Echo acquisition and reporting

There was an endeavour to perform the detailed echocardiogram on the same day and in the same centre as the CMR for patient ease and also to allow valid temporal comparison between the two investigations. The echo was performed and reported

according to a standardised protocol and according to the best practice described in Chapter 3. The same GE Vivid 7 machine was used for all scans with images transferred to EchoPAC clinical workstation for post analysis and reporting. Only the two echocardiographers trained in the specifics of the acquisition protocol would perform the scans. Measurements included cardiac chamber sizes, LV wall thickness and mass, full LV systolic and diastolic function assessment, LV strain imaging by speckle tracking, pulmonary vein flow Dopplers, RV function with TAPSE, IVC assessment for size and collapsibility and estimated PASP. These were all performed using best practice protocols described in the literature review section. The strain imaging, not previously described, was performed according to best practice. All apical LV images were optimised for best quality, trying to ensure that the endo and epicardial surfaces of all walls were visualised over three-five cardiac cycles. The three-chamber view was used initially so that the aortic valve closure time could be confirmed visually. Thereafter the two-chamber and four-chamber views were analysed. Points were marked manually at the mitral valve annulus and LV apex before an automated tracker package marked the endocardium at points in between. These were adjusted manually when necessary and the width of the tracker optimised. At least 15 of the 17 segments had to be of acceptable quality according to the analysis package in order to use the final global strain measurement.

Final documented results were as a result of measurements over an average of at least three heart beats in patients with sinus rhythm and over an average of five cardiac cycles in patients with atrial fibrillation.

Inter-observer assessment of LVEF was not formally tested as part of this study but has been done so at a departmental level in both the echo and CMR departments in the past for internal validation purposes and no concerns highlighted. As this was a pragmatic assessment of everyday practice, a formal assessment of inter and intra-observer variability in scan recording and reporting was not performed.

Patient supervision and responsibility for care

Each patient was under the clinical supervision of the heart failure team (a consultant cardiologist, nurse specialist and non-consultant medical staff) who was responsible for the patients' care. Medical management of heart failure was according to current clinical NICE/ESC standards in all patients and all imaging results were sent to the treating clinician in order to guide further management.

Consent

Those patients given an initial diagnosis of HFREF, HFPEF or HFNMSD were eligible to consent to have their data kept on the research database according to the inclusion and exclusion criteria listed above. The clinician in charge of the patient's care would briefly explain the research to the individual at the end of their 1st clinic appointment, and provide a basic information leaflet to those eligible to be involved. Most patients received the new diagnosis of heart failure or possible heart failure at this first clinic, and being a major diagnosis for most, it was felt to be inappropriate to talk of the research in any detail at this time. As such this discussion was kept very brief.

Most patients diagnosed with heart failure would have a follow-up appointment organised before or around 3 months, and formal written consent was sought at this return visit by a trained research nurse. Approximately 2 weeks prior to the return clinic visit a detailed participant information sheet was sent to the patient's home. On the return visit a verbal discussion detailing the database research objectives and methods was undertaken by the research nurse, and any questions answered. If agreeable, patients were consented using a standardised written consent form. The research nurse obtained consent wherever possible but in those rare circumstances when a research nurse was not available this task was delegated to another competent individual with GCP training, as per the research team's responsibilities log.

Those individuals with heart failure that were discharged from follow-up, who did not wish to return to the hospital, or were too frail to return to the hospital, and who expressed willingness to participate in the database, could be visited at home by the research team, or have the consent form sent to their home to sign and return. Those patients that died before formal consent could have been obtained had their data input to the database under the Research Governance Framework (RGF) permission.

Participants consented to allow the research team to keep personal identifiable information and routine clinical data on a secure computer database indefinitely, with a view to analysis for heart failure research. At the time of consent participants are also asked if they want a summary of study results. This is documented and the results of this study will be distributed on completion.

Consent was not obtained when patients did not have capacity to make this decision. Those whose first language is not English required an interpreter and in this circumstance a fully trained and accredited translator was present at the time of any discussions or investigations, and to translate any documentation including the patient information leaflet.

Patients were advised that they are free to refuse consent or withdraw consent from the study at any time and those who were uncertain about consenting were offered a further period of time to consider and discuss with family members and/or GP.

Those given a diagnosis of Heart Failure due to another cause or Non Heart Failure were often immediately discharged and were not asked to consent for data collection nor sent a participant information sheet.

Data Collection

The following data were recorded for each consenting participant:

- Name, unit number, and date of birth

- Observations and examination findings of congestion

- Symptom profile

- Medical history

- Results of quality of life questionnaire

- Blood results

- ECG results

- Initial basic echo parameters

- Subsequent echo and CMR measurements

- Heart failure related treatments

These data were taken directly from the written template in the hospital notes, clinic letter information, biochemical and imaging reports or directly from imaging raw data. With regards to BNP, the laboratory's coefficient of variation has been assessed at three levels and is as follows:

Level 1 38.0 pg/ml with coefficient of variation of 3.3%

Level 2 450 pg/ml with coefficient of variation of 0.87%

Level 3 1490 pg/ml with coefficient of variation of 1.56%

Data storage, custody and control

Data were stored onsite at Darlington Memorial Hospital. The database is on a secure password-protected area of the Trust server and actually consists of two separate

databases. The first is a list of participant names, unit numbers and date of birth alongside a study number. Passwords to this database are only available to Professor J Murphy, Professor A Fuat, Dr J Crilley, the cardiology research fellow and research nurse or research secretary that would require access for data input. These passwords require changing on a regular basis as per Trust policy. The second database has the participant study number and initials but no other identifying personal information, and alongside this all the clinical data listed above. Passwords for this semi-anonymised database are available to named individuals as determined by Professor Murphy and would generally include Trust or university clinicians, researchers or staff with expertise required to conduct research such as statisticians.

The databases were constructed on a Microsoft Excel program following Excel training sessions at Durham University, online training and the advice and scrutinisation of the I.T learning and development officer at the Trust to maximise effective and valid data input. Comprehensive formulas, data validation methods, drop down choices and protected cells make it as robust as possible and to avoid accidental erroneous data input or removal.

The databases are copied for back-up purposes on a regular basis, and any previous copies erased at the same time. The databases are kept in different places to reduce the likelihood of any data security breach but it remains possible to link the personal data from one database with the clinical data on the other, which is necessary when follow-up data input needs correlating for the same person.

Data were analysed on site at Darlington Memorial Hospital according to Caldicott guidelines and standards. When needed to be taken off site for statistician analysis then only the anonymised data were used and transferred using a Trust-provided password-protected memory stick.

Data analysis and statistical packages

Data were initially stored on Excel spreadsheets in a format conducive with easy transfer to an SPSS package, all the while trying to ensure that missing data and non-measurable data were coded appropriately and separately rather than leaving blank fields. The introduction to SPSS provided by Durham University was helpful and thereafter wise words from Dr Douglas Wilson and the Information Technology team at Darlington hospital allowed comprehensive planning of the data collection from the outset in order to facilitate analysis later. All data analysis was performed using SPSS with the exception of the Deming regression analyses and Bland-Altman plots which were not provided by the SPSS package. These were performed on the reputable "Medcalc"

online application, with double checking of initial results to ensure accuracy. The prospective observational data were generally descriptive with basic average and percentage calculations. Comparison of demographics between different groups was then performed using the Student's t, Mann-Whitney U or Fisher's exact test depending upon whether the data were parametric, non-parametric or categorical. The statistics behind the assessment and development of a new RWMSI equation, and LGE to predict prognostic coronary disease was more complex and the rationale for different statistical methods and approaches are explained in the relevant methodology sections below. University statistician Dr Douglas Wilson helped at all stages of the statistical methodology and interpretation. His guidance was invaluable and meant that results were double checked for accuracy.

Ethical considerations

This research was subject to the local County Durham and Darlington NHS Foundation Trust Research and Development Department approval and thereafter National NHS Research Ethics Service (NRES) Committee South Central-Oxford C approval before Durham University SMPH ethics sub-committee approval. This was a lengthy and repetitive process with a variety of set-backs to be overcome along the way. It was particularly useful to canvas opinion via peer review and the patient group workshop, and the advice from the Trust's Research and Development manager was invaluable for successful engagement in the local submission process and IRAS.

A diagnosis of heart failure can be a major life event for an individual and as such it was deemed inappropriate to approach people for consent to participate in the study at the initial clinic visit. This meant that people were approached on their return visit and had the limitation of excluding the subgroup of patients that did not receive a follow-up hospital appointment (most often due to frailty) or those who died before follow-up. With the realisation that this would lead to a biased subset for analysis an amended protocol to allow a modified consent process was submitted to the Oxford REC and local Research and Development unit, and approved so that such individuals could be visited at home by the research team, or have the consent form sent to their home to sign and return. Those patients that died before formal consent could be obtained would have their data inputted under the Research Governance Framework (RGF) permission.

It became an ethical quandary to know whether to perform the CMR and echocardiogram on the same day. The scans can be long and as such tiring for the patient to have both on the same day. However it avoids a repeat visit for the patient and from a research perspective is preferred because of the close temporal relationship when comparing the different methods. Because of this ethical quandary, opinion was canvassed from the
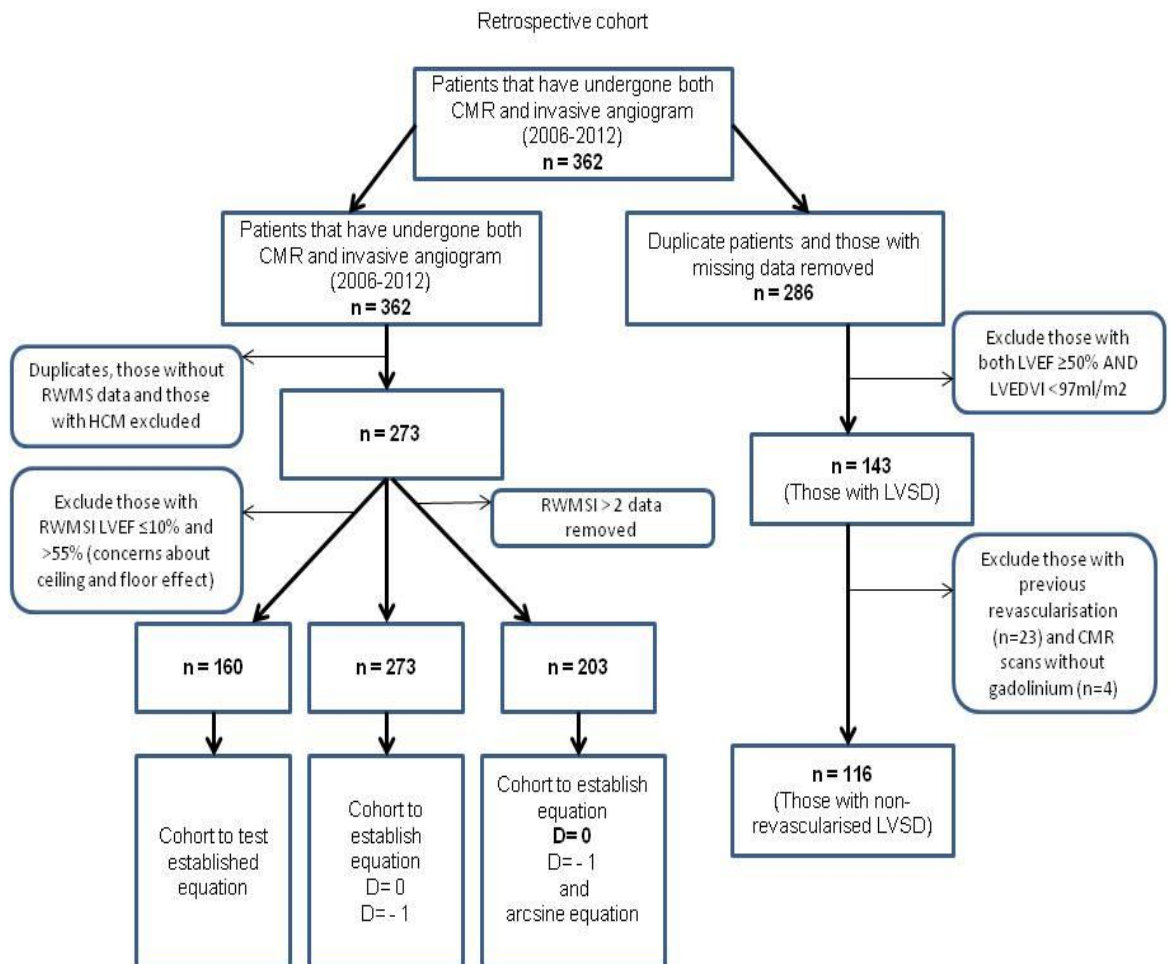
heart failure support group and the consensus was that same day scans was the preferred strategy. However, if an individual would prefer to have the scans on separate days for any reason then this would be arranged.

It was felt important to acknowledge patients contribution to the study by taking the time to produce a summary of any results for those that wanted it. As such patients were asked if they wanted this at the time of consent. Whilst many had no interest in receiving such information, the gesture was warmly received by a number of individuals who commented on how refreshing this approach was.

Retrospective cohort

This relates to the cohort used to investigate the performance of current RWMSI equations and consider new equations if necessary (with a view to subsequent validation in a prospective cohort), and whether the presence and degree of subendocardial LGE reliably predicts CAD on angiography. It is a different group from the prospective heart failure clinic cohort. The consort diagram for these two retrospective analyses is shown in Figure 15 and will be referred to in its various components throughout the rest of the methodology and results section for clarification of the patient cohort being examined in each section.

Figure 15. Consort diagram of retrospective analyses

Retrospective cohort

Patients that have undergone both CMR and invasive angiogram (2006-2012) n = 362

Patients that have undergone both CMR and invasive angiogram (2006-2012) n = 362

Duplicate patients and those with missing data removed n = 286

Duplicates, those without RWMS data and those with HCM excluded

Exclude those with both LVEF ≥50% AND LVEDVI <97ml/m2

n = 273

n = 143 (Those with LVSD)

Exclude those with RWMSI LVEF ≤10% and >55% (concerns about ceiling and floor effect)

RWMSI >2 data removed

Exclude those with previous revascularisation (n=23) and CMR scans without gadolinium (n=4)

n = 160

n = 273

n = 203

n = 116 (Those with non-revascularised LVSD)

Cohort to test established equation

Cohort to establish equation D= 0 D= - 1

Cohort to establish equation D= 0 D= - 1 and arcsine equation

Since the initiation of the CMR service at Darlington Memorial Hospital there have been a number of patients who have undergone both CMR and invasive X-ray coronary angiogram within a relatively short time span of each other. The retrospective cohort essentially incorporates these individuals.

The patient demographics of everyone that has ever had a X-ray angiogram and all those who have ever had a CMR are kept on separate databases, the newest being the CMR database which was set up in 2006 when the service began. Both databases are kept within the cardiology department for audit purposes.

Combining these two databases allowed identification of those that had undergone both a CMR and X-ray angiogram and the dates when the investigations occurred. A new database was created containing only these individuals. The full reports from both investigations were then reviewed, and a dataset of information established.

Invasive X-ray coronary angiography had been performed and reported on the same day by a consultant cardiologist. The presence and degree of any coronary stenoses were labelled on a detailed pictorial display of the coronary arteries along with a written description.

CMR scanning and reporting was performed in the same manner as described above for the prospective cohort.

Database Construction

This retrospective database was created in Microsoft Excel in a password protected environment within the NHS Trust server. Individuals were given a study number and when patient identifiable information was no longer required it was removed from the database. The data compiled included:

- Date of CMR and X-ray angiogram

- Age at the time of X-ray angiogram

- Sex of patient

- Time between investigations in days and which study came first

- Indication for CMR and angiogram

- CMR results

- X-ray angiogram results

The indication for undertaking the CMR and X-ray angiogram were not always clear or standardised. Establishing a standardised set of indications was helpful for consistent data entry, and included:

- Heart failure

- Viability

- Ischaemia

- Troponin positive chest pain

- Constriction or restriction

- Congenital Heart disease

- Hypertrophic cardiomyopathy

- Left ventricular hypertrophy

- Cardiac tumour

- Valve disease

- Ventricular fibrillation/tachycardia

In cases where the indication was unclear, a review of medical notes, blood and echo results was undertaken to decide upon the most likely referral reason.

The data used from the CMR report included chamber measurements and ejection fraction (with indexing to body surface area when able). A regional wall motion numerical score (RWMS) was substituted for the colour interpretation of the wall motion for each of the AHA 17 segments of the LV. The numerical score given depended upon the RWMS analysis being tested. The pattern of late enhancement was established and if subendocardial, graded as either normal (not present) ("0"), or present <50% thickness ("0.5"), or >50% thickness ("1") for all 17 segments. The stress perfusion results were described as simply normal ("N") or having a defect ("D") for each of the 17 segments. When segments were not seen or reported the number "99" was used within the numerical datasets, and the letter "z" used within alphabetic datasets to represent missing data and allow a smoother transition into the SPSS package later. Tests not

performed or abandoned were given different codes to differentiate them from other missing data.

The results of the X-ray angiogram were documented; specifically maximum percentage stenosis of the LMS and proximal LAD, and then of the LAD territory, LCx territory and RCA territory. Stenosis in a "territory" generally referred to that in the main coronary artery, however, if a large diagonal or OM had more profound disease than the main vessel this would be documented as the worst stenosis. These were given numerical percentage values exactly as described on the angiogram report. Another column of data to document unusual features from the X-ray angiogram was also created to include information such as whether the patient had grafts, stents or valve disease. This should have picked up all of those who had undergone previous revascularisations.

Regional wall motion score index to predict CMR LVEF

Regional wall motion scoring index is performed by assigning a score to each of the segments of the 16-segment American Heart Association (AHA) model for the assessment of regional LV function. It is sometimes used in clinical echo practice because of the difficulties performing Simpson's Biplane measures and it is simple to perform. Appraisals of RWMSI have demonstrated good correlation with cardiac MRI LVEF but this has only been looked at over a wide range of ejection fractions and sub group analysis was limited by small group numbers. It tends not to be employed in CMR reporting because the LV endocardium clarity means that LVEF can be easily calculated by the well practised method of endocardial tracing. Various scoring systems have been used but the generally accepted method is to give a score of 1 to 4 depending upon the wall motion in each segment (198):

1 = Normal wall motion

2 = Hypokinetic

3 = Akinetic

4 = Dyskinetic

The wall motion score index takes the sum of these scores and divides it by the number of segments observed. The entire myocardium (except for the apical cap) is taken into account as opposed to the Simpson's Biplane assessment which does not look at the function of the inferior and anterior walls. One of the drawbacks to this scoring system is that it has an inverse relationship to the calculated LVEF, requiring a computerised equation to convert one to another, and making its application difficult in clinical practice. This is due to the fact that better contracting myocardium has a lower score than

dysfunctional myocardium in most scores. Some teams have validated a scoring system where more positive scores represent better contracting myocardium but the scores were sub-divided for different degrees of hypokinesis thus increasing their complexity (137, 199). One of these studies validated a 2D RWMSI against 3D echo LVEF (199), the other against CMR LVEF (137). However the spread for level of agreement was not probably not clinically acceptable and it is also worth noting that previous correlation calculations may be skewed by the ceiling effect of the RWMSI (i.e. a positively scoring RWMSI described above could not exceed the score given to a normokinetic segment, e.g. 3x16/16=3) whereas Simpson's Biplane or CMR LVEF is not restrained by the same ceiling cut-off.

My experience is that this positively correlating calculation seems to be a reasonable representation in those with normal, mildly impaired or moderately impaired LV systolic function, but that it over-exaggerates the degree of LV impairment in those with severe LV systolic impairment, resulting in much lower ejection fractions using RWMSI compared with endocardial tracing using CMR.

In current clinical work the previously validated equation,

RWMSI LVEF = (Total RWMS/16) x 30,

is often used alongside a simplified RWMS where normal wall motion = 2, hypokinesis = 1, akinesis = 0 and dyskinesis = 0 or -1 (137). The denominator of 16 is used rather than 17 because in many centres only a 16 segment LV model is used, missing out the very apical segment. My experience was that this calculation seemed to be a reasonable representation in those with normal, mildly impaired or moderately impaired LV systolic function, but that it may over-exaggerate the degree of LV impairment in those with severe LV systolic impairment. This would result in much lower ejection fractions using RWMSI compared with endocardial tracing using CMR.

One aim, using the retrospective database of information, was to test the hypothesis that the RWMSI equation above provides an accurate reflection of CMR LVEF and heart failure severity group across all the degrees of LV impairment. If not, it would be important to consider and define alternative equations and investigate whether these could provide a better representation of CMR measures.

The initial dataset included 362 names. Those with missing CMR or angiogram data, or those with very focused studies where the data above were not collected, and those with repeat datasets due to a different hospital number were all excluded from the database. A subsequent seven individual datasets were removed because of missing RWMS data.

The RWMSI equation described above will have a ceiling effect whereby the maximum possible LVEF is 60% (RWMSI LVEF = (32/16) x 30). Discrepancies with those with CMR endocardial LVEF > 60% are therefore evident. In order to minimise these discrepancies I opted to remove all those patients with an indication of hypertrophic cardiomyopathy from the database as such individuals have a supra-normal LVEF almost universally. This resulted in the removal of six datasets, leaving 273 patients for analysis (see flowchart, Figure 16 below). The study was considered by the NHS Health Research Authority (HRA) screening tool and individual patient consent was not required.

Figure 16. Patient selection for RWMSI equation development: adapted from consort diagram (Figure 15).
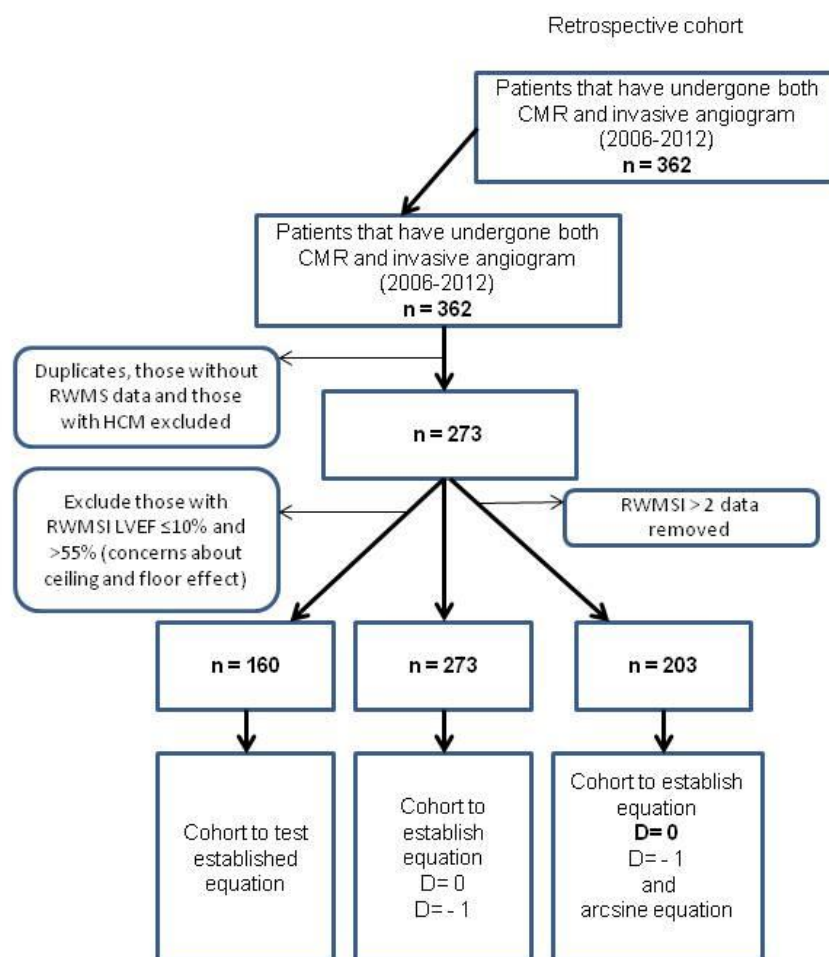
The indication for CMR was varied, incorporating all the subgroups described above. The RWMSI LVEF was calculated for every individual according to a 16 segment model, excluding the very apical segment in all, and using the equation above. The simplified RWMS whereby normal = 2, hypokinetic =1 and, akinetic and dyskinetic = 0 was employed. Deming regression analysis was performed as well as Bland Altman agreement plots of RWMSI LVEF versus CMR LVEF. This was initially performed in the entire study population of 273 individuals but the impact of the ceiling effect of the equation was notable visually on the charts with a dense clustering of RWMSI LVEF at the 60% level. As such, the data were reanalysed only for those with a RWMSI LVEF >10% and ≤55% in an attempt to overcome concerns about a ceiling or floor effect that might skew the analysis. This reduced the sample size to 160 subjects. The data were also depicted by heart failure subgroup from the CMR LVEF according to the British Society of Echocardiography reference ranges (Normal LVEF ≥55%, mild impairment 45 to 54%, moderately impaired 36 to 44%, and severe <35%).

The Deming regression analysis was used in preference to standard regression analysis as this method would take into account the variation within both variables, acknowledging that even the gold standard CMR endocardial LVEF will have inherent variance (200). The Bland Altman plot is a means of assessing agreement between two methods of clinical measurement (201, 202), rather than simply the strength of a relationship (be that one which lies along the line of equality or not) as depicted by a correlation or regression analysis. It was used as a means of assessing this equation in the previous validation study (137) and in that study the limits of agreement suggested that the RWMSI LVEF could be 9% higher or 14% lower the CMR endocardial LVEF.

Separate Deming regression analyses were performed on the individual heart failure subgroups (normal, mild, moderate or severe LV impairment by BSE criteria) according to the CMR endocardial LVEF and the difficulties with this are examined in the results section below.

Following this analysis, a better fit equation was calculated and novel RWMSI LVEF equations were constructed from the best-fit Deming regression lines for four different datasets, adjusted according to whether the RWMS allocated a score of 0 versus -1 to a dyskinetic segment, and thereafter either incorporating or removing all those with a RWMSI of 2 (Figure 16).

Most previous RWMSI calculations have tended to allot a score of -1 to a dyskinetic segment and thus it was necessary to test this scoring method. A RWMSI of 2 would mean that all the walls of the heart have normal contractility and it should logically follow

that any LVEF should be at least 55% (i.e. at the lowest end of the normal range) in all these cases. In practice this may not always be the case but in this sample there were 70 individuals that had a RWMSI of 2 and all but one had an CMR endocardial tracing LVEF of ≥ 55%, (outlier LVEF = 52%). The range of LVEF in this group was varied, with a mean LVEF of 70%. Theoretically incorporating all the data could produce a regression equation that would allow a RWMSI of 2 to result in a RWMSI LVEF of < 55%. This seemed counterintuitive and one way to avoid this was to remove all those with a RWMSI =2 and accept that these should always represent an LVEF ≥55% but could not be defined with any more accuracy. The decision then came whether to remove or keep the group with a RWMSI = 2 for the regression equation for the rest of the data since each method would bias the regression line differently.

Given these different considerations, equations were derived for four different datasets:

1.   Dyskinetic segments = 0, and all RWMSI data used (including RWMSI = 2)

2.   Dyskinetic segments = 0, and only RWMSI < 2 data used

3.   Dyskinetic segments = -1, and all RWMSI data used (including RWMSI = 2)

4.   Dyskinetic segments = -1, and only RWMSI < 2 data used

The aim was to identify which dataset provided an optimal relationship between the RWMSI and the CMR endocardial LVEF, by way of the difference in the means and confidence intervals.

The distribution of the RWMSI data was positively skewed by the large numbers with a RWMSI of 2. However, even with this group removed, the data were not normally distributed and it was possible that linear equations would not be representative of the relationship between RWMSI LVEF and CMR endocardial LVEF. Attempts to transform the data into a more normal distribution using logarithmic and trigonometric methods were undertaken and the most successful method was taken forward to perform another Deming regression analysis and a further equation identified.

In addition, the equations established above were simplified to be more clinically useful. The final selection of equations are listed and explained in the results section.

The performance of all the equations were compared on the same cohort of subjects, for the full data set and then for each heart failure subgroup (normal, mildly impaired, moderately impaired, and severely impaired according to CMR LVEF) for data that

included RWMSI = 2, and then those where RWMSI = 2 were excluded. This was done by comparing the mean RWMSI LVEF (with confidence intervals) of each equation with CMR endocardial LVEF values. Subsequent paired analysis of heart failure group allocations by the different equations versus CMR LVEF was performed. The LVEF determined a heart failure grouping according to BSE criteria (1=severe (LVEF ≤ 35%), 2=moderate (LVEF 36-44%), 3=mild (LVEF 45-54%), 4=normal (LVEF ≥ 55%). The notion was that performance according to heart failure group allocations may allow a more clinically relevant interpretation of the equations' performance. It also provides an alternative method of comparison to support any conclusions, acknowledging that using the same set of data for hypothesis generation and then hypothesis testing has significant limitations. Indeed, despite multi-method hypothesis testing any findings would need to be validated with a future cohort of different patients.

Wilcoxon (matched pairs) signed rank analysis of the heart failure groups created by the different equations versus CMR LVEF was attempted but was unhelpful. The ranking system, that is inherent in this statistical method, produced dramatic differences in the level of significance of the equations depending upon whether the middle or outside heart failure subgroups groups were analysed. The lowest and highest group could not have data that were negatively or positively ranked respectively because they were at the lower and upper ends of the ranking system. The two middle groups could have rankings in either direction. Whether the group was an inner or outer heart failure group in the ranking system seemed to be the most relevant variable to the significance results of the test. Instead, a test that considered simply whether the heart failure group allocation was correct or incorrect (irrelevant of positive or negative ranking) was performed using cross-tabulation and Kappa measure of agreement, and the different levels of agreement for the equations were compared. Once again this was initially performed with the whole dataset but the high levels of agreement in the "normal" subgroup, with large "normal" subgroup numbers appeared to be skewing the picture for the other subgroups. Therefore, repeat analysis was done for only those 203 individuals with a RWMSI < 2, removing the group of people with the equation's ceiling RWMSI LVEF and reducing the skewing effect.

After review of the semi continuous and categorical agreement between the various RWMSI LVEF equations and CMR LVEF, the best fit equations, taking into account clinical usability were identified. These were then prospectively tested using Bland Altman plots of echo RWMSI LVEF and CMR LVEF for studies performed on the same day in the prospective heart failure cohort. Categorical analysis was also performed to assess the concordance of heart failure group allocation by the different methods. The
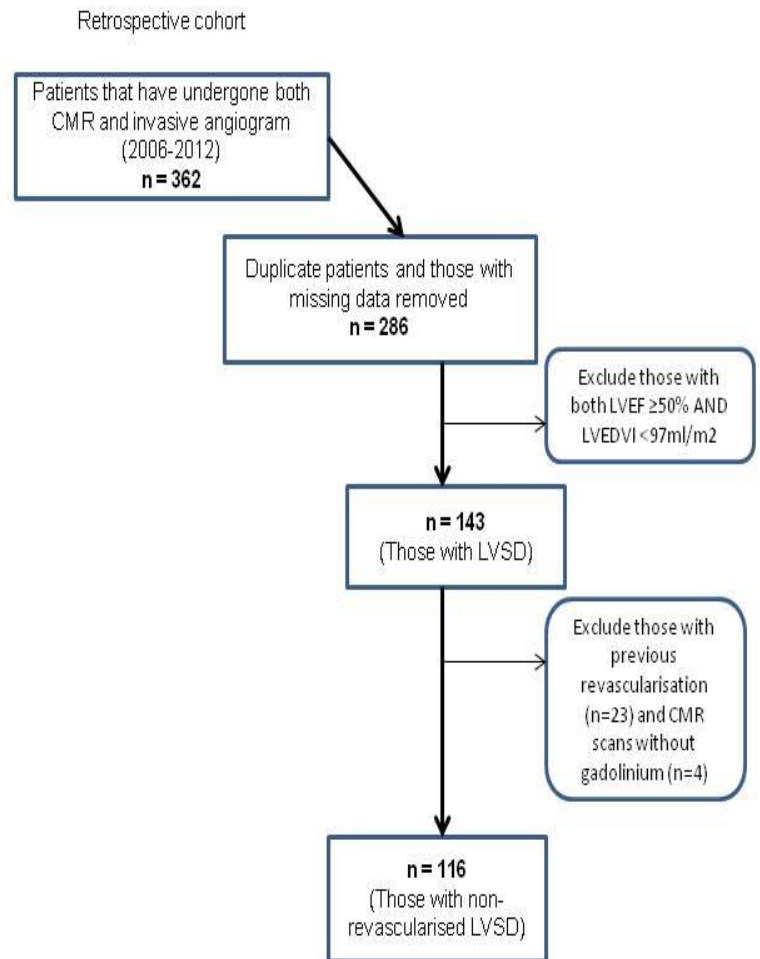
results were then compared against the accuracy of those for the Simpson's Biplane method of LVEF.

LGE CMR to predict prognostic coronary artery disease

The evidence for the predictive value of LGE CMR alone to detect prognostic CAD in a heart failure population is lacking, and understanding local performance is important. The aim in this analysis was to assess whether the absence of subendocardial LGE could reliably exclude prognostic CAD in a population with LV systolic dysfunction.

The European Society of Cardiology (ESC) definition of HFREF (6) was applied to the retrospective dataset of 286 people, and those with LV ejection fraction (LVEF) <50% or LV end-diastolic volume index (LVEDVI) ≥ 97ml/m^2 on CMR, or with a previous echocardiogram suggesting LV systolic impairment for which CMR had been requested to further differentiate the cardiomyopathy were selected. This latter group were identified by looking through the previous echos of those with a heart failure or viability indication for CMR but with normal CMR LV parameters. This resulted in a group of 143 individuals. Of these, those with a history of previous revascularisation (23 people), and those who did not receive gadolinium at the time of CMR (4 people) were excluded. A final total of 116 patients were included for analysis (Figure 17). The study was considered by the NHS Health Research Authority (HRA) screening tool and individual patient consent was not required.

Figure 17. Patient selection for retrospective analysis of CMR LGE with invasive angiography: adapted from consort diagram (Figure 15).

Retrospective cohort

Patients that have undergone both CMR and invasive angiogram (2006-2012)
n = 362

Duplicate patients and those with missing data removed
n = 286

Exclude those with both LVEF ≥50% AND LVEDVI <97ml/m2

n = 143
(Those with LVSD)

Exclude those with previous revascularisation (n=23) and CMR scans without gadolinium (n=4)

n = 116
(Those with non-revascularised LVSD)

A definition of prognostic coronary disease was established as described in the literature review section:

- LMS ≥ 50% stenosis

- Proximal LAD ≥ 75% stenosis

- Two or three vessel disease with ≥ 70% stenosis of a main epicardial vessel (defined as main LAD or large secondary branch, main LCx or large secondary branch or main right coronary artery excluding branches)

The definition of prognostic CAD was applied to the X-ray angiogram reports so that two groups were established: those with prognostic CAD and those without. These angiogram reports had been finalised by a single Consultant performing the study on the day of the study and formal inter and intra-observer variability was not tested. The presence or absence of subendocardial LGE was determined from the CMR report and two groups were established: those with subendocardial LGE and those without. A subendocardial LGE Total Score was calculated for each scan with a view to evaluating whether the total amount of LGE could help predict the likelihood of prognostic CAD in positive CMR scans. A value of 1 was given for one AHA segment with 50 to100% transmural enhancement, and 0.5 for one AHA segment with <50% transmural enhancement. A maximum Score of 17 would represent transmural LGE in every AHA segment. The basic demographics of the study population and comparison of demographics between the prognostic CAD positive versus CAD negative groups was performed. Continuous variables were expressed as mean ± standard deviation unless otherwise specified. To analyse the accuracy of LGE CMR to detect prognostic CAD we assessed sensitivity, specificity, positive and negative predictive value and diagnostic accuracy, with 95% confidence intervals. The rates of false positives and false negatives were calculated and case analysis of each group undertaken.

Results

Rather than breaking this into prospective and retrospective analyses, the results are displayed in an order consistent with the "Specific sub-questions to be addressed" section above. In some cases the combination of prospective and retrospective results are complementary and thus will be displayed together and labelled as such.

Q1. What is the diagnostic profile of a newly diagnosed heart failure population in the County Durham and Darlington NHS Foundation Trust?

How would the group divisions differ using different LVEF thresholds to diagnose HFREF?

The newly created, comprehensive diagnostic pathway using current best evidence for the diagnosis of heart failure with reduced ejection fraction (HFREF) and heart failure with preserved ejection fraction (HFPEF) (Figure 13) was applied prospectively to all 319 new patients attending our heart failure clinic between May 2013 and July 2014. In order to get a generalised overview of a generic population presenting to the heart failure clinic all 319 people were initially included. Many of these did not undergo CMR or repeat echo assessment but to include only these in the initial overview would have presented a biased population. Instead the data for this subset will come later. In this overview only clinician history, examination findings, ECG, basic initial echo, and BNP alone were used to define the groups. Figure 18 below shows the adapted prospective consort diagram to demonstrate the group being analysed (highlighted in red).

Figure 18. Adapted prospective consort diagram (Figure 14)
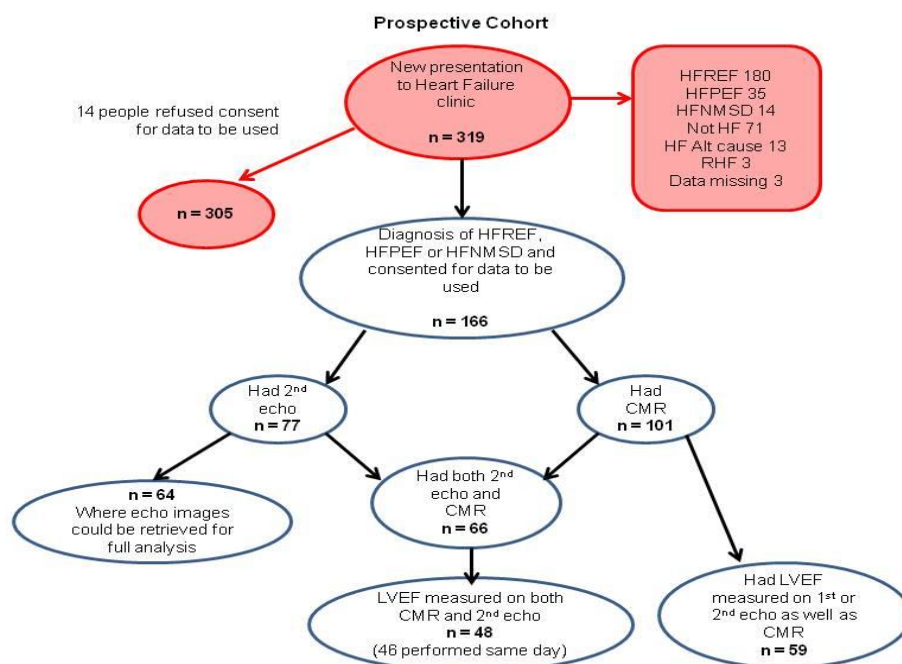
Whilst it was recommended that referral to the clinic incorporated an elevated BNP, GPs also had open access to transthoracic echo and many wanted an opinion based on clinical suspicion alone. As such the referral mechanisms were varied. In total, 58% had a BNP performed prior to clinic attendance. 54% of those referred had a BNP > 35 pg/ml and 47% of those referred had a BNP > 100 pg/ml prior to clinic attendance. BNP was also measured in clinic and data analysis later uses these measurements.

Of the 319 new patients, 245 were deemed to have heart failure clinically (combined HFREF, HFPEF, HFNMSD, HF alt cause and Right HF groups). Of these 245 individuals 73% met our diagnostic criteria for HFREF, and only 14% met the diagnostic criteria for HFPEF (20% if those with no major structural disease were included within the HFPEF heading) (Figure 19). This is a very different balance of HFREF to HFPEF when compared with other nationally published data and almost certainly represents discrepancies in LVEF diagnostic thresholds to define HFREF. Indeed Figures 22 and 23 below demonstrate how differing LVEF cut-offs affect the prevalence and ratios of HFREF to HFPEF in this heart failure community.

Figure 19. Schematic overview of diagnoses in the prospective cohort attending the heart failure clinic.
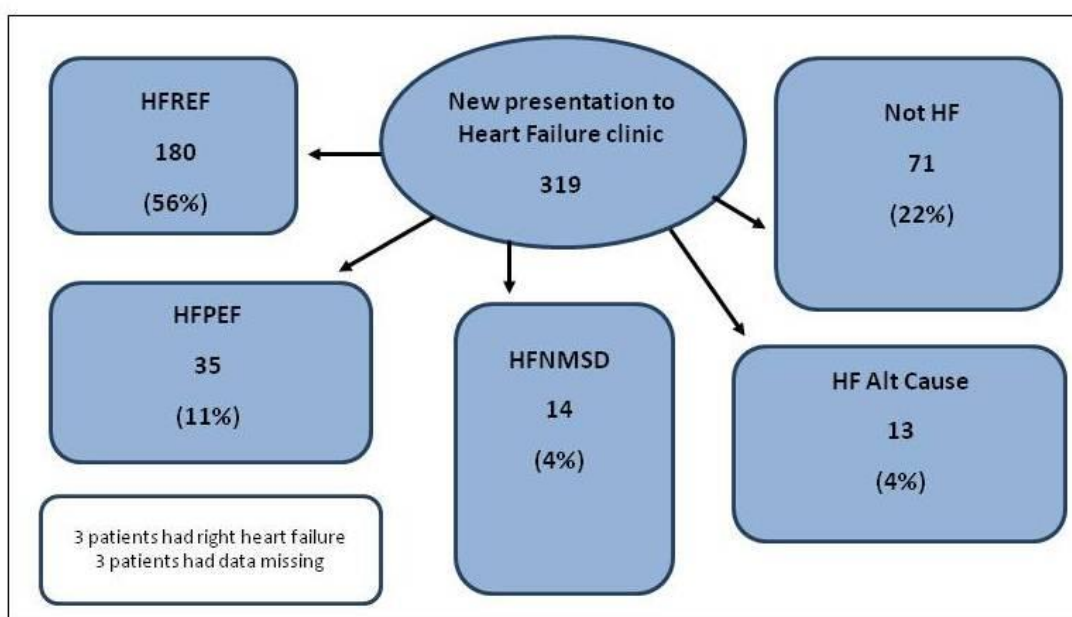
HFREF, Heart failure with reduced ejection fraction; HFPEF, Heart failure with preserved ejection fraction; HFNMSD, Heart failure with no major structural disease; HF Alt cause, Heart failure due to an alternative cause; Not HF, Not heart failure.

The characteristics of the population attending the heart failure clinic are described in Figure 20 below. Only those fourteen individuals that refused to consent for the

collection of their data were excluded from this analysis. Thereafter the significance of differences between the demographics of the HFREF and HFPEF populations are explored in Figure 21.

Figure 20. Demographics of the population attending the heart failure clinic (and subdivided according to heart failure grouping).

	All patients attending HF clinic	HFREF (LVEF<55%)	HFPEF	Not HF
Number	319 (305) (14 refused consent for data to be used)	180 (169) (11 refused consent for data to be used)	35 (33) (2 refused consent for data to be used)	71
% DMH clinic	57%	58%	80%	42%
% Female	47%	38%	57%	58%
Mean BNP (pg/ml)	340	434	298	151
BNP>35 (pg/ml)	92%			
BNP>100 (pg/ml)	76%			
% Previous MI	25%	31%	21%	15%
% Previous HF admission	15%	24%	6%	1.4%
% Permanent AF	35%	34%	62%	21%
% Dyspnoea present	85%	89%	91%	67%
% Oedema present	62%	58%	91%	44%
% Loop diuretic use	52%	54%	53%	32%
% Thiazide diuretic use	12%	10%	12%	14%

Figure 21 below compares the demographics of the HFREF and HFPEF groups, as designated by the diagnostic flow chart in figure 13. Similarly to other published literature, those with HFPEF were statistically more likely to be older, diabetic, hypertensive (systolic BP only) and to have permanent atrial fibrillation than those with HFREF. In accordance with other published data, there was also a much higher preponderance of females in the HFPEF group, although this didn't reach statistical significance (P=0.06). Those with HFREF were statistically more likely to have bundle branch block and to have had a previous hospital admission with heart failure. There was no significant difference in BNP level, body mass index, or prevalence of ischaemic heart disease or COPD. Interestingly, despite the higher rates of previous hospital admission in the HFREF group, the subjective assessment of quality of life by way of the Minnesota score was identical between the groups.

Figure 21. Comparison of demographics between the HFREF and HFPEF groups.

According to diagnostic flow chart (Figure 13)					
	Based on initial echo (LVEF<55% (≥"mild LVSD") or LVEDVI≥97ml/m^2)				
	HFREF (LVEF<55%)	HFPEF	HFREF vs HFPEF	OR where significant	Test used	
Number	180	35				
Mean BNP (pg/ml)	434	298	P=0.06 NS		Student's t	
Average age	73	81	P<0.001 *		Student's t	
Mean BMI	29.5	31.1	P=0.14 NS		Student's t	
%Female	38.3%	57.1%	P=0.06 NS	OR 2.1 (95% CI 1.0 to 4.5)	Fisher's Exact	Phi = 0.14 (little/no association)
%IHD	33.1%	23.5%	P=0.32 NS		Fisher's Exact	
%Diabetes	25.7%	47.1%	P=0.02*	OR 2.6 (CI 1.2 to 5.5)	Fisher's Exact	Phi =0.18 (little/no association)
%COPD	22.8%	32.4%	P=0.27 NS		Fisher's Exact	
%Permanent AF	33.9%	61.8%	P=0.003 *	OR 3.1 (CI 1.5 to 6.6)	Fisher's Exact	Phi =0.21 (little/no association)
%BBB	34.1%	11.8%	P=0.008*	OR 0.26 (CI 0.09 to 0.77)	Fisher's Exact	Phi = -0.18 (little/no association)
%Previous HF admission	23.5%	6.1%	P=0.03 *	OR 0.21(CI 0.05 to 0.92)	Fisher's Exact	Phi = -0.16 (little/no association)
Mean Minnesota score	40.7	40.7	P=1.00 NS		Student's t	
%HTN	67.1%	82.4%	P=0.10 NS		Fisher's Exact	
Systolic BP (mmHg)	133.0	144.0	P=0.01 *		Student's t	
Diastolic BP (mmHg)	77.0	77.0	P=0.96 NS		Student's t	

Fisher's Exact test performed on frequencies not percentages. *, Statistically significant; NS, Non significant; OR, Odds ratio; LVEF, Left ventricular ejection fraction; LVSD, Left ventricular systolic dysfunction; LVEDVI, Left ventricular end-diastolic volume index; HFREF, Heart failure with reduced ejection fraction; HFPEF, Heart failure with preserved ejection fraction; BNP, Brain natriuretic peptide; BMI, Body mass index; IHD, Ischaemic heart disease; COPD, chronic obstructive pulmonary disease; AF, Atrial fibrillation; BBB, Bundle branch block.

When different LVEF thresholds were employed the numbers and ratio of HFREF to HFPEF altered substantially (Figure 22 and Figure 23). LVEF threshold of <40% produced a ratio of HFREF to HFPEF of 1.3:1 (1.2:1 if those with no major structural disease were included within the HFPEF heading) which is much more in keeping with current perceptions about an epidemic of HFPEF but reflects the fact that many of those currently diagnosed with HFPEF have a definite reduction in LVEF that could account for their presentation.

Figure 22. Breakdown of heart failure population according to a contemporary diagnostic framework and utilising different LVEF thresholds for HFREF.

LVEF threshold for HFREF		Total	HFREF	HFPEF	HFNMSD	HF Alt cause	RHF		HFPEF and HFNMSD		Ratio of HFREF to HFPEF
LVEF <55%	Number	245	180	35	14	13	3		49		5.1 : 1
	% of total	100%	**73%**	**14%**	5.7%	5.3%	1.2%		**20%**		
LVEF <50%	Number	245	163	52	14	13	3		66		3.1 : 1
	% of total	100%	**67%**	**21%**	5.7%	5.3%	1.2%		**27%**		
LVEF <45%	Number	245	141	74	14	13	3		88		1.9 : 1
	% of total	100%	**58%**	**30%**	5.7%	5.3%	1.2%		**36%**		
LVEF <40%	Number	245	123	92	14	13	3		106		1.3 : 1
	% of total	100%	**50%**	**38%**	5.7%	5.3%	1.2%		**43%**		

LVEF, Left ventricular ejection fraction; HFREF, Heart failure with reduced ejection fraction; HFPEF, Heart failure with preserved ejection fraction; HFNMSD, Heart failure with no major structural disease; HF Alt cause, Heart failure due to an alternative cause; RHF, Right heart failure.

Figure 23. Differing ratios of HFREF to HFPEF according to varying LVEF thresholds.

LVEF threshold for a diagnosis of HFREF	Ratio of HFREF to HFPEF	Ratio of HFREF to HFPEF + HFNMSD
LVEF <55%	5.1 : 1	3.7 : 1
LVEF <50%	3.1 : 1	2.5 : 1
LVEF <45%	1.9 : 1	1.6 : 1
LVEF <40%	1.3 : 1	1.2 : 1

LVEF, Left ventricular ejection fraction; HFREF, Heart failure with reduced ejection fraction; HFPEF, Heart failure with preserved ejection fraction; HFNMSD, Heart failure with no major structural disease.

Q2. What is the diagnostic profile of this newly diagnosed heart failure population when incorporating routine CMR and comprehensive 2D echocardiography according to a contemporary diagnostic framework?

a. Does this differ from the diagnostic profile of the heart failure population using routine echocardiography alone?

b. Do echo and CMR measurements of LVEF correlate?

Of the 319 people that attended the heart failure clinic between May 2013 and July 2014 a total of 166 were given a diagnosis of heart failure by way of HFREF, HFPEF or HFNMSD according to the flowchart in Figure 13 and provided consent for their data to be used for further analysis.

All of these 166 patients had an initial basic clinical echo performed. Thereafter, 77 went on to have a second, more detailed, echo performed, and 101 went on to have a CMR performed. In 66 of these 101 individuals a second echo was also performed. Figure 24 shows the adapted prospective consort diagram for clarification of the population being referred to for this analysis. Thereafter, Figure 25 demonstrates how the diagnostic subgroups alter for this population of 166 individuals following further detailed echo and thereafter CMR examination.

Figure 24. Prospective population being analysed (adapted from Figure 14)
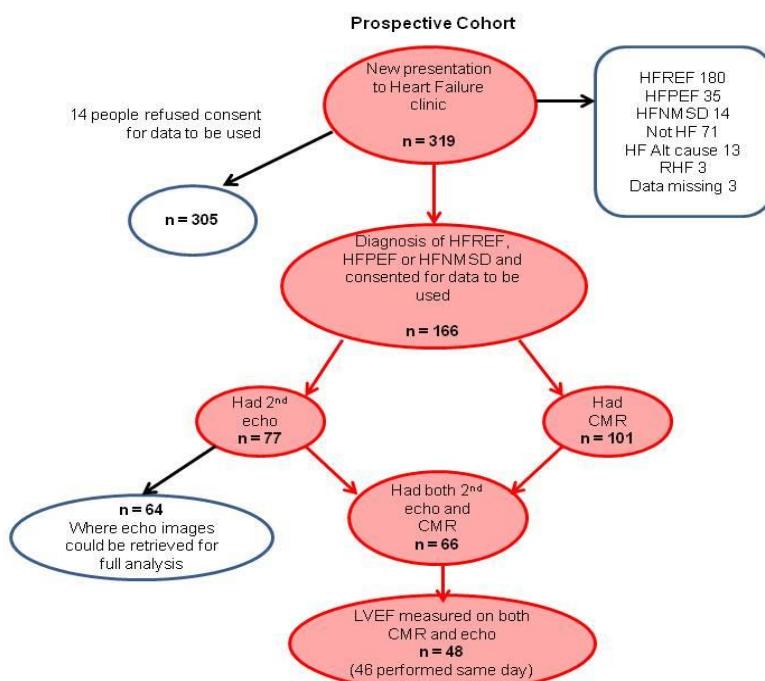
Figure 25. Change in the distribution of diagnostic sub-groups following different investigations.

Diagnostic Group according to HF flow chart	Number in group according to 1st echo	% of total according to 1st echo	Number in group according to 2nd echo	% of total according to 2nd echo	Number in group after CMR +/- 2nd echo	% of total according to CMR +/- 2nd echo
HFREF	134	81%	57	74%	61	60%
HFPEF	21	13%	14	18%	25	25%
HFNMSD	2	1%	6	8%	15	15%
HFNMSD (insuff measures)	9	5%	0	0%	0	0%
Total	166	100%	77	100%	101	100%

CMR, cardiac magnetic resonance; HFREF, Heart failure with reduced ejection fraction; HFPEF, Heart failure with preserved ejection fraction; HFNMSD, Heart failure with no major structural disease.

The overall appearance is one where by more detailed imaging seems to revoke the diagnosis of HFREF, particularly following CMR. Instead these individuals are re-labelled as HFPEF or HFNMSD. In order to delve into the detail of how the second echo and CMR affect diagnosis a more in depth analysis has been performed below looking at the subsets of people that have had these investigations.

Impact of the second echo

The second echo comprised of a more comprehensive imaging protocol than the first echo, including an attempt to get a Simpson's Biplane LVEF, biplane left atrial volumes and all the other markers of diastolic function depicted in the diagnostic flow diagram. A total of 77 patients had a second echo performed and the breakdown of diagnoses and individual changes to diagnosis is depicted below in Figure 26 and Figure 27.

Figure 26. Changes to diagnostic profile of the heart failure population following the second echo.

Diagnostic Group	Number according to 1st echo	Number according to 2nd echo	Net population change in diagnostic subgroup after CMR
HFREF	60	57	-3
HFPEF	11	14	+3
HFNMSD	6 (4 insufficient measures)	6 (0 insufficient measures)	No change
Total	77	77	NA

HFREF, Heart failure with reduced ejection fraction; HFPEF, Heart failure with preserved ejection fraction; HFNMSD, Heart failure with no major structural disease.

Figure 27. Schematic representation of individual changes to diagnoses following the second echo.
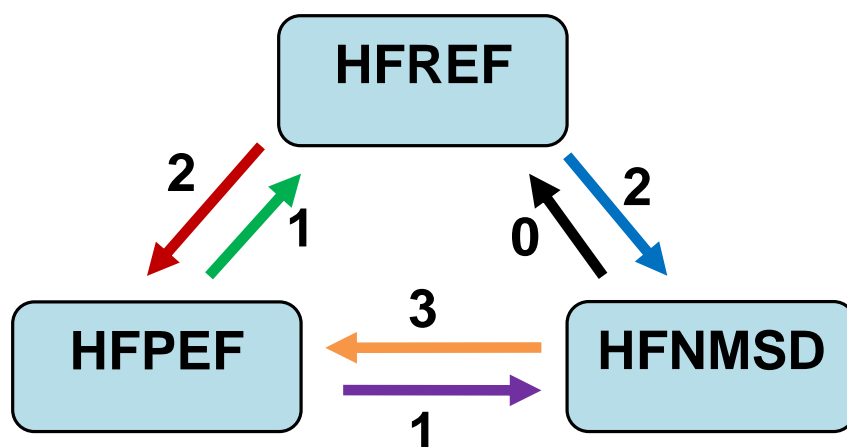
Although the net movement across groups was that 3 patients moved from the HFREF to the HFPEF group there were actually 9 separate changes in diagnosis to create this net change. This accounts for 12% (9/77 x 100) of the total group observed. The flow chart above demonstrates these individual changes and Figure 28 below explains the rational for each change. The colours correspond to the arrows on the flow diagram for ease of interpretation.

Figure 28. Rationale for changes in diagnostic group following second echo

Study No	Diagnosis after 1st clinic review and 1st echo	Diagnosis after 2nd echo	Rational for why the diagnosis changed
59	HFREF	HF and NMSD	LVEF improved ≥55% and no BNP to diagnose HFPEF
191	HFREF	HF and NMSD	LVEF ≥55% and doesn't meet HFPEF parameters
149	HFREF	HFPEF	LVEF improved ≥55% and raised E/e' and severe LA dilatation diagnose HFPEF
197	HFREF	HFPEF	LVEF ≥55% and E/e' 15 with LAVI >40 and AF
62	HFPEF	HF and NMSD	E/e' reduced to <15 and no other secondary supporting features for HFPEF
195	HFPEF	HFREF	LVEF reduced to <55% on 2nd echo
78	HF NMSD (insufficient HFPEF measures)	HFPEF	E/e' measures done and >15 as well as high BNP
235	HF NMSD (insufficient HFPEF measures)	HFPEF	E/e' performed and 14 with LAVI >40 and AF
1	HF NMSD (insufficient HFPEF measures)	HFPEF	E/e' measured and >15 and BNP elevated

HFREF, Heart failure with reduced ejection fraction; HFPEF, Heart failure with preserved ejection fraction; HFNMSD, Heart failure with no major structural disease; LVEF, Left ventricular ejection fraction; BNP, Brain natriuretic peptide; LA, Left atrium; AF, Atrial fibrillation; E/e', ratio of the mitral inflow E wave to the tissue Doppler e' wave.

Four individuals had the diagnosis of HFREF revoked following the second echo, and only one individual had this diagnosis instated. Numbers are small and it is impossible to draw statistically significant conclusions. Indeed the changes may all reflect valid differences in inter and intra-observer variability in measurements of LVEF. However, one can postulate other reasons for these trends. It may be that a formal Simpson's Biplane LVEF tends to be higher than the more commonly used eyeball assessment of LVEF in the first echo. However, it is worth noting that there is a temporal change between the first and second echo. Many of the HFREF group will have been started on an ACE-inhibitor and beta blocker and perhaps the more likely reason for this difference is that the LVEF improved due to drug therapy started after the first echo. Unfortunately it was impossible to obtain the information about changes in drugs between initial and follow-up imaging as drug lists at the time of follow-up scans were not recorded. Only one of the four individuals that had an increase in the LVEF between the two echo studies (study numbers 59, 191, 149 and 197 in Figure 28 above) had a specific numerical value given to the LVEF at the time of the first echo. The others were simply an eyeball assessment of whether the LVEF appeared normal, mild, moderately or severely

impaired. In this regard, two of the initial studies were graded as mildly impaired, one as moderately impaired and one as severely impaired.

Three individuals had the diagnosis of HFNMSD converted to HFPEF as a result of full diastolic measures being performed on the second echo but only one to the contrary. Whilst some may argue that all those with clinical heart failure but preserved ejection fraction should be labelled as HFPEF (negating the need for a detailed echo), 6 of the 21 with a normal LVEF following the second echo did not have sufficient abnormalities to support a diagnosis of heart failure according to this inclusive diagnostic framework.

Impact of the CMR

Of the 101 individuals who had a CMR performed there were 22 separate changes in diagnosis following this investigation according to the diagnostic framework in Figure 13. This accounts for 22% (22/101 x 100) of the total group observed. Figure 29 and Figure 30 demonstrates these individual changes and Figure 31 explains the rational for each change.

Figure 29. Impact of CMR on the diagnostic profile of the heart failure population.

Diagnostic Group	Number according to 1st or 2nd echo (2nd echo takes preference)	Number according to CMR	Net population change in diagnostic subgroup after CMR
HFREF	77	61	-16
HFPEF	16	25	+9
HFNMSD	8	15	+7
Total	101	101	NA

Comparison made with the second echo or 1st echo when 2nd echo wasn't performed. HFREF, Heart failure with reduced ejection fraction; HFPEF, Heart failure with preserved ejection fraction; HFNMSD, Heart failure with no major structural disease.

Figure 30. Schematic representation of individual changes to diagnoses following the CMR.
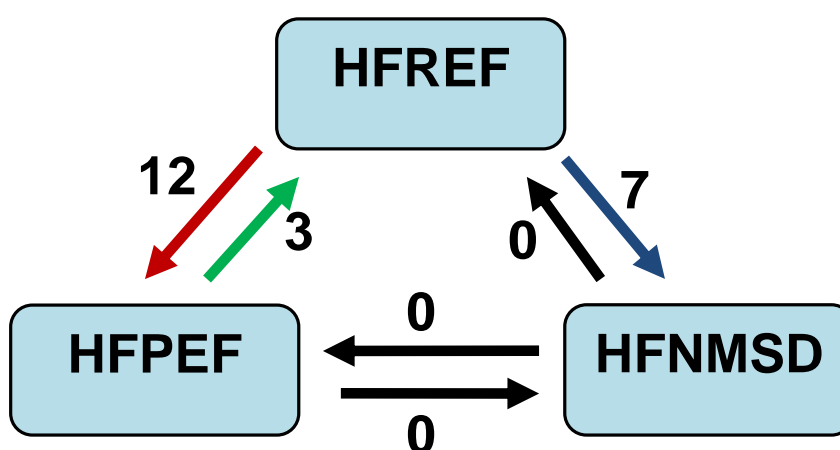
Figure 31. Rationale for changes in diagnostic group following CMR.

Study No	Diagnosis after 1st or 2nd echo (2nd echo takes preference)	Diagnosis after CMR	Rationale for why the diagnosis changed
10	HFREF	HF and NMSD	LVEF ≥55% and LVEDVI<97 and echo diastolic parameters NMSD
28	HFREF	HF and NMSD	LVEF ≥55% and LVEDVI<97 and echo diastolic parameters NMSD
188	HFREF	HF and NMSD	LVEF ≥55% and LVEDVI<97 and does not meet HFPEF parameters
212	HFREF	HF and NMSD	LVEF ≥55% and LVEDVI<97 and does not meet HFPEF parameters
255	HFREF	HF and NMSD	LVEF ≥55% and LVEDVI<97 and does not meet HFPEF parameters
289	HFREF	HF and NMSD	LVEF ≥55% and LVEDVI<97 and does not meet HFPEF parameters
311	HFREF	HF and NMSD	LVEF ≥55% and LVEDVI<97 and does not meet HFPEF parameters
87	HFREF	HFPEF	LVEF ≥55% and LVEDVI<97 and BNP with AF meet HFPEF criteria
119	HFREF	HFPEF	LVEF ≥55% and LVEDVI<97 and BNP and E/e' meet HFPEF criteria
161	HFREF	HFPEF	LVEF ≥55% and E/e' >15 meet HFPEF criteria
172	HFREF	HFPEF	LVEF ≥55% and E/e' 14 with LAVI >40 meet HFPEF criteria
189	HFREF	HFPEF	LVEF ≥55% and E/e' >15 meet HFPEF criteria
217	HFREF	HFPEF	LVEF≥55% and E/e' >15 meet HFPEF criteria
222	HFREF	HFPEF	LVEF≥55% and E/e' >15 meet HFPEF criteria
254	HFREF	HFPEF	LVEF≥55% and E/e' >15 meet HFPEF criteria
263	HFREF	HFPEF	LVEF≥55% and BNP>200pg/ml with AF meet HFPEF criteria
275	HFREF	HFPEF	LVEF≥55% and BNP>200pg/ml with AF meet HFPEF criteria
283	HFREF	HFPEF	LVEF≥55% and E/e'>8 with AF meet HFPEF criteria
306	HFREF	HFPEF	LVEF≥55% and E/e'>8 with AF and elevated BNP meet HFPEF criteria
133	HFPEF	HFREF	LVEF<55% on CMR
149	HFPEF	HFREF	LVEF <55% on CMR (NB 1st echo suggested HFREF but 2nd echo suggested HFPEF)
197	HFPEF	HFREF	LVEF <55% on CMR (NB 1st echo suggested HFREF but 2nd echo suggested HFPEF)

HFREF, Heart failure with reduced ejection fraction; HFPEF, Heart failure with preserved ejection fraction; HFNMSD, Heart failure with no major structural disease; LVEF, Left ventricular ejection fraction; LVEDVI, Left ventricular end-diastolic volume index; BNP, Brain natriuretic peptide; LA, Left atrium; LAVI, Left atrial volume index; AF, Atrial fibrillation; E/e', ratio of the mitral inflow E wave to the tissue Doppler e' wave.

In the group of 66 individuals that had both a second echo and CMR there were 9 separate changes in diagnosis following CMR. This accounts for 14% (9/66 x 100) of the total group observed. Figure 32 and Figure 33 below demonstrate these individual changes and Figure 34 below explains the rationale for each change.

Figure 32. Impact of CMR to the diagnostic profile of the heart failure population (comparison with only those that had a second echo).

Diagnostic Group	Number according to 2nd echo	Number according to CMR	Net population change in diagnostic subgroup after CMR
HFREF	47	44	-3
HFPEF	13	14	+1
HFNMSD	6	8	+2
Total	66	66	NA

HFREF, Heart failure with reduced ejection fraction; HFPEF, Heart failure with preserved ejection fraction; HFNMSD, Heart failure with no major structural disease.

Figure 33. Schematic representation of individual changes to diagnoses following the CMR (comparison with only those that had a second echo)

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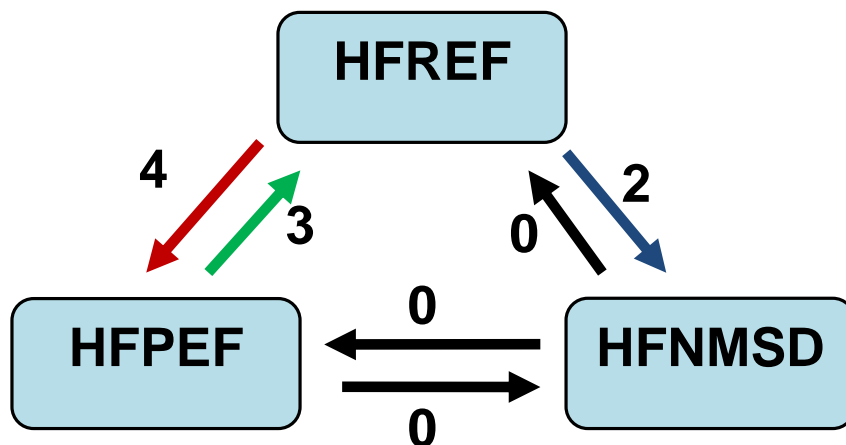
Figure 34. Rationale for changes in diagnostic group following CMR (comparison with only those that had a second echo)

Study Number	Diagnosis after 2nd echo	Diagnosis after CMR	Why CMR changed diagnosis
28	HFREF	HF and NMSD	LVEF ≥55% and LVEDVI<97 and echo diastolic parameters NMSD
188	HFREF	HF and NMSD	LVEF ≥55% and doesn't meet HFPEF parameters
161	HFREF	HFPEF	LVEF ≥55% and E/e' >15 meet HFPEF criteria
172	HFREF	HFPEF	LVEF ≥55% and E/e' 14 with LAVI >40 meet HFPEF criteria
222	HFREF	HFPEF	LVEF ≥55% and E/e' >15 meet HFPEF criteria
119	HFREF	HFPEF	LVEF ≥55% and LVEDVI<97 and BNP and E/e' meet HFPEF criteria
133	HFPEF	HFREF	LVEF <55% on CMR
149	HFPEF	HFREF	LVEF <55% on CMR (NB 1st echo suggested HFREF but 2nd echo suggested HFPEF)
197	HFPEF	HFREF	LVEF <55% on CMR (NB 1st echo suggested HFREF but 2nd echo suggested HFPEF)

HFREF, Heart failure with reduced ejection fraction; HFPEF, Heart failure with preserved ejection fraction; HFNMSD, Heart failure with no major structural disease; LVEF, Left ventricular ejection fraction; LVEDVI, Left ventricular end-diastolic volume index; BNP, Brain natriuretic peptide; LAVI, Left atrial volume index; E/e', ratio of the mitral inflow E wave to the tissue Doppler e' wave.

The impact of the CMR to alter diagnosis was entirely related to discrepancies in the LVEF compared with echo and this finding was replicated (although on a smaller scale) even for those 63% where the echo and CMR were performed on the same day. However, whereas 86% of those 101 patients given an alternative diagnosis after CMR were due to an upgrade in the LVEF with CMR, this was only true of 66% of the 66 patients that had a second echo. Once again, this is probably due to the fact that most of the second echos were performed on the same day as the CMR, and certainly, as a group, had a much closer temporal relationship to the CMR than the first echo. Similarly to the differences described between the first and second echo this probably reflects an improvement in LVEF after the initiation of drug therapy. Once again, an alternative explanation is that a formal Simpson's Biplane LVEF (performed more commonly on the second echo) tends to be higher than the more commonly used eyeball assessment of LVEF on the first echo.

The next thing to consider is whether the CMR LVEF is universally higher than the Simpson's Biplane echo LVEF due to measuring technique differences. Thereafter are the differences in the diagnostic groups simply due to the echo cut of normal LVEF ≥55%

being incorrectly applied to the CMR data, when a higher LVEF cut-off for normal should be used instead?

The first thing to appreciate is that a formal Simpson's Biplane LVEF is only achievable in about three quarters of cases. Of those 77 people that had a second echo, where the need to achieve a Simpson's Biplane LVEF was emphasised and encouraged, in only 57 (74%) was this possible. In 26% of cases suboptimal image quality due to poor endocardial definition, patient related factors or rhythm disturbances made accurate LVEF measurements impossible. Conversely, CMR can provide this measurement almost universally. Of those 101 people that had a CMR scan, a LVEF was able to be performed in 100/101 cases (99%). The one case where LVEF could not be performed was due to the patient being unable to tolerate the scan due to claustrophobia and an early termination to the imaging.

There were 48 people that had a CMR and second echo, both of which measured LVEF and a comparison of the results was performed (see adapted consort diagram Figure 35).

Figure 35. Adapted consort diagram (Figure 14) of group being analysed
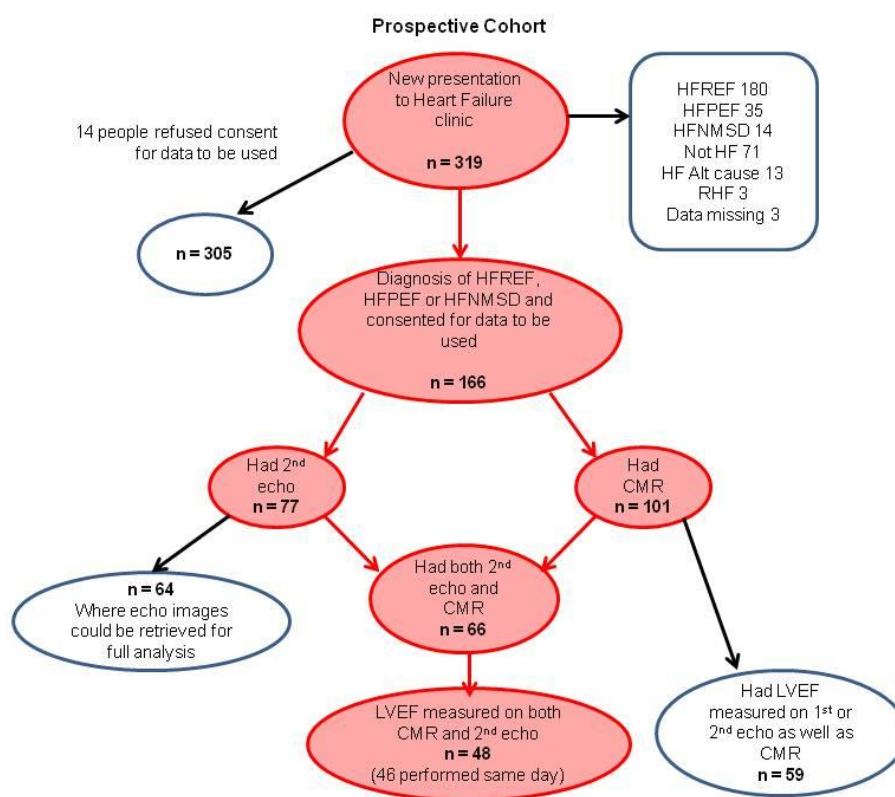
Nearly all of these scans (46 out of 48) were performed on the same day as the CMR and all are referred to as such in the following analyses for ease of interpretation. Although a similar analysis was performed on the 59 people that had a CMR and first or second echo with measured LVEF it was felt that comparison with only the second echo data would be more robust to help exclude temporal related differences from the first echo. This is demonstrated by the Deming regression analysis below (Figure 36) and subsequently by Bland Altman plots of absolute differences in the LVEF (units are a percentage) (Figure 37) as well as percentage differences in the LVEF for the two methods (Figure 38).

Figure 36. Deming regression analysis of CMR LVEF versus TTE Biplane LVEF for scans performed on the same day.
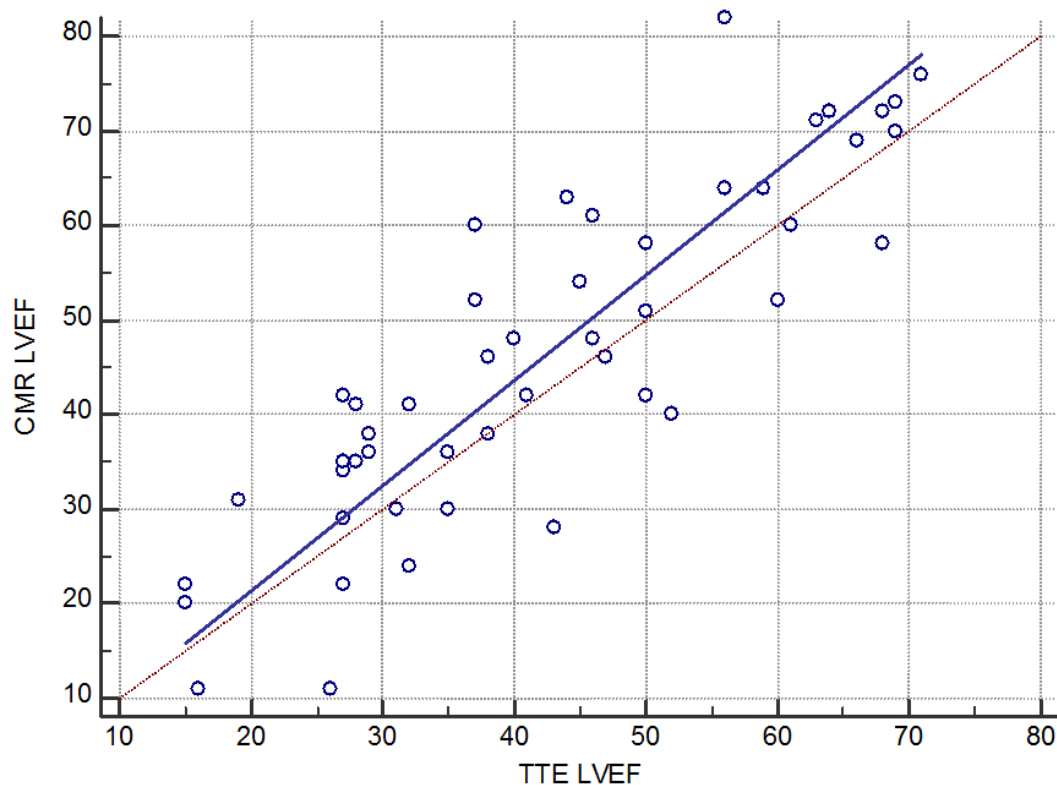
n = 48. CMR, Cardiac magnetic resonance; TTE, Transthoracic echocardiography; LVEF, Left ventricular ejection fraction.

The Deming regression analysis providing the mean regression parameter and its 95% confidence interval demonstrated that the two methods were highly comparable (Slope 1.11, 95% CI 0.93 to 1.30, intercept -0.85, 95% CI -8.9 to 7.2) (please note that this Figure does not start at the origin). However, the Bland-Altman plot (Figure 37) shows how the echo LVEF would be lower than the CMR LVEF with a mean difference of -3.9 percentage units (95% CI -6.5 to -1.3) or alternatively by a mean percentage difference of -4.1% (95% CI -12.7 to 4.5).

Figure 37. Bland-Altman methods comparison plot of CMR LVEF versus TTE Biplane LVEF for scans performed on the same day.
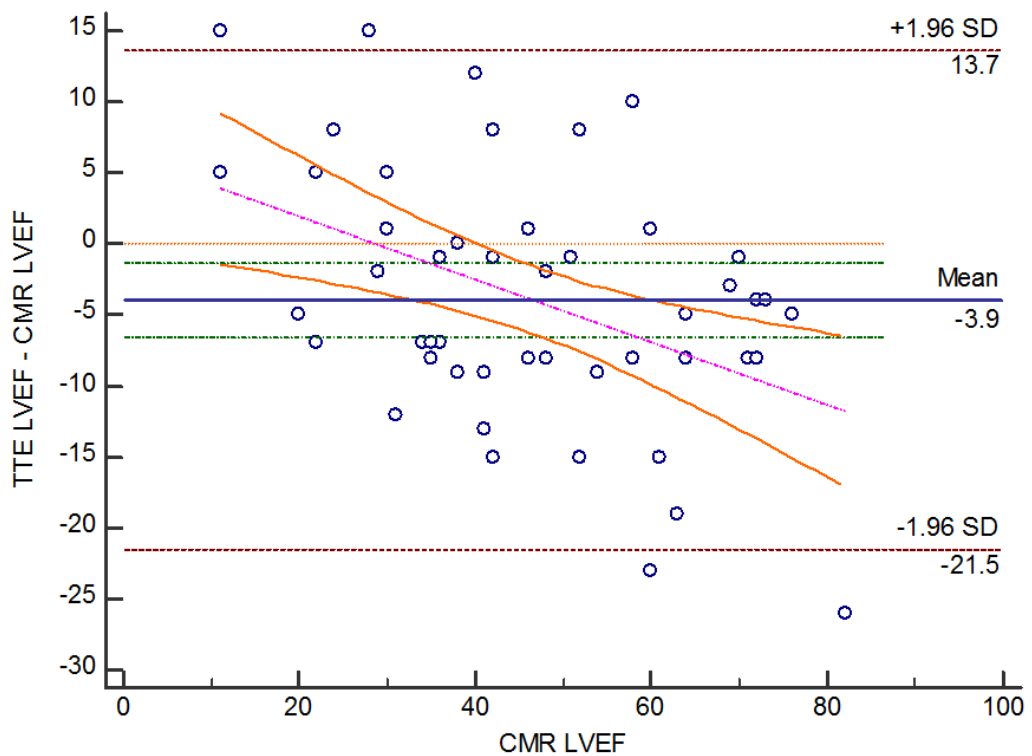
N=48. CMR, Cardiac magnetic resonance; TTE, Transthoracic echocardiography. LVEF, Left ventricular ejection fraction.

Figure 38. Percentage difference Bland-Altman methods comparison plot of CMR LVEF versus TTE Biplane LVEF for scans performed on the same day.
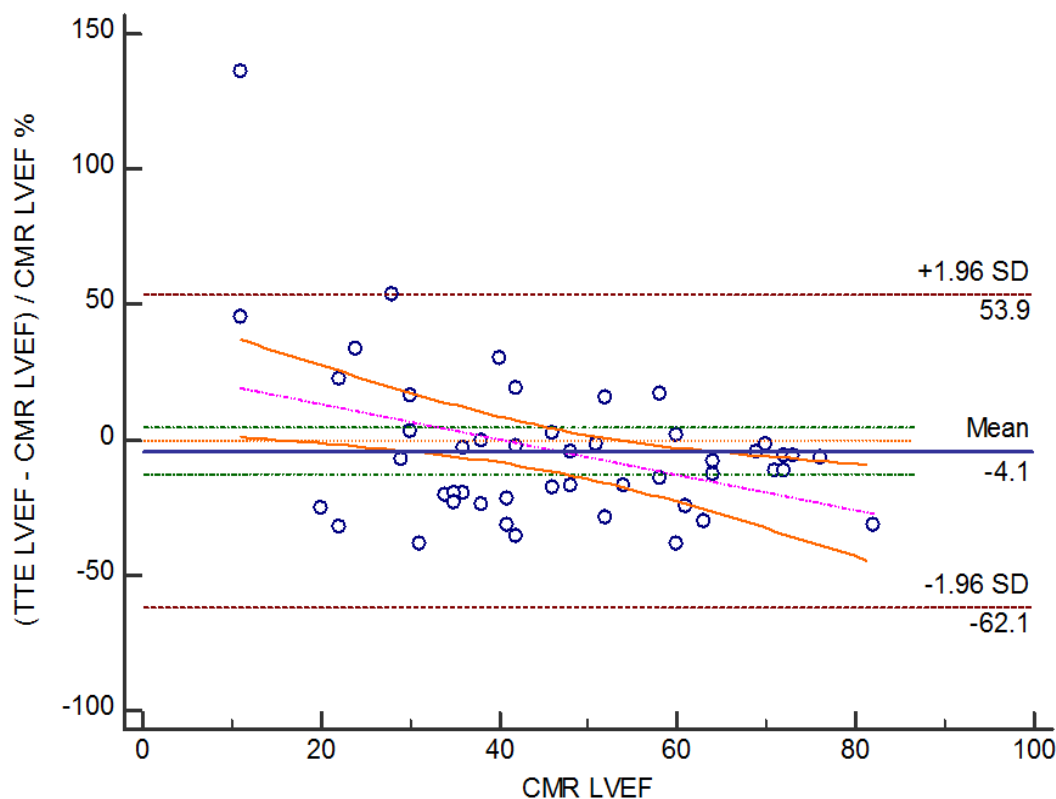
N=48. CMR, Cardiac magnetic resonance; TTE, Transthoracic echocardiography. LVEF, Left ventricular ejection fraction.

This percentage difference Bland Altman plot (Figure 38) also suggests that echo LVEF underestimates CMR LVEF to a greater extent, the higher the LVEF. The absolute unit difference Bland Altman plot 1.96 standard deviation limits of agreement show how the echo LVEF is between 13.7% units higher or 21.5% units lower than the MRI endocardial LVEF. Whilst the numbers compared are small, this wide discrepancy in measured LVEF at the equivalent of two standard deviations suggests that the two methods are not adequately reproducible for use in clinical practice.

In order to achieve a better appreciation for why the Simpson's Biplane echo measurement differ to CMR LVEF, beyond the fact the measurement techniques seem to result in an average 3.9% units higher LVEF with CMR, other variables were investigated. This included the presence of AF, ectopy, bundle branch block, BMI, being a poor echo or CMR subject for imaging for other reasons, and temporal factors. Because the numbers for each variable were small a comparison for all 59 people that had a CMR and first or second echo with measured LVEF was performed with the

expectation that the higher numbers would be more robust for statistical analysis. The incidence of these different variables in a group where the difference in LVEF was >10% between echo and CMR, versus a group where the LVEF differed by ≤10% was compared. The adapted consort diagram in Figure 39 demonstrates the population being analysed for this and the results are shown below in Figure 40.

Figure 39. Adapted consort diagram (Figure 14) of population being analysed for variations in CMR and TTE LVEF
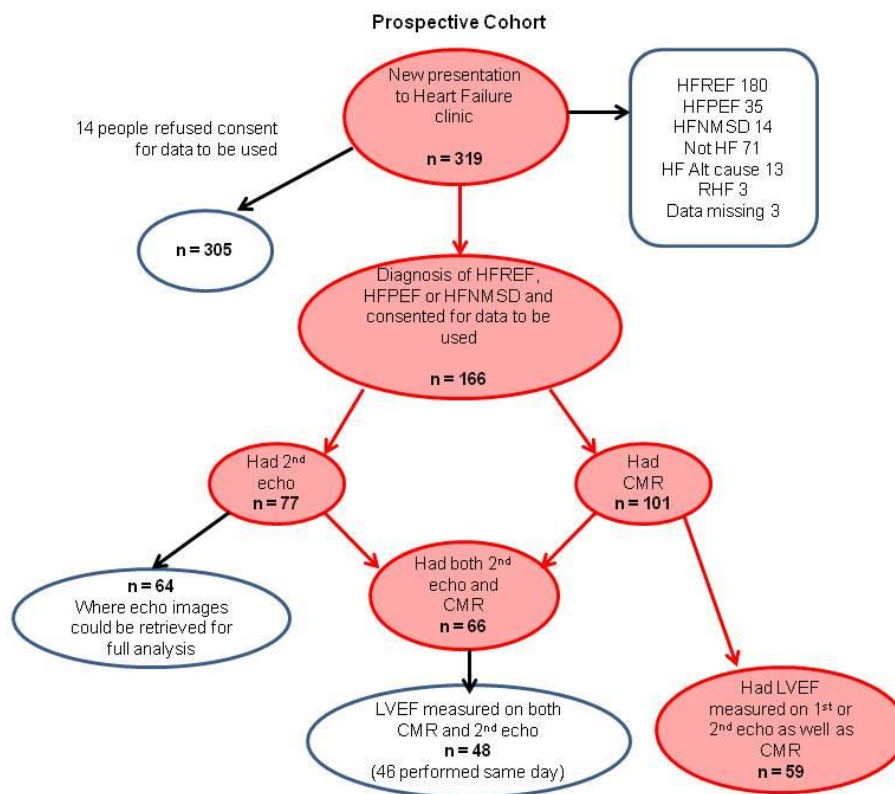
Figure 40. Exploring variables that may contribute to >10% differences in CMR vs TTE LVEF.

		LVEF Differs >10%	LVEF differs ≤10%	P Value	Odds Ratio	Association
Total number		16	43	NA	NA	
Variable	AF	2 (12.5%)	19 (44.2%)	P=0.03* (Fisher's Exact)	OR 0.18 (95%CI 0.04 to 0.89)	Little or no assoc
	Ectopy present (if not in AF)	7 (43.8%)	6 (14.0%)	P=0.03* (Fisher's Exact)	OR 4.80 (CI 1.2 to 17.8)	Weak positive assoc
	BBB	7 (43.8%)	10 (23.3%)	P=0.12 NS (Fisher's Exact)		
	Mean BMI	25.6	29.5			
	Poor echo subject	0 (0%)	7 (16%)			
	Poor CMR subject	6 (37.5%)	6 (14.0%)			
	Mean No of days between scans	19	8	P=0.02* (Mann-Whitney U)		
	Median No of days between scans	0	0			
	Scans done on same day	9 (56.2%)	37 (86.0%)	P=0.03 * (Fisher's Exact)	OR 0.21 (CI 0.06 to 0.77)	Weak negative relationship

LVEF, Left ventricular ejection fraction; OR, Odds ratio; CI, Confidence interval; BMI, Body mass index; IHD; AF, Atrial fibrillation; BBB, Bundle branch block; NS, Non significant; *, P value significant.

This result shows once again that the temporal relationship to the scans is important in that there was a significantly fewer scans performed on the same day in the group where the LVEF differed by >10%, and that the mean number of days between scans was significantly higher in the group where the LVEF differed by >10%.

The only other variables that showed a positive association with a difference in LVEF of > or ≤10% was the presence of ectopy or AF. The group where the LVEF differed by >10% was more likely to have ectopy but less likely to have AF. Both relationships are only weakly positive and these findings seem at odds with each other. A plausible

explanation for why ectopy causes a worse association and AF causes a better association between echo and CMR LVEF is difficult to postulate. If true, the only seemingly possible explanation is that echo measures in AF are averaged and so result in a better comparison with CMR, where as the ectopic beats may not have been recognised on the echo assessment and thus erroneous (non-representative) measurements performed.

Based upon the analysis of CMR LVEF versus TTE Simpson's Biplane LVEF performed on the same day there is an apparent fixed difference between the measurements, with a mean 3.9% increase from the TTE result to the CMR result. This is also borne out by the differences in guideline normal ranges for TTE LVEF in the NORRE study (mean LVEF of 63.9% (2SD range of 56.5 to 71.7%)) (67) versus CMR LVEF (mean 69% for female over 35 years, mean 71% male over 35 years, 2SD range incorporating both male and female of 57% to 83%) (142). Establishing whether the cases where a HFREF diagnosis was revoked by CMR LVEF can be explained by this mean discrepancy in LVEF due to imaging technique would be valuable and would mean different cut-offs for HFREF need to be established and recognised within the clinical community to avoid confusion. If this is not the situation then the CMR scan has an added impact on the diagnosis, above and beyond what echo imaging can offer.

There were 19 people who had the diagnosis of HFREF revoked by CMR (6 in the group that had a 2nd echo on the same day as the CMR for a better temporal comparison). Figure 41 below shows the results for the CMR LVEF in these cases.

From this analysis one can see that three of these 19 patients had a diagnosis of HFREF revoked due to the CMR LVEF being interpreted with TTE reference ranges, and would have otherwise remained in the HFREF classification if the CMR reference ranges had been used. However this still leaves the majority of the group (16 of these 19 patients) with a normal LVEF according to CMR reference ranges and represents a true impact that CMR imaging has on the diagnosis. It is worth acknowledging that a true change in diagnosis occurred for 5 of the 6 patients that had the echo and CMR on the same day, in keeping with the suggestion that the difference in diagnosis is not simply due to a temporal difference in imaging.

Figure 41. Analysis of patients that had the diagnosis of HFREF revoked by CMR imaging.

Study Number	Sex	Age	CMR LVEF	CMR & TTE same day?	Is CMR LVEF below the CMR normal reference range?(142) Male ≥35yrs < 59% Female ≥ 35yrs < 57%
28	F	72	61	Yes	No
188	M	57	72	Yes	No
161	F	83	60	Yes	No
172	M	67	63	Yes	No
222	F	80	58	Yes	No
119	F	47	55	Yes	Yes
10	F	82	57	No	No
212	M	74	59	No	No
255	F	60	62	No	No
289	M	64	61	No	No
311	M	67	57	No	Yes
87	F	84	61	No	No
189	M	73	69	No	No
217	F	77	58	No	No
254	M	85	66	No	No
263	M	81	66	No	No
275	F	75	59	No	No
283	M	69	56	No	Yes
306	M	81	63	No	No

Impact of CMR for understanding the underlying aetiology of heart failure

CMR uses late gadolinium contrast to demonstrate areas of fibrosis or infarction in the myocardium. This is an attribute confined to CMR and is beyond the diagnostic capabilities of echo. To investigate whether this component of the CMR investigation provided additional information to the understanding of the underlying aetiology of heart failure, the diagnosis suggested before the CMR (based upon clinical history, past medical history, risk factors for ischaemic heart disease examination, ECG and echo findings) was compared against the diagnosis given by CMR. The population being studied here is again depicted in the adapted consort diagram below (Figure 42) for clarification.

Figure 42. Adapted consort diagram (Figure 14) of population being analysed for the impact of CMR on the understanding the aetiology of heart failure
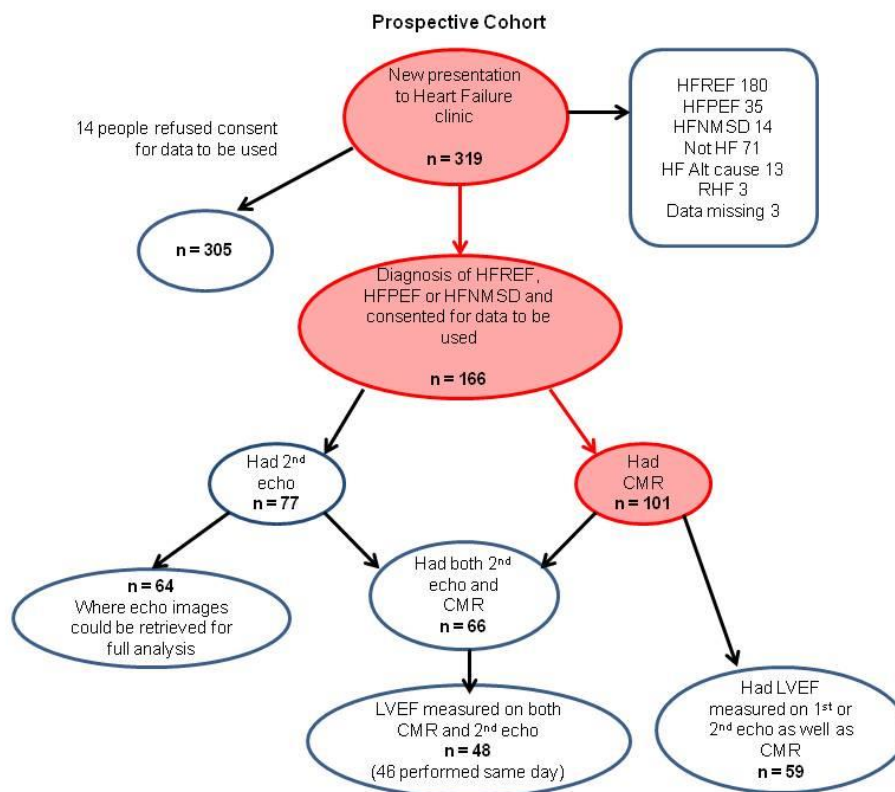
The groups are divided according to heart failure grouping following CMR. In those 61 individuals with a diagnosis of HFREF, subendocardial LGE was present in 26 cases (42%) to suggest previous infarcts. CMR had additive useful clinical value beyond the clinical and echo assessment by confirming or refuting infarcts in those suspected of having HFREF due to IHD, and thereafter suggesting viability or lack of viability in those where infarcts were present and this is shown on the HFREF flow chart below (Figure 43). In the 26 cases suspected of having IHD, LGE confirmed infarcts in 18 cases, demonstrating viability in eight of these. In the other eight cases without subendocardial LGE there was one case with RWMA features to suggest possible underlying IHD. The remaining cases had no features to support IHD and no other features to provide a positive alternative diagnosis other than dilated cardiomyopathy (DCM), although LBBB was present in half to account for some of the LV impairment. CMR also had additive value for those with HFREF but where there was no suspicion of IHD. This was the case in 34 patients and in eight of these cases subendocardial LGE was present to suggest a previous infarct, six of whom had viability, and this group may benefit from angiography assessment. 21 of these 34 individuals had no evidence of an infarct and in these cases it is also noteworthy that there were no other significant changes or RWMA to suggest

IHD as a cause. There were seven individuals within the entire HFREF population that demonstrated LGE in a non subendocardial distribution resulting in a differential diagnosis including myocarditis and sarcoidosis.

**Figure 43. Impact of CMR LGE imaging for understanding the underlying aetiology in the HFREF group.**
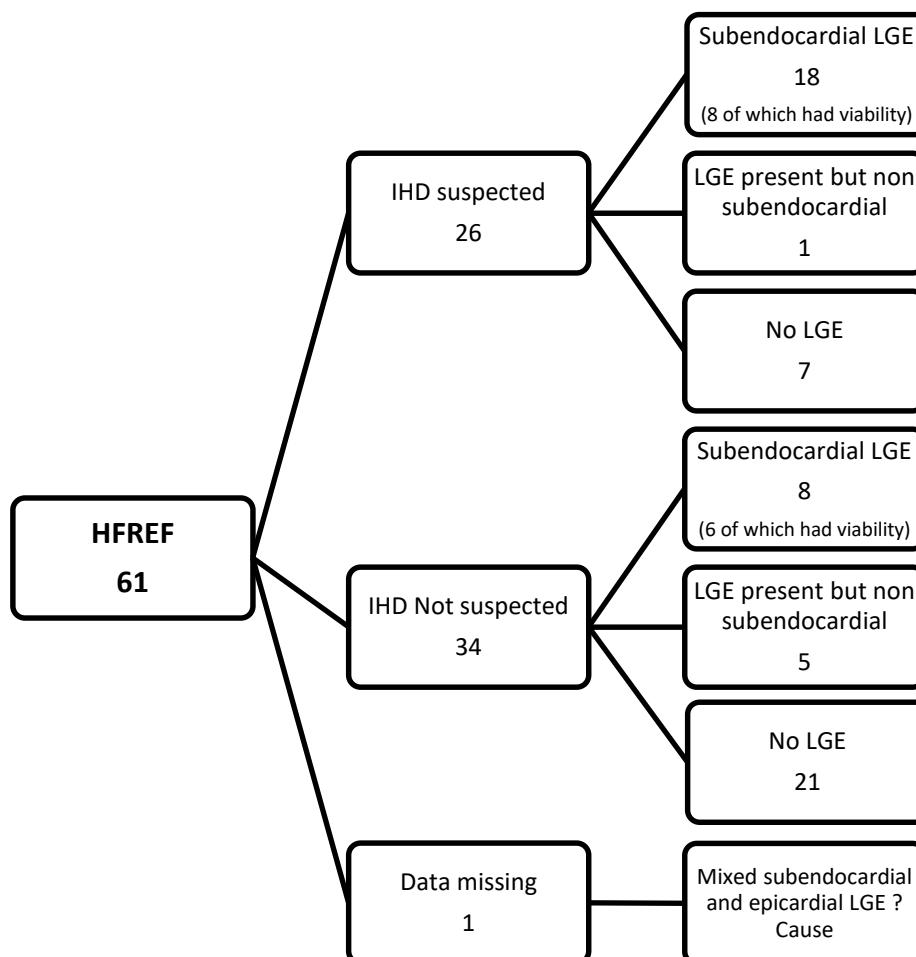
HFREF, Heart failure with reduced ejection fraction; IHD, Ischaemic heart disease; LGE, late gadolinium enhancement (subendocardial LGE representative of myocardial infarction).

In those 25 individuals with a diagnosis of HFPEF, subendocardial LGE was present in five cases (20%) to suggest previous infarcts. CMR had additive value beyond the clinical and echo assessment by confirming or refuting infarcts in those suspected of having IHD, and thereafter suggesting viability or lack of viability as shown in the HFPEF flow chart (Figure 44). In the seven cases of suspected IHD, LGE confirmed infarcts in two cases. Despite there being no infarcts in the other five cases, three of these had RWMA that might prompt further assessment of ischaemia. There were then 18 cases where IHD was not suspected and in three of these cases the CMR identified infarcts

and this group may benefit from angiography. In the other 15 cases without subendocardial LGE there were no other features to prompt a search for underlying IHD but in one case the possibility of apical hypertrophic cardiomyopathy was raised where it hadn't been following echo. There were two individuals within the entire HFPEF population that demonstrated LGE in a non subendocardial distribution resulting in a differential diagnosis of healed myocarditis.

Figure 44. Impact of CMR LGE imaging for understanding the underlying aetiology in the HFPEF group.
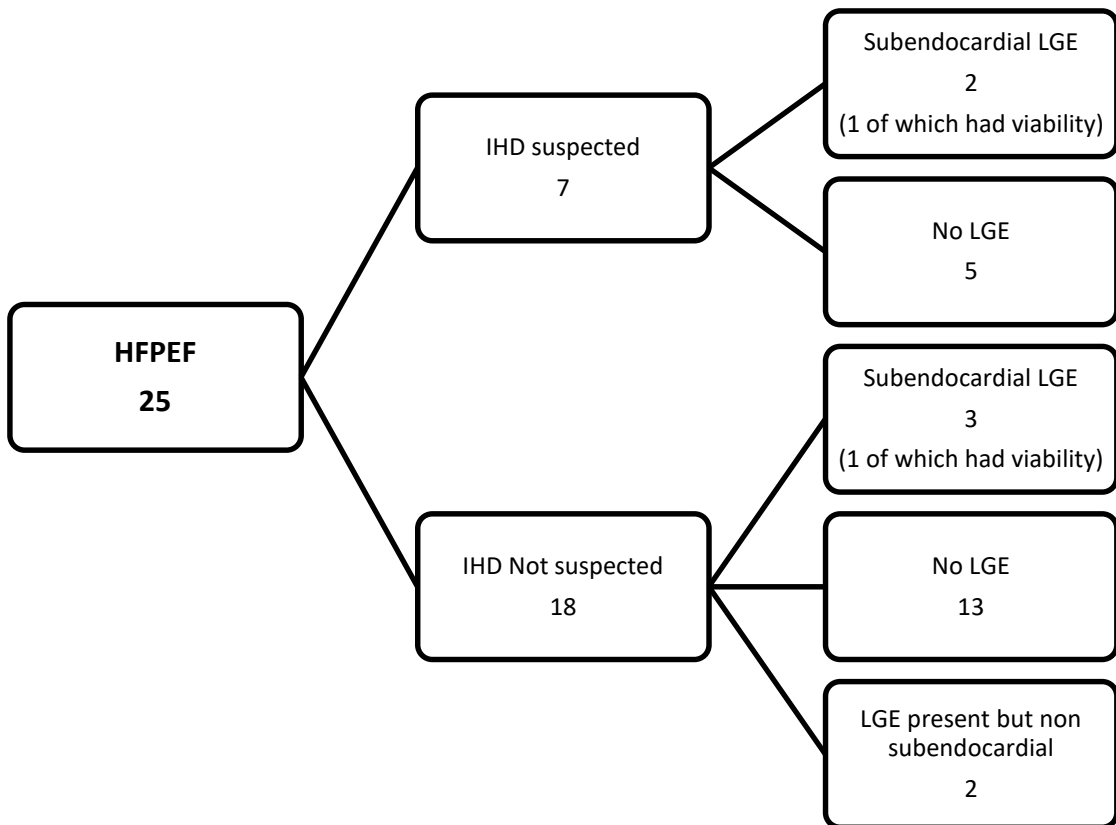
HFPEF, Heart failure with preserved ejection fraction; IHD, Ischaemic heart disease; LGE, late gadolinium enhancement (subendocardial LGE representative of myocardial infarction).

In those 15 individuals with a diagnosis of HFNMSD, subendocardial LGE was present in six cases (40%) to suggest previous infarcts (Figure 45). This is a much higher proportion than the HFPEF group and raises the possibility of IHD, rather than heart failure, being the cause of symptoms in this population. In the six cases of suspected IHD, LGE confirmed infarcts in five cases. There were then nine cases where IHD was not suspected and CMR identified infarcts in one of this group. In the other eight cases without subendocardial LGE, five had no significant abnormality at all on CMR. The

other three had a variety of left ventricular hypertrophy, left atrial enlargement and minor regional wall abnormalities but nothing specific to confirm an underlying aetiology for the symptoms.

Figure 45. Impact of CMR LGE imaging for understanding the underlying aetiology in the HFNMSD group.
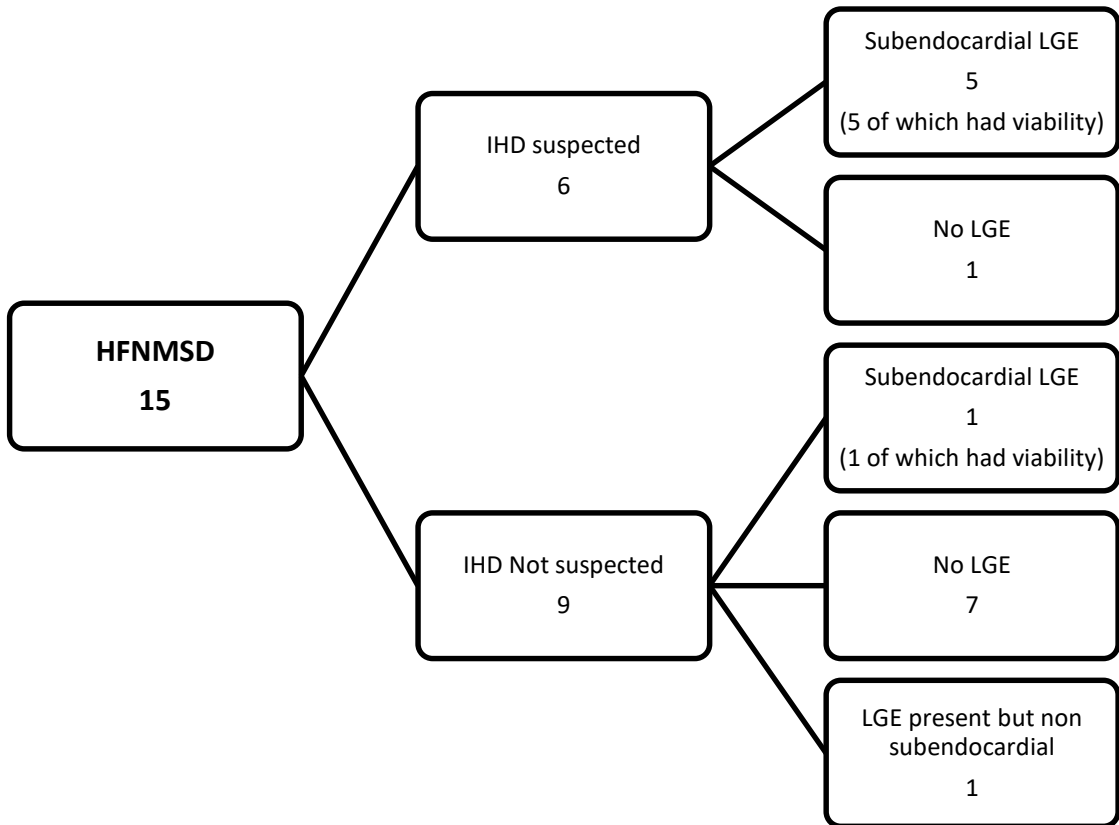
HFNMSD, Heart failure with no major structural disease; IHD, Ischaemic heart disease; LGE, late gadolinium enhancement (subendocardial LGE representative of myocardial infarction).

Q3. What are the most useful diastolic criteria to confirm a diagnosis of HFPEF?

The population being analysed for this is those 64 individuals that had a second echo where the images could be retrieved and full analysis was attempted (see adapted consort diagram, Figure 46).

Figure 46. Adapted consort diagram (Figure 14) of population being studied to assess the most useful diastolic criteria to confirm a diagnosis of HFPEF
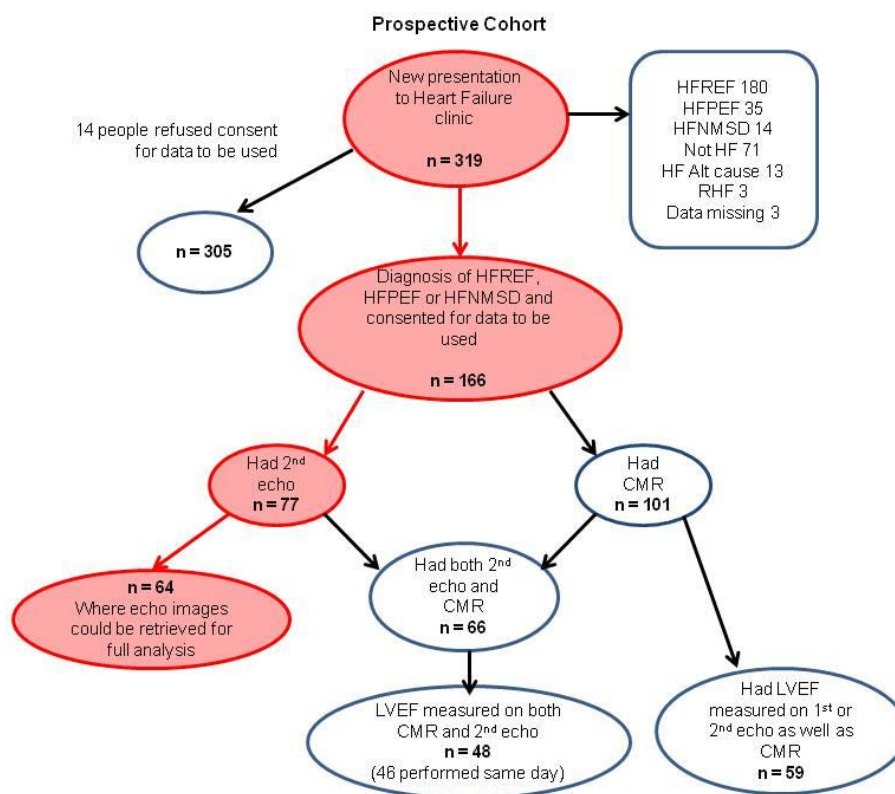
The ease with which the HFPEF echo parameters could be measured are depicted in Figure 47 below. The measures marked with an asterisk (*) are the ones that require normal sinus rhythm and so the percentage achievement should be interpreted from this population when comparing the different techniques.

Figure 47. Identifying which HFPEF echo parameters can be readily obtained.

Measure	Total that had second echo	Number in NSR	Number where measure achieved	% where measure achieved	Number where measure achieved when in NSR	% where measure achieved when in NSR
LV Mass	64	41	51	80%	31	76%
Biplane LA Volume	64	41	59	92%	38	93%
e' any	64	41	62	97%	41	100%
E/e' any	64	41	62	97%	41	100%
* E/A	64	41	40	63%	40	98% *
DCT	64	41	64	100%	41	100%
IVRT	64	41	50	78%	32	78%
*PV Doppler	64	41	32	50%	29	71% *
*S/D	64	41	32	50%	29	71% *
*Ard-Ad	64	41	24 (and in no case was the value +ve)	38%	24	59% *
CF Propagation velocity	64	41	55	86%	33	80%

*, measurements require normal sinus rhythm. NSR, Normal sinus rhythm; LV, Left ventricle; LA, left atrium; E/e', ratio of the mitral inflow E wave to the tissue Doppler e' wave; E/A, ratio of early to late diastolic mitral inflow waves; e', early Tissue Doppler diastolic velocity of mitral annulus; DCT, Deceleration time; IVRT, Isovolumic relaxation time; PV, Pulmonary vein; S/D, Ratio of peak velocities of the S and D waves of pulmonary vein flow; Ard-Ad, atrial flow reversal time (subtraction of duration of the A wave on pulsed wave Doppler through the mitral valve from the duration of the Ar wave in the pulmonary vein inflow; CF, Colour flow.

The e', E/e', and deceleration time (DCT) of the E wave could be measured in 100% of cases, closely followed by the E/A ratio in 98% of cases when an individual was in normal sinus rhythm, and thereafter left atrial volume in 93% of cases. The other parameters were not so easy to obtain and the Ard-Ad measure utilising the reverse flow wave from the pulmonary vein Doppler trace along with the A wave Doppler from mitral valve forward flow was only possible in 59% of cases (discarding those in AF where the measurement would not have been possible). Thereafter the results from these 24 cases showed no value where the result was positive and so either the measurement was being performed incorrectly (reflecting significant limitations in its use) or in no cases was it helpful to establish a diagnosis of HFPEF.

Out of the 101 patients that went on to have a CMR, 25 individuals were finally labelled with a diagnosis of HFPEF (Figure 29). All of these individuals would have had an LVEF ≥55% and LVEDVI ≥97ml/m^2 on the CMR. Thereafter the measurements that positively

enforced the diagnosis of HFPEF are all listed in Figure 48 and on a case by case basis. Figure 49 then summarises these individual cases into groups of diagnostic parameters to better demonstrate which markers appear to be most useful.

The findings would suggest that various combinations of E/e', BNP, the presence of AF and left atrial volume index (LAVI) are the key components to diagnosing HFPEF. LV mass index was supportive in only one case. The E/A ratio in combination with deceleration time (DCT) and the Ard-Ad measurements were never supportive of a diagnosis of HFPEF. In light of the difficulty measuring left ventricular mass on echo (only possible in 76% of focused echo studies) and the fact that this appears to be of minimal value for the diagnosis of HFPEF it is reasonable to conclude that only E/e' and LAVI need to be carried out in routine clinical echo exams for the identification of HFPEF.

Other than to substantiate the LVEF and LV volume, in no cases did CMR positively contribute to the diagnosis of HFPEF where echo parameters couldn't, specifically by way of measurement of LV mass or left atrial size.

Figure 48. Rationale for the diagnosis of HFPEF on a case by case basis.

Study Number	Diagnosis after CMR	Rationale for diagnosis of HFPEF
60	HFPEF	E/e' > 15
161	HFPEF	E/e' > 15
187	HFPEF	E/e' > 15
189	HFPEF	E/e' > 15
217	HFPEF	E/e' > 15
54	HFPEF	E/e' > 15, also AF
222	HFPEF	E/e' > 15 and LVMI
1	HFPEF	E/e' > 15 and BNP > 200pg/ml
78	HFPEF	E/e' > 15, also BNP >200pg/ml
254	HFPEF	E/e' > 15, also BNP >200pg/ml
119	HFPEF	BNP > 200pg/ml and E/e' > 8
206	HFPEF	BNP > 200pg/ml and E/e' > 8
272	HFPEF	BNP > 200pg/ml and E/e' > 8
306	HFPEF	BNP > 200pg/ml or E/e' > 8 and AF
198	HFPEF	BNP > 200pg/ml or E/e' > 8 and AF,
204	HFPEF	BNP > 200pg/ml or E/e' > 8 and AF and severe LA dilation
171	HFPEF	BNP >200pg/ml or E/e' > 8 with AF and LAVI >40
263	HFPEF	BNP > 200pg/ml and AF
275	HFPEF	BNP > 200pg/ml and AF
87	HFPEF	BNP > 200pg/ml and AF and severe LA dilation
35	HFPEF	E/e' > 8 and AF
41	HFPEF	E/e' > 8 and AF
283	HFPEF	E/e' > 8 with AF
61	HFPEF	E/e' > 8 and AF and LAVI > 40
172	HFPEF	E/e' > 8 and LAVI > 40

HFPEF, Heart failure with preserved ejection fraction; E/e', ratio of the mitral inflow E wave to the tissue Doppler e' wave; F, Atrial fibrillation; LVMI, Left ventricular mass index; BNP, Brain natriuretic peptide; LA, Left atrium; LAVI, Left atrial volume index.

Figure 49. Establishing which HFPEF diagnostic criteria appear to be utilised most.

Rationale for diagnosis of HFPEF			Number where this rationale was valid	Percentage of total (n=25) cases where this rationale was valid
Average E/e' > 15 as sole rationale			**10**	**40%**
Average E/e' ≥ 8 with other supporting criteria			**17**	**68%**
Supporting criteria for E/e' ≥ 8	BNP > 200pg/ml	10		40%
	AF	9		36%
	LAVI > 40	4		16%
	LVMI	1		4%
BNP > 200 with other supporting criteria			**13**	**52%**
Supporting criteria for BNP > 200pg/ml	E/e' ≥ 8	10		40%
	AF	7		28%
	LAVI > 40	3		12%

HFPEF, Heart failure with preserved ejection fraction; E/e', ratio of the mitral inflow E wave to the tissue Doppler e' wave; F, Atrial fibrillation; LVMI, Left ventricular mass index; BNP, Brain natriuretic peptide; LA, Left atrium; LAVI, Left atrial volume index.

Q4. How many of those given a diagnosis of not having heart failure by a clinician would have met the HFREF or HFPEF diagnostic criteria?

The "Not Heart Failure" group represented 71 patients of the total 319 that attended the heart failure clinic. These are identified in the adapted consort diagram below (Figure 50).

Figure 50. Adapted consort diagram (Figure 14) of those deemed not to have heart failure for analysis in this sub-section
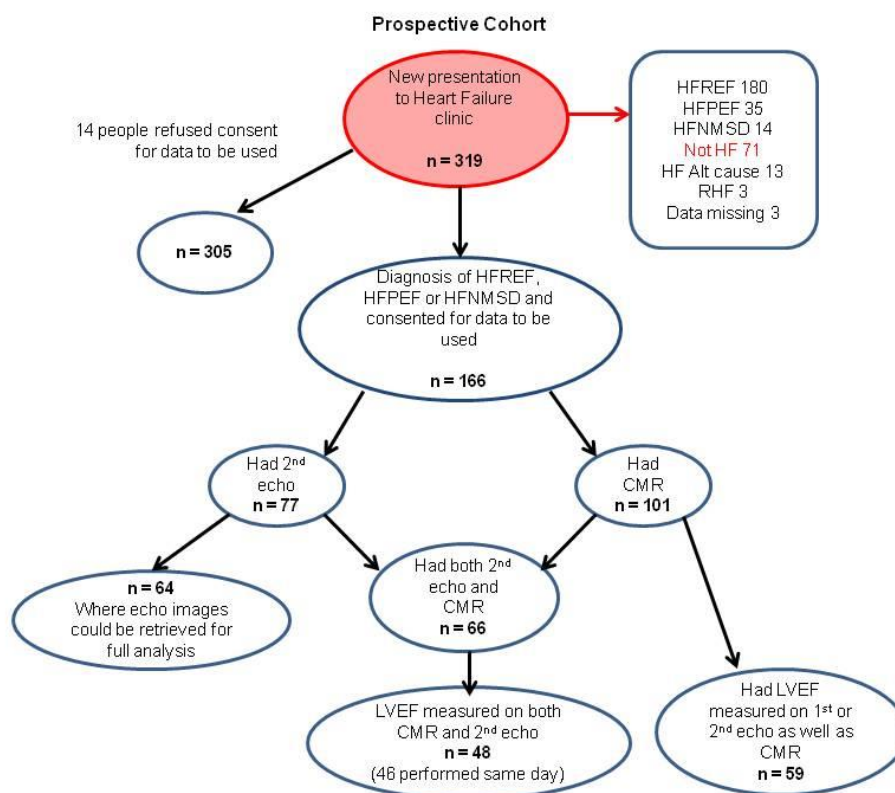
Of these, 16 did not have symptoms associated with heart failure and the referral reasons included new AF, angina, palpitations, abnormal echo but asymptomatic etc. 53 did have symptoms of HF with dyspnoea being the predominant symptom in 44 cases, oedema the predominant symptom in 9 cases and data missing in 2 cases. The clinician's opinion in all these cases was that the symptoms were not as a result of heart failure, but as a result of a variety of other causes listed in Figure 51 and Figure 52 below.

Figure 51. Postulated causes of dyspnoea in those deemed not to have heart failure by the clinic physician.

Causes of symptoms according to clinician when dyspnoea was the predominant symptom	
Primary respiratory	15
Isolated atrial fibrillation	5
Rhythm disturbance other than atrial fibrillation	4
Anxiety	4
Obesity	5
Non cardiac pleural effusion	2
Pulmonary Embolism	1
Valve disease	1
Anaemia	1
Old age/general frailty	1
Ticagrelor	1
Chronic fatigue syndrome	1
Not specified	2
Data missing	1
Total	44

Figure 52, Postulated causes of peripheral oedema in those deemed not to have heart failure by the clinic physician.

Causes of symptoms according to clinician when oedema was the predominant symptom	
Lymphoedema	2
Drug Induced (Calcium channel blocker)	3
Infective/inflammatory leg pathology	1
Venous insufficiency	2
Not specified	1

The demographics of the 71 patients deemed not to have heart failure showed the average (mean) age to be 74 years which lies between the mean age of the HFREF and HFPEF groups. 41 (58%) were female which is most similar to the demographics of the HFPEF group where 57.1% of the group were female, and higher than the HFREF group where only 38.3% were female. 29 of the 71 (41%) were taking some form of loop or thiazide diuretic and at least 13 (18%) had atrial fibrillation or atrial flutter (4 datasets missing). 50 of the 71 patients completed the Minnesota questionnaire with a mean

score of 48, which is higher than the mean score of 40.7 for both the HFREF and HFPEF groups (as diagnosed following the first echo) reflecting a subjective feeling of a poorer quality of life. However, the mean BNP was lower than that of the HFREF and HFPEF groups as depicted in Figure 53 below. Out of the 53 with dyspnoea or oedema put down to non heart failure causes, 35 had a BNP >35pg/ml, 28 had a BNP >100pg/ml and 9 had a BNP >200pg/ml. The highest BNP was 890pg/ml for a patient deemed to not have any symptoms of heart failure, in NSR but with mild impairment of LVEF on echo.

Figure 53. Comparison of BNP levels in the non heart failure groups according to the presence or absence of symptoms, and the HFREF and HFPEF groups.

Group	Mean BNP Level (pg/ml)	Median BNP (pg/ml)	% of group with BNP measured
Entire non HF group	151	114	75%
Those without symptoms	175	23	56%
Those with symptoms	134	119	76%
Dyspnoea predominant symptom	133	107	75%
Oedema predominant symptom	139	134	100%
HFREF group (based on initial echo LVEF<55%, or LVEDVI ≥97ml/m^2)	382		
HFPEF group (based on initial echo LVEF<55%, or LVEDVI ≥97ml/m^2)	298		

Of the 53 with dyspnoea or oedema 1 would meet the diagnostic criteria for HFREF due to a mildly reduced LVEF, and 13 would meet the diagnostic criteria for HFPEF (at least 25%) according to the flow chart definitions (Figure 13), noting that 15 patients had insufficient data measured to exclude a diagnosis of HFPEF by my flow diagram because either an E/e' or BNP had not been measured. The rationale for meeting the HFPEF criteria in these cases is listed in Figure 54 below and tends to be related to a combination of E/e' > 8, the presence of AF, a dilated left atrium and a raised BNP. Interestingly, only 4 patients had a BNP < 35pg/ml, normal ECG and entirely normal echo as defined by my flow chart.

Figure 54. Rationale for meeting HFPEF criteria in those deemed not to have heart failure.

Study No of those with "Not HF" that would have met diagnostic criteria for HFPEF	Rationale why HFPEF criteria were met
11	E/e' > 8, AF
12	E/e' > 8, AF, severe LA dilatation
18	BNP >200 pg/ml and AF
25	BNP >200 pg/ml and severe LA dilatation
51	E/e' > 8, AF and severe LA dilatation
66	E/e' >8 and BNP > 200 pg/ml
128	E/e' >15
139	BNP > 200 pg/ml and AF and severe LA dilation
142	E/e' > 8, severe LA dilation and BNP >200pg/ml
239	E/e' >8 and AF
258	E/e' >15 also BNP > 200 pg/ml
259	E/e' > 8, AF and severe LA dilatation
274	E/e' > 8 and AF

HFPEF, Heart failure with preserved ejection fraction; E/e', ratio of the mitral inflow E wave to the tissue Doppler e' wave; AF, Atrial fibrillation; BNP, Brain natriuretic peptide; LA, Left atrium; LAVI, Left atrial volume index.

Q5. Is there systolic dysfunction other than reduced LVEF in those with HFPEF?

Similarly to the HFPEF parameters it is worth considering which markers of systolic dysfunction could be readily obtained with echo. Once again the 64 people that had a second echo where the images could be retrieved and full analysis was attempted (Figure 46) are displayed (Figure 55). The measures marked with an asterisk (*) are the ones that require normal sinus rhythm and so the percentage achievement should be interpreted from this population when comparing the different techniques.

Figure 55. Identifying which measures of systolic function could be readily obtained with echo.

Measure	Total that had second echo	Number in NSR	Number where measure achieved	% where measure achieved	Number where measure achieved when in NSR	% where measure achieved when in NSR
LVEF (Simpson's Biplane)	64	41	48	75%	31	76%
RWMS	64	41	60	94%	40	98%
GLS	64	41	42	66%	28	68%
S' any	64	41	63	98%	41	100%
MAPSE	64	41	62	97%	40	98%
*Tei using PW Doppler	64	41	46	72%	40	98% *
CO using PW Doppler	64	41	62	97%	39	95%

*, measurements require normal sinus rhythm; NSR, Normal sinus rhythm; LVEF, Left ventricular ejection fraction; RWMS, Regional wall motion score; GLS, Global longitudinal strain; S', tissue Doppler measure of mitral annular systolic motion; MAPSE, Mitral annular plane systolic excursion; Tei, myocardial performance index; PW, Pulsed wave; CO, Cardiac output.

Subset analysis of 25 patients who maintained a diagnosis of HFPEF (LVEF ≥55%) following cardiac MRI (Figure 29) showed that 76% had other convincing markers of LV systolic dysfunction despite a normal LVEF. Figure 56 shows the number of parameters supporting some form of LV systolic dysfunction and then qualifies these.

Only six of the 25 patients diagnosed with HFPEF had no signs of LV systolic dysfunction. The other 19 patients showed a varying number of parameters of systolic dysfunction ranging from seven to one, and this is in the context of a HFPEF group with a high cut-off LVEF <55% for the diagnosis of HFREF. As opposed to the current common opinion that 50% of the heart failure community have HFPEF this demonstrates

that only 25/101 (25%) or 25+15=40/101 = 39% (when including those labelled as HFNMSD) have a normal LVEF when an appropriate LVEF is applied (i.e. <55%), and that in the majority of cases of HFPEF (76%) there are other convincing markers of LV systolic dysfunction despite a normal LVEF.

When applying the 2013 British Society of Echocardiography (BSE) protocol for the diagnosis and grading of diastolic dysfunction (129) to this cohort of 25 patients with HFPEF, grade 2 diastolic dysfunction (11 of the 25 cases) was the most frequent finding. Thereafter one individual was graded as grade 1 dysfunction, one individual as grade 1-2 dysfunction and two as normal in terms of diastolic dysfunction. In the remaining ten cases, seven had data that were conflicting so that a grading could not be allocated and three had insufficient parameters measured.

Of those with no evidence of systolic dysfunction, three had evidence of grade 2 diastolic dysfunction and in the other two cases; one had insufficient parameters measured to comment on and one had conflicting results making it difficult to reach a conclusion.

Figure 56. Prevalence and assessment of measures of LV systolic dysfunction in those individuals with HFPEF.

Systolic dysfunction?	No of parameters supporting LV Systolic dysfunction	Rationale for systolic dysfunction
Yes	10	LBBB, reduced RWMSI and CI by echo and CMR, reduced MAPSE, S' septal and lateral, GLS and abnormal Tei
Yes	8	LBBB, reduced RWMSI by echo and CMR, reduced CI on echo, reduced GLS, S', abnormal Tei and evidence of previous infarct on LGE
Yes	7	LBBB, reduced RWMSI on echo and CMR, reduced CI on echo, reduced GLS and S' with abnormal Tei
Yes	6	Reduced RWMSI on echo and CMR, reduced S' septal and lateral, reduced CI on echo, and abnormal Tei
Yes	6	Reduced CMR RWMSI, reduced CI echo and CMR, echo GLS, MAPSE and evidence of previous infarct on LGE,
Yes	6	Reduced RWMSI on echo and CMR, MAPSE, CI on echo and CMR and abnormal Tei
Yes	5	Reduced MAPSE, S', abnormal Tei, and reduced CI on echo and reduced RWMSI on CMR
Yes	4	Reduced MAPSE, CI by echo and CMR and RBBB
Yes	3	Reduced GLS, MAPSE and CI on CMR
Yes	3	LBBB, reduced RWMSI by CMR and subendocardial LGE to suggest previous infarct
Yes	3	Reduced RWMSI and CI by CMR and subendocardial LGE to suggest previous infarct
Yes	2	Reduced RWMSI and CI by CMR with some subendocardial LGE
Yes	2	Reduced CI and RWMSI on CMR
Yes	1	CMR RWMSI reduced but this is subjective. All other systolic parameters are normal. The echo RWMSI from the same day was normal.
Yes	2	Reduced RWMSI and CI by CMR
Yes	1	Reduced RWMSI on CMR
Yes	1	CMR RWMSI reduced but this is subjective and in AF
Yes	1	Reduced RWMSI by CMR and although this is subjective there are no other echo parameters performed to contradict this
Yes	1	Reduced RWMSI by CMR and although this is subjective there are no other echo parameters performed to contradict this
Probably not	3	Borderline MAPSE, borderline reduced CI on echo and CMR but normal GLS, RWMSI, S' and Tei
No	0	
No	0	
No	0	
No	0	
No	0	

LV, Left ventricle; LBBB, Left bundle branch block; RWMSI, Regional wall motion score index; CI, Cardiac index; GLS, Global longitudinal strain; S', tissue Doppler measure of mitral annular systolic motion; MAPSE, Mitral annular plane systolic excursion; Tei, myocardial performance index; LGE, late gadolinium enhancement; RBBB, Right bundle branch block; CMR, Cardiac magnetic resonance.

By comparison, in those 15 individuals labelled as HFNMSD (Figure 29) (discussed in more detail in the following section) only one individual met the criteria for grade 2 diastolic dysfunction. In the other cases the grading was more in keeping with grade 1 dysfunction with a noticeable prevalence of E/A<1 associated with a DCT >230 with reduced e' but generally a left atrium that was normal in size and a normal or borderline E/e' measure suggesting impaired ventricular relaxation but not to the extent of causing elevated LV diastolic pressures and left atrial dilatation at rest.

Diastolic dysfunction is a common contributor to those with HFPEF, however so is systolic dysfunction. The fact that so many individuals were unable to be classified by the BSE grading protocol due to conflicting results suggests significant limitations to applying this in daily practice.

Q6. Is there systolic or diastolic dysfunction in those diagnosed as HFNMSD?

In the 101 individuals that went on to have a CMR (consort Figure 42), 15 were finally labelled as HFNMSD. All had at least one echo and 8 had a second echo performed. The rationale behind this diagnosis was that all individuals had symptoms or signs of heart failure along with either an abnormal ECG, elevated BNP, or echo abnormalities suggestive but not diagnostic of HFREF or HFPEF. In addition, a CMR and either a full echo protocol was performed and excluded HFREF and HFPEF, or a full echo HFPEF assessment could not or was not undertaken. Figure 57 below qualifies this better and it is noteworthy that even in those where a diagnosis of HFPEF could not be fully excluded due to a lack of HFPEF measures, these measures were PV Doppler, LV mass or LAVI. These were all likely to be irrelevant to the diagnosis if one considers the impact of these measures in the group diagnosed with HFPEF (discussed in the results section for question 3 earlier). PV Doppler made no positive contribution to the diagnosis in any cases, and LV mass did so in only one case. Whilst LAVI is an important measure and was not performed in 8 of these HFNMSD cases, the visual assessment of the left atrium was no greater than moderately dilated for any (as opposed to the severely dilated volume that a LAVI of >40ml/m^2 would indicate).

Nevertheless, a more detailed analysis for the presence of systolic or diastolic dysfunction in this group of 15 patients with symptoms or signs of heart failure is interesting. Only two individuals have no convincing evidence of an abnormality on echo or CMR. In six individuals there is compelling imaging evidence to support both systolic dysfunction and diastolic dysfunction that is out with the criteria to diagnose HFREF or HFPEF. A further three individuals have evidence of systolic dysfunction alone, and a further four have evidence of diastolic dysfunction alone. Obviously some of the cases are more compelling than others and whilst some of the decision making is subjective there are definite cases where the collective imaging abnormalities are convincing. The numbers of abnormal imaging parameters are quantified and qualified in Figure 58 and 59 below to help guide the reader with the assimilation of this information and I draw attention to the fact that six of these individuals have late gadolinium enhancement in the subendocardium to suggest a previous infarct.

Figure 57. Qualifying the HFNMSD group.

Rationale	Number of people HFNMSD explained by this rationale			% of total HFNMSD group explained by this rationale
HFREF and HFPEF fully excluded by diagnostic pathway	2			13%
HFREF excluded but HFPEF could not be entirely excluded because various measurements not attempted:	8	BNP	1	53%
		PV Doppler	7	
		LV Mass	7	
		LAVI	6	
HFREF excluded but HFPEF could not be entirely excluded because various measurements attempted but could not be measured:	5	PV Doppler	5	33%
		LV Mass	4	
		LAVI	2	
Total	15			100%

HFREF, Heart failure with reduced ejection fraction; HFPEF, Heart failure with preserved ejection fraction;

BNP, Brain natriuretic peptide; LV, Left ventricle; LAVI, Left atrial volume index; PV, Pulmonary vein.

Figure 58. Quantification of abnormal systolic and diastolic parameters in HFNMSD group.

Study No	Systolic dysfunction?	No of parameters supporting LV Systolic dysfunction	Any evidence of diastolic dysfunction?	No of parameters contributing to this (E/A and DCT count as 1)
8	Yes	3	Yes	3
28	Yes	7	Yes	5
59	Yes	4	Yes	4
188	Yes	6	Yes	1
191	Yes	5	Yes	3
289	Yes	2	Yes	1
255	Yes	3	No	0
136	Yes	2	No	0
311	Yes	2	No	0
9	Probably not	1	Yes	2
135	Probably not	2	Yes	4
62	No	0	Yes	4
243	No	0	Yes	1
212	Probably not	1	No	0
10	Probably not	1	No	0

DCT, Deceleration time; LV, Left ventricle.

Figure 59. Qualification of abnormal systolic and diastolic parameters in HFNMSD group.

Study No	Rationale for systolic dysfunction	Rationale for diastolic dysfunction
8	Abnormal CMR RWMSI, CMR CI, TTE CI	Abnormal e' septal and lateral and E/A
28	LBBB, Reduced RWMSI by echo and CMR, reduced CMR CI, reduced S' and MAPSE and abnormal Tei, although normal GLS	Abnormal e' septal and lateral, E/A and DCT, IVRT, and CF propagation velocity
59	Reduced RWMSI by echo and reduced CI by echo and CMR, with reduced S'	Abnormal e' septal and lateral, E/A and DCT, and CF propagation velocity
188	Reduced S' lateral and septal walls, CI by echo and CMR, abnormal Tei and LGE to suggest infarct	Abnormal e' septal only
191	Reduced RWMSI and CI by CMR with reduced S', an abnormal Tei and LGE to suggest previous infarct	Abnormal e' septal and lateral, and E/A and DCT
289	CMR RWMSI reduced and LGE to suggest previous infarct	Abnormal LAVI
255	LBBB, CMR RWMSI reduced and LGE to suggest previous infarct	
136	CMR RWMSI reduced and LGE to suggest previous infarct	
311	CMR RWMSI reduced and LGE to suggest previous infarct	
9	Only echo CI abnormal, CMR CI normal	Abnormal E/A and IVRT
135	Borderline MAPSE and the reduced CI on echo are not upheld by CMR. Other parameters normal	Abnormal e' septal and lateral, LAVI, and E/A and DCT
62		Abnormal e' septal and lateral, IVRT and CF propagation velocity
243		Abnormal LAVI
212	Only CMR CI abnormal, no RWMS abnormalities and no echo parameters to back up the reduced CI	
10	Only CMR CI abnormal, no RWMS abnormalities and no echo parameters to back up the reduced CI, Although normal GLS	

CMR, Cardiac magnetic resonance; TTE, Transthoracic echo; CI, Cardiac index; RWMSI, Regional wall motion score index; LGE, late gadolinium enhancement; LBBB, Left bundle branch block; GLS, Global longitudinal strain; S', tissue Doppler measure of mitral annular systolic motion; MAPSE, Mitral annular plane systolic excursion; Tei, myocardial performance index; E/A, ratio of early to late diastolic mitral inflow waves; e', early tissue Doppler diastolic velocity of mitral annulus; DCT, Deceleration time; IVRT, Isovolumic relaxation time; CF, Colour flow.

Whilst these patients may have insufficient abnormalities to diagnose HFREF or HFPEF, all have clinical symptoms or signs that could be in keeping with heart failure and an average elevated Minnesota score of 43. Ten have significant ECG changes that could be consistent with ischaemic heart disease, or else LBBB or ectopy. Eight had a first echo which showed a reduced visual assessment of LV function and seven had a regional wall motion abnormality on CMR despite a normal LVEF. Six have the suggestion of a previous infarct on late gadolinium CMR imaging and three went on to have an invasive angiogram, all of which demonstrated significant coronary artery disease requiring revascularisation. Whilst angiograms or ischaemia stress testing were only performed in a very small number of these individuals the collective information above raises serious questions about whether these could represent a group with symptoms due to dynamic ischaemia that would benefit from some form of routine stress testing, or exercise/cardiopulmonary exercise testing with ECG monitoring to better assess them.

Q7. If current CMR and echo measurements of LVEF do not correlate can this be improved upon using a regional wall motion score index (RWMSI) equation?

Regional wall motion score index to predict CMR LVEF

Please refer to the methodology section under the same subheading to recount the methods of this data analysis. Consort diagram (Figure 16) describes the population being retrospectively studied in this section.

Assessing the precision of the RWMSI equation used current practice

Deming regression analysis (Figure 60) and Bland Altman agreement plots (Figure 61) of RWMSI LVEF versus CMR LVEF for the previously validated equation "RWMSI LVEF = (Total RWMS/16) x 30" were performed for the 160 individuals with a RWMSI LVEF >10% and ≤55%, and with data created using the simplified RWMS whereby normal = 2, hypokinetic =1 and, akinetic and dyskinetic = 0, and using a 16 segment model. The alternative way of writing this equation would be:

 RWMSI LVEF = RWMSI (dyskinetic score=0) x 30

In these plots CMR LVEF is represented by MRI LVEF instead. This work formed the basis of a poster abstract in the European Society of Cardiology (ESC) Heart Failure Conference in Athens, May 2014.

Figure 60. Deming regression analysis of RWMSI LVEF vs CMR (MRI) LVEF for the equation "RWMSI LVEF = (Total RWMS/16) x 30"

Key for Figures 60 and 61.

◯ = Severe LVSD heart failure group

🟥 = Moderate LVSD heart failure group

⚫ = Mild LVSD heart failure group

△ = Normal LV function
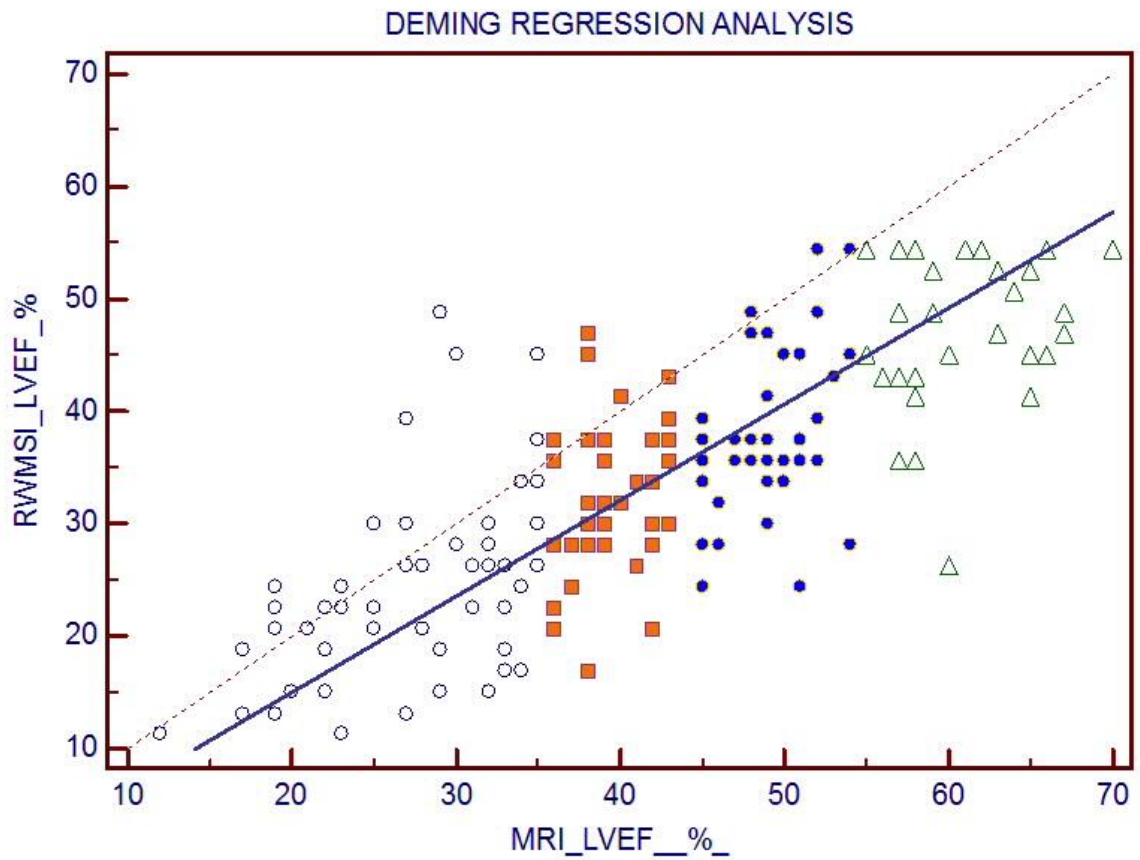
RWMSI, Regional wall motion score index; MRI, Cardiac magnetic resonance, otherwise referred to as CMR throughout the rest of the thesis; LVEF, Left ventricular ejection fraction.

The Deming regression analysis providing the mean regression parameter and its 95% confidence interval demonstrated that the two methods were highly comparable (Slope 0.85, 95% CI 0.77 to 0.94, intercept -2.1, 95% CI -5.95 to 1.75). However, the mean CMR/MRI LVEF = 42.4% (coefficient of variation 30.5%) compared with a mean RWMSI LVEF of 34% (coefficient of variation 32.4%), and the Bland-Altman plot confirms how the RWMSI LVEF would underestimate the CMR LVEF with a mean difference of 8.3% units.

Figure 61. Bland-Altman plot of RWMSI LVEF vs CMR (MRI) LVEF for the equation "RWMSI LVEF = (Total RWMS/16) x 30"
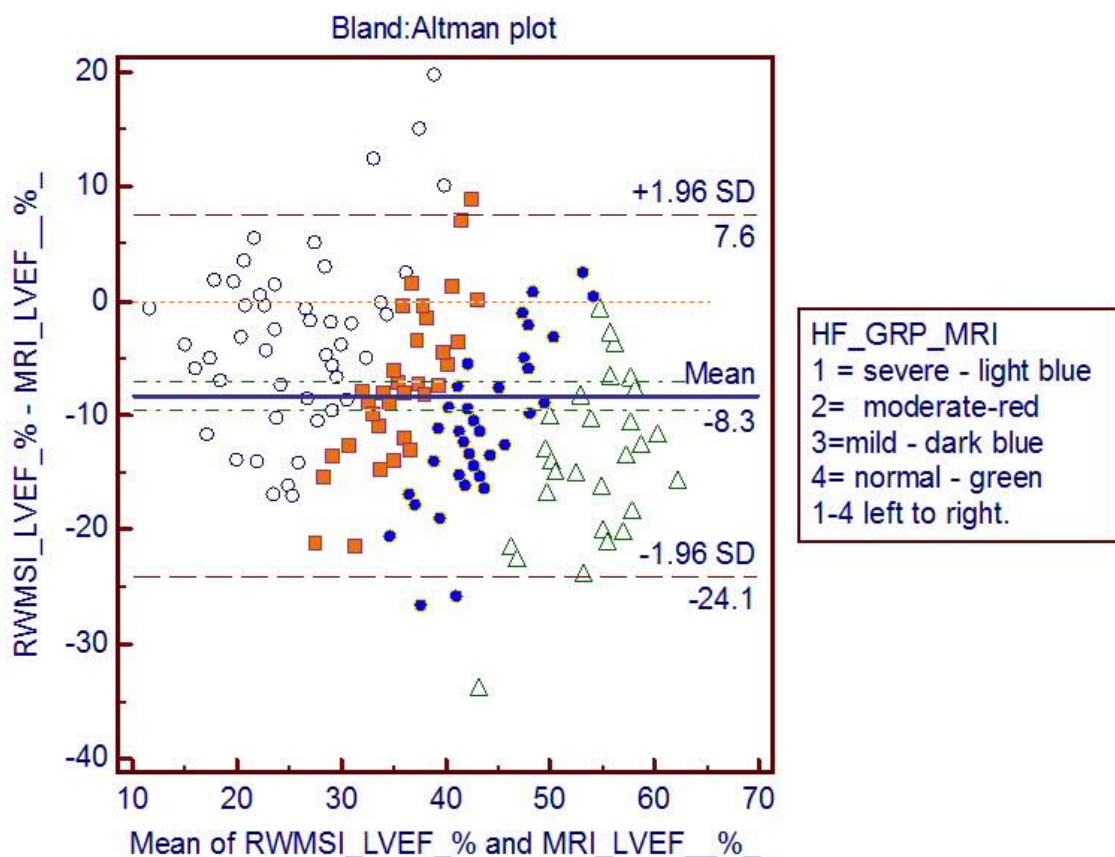
RWMSI, Regional wall motion score index; MRI, Cardiac magnetic resonance, otherwise referred to as CMR throughout the rest of the thesis; LVEF, Left ventricular ejection fraction.

On both figures the differently coloured and differently shaped plots depict the different heart failure subgroups according to CMR endocardial LVEF measurement and provide a visual appreciation of the relationship between the two methods of LVEF calculation in each group. Interestingly, from the Bland Altman plot in particular it appears that those with more severe LV impairment may have the LVEF underestimated to a lesser extent

than other groups by this RWMSI equation. This observation would be the opposite of the initial clinical suspicion.

The previous validation study for this equation, which applied a score of -1 for a dyskinetic segment as opposed to 0, suggested that the RWMSI LVEF could be 9% higher or 14% lower the averaged RWMSI LVEF and CMR endocardial LVEF (137). However the very nature of averaging the two methods LVEF means the authors did not consider the data in the setting of CMR being the gold standard measurement, as it has been deemed to be. It is no surprise therefore that in this analysis the limits of agreement show how this RWMSI equation may produce an LVEF that is between 8% higher or 24% lower than the MRI endocardial LVEF. Such ranges of discrepancy between methods would be unacceptable for clinical purposes, resulting in heart failure group classifications that could be markedly different from one another using the two techniques.

Assessment of the RWMSI LVEF performance within each individual heart failure subgroup was attempted using separate Deming regression analyses on the normal, mild, moderate and severe subdivisions. In this setting Deming regression analysis did not support a consistent relationship between the RWMSI LVEF and CMR endocardial LVEF in any of the sub groups. This is inconsistent with the overall analysis and perhaps the most likely explanation is based upon the statistical rules that the likelihood of finding a significant level of agreement depends on the range and spread of the sample being tested. Whilst the large group analyses had sufficient range and spread of data to establish a statistically valid correlation, the narrower range and spread of the sample in subgroup analysis meant that valid continuous correlation analysis could not be achieved. A major contributor to this was the nature of the RWMSI LVEF equation that meant that the LVEF figures produced would always be of a semi-continuous nature. As such, this method of subgroup analysis was abandoned.

Constructing new linear equations

Whilst the mean LVEF difference of 8.3%, and wide limits of agreement means that this equation is unlikely to be clinically acceptable, the fact that there is good correlation between the two methods overall lends itself to the development of an equation that could improve the accuracy of the RWMSI LVEF simply by the addition of 8 to the original equation i.e:

RWMSI LVEF = RWMSI (D=0) x 30 + 8,

whereby D=0 represents the score given to dyskinetic segments for this equation.

Another four separate possible equations were constructed from the best-fit Deming regression lines between the RWMSI and CMR LVEF by adjusting the dataset according to whether the RWMS allocated a score of 0 versus -1 to a dyskinetic segment, and thereafter either incorporating or removing all those with a RWMSI = 2, see consort diagram (Figure 62).

Transforming the data to obtain a more normal distribution

The distribution of the entire dataset is positively skewed by the large numbers with a RWMSI =2. Even with the group with a RWMSI = 2 removed from the population, the data were not normally distributed and it was possible that linear equations would not be representative of the relationship between RWMSI LVEF and CMR endocardial LVEF.

Attempts to transform the data into a more normal distribution using logarithmic and trigonometric methods were undertaken. The most successful method was an arcsine transformation of the RWMSI/2, although there remained a visible positive skew to the dataset even after this transformation.

A further Deming regression analysis was applied to this transformed data and a further equation constructed. The resulting equation was:

arcsine(RWMSI (D=0)/2) x 46.5 + 12

Simplified equations for clinical use

Many of the equations established above would be difficult to remember for quick everyday use in clinical practice. Rounded figures would be more amenable to daily application and so some of the more complex equations were simplified and adapted equations were created below with a view to comparing whether the subtle differences had a clinically relevant effect on their precision. A final selection of eleven equations was then ready to be assessed for their precision compared with CMR LVEF. These are fully listed and explained by the consort diagram below (Figure 62) and Figure 63.

Figure 62. Flow diagram of equation creation
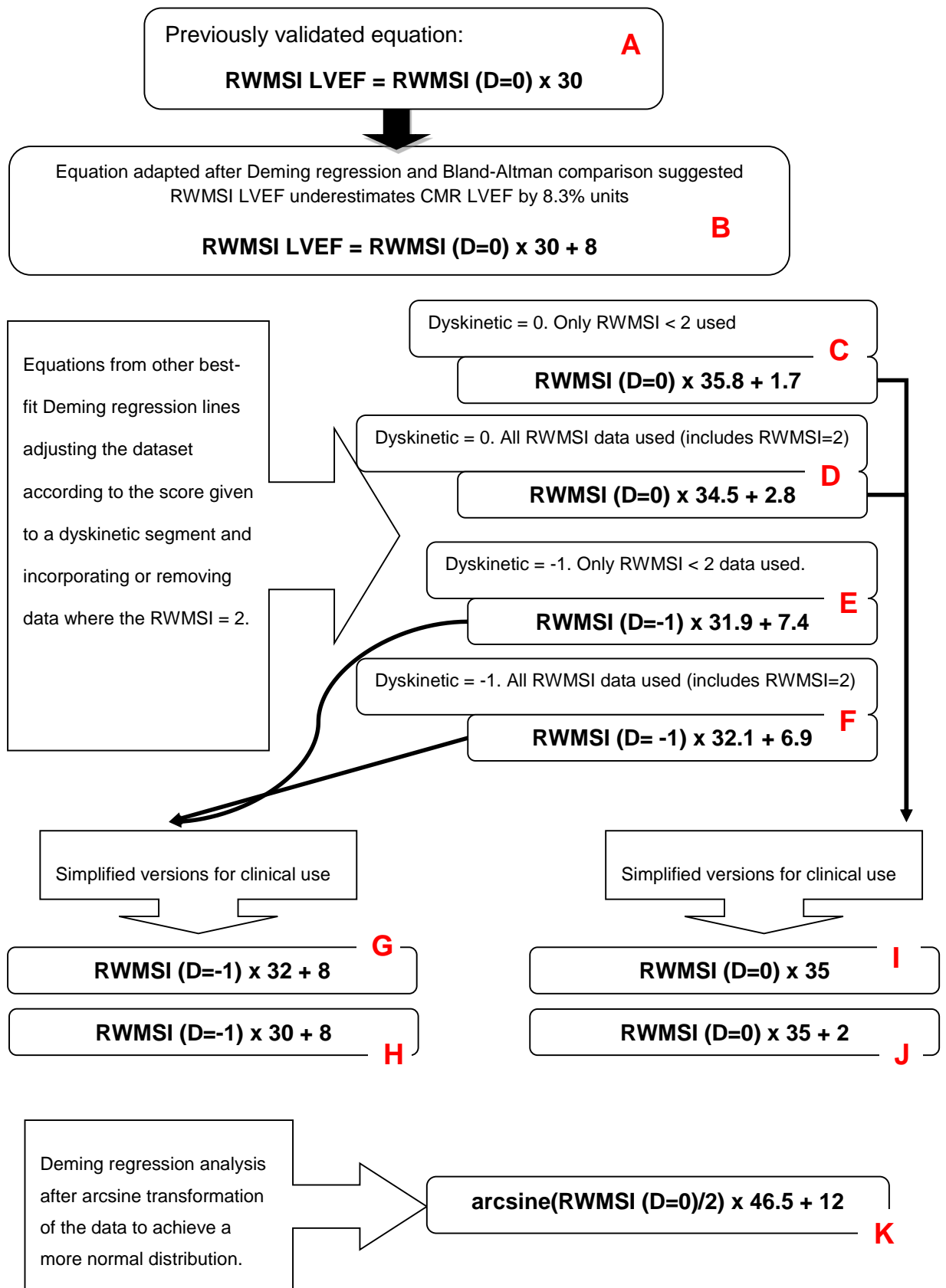
Figure 63. Table of equations labelled alphabetically for simplicity.

RWMSI LVEF Equation	Alphabetical representation
RWMSI (D=0) x 30	A
RWMSI (D=0) x 30 + 8	B
RWMSI (D-0) x 35.8 + 1.7	C
RWMSI (D=0) x 34.5 + 2.8	D
RWMSI (D=-1) x 31.9 + 7.4	E
RWMSI (D=-1) x 32.1 + 6.9	F
RWMSI (D=-1) x 32 + 8	G
RWMSI (D=-1) x 30 + 8	H
RWMSI (D=0) x 35	I
RWMSI (D=0) x 35 + 2	J
Arcsin(RWMSI/2) (D=0) x 46.5 +12	K

Testing and comparing the precision of these new equations

The performance of all the equations were compared on the same cohort of subjects, for the full data set (RWMSI = 2, and then those where RWMSI = 2 were excluded) and then subgroups (normal, mildly impaired, moderately impaired, and severely impaired according to CMR LVEF). This was done by comparing the mean RWMSI LVEF (with confidence intervals) of each equation with CMR endocardial LVEF values. The estimated standard error given in this exploratory analysis was calculated using standard methods of analysis. Bootstrapping was explored but since it made only a minor bias to the dispersion it was not incorporated in the analysis. The bootstrapping method assumes the population is the sample and so resamples with replacement 1000 times in this example. In general, this technique is used for relatively small samples, e.g. n<40.

It became apparent that every equation (excluding the original equation used in current practice) results in a higher LVEF in the severe group than that produced by the CMR. This was a useful observation. The severe group is the one most likely to be affected by the alterations in the dyskinesis score (because the more normal the contraction of the heart the less likely it is to have dyskinetic segments). Thus if there is an equation that scores dyskinesis as 0 and performs well in all the other subgroups, it is plausible that this may also perform equally as well in these groups if the dyskinesis score is changed to -1, but even better in the severe LV impairment group. Visually one possibility is

equation J, or "RWMSI (D=0) x 35 + 2" due to the consistent reliable representation of the CMR LVEF across all the other subgroups. This is also a relatively simple formula that could be readily used in clinical practice. This equation was adapted using a dyskinesis score of -1 to create a final equation to be tested "RWMSI (D=-1) x 35 + 2" (equation L). The graphs below (Figure 64-69) provide a visual comparison of effectiveness of the various equations as discussed in this synopsis with the newly adapted equation L shown in red at the end of each graph.

Figure 64. Equation comparison of mean LVEF for all data

Previous and new equation comparison of mean LVEF with 95% CI
Data for all heart failure subgroups (full dataset)
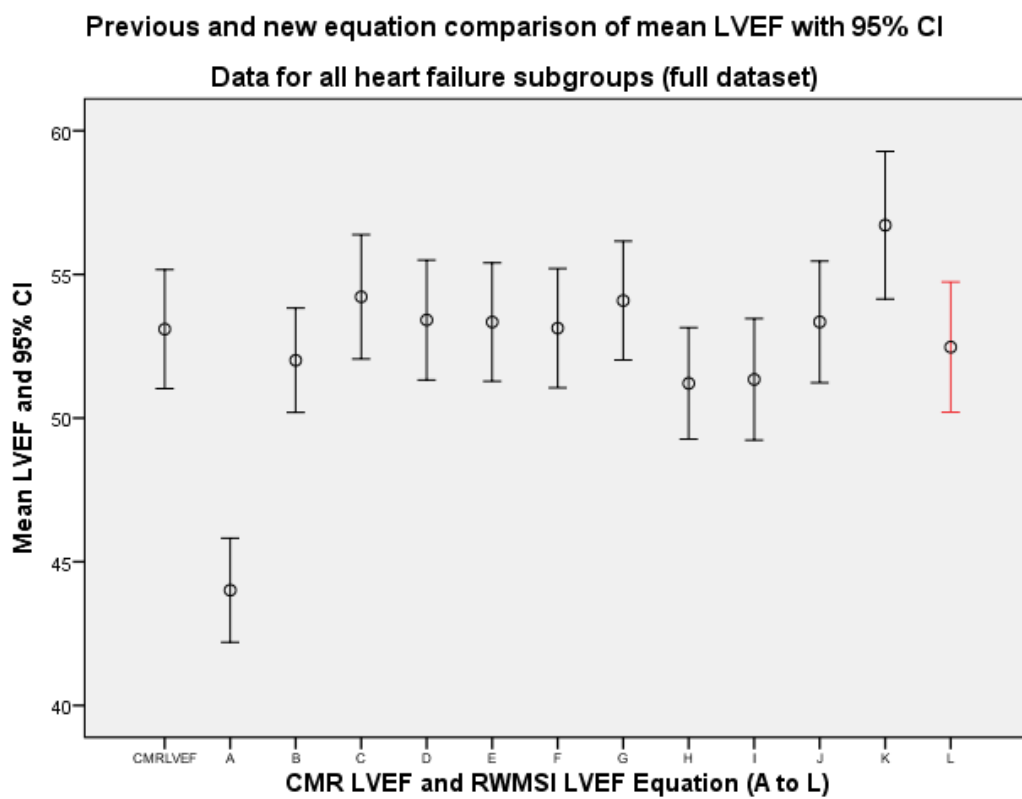
Figure 65. Equation comparison for all data, excluding those with RWMSI =2.

Previous and new equation comparison of mean LVEF with 95% CI

Data for all heart failure subgroups excluding those with RWMSI = 2.
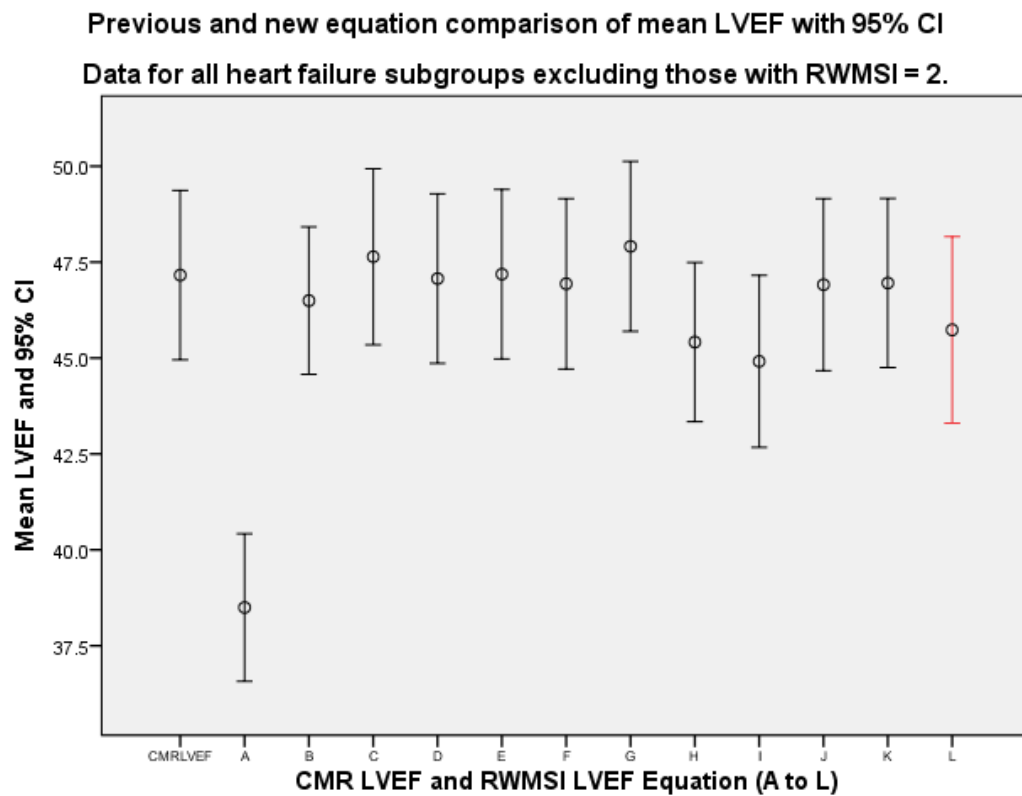
Figure 66. Equation comparison for those with normal systolic function.

Previous and new equation comparison of mean LVEF with 95% CI

Data for all those with normal LV systolic function (LVEF>=55%)

147
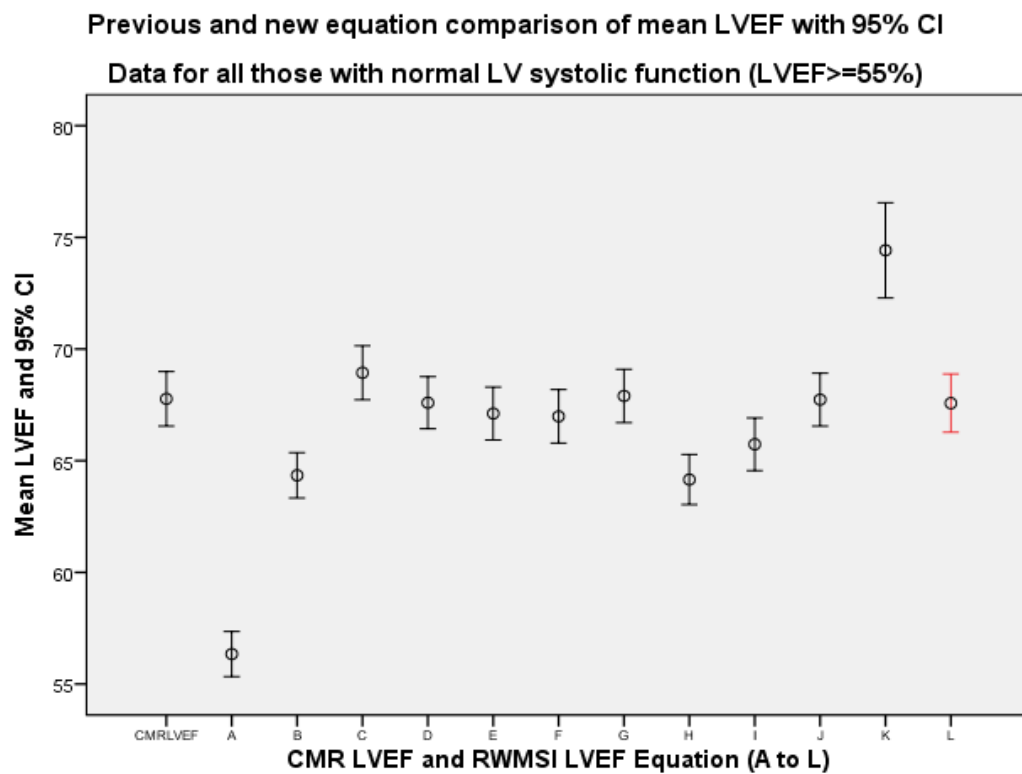
Figure 67. Equation comparison for those with mild LV impairment.

Previous and new equation comparison of mean LVEF with 95% CI

Data for all those with mild LV systolic impairment (LVEF 45-54%)
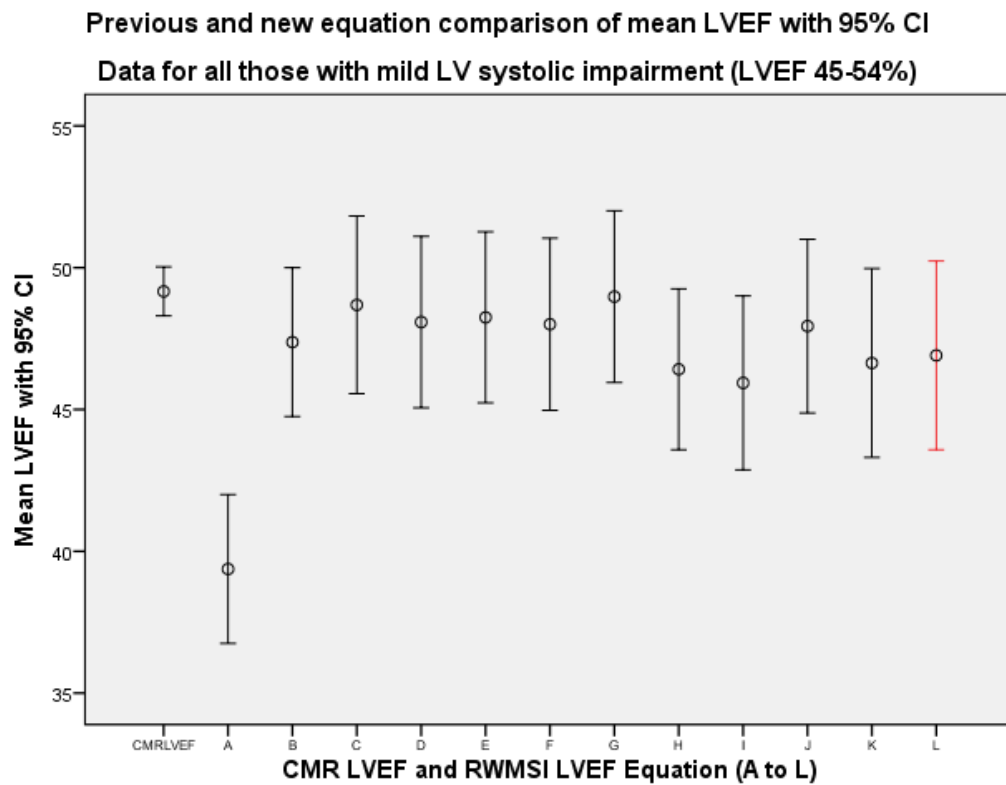
Figure 68. Equation comparison for moderate LV impairment.

Previous and new equation comparison of mean LVEF with 95% CI

Data for all those with moderate LV systolic impairment (LVEF 36-44%)
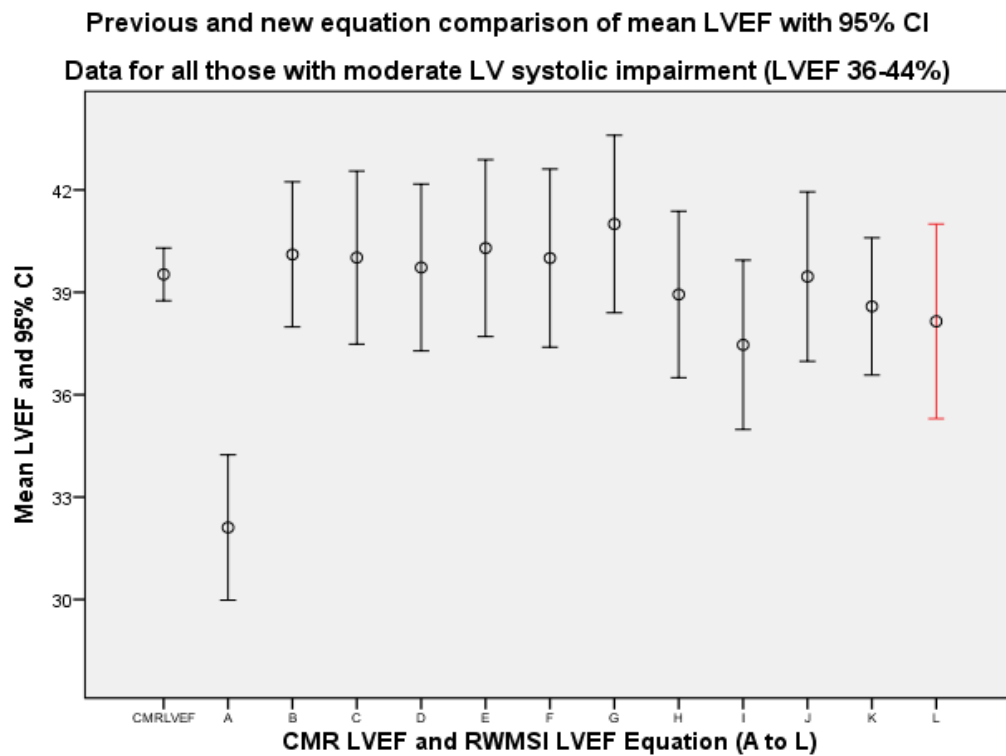
Figure 69. Equation comparison for those with severe LV impairment.
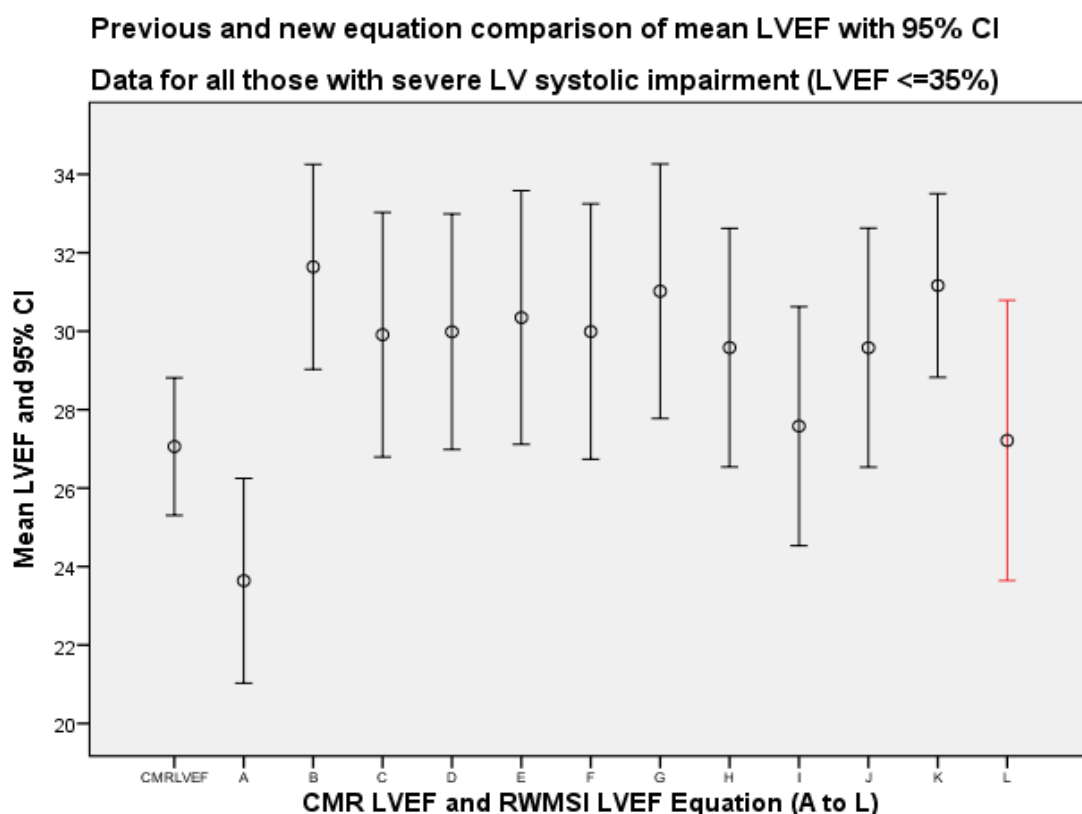
Previous and new equation comparison of mean LVEF with 95% CI

Data for all those with severe LV systolic impairment (LVEF <=35%)

Paired analysis of heart failure group allocations by the different equations versus CMR LVEF was performed using cross-tabulation and Kappa measure of agreement. The LVEF determined a heart failure grouping according to BSE criteria (1=severe (LVEF ≤ 35%), 2=moderate (LVEF 36-44%), 3=mild (LVEF 45-54%), 4=normal (LVEF ≥ 55%). This was initially performed with the whole dataset but the high levels of agreement in the "normal" subgroup, with large "normal" subgroup numbers appeared to be skewing the picture for the other subgroups. Therefore, repeat analysis was done for only those 203 individuals with a RWMSI < 2, removing the group of people with the equation's ceiling RWMSI LVEF and reducing the skewing effect (Figure 70).

Figure 70. Comparison of CMR LVEF vs equation LVEF using Kappa measure of agreement.

	Kappa measure of agreement with CMR LVEF HF Group	Asymp Std Error[a]	Approx T[b]
Equation A	0.369	0.043	9.367
Equation B	0.527	0.044	12.887
Equation C	0.494	0.044	11.945
Equation D	0.494	0.044	11.945
Equation E	0.503	0.044	12.184
Equation F	0.503	0.044	12.184
Equation G	0.491	0.044	11.972
Equation H	0.494	0.044	12.063
Equation I	0.470	0.043	11.480
Equation J	0.492	0.044	11.947
Equation K	0.481	0.044	11.808
Equation L	0.454	0.044	11.009

a, not assuming the null hypothesis; b, using the aymptotic standard error assuming the null hypothesis.

With the RWMSI = 2 group removed from analysis only three equations had a Kappa level of >0.5 to suggest a good level of agreement. Two of these were the equations derived from the Deming regression curves when a dyskinesis score of -1 was applied, and were relatively complex from the perspective of daily clinical application. Indeed the level of agreement is probably not sufficient to justify abiding the complexities of these equations for clinical use. The other was Equation B, which was the original equation adapted after the Bland Altman assessment suggested 8% should be added to the answers, and using a dyskinesis score of 0. This had the highest Kappa level of agreement and was actually a more simple equation for clinical application. The visual

interpretation of the effectiveness of this equation (Equation B) is shown in the colour bar chart (Figure 71), and demonstrates the distribution of the heart failure groups according to CMR LVEF within each RWMSI LVEF grouping.

Figure 71. Pictorial bar chart display of the equation with the best Kappa agreement with CMR LVEF.

Bar chart display of Equation B (RWMSI (D=0) x 30 +8) performance against CMR LVEF for approriate HF Group selection.
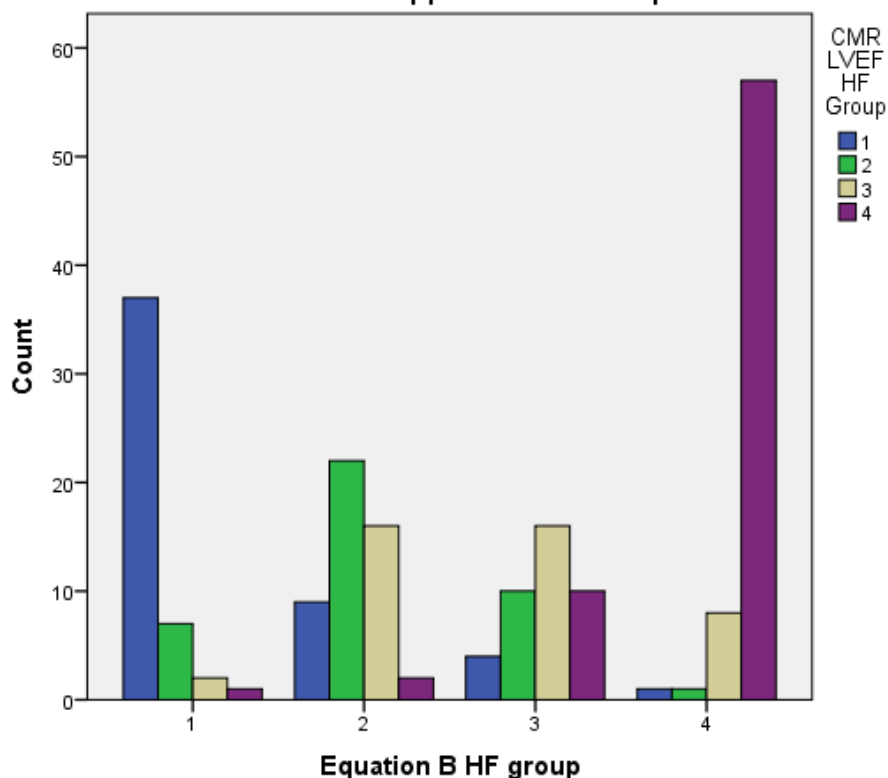
(1=severe (LVEF ≤ 35%), 2=moderate (LVEF 36-44%), 3=mild (LVEF 45-54%), 4=normal (LVEF ≥ 55%).

The equations' performances by the heart failure group allocation, as well as the individual value of LVEF, are both clinically relevant. From the Kappa information it appears that Equation B (RWMSI (D=0) x 30 + 8) is the most useful. Although one may initially assume this is due to the large numbers with a normal LVEF skewing the data to enhance the performance of an equation that favours a higher LVEF, actually Equation B fared better than the other equations in the mild and moderately impaired heart failure groups. However, the visual interpretation of the mean LVEF with confidence intervals shows how Equation B overestimates the LVEF in those with severe LV impairment more than a number of other equations. The most recently constructed equation (equation L), incorporating a dyskinesis score of -1 definitely improved the LVEF representation in the severe group as had been postulated. Unfortunately, employing this dyskinesis score of -1 also had an effect in the other groups so that it reduced the LVEF sufficiently (and

particularly when it was close to the boundary between mild and moderate LV dysfunction) so that enough people were incorrectly classified in a worse heart failure group to reduce the Kappa level to <0.5, and meaning that it was less effective in the heart failure group analyses.

Each equation has its own pros and cons when spanned across the entire LVEF range. Perhaps a linear equation is not the most appropriate method of converting a RWMSI into LVEF. Perhaps the fact that the LVEFs produced by the RWMSI are only semi-continuous (due to the 16 segment division) means they lack accuracy for the categorical group analysis, particularly in the middle range groups (mild and moderate LV impairment) which only span 9 or 10% units, and boundaries easily traversed. It should also be remembered that the same set of data has been used for hypothesis generation and hypothesis in this analysis with the inherent limitations this brings. As such prospective validation was attempted with the three equations that were most representative of CMR endocardial LVEF.

Prospective validation of the RWMSI equations to predict CMR LVEF

Equations for prospective validation

The three equations taken forward and the rationale for their inclusion are listed below in Figure 72.

Figure 72. Equations for prospective validation

	Equation	Rationale for taking forward to prospective analysis
B	RWMSI (D=0) x 30 + 8	Best Kappa agreement
H	RWMSI (D= -1) x 30 + 8	An equation with D= -1 with better Kappa agreement in the heart failure group analysis than equation L. Better representation of the HF group and LVEF at the lower end of the LVEF spectrum.
L	RWMSI (D=-1) x 35 + 2	Best representation of the severe heart failure group LVEF and similar representation of LVEF in the normal, mild and moderate groups compared with other equations

All those that underwent echo and CMR on the same day that had valid consent for the use of the data, and that had a CMR LVEF performed and an echo RWMSI performed using at least 15 of the 16 regional segments were included for analysis. This resulted in a total of 59 datasets. The CMR LVEF was then compared with these three equation calculated LVEFs by way of Bland Altman plots. These were then compared against the Simpson's Biplane echo LVEF Bland Altman plot displayed earlier in the section labelled "Do echo and CMR measurements of LVEF correlate?" This was a marginally different cohort, comprising the 48 individuals that had a second echo as well as a CMR (46 of which were performed on the same day) and had Simpson's Biplane LVEF performed.

Thereafter, categorical assessment of concordance with CMR heart failure group allocation, based on the BSE criteria (1=severe (LVEF ≤ 35%), 2=moderate (LVEF 36-44%), 3=mild (LVEF 45-54%), 4=normal (LVEF ≥ 55%), was performed for each equation and then also compared with a similar analysis for the cohort of 48 individuals using Simpson's Biplane echo LVEF method.

Would any of the RWMSI equations be an improvement on the echo Simpson's Biplane representation of CMR LVEF? Figures 73-75 are Bland-Altman plots comparing the three prospective equations with CMR LVEF. Figure 76 is a Bland-Altman plot comparing transthoracic echo Simpson Biplane LVEF with CMR LVEF.

Figure 73. Bland-Altman plot comparing equation B with CMR LVEF.
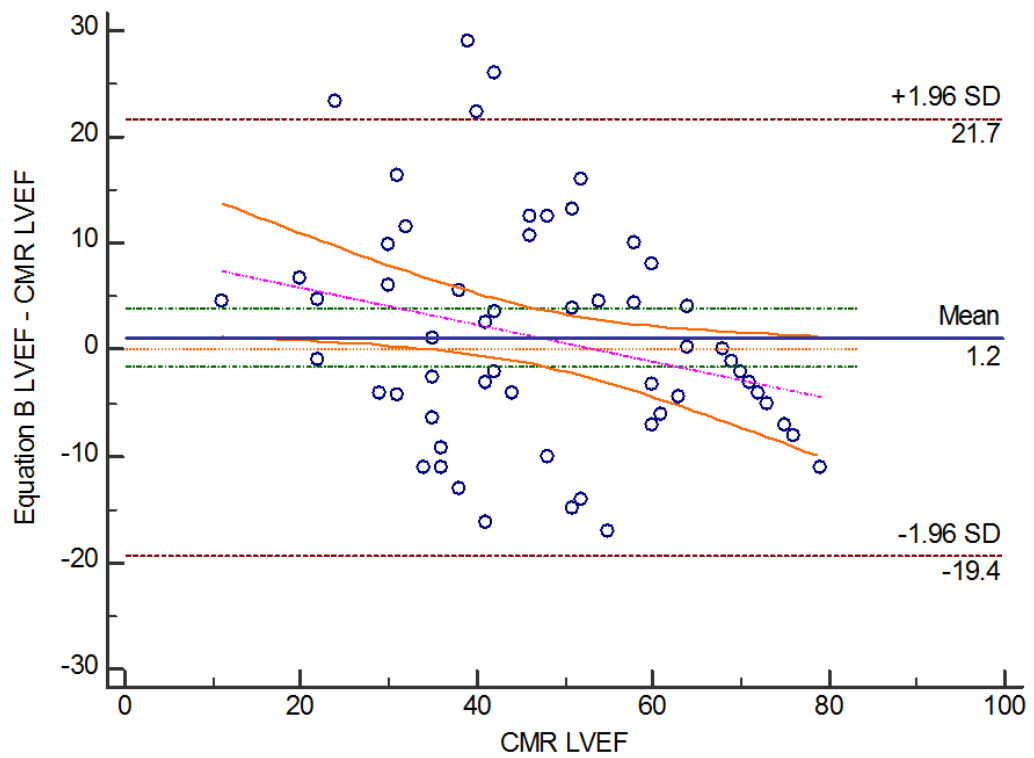
Figure 74. Bland-Altman plot comparing equation H with CMR LVEF.
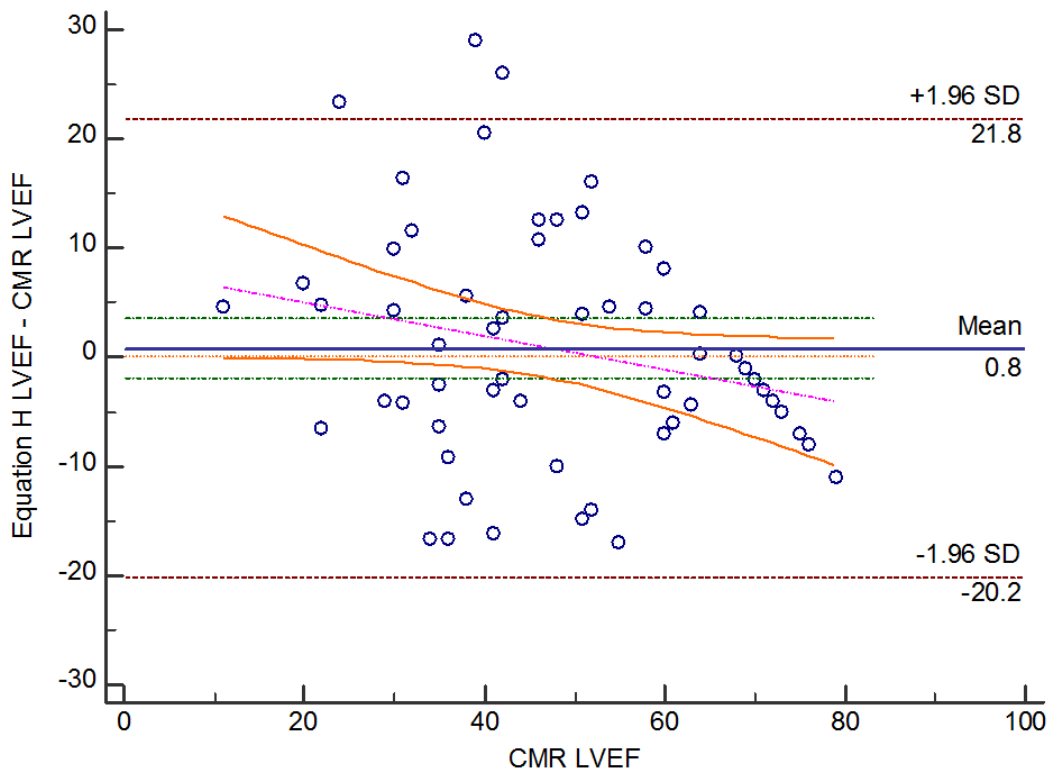
Figure 75. Bland-Altman plot comparing equation L with CMR LVEF.
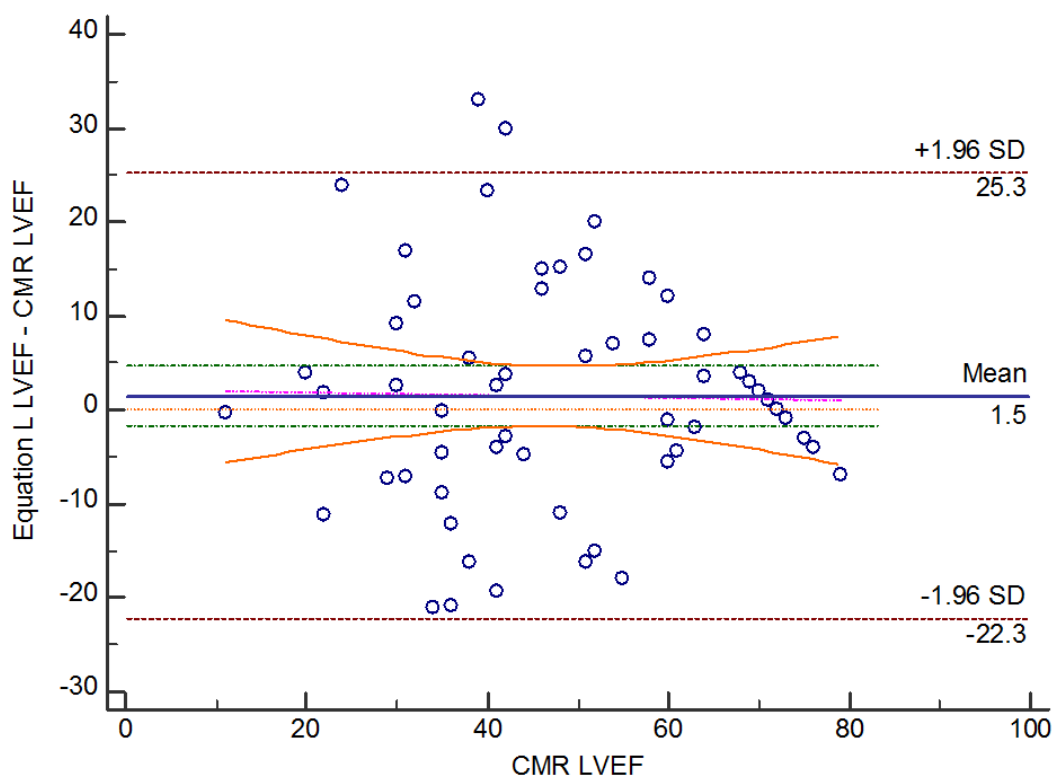
Figure 76. Bland-Altman plot comparing TTE Biplane LVEF with CMR LVEF.
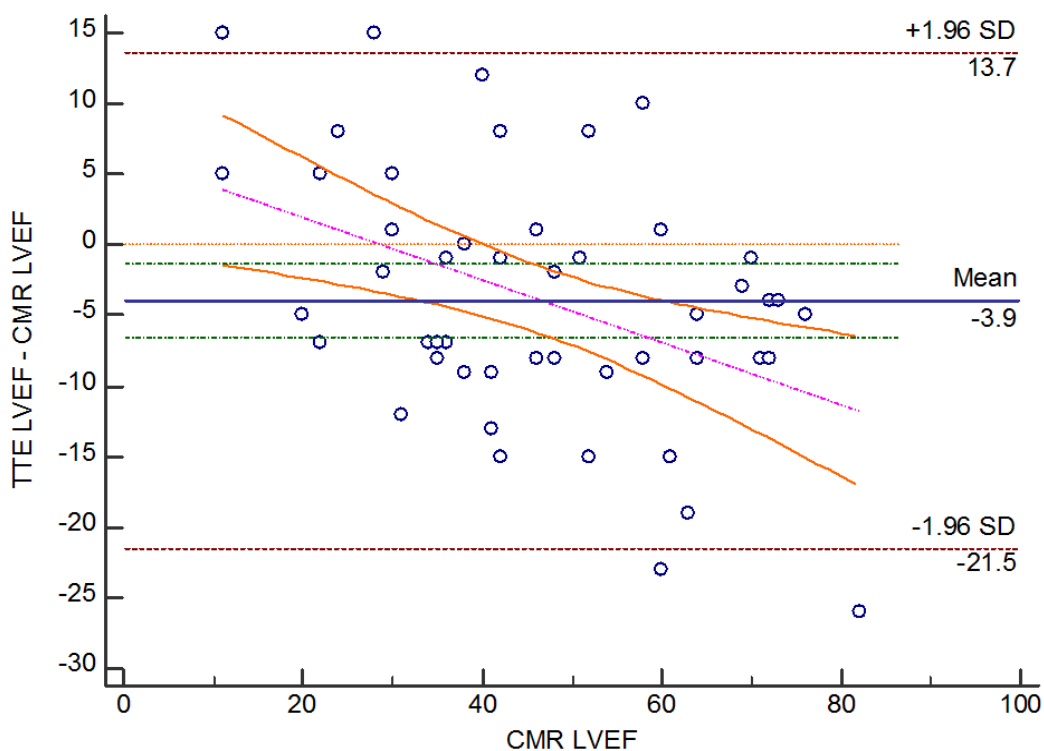
The Bland Altman plots are plotted with CMR LVEF on the X-axis as this is deemed to be the gold standard. This is different from the method where the two methods being tested are averaged but this should only happen when the gold standard is not known. They demonstrate the mean difference between the two methods tested with associated confidence intervals and also the 1.96 standard deviations around this mean.   The associated table (Figure 77) summarise these numerical values adjacent to each other to ease comparison. The results demonstrate that the TTE Simpson's Biplane LVEF is on average of -3.9% units below that of the CMR LVEF and the regression line demonstrates that this is proportional to the LVEF so that the underestimate is more pronounced the higher the LVEF, and indeed may tend to overestimate the LVEF and very low LVEFs.

In comparison, all RWMSI equations produce an LVEF that is on average higher than the CMR LVEF, minimally with equation H at +0.8% units, and maximally with equation L at +1.5% units. Equation B and H both have down sloping regression lines similar to the Simpson's Biplane analysis so that they overestimate the CMR LVEF at lower LVEFs and underestimate it at higher LVEFs. However, this is less pronounced with Equation H (-0.1554 versus -0.1747) which may reflect the use of a dyskinesis score of -1 which makes it more reliable for those with lower LVEFs. Equation L has a much flatter regression line so that the 1.5% units overestimate of CMR LVEF is more consistent across the range of LVEFs but the payoff is a wide standard deviation so that the CMR LVEF can be 25.3% units above or 22.3% units below Equation L LVEF to incorporate two standard deviations of data. Indeed all the equations have a standard deviation range greater than that for the TTE Simpson's Biplane LVEF.

Figure 77. Table explaining the results of the Bland-Altman plots for equations B, H and L and TTE Biplane LVEF.

Equation / Method	Mean difference in results (Method–CMR LVEF)	95% Confidence Interval	SD Range	Regression line pattern	Interpretation of the plot
Equation B (n=59)	+1.2	-19.4 to +21.7	41.1	Downsloping	Equation B tends to overestimate the CMR LVEF at lower LVEFs and underestimate the CMR LVEF at higher LVEFs.
Equation H (n=59)	+0.8	-20.2 to +21.9	42.1	Downsloping	Equation H tends to overestimate the CMR LVEF at lower LVEFs and underestimate the CMR LVEF at higher LVEFs. The slope of the regression line is less than Equation B probably due to the use of D=-1 in Equation H which makes it more reliable for those with lower LVEFs.
Equation L (n=59)	+1.5	-22.3 to +25.3	47.6	Horizontal	Equation L produces an LVEF that is on average 1.5% units higher than CMR and this is consistent across the range of LV function/LVEF but with the widest 2SD range.
TTE Simpson's LVEF (n=48)	-3.9	-21.5 to +13.7	35.2	Downsloping	TTE produces an LVEF that is on average -3.9% units below that of CMR. The regression line demonstrates that this is proportional to the LVEF so that the TTE underestimate is more pronounced the higher the LVEF, and indeed may tend to overestimate the LVEF at very low LVEFs.

SD, Standard deviation.

The categorical assessment of the percentage of cases that are concordant with CMR LVEF heart failure grouping also favours the TTE Simpson's Biplane LVEF method, demonstrating the highest concordance at 65% (Figure 78).

Figure 78. Comparison of equation and TTE Biplane LVEF performance with CMR LVEF according to concordance with heart failure grouping.

Method of LVEF	Number of cases concordant with CMR heart failure grouping (normal, mild, moderate or severe)	Total number of cases	Percentage concordance with CMR heart failure grouping
Equation B	33	59	56%
Equation H	34	59	58%
Equation L	36	59	61%
TTE Simpson's	31	48	65%

Whilst TTE Simpson's Biplane LVEF may underestimate CMR LVEF by 3-4% this phenomenon is now increasingly recognised amongst cardiologists. With this in mind, the fact that the standard deviation range is much smaller and categorical heart failure groupings superior than any of the RWMSI equation results, it is reasonable to conclude that the Simpson's Biplane LVEF should be used in preference to all of the RWMSI equations for an echo assessment of LVEF. If this is not possible due to poor endocardial definition etc then Equation L (RWMSI (D=-1) x 35 + 2) should be used as the preferred RWMSI equation due to its superior performance in the categorical assessment of the heart failure groups and it's consistent similar representation of CMR LVEF across the range of LVEFs. However, it should be borne in mind that this equation has a wide standard deviation associated with it.

Q8. How does routine CMR affect the understanding about the underlying aetiology for the heart failure?

a) What is the frequency of ischaemic versus non-ischaemic aetiology pre versus post CMR?

b) Can the presence and degree of subendocardial LGE reliably predict CAD on angiography in a retrospective cohort?

c) What is the prevalence and degree of non-subendocardial LGE in the heart failure cohort?

As previously described in the section exploring the impact of CMR to understand the underlying aetiology, the presence of subendocardial LGE reflects infarcts in 42% of the HFREF subgroup, 20% of the HFPEF subgroup and 40% of the HFNMSD subgroup. However, in the majority of the prospective cohort invasive coronary was not performed to corroborate or refute these CMR findings, or to establish whether significant coronary artery disease can be present despite the absence of subendocardial LGE.

The degree of LGE was not explored in the above analysis and the expectation would be that there would be more in those where the LVEF is reduced (i.e. the HFREF cohort) to account for the significant LV impairment. This comparison is explored in Figures 79 below, using the cohort of 101 patients that had a CMR and consented to their data being used (consort Figure 42), and demonstrates that the average LGE score of those with LGE is highest in the group with HFREF, followed by the HFPEF and HFNMSD respectively. Student's t tests were performed to observe if there was a significant difference in the LGE score between the HFREF versus HFPEF groups and thereafter the HFPEF versus HFNMSD groups in only those cases where LGE was present (Figure 80-81). The difference between the HFREF and HFPEF and thereafter the HFPEF and HFNMSD group was not statistically significant.

Figure 79. HFREF vs HFPEF and HFNMSD: the presence, location and amount of LGE.

Diagnosis	Number in Group	Presence of LGE (any distribution)			LGE present (predominantly subendocardial)		LGE present (predominantly non-subendocardial)	
		Total Number	Average LGE score of all data	Average LGE score of those with LGE	Total Number	Average LGE Score	Total Number	Average LGE Score
HFREF	61	33	2.615	4.833	25	5.800	8	1.813
HFPEF	25	7	0.600	2.143	4	2.250	3	2.000
HFNMSD	15	7	0.923	1.714	6	1.917	1	0.500
Total	101	47	1.884	3.968	35	4.729	12	1.750

HFREF, Heart failure with reduced ejection fraction; HFPEF, Heart failure with preserved ejection fraction; HFNMSD, Heart failure with no major structural disease; LGE, Late gadolinium enhancement.

Figure 80. Comparison of LGE score between HFREF and HFPEF groups (when LGE present).

	Diagnosis	N	Mean	Std. Deviation	Std. Error Mean
LGE Score	HFREF	33	4.8	3.9	0.69
	HFPEF	7	2.1	2.0	0.76

Student's t test (independent variables, 2-sided), P =0.092 NS

Figure 81. Comparison of LGE score between HFPEF and HFNMSD (when LGE present)

	Diagnosis	N	Mean	Std. Deviation	Std. Error Mean
LGE Score	HFPEF	7	2.1	2.0	0.76
	HFNMSD	7	1.7	1.6	0.61

Student's t test (independent variables, 2-sided), P =0.671 NS

Further similar analysis was performed for the subgroups of subendocardial LGE and non subendocardial LGE but there was no statistical difference in the LGE score. It is noteworthy however that although there is more subendocardial LGE in the HFREF group compared with the HFPEF group the opposite is true of non subendocardial LGE which would be in keeping with a fibrotic infiltrative mechanism of pathology in the HFPEF group.

LGE CMR to predict prognostic coronary artery disease

The aim in this analysis was to assess whether the absence of subendocardial LGE could reliably exclude prognostic CAD in a population with LV systolic dysfunction. In order to get a large enough dataset, it was performed on the retrospective cohort of 116 people who had undergone both CMR and invasive angiography and who had an LV ejection fraction (LVEF) <50% or LV end-diastolic volume index (LVEDVI) ≥ 97ml/m^2 on CMR, or with a previous echocardiogram suggesting LV systolic impairment for which CMR had been requested to further differentiate the cardiomyopathy. The consort diagram referring to this group can be revisited in Figure 17.

A definition of prognostic coronary disease at angiography was:

- LMS ≥ 50% stenosis

- Proximal LAD ≥ 75% stenosis

- Two or three vessel disease with ≥ 70% stenosis of a main epicardial vessel (defined as main LAD or large secondary branch, main LCx or large secondary branch or main right coronary artery excluding branches)

This was applied to the X-ray angiogram reports so that two groups were established: those with prognostic CAD and those without. The presence or absence of subendocardial LGE was determined from the CMR report and two groups were established: those with subendocardial LGE and those without. A subendocardial LGE Total Score was calculated for each scan with a view to evaluating whether the total amount of LGE could help predict the likelihood of prognostic CAD in positive CMR scans. A value of 1 was given for one AHA segment with 50 to100% transmural enhancement, and 0.5 for one AHA segment with <50% transmural enhancement. A maximum score of 17 would represent transmural LGE in every AHA segment.

The baseline characteristics are shown in Figure 82. Mean age was 64 years and 78% were male. Mean LVEF was 40% and LVEDVI 114ml/m^2. The indication for CMR was varied, with the majority (79%) investigated for heart failure or myocardial viability.

History of previous myocardial infarction was generally unknown but those with previous revascularisation were excluded.

Figure 82. Baseline Characteristics of the retrospective cohort, differentiated by the presence or absence of prognostic coronary artery disease.

Characteristic	Entire Group	Prognostic CAD present	Prognostic CAD absent
Number of patients (%)	116 (100%)	55 (47%)	61 (53%)
Age (SD)	64 (± 9)	67 (± 8)	61 (± 10)
Male Sex (%)	90 (78%)	47 (86%)	43 (71%)
Median time between investigations (days)	42	41	44
CMR performed before X-ray angiogram (%)	48 (41%)	17 (31%)	31 (51%)
Indication for CMR (%)			
Heart Failure/Viability assessment	92 (79%)	43 (78%)	49 (80%)
Suspected ischaemia	14 (12%)	11 (20%)	3 (4.9%)
VF/VT	3 (2.6%)	1 (1.8%)	2 (3.3%)
Troponin positive chest pain	4 (3.4%)	0	4 (6.6%)
Valve disease assessment	2 (1.7%)	0	2 (3.3%)
LVH	1 (0.9%)	0	1 (1.6%)
CMR LVEF (%) (SD)	40% (12)	41% (11)	39% (14)
CMR LVEDVI (ml/m^2) (SD)	114 (31)	116 (33)	112 (30)
Subendocardial LGE present (%)	89 (77%)	55 (100%)	34 (56%)
LGE Total Score (mean of all scans) (SD)	4.1 (3.5)	6 (2.7)	2.4 (3.2)
LGE Total Score (mean of scans with LGE present) (SD)	5.3 (3.0)	6.0 (2.7)	4.3 (3.2)

CAD, Coronary artery disease; CMR, Cardiac magnetic resonance; VF/VT, ventricular fibrillation/ventricular tachycardia; LVH, Left ventricular hypertrophy; LVEF, Left ventricular ejection fraction; LVEDVI, Left ventricular end-diastolic volume indexed to body surface area; LGE, Late gadolinium enhancement; SD, standard deviation. The maximum LGE Total Score = 17 if all segments are transmurally infarcted.

Median time between CMR and angiogram was 42 days and in 41% of cases the LGE CMR was performed before the X-ray angiogram. The diagnostic performance of LGE CMR to predict prognostic CAD is demonstrated in Figure 83 and 84. The prevalence of prognostic CAD was high at 47% (95% CI 38 to 57%). The presence of ≥1 segment of subendocardial LGE detected prognostic CAD with a sensitivity of 100% (95% CI, 92 to 100%). This meant there were no false negative results in this cohort with a high prevalence of prognostic CAD. For any particular negative test the probability of a false negative result is 0 to 16%. Specificity was low at 44% (95% CI 32 to 57%) with a false positive rate of 38% (95% CI 28 to 49%) but this reflects the large number of people with single vessel disease sufficient to cause an infarct, yet insufficient to justify prognostic CAD.

Figure 83. Diagnostic performance of LGE CMR to predict prognostic CAD.

		X-ray angiogram		Total
		Prognostic CAD present	Prognostic CAD absent	
CMR	Subendocardial LGE present	55 (TP)	34 (FP)	89
	Subendocardial LGE absent	0 (FN)	27 (TN)	27
	Total	55	61	116

CAD, Coronary artery disease; CMR, Cardiac magnetic resonance; LGE, Late gadolinium enhancement; TP, True positive; FP, False positive; FN, False negative; TN, True negative.

Figure 84. Diagnostic parameters of LGE CMR to predict prognostic CAD.

	Performance of LGE CMR (95% Confidence Interval)
Prevalence of prognostic CAD	47% (38 to 57%)
Sensitivity	100% (92 to 100%)
Specificity	44% (32 to 57%)
Positive Predictive Value	62% (51 to 72%)
Negative Predictive Value	100% (84 to 100%)
Probability of False Negative	0% (0 to 16%)

LGE CMR, Cardiac magnetic resonance with late gadolinium enhancement sequences; CAD, Coronary artery disease.

The sub-analysis of those with false positive LGE CMR investigations is demonstrated in Figure 85. Over half of these 34 cases (18 patients, 53%) had single vessel CAD severe enough to explain the infarct shown on LGE CMR (14 with ≥ 90% stenosis and 4 with less severe disease but the combination of the clinical history and CAD providing justification for an infarct). Out of the remaining 16 cases, three had LGE in a distribution in keeping with an infarct and seven had LGE in a non-infarct or multiple territory distribution, or only a single AHA segment. All of these patients had normal coronaries or only minor CAD. The predominant differential diagnosis for this group includes true myocardial infarction with recanalization of an occluded artery, coronary spasm, microvascular disease or emboli featuring as likely culprits, or alternatively, infiltrative diseases such as cardiac sarcoid. There were six cases where the presence of subendocardial LGE was dubious and probably not real in light of the X-ray angiogram findings and clinical presentation.

The mean LGE Score for those with LGE and with prognostic CAD (6.0, SD 2.7) was compared with the mean LGE Score for those with LGE but without prognostic CAD (4.3, SD 3.2) using the Mann-Whitney U Test. This demonstrated a significant difference between the LGE Scores (p=0.007) suggesting that those with smaller LGE scores may be less likely to have prognostic CAD. Indeed the 16 cases with LGE but normal or only minor CAD had a mean LGE Score of only 1.9 (SD 1.4).

In the remaining group of 27 patients with true negative results, i.e. non-prognostic coronary disease and no subendocardial LGE, LGE in a midwall or epicardial pattern was seen in 56% of patients (15 patients). Proposed aetiology for the cause of cardiomyopathy in this groups included idiopathic dilated cardiomyopathy, myocarditis, cardiac sarcoid, ARVC with LV involvement and vasculitis. In one of these cases there was 100% occlusion of a coronary artery at X-ray angiography but no evidence of an infarct on LGE CMR. In this case of mid RCA occlusion, the LGE CMR was performed four months before the X-ray angiogram. In the interim period the patient developed exertional chest pain followed by an episode that would be in keeping with a myocardial infarction clinically, and could explain the discrepancy between the imaging studies.

The absence of subendocardial LGE reliably excluded prognostic CAD in a population with LV systolic dysfunction with no false negative results. This is a reassuring demonstration of how CMR scanning using gadolinium late enhancement protocols, without proximal coronary artery imaging, can be used as a screening tool to exclude prognostic CAD and avoid unnecessary invasive X-ray angiography in patients with LV systolic dysfunction.

The high false positive rate of 38% for LGE CMR can be explained by significant single vessel CAD in over half of the cases. Thereafter, in some of the remaining false positive cases a myocardial infarction may be the cause of the LGE but without demonstrable CAD on X-ray angiography. The total LGE Score may aid as a helpful indicator of whether prognostic or indeed any significant CAD will be present on X-ray angiography but requires further investigation.

Figure 85. Case analysis of False Positive Results.

Assessment of False Positive Cases	Numbers	Imaging and clinical details
	(% of FP group)	AHA 17 segment model: Black = subendocardial LGE. Half-filled segments < 50% transmural. x = not described. Grey differentiation according to different coronary territories:
		☐ LAD territory, ☐ RCA territory, ■ Cx territory
		Outer numbers represent maximum % stenosis of main vessel supplying that territory
X-ray angiogram CAD ± clinical history suggest MI in area of LGE		All cases had LGE predominantly in the territory supplied by the diseased single vessel
Single main vessel CAD ≥ 90% stenosis	14 (41%)	
CAD in coronary territory (but <90% stenosis of main relevant vessel) ± clinical history suggestive of MI	4 (12%)	

a) History of chest pain suggestive of MI 3 months earlier.
b) Suggestion of a stenosed OM3 vessel at X-ray angio in left dominant system.
c) Delayed presentation with chest pain and ECG consistent with inferior STEMI. Anomalous RCA origin with moderate diffuse mid RCA disease on angiogram.
d) 50% LAD stenosis. Prosthetic MVR in situ with mitral regurgitation.

Convincing LGE predominantly in coronary artery distribution to suggest an infarct. CAD not in keeping with this.	3 (9%)	 e) f) g)
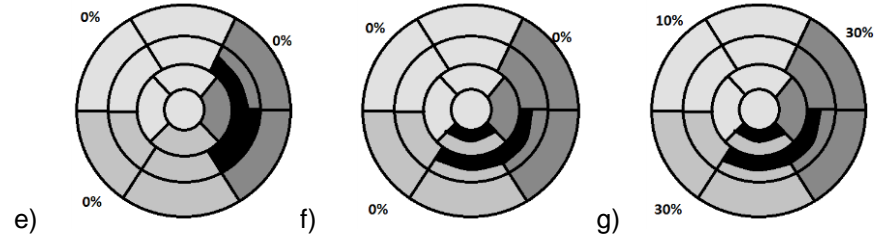
e) Troponin positive chest pain. Convincing LGE in LCx. Normal coronaries.
f) Convincing LGE in posterolateral wall and associated RWMA. Normal coronaries. In AF.
g) Dilated cardiomyopathy. LBBB. RWMA in area of LGE. Mildly atheromatous proximal LCx with slow flow and distal LCx disease with very small OM.

Convincing subendocardial LGE in non-infarct distribution, multiple territories, or only a single AHA segment	7 (20%)	 h) i) j) k)

l)   m)   n)
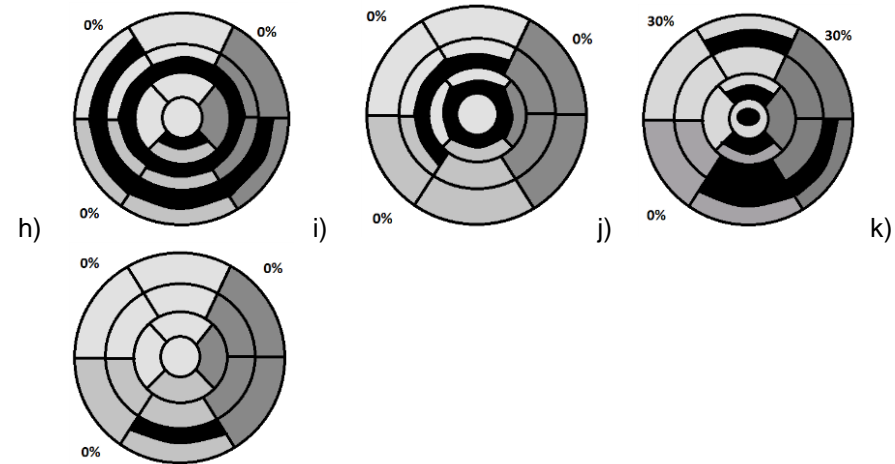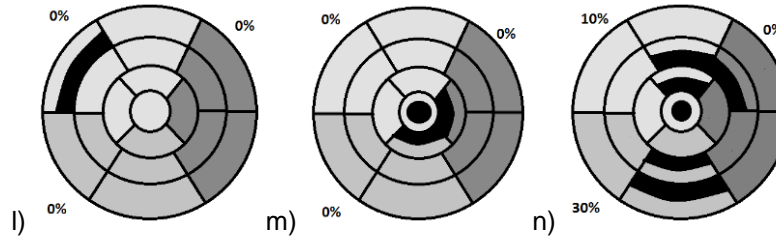
h)   Extensive convincing LGE in multiple territories with normal angiogram.
i)   Convincing subendocardial LGE in all coronary territories. Normal coronaries.
j)   Troponin positive chest pain. Inferior wall RWMA. LGE affecting RCA territory in particular but also isolated patch in LAD and LCx territory. Normal coronaries.
k)   LBBB and dilated cardiomyopathy with chest pains. Wall thinning in area of LGE.
l)   Dilated cardiomyopathy. LGE not associated with RWMA. Normal coronaries.
m)   Dilated cardiomyopathy with atrial fibrillation. RWMA in area of LGE.
n)   Troponin positive chest pain. Subendocardial LGE in anterior and inferior walls.

Dubious subendocardial LGE	6 (18%)

FP, False positive; CAD, Coronary artery disease; CMR, Cardiac magnetic resonance; LGE, Late gadolinium enhancement; MI, Myocardial Infarction; AHA, American Heart Association; LAD, Left anterior descending artery; LCx, Left circumflex vessel; RCA, Right coronary artery; OM, Obtuse marginal vessel; RWMA, Regional wall motion abnormality; AF, Atrial fibrillation; LBBB, Left bundle branch block; STEMI, ST segment elevation myocardial infarction; ECG, Electrocardiograph; MVR, Mitral valve replacement

Discussion

Main findings and conclusions

The aim of this study was to differentiate the demographics and imaging characteristics of a heart failure population using a comprehensive transthoracic echo protocol and routine cardiac magnetic resonance (CMR) imaging, and to assess the clinical value of routine CMR in this population.

This study shows that heart failure with preserved ejection fraction (HFPEF) is not the epidemic previous literature would have us believe. It is over-diagnosed in current practice due to lax definitions and inappropriately low left ventricular ejection fraction (LVEF) cut-offs.

The ratio of heart failure with reduced ejection fraction (HFREF) to HFPEF alters substantially when different LVEF thresholds are employed. In light of validated normal ranges, this study insisted that a LVEF threshold of <55% would be diagnostic of HFREF. In doing so it demonstrated that HFREF occurred in 73% of heart failure cases whereas HFPEF accounted for only 14% of cases. This is vastly removed from current perceptions about a 50:50 split and whilst recognising that HFPEF is not uncommon, it is not be the epidemic it was previously portrayed as.

CMR has a substantial impact on the diagnostic profile of the heart failure population. In this study, incorporating CMR into the routine assessment of newly diagnosed heart failure patients changed diagnoses in 22% of cases (14% of cases for those who had an echo performed on the same day). Firstly, this study demonstrates that CMR LVEF averages 3.9% units higher than Simpson's Biplane LVEF with echo and diagnoses of HFREF will be inadvertently revoked if modality specific normal ranges are not taken into account. However, even if one were to use the method specific LVEF cut-offs to diagnose HFREF (i.e. <55% for echo and <57% for CMR) there is still a discernible impact of routine CMR on the diagnostic profile of the heart failure community. In general CMR revokes the diagnosis of HFREF, and does so to a greater extent than is accounted for by the temporal improvement in LVEF whilst waiting for the CMR scan.

Six of the 66 individuals who had an echo and CMR on the same day had their diagnosis of HFREF revoked by a CMR. In 5 of these 6 cases this change in diagnosis would have been upheld when applying imaging modality specific LVEF normal ranges. This represents the true impact of CMR on the diagnostic profile of a heart failure community out with discrepancies due to temporal changes and modality specific normal ranges. The presence of ectopy may contribute to different results between the different imaging

modalities but again does not fully explain the discrepancy and thus intrinsic, non-definable, investigation specific factors also seem to be at play. It seems from this analysis that the CMR scan does indeed have an added impact on the diagnosis, above and beyond what echo imaging can offer. Whether this justifies the routine use of CMR in the setting a heart failure clinic can be debated, but a full economic assessment would be warranted as part of this process, and is out with the scope of this thesis.

Attempts to identify a superior comparator by way of regional wall motion scoring index (RWMSI) LVEF in this analysis was fruitless, the conclusion being that a Simpson's Biplane assessment of LVEF is superior to any of the RWMSI equations tested. This said, where Simpson's Biplane LVEF is not possible due to poor endocardial definition, then the Equation "RWMSI (D=-1) x 35 + 2" should be used as the preferred RWMSI equation, bearing in mind a wide standard deviation associated with it.

CMR with LGE has the additive clinical value of confirming or refuting infarcts, and thereafter determining viability. This is an attribute confined to CMR and is beyond the diagnostic capabilities of echo. The presence of subendocardial LGE in this study suggest infarcts in 42% of those with HFREF, 20% of those with HFPEF, and 40% of those with heart failure with no major structural disease (HFNMSD). It identifies infarcts in a sizeable number of patients for whom there was no suspicion of ischaemic heart disease (IHD) and raises the novel concept that ischaemia may account for symptoms in many of those with HFNMSD. It also demonstrates an impressive ability to exclude prognostic coronary disease whereby the absence of subendocardial LGE excluded prognostic coronary disease in 100% of cases. In HFPEF and HFNMSD patients, the identification of infarcts might reasonably be expected to change further management and treatment. Whilst at present this would not be not be the case in the HFREF population, it does provide diagnostic information as to the underlying cause of the LV impairment.

LGE in a non-subendocardial distribution was prevalent in both the HFREF and HFPEF community but with a greater average burden in the HFPEF group and may support the postulated fibrotic infiltrative mechanism of pathology in this group. Additionally, LGE in a non-subendocardial distribution established aetiology including myocarditis and sarcoidosis that were not detected with echo alone. Furthermore, CMR visualises the endocardial borders and cardiac apex with better clarity than transthoracic echo, and in this study resulted in a diagnosis of apical hypertrophic cardiomyopathy that would have otherwise gone undetected.

A number of characteristics differ significantly between the HFREF and HFPEF groups, supporting the theory that the diseases represent distinct pathological entities. Similar

to other published literature, those with HFPEF were older, and more often diabetic, hypertensive and with permanent atrial fibrillation. There was also a trend towards more females in the HFPEF community. Those with HFREF were more likely to have LBBB and were also more likely to have had a previous hospital admission with heart failure than those with HFPEF. Interestingly however, identical Minnesota scores suggest that both groups have a similar subjective experience of their symptoms and impact on their quality of life. Similar BNP levels between the groups also give credence to this HFPEF community having symptoms as a result of cardiac disease.

Experts that believe that symptoms in a HFPEF community are due to non-cardiac causes (e.g. COPD and obesity) may have been misled by older studies with lax defining HFPEF criteria. A key feature of this study was that there were strict defining criteria for HFPEF. This included a requirement for echo evidence of elevated LV diastolic pressures or elevated biomarkers +/- diastolic dysfunction, as opposed to simply the absence of a reduced ejection fraction. Those with non-cardiac causes for their symptoms should have been better weaned out, leaving a purer HFPEF community. This is reflected in the fact that rates of COPD and raised BMI are similar between the HFREF and HFPEF groups and that the mean BNP was lower for the group deemed not to have heart failure than that of the HFREF and HFPEF groups. Interestingly, the mean Minnesota questionnaire score was higher in the group deemed not to have heart failure (48 versus 40.7 for both the HFREF and HFPEF groups), reflecting a subjective feeling of a poorer quality of life in this subset of people.

Whilst some may argue that all those with clinical heart failure but preserved ejection fraction should be labelled as HFPEF (negating the need for a detailed echo), 6 of the 21 deemed to have heart failure clinically, but with a normal LVEF following the second echo, did not have sufficient abnormalities to support a diagnosis of heart failure according to this inclusive diagnostic framework and the difference in HFPEF population demographics between this cohort and others' series adds weight to justifying a set of positive diagnostic criteria.

The diagnosis of HFPEF is not standardised and all current protocols are deficient. Exploration and analysis of such measures in the prospective cohort demonstrated that E/e' and left atrial volume index (LAVI) were the most helpful echo measures to aid decision making about a diagnosis of HFPEF in that both could be measured in well over 90% of cases, are applicable in those with atrial fibrillation (a common finding in the HFPEF community), are not age dependent, and are not subject to the pseudonormalisation phenomenon that affects other parameters. Pulmonary vein Dopplers have been increasingly advocated as a useful tool for the diagnosis of HFPEF

but in this cohort they were achievable in less than three quarters of echo scans and thereafter, the well reported Ard-Ad was of no diagnostic value in any cases. Left ventricular mass was also unhelpful in that it could only be obtained in 76% of cases and positively contributed to the diagnosis in only one situation. The E/A ratio in combination with deceleration time (DCT) were never supportive of a diagnosis of HFPEF. Overall E/e', BNP, the presence of atrial fibrillation and left atrial volume index were the key components to the diagnosis of HFPEF.

The cause and mechanism of HFPEF remains unclear and this study helped clarify the contribution of systolic versus diastolic dysfunction versus simply the presence of atrial fibrillation. The prevalence of systolic dysfunction in this HFPEF cohort with an LVEF ≥55% was 76% (19 of 25 cases), with most cases having 3-10 simultaneous measures supporting systolic dysfunction. Diastolic dysfunction is also a common finding in those with HFPEF, and in general the grade of this dysfunction is worse than that in the HFNMSD cohort. However, there appears to be significant limitations to current diastolic grading protocols whereby many cannot be classified due to conflicting results, limiting the applicability of such protocols in daily practice.

Three quarters of those deemed "not heart failure" by the clinician after the initial consultation had symptoms of dyspnoea or peripheral oedema. Of these, one patient had mildly reduced LVEF and at least 25% would have met the diagnostic criteria for HFPEF with only 4 patients having a BNP < 35pg/ml, normal ECG and entirely normal echo. Such findings suggest that clinicians are not as good at correctly excluding heart failure by clinical assessment as they think and perhaps there should be more reliance on imaging for diagnostic exclusion. Equally, in the 101 individuals that went on to have a CMR, 15 were finally labelled as HFNMSD also supporting the fact that clinical diagnosis of heart failure has limitations when compared with resting imaging. In this latter group of "false positives" however, there is the potential that this imaging strategy is sub-diagnostic for HFPEF due to a lack of an exercise assessment of cardiac function and haemodynamic parameters. The other real possibility is that angina as opposed to heart failure could explain their symptomatology in a number or all of these cases.

Perhaps heart failure should be identified by the presence of markers that demonstrate a failing heart such as clinical signs (of pulmonary oedema or pedal oedema) raised biomarkers, and elevated left ventricular end diastolic pressure or pulmonary venous pressures at rest or on exercise. Thereafter the cause should be classified by the cardiac abnormality or abnormalities and thence suspected underlying aetiology. The absence of an abnormality should not be a defining feature, so that HFPEF would no longer be a valid diagnosis. Identifying the absence of a pathology in a failing heart is ultimately not

useful for explanations or management strategies which require inclusive criteria. Such a strategy enables the physician to become indifferent in their appreciation for the alternative causes of the heart failure, and fosters a lackadaisical attitude to identifying and exploring them in more detail.

Instead I propose a diagnostic framework that describes the causes of heart failure as:

1) Heart Failure due to LV systolic dysfunction with reduced ejection fraction (due to ischaemic heart disease, "dilated cardiomyopathy", etc)

2) Heart Failure due to LV systolic dysfunction with preserved ejection fraction

3) Heart Failure due to primary LV diastolic dysfunction

4) Heart Failure due to valvular disease (isolated or mixed)

5) Heart Failure due to another specified structural disease (e.g. specified congenital heart disease)

6) Heart failure with no major structural disease

Limitations of the results and study design

Much of the analysis was performed on data collected prospectively with the robustness that this brings.

Despite comprehensive planning there were circumstances where data were not measured, collected or recorded as robustly as initially proposed but these were generally identified early because of continuous appraisal of the data and as such these problems were rectified early. A specific example includes BNP levels not being taken on the clinic blood test and so a new blood form was created for each patient with BNP requested, along with a comment to include a separate bottle for the test. In most situations there did not appear to be a specific factor that could result in biased data.

The initial echo was often performed prior to patients attending the heart failure clinic and as such the majority of these patients had an eyeball visual assessment of the LVEF according to normal, mild, moderate or severe groupings rather than a Simpsons Biplane assessment. This limits comparison between the first echo and subsequent imaging to some extent, although a qualitative grading of mild, moderate or severe impairment does represent a narrow numerical range of LVEF for comparison.

It was impossible to obtain the information about changes in drugs between initial and follow-up imaging as drug lists at the time of CMR or follow-up echo were not recorded. Subsequent clinic attendance varied from weeks to months after the repeat imaging and drug titration regimes were not clearly defined in follow-up letters to allow for accurate assessment of drug changes. Whilst it would be interesting to assess if improvements

in LVEF correlated with heart failure drug titration, small numbers are likely to have prohibited formal statistical credence.

Inter-observer assessment of LVEF was not formally tested as part of this study but has been done so at a departmental level in both the echo and CMR departments in the past for internal validation purposes and no concerns highlighted. As this was a pragmatic assessment of everyday practice, a formal assessment of inter and intra-observer variability in scan recording and reporting was not performed but the potential limitations of not doing so are acknowledged. This similarly applies to the angiogram analysis, which was performed by a single Consultant, (although the Consultant reporting would differ with differing scans).

The cohort of patients attending the heart failure clinic consisted of a high proportion of frail elderly, particularly in the HFPEF cohort. This introduced bias into the consent process whereby the more frail the individual, the less likely they were to attend again and be available for consent. Those with dementia or lacking capacity couldn't be included and even when there wasn't a formal diagnosis of such, general frailty meant that many of the elderly individuals simply didn't want the extra bother of considering what the research involved. With this in mind, the analysis for the overall demographic profile of the heart failure community was done on the entire population, hopefully avoiding such biases. Thereafter, the specific imaging analyses were performed only for those where consent was given or data approved for use by the modified research application.

An exercise assessment would have provided a better objective assessment of an individual's exercise capacity as well as allow a more relevant imaging assessment of cardiac function at those times when many patients are most symptomatic. However this was not performed for a variety of reasons. Firstly, many patients were simply too frail to complete a basic six minute walk. This was tried with the first ten patients but concerns for patient safety meant that this was discontinued. Concerns were perhaps exaggerated because the only space available to perform such tests was in the middle of the busy patient clinic or cardiac investigations unit with numerous distractions and with risk of collisions. The lack of adequate space in the hospital environment was frustrating. With regards to exercise during imaging, time limitations, patient frailty, lack of operator experience and lack of exercise bike or pedals on imaging beds meant that this was impossible.

The fact that the CMR was not performed on the day of the heart failure clinic, but instead around six weeks after diagnosis allowed stabilisation of symptoms but introduced a temporal discrepancy between the first echo and CMR. This was overcome in those that

went on to have a second echo on the same day as the CMR but numbers were more limited.

Not all those diagnosed with heart failure went on to have a CMR. Only 101 of the 166 patients did so. The reasons for not proceeding with a CMR were varied ranging from claustrophobia, general frailty, contraindications e.g. pacemaker, end stage renal failure or other reasons that meant the physician felt that the scan would not be tolerated, but may result in a select group proceeding with the CMR investigation.

Those thought not to have heart failure but with pedal oedema or raised BNP etc were discharged without CMR. The initial suggested protocol had indicated that such people be scanned but when this was put into practice the clinician was so confident to exclude the diagnosis of heart failure that they felt it unnecessary to obtain a CMR scan. However, this is a very interesting group of patients where clinician impression may be surpassed by imaging results, and CMR scanning in this cohort would have been interesting and informative.

Regarding the creation of an optimal RWMSI equation to accurately reflect the CMR LVEF, many of the limitations have been discussed in the relevant results section above. Firstly, the RWMSI equation was formulated from CMR images as opposed to echo images. It was only later in the prospective cohort where echo images were used to create the RWMSI LVEF. Whilst it was a false pretence to substitute CMR for echo imaging for the equation creation, theoretically there shouldn't be a difference in the depiction of regional wall function between the two modalities, but this cannot be completely excluded. Concerns about a ceiling or floor effect that might skew the analysis meant that the data were reanalysed on a subset excluding those that might be affected but this reduced the sample size to 160 subjects. Semi quantitative data versus quantitative data posed statistical analysis difficulties as previously discussed and as such some statistical methods had to be abandoned.

With regards to the analysis of whether subendocardial LGE could exclude prognostic CAD in a population with LV systolic dysfunction, this cohort was retrospectively collected and analysed and the results should be interpreted with this in mind. Although the CMR and X-ray angiogram scans were reported independently of each other there was no formal blinding process. The cohort all had imaging evidence of reduced LVEF or LV dilatation and identification of the cause of heart failure or a viability assessment was the predominant reason for CMR referral. As such, the group characteristics are likely to reflect that of a newly diagnosed heart failure population with LV systolic dysfunction with the exception of any bias that led to X-ray angiography being requested universally in this study group. In this regard, the high prevalence of prognostic CAD is

not reproduced by other groups that observed all newly diagnosed heart failure patients, and so does suggests that some bias for X-ray angiogram referral may be at play. These high prevalence rates of prognostic CAD will result in better negative predictive values than populations with lower rates of prognostic CAD and this should be borne in mind when extrapolating the results. There remains the theoretical concern that significant coronary disease might cause a hibernating myocardium but without fibrosis or LGE. Alternatively non-ischaemic causes of cardiomyopathy can result in fibrosis and LGE in a subendocardial distribution that might raise concerns about the presence of significant CAD where there is none. Both of these scenarios have been demonstrated in trials to date and might result in unacceptable levels of false positive or false negative results, although in practice these scenarios seem to be rare.

There is no standard definition for significant CAD amongst the LGE CMR studies. The definition for prognostic CAD in this study is based on current guidelines and respected trial data. It did not incorporate single vessel disease and used lower cut-offs for two or three vessel disease than other trials with prognostic like definitions ($\geq$70% stenosis of > 1 main epicardial coronary artery as opposed to $\geq$75% stenosis). Each definition brings a different clinical implication to the sensitivity results. Defining ischaemic cardiomyopathy using single vessel disease may be less reliable and prone to bystander disease than multi-vessel disease. Additionally, the argument to identify single vessel disease to make changes to medical management by way of antiplatelet and lipid lowering therapy is contentious in a heart failure population. Although indications for revascularisation in heart failure are also debatable, defining significant CAD using a prognostic approach would be more relevant to future management. Whilst acknowledging that the visual grading of vessel stenosis on X-ray angiography does not incorporate a functional assessment of the stenosis, isolated X-ray angiography continues to be employed to grade CAD in daily clinical practice, justifying it as the comparator, especially in a screening tool setting.

Previous groups that have shown moderate ability of LGE CMR to detect CAD used diagnostic thresholds for significant CAD that were less severe than our study and included non-prognostic single vessel disease. It is entirely plausible that such lesser degrees of CAD may not have had a functional impact on cardiac function accounting for the lower sensitivity of LGE. Those with 100% sensitivity have been in cohorts with confirmed myocardial infarctions or have included CMR proximal coronary artery imaging in the protocol. This is the first known study to compare LGE CMR without proximal coronary artery imaging with prognostic CAD.

Applicability of the results: translation into clinical practice

This is a single centre study and incorporates the inherent limitations and potential for bias that this brings. The population is localised to the county Durham and Darlington area with the patient specific characteristics influenced by this locality. Despite this, the locality is large with a diverse population from a variety of socioeconomic backgrounds and probably representative of general heart failure populations across the United Kingdom. The physicians identifying and managing the patient cohort are all part of the same team and subject to similar policies, procedures, and way of working that may differ in other institutions. This also applies to the other members of the clinical and imaging team. Despite this, there is more than one physician involved in the diagnosis and management of the patients and they do so according to national policy and guidelines, as well as the standardised study diagnostic protocol based upon international consensus and best evidence. The echocardiographers have all undergone nationally approved and accredited training and examination and continue to be members of the British Society of Echocardiography requiring continued reaccreditation and national meeting attendance. CMR image acquisition takes place on a GE scanner whereas many other centres may use a Phillips or Siemens machines however, image acquisition is similar across the range of CMR machines. Reporting of the CMR scans was performed by two Consultants both of whom participate in regular regional CMR meetings for continued professional development and ensuring that reporting habits are consistent with regional colleagues.

The questions posed are extremely clinically relevant and apply to day to day diagnosis and management of patients with heart failure or symptoms suggestive of heart failure. The findings are particularly relevant to a UK population which is steadily increasing in average age, with the need for a better understanding of HFPEF in particular. The results are also particularly relevant to UK cardiology practice which has a steadily increasing CMR workload with demands from commissioners to demonstrate clinical effectiveness and cost benefit.

Reflections on the questions considered, Were the aims and objectives met and question answered?

The main rationale for this study was to identify whether incorporating routine CMR, alongside comprehensive echocardiography, into the initial screening of patients with heart failure could provide clinically important information to complement basic echocardiography findings. In this regard essentially all of the specific sub-questions for this study have been investigated and answered.

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It has demonstrated epidemiological information to refute the current presumed spectrum of pathology in the heart failure population and explored the reasons behind different prevalence data. It has demonstrated how a comprehensive HFPEF diastolic framework can be applied, how its' application affects the profile of the heart failure community and established which parameters are the most useful to confirm a diagnosis of HFPEF. It has established how many of those given a diagnosis of not having heart failure by a clinician would have met the HFREF or HFPEF diagnostic criteria and identified the prevalence of systolic dysfunction other than reduced LVEF in those with HFPEF. It has shown how CMR can alter diagnosis by reclassifying LVEF in individuals and delved into the comparability of CMR and echo LVEF measures why they may differ. It has also demonstrated how CMR aids the differentiation of the underlying cause of heart failure by way of late enhancement, particularly in the HFREF population. It has demonstrated the predictive value of LGE CMR to detect prognostic CAD in a local cohort. It has clarified that the assessment of LVEF using a regional wall motion scoring index (RWMSI) should not be readily performed. All of the findings have some degree of limitation which has been explored in the individual sections above. The study did not look at whether CMR could clarify some already accepted measures of diastolic dysfunction to aid diagnosis in unclear groups, nor demonstrate novel imaging findings that help to describe heart failure by way of new defining criteria. In this regard it became apparent that this was too ambitious a goal that would require new CMR techniques never applied by the CMR radiographers and as such it was abandoned. However, recognising these limitation and exceptions, in the main the aims and objectives of this study have been achieved.

Future considerations

A revision in the current diagnostic framework for heart failure should be considered as described above with a focus on positive identification of pathology rather than the absence of pathology as is currently advocated with the HFPEF diagnosis. Thereafter the cause should be classified by the cardiac abnormality or abnormalities and thence suspected underlying aetiology. The threshold for a diagnosis of HFREF needs to be formally agreed by regulatory bodies but I would advocate a cut-off of 55%.

All echo scans for a heart failure indication should incorporate reliable and reproducible indexed left atrial volumes, E/e' measures, an appreciation for left ventricular hypertrophy and other markers of systolic function, (in particular MAPSE, S' and global longitudinal strain) when LVEF is deemed to be normal. Cardiac Magnetic Resonance provides useful additional information to transthoracic echo and there is rationale for this imaging modality to be used in all patients presenting with heart failure to better assess LVEF,

identify or exclude significant underlying coronary artery disease, and identify or clarify underlying aeitiology such as myocarditis, dilated cardiomyopathy, hypertrophic cardiomyopathy, or sarcoidosis etc.

This study has raised important questions for future consideration. The suggestion that coronary artery disease and cardiac ischaemia may be contributing to the presentation and symptomatology of the HFNMSD group in particular is worthy of further investigation. In addition, incorporating a formalised exercise assessment of patients presenting as HFPEF or HFNMSD and assessing left ventricular systolic and diastolic function and haemodynamics during such exercise is of interest. The current assessment of resting parameters alone has readily postulated limitations in a group where exercise limitation is often the main presentation. The influence of the left atrium by way of size but also function is increasingly postulated and better assessment of left atrial haemodynamics including left atrial strain may be important and should be investigated in more detail. There is the potential for CMR T1 mapping in heart failure community in the future and might better explore the postulated fibroinfiltrative mechanism of LV dysfunction in the HFPEF group in particular. A prospective comparison of subendocardial late gadolinium enhancement with invasive coronary angiography (and without the use of proximal CMR coronary angiography) is now necessary to comprehensively advocate the use of contrast CMR to exclude prognostic coronary disease in a heart failure population.

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List of figures

Appendices

Ethical approval documents – CDDFT REC

County Durham and Darlington **NHS**
NHS Foundation Trust

Research and Development Department
Darlington Memorial Hospital
Pierremont Unit
Hollyhurst Road
Darlington
DL3 6HX

Tel: 01325 743458

All studies are subject to the requirements of the DoH's Research Governance Framework 2005 Second Edition and subsequent amendments. If you have not read this document, or are unfamiliar with its contents you are strongly advised to refer to it before commencing with any research or data collection. You may not commence data collection until you have written formal authorisation from the Chair of the Research Review Board and an appropriate ethics committee.

08 October 2013

Ethics Committee

Dear Ethics Chair

Re: An Enhanced Clinical Heart Failure Service (Research Database)
MED-271-2013

Please find enclosed the above titled study for Ethics Review as evidence of IRAS Question A54. This project has been through the Trust's peer review process and has been given provisional approval by the Trust's Research Review Board. We have enclosed copies of correspondence for your information.

If you have any further queries please contact the R&D Office.

Yours sincerely

Professor Y Yiannakou
Chair – Research Review Board

Enc.

with you ❤ all the way

4 - Trust Support Letter.doc

Ethical approval documents – Durham University

Durham
University
School of Medicine,
Pharmacy and Health

Shaped by the past, creating the future

Dr David Ekers
Clinical Senior Lecturer
Chair, School of Medicine, Pharmacy and Health Ethics Sub-Committee

Dr Alexandra Thompson
School of Medicine, Pharmacy and Health
Durham University

12th August 2014

Dear Alexandra

Re: Ethics Application ESC2/2013/04
Cardiac magnetic resonance in heart failure: re-evaluating causes and definitions

Thank you for sending the above application to the School of Medicine, Pharmacy and Health Ethics Committee for ethical review. The project was reviewed at a committee meeting on 20th February 2013. The application has approval from the South Central-Oxford C NRES committee, you have provided confirmation that CDDFT will Sponsor your project and it has approval by the NHS data monitoring committee responsible for the project. I have reviewed this application based upon the recommendations of your previous application and I am satisfied that all suggestions have been attended to. I can therefore confirm Durham University ethical approval for the study.

Approval is given subject to the following:

- That data generated for this study is maintained and destroyed as outlined in this proposal and in keeping with the Data Protection Act.

- If you make any amendments to your study, these must be approved by the School committee prior to implementation.

- At the end of the study, please submit a short end of study report (ESC3 form) to the School ethics committee.

Please do not hesitate to contact me should you have any questions.

Kind regards

David Ekers

Page 1 of 1

Ethical approval documents – NHS HRA NRES Committee

Initial approval document

NHS
Health Research Authority

NRES Committee South Central - Oxford C
Bristol REC Centre
Level 3, Block B
Whitefriars Building
Lewins Mead
Bristol
BS1 2NT
Telephone: 01173 421383
Facsimile: 01173 420455

18 December 2013

Professor Jerry Murphy
County Durham and Darlington NHS Foundation Trust
Cardiology Department
Darlington Memorial Hospital
Darlington
DL3 6HX

Dear Professor Murphy

Title of the Research Database:	**Characterising a newly diagnosed heart failure population**
REC reference:	**13/SC/0594**
IRAS project ID:	**138143**

Thank you for your letter of 16 December 2013, responding to the Committee's request for further information on the above research database and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Manager Lauren Allen, nrescommittee.southcentral-oxfordc@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion of the above research database on the basis described in the application form and supporting documentation as revised.

Duration of ethical opinion

The favourable opinion is given for a period of five years from the date of this letter and provided that you comply with the standard conditions of ethical approval for Research Databases set out in the attached document. You are advised to study the conditions carefully. The opinion may be renewed for a further period of up to five years on receipt of a fresh application. It is

suggested that the fresh application is made 3-6 months before the 5 years expires, to ensure continuous approval for the research database.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Covering Letter		23 October 2013
Covering Letter		05 December 2013
Other: RRB Research Governance Approval Response Letter		08 October 2013
Other: First Clinic Patient Letter	2.0	01 August 2013
Other: 1st Clinic Documentation	2.0	01 August 2013
Other: 3 month Clinic Documentation	2.0	01 August 2013
Other: Chief Investigator CV	2013	28 October 2013
Other: Research Fellow CV	2013	28 October 2013
Other: Letter to GP For Database	Version 1.0	01 December 2013
Other: Standard Operating Procedure for Heart Failure Database Steering Committee	Version 1.0	01 December 2017
Participant Consent Form	Version 3.0	01 December 2013
Participant Information Sheet	Version 3.0	01 December 2013
Protocol for Management of the Database	Version 3.0	01 December 2013
REC application		23 October 2013
Response to Request for Further Information		16 December 2013

Research governance

Under the Research Governance Framework (RGF), there is no requirement for NHS research permission for the establishment of research databases in the NHS. Applications to NHS R&D offices through IRAS are not required as all NHS organisations are expected to have included management review in the process of establishing the database.

Research permission is also not required by collaborators at data collection centres (DCCs) who provide data under the terms of a supply agreement between the organisation and the database. DCCs are not research sites for the purposes of the RGF.

Database managers are advised to provide R&D offices at all DCCs with a copy of the REC application for information, together with a copy of the favourable opinion letter when available. All DCCs should be listed in Part C of the REC application.

NHS researchers undertaking specific research projects using data supplied by a database must apply for permission to R&D offices at all organisations where the research is conducted, whether or not the database has ethical approval.

Site-specific assessment (SSA) is not a requirement for ethical review of research databases.

Health Research Authority

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

Here you will find links to the following:

a) Providing feedback. You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.
b) Annual Reports.   Please refer to the attached conditions of approval.
c) Amendments.   Please refer to the attached conditions of approval.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

13/SC/0594	Please quote this number on all correspondence

Yours sincerely

PP J Muller

Professor Nigel Wellman
Chair

E-mail: nrescommittee.southcentral-oxfordc@nhs.net

Enclosures: *Approval conditions*

Copy to: *Dr Robin Mitchell, County Durham and Darlington NHS Foundation Trust*

Amendments approval document 1

NHS
Health Research Authority

NRES Committee South Central - Oxford C
Bristol REC Centre
Level 3, Block B
Whitefriars Building
Lewins Mead
Bristol
BS1 2NT
Telephone: 01173 421383

30 April 2014

Professor Jerry Murphy
County Durham and Darlington NHS Foundation Trust
Cardiology Department
Darlington Memorial Hospital
Darlington
DL3 6HX

Dear Professor Murphy

Title of the Database:	**Characterising a newly diagnosed heart failure population**
REC reference:	**13/SC/0594**
Amendment number:	**Substantial Amendment 1: 16.04.14**
Amendment date:	**16 April 2014**
IRAS project ID:	**138143**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The Sub-Committee had no objection to the minor changes to the PIS and Consent forms and were also happy for others beyond the research nurses to take consent, providing they are GCP trained and everything is properly recorded. The Sub-Committee were also happy with the home visits and postal consent as long as the data from deceased patients is used anonymously.

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Notice of Substantial Amendment	Substantial Amendment 1: 16.04.14	16 April 2014
Covering Letter		09 April 2014
Protocol for Management of the Database	4.0	15 April 2014
Participant Information Sheet	4.0	15 April 2014
1st Clinic Document	3.0	15 April 2014

A Research Ethics Committee established by the Health Research Authority

Membership of the Committee

The members of the Ethics Committee who took part in the review are listed on the attached sheet.
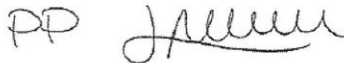
Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

| 13/SC/0594 | Please quote this number on all correspondence |

Yours sincerely

PP *[signature]*

Professor Nigel Wellman
Chair

E-mail: nrescommittee.southcentral-oxfordc@nhs.net

| Enclosures: | *List of names and professions of members who took part in the review* |
| Copy to: | *Dr Robin Mitchell, County Durham and Darlington NHS Foundation Trust* |

Amendments approval document 2

NHS
Health Research Authority
South Central - Oxford C Research Ethics Committee
Level 3, Block B
Whitefriars Building
Lewins Mead
Bristol
BS1 2NT

Telephone: 0207 104 8049

08 September 2016

Professor Jerry Murphy
County Durham and Darlington NHS Foundation Trust
Cardiology Department
Darlington Memorial Hospital
Darlington
DL3 6HX

Dear Professor Murphy

Title of the Database:	An enhanced clinical heart failure service (Research database)
REC reference:	13/SC/0594
Amendment number:	Amendment number 2 (AM02)
Amendment date:	01 August 2016
IRAS project ID:	138143

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Covering letter on headed paper [Further approval request]		10 August 2016
Notice of Substantial Amendment (RD) [IRAS substantial amendment form Aug 2016]	Amendment number 2 (AM02)	01 August 2016
Protocol for management of the database [NHS Protocol, version 5.0 August 2016 changes highlighted]	5.0	11 August 2016

Membership of the Committee

The members of the Ethics Committee who took part in the review are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

13/SC/0594	Please quote this number on all correspondence

Yours sincerely

Pp Professor Nigel Wellman
Chair

E-mail: nrescommittee.southcentral-oxfordc@nhs.net

Enclosures:	*List of names and professions of members who took part in the review*
Copy to:	*Dr Robin Mitchell, , County Durham and Darlington NHS Foundation Trust Confidentiality Advice Team*

Letter to Patients prior to attending clinic

with you ◆ all the way   County Durham and Darlington **NHS**
NHS Foundation Trust

Collection and analysis of routine clinical data on patients with newly diagnosed heart failure

County Durham and Darlington Foundation Trust and run weekly heart failure clinics and all new patients have a number of tests. Currently the results of these tests stay in your notes. We would like to put all the information from every patient into one large computer database. We hope this will allow us to understand the different types of heart failure better. We would like to invite you to participate in this research by allowing us to put your clinical information into this database.

You don't need to do anything now. An information sheet will be sent out to you before your next clinic review. This will have more detail and explain why we want to do the research and what would be involved. If you want to be involved we will go through everything with you, and answer any questions at your next clinic review. Don't worry if you don't want to be involved. It will not affect your normal care.

Version 2.0, August 2013

Consent Form

CONSENT FORM

Collection and analysis of data from an enhanced clinical heart failure service

Researchers: Professor J Murphy, Professor A Fuat, Dr J Crilley

Patient identification Addressograph

Please initial box

1. I have read and understand the information sheet dated (version 4.0) for the above study and have had the opportunity to ask questions and have had these answered in full. ☐

2. 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. ☐

3. I agree to take part in the above study and have my personal identifiable information and routine clinical data placed on a secure computer database indefinitely for future analysis. ☐

4. I understand that my medical notes and data collected for the study may be looked at by individuals from regulatory authorities or the NHS Trust. Where it is relevant to my participating in the research I give consent for such individuals to access my records. ☐

5. I agree to my Consultant and GP being informed of my participation in the study. ☐

6. I agree to being contacted in the future if further information is required, or for follow-up information to be obtained from my hospital notes or GP records. ☐

Name of patient:	Date:	Signature:
Name of person taking consent:	Date:	Signature:
Researcher:	Date:	Signature:

The patient wishes to receive a summary report of the results of any studies? ☐

Version 4.0, April 2014   1   Research

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GP Letter

with you ◆ all the way County Durham and Darlington **NHS**
NHS Foundation Trust

Regarding: Professor J Murphy
                                                    Cardiology Department
              DOB   Darlington Memorial Hospital
                                                    Hollyhurst Road
              Hosp No: Darlington
                                                    DL3 6HX
              Date: 01325 743235

Dear Dr

This is to inform you that the patient above is considering a request to have their clinical data placed on the County Durham and Darlington NHS Foundation Trust heart failure database. This is a clinical computer database of routine clinical data collected at the time of the heart failure clinics, along with relevant investigation results, and follow-up information. The data may be used for future audit and research under the guidance of Professor J Murphy, and a local heart failure steering committee. This study has been given a favourable opinion by the South Central-Oxford C Research Ethics Committee and is a continuous study of all new patients diagnosed with heart failure due to a reduced or preserved ejection fraction seen for the first time in the heart failure clinic. The aim is to establish a better understanding of the spectrum of pathology in the local heart failure population and provide a database of imaging and other demographics for a generic heart failure population.
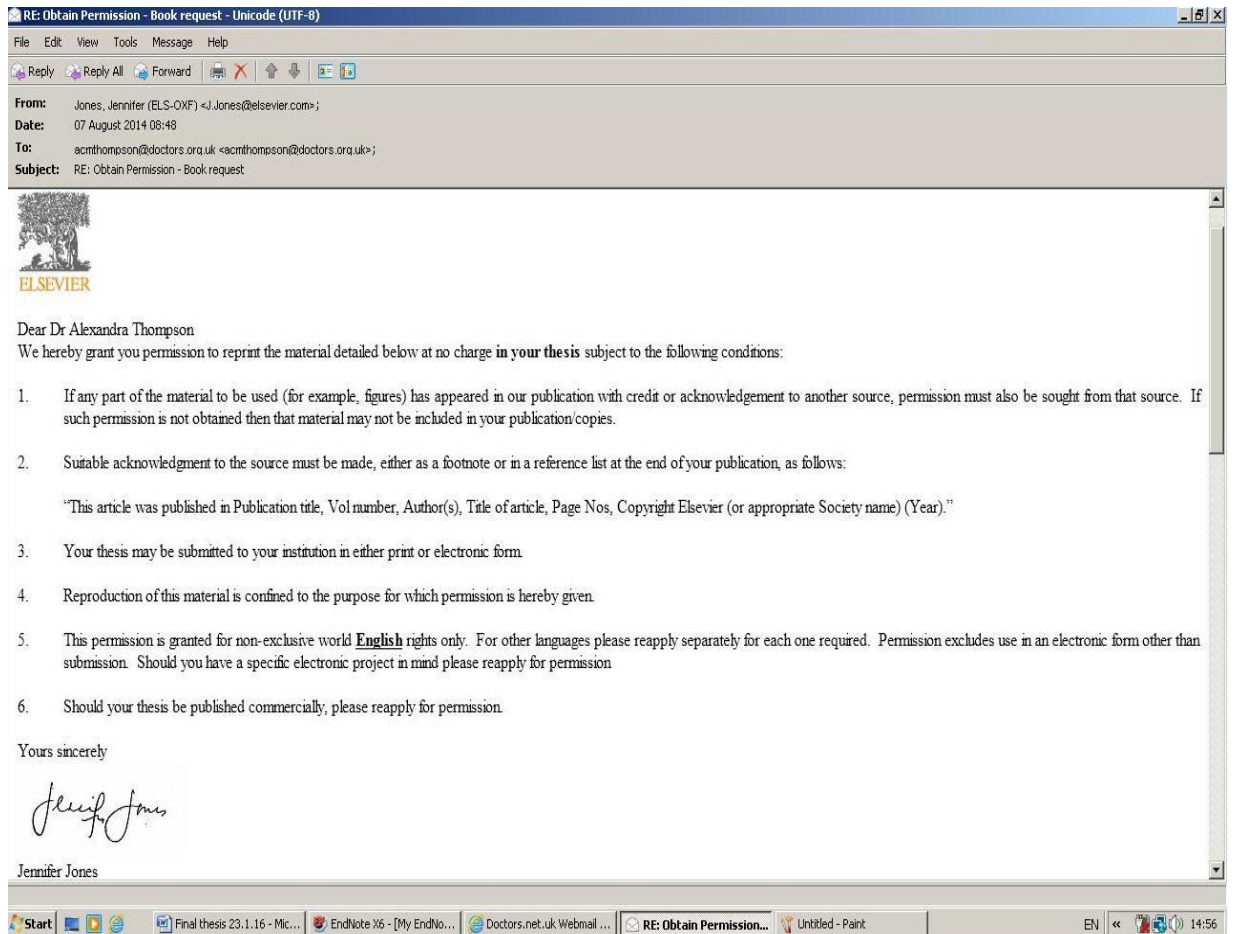
Please find enclosed a copy of the patient information leaflet. If you have any questions or queries please contact me on the address or phone number above.

Yours sincerely,

Professor J Murphy

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Version 1.0, December 2013

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Copyright permission for use of images

This permission applies for the print or electronic replication of up to 15 images from the Textbook of Clinical Echocardiography; ISBN: 978-1-4160-5559-4, 2009 by CM Otto; pages125-181 (Chapter numbers 6 and 7, Left and right ventricular systolic function and ventricular diastolic filling and function) (203).

Postgraduate Conference Award

School of Medicine, Pharmacy and Health

Doing it Stockton-style!!

MAY/JUNE/JULY 2014
Issue 4

SMurPH POSTGRADUATE NEWS

IS NO NEWS GOOD NEWS?

As you can see this is a combined issue covering May, June, and July. The reason? There was not enough news to fill a newsletter for each of those months. As the holiday season moves in to top gear there isn't a huge amount of news for August either—so this issue is mainly a round-up of what has already happened!

PGR CONFERENCE

The PGR Conference took place on 17 June 2014 and it went very well. Before lunch four PhD students completed their Confirmation Review by presenting their posters, and after lunch another four students made oral presentations as part of their Completion Review. A prize (a £25 Amazon voucher) was awarded to the student who made the best oral presentation (as voted by the attendees) and the winner was Alex Thompson, with her presentation *Heart failure? To be confirmed*. Congratulations to Alex, well done to all the student presenters, and a big thank you to everyone who attended.

Next year's PGR Conference will take place on 16 June 2015—please put the date in your diaries now!

PGR INDUCTION

CONGRATULATIONS...

... to *Rachel Stocker* who passed her viva in May, and *Drew Tootal* who was awarded his MSc in June.
Well done, both!

BEST WISHES...

... to *Prav Rajasekhar* who will be having his viva on 8 August! We'll be thinking of you, Prav!

School of Medicine, Pharmacy and Health

POSTGRADUATE CONFERENCE

Alex Thompson

Award for the best presentation as voted for by the attendees

Signature

Date 17 June 2014

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