University of Southampton

Faculty of Medicine

Role of Cardiovascular Magnetic Resonance Imaging and Tissue Characterisation in Cardiac Reverse Remodelling

by

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Thesis for the degree of Doctor of Medicine (DM) in Human Development and Health

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Abstract

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Cardiovascular Magnetic Resonance (CMR) imaging is recognised as the gold standard for functional cardiac assessment. Tissue characterisation assessment of myocardial diffuse fibrosis with T1 mapping and estimation of Extracellular Volume (ECV) is increasingly recognised for its role in clinical diagnosis and holds potential as a non-invasive biomarker for risk stratification, predicting prognosis, or monitoring response to therapy.

Over the last decade, the landscape of Heart Failure with reduced Ejection Fraction (HFrEF) medical therapy has changed significantly with the introduction of ARNI and SGLT2 inhibitors. In this thesis, I describe the marked beneficial Left Ventricular (LV) and left atrial reverse remodelling effects, as well as changes in tissue characteristics after optimisation to contemporary HFrEF therapy, evaluated with CMR for the first time. There were significant reductions in both native and post-contrast septal and global T1 values across time. There was no reduction in ECV but instead, reductions in both absolute LV cell and matrix volumes, and LV mass were found. In this cohort, reductions in LV volumes resulted in an increase in median LVEF by 12 points. 59% no longer met criteria for complex device implantation after 6 months.

I also describe the association between baseline CMR tissue characteristics with prognosis and cardiac reverse remodelling, in two discrete Heart Failure cohorts. PREDICT-HF included patients hospitalised with a new Heart Failure diagnosis, initiated on therapy and followed up over 24 months. Higher septal native T1 values were found to be significantly associated with adverse outcome in this cohort. The ENVI study included patients with symptomatic severe LVEF <35% despite 3 months of conventional therapy, optimised to contemporary HFrEF therapy. Those who experienced beneficial reverse remodelling to an LVEF >35% after 6 months were found to have lower septal native T1 values, lower absolute LV matrix and cell volumes, and LV mass at baseline.

Table of Contents

Table of Tables

Table of Tables

Table of Figures

Table of Figures

Table of Figures

Table of Figures

Research Thesis: Declaration of Authorship

Print name: **DR ALICE W ZHENG**

Title of thesis: **Role of Cardiovascular Magnetic Resonance Imaging and Tissue Characterisation in Cardiac Reverse Remodelling**

I declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

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   Zheng A, Adam R, Peebles C, Harden S, Shambrook J, Abbas A, Vedwan K, Adam G, Haydock P, Cowburn P, Young C, Long J, Walkden M, Smith S, Greenwood E, Olden P, Flett A. Effect of optimisation to contemporary HFrEF medical therapy with sacubitril/valsartan (Entresto) and dapagliflozin on left Ventricular reverse remodelling as demonstrated by cardiac magnetic resonance (CMR) Imaging: the ENVI study. Open Heart. 2024 Dec 2;11(2):e002933

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Definitions and Abbreviations

ACC ..... American College of Cardiology

ACE-I ..... Angiotensin-Converting Enzyme Inhibitor

AHA ..... American Heart Association

ALP ..... Alanine Transaminase

ALT ..... Alkaline Phosphatase

ARB ..... Angiotensin II Receptor Blocker

ARNI ..... Angiotensin Receptor Neprilysin Inhibitor

AUC ..... Area Under the Curve

BMI ..... Body Mass Index

BNP ..... B-type Natriuretic Peptide

BSA..... Body Surface Area

bSSFP ..... balanced Steady State Free Progression

CI ..... Confidence Interval

CO ..... Cardiac Output

CMR ..... Cardiovascular Magnetic Resonance

CRT..... Cardiac Resynchronisation Therapy

CRT-D ..... Cardiac Resynchronisation Therapy-Defibrillator

CRT-P ..... Cardiac Resynchronisation Therapy-Pacemaker

CT..... Computed Tomography

DBP ..... Diastolic Blood Pressure

DCM ..... Dilated Cardiomyopathy

DTPA..... Diethylenetriaminepentaacetic Acid

EACVI ..... European Association of Cardiovascular Imaging

ECG ..... Electrocardiogram

ECV ..... Extracellular Volume

ECM..... Extracellular Matrix

EDV(i) ..... End Diastolic Volume (indexed)

EF ..... Ejection Fraction

eGFR ..... estimated Glomerular Filtration Rate

ESV(i)..... End Systolic Volume (indexed)

ESC ..... European Society of Cardiology

FWHM..... Full Width Half Max

GMDT ..... Guideline Directed Medical Therapy

GE ..... Gradient Echo

HbA1c..... Haemoglobin A1c (glycated haemoglobin)

HF ..... Heart Failure

HFrEF ..... Heart Failure with reduced Ejection Fraction

HFmrEF ..... Heart Failure with mildly reduced Ejection Fraction

HFpEF..... Heart Failure with preserved Ejection Fraction

HR ..... Hazard Ratio

HRA ..... Health Research Authority

ICD ..... Implantable Cardioverter-Defibrillator

ICM..... Ischaemic Cardiomyopathy

IHD ..... Ischaemic Heart Disease

IQR ..... Interquartile Range

KCCQ ..... Kansas City Cardiomyopathy Questionnaire

LA ..... Left Atrium

LAV(i) ..... Left Atrial Volume (indexed)

LBBB..... Left Bundle Branch Block

LCD ..... Liquid Crystal Display

LV ..... Left Ventricle

LVEF ..... Left Ventricular Ejection Fraction

MAG ..... Magnitude-based

MAGGIC..... Meta-Analysis Global Group in Chronic Heart Failure

MI ..... Myocardial Infarction

MLWHF..... Minnesota Living with Heart Failure Questionnaire

MMP ..... Matrix Metalloproteinases

MMSE ..... Mini Mental State Examination

MOLLI ..... Modified Look-Locker Inversion recovery

NICE ..... National Institute for Health and Care Excellence

NICM ..... Non-Ischaemic Cardiomyopathy

NNT ..... Number Needed to Treat

NSVT..... Non Sustained Ventricular Tachycardia

NTproBNP ..... N-terminal prohormone of brain natriuretic peptide

NYHA..... New York Heart Association

MRA..... Mineralocorticoid Receptor Antagonist

OMT..... Optimal Medical Therapy

PINP ..... Procollagen type I N-terminal Propeptide

PIIINP ..... Plasma Procollagen type III aminoterminal Peptide

PSIR..... Phase-Sensitive Inversion Recovery

PVC ..... Premature Ventricular Contraction

QA ..... Quality Assurance

QOL..... Quality of Life

RAAS..... Renin-Angiotensin-Aldosterone System

RBBB ..... Right Bundle Branch Block

RCT..... Randomised Controlled Trial

REC ..... Research Ethics Committee

ROI ..... Region of Interest

ROC..... Receiver Operating Characteristic

RV..... Right Ventricle

RVEF..... Right Ventricular Ejection Fraction

SAX..... Short Axis

SCMR ..... Society for Cardiovascular Magnetic Resonance

SD ..... Standard Deviation

SBP..... Systolic Blood Pressure

ShMOLLI ..... Shortened Modified Look-Locker Inversion recovery

SNS ..... Sympathetic Nervous System

SV(i)..... Stroke Volume (indexed)

SGLT2 I ..... Sodium-Glucose Cotransporter-2 Inhibitor

sST2..... soluble ST2 protein

T1MES ..... The T1 mapping and ECV Standardisation Program phantom

TI ..... Inversion Time

TIMP ..... Tissue Inhibitors of Matrix Metalloproteinases

TGFβ..... Transforming Growth Factor β

TTE ..... Transthoracic Echocardiogram

UHS..... University Hospital Southampton NHS Foundation Trust

UK ..... United Kingdom

VT..... Ventricular Tachycardia

6MWT ..... 6 Minute Walk Test

Chapter 1 Cardiovascular Magnetic Resonance Imaging (CMR) and Remodelling in Heart Failure: INTRODUCTION

1.1 Heart Failure

1.1.1 Definition and Terminology

Heart failure (HF) is a common and heterogenous syndrome characterised by a triad of cardinal symptoms, namely breathlessness, ankle swelling and fatigue and may be accompanied by clinical signs e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema. It is caused by structural and/or functional abnormality of heart function resulting in elevated intracardiac pressures and/or inadequate cardiac output. (1)

HF is divided into subtypes based on the measured Left Ventricular Ejection Fraction (LVEF), normally by echocardiography as a first-line imaging modality. The original randomised controlled trials of HF treatments demonstrated significant improvement in outcomes in patients with a LVEF ≤40%, hence providing the threshold LVEF for the terminology of Heart Failure with reduced Ejection Fraction (HFrEF). The syndrome of HF in fact spans the whole range of LVEF, and the updated 2021 European Society of Cardiology (ESC) guidelines provide the following definitions of the three categories. Patients with symptoms ± signs and LVEF 41-49% are termed Heart Failure with mildly reduced Ejection Fraction (HFmrEF) and greater than 50% termed Heart Failure with preserved Ejection Fraction (HFpEF). **(Table 1.1)** (1)

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricle; LVEF = left ventricular ejection fraction.
[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in optimally treated patients.
[b]For the diagnosis of HFmrEF, the presence of other evidence of structural heart disease (e.g. increased left atrial size, LV hypertrophy or echocardiographic measures of impaired LV filling) makes the diagnosis more likely.
[c]For the diagnosis of HFpEF, the greater the number of abnormalities present, the higher the likelihood of HFpEF.

Table 1.1 Definitions of Heart Failure with reduced Ejection Fraction, mildly reduced Ejection Fraction and preserved Ejection Fraction. Reproduced from McDonagh TA et al. (1)

1.1.2 Epidemiology

The incidence (number of newly diagnosed cases in a population within a specified time period), of HF in Europe is approximately 5/1000 person-years in the adult population. (2) In the United Kingdom, despite a moderate decline in standardised (age-adjusted) incidence, presumably reflecting improved management of cardiovascular disease, the absolute prevalence (proportion of a population with the diagnosis at a given time period) of HF increased by 23% between 2002 to 2014. This is largely due to an increase in population size and age; the burden of heart failure is now similar to the four most common causes of cancer combined. (3) The prevalence of HF is 1-2% of adults and increases with age; from around 1% in those under 50 years to >10% in those 70 years and over. (4) In 2017, the global prevalence of cases was 64.3 million. (5) Prevalence is also likely to be underestimated as studies only usually include those recognised and diagnosed HF cases. (6)

1.1.3 Aetiology

The aetiology of HF is extremely diverse. Globally, the leading cause of HF is ischaemic heart disease caused by coronary artery disease (26.5%), followed by hypertension (26.2%), Chronic Obstructive Pulmonary Disease (23.4%) and other cardiomyopathies (6.5%). (5) Numerous other cardiac e.g. valvular disease and arrhythmias and non-cardiac pathologies e.g. infective, metabolic and infiltrative diseases can cause or contribute to HF, and can result in a variety of initial clinical presentations.

In addition, many patients have multiple co-morbidities such as hypertension, diabetes mellitus, chronic kidney disease and atrial fibrillation. HFpEF represents a complex and heterogenous patient group, where the aetiology of HF is largely related to co-morbidities. (7)

1.1.4 Diagnosis

The diagnosis of HF requires the presence of symptoms and/or signs, in addition to objective evidence of cardiac dysfunction. The diagnosis is more likely if the patient has a history of cardiac disease, hypertension, diabetes mellitus, alcohol misuse, chronic kidney disease or has a family history of cardiomyopathy or sudden cardiac death. (1) The development of symptoms generally results from the reduction in cardiac output and clinical signs are typically secondary to elevated filling pressures. **(Table 1.2)**

Symptoms	Signs
▶ Shortness of breath/dyspnoea ▶ Reduced exercise tolerance ▶ Fatigue ▶ Ankle swelling ▶ Orthopnoea ▶ Paroxysmal nocturnal dyspnoea	▶ Elevated jugular venous pressure ▶ Third heart sound (gallop rhythm) ▶ Laterally displaced apical impulse ▶ Pulmonary crepitations ▶ Peripheral oedema

Table 1.2 Common symptoms and signs of Heart Failure. Reproduced with permission from Haydock et al. (7)

The symptomatic severity of HF is most commonly described using the New York Heart Association (NYHA) functional classification. **(Table 1.3)**

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results undue breathlessness, fatigue, or palpitations.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.

Table 1.3 New York Heart Association (NYHA) functional classification based on severity of symptoms and physical activity. Reproduced from McDonagh TA et al. (1)

After taking a thorough history and clinical examination, the 2021 ESC guidelines recommend that patients with suspected HF have key investigations including Electrocardiogram (ECG) and Echocardiography. Echocardiography not only determines the LVEF but also provides information such as chamber size, wall thickness, regional wall abnormalities, valvular and diastolic function, offering clues to the aetiology. (8)

Measurement of natriuretic peptides serum B-type natriuretic peptide (BNP) or its N-terminal component (NTproBNP) are recommended as an initial diagnostic test, particularly in the non-acute setting and can be used as a gate keeper for echocardiography. (7)

BNP is released from the myocardium as a physiological response to elevated filling pressures and wall stress. Natriuretic peptides promote natriuresis, diuresis, vasodilatation, improved myocardial relaxation and reduced myocardial fibrosis. (9) They oppose the effects of an activated renin-angiotensin-aldosterone and sympathetic nervous systems and are important in attempting to regulate and restore normal loading conditions.

Natriuretic peptides are highly sensitive but are poorly specific for heart failure and should always be interpreted in conjunction with the clinical context. Very low natriuretic peptide levels have a very high negative predictive value and can exclude a HF diagnosis. There are however, many cardiac and non-cardiac causes of elevated natriuretic peptides including Atrial Fibrillation, increasing age, metabolic abnormalities, acute and chronic kidney disease. Levels can be disproportionately low in obese patients (BMI ≥30 kg/m2) both with and without HF. (10)

Further investigations to determine the aetiology of HF should be guided by clinical suspicion in choosing the appropriate test. This could include Cardiac Magnetic Resonance (CMR) imaging, invasive or Computed Tomography (CT) coronary angiography, right and left heart catheterisation, infectious disease serology, biochemical or immunological testing. (1)

1.1.5 HFrEF Pharmacotherapy

The goals of treatment for patients with HFrEF are to reduce mortality, prevent HF hospitalisations and achieve improvement in functional status and quality of life. Multiple randomised controlled trials spanning 30 years have radically changed the landscape of HFrEF management and have had major impact on clinical outcomes.

In HFrEF, there is overactivation of the renin-angiotensin-aldosterone (RAAS) and sympathetic nervous systems. **(Figure 1.1)** This neurohormonal axis is initially activated as an adaptive response to promote arteriolar vasoconstriction and maintain cardiac output, but becomes inappropriate and pathological in HF, resulting in salt and water retention, volume overload and the downstream effects of HF. Modulation of this maladaptive axis forms the foundation for pharmacotherapy for patients with HFrEF.

The cornerstones of HFrEF pharmacotherapy consist of a triad of ACE-I or ARB/ARNI, a beta-blocker and a mineralocorticoid receptor antagonist (MRA), along with the latest addition of sodium-glucose co-transporter 2 (SGLT2) inhibitors. (1)

Pharmacotherapy forms the foundation for HFrEF management and should be fully optimised in a timely fashion, before moving onto consideration of Cardiac Rhythm Management strategies i.e. cardiac devices **(Figure 1.2)**. Medications are started at low doses and then titrated up to maximum tolerated doses by members of the multidisciplinary HF team, namely Heart Failure Nurse Specialists, who have a key role in patient education, engagement and monitoring.

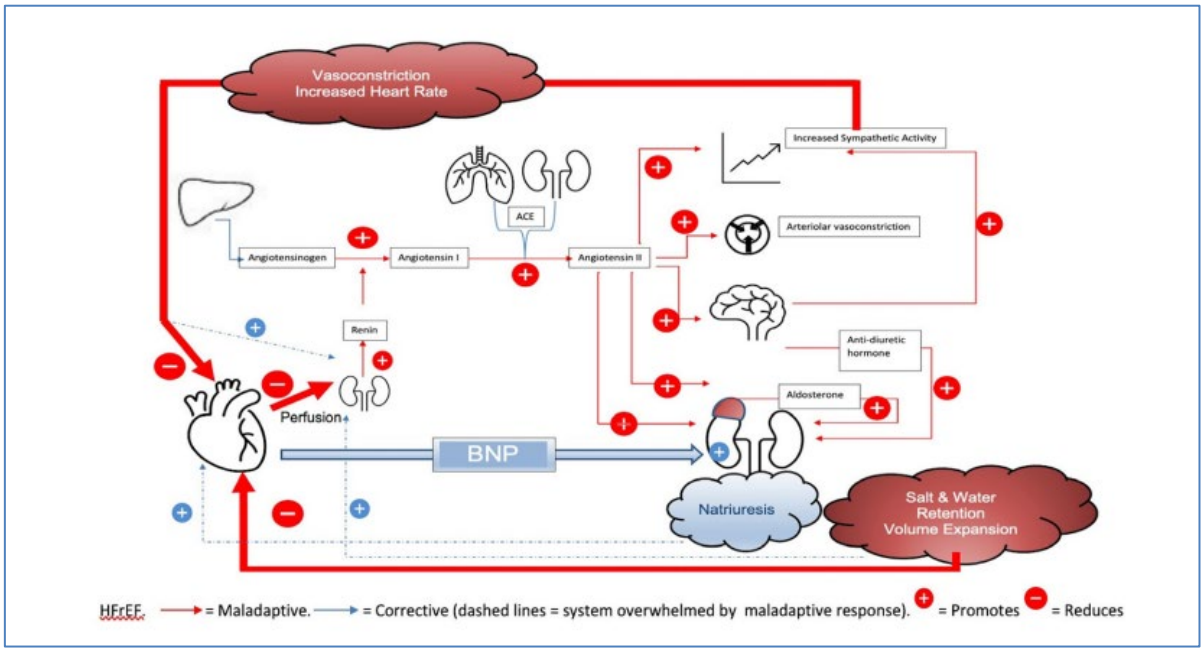

Figure 1.1 Overview of homeostatic mechanisms in HFrEF. BNP, B-type Natriuretic Peptide; HFrEF, Heart Failure with reduced Ejection Fraction. Reproduced with permission from Haydock et al. (7)

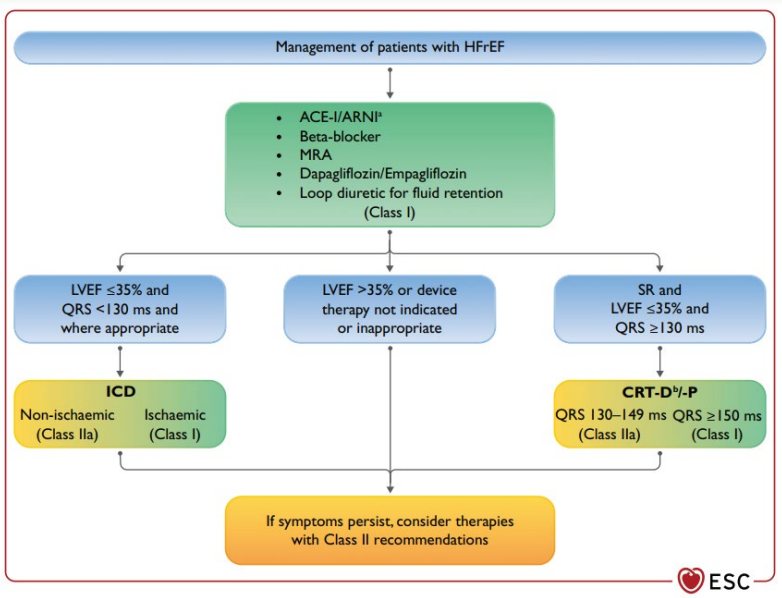

Figure 1.2 ESC 2021 Therapeutic algorithm of Class I Therapy Indications for a patient with HFrEF. Class I=green. Class IIa=Yellow. Reproduced from McDonagh TA et al. (1)

1.1.5.1 Angiotensin-converting enzyme Inhibitors (ACE-I)

Angiotensin-converting enzyme inhibitors (ACE-I) inhibit the conversion of Angiotensin I to Angiotensin II and are recommended as first line treatment for all patients with HFrEF. In the early 1990's ACE-I were the first class of drugs shown to significantly reduce mortality (~20%) and hospitalisation from HF (~20%). (11,12) In those patients who cannot tolerate ACE-I, most commonly due to the recognised side effect of a dry cough, Angiotensin II Receptor Blockers (ARB) have been historically prescribed as an alternative. (13) The mortality benefit of ARBs is less robust and with the arrival of the Angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril/valsartan (Entresto), switchover to ARNI is preferred instead.

1.1.5.2 Beta Blockers

Overactivity of the sympathetic nervous system causing vasoconstriction and increased heart rates occur in HF, as the body attempts to main cardiac output **(Figure 1.1)**. This inappropriate overactivity of the sympathetic nervous system state may worsen any underlying ischaemia, as well as increase the risk of arrhythmias. Beta adrenergic receptor blockers have been shown to confer a significant mortality and morbidity benefit, compared to placebo (relative mortality reduction of 35%) and are recommended for all patients with stable HFrEF, in addition to an ACE-I. (14,15)

1.1.5.3 Mineralocorticoid Receptor Antagonists (MRA)

Mineralocorticoid receptor antagonists (MRA) oppose the effects of aldosterone within the sustained and overactive RAAS in HF. Aldosterone promotes sodium retention, loss of potassium, activates the sympathetic nervous system and causes myocardial and vascular remodelling and fibrosis. (16,17)

The landmark RALES study showed that the MRA spironolactone, when added to ACE-I in combination therapy demonstrated a ~30% relative reduction in risk of death, and a 35% risk reduction in HF hospitalisations, compared to placebo in patients with severe HF. (18) In the post-MI HF population (EPHESUS), treatment with eplerenone showed a relative risk reduction in mortality of 15%, as well as a risk in reduction of HF hospitalisation and sudden cardiac death. (19)

1.1.5.4 Angiotensin receptor-neprilysin inhibitor (ARNI)

Sacubitril/valsartan (Entresto) consists of a neprilysin inhibitor sacubitril and the Angiotensin Receptor Blocker valsartan and is classed as an angiotensin receptor-neprilysin inhibitor (ARNI). Neprilysin degrades natriuretic peptides, and therefore its inhibition enhances the protective actions of circulating BNP, described previously.

The landmark trial PARADIGM-HF (2014) was terminated early, having shown a clear benefit of sacubitril/valsartan (Entresto) in patients with HFrEF compared to enalapril (ACE-I). After a median follow up of 27 months, there was a demonstrated reduction in risk of all-cause mortality (HR 0.84; 95% CI 0.76-0.93; p <0.001; NNT 36), cardiovascular death and heart failure hospitalisation (HR 0.80; 95% CI 0.73-0.87; p <0.001; NNT 21) as well as an improvement in quality of life and symptoms. (20)

So powerful was the effect that Entresto was put on the UK Early Access to Medicine Scheme, enabling its use before licensing, with subsequent national and international heart failure guideline updates. Sacubitril/valsartan (Entresto) has since been incorporated into best practice. The 2016 ESC HF guidelines recommended it as a replacement for ACE-Inhibitor in ambulatory patients with HFrEF who remain symptomatic despite the conventional combination of ACE-Inhibitor, beta-blocker and mineralocorticoid receptor antagonist. (21)

National Institute for Health and Care Excellence (NICE) guidelines recommend sacubitril/valsartan (Entresto) for those patients with NYHA II-IV symptoms and LVEF ≤35%, who are already taking stable doses of ACE-I/ARB. (22) This approach currently remains common practice among HF clinicians.

Two studies have since examined the use of ARNI in hospitalised patients, a proportion of whom were ACE-I/ARB naïve and shown to be safe, as well as a reduction in subsequent cardiovascular death or HF hospitalisation, compared to enalapril. (23,24)

As a result, the 2021 updated ESC HF guidelines have reiterated its previous recommendation but with an addition of

> "...however, an ARNI may be considered as a first-line therapy instead of an ACE-I"

as a class IIb recommendation (level of evidence B). (1)

1.1.5.5 Sodium-glucose cotransporter 2 Inhibitors (SGLT2 inhibitors)

SGLT2 inhibitors are a group of anti-diabetic hypoglycaemic agents that block the SGLT2 cotransporters in the proximal renal tubules, inhibiting glucose reabsorption and promoting glycosuria. There is also accompanying sodium excretion which reduces intraglomerular pressure, central to its nephroprotective effects. Other potential beneficial mechanisms such as reduction in tubular inflammation and hypoxia have been proposed. (25)

DAPA-HF demonstrated a ~25% reduction in relative risk with Dapagliflozin treatment compared to placebo, in a combined primary endpoint of worsening HF or cardiovascular death in HFrEF patients with and without diabetes, despite optimal medical therapy. There were reductions in each component of the primary endpoint with a 30% risk reduction in heart failure hospitalisations and 18% risk reduction in cardiovascular death. (26) EMPEROR-Reduced also demonstrated a 25% risk reduction in the same primary endpoint with Empagliflozin vs. placebo but the result was driven by reduction in risk of HF hospitalisation. There was no significant risk reduction in cardiovascular death. (27) As a result of both trials, SGLT2 inhibitors are now widely considered the “fourth pillar” of HFrEF pharmacological management, regardless of diabetes status.

1.1.6 Cardiac Rhythm Management in HF (Implantable Devices)

1.1.6.1 Implantable Cardioverter-Defibrillators (ICD)

Patients with HFrEF are at risk of death from cardiac arrhythmias. Implantable Cardioverter-Defibrillators (ICD) are effective at detecting and treating life-threatening ventricular arrhythmias. Landmark trials MADIT I and MADIT II concluded that there was a significant mortality benefit for prophylactic ICD implantation in patients with HFrEF post myocardial infarction. (28,29) SCD-HeFT demonstrated a 23% relative risk reduction in mortality with ICD therapy compared to Amiodarone, and placebo, in patients with HFrEF of both ischaemic and non-ischaemic aetiology. (30)

These ICD trials however pre-date the recent advancements of HF medical therapy (ARNI and SGLT2 inhibitors). An analysis of over 40,000 patients from 12 HFrEF trials showed a decline of 44% in rates of sudden cardiac death between 1995 and 2014. This is almost certainly due to the cumulative benefits of improved evidence-based pharmacotherapy in HF over time, as well as Cardiac Resynchronisation Therapy (CRT). (31)

The recent DANISH trial concluded that ICDs conferred no significant improvement in overall risk of all-cause mortality in patients with HFrEF due to non-ischaemic cardiomyopathy (NICM). The rates of sudden cardiac death in this study were low (70 out of 1116 patients over 5 years). (32)

Updated guidelines recommend a primary prophylactic ICD for NYHA II-III patients with EF ≤35% despite ≥ 3 months of optimal medical therapy (OMT), provided they are expected to have good functional status > 1year. (Class IA indication for ischaemic cardiomyopathy; Class IIa for non-ischaemic aetiology). **(Figure 1.2)** (1)

1.1.6.2 Cardiac Resynchronisation Therapy (CRT)

In symptomatic patients with EF ≤35% despite OMT and a broad QRS complex (≥130ms) on ECG, Cardiac Synchronisation Therapy (CRT) should be considered. **(Figure 1.2)** CRT reduces morbidity and mortality in appropriately selected patients. (33) The decision between a cardiac resynchronisation-pacemaker (CRT-P) or cardiac resynchronisation-defibrillator (CRT-D) is specific to the patient and should made through a shared decision-making process.

1.1.7 Prognosis

Outcomes for patients with HF have improved significantly since the initial treatment trials and along with increased HF therapy prescriptions, survival and hospitalisation rates have improved between 1980's and 2000. (34–36)

Overall prognosis is however extremely poor and from 2000 onwards, this previous trajectory of improvement appears to plateau off and mortality remains high. In the Olmstead County Minnesota cohort, mortality was 20% at 1 year and 53% at 5 years, regardless of HFrEF or HFpEF diagnosis. 54% of deaths were attributed to non-cardiovascular causes and did not decline with time, highlighting the need to manage these complex patients with multiple co-morbidities holistically. (37)

The 2020/21 UK Heart Failure audit reported an inpatient mortality of 9.2% and a 1-year mortality of 39%. (38) Repeat hospitalisations after a diagnosis of HF are extremely common with 67%, 54% and 43% of patients hospitalised ≥2, ≥3 and ≥4 times respectively in Olmsted County, with less than half due to cardiovascular causes. (39)

1.2 Role of Cardiovascular Magnetic Resonance Imaging (CMR) in HF

1.2.1 Strengths of Cardiovascular Magnetic Resonance (CMR)

Cardiovascular Magnetic Resonance (CMR) has emerged as a key non-invasive imaging technique and plays an integral role in the evaluation of patients with HF. CMR is the gold standard for accurately assessing Left Ventricular (LV) and Right Ventricular (RV) volumes, mass, function and cardiac anatomy with excellent reproducibility, compared to other imaging modalities. (40–42) Unlike echocardiography, Ejection Fractions (EF) with CMR are calculated by true volumetric evaluation, without geometric assumption of the ventricle hence resulting in higher reproducibility and accuracy. (43) The right ventricle can also be accurately assessed despite its complex and highly variable shape. (42) CMR offers superior image quality with high spatial resolution and an unrestricted view of the heart. There is no ionising radiation risk to the patient, with a typical study taking around 45 minutes and generally well tolerated.

In addition to evaluation of cardiac function, CMR can provide a wealth of information from tissue characterisation. It can identify pathological tissue characteristics such as oedema and scar providing enhanced diagnostics into the aetiology of HF, assess viability of myocardium and offer information of prognostic value. (43,44)

Understanding the aetiology of HF is fundamental for management of the patient and their prognosis. The unique ability to characterise scar distribution with CMR gives it superiority over other modalities when investigating the cause of HF. (45)

As a result of these strengths, studies have shown that CMR has had increasingly significant influence on decision making within routine clinical care. (46,47) One study centre reported CMR having “significant clinical impact” in 65% of HF patients scanned, resulting in a completely different diagnosis in 30% and a change in management in 52% of patients. (46)

1.2.2 Late Gadolinium Enhancement (LGE)

The ability of the Late Gadolinium Enhancement (LGE) technique on CMR to detect focal myocardial fibrosis, or scar, associated with damaged myocardium has been validated with histopathological studies in animal models of Ischaemic Cardiomyopathy, biopsies and in explanted hearts. (48–50) In clinical practice, LGE-CMR has become the non-invasive gold standard technique for visualising focal myocardial scar in a range of cardiac conditions and differentiating between ischaemic and non-ischaemic aetiologies of cardiomyopathy. (51)

Gadolinium, chelated to diethylenetriaminepentaacetic acid (DTPA), is a paramagnetic extracellular contrast agent. It enters the extracellular tissue space but not the intracellular space. In healthy, undamaged myocardium, myocardial cell membranes are intact and the extracellular space is small; the Gadolinium is 'washed in' and 'washed out' quickly (within minutes). In damaged myocardium, extracellular space is expanded due to myocardial cell rupture in the case of acute myocardial infarction, or due to collagen deposition in chronic fibrosis. The Gadolinium therefore accumulates in this expanded extracellular space and is "washed out" far slower (> 30 minutes), resulting in an increased concentration which is imaged with the LGE technique and differentiates between healthy and scarred tissue. (45) (**Figure 1.3**)

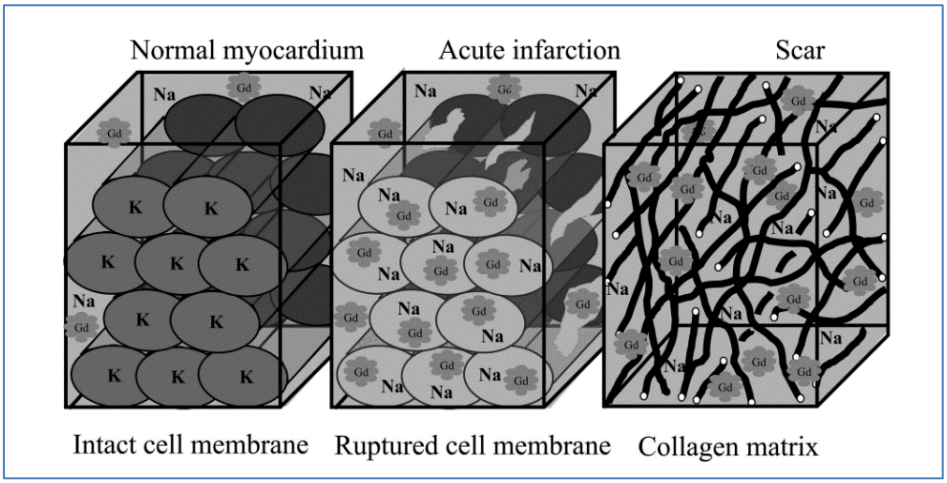

Figure 1.3 Gadolinium contrast distribution in normal myocardium, acute myocardial infarction and chronic scar. Reproduced with permission from Kim RJ et al.(45)

Gadolinium shortens the T1 time. This is the time taken for excited protons (after application of a radiofrequency pulse) for longitudinal recovery and return to equilibrium, realigning with the external magnetic field. T1-weighted inversion recovery sequences detect differences in T1 times and therefore damaged myocardium (scar) will appear hyper-enhanced and bright, contrasting to healthy myocardium in images acquired typically 10-20 minutes after contrast administration.

Good quality LGE images however require optimisation and selection of the correct inversion time (TI). This is the time to null the magnetisation signal of the normal myocardium (so healthy myocardium appears black), achieving the greatest contrast in image intensity between healthy and scar tissue. Selecting the correct TI time is achieved most reproducibly using a TI scout sequence. (52)

1.2.3 LGE Distributions and Aetiology

Specific patterns of fibrosis and scarring as identified by LGE on CMR, caused by different non-ischaemic and ischaemic cardiac disease processes have been well described. **(Figure 1.4)**

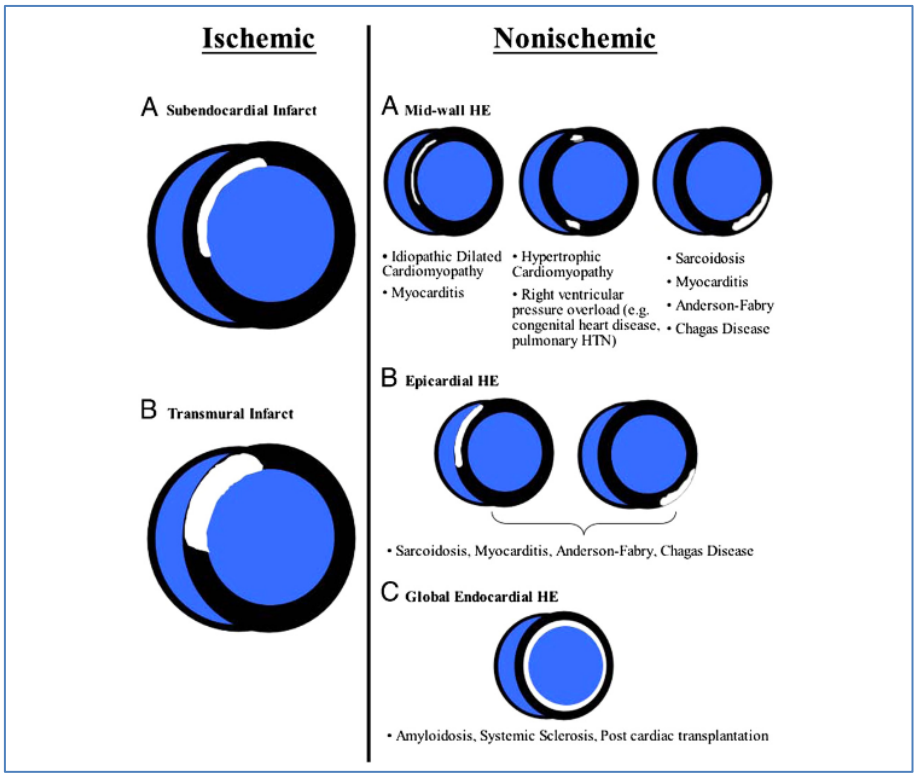

Figure 1.4 Schematic representation of LGE patterns characteristic for ischaemic and non-ischaemic disorders. Reproduced with permission from Shah et al. (51)

In ischaemic cardiomyopathy, there is always hyperenhancement involving the subendocardium, in a coronary distribution. In contrast, non-ischaemic aetiologies of cardiomyopathy generally demonstrate mid-wall or epicardial distributions of LGE, across multiple coronary territories. (51)

Up to 13% of patients diagnosed with Dilated i.e. Non-Ischaemic Cardiomyopathy with unobstructed coronary arteries on angiography, were found to have areas of subendocardial or transmural areas of LGE on CMR, evidence of previous infarct. These cases could have represented spontaneous recanalisation of the coronary artery, or embolic infarction. The original clinical diagnosis in this subgroup was therefore incorrect, having important therapeutic implications. (53,54)

Visual assessment is sufficient for most clinical indications and assessment of LGE presence, location, pattern, coronary territory and average extent (%) of transmural involvement is now standard as part of CMR assessment. Multiple methods exist for quantitative assessment of LGE extent including manual planimetry, Full Width Half Max (FWHM) and n-SD techniques. The FWHM method has been demonstrated in few studies to be most reproducible and comparable to manual quantification. (55,56) There is at present, no Society for Cardiovascular Magnetic Resonance (SCMR) task force consensus as to which quantitative LGE method is the optimum method. (57)

1.2.4 LGE and Prognosis

The inverse relationship between the extent of transmural LGE and subsequent recovery of contractile function post coronary revascularisation was initially described in 2000. (58) Subsequent studies have confirmed that the transmural extent of infarct as shown by LGE on CMR can predict likelihood of regional functional recovery post coronary revascularisation, in both acute and chronic settings i.e. predicting myocardial viability. >75% of transmural scarring suggests non-viability of that segment. (59–61)

The presence of LGE scar and its prognostic implications in terms of adverse outcome has been extensively described in a whole range of cardiac conditions including myocarditis (62), Hypertrophic Cardiomyopathy (63,64) and amyloidosis (65) A number of studies have shown that extent of myocardial scar by LGE is predictive of arrhythmic risk, irrespective of LVEF and that infarct size could be a better predictor of arrhythmias than LVEF. (66) In one study, patients with LVEF >30% with significant scarring (>5% of left ventricular mass) were a high-risk cohort similar to those with LVEF ≤30%. Conversely, those patients with LVEF ≤30% but no scarring were found to be a low-risk cohort, with a similar risk to patients with EF >30%. (67)

From a meta-analysis of 34 studies of over 4500 patients with Non-Ischaemic Cardiomyopathy, LGE was found in 44.8% of patients. Patients with LGE had increased cardiovascular mortality (Odds Ratio 3.40; 95% CI (2.04-5.67), ventricular arrhythmias (Odds Ratio 4.52; 95% CI 3.41 to 5.99) and HF rehospitalisation (Odds Ratio 2.66; 95% CI 1.67 to 4.24), compared to those without LGE on CMR. (68)

The presence of LGE and scar has also been shown to have implications in which patients respond to heart failure therapy, and which patients do not. This is further discussed **in Chapters 4.1** and **7.1.**

1.2.5 Quantitative Cardiovascular Magnetic Resonance (CMR) Metrics

1.2.5.1 Volumetric Parameters and Cardiac Function

There is a large body of evidence demonstrating and validating the excellent ability of CMR to assess both left and right ventricular volumes and function with accuracy, interstudy, inter- and intraobserver reproducibility. CMR is the gold standard method for calculating left (and right) ventricular volumetric parameters and hence, global systolic function, including end diastolic volume (EDV), end systolic volume (ESV), stoke volume (SV), cardiac output (CO), ejection fraction (EF) as well as left ventricular muscle mass. (50,69) Values are reported in absolute values, as well as indexed to Body Surface Area (BSA) (/m2).

Cardiac volumes and visual assessment of regional wall motion abnormalities are performed using standard CMR cine images which are processed by post-processing software. Cine imaging consists of acquisition of the same slice position through different phases of the cardiac cycle, during breath-holds. The modern k-space-segmented balanced steady state free precession (bSSFP) sequence is the technique of choice as it provides high Signal to Noise Ratio and excellent contrast between the myocardium and the blood pool. Normal values have been published for different field strengths, imaging sequences, post-processing approaches, age, sex and ethnicity groups. (70) It is recognised that smaller sets of normal values are available for bSSFP technique, compared to conventional Gradient Echo sequences and that reference values differ between techniques, so the appropriate reference ranges need to be selected. (50)

A standardised cine imaging acquisition protocol as defined in SCMR Standardised Protocols is as follows:

- Short axis (SAX) stack of slices covering both Left and Right Ventricles from base to apex. (Slice thickness 6-8mm, with or without 2-4mm interslice gaps, making total 10mm slices). **(Figure 1.5)**
- Long axis cine images of the Left Ventricle – 4-chamber, 3-chamber, and 2-chamber views, more views optional.
- Long axis cine images of the Right Ventricle – vertical long axis RV view aligned with tricuspid valve inflow, and Right Ventricular Outflow Tract view.

In patients with irregular heart rhythms, or struggle with breath-holds, real-time cine image methods can be used, although quantification of absolute LV volumes are typically less accurate and precise with this method. (71)

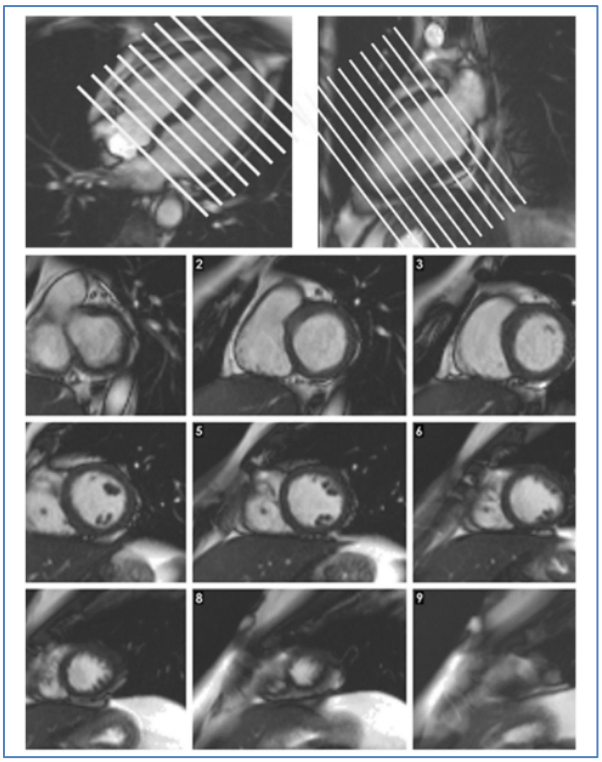

Figure 1.5 Top panel- Planning of short axis image plane parallel to the mitral valve in the 4-chamber long axis plane (left) and 2-chamber long-axis plane (right).
Bottom panel - 9 short axis cine slices shown from base (top left) to apex (bottom right). Reproduced with permission from Kramer et al. (71)

Most software use a combination of semi-automated with manual correction of contours of the short axis stack. Automatic contour delineation algorithms must be checked. With automated segmentation algorithms, ventricular volumes through all phases of the cardiac cycle can be evaluated. It is however, the endocardial and epicardial LV borders at the End-Diastolic phase (largest LV blood volume-EDV) and End-Systolic phase (smallest LV blood volume-ESV) that are confirmed, and using those the SV, CO, EF and mass calculated. (72)

The impact of differing acquisition techniques and analysis strategies on left ventricular volumetric function and mass results have been described. The inclusion or exclusion or papillary muscle mass significantly affects Left Ventricular volume and mass analyses but there is currently no universally accepted approach. (69) Papillary muscles and trabeculae should be assigned to the bloodpool for LV volume assessment but ideally should be added to the myocardial mass calculation. It is recognised however, that users can exclude papillary muscles from myocardial mass, as long as correct reference ranges are used. **(Figure 1.6).** (70,72)

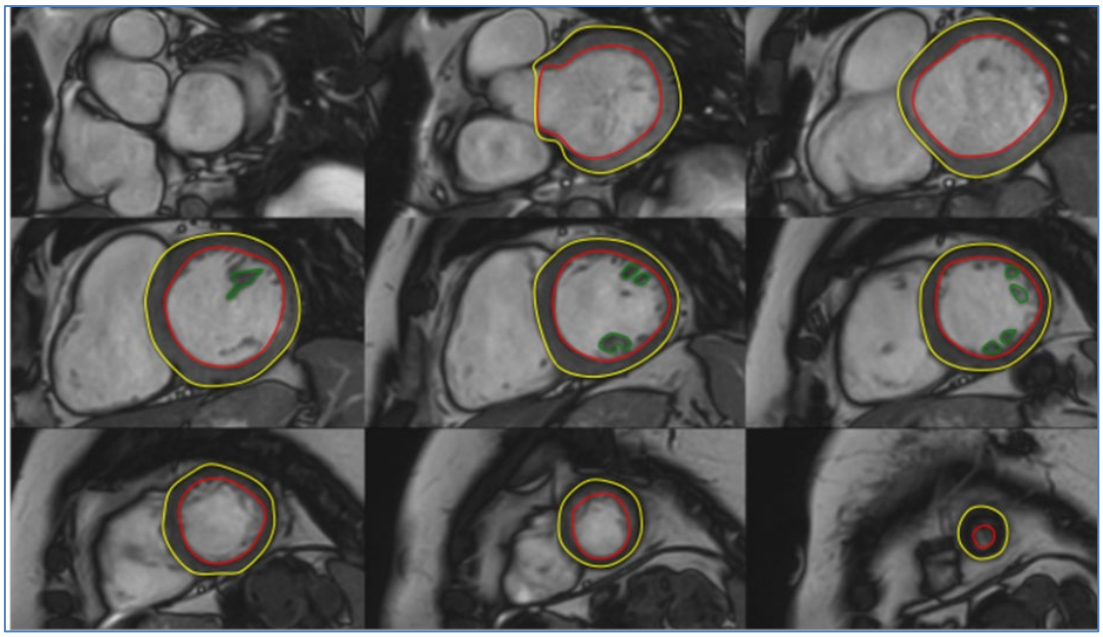

Figure 1.6 LV endocardial (red) and epicardial (yellow) contouring. LV papillary muscle (green) has been isolated and added to LV mass. Reproduced with permission from Kawel-Boehm N et al. (70)

Along with calculated myocardial mass, left ventricular wall thickness to assess for hypertrophy can be measured either from the basal short axis slice or the 3-chamber view. Both approaches have good reproducibility. (72)

1.2.5.2 Left Atrial (LA) Volumetric Assessment and Implications

There is limited consensus about how to measure LA volumes on CMR. Software can semi-automatically track the LA area and length in 2-chamber and 4-chamber cine views. In practice, the bi-plane area-length method is most commonly used. An alternative is the modified Simpson's method, analogous to LVEF calculation, which requires a dedicated stack of atrial cines. (70)

Maximum and minimum atrial volumes can be evaluated on the last cine image before opening of the mitral valve and the first image after closure of the mitral valve, respectively. The left atrium has a biphasic volume-time curve and calculation of the Total Emptying Fraction (global function), Passive Emptying Fraction (conduit function) and Active Emptying Fraction (booster pump function) of the left atrium is possible. Inter-study reproducibility of LA volumetric assessment although less well-established compared to LV assessment, has been shown to be good, with calculation of Total Emptying Fraction being more reproducible than the other two. (73,74)

There is a well- known association between increased LA size and all-cause mortality in both general and high-risk populations (stroke, Dilated Cardiomyopathy, and post Myocardial Infarction). Most studies are based on echocardiographic data. (75–78) This finding has been replicated in a retrospective multi-centre study with CMR, analysing over 10,000 patients referred for a clinically indicated CMR. They found that moderate (63-73 ml/m2) and severe (>73 ml/m2) enlargement of the left atrium was independently associated with all-cause mortality. (79)

Some CMR studies have demonstrated LA Emptying Fraction as a predictor for appropriate ICD shock therapy with or without sudden cardiac death. They however did not include multivariable analysis incorporating LVEF and had overall fairly small numbers of primary endpoints. (80,81) A retrospective multi-centre study of 392 patients with ischaemic and non-ischaemic cardiomyopathy undergoing CMR prior to ICD implantation defined a harder endpoint of a composite of appropriate ICD shock or all-cause death. It found that LA volume and function were univariate, but not independent predictors of the primary outcome once multivariable analysis (including the more established variables of LVEF and LGE) was performed. (82)

LA volume has been shown to be a predictor of HF development, regardless of LVEF in the ≥ 65 year old population. (83) In analysis of the SOLVD (Studies of Left Ventricular Dysfunction) studies and registries of 1172 patients, LA dimension on echocardiography was found to be a predictor of mortality and cardiovascular hospitalisation after adjusting for LVEF, NYHA and ischaemic aetiology. (84) In a meta-analysis of 18 HF studies of 1157 patients, LA area was found to be a powerful predictor of death or HF hospitalisation in patients with HFrEF, independent of LV systolic and diastolic function. (85)

1.2.5.3 T1 Mapping and Extracellular Volume (ECV)

In contrast to LGE imaging, which identifies areas of focal myocardial fibrosis and scar, CMR is able to directly assess diffuse myocardial fibrosis with T1 mapping. T1 mapping allows estimation of myocardial Extra Cellular Volume (ECV), a validated surrogate marker of fibrosis. (86,87) This relatively novel technique has, over the last decade or so, been extensively studied and has been shown to have clinical value from large scale clinical outcomes trials, holding potential as a biomarker for risk stratification and monitoring therapy.

Parametric mapping is now recommended by SCMR and EACVI as part of the evaluation of patients being investigated for cardiac diseases including potential iron overload, amyloidosis, Anderson-Fabry disease, myocarditis and heart failure.

Clinical reporting of T1 values should only be referenced against the site-specific normal reference ranges, where acquisition and evaluation are performed in a standardised manner. (88)

T1 measures the longitudinal (spin-lattice) relaxation time and T1 mapping refers to the pixelwise illustration of these T1 relaxation times on a map. The most established and popular method is the Modified Look-Locker Inversion recovery (MOLLI) pulse sequence which obtains T1 values in a single breath-hold over 17 heartbeats. The shortened MOLLI (ShMOLLI) sequence allows a shortened breath-hold of only 9 heartbeats. (89)

Native T1 mapping refers to this quantitative tissue characterisation technique at baseline i.e. before the use of contrast. Most commonly, increased water content e.g. inflammation and acute infarct causing tissue oedema and increased interstitial space e.g. fibrosis causes increased native T1 values. Low native T1 values are most commonly caused by fat deposition e.g. lipomatous metaplasia or iron overload. (89)

In those patients without severe kidney impairment, the administration of Gadolinium-DTPA contrast and repeat acquisition of T1-mapping (typically >10 min post-contrast) allows the comparison and calculation of myocardial Extracellular Volume (ECV). In contrast to native T1, areas of myocardial fibrosis and scar have shortened post-contrast T1 values, caused by the higher Gadolinium distribution within the increased extracellular space. (69)

Measurement of pre- and post-contrast T1 values, along correction for red blood cell density in the blood pool (Haematocrit) allows the estimation of ECV (%) using the following formula: (89)

$$ECV = (1 - haematocrit)\frac{\frac{1}{post\ contrast\ T1\ myo} - \frac{1}{native\ T1\ myo}}{\frac{1}{post\ contrast\ T1\ blood} - \frac{1}{native\ T1\ blood}}$$

The mean normal ECV in healthy individuals has been reported as 25.3±3.5% [1.5T] and higher in women than men. (90) The clinical causes of an increased and decreased ECV are shown below. **(Figure 1.7)**

Myocardial ECV can be calculated for regions of interest (ROI), most accurate in the mid-wall, or visualised as ECV maps. Examples of CMR multiparametric tissue characterisation (Native T1, LGE and ECV) in cardiomyopathies are shown below. **(Figure 1.8)**

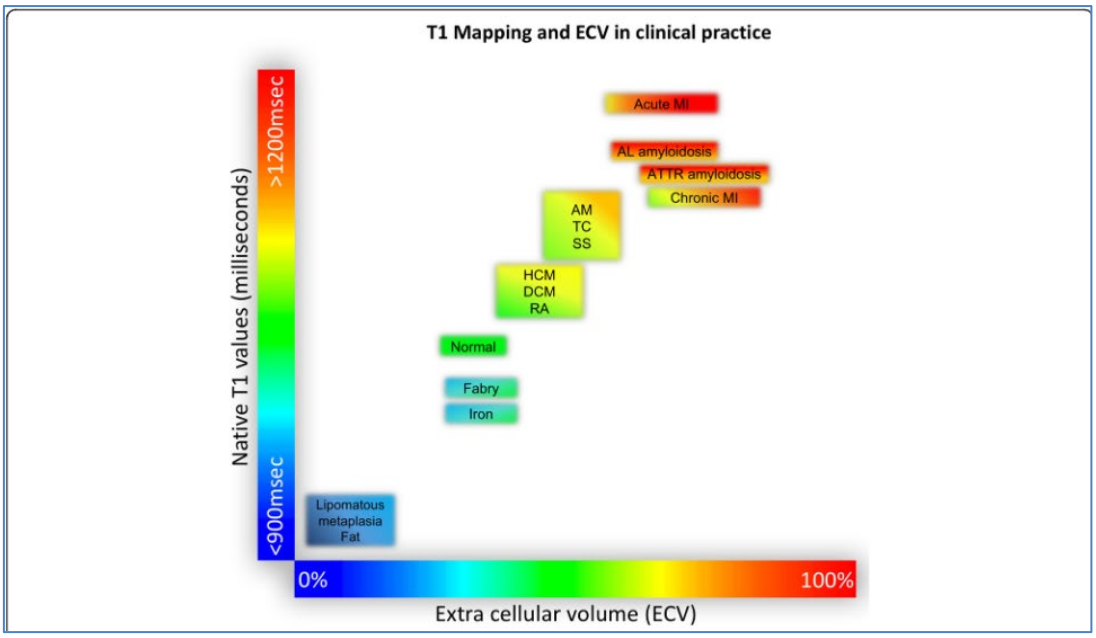

Figure 1.7 Changes in T1 and ECV in different myocardial diseases. T1 values refer to MOLLI-based techniques at 1.5T. Reproduced with permission from Messroghli DR et al. (88)

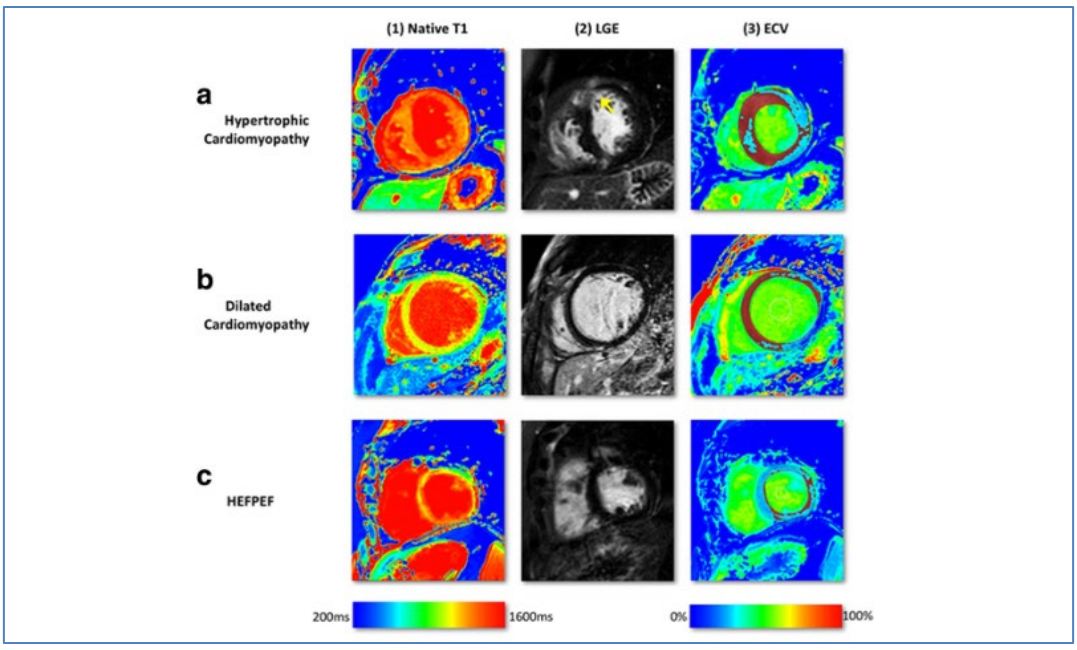

Figure 1.8 T1 mapping using MOLLI pulse sequence at 1.5T. Red areas on ECV maps represent ECV >30%. **a**. Hypertrophic Cardiomyopathy showing diffuse and heterogenous LGE in anterior wall. Diffusely raised native T1 and higher ECV. **b**. Dilated Cardiomyopathy with no LGE but raised native T1 values in septum and raised ECV. **c**. HFpEF with raised native T1 with no LGE and patchy areas of raised ECV. Reproduced with permission from Haaf et al. (89)

Only approximately 30% of patients with Dilated (Non-Ischaemic) Cardiomyopathy have the characteristic mid-wall stripe pattern of LGE on CMR. (91) In NICM, it has been shown that native T1 is increased, even in segments without LGE, and actually correlate with the thinnest myocardial wall segments. (92)

A number of studies have demonstrated that elevated T1 values and ECV are predictors of worse outcome, independent of LVEF and LGE, in patients with NICM, amyloidosis and mixed patient cohorts. (93–97) Tissue characterisation by T1 mapping has the advantage of being a non-invasive assessment of diffuse fibrosis and perhaps has the potential to guide or predict response to therapy. This, along with its potential role as a biomarker for predicting long term prognosis requires further investigation.

1.3 Cardiac Remodelling

1.3.1 Adverse Remodelling

Cardiac remodelling can be described as a process of changes to the heart size, shape or function caused by underlying genomic expression, molecular, cellular, and interstitial alterations, as a result of physiological or pathophysiological stimuli such as injury (e.g. myocardial infarction), inflammation (e.g. myocarditis), changes in haemodynamic load (e.g. aortic stenosis, hypertension) and neurohormonal activation (as seen in heart failure). (98) Remodelling does not only affect the Left Ventricle (LV) however it is LV remodelling in the context of patients with HFrEF that has been most extensively studied to date.

Early work into understanding Left Ventricular (LV) remodelling began in rat models of Myocardial Infarction (MI). Rats with larger induced infarctions had substantially greater LV ventricular enlargement and higher mortality, compared to smaller infarctions. The LV remodelling process began rapidly after insult and continued to progress, augmented by an additional 30% at 3 months post infarct, suggesting progressive changes of the non-infarcted regions contributed to the overall remodelling process. The same investigators went on to demonstrated that ACE Inhibition with captopril, initiated soon after inducing the MI, attenuated the remodelling process and improved survival, paving the way for the cascade of human studies that followed. (99,100)

Adverse remodelling is characterised by varying degrees of loss of healthy myocytes, development of hypertrophy and interstitial fibrosis. Remodelling may continue for months to years after the initial insult and as it does, the heart's geometry changes from elliptical to more spherical with increasing dimensions, volume and mass, all of which may adversely affect its systolic and diastolic function. Enlargement and spherical change in left ventricular shape can also cause functional (secondary) incompetence of the mitral valve which exacerbates the increase in preload and dilatation. (101)

Reverse remodelling describes the improvement in heart geometry and or function, where the left ventricle reverts closer to normal structure and is associated with improved cardiac function and prognosis. There is, however, a lack of standardised definition as studies have been heterogenous in their participant populations, imaging modalities, parameters measured and criteria to define reverse remodelling. It should also be noted that although there may be improvement in ventricular size and function, much of the histological damage remains. (102)

1.3.2 Mechanisms of Adverse Remodelling

1.3.2.1 Ischaemic Injury

Post Myocardial Infarction, the initial process of remodelling, repairing the necrotic area and the formation of scar is intended to be beneficial, as an attempt to maintain cardiac output. Ischaemic insult results in the injury and death of myocytes through necrosis and apoptosis within the affected coronary territory, but progressive remodelling changes occur in both infarcted and non-infarcted tissue.

Myocardial necrosis results in the release of many cytokines, an early influx of macrophages and other inflammatory cells, which leads to the breakdown of the collagen scaffolding that helps maintain the original myocardial integrity. This leads to regional thinning and dilatation of the myocardium within the infarcted area. Fibroblasts then proliferate and begin to deposit a new collagen matrix at the site of injury, contributing to the scar formation process, along with reorganisation of the Extracellular Matrix (ECM) and fibrosis formation.

Following the acute event, the non-infarcted myocardium experiences increased load and undergoes a process of eccentric remodelling. The cardiac myocytes assemble into contractile units in series, resulting in elongation, relative wall thinning and an increase in Left Ventricular cavity size. (103)

This is a remodelling compensatory mechanism aiming to preserve cardiac output, however it becomes maladaptive as increasing LV volumes result in increasing wall stress and further dilatation, as well as an increase in myocardial oxygen demand. As the preload increases without the ability to increase contractility, the result is a reduction in LVEF, and the development of Ischaemic Cardiomyopathy. (104)

The interactions between different components of cardiac remodelling in the context of Ischaemic Cardiomyopathy are shown schematically below. **(Figure 1.9)**

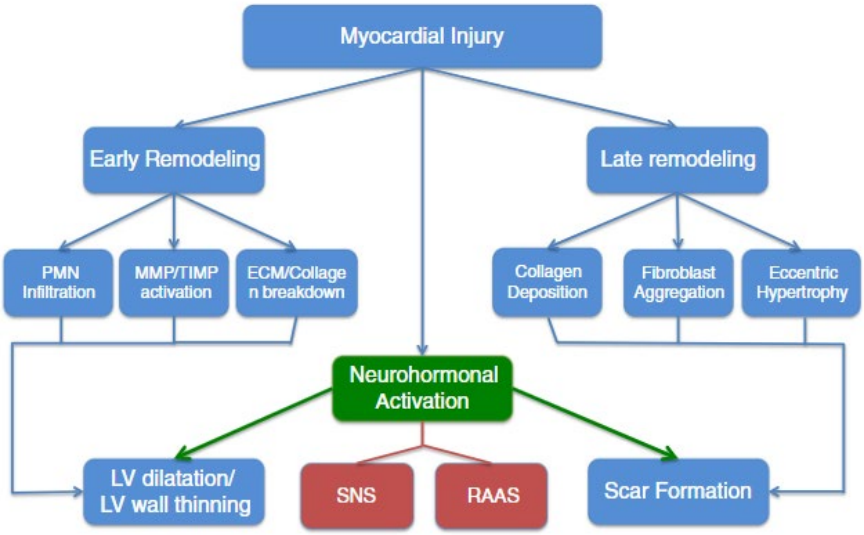

Figure 1.9 Major Interactions between cellular, extracellular and neurohormonal components in the development of post-Myocardial Infarction cardiac remodelling. Reproduced from Bhatt et al. (104)

1.3.2.2 Myocardial Fibrosis

Fibrosis generally refers to the deposition of Type I and Type III collagen along with Extracellular Matrix (ECM) remodelling and cross-linking, resulting in an altered structure, stiffening and reduced elasticity of the heart. Myocardial fibrosis can be classified into three categories; replacement fibrosis which occurs following myocyte injury such as post infarction, reactive fibrosis which is a more diffuse distribution of collagen in the ECM such as in NICM and infiltrative interstitial fibrosis, accumulation of non-collagenous materials such as amyloid deposition, or iron (105).

The process of fibrogenesis, which is initiated following the activation of cardiac fibroblasts, is a complex and multi-step phenomenon. Many immune cells including macrophages, mast cells and lymphocytes are involved in this process by secreting pro-fibrotic mediators such as cytokines and growth factors, which not only activate fibroblasts, but recruit more inflammatory cells to the site of injury. Vascular endothelial and smooth muscle cells are capable of secreting fibroblast activating factors. Injured cardiomyocytes in response to stress, respond by triggering inflammatory and fibrogenic pathways.

A vast number of inflammatory cytokines and growth factors have been demonstrated to play a role in cardiac fibrosis and remodelling in both in vitro and in vivo animal model studies and their exact mechanisms are being continually studied. It is beyond the scope of this introduction to review them in detail here.

Activated fibroblasts are the key step to myocardial fibrosis. They recruit inflammatory cells, produce large amounts of ECM proteins e.g. type I and type III collagen, and determine ECM remodelling by producing Matrix Metalloproteinases (MMPs) as well as their inhibitors. (106)

Under cardiac stress and injury, activated fibroblasts convert to an “over-active” phenotype known as myofibroblasts. These myofibroblasts express novel markers, contractile activity, and demonstrate a pronounced and prolonged increase in production of ECM components such as collagen and fibronectin. (107,108)

Multiple changes occur in the ECM during the fibrogenic process. As well as increased protein production, there is increased synthesis of MMPs and relative downregulation of Tissue Inhibitors of MMPs (TIMPS), which results in the ECM being actively turned over. The balance between MMPs and TIMPs is coordinated through a vast system of transcription factor and enzyme signalling pathways. (109)

1.3.2.3 The role of Neurohormonal Pathways in Adverse Remodelling

In HF regardless of aetiology, the Renin-Angiotensin-Aldosterone (RAAS) system and Sympathetic Nervous System (SNS) are overactive and maladaptive, as described previously. This neurohormonal axis plays a critical role in the development of adverse cardiac remodelling, myofibroblast activation and fibrosis.

Angiotensin II is a potent activator of cardiac fibroblasts, with multiple studies demonstrating it stimulates fibroblast proliferation and migration, inhibits fibroblast apoptosis and promotes myofibroblast transdifferentiation.

It stimulates myofibroblast cell adhesion and ECM structural protein production, synthesis of collagen and connective tissue growth factors. These effects are mediated through the binding of Angiotensin II to the Angiotensin II Type 1 receptor (AT1 receptor) which stimulates expression of Transforming Growth Factor β (TGFβ). Blockade of RAAS could therefore attenuate or inhibit the process of cardiac fibrosis. (106,108)

1.3.3 Prognostic Relevance of Cardiac Remodelling in Heart Failure

Remodelling, as described above, is biologically involved in the development and progression of HF. Enlargement of the Left Ventricle and reduced Ejection Fraction are well recognised negative prognostic markers in patients with HF. (101) Increased LV volumes as assessed by echocardiography have been described as strong predictors of both development of, and survival in Heart Failure. (99,110) Reverse remodelling has therefore been proposed as a possible surrogate marker for efficacy of HF therapy. Treatments that result in reverse remodelling should be effective in reducing adverse outcomes within the HF patient cohort.

A meta-analysis examining the association between 30 placebo-controlled randomised controlled trials (RCTs) evaluating the effect of drug or device HF therapies on mortality, and 88 studies of those same therapies on remodelling parameters from imaging studies; found that short-term therapeutic effects of the therapies on LV remodelling was associated with longer-term trial level effects on mortality. Favourable change in LV remodelling i.e. increase in LV Ejection Fraction (EF), reduction in End Diastolic Volume (EDV) and reduction in End Systolic Volume (ESV), was associated with reduced mortality risk. (111)

Patients who do undergo reverse remodelling and clinical improvement or apparent “recovery” on heart failure medications should not however, have their medications withdrawn. TRED-HF demonstrated that 44% of patients who had improved EF to >50%, normalised LVEDVs and low serum NTproBNP on HF therapy, experienced a relapse of dilated cardiomyopathy 6 months after medication withdrawal. (112)

Morbidity and mortality in Heart Failure result from a complex process with a multitude of factors at play; and is unlikely to be predicted by any single parameter. Developing our understanding of a whole range of biomarkers and prognostic indicators, increases our overall understanding of risk stratification in this complex patient cohort.

1.3.4 Heart Failure Therapies and Reverse Remodelling

1.3.4.1 ACE Inhibitors

The clinical morbidity and mortality benefit for ACEIs in the treatment of patients with HFrEF is well evidenced however, relatively few studies have isolated the remodelling process i.e. change in LV volume, in examining its relation to outcome.

The landmark Survival and Ventricular Enlargement (SAVE) trial demonstrated a significant reduction in morbidity and mortality among patients post-MI with EF ≤40% randomised to captopril vs placebo. An echocardiographic sub-study of SAVE showed at 1 year there was an attenuation of LV area enlargement in the patients treated with captopril, which was associated with a reduction of adverse events (risk reduction of 35%). Interestingly, they found that increased baseline LV areas and larger increases in LV areas at 1 year (i.e. more adverse remodelling) were predictors of cardiovascular mortality and adverse outcome, regardless of whether patients were in the treatment or placebo group. (113)

The Studies of Left Ventricular Dysfunction (SOLVD) trial showed that enalapril reduced mortality and HF hospitalisation for NYHA II-III patients with chronic HF and EF ≤35%. A radionuclide ventriculography sub-study found that patients randomised to enalapril had relatively early reduction in LV volumes (EDV and ESV) which was maintained to approximately 3 years. In contrast, patients treated with placebo had a steady increase in LV volumes. (114)

1.3.4.2 Beta Blockers

The beneficial effect of beta blockers on reducing morbidity and mortality in patients with HFrEF is overwhelming. In terms of remodelling, treatment with beta blockers have demonstrated significant and sustained improvements in cardiac remodelling parameters; decreased LV volumes and mass, improvement in LV geometry, increased Ejection Fraction and prevention of progressive LV dilatation. (115–118)

It must be remembered however, that almost all patients enrolled into these beta blocker Heart Failure studies were already taking regular ACE Inhibitors and therefore the significant effects they have shown on reverse remodelling is on the background of RAAS inhibition.

1.3.4.3 Mineralocorticoid Receptor Antagonists (MRA)

Although the clinical survival benefit of MRAs in patients with HF both ischaemic and non-ischaemic is well established, the evidence with respect to LV remodelling however is more limited and show mixed results. (18,19)

A small study of stable patients with Non-Ischaemic HFrEF found that 4 months of spironolactone improved left ventricular volume and mass; and was associated with decreased plasma levels of BNP and the fibrotic marker Plasma Procollagen type III aminoterminal peptide (PIIINP). (119)

A larger multicentre study however, randomised clinically stable NYHA II/III patients with HFrEF already treated with ACEI and beta blockers, to eplerenone vs. placebo and found after 36 weeks, no significant difference on parameters of LV remodelling (indexed LVEDV or indexed LVESV). They did find a reduction in serum levels of collagen turnover marker Procollagen type I N-terminal propeptide (PINP)and BNP, but no significant difference in PIIINP levels. (120)

A sub-study that retrospectively analysed a subgroup of 261 patients from the landmark RALES study measured serological markers of Extracellular Matrix turnover at baseline and at 6 months. They found that high baseline serum levels of markers of fibrosis (including PINP and PIIINP) were associated with worse patient outcome (death and hospitalisation) and that levels of these serum markers decreased with spironolactone treatment; suggesting that antagonism of aldosterone stimulated collagen synthesis may be one of the mechanisms contributing to clinical benefits seen of spironolactone. (121)

A sub-study of EPHESUS also measured serum levels of collagen biomarkers in 476 patients and found that high levels of type 1 collagen telopeptide (a marker of cardiac collagen degradation) and BNP at baseline were associated with worse outcome. They found the eplerenone group had decreased serum levels of PINP and PIINP at 6 months. (122)

1.3.4.4 Angiotensin Receptor Neprilysin Inhibitor (ARNI)

The exact mechanisms by which sacubitril/valsartan (Entresto) achieves its profound clinical benefit in HFrEF are not fully understood. Recent data does however support the notion that cardiac reverse remodelling forms part of the explanation. Several small early studies reported an improvement in left ventricular volumes and LVEF after the initiation of ARNI therapy.

These were included in a meta-analysis of 20 studies (over 10,000 patients) which showed that sacubitril/valsartan was associated with a decrease in LVEDV and LVESV, and an increase in LVEF of approximately 5% in HFrEF patients, compared with traditional ACEI/ARB therapy. The authors however recognised the limitations of this meta-analysis in that some studies included were conference abstracts, and only 7 compared ARNI to ACEI/ARBs. (123)

PROVE-HF was a multi-centre prospective single group open label study of 794 patients with HFrEF treated with sacubitril/valsartan. 76% of patients were previously established on ACEI/ARB and were switched over to sacubitril/valsartan, with 65% of patients reaching the target dose of 97/103mg BD by the end of the study. Patients had a blinded echocardiogram at baseline, 6 months and 12 months, along plasma NTproBNP levels measured at each study visit.

The study found at 6 months, patients had a mean LVEF increase of 5.2% (95% CI, 4.8% to 5.6%. P <0.001). At 12 months, they reported a mean LVEF increase of 9.4% (95% CI, 8.8% to 9.9%. P<0.001); with 75% of patients experiencing an LVEF increase of ≥4.9% and 25% of patients experiencing an LVEF increase of ≥13.4%.

At 6-months and 12-month timepoints, they reported reductions in mean LVEDVi -6.65ml/m2 (95% CI, -7.11 to -6.19. P<0.001) and -12.25ml/m2 (95% -12.92 to -11.58. P<0.001) respectively; and reductions in LVESVi of -8.67ml/m2 (95% CI, -9,18 to -8.15. P<0.001) and -15.29ml/m2 (95% CI, -16.03 to -14.55. P<0.001) respectively. Mean indexed LA volumes were also found to have decreased at these timepoints and in post-hoc analysis, so did mean indexed LV masses.

Whilst recognising the inherent limitations of observational studies, PROVE-HF demonstrated echocardiographic changes consistent with beneficial reverse remodelling in patients with HFrEF following sacubitril/valsartan treatment from as early as 6 months, sustained and actually amplified by 12 months. (124) The improvement in parameters of reverse remodelling were associated with a reduction in NTproBNP across the 12-month study period.

A sub-study of the PROVE-HF cohort demonstrated a rapid and significant improvement in patient reported health status using the Kansas City Cardiomyopathy Questionnaire (KCCQ-23), significantly related to change in plasma NTproBNP levels in an inverse fashion. (125) Several other subgroup analyses of PROVE-HF have been performed to understand reverse remodelling differences in sex and race. 28.5% of the PROVE-HF cohort were women. The degree of reverse remodelling was found to be similar between men and women, but the effects were apparent earlier in women, in association with a more rapid early decline of NTproBNP. (126)

22.7% and 14.9% of the PROVE-HF cohort were Black or Hispanic patients respectively. Black and Hispanic patients were found to have lower NTproBNP levels at baseline compared to White patients. After treatment with sacubitril/valsartan however, there were similar reductions seen in NTproBNP levels and similar improvements in LVEF, LVEDVi and LVESVi across all three race/ethnicity groups. (127)

EVALUATE-HF was a randomised double-blind trial of 464 patients with HFrEF treated with sacubitril/valsartan or enalapril for 12 weeks, looking to investigate the potential early beneficial effects of ARNI on central aortic stiffness and cardiac remodelling. They found no statistical difference between groups for aortic impedance, however the prespecified secondary endpoints demonstrated greater reductions from baseline in the sacubitril/valsartan group of LVEDVi, LVESVi and LAVi, as well as improvement in diastolic function compared to enalapril. There was however, no difference demonstrated between groups in LVEF at the 3 month stage. (128)

Similar to some of the earlier MRA studies described above, a sub-study of PARADIGM-HF analysed the effect of sacubitril/valsartan on biomarkers of Extracellular Matrix homeostasis and collagen synthesis, and their association with the PARADIGM-HF primary outcome (cardiovascular death or HF hospitalisation). They found that in patients with HFrEF, baseline levels of biomarkers of ECM homeostasis, collagen synthesis and profibrotic signalling were higher than reference values. Higher baseline levels of the profibrotic biomarkers soluble ST2 (sST2), TIMP-1 and PIIINP were associated with worse outcome.

8 months after randomisation, levels of aldosterone, soluble ST2, TIMP-1, PINP, PIIINP and MMP-9, had decreased more in the sacubitril/valsartan patient group compared with enalapril. There was also a significant relationship between the reduction of ssT2 and TIMP-1 levels from baseline, and reduced rates of the primary outcome. The study concluded that profibrotic signalling biomarkers are altered in HFrEF, are prognostically important and were significantly decreased by sacubitril/valsartan, suggesting a reduction in profibrotic signalling as a contributing mechanism to its clinical efficacy. (129)

In animal studies of induced MI mouse models, sacubitril/valsartan has been found to attenuate adverse cardiac remodelling, degree of fibrosis and post-infarct cardiac dysfunction. (130,131) One recent study investigated the Wnt/β-catenin signalling pathway which is involved in myocardial repair post-infarct, cardiac fibrosis and adverse remodelling processes. This signalling pathway was found to be activated in post-MI mice and was shown to be inhibited by sacubitril/valsartan. (131)

In a sub-analysis of the PARADIGM-HF mortality data, 44.8% (n=561) of cardiovascular deaths were classified as "sudden death" and treatment with sacubitril/valsartan resulted in a relative risk reduction of 20%, compared with enalapril (HR 0.80, 95% CI 0.68-0.94. P=0.008). (132)

An anti-arrhythmic effect has been described in two prospective studies of HFrEF patents with ICD/CRT-Ds in situ and remote monitoring. Following switchover from ACE-I/ARB to sacubitril/valsartan therapy, episodes of non-sustained ventricular tachycardia (VT), sustained VT and appropriate ICD shocks were significantly decreased. (133,134)

The mechanisms behind this apparent anti-arrhythmic effect are not well understood. One of the aforementioned studies defined reverse remodelling as an improvement in LVEF ≥5% and found that patients with a greater degree of LVEF improvement following sacubitril/valsartan treatment (i.e. improvement of LVEF >5%), experienced a lower burden of NSVT and hourly premature ventricular contractions (PVC). The significant reduction in PVC burden seen after sacubitril/valsartan treatment, possibly due to beneficial remodelling, was associated with an improvement in percentage of biventricular pacing in those patients with <90% biventricular pacing at baseline. (135)

Another relatively small prospective study found treatment with sacubitril/valsartan resulted in a reduction in QTc interval and QRS duration on ECG and a reduction in mechanical dispersion index (standard deviation of time to peak negative LV Global Longitudinal Strain) on echocardiography at 6 months. (136) Mechanical dispersion index has been shown in pilot studies to correlate with ventricular arrhythmic burden in patients with HFrEF, supporting the notion that favourable myocardial reverse remodelling with sacubitril/valsartan may contribute to lessening the arrhythmic burden. (137)

Sacubitril/valsartan is known to promote natriuresis, reduce LV volumes and end diastolic pressures, as well as improve functional mitral regurgitation. Elevated LV filling pressures and natriuretic peptide levels are predictors of ventricular arrhythmias and appropriate ICD therapies in patients with HFrEF. The unloading of the LV seen in beneficial reverse remodelling with sacubitril/valsartan treatment could also be a contributing factor to reduction in arrhythmias. (138)

1.3.4.5 SGLT2 Inhibitors

There are several published animal studies investigating the effect of SGLT2 Inhibitor Dapagliflozin on cardiac remodelling, fibrosis and function, as well as its effects on specific signalling pathways and inflammatory cytokines involved in these processes.

The results suggest that Dapagliflozin could play a role in attenuating these processes in animal models. (139–141)

One meta-analysis examining the effects of SGLT2 inhibitors on cardiac remodelling included RCTs evaluating patients with Type 2 Diabetes and/or Heart Failure. This found that favourable cardiac remodelling was only significant in the subgroup of patients with HFrEF and that treatment with SGLT2 inhibitors, particularly Empagliflozin, improved LVEF, LV mass and volume parameters as assessed by echocardiography, regardless of diabetic status. (142) Another meta-analysis which only included HFrEF patients (25% with diabetes) demonstrated that SGLT2 inhibitors resulted in reverse remodelling in the form of improved LVEDV, LVESV and LAVi but only a non-significant trend in LVEF increase and LV mass reduction. (143)

A recent meta-analysis of 5 randomised CMR imaging trials comparing SGLT2 inhibitors to placebo in patients with HF and/or diabetes found that SGLT2 inhibitor treatment was associated with a reduction in LV mass as assessed by CMR, but no difference in LV Mass indexed to BSA, LV volume parameters nor LVEF. There was however significant heterogeneity between the studies included, with relatively small sample sizes and differing durations of treatment. (144)

With the advent of CMR parametric mapping techniques as discussed previously, studies are now starting to use T1 mapping and ECV as measures of diffuse myocardial fibrosis as an endpoint in determining the antifibrotic effects of therapies. (145)

A meta-analysis of a small number CMR studies evaluated the effect of empagliflozin on diffuse myocardial fibrosis by CMR T1 mapping. The analysis of studies that compared Extracellular Volume (ECV) before and after treatment with empagliflozin or placebo, showed a pooled effect of weighted mean differences in favour of empagliflozin. There was no statistical difference in change of native T1 values between groups. The studies included were however small in sample size, only 2 studies included patients with HFrEF and only 3 studies reported ECV before and after empagliflozin or placebo treatment. (146)

1.4 Research Objectives

This research aimed to investigate the role of Cardiac Magnetic Resonance (CMR) imaging in the management of two cohorts of Heart Failure patients; those hospitalised with a new diagnosis of Heart Failure (PREDICT-HF) and those with chronic HFrEF, who had not demonstrated reverse remodelling despite 3 months of "conventional" HFrEF medical therapy (The ENVI Study).

PREDICT-HF, a proof of concept pilot study, aimed to investigate whether baseline T1 parametric mapping values and Extracellular Volume (ECV), both novel CMR tissue characterisation biomarkers, correlate with adverse outcome, response to guideline-directed HF therapy in the form of cardiac reverse remodelling in patients hospitalised with newly diagnosed HF.

The ENVI study aimed to investigate the effects of optimisation from conventional to contemporary HFrEF medical therapy with sacubitril/valsartan (Entresto), on CMR volumetric and tissue characterisation parameters, and rates of complex device implantation.

The final aim was to evaluate whether there was any significant variability in T1 value measurements over time from the same CMR scanner, using T1MES phantom technology.

Chapter 2 GENERAL METHODOLOGY

2.1 Cardiovascular Magnetic Resonance

All patients were scanned using a 1.5 Tesla Siemens Sola CMR scanner (Erlangen, Germany) using prospective ECG gating and standard imaging acquisition protocols. (71) All scans were performed at University Hospital Southampton (UHS) between April 2018 and March 2023.

CMR analysis was performed on CVI42® version 5.10.1 software (Circle, Calgary, Canada). All patient scan data were anonymised, and analysis of baseline and follow up scans were performed during independent sessions.

2.1.1 Cardiomyopathy Protocol and Acquisition

A standardised cardiomyopathy protocol was used for all CMR scans. In brief, localiser acquisitions to position and align the true long and perpendicular short axis of the ventricle were taken. Balanced steady state free precession (bSSFP) cine imaging was performed with breath hold at end expiration. Long axis cines for LV 4-chamber, 2-chamber, 3-chamber and RV 2-chamber were acquired, followed by pre-contrast T1 mapping of long axis 4-chamber and at 2 levels of short axis (basal and mid) slices; and T2 mid-level short axis map.

The T1 mapping (Siemens MyoMaps) sequence used was a Modified Look Locker Inversion recovery (MOLLI) with diastolic acquisition in one breath hold with inline motion correction. The validated MOLLI acquisition sequences used were 5(3)3 pre-contrast and 4(1)3(1)2 post-contrast to generate T1 mapping.

Gadovist ® contrast was given at 0.15mmol/kg dose and short-axis cines acquired followed by Mitral and Aortic flow. Late Gadolinium acquisition comprised of TI-scout (inversion time) sequence and Magnitude-based (MAG) LGE short axis slices (at same position as cines), 2-chamber, 3-chamber and 4-chamber along with single shot PSIR short-axis stack (phase-sensitive inversion recovery).

Lastly, Post-contrast T1 maps were generated in the same positions as pre-contrast maps.

2.1.2 Ventricular Volumetric, Mass and Function Analysis

Biventricular volume analysis was calculated from the short axis cine stack using CVI42® semi-automated LV and RV analysis package. Mitral and tricuspid annular planes were specified throughout the cardiac cycle in both 4 chamber, 2 chamber and 3 chamber planes and short axes slices defined for volume analysis. **(Figure 2.1)**

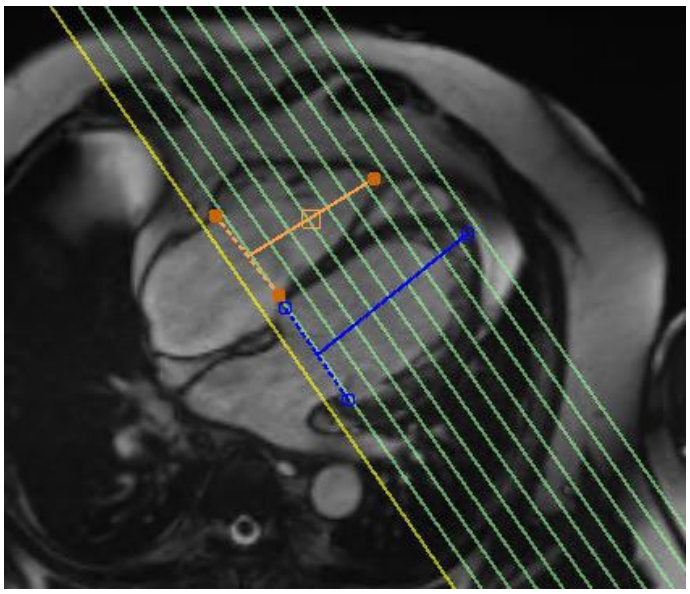

Figure 2.1 Left Ventricular (blue) and Right Ventricular (orange) long-axis delineation on 4-chamber long axis view. Perpendicular lines show position of short axis slices.

LV endocardial and epicardial borders were defined semi-automatically, however manual adjustments were sometimes required. The papillary muscles were assigned to the blood pool for calculation and were also not included in LV mass calculation. RV endocardial border was also delineated semi-automatically with manual correction if required. **(Figure 2.2)**

End-diastolic and End-systolic phases were identified, giving calculated End-Diastolic Volumes (EDV) and End-Systolic Volumes (ESV) both in absolute values and indexed to Body Surface Area (BSA). Stroke Volumes (SV) was calculated automatically from the difference between EDV and ESV and Ejection Fraction calculated by dividing SV by EDV and multiplied by 100.

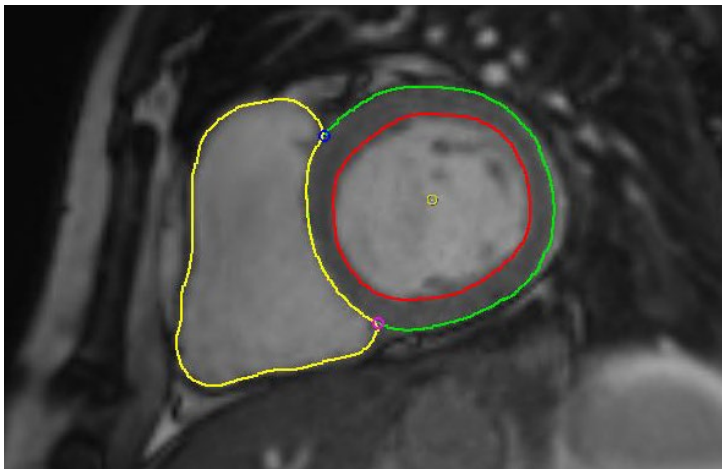

Figure 2.2 Left Ventricular endocardial (red) and epicardial (green) contours. Right Ventricular endocardial (yellow) contour. Superior Right Ventricular Insertion Point (blue dot) and inferior Right Ventricular Insertion Point (pink dot).

2.1.3 Atrial Analysis

Atrial analysis was performed using CVI42® atrial analysis package by manually delineating the left atrial areas in the 4-chamber and 2 chamber views in order to give a biplanar calculated LA volume at LV end-systole, also indexed to BSA. **(Figure 2.3)**

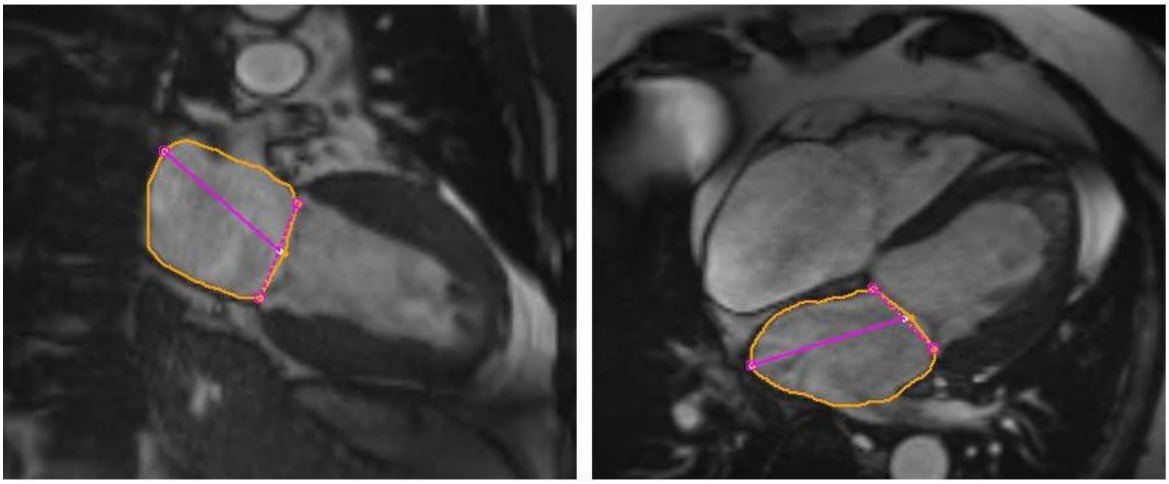

Figure 2.3 Left Atrial contour delineated in 2-chamber and 4 chamber views.

2.1.4 Late Gadolinium Enhancement – Analysis and Quantification

Left Ventricular Late Gadolinium Enhancement (LGE) (focal scar) was analysed both qualitatively and quantitatively. Qualitative analysis of MAG/PSIR short axis slices was performed with visual assessment for presence or absence of LGE.

If present, diagnosis was classified as either ischaemic (sub-endocardial or transmural LGE) cardiomyopathy or non-ischaemic cardiomyopathy (mid-wall or sub-epicardial LGE) based on the predominant LGE pattern.

If LGE was absent, the diagnosis was classified as non-ischaemic cardiomyopathy without scar.

Quantitative LGE was initially performed using the validated semi-automated Full Width Half Maximum (FWHM) detection method. The LV endocardial and epicardial borders were manually drawn and superior RV Insertion Point selected. A Region of Interest (ROI) of maximum signal i.e. brightest area of LGE enhancement was selected manually, giving a calculation of LGE quantification (% mass). **(Figure 2.4)**

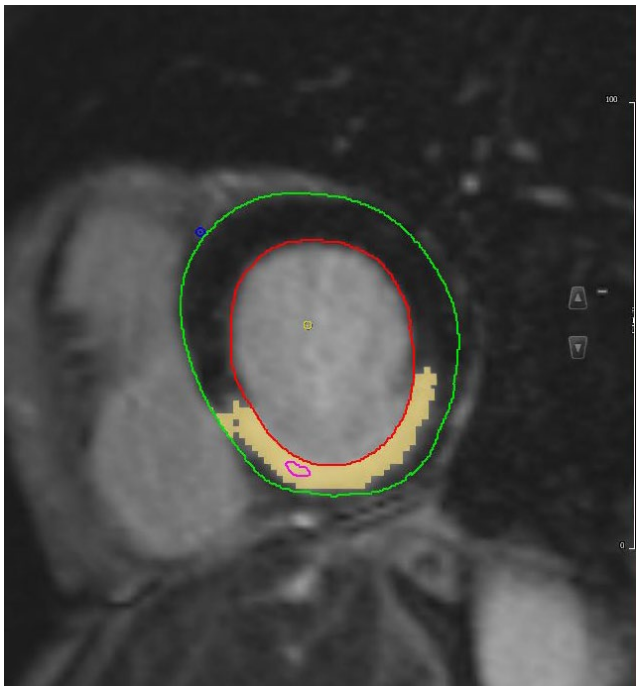

Figure 2.4 FWHM method for LGE quantification. LV endocardial (red) and epicardial (green) contours are delineated. Superior Right Ventricular insertion point (blue dot) and maximum LGE signal strength sampled (pink).

Unfortunately, the FWHM method proved to overestimate LGE burden in many study scans and therefore, areas which had been highlighted by this method as LGE present but were visually assessed to be absent, were then excluded manually. The LGE quantification analysis technique for these studies therefore equated to manual LGE planimetry quantification technique. As previously discussed, there is currently no consensus as to which method is best for quantitative assessment. (57)

2.1.5 T1 Mapping and ECV – Analysis

Two short-axis LV slices (basal and mid-level) were acquired for pre-contrast and post-contrast T1 parametric mapping. Local T1 reference ranges for normal subjects using the acquisition sequences above had been previously established.

Each slice was segmented into 6 segments, giving a total of 12 segments corresponding to segments 1-12 of the American Heart Association (AHA) 17 cardiac segment model. (147)

A Region of Interest (ROI) was manually drawn within the basal or mid-level septum (segment 2/3 or 8/9) for native (pre-contrast) and post-contrast T1 value measurements. The ROI was selected in an area of myocardium *away* from visible LGE. A sample for bloodpool T1 value pre- and post-contrast was manually drawn on both slices, away from papillary muscles. **(Figure 2.5)**

The Haematocrit (Hct) value was obtained from the patient's blood test at their baseline research clinic visit and used for calculation of ROI Extracellular Volume (ECV) using the validated calculation below.

$$ECV = (1 - haematocrit)\frac{\frac{1}{post\ contrast\ T1\ myo} - \frac{1}{native\ T1\ myo}}{\frac{1}{post\ contrast\ T1\ blood} - \frac{1}{native\ T1\ blood}}$$

In addition to the septal ROI, "whole heart" Global Myocardial T1 and ECV values were calculated from 2 level (12 segments) pre- and post-contrast T1 maps using CVI42® software.

This technique of utilising multi-level circumferential regions of interest (ROI) ensuring a larger sample of myocardium for T1 analysis and ECV calculation, and its technical feasibility in cardiomyopathy patients regardless of aetiology, is described in prior work from our Research Group. (148)

For both short axis slices (12 segments), left ventricular epicardial and endocardial contours were manually drawn on pre-contrast and post-contrast maps. An equal offset from both contours of 30% was selected (value previously used by our group). A circumferential offset of 10% has been previously used in healthy cohorts. (149) As our cohort consisted of patients with cardiac pathology, left ventricular dilatation and potentially myocardial thinning, a 30% offset was chosen to reduce partial volume effect. **(Figure 2.6)**

The pre- and post-contrast mean T1 (ms) values for the individual 12 segments at basal and mid-level, along with the corresponding (basal and mid-level) bloodpool mean T1 values were recorded and used to calculate a mean basal, mid-level and subsequent "whole heart" Global T1 and ECV (%), representing total myocardial fibrosis.

Global T1 and ECV is still very much an emerging field with focal myocardial fibrosis (LGE) and diffuse fibrosis (T1 mapping and ECV %) have been previously described in isolation in the literature. Estimations of "whole heart" Global ECV (%) *excluding* LGE were therefore also calculated for participants in The ENVI Study. This was calculated by comparing the 2 short-axis T1 maps with the corresponding slice position of short-axis LGE imaging. Any myocardial segments containing LGE were excluded from the overall mean native and post-contrast T1 (ms) and ECV (%) calculations.

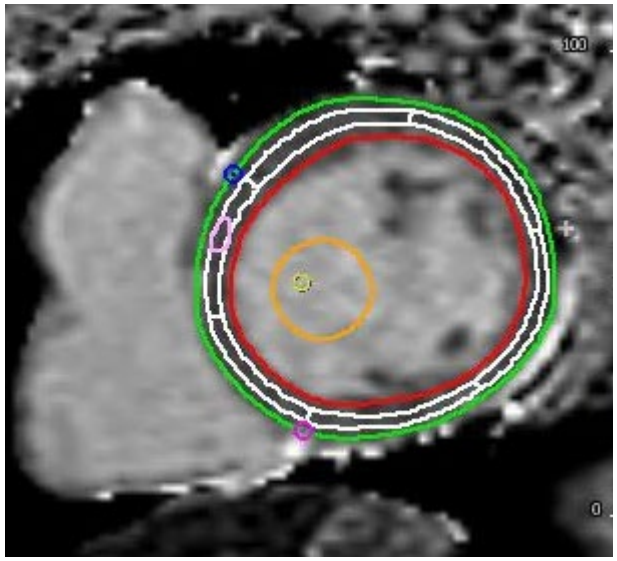

Figure 2.5 Left Ventricular endocardial (red) and epicardial (green) contours with equal offset applied (white) and 6-segments. Superior Right Ventricular Insertion Point (blue dot) and inferior Right Ventricular Insertion Point (purple dot). Septal ROI (pink sample) and bloodpool ROI (orange sample).

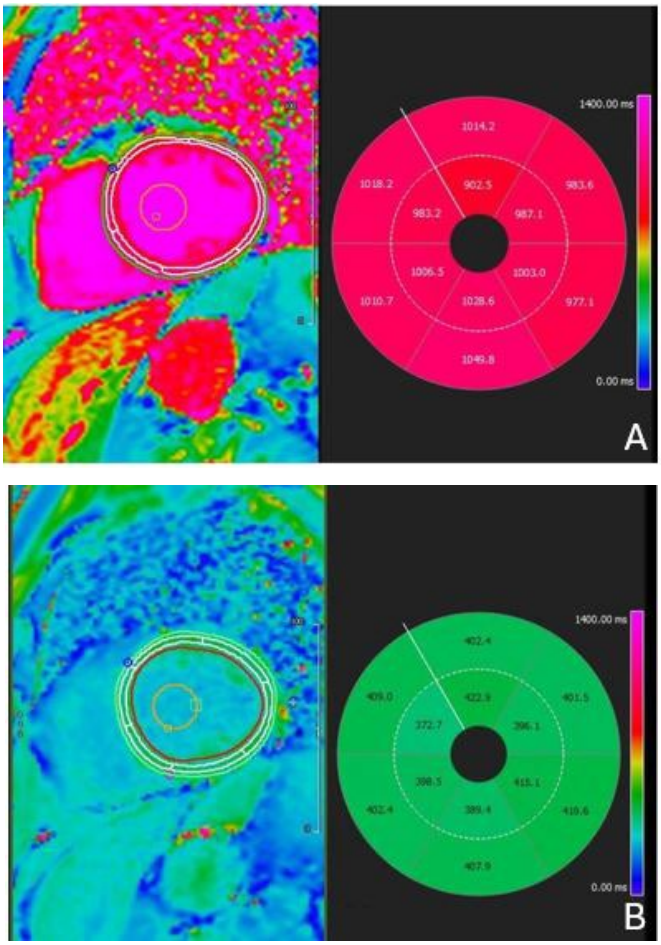

Figure 2.6 Pre-contrast (A) and Post-contrast (B) T1 maps showing T1 values for each of 12 segments.

2.2 Patient Clinical Data

Following informed consent and study enrolment, patient clinical data was collected prospectively during baseline and each follow up study clinical consultations. Past medical history and medication data was corroborated using the University Hospital Southampton (UHS) digital Electronic Patient Records (CHARTS) and Care and Health Information Exchange (CHIE) information linked from Primary Care.

The following data points were recorded:

2.2.1 Demographic and Clinical Data

- Age and Sex
- Weight (kg) and height (cm)
- NYHA Functional Class Status (I-IV)
- Blood Pressure, pulse and oxygen saturations
- Past Medical History
- Medication History
- Blood tests (specified in Results Chapters)
- 12-lead Electrocardiogram (rhythm, rate, QRS duration, presence of LBBB or RBBB)
- Transthoracic Echocardiogram (parameters specified in Results Chapters)

2.2.2 Six Minute Walk Test (6MWT)

Patients completed a supervised 6 Minute Walk Test (modified 10 metre track) at baseline and at subsequent follow up assessments.

Resting heart rate, BP and oxygen saturations were measured before starting. Patients were instructed to walk the course at their own pace, attempting to cover as much distance as possible in 6 minutes. A verbal update was given at every minute. Patients were allowed to rest if required, and were encouraged to continue if able, or terminate the test early if required.

At the end of the 6 minutes, the distance was measured. Any symptoms such as shortness of breath, fatigue or dizziness were recorded. Reasons for declining the 6MWT were also recorded. Heart rate, BP and oxygen saturations were repeated during recovery.

2.2.3 Kansas City Cardiomyopathy Questionnaire (KCCQ-12)

Patients completed a Kansas City Cardiomyopathy (KCCQ-12) questionnaire at baseline and at follow up. The KCCQ-12 was developed as a shorter version of the original 23-item instrument and is well-validated, reproducible and widely used to collect patient-reported symptoms, function and quality of life.

2.2.4 Clinical Outcome Data

Clinical outcome data was collected for the specified study follow up period from UHS Electronic Patient Records (CHARTS). Data points included:

- Date of hospital admission/re-admissions during study period
- Reason for re-admission e.g. heart failure hospitalisation
- Device implantation – device type, date of implant
- All-cause mortality and date of death

2.3 Statistics

All statistical tests were performed using IBM® SPSS® software package version 27.

Normally distributed (parametric) continuous variables are presented as mean ± standard deviation (SD). Non-normally distributed (non-parametric) continuous variables are presented as median (interquartile range; IQR). Categorical variables are reported as number and percentage frequencies.

The statistical tests used are detailed below:

- Normality testing:
    - Shapiro-Wilk test, correlated with visual histogram assessment
- Normally distributed (parametric) continuous variables:
    - Independent 2 sample t-test (2 tailed) (unpaired data)
    - Paired t-test (paired data)
- Non-normally distributed (non-parametric) continuous variables:
    - Mann-Whitney U test (unpaired data)
    - Wilcoxon signed ranks test (paired data)
- Categorical values:
    - Fisher's exact test as sample size is small and >20% expected counts <5.

- Survival analysis (Hazard Ratio):
    - Kaplan Meier Analysis

2.4 Ethics

All research was conducted between April 2018 and March 2023 at University Hospital Southampton (UHS) with Research & Development (R&D) sponsorship.

Health Research Authority (HRA) approval was granted for both prospective studies.

- REC Reference: 18/LO/0506, IRAS ID 241841
- REC Reference: 21/WM/0073, IRAS ID 288602

Chapter 3 RESULTS 1: Using cardiovascular magnetic resonance tissue characterisation to PREDICT clinical outcomes, and response to therapy in hospitalised Heart Failure patients: PREDICT-HF - Adverse Outcome Analysis

3.1 Acknowledgement

Dr Robert Adam, under the supervision of Dr Andrew Flett, was responsible for the concept, ethics application, study design, recruitment of participants and the initial 6-month follow ups for the PREDICT-HF study before finishing his time in research. The PREDICT-HF study data was not included in his MD thesis.

From February 2020, Dr Alice Zheng commenced research and took over the PREDICT-HF study, completing all subsequent participant clinical follow up appointments, clinical data and sample collections, all clinical and CMR data analyses, statistical analyses and manuscript write ups.

3.2 Introduction

Multiple prognostic indicators in Heart Failure have been identified over the past decades of research and reflect the complexity and co-morbidity of this patient cohort. **(Table 3.1)**

Left Ventricular Ejection Fraction (LVEF) has however, emerged and remains the sole parameter defining classification and inclusion criteria for most clinical trials, and the arbiter for offering HF therapies. There is a recognised need for development of improved risk stratification strategies that deliver a more personalised care for patients with Heart Failure.

CMR with its ability to accurately assess tissue characterisation non-invasively, places this imaging modality at the forefront of efforts to establish individualised Heart Failure care when it comes to both pharmacological and device therapy.

Demographic	Older age, male sex, low socio-economic status
Clinical	Body weight, advanced NYHA Class, short-6-minute walk test, reduced muscle strength, poor quality of life, low blood pressure, evidence of fluid overload, frailty, heart failure hospitalisation, aborted cardiac arrest
Co-morbidities	Ischemic heart disease, previous TIA/CVA, peripheral artery disease, diabetes, anaemia, iron deficiency, COPD, renal failure, liver dysfunction, sleep apnoea, depression
Electrophysiological	High resting heart rate, atrial fibrillation, ventricular arrhythmias, broad QRS
Biological	Low sodium, increased urea, increased creatinine, low haemoglobin, increased troponin, increased natriuretic peptide increased high sensitivity CRP
Imaging	Low LVEF, LV dilatation, severe diastolic dysfunction, high LV filling pressures, mitral regurgitation, aortic stenosis, LVH, left atrial dilatation, RV dysfunction, pulmonary hypertension, ventricular dyssynchrony

Table 3.1 Biomarkers of worse prognosis in patients with Heart Failure. Reproduced from PREDICT-HF protocol.

The association between Late Gadolinium Enhancement (detecting focal fibrosis) in particular, and the potential emerging role of parametric mapping (detecting diffuse myocardial fibrosis) techniques to inform clinical prognosis has been discussed above in 1.2.4 and 1.2.5.3.

3.3 Methods

3.3.1 Study Rationale

PREDICT-HF was the first prospective study to investigate novel CMR tissue characterisation biomarkers and correlate to adverse outcome and response to therapy in a cohort of patients hospitalised with a new diagnosis of Heart Failure.

3.3.2 Study Hypotheses

1. Increased Left Ventricular focal (LGE) and diffuse fibrosis (T1 values and ECV) identified by CMR at baseline is associated with adverse outcome (all-cause mortality and heart failure hospitalisations) in patients hospitalised with a new diagnosis of Heart Failure.
2. Increased Left Ventricular Focal (LGE) and diffuse fibrosis (T1 values and ECV) identified by CMR at baseline is negatively associated with response and beneficial reverse remodelling to Heart Failure therapies, in patients hospitalised with a new diagnosis of Heart Failure.

3.3.3 Study Sample Size

The PREDICT-HF study was designed as a pilot, proof of concept study. Given the relative paucity of data relating to the role of fibrosis and outcomes at the time of study design, a sample size of 150 was initially chosen pragmatically. This was based on HF admission statistics at UHS (approx. 800/year), anticipating 50% eligibility and a 40% uptake, allowing for a 5% drop-out.

The Samsung S-PATCH cardiac monitoring device used for the sub-study was taken over by Wellysis during study recruitment. Rebranding of the S-PATCH device required undergoing an international process of obtaining a new CE mark, resulting in suspension of study recruitment in May 2019. This process unfortunately could not be resolved in a timely fashion before the Covid-19 pandemic in 2020. The final recruitment number therefore remained at n=47.

3.3.4 Inclusion and Exclusion Criteria

All patients admitted to University Hospital Southampton (UHS) with a new primary diagnosis of Heart Failure were considered for eligibility. The diagnosis of Heart Failure was confirmed by a senior Cardiologist with a subspecialty interest in Heart Failure following detailed review of the patient's clinical history, examination findings and investigations using the following diagnostic criteria:

- Signs and symptoms of Heart Failure
- LVEF ≤50% **or** plasma concentrations of NTproBNP >400pg/mL if in sinus rhythm or >1000pg/mL if in Atrial Fibrillation/Flutter and being treated with either oral or intravenous furosemide >40mg/day or equivalent at time of inclusion

Inclusion Criteria:

- Age ≥18 years
- First hospital admission with a diagnosis of Heart Failure
- Able and willing to provide informed consent
- Able to undergo CMR

Exclusion Criteria:

- Known or subsequent diagnosis of amyloidosis, sarcoidosis or hypertrophic cardiomyopathy
- Severe valve disease of any type requiring inpatient surgery

- Heart transplant recipient or admitted for cardiac transplantation/left ventricular assist device
- Clinically apparent myocardial ischaemia which requires revascularisation
- Myocardial infarction or revascularisation within the previous 60 days
- Intracardiac mass requiring surgery
- Active endocarditis
- Septicaemia
- Pregnancy
- Life expectancy <2 years secondary to any other cause (e.g. malignancy)
- Active treatment with chemotherapy
- Severe renal failure (eGFR <30ml/min/1.73m^2)

3.3.5 Study Design

PREDICT-HF was a single centre observational study conducted at University Hospital Southampton.

Consecutive eligible patients hospitalised between April 2018 and April 2019 with a new primary diagnosis of Heart Failure were recruited and written informed consent was obtained. Initial assessment of LV Ejection Fraction for study inclusion was performed by Transthoracic Echocardiogram (TTE) at time of admission.

All participants then underwent a comprehensive CMR scan to non-invasively establish their cardiac anatomy, function and individual myocardial tissue characteristics during their initial presentation hospital admission.

Participants were managed according to best practice 2016 international HF European Society of Cardiology guidelines (21) and underwent comprehensive clinical reviews at 6, 12-18***** and 24-30***** months. **(Figure 3.1)**

Of note, the PREDICT-HF study (including completed follow up period) pre-dated the subsequent updates of HF guidelines and introduction of the ARNI sacubitril/valsartan and dapagliflozin.

***Due to Covid-19 pandemic restrictions in 2020 and national guidance to discontinue non-emergency face-to-face hospital visits during this time; affected participants had their 12- and 24-month reviews conducted via telephone and their face-to-face clinical assessments postponed to 18- and 30-months respectively.**

NB: All patients were offered to participate in an optional heart rhythm and rate monitoring sub-study with continuous electrocardiographic monitoring for up to 2 days prior to discharge and up to 30 days immediately post-discharge using a Samsung S-PATCH device.

The sub-study S-PATCH rhythm data has not been included in this thesis and will form a separate future manuscript.

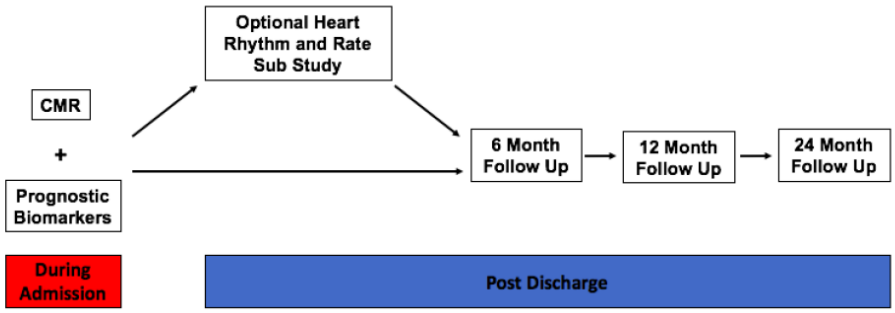

Figure 3.1 PREDICT-HF Study Timeline (reproduced from PREDICT study protocol).

A range of validated investigations to comprehensively assess clinical status, function and other recognised Heart Failure prognostic biomarkers were performed with each study participant at baseline and at each subsequent assessment time point. These included detailed clinical and medication history, clinical examination, ECG, TTE and blood tests including full blood count, renal, liver and bone profile, full cardiomyopathy screen and NTproBNP.

Additional assessments included 6 Minute Walk Test (6MWT), Minnesota Living with Heart Failure questionnaire (MLWHF), grip strength and Mini Mental State Examination (30 points). **(Figure 3.2)**

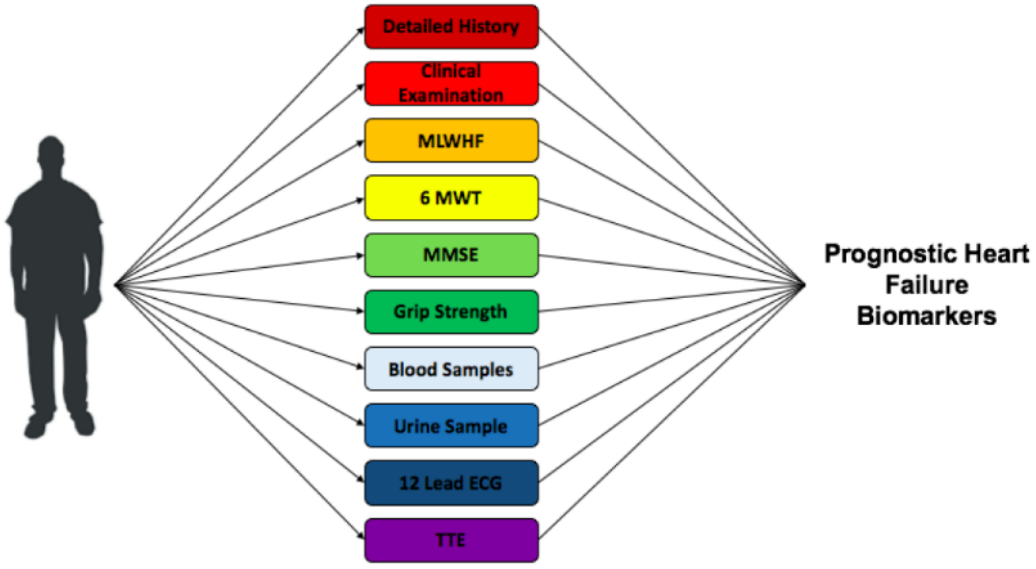

Figure 3.2 PREDICT-HF study assessments. MMSE= Mini Mental State Examination, MLWHF= Minnesota Living with Heart Failure Questionnaire, 6MWT= 6 Minute Walk Test, ECG= Electrocardiogram, TTE= Transthoracic Echocardiogram

All clinically relevant event data, specifically any complex device therapy, rehospitalisation and all-cause mortality were recorded for each participant throughout the study period.

3.3.6 Method – Adverse Outcome Analysis

Hypothesis 1: Increased Left Ventricular focal (LGE) and diffuse fibrosis (T1 values and ECV) identified by CMR at baseline is associated with adverse outcome (all-cause mortality and heart failure hospitalisations) in patients hospitalised with a new diagnosis of Heart Failure.

Adverse Outcome was defined as **all-cause mortality or Heart Failure hospitalisation** during the study follow up period.

CMR parameters including baseline Left Ventricular (LV) volumes and LV Ejection Fraction (LVEF), presence of Late Gadolinium Enhancement (LGE), LGE distribution pattern and quantification as % LV mass, septal Region of Interest (ROI) T1 and ECV (%) values and Global T1 and ECV (%) values were compared between those participants who had an adverse outcome during the study follow up period, and those who had not.

Left Atrial (LA) volume and Right Ventricular (RV) volumes were also compared between adverse outcome and no adverse outcome groups.

Full methods of CMR volumetric, function and tissue characterisation analysis techniques are described in **Chapter 2.**

A Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) score incorporating 13 independent predictors to predict 1 and 3 year mortality in HF patients was calculated for each participant at each assessment stage. (150)

3.3.7 Statistics

All statistical tests were performed on IBM® SPSS® software package version 27. All variables for each group were tested for normality using Shapiro-Wilk test, and correlated with visual assessment of data histogram.

For continuous variables, results were reported as mean ± standard deviation (SD) for normally distributed (parametric) data and median (interquartile range) for non-parametric data. Categorical variables were reported as number and percentage frequencies; n (%).

Independent 2 sample t-test was used to compare continuous parametric variables and Mann-Whitney U test for continuous non-parametric variables. Fisher's exact test was used to compare categorical variables as the overall sample size is small and >20% expected counts were <5.

For analysis of >2 dependent non-parametric variables e.g. LVEF and NTproBNP change across time, Friedman's test was used to test whether there was an overall significant difference. Wilcoxon post-hoc testing was then carried out to determine exactly which paired groups differ statistically (i.e. between which two timepoints). Bonferroni correction was used to adjust the α value and reduce the risk of a Type 1 error when making multiple comparisons.

A p value of ≤0.05 was considered statistically significant.

3.4 Results

A total of 47 participants were recruited to PREDICT-HF between April 2018 and April 2019. Three participants subsequently met exclusion criteria (diagnosis of Hypertrophic Cardiomyopathy, diagnosis of severe Aortic Stenosis and one transpired to have been admitted with HF before). One participant chose to withdraw their consent for participation.

The original protocol stated assessment of each participant at baseline, 6 months, 12 months and 24 months. Due to the Covid-19 pandemic in 2020 and the suspension of face-to-face clinical review during that time, 7 participants had a telephone review only at 12 months, with face to face collection of research data at 18 months, and 20 participants had telephone review only at 24 months with face to face collection of research data at 30 months. Approval for this study amendment was granted by the Research Ethics Committee (REC).

The median follow up of 43 participants was 24.4 months. Overall, the population was relatively young with a mean age of 67±12 years and mostly male (70%). 41 participants (95%) were diagnosed with HF with reduced EF (HFrEF) and 2 (5%) with HF with preserved Ejection Fraction (HFpEF). Nine participants (21%) experienced an adverse outcome (including 6 deaths) during the follow up period.

3.4.1 Baseline Characteristics

Baseline clinical, biochemical characteristics, NYHA functional class and MAGGIC score between the Adverse Outcome and No Adverse Outcome groups were similar. There was very high uptake of Heart Failure medical therapy in both groups.

There was a higher proportion of participants in the Adverse Outcome group with a diagnosis of Ischaemic Cardiomyopathy, compared to the No Adverse Outcome group (67% vs. 18%; p=0.008). Conversely, there was a higher proportion of participants with a diagnosis of Non-Ischaemic Cardiomyopathy in the No Adverse Outcome group (79% vs. 22%, p=0.003). **(Table 3.2)**

	All (n=43)	No Adverse Outcome (n=34)	Adverse Outcome (n=9)	*p* Value
Clinical parameters				
Age (years)	67±12	66±12	72±14	0.159
Male, n (%)	30 (70%)	24 (71%)	6 (67%)	1.000
BMI (kg/m^2)	28.2±4.5	28.4±4.5	27.9±4.8	0.802
SBP (mmHg)	128±22	127±21	135±23	0.326
DBP (mmHg)	78±13	78±14	78±10	0.956
Heart Rate (beats/min)	90 (68-110)	90 (77-112)	73 (64-100)	0.428
NICM, n (%)	29 (67%)	27 (79%)	2 (22%)	**0.003**
ICM, n (%)	12 (28%)	6 (18%)	6 (67%)	**0.008**
HFpEF, n (%)	2 (5%)	1 (3%)	1 (11%)	0.379
MAGGIC score	20±6	20±7	22±4	0.329
MAGGIC 1 year risk (%)	12±7	11±7	13±4	0.621
MAGGIC 3 year risk (%)	27±13	27±14	30±9	0.510
NYHA functional class				
I, n (%)	0 (0%)	0 (0%)	0 (0%)	
II, n (%)	25 (58%)	20 (59%)	5 (56%)	1.000
III, n (%)	18 (42%)	14 (41%)	4 (44%)	1.000
IV, n (%)	0 (0%)	0 (0%)	0 (0%)	
Comorbidity				
Hypertension, n (%)	23 (53%)	16 (47%)	7 (78%)	0.142
Diabetes Mellitus, n (%)	13 (30%)	10 (29%)	3 (33%)	1.000
IHD n (%)	12 (28%)	6 (18%)	6 (67%)	**0.008**
Atrial Fibrillation, n (%)	16 (37%)	12 (35%)	4 (44%)	0.706
Current smoking, n (%)	10 (23%)	9 (26%)	1 (11%)	0.659
Laboratory data				
NTproBNP (ng/L)	5420 (2650-7761)	5456 (2382-7401)	4948 (2121-9247)	0.929
Haemoglobin (g/L)	133±19	134±18	130±24	0.523
Urea (mmol/L)	8.3±2.8	7.9±2.8	9.8±2.3	0.062
Creatinine (umol/L)	96±28	92±28	111±24	0.075
Iron (nmol/L)	10 (7-16)	11 (7-16)	9 (6.5-21.75)	0.754

Drugs				
ACEI/ARB, n (%)	43 (100%)	34 (100%)	9 (100%)	
Beta Blockers, n (%)	42 (98%)	33 (97%)	9 (100%)	1.000
MRA, n (%)	35 (81%)	28 (82%)	7 (78%)	1.000
Loop Diuretics, n (%)	37 (86%)	29 (85%)	8 (89%)	1.000

Table 3.2 Baseline characteristics for all PREDICT-HF participants, No Adverse Outcome group vs. Adverse Outcome group.

BMI=Body Mass Index, SBP= Systolic Blood Pressure, DBP= Diastolic Blood Pressure, NICM= Non-Ischaemic Cardiomyopathy, ICM= Ischaemic Cardiomyopathy, HFpEF= Heart Failure with preserved Ejection Fraction, MAGGIC= Meta-Analysis Global Group in Chronic Heart Failure, NYHA= New York Heart Failure Association functional classification, IHD=Ischaemic Heart Disease, ACEI/ARB=ACE-inhibitors/Angiotensin II Receptor Blockers, MRA= Mineralocorticoid Receptor Antagonists.

3.4.2 LV Ejection Fraction and NTproBNP

With best practice guideline-directed HF therapy (2016), there was an increase in Left Ventricular EF (LVEF) (%) across the whole cohort as measured by echocardiography. The increase in median LVEF occurred predominantly within the first 6 months of initiation of HF therapy from 20% (IQR 15-35%) to 47% (IQR 31-56%) ($p<0.001$). Thereafter, there was no significant difference in median LVEF between any of the other follow up timepoints. **(Figure 3.3)**

On comparison of baseline echocardiography, the No Adverse Outcome group had a lower median baseline LVEF compared to the Adverse Outcome group (18% (IQR 15-30%) vs 35% (IQR 20-48%); $p=0.038$). Despite this, the No Adverse Outcome responded to HF therapy and there was no difference in the median LVEF between groups in subsequent 6-month, 12-18 month and 24–30 month echocardiograms. **(Table 3.3)**

Timepoint	Median LVEF (%)	No Adverse Outcome (n=34)	Adverse Outcome	*p* Value	Adverse Outcome (n)
Baseline LVEF (%)	20 (15-35)	18 (15-30)	35 (20-48)	**0.038**	9
6 month LVEF (%)	47 (31-56)	46 (30-55)	50 (40-60)	0.465	7
12-18 month LVEF (%)	50 (40-56)	50 (39-55)	55 (45-61)	0.178	7
24-30 month LVEF (%)	50 (41-57)	50 (40-55)	58 (33-60)	0.49	4

Table 3.3 Median LV Ejection Fraction (LVEF) (%) by Echocardiography (TTE) across study follow up period for all participants, No Adverse Outcome vs. No Adverse Outcome groups. Number of participants (n) alive in the Adverse Outcome group decreased across review timepoints.

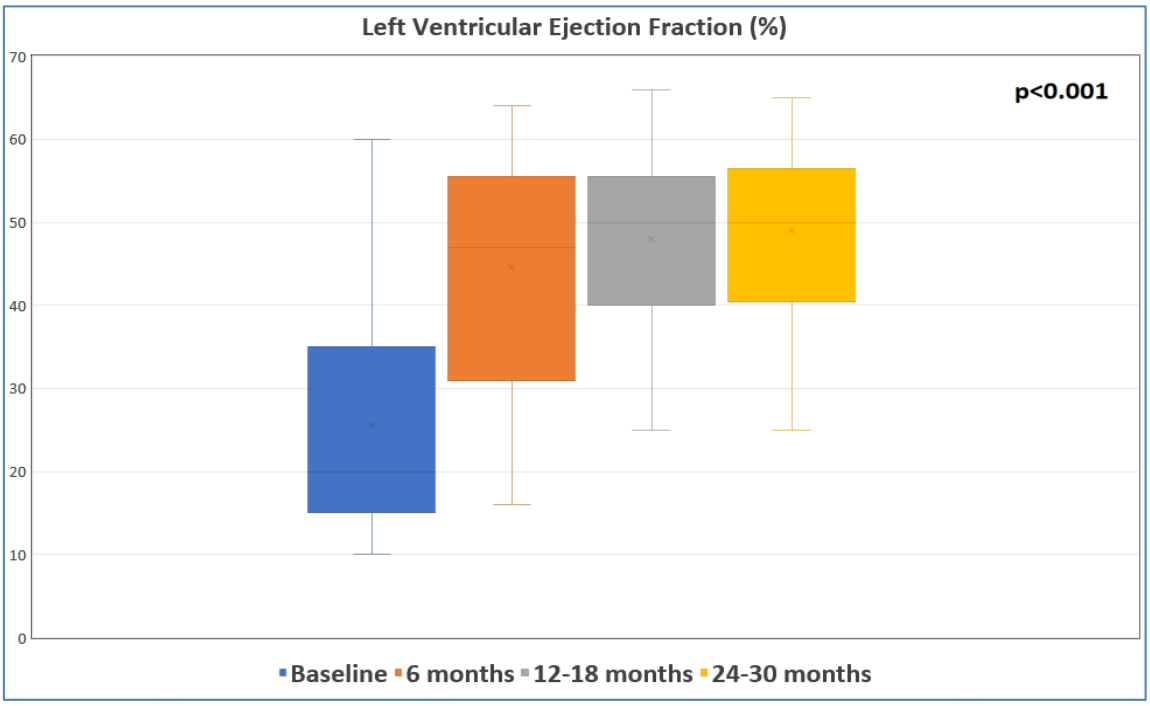

Figure 3.3 Median LV Ejection Fraction (%) by Echocardiography of all participants (n=43) across study follow up period.

There was a reduction in median NTproBNP levels in all participants across the study follow up period. Similarly to LVEF change, the significant decrease in median NTproBNP levels occurred within the first 6 months of HF therapy. Whole cohort median NTproBNP reduced from 5420 (IQR 2650-7761) ng/L to 620 (IQR 250-1993) ng/L (p<0.001) between baseline and 6 months. Subsequent median NTproBNP levels at 6, 12-18 and 24-30 months plateaued. **(Figure 3.4)**

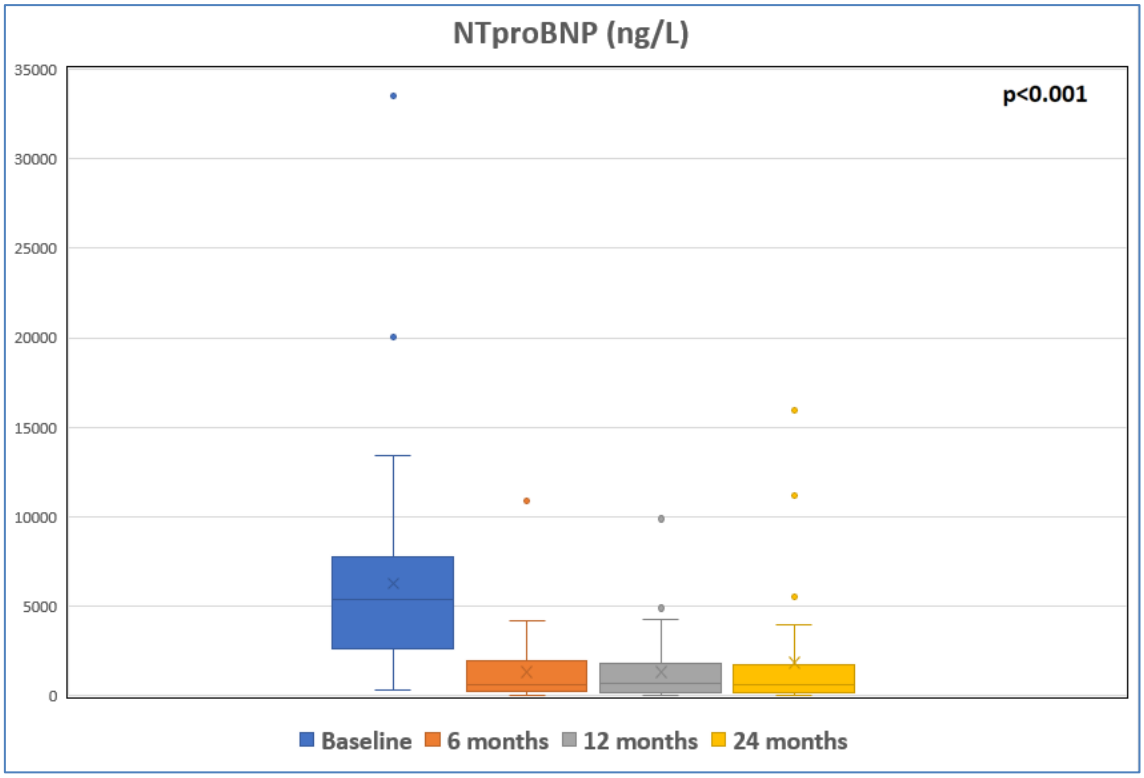

Figure 3.4 Median NTproBNP (ng/L) of all participants (n=43) across study follow up period.

There was no significant difference in median NTproBNP levels between the Adverse Outcome and No Adverse Outcome groups at either baseline, or any of the subsequent follow up timepoints. There was trend towards higher NTproBNP levels in the Adverse Outcome group at 6, 12-18 months and 24-30 months but this did not meet statistical significance. **(Table 3.4)**

This was likely due to the small sample sizes of the Adverse Outcome group, which reduced further with time.

Timepoint	Median NTproBNP (ng/L)	No Adverse Outcome (n=34)	Adverse Outcome	*p* Value	Adverse Outcome (n)
Baseline	5420 (2650-7761)	5456 (2382-7401)	4948 (2121-9247)	0.929	9
6 month	620 (250-1993)	465 (187-1878)	1510 (828-2253)	0.084	8
12-18 month	688 (174-1881)	624 (137-1772)	1110 (376-3371)	0.219	7
24-30 month	641 (197-1736)	541 (181-1412)	1978	0.266	3

Table 3.4 Median NTproBNP (ng/L) across study follow up period for all participants, No Adverse Outcome group vs. Adverse Outcome group. Number of participants (n) alive in the Adverse Outcome group decreased across review timepoints.

3.4.3 Cardiac Magnetic Resonance (CMR) Parameters

At baseline, the median LVEF as measured by CMR of the whole cohort was 24% (IQR 20-37%). Baseline CMR LVEF was not significantly different between Adverse Outcome and No Adverse Outcome groups.

The Adverse Outcome group had lower baseline mean indexed Left Ventricular End Diastolic Volume (LVEDV i) 78±16 vs 106 ±32 ml/m^2; p=0.014 and lower mean indexed Left Ventricular End Systolic Volume (LV ESV i) 52±16 vs 79±32 ml/m^2; p=0.017 compared to the No Adverse Outcome group.

The Adverse Outcome group had lower baseline mean indexed LV Mass (LV Mass i) 73±19 vs 90±20ml/m^2; p=0.036 and lower mean index LA volume (LAV i) 42±15 vs 59±20 ml/m^2 ; p=0.025 compared to the No Adverse Outcome group. **(Figure 3.5)**

There were no differences in baseline mean indexed Right Ventricular Volumes and RVEF (%) between groups.

28 (65%) participants had Late Gadolinium Enhancement present on their baseline CMR at the time of hospitalisation with a new diagnosis of Heart Failure. Half (n=14) had an ischaemic (sub-endocardial or transmural) pattern of LGE, and half had a non-ischaemic (mid-wall or epicardial) pattern of LGE.

There was no significant difference found between Adverse Outcome and No Adverse Outcome groups either in terms of proportion of participants with LGE present (78 vs. 62%; p=0.458) nor as quantified LGE mass (as % LV mass) via manual quantification method (12% (IQR 2-22%) vs 5% (IQR 0-15%); p=0.306).

There was however, a significantly higher proportion of participants in the Adverse Outcome group with an ischaemic pattern of Late Gadolinium Enhancement (67% vs 24%; p=0.040).

Native septal Region of Interest (ROI) T1 (ms) was significantly higher in the Adverse Outcome group compared with the No Adverse Outcome group (1035ms vs.996ms p=0.045). **(Figure 3.6)**

There were no differences found in Septal (ROI) ECV, Whole Heart Native T1 (ms) or Whole Heart ECV between groups. **(Table 3.5)**

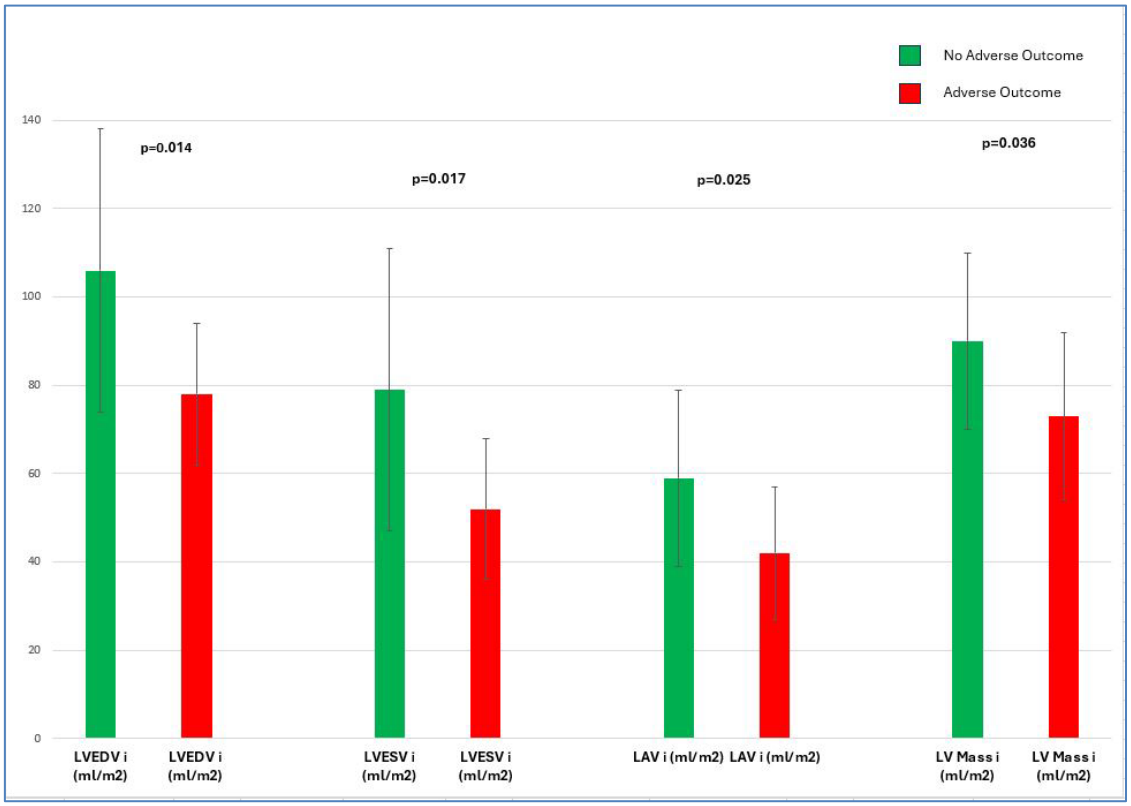

Figure 3.5 Comparison between mean baseline indexed CMR volumetric and mass parameters between No Adverse Outcome vs Adverse Outcome groups.

CMR parameter	All (n=43)	No Adverse Outcome (n=34)	Adverse Outcome (n=9)	*p* Value
LVEDV i (ml/m^2)	100±31	106±32	78±16	**0.014**
LVESV i (ml/m^2)	73±31	79±32	52±16	**0.017**
LV Mass i (g/m^2)	86±21	90±20	73±19	**0.036**
LVEF (%)	24 (20-37)	23 (19-32)	33±14	0.339
RVEDV i (ml/m^2)	70±25	71±25	68±27	0.707
RVESV i (ml/m^2)	45±23	46±24	44±21	0.822
RVEF (%)	38±14	38±14	36±13	0.624
LAV i (ml/m^2)	56±20	59±20	42±15	**0.025**
LGE presence, n (%)	28 (65%)	21 (62%)	7 (78%)	0.458
Ischaemic LGE, n (%)	14 (33%)	8 (24%)	6 (67%)	**0.040**
Non-Ischaemic LGE, n (%)	14 (33%)	13 (38%)	1 (11%)	0.231
LGE mass (% LV mass)	7 (0-15)	5 (0-15)	12 (2-22)	0.306
Septal ROI Native T1 (ms)	1002 (969-1034)	996 (969-1015)	1035 (999-1062)	**0.045**
Septal ROI Post contrast T1 (ms)	426±51	428±52	415±51	0.493
Septal ROI ECV (%)	28±5	28±5	29±6	0.997
Whole Heart Native T1	1016±42	1018±35	1008±66	0.559
Whole Heart Post Contrast T1	406±58	411±58	390±56	0.348
Whole Heart ECV (%)	31±5	31±4	32±7	0.731

Table 3.5 CMR parameters for all participants, No Adverse Outcome group vs. Adverse Outcome group.

3.4.4 Septal Region of Interest (ROI) Native T1

The median Native T1 (ms) of the septal ROI (Regional of Interest) was higher 1035 (IQR 999-1062) ms vs.996 (IQR 969-1015) ms in the Adverse Outcome group compared to the No Adverse Outcome group (p=0.045). **(Figure 3.6)**

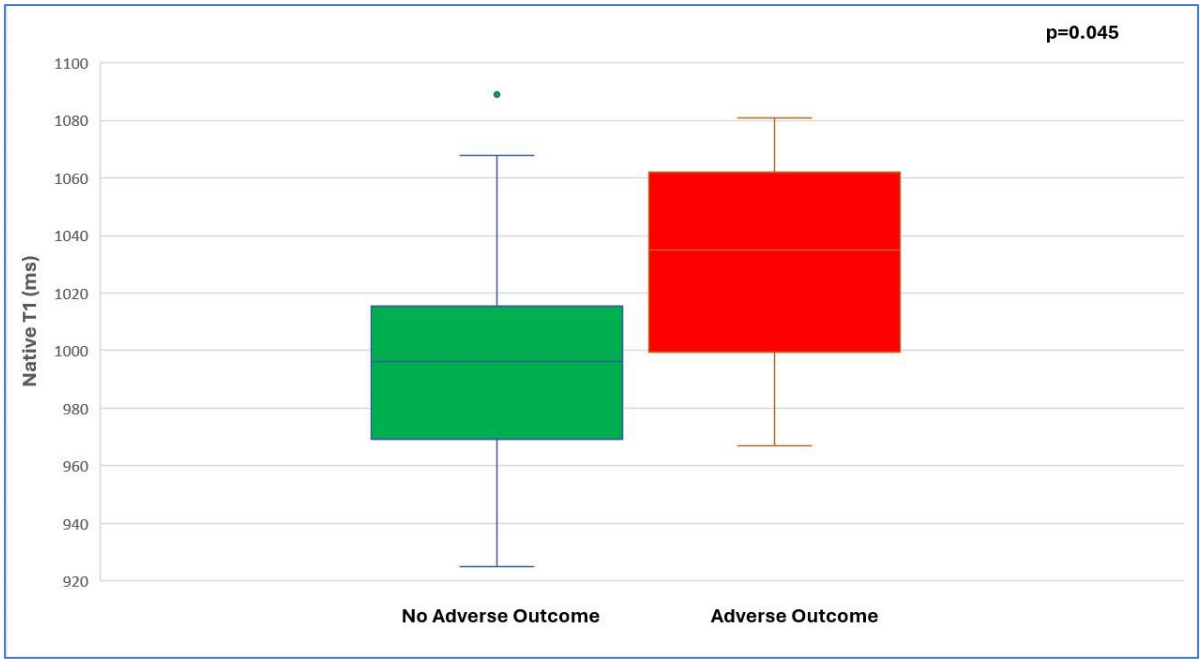

Figure 3.6 Median Septal (ROI) Native T1 (ms) comparison between No Adverse Outcome vs Adverse Outcome groups.

Receiver Operating Characteristic (ROC) curve analysis of the Septal ROI Native T1 values gave the optimum Cut-Off value of 1022ms with a sensitivity of 78% and a specificity of 82%. Area Under the Curve (AUC) showed that Septal ROI Native T1 value was an acceptable discriminator for Adverse Outcome in this study cohort with an AUC of 0.72 (95% CI 0.49 – 0.95; p=0.045). **(Figure 3.7)** (151)

Kaplan-Meier survival analysis was performed comparing those participants with septal ROI Native T1 <1022ms and those participants with septal ROI Native T1 >1022ms on their baseline CMR. There was an adverse event-free survival benefit favouring the lower T1 value group (<1022ms) (HR 11.4; 95% CI 2.34-55.48; p=0.003). **(Figure 3.8)**

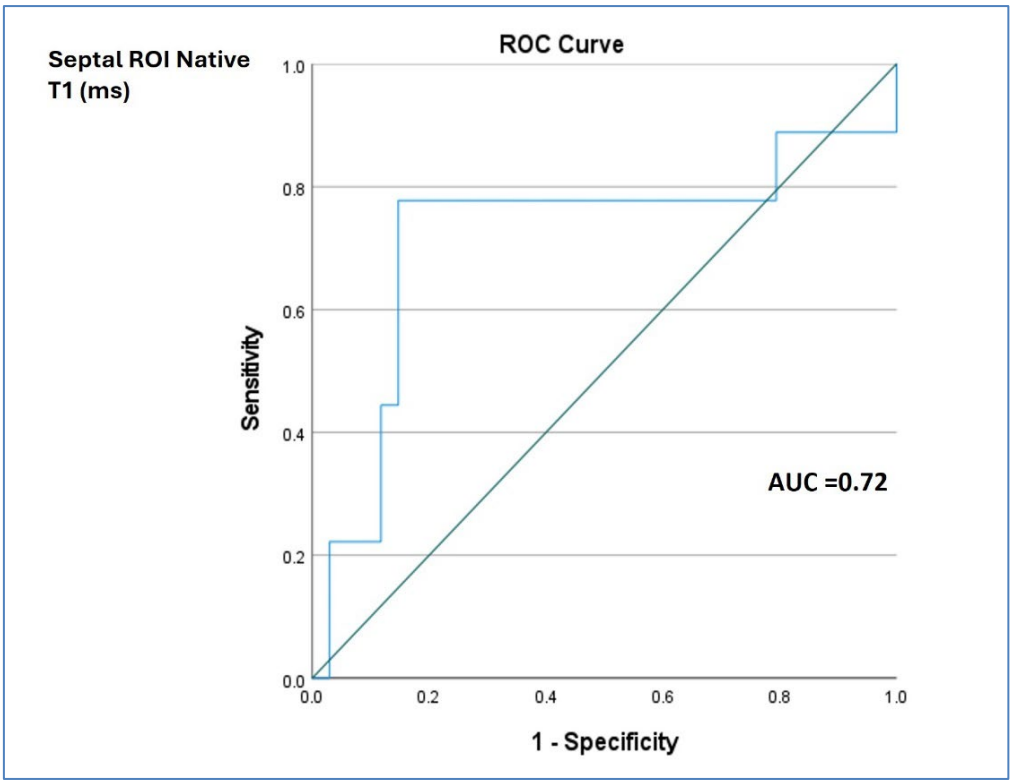

Figure 3.7 Receiver Operator Characteristics (ROC) Analysis for Septal ROI Native T1 value (ms) as a predictor for Adverse Outcome in study cohort. AUC = Area Under Curve.

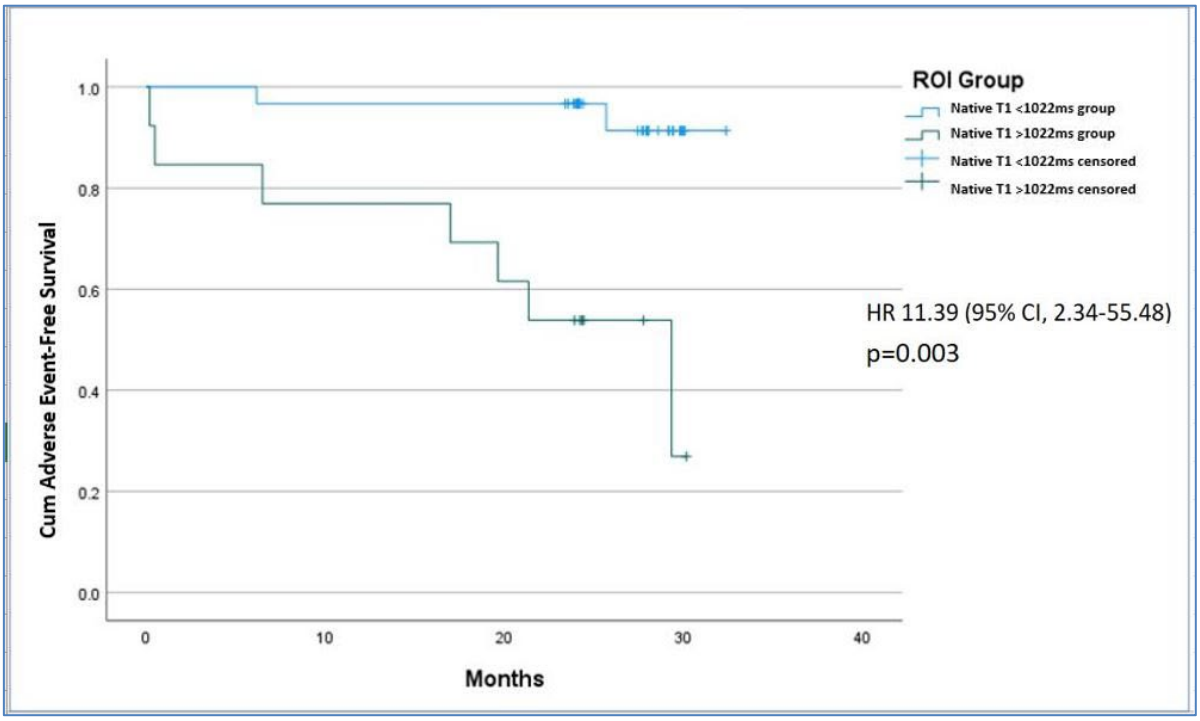

Figure 3.8 Kaplan-Meier Adverse Event-Free Survival Analysis between Septal (ROI) Native T1 <1022ms and Septal (ROI) Native T1 >1022ms. HR=Hazard Ratio; p value=0.003.

3.5 Discussion

Although CMR prognostic biomarkers have been previously investigated in different cardiomyopathy cohorts, this was the first study to evaluate these novel CMR biomarkers in a real-world cohort presenting with decompensated heart failure at time of diagnosis requiring hospital admission, including both HFrEF and HFpEF. Standard practice currently does not include routine CMR examination at time of admission, with a new Heart Failure diagnosis made on clinical history, examination and echocardiographic assessment.

The PREDICT-HF study prospectively followed up a cohort of patients hospitalised with a new diagnosis of Heart Failure for over 24 months, managed as per standard HF guidelines including medical and device therapy, all of whom underwent a baseline CMR.

There were significant improvements in LV Ejection Fraction (%) and plasma NTproBNP (ng/L) seen predominantly within the first 6 months of HF therapy initiation and sustained through the follow up period of 2 years.

Participants who experienced an adverse outcome (all-cause mortality or HF hospitalisation) had smaller left ventricles on volumetric and mass assessment at baseline. Conversely, participants who did not experience an adverse outcome had more dilated left ventricles. This likely reflects to some extent, the underlying aetiology of their cardiomyopathy, with dilated Non-Ischaemic Cardiomyopathy experiencing less adverse outcome.

There were no statistical differences found between either proportion of participants with Late Gadolinium Enhancement present or between quantified LGE mass (as % cardiac mass) between those who experienced Adverse Outcome and those who did not. LGE is known to portend to worse prognosis and the small study sample size overall and subsequent small number of event rates are likely to contribute to this finding. The pattern of LGE (i.e. aetiology of cardiomyopathy) was however, significantly different between groups. An ischaemic (subendocardial or transmural) scar pattern was associated with a worse prognosis.

Septal Native T1 (ms) was found to be acceptable discriminating marker in predicting prognosis in this cohort. There was significant difference in median septal Native T1 between those who experienced adverse outcome and those who did not. Participants with a septal native T1 >1022ms had an increased risk of adverse outcome (HR 11.4; 95% CI 2.34-55.48; p=0.003) compared to those with septal Native T1 <1022ms.

Native T1 values are influenced by a number of factors including field strength, pulse sequence, cardiac phase and therefore “normal T1 values” are specific to each scanner and local acquisition set-up. A native septal T1 value of 1022ms is still within the normal range specified for the scanner and local set-up at UHS. A higher septal native T1 value could reflect higher levels of water content (e.g. inflammation or oedema) or increased interstitial space (e.g. fibrosis) at baseline and is a composite of both myocyte (intracellular) and ECV signals. (152)

There were no differences found between calculated septal ECV (%), whole heart native T1 values or whole heart ECV (%) between groups. It is possible that native septal T1 value at baseline is a more sensitive biomarker.

3.6 Limitations

The main limitation of this study was relatively small sample size in a single centre and therefore even smaller event rates, when comparing Adverse Outcome and No Adverse Outcome groups. This may account for the lack of statistical significance in comparing quantification of LGE (% mass) between groups.

The calculated Hazard Ratio between septal Native T1 value above and below 1022ms therefore does need to be interpreted with this limitation in mind.

The applicability and significance of “Whole Heart” T1 values and ECV (%) including areas of LGE is not yet well established. Its technical feasibility as a method to quantify total myocardial fibrosis has been described in previously by our group. (148) The clinical and prognostic implications of this method merits further investigation.

The PREDICT-HF study was designed as proof of concept and hypothesis generating in this cohort and further studies in larger cohorts with sufficient power are required.

3.7 Conclusion

In a cohort of all-comer hospitalised patients with a new diagnosis of Heart Failure and followed up over a 24-month period, there was an overall high rate of combined all-cause mortality and Heart Failure Hospitalisation. We have found that higher septal native T1 values (ms) and an ischaemic pattern of Late Gadolinium Enhancement on baseline CMR were significantly associated with worse outcome.

Chapter 4 RESULTS 2: Using cardiovascular magnetic resonance tissue characterisation to PREDICT clinical outcomes, and response to therapy in hospitalised Heart Failure patients: PREDICT-HF - Reverse Remodelling Analysis

4.1 Introduction

Adverse cardiac remodelling results from an insult such as myocardial infarction, or as seen in Heart Failure (HF), maladaptive neurohormonal activation. Reverse Remodelling describes an improvement in cardiac geometry; the left ventricle (LV) recovers more normal structure with improved function and better outcome, as discussed in **section 1.3.3**.

There is however no standardised definition of Reverse Remodelling with multiple criteria from different studies involving changes in Left Ventricular diameters or volumes and LVEF with arbitrarily defined cut-offs. (153)

Studies specifically investigating CMR biomarkers in the context of response to HF therapy and cardiac reverse remodelling are emerging.

An early study of patients with chronic heart failure (both Ischaemic and Non-Ischaemic Cardiomyopathy) treated with beta blockers in addition to ACEI/ARB, demonstrated an inverse relationship between extent of scarring at baseline, as assessed by LGE CMR, and the likelihood of contractile improvement at 6 months. Multivariate analysis showed that the amount of dysfunctional but viable myocardium was a predictor of change in LVEF. (154)

Another study included only Non-Ischaemic Cardiomyopathy patients (65% had LGE scar at baseline) and treated them with carvedilol. They demonstrated that although there was an improvement in LVEF in both LGE negative and positive groups at 6 months, there was a significant difference between the groups. The absence of scar (LGE negative group) predicted a greater response to carvedilol therapy in both LVEF and LV reverse remodelling parameters on echocardiography. (155)

These findings have been supported by a number of subsequent studies of patients with Non-Ischaemic Cardiomyopathy, which show that the presence of myocardial fibrosis detected by LGE on CMR is independently associated with failure of LVEF improvement, and that its absence is a predictor of beneficial reverse remodelling. (156–160) There is also a well described correlation between increased LGE burden and non-response to Cardiac Resynchronisation Therapy (CRT). (161–164)

The role of T1 mapping in the context of response to HF therapy and cardiac reverse remodelling is not well described. A single-centre retrospective study from Tokyo looked to determine whether T1 mapping could predict reverse cardiac remodelling (defined as LVEF improvement ≥10% from baseline) in 33 patients with NICM. They found no association between native or post contrast T1 values and change in LVEF but did find a significant negative correlation between ECV and improvement in LVEF at 6 months. Comparing the LVEF improvement and non-improvement groups, native T1 and ECV were significantly lower at baseline in the LV improvement group. There were no deaths during the 34 month follow up period, but they reported a higher incidence of HF hospitalisation in the group with higher ECV. (165)

An observational study from China prospectively recruited 157 patients with NICM who underwent baseline and follow up CMRs after a minimum of 12 months of guideline directed medical therapy. They found that patients who demonstrated LV reverse remodelling (defined as an increase in LVEF >10% to the final value of ≥35% and a relative decrease in LVEDV of >10%) showed a significant decrease in native T1 values, indexed matrix volume and indexed cell volume during the follow up period, but no difference in calculated ECV. They also found that lower ECV, as well as absence of LGE at baseline were significant predictors of LV reverse remodelling. (166)

Our understanding of parametric mapping and the significance of the values derived are continuously evolving. A recent study retrospectively analysed a cohort of 113 NICM patients and found that the proportion achieving LV reverse remodelling on medical therapy was significantly lower in those patients with high mean T1 and high T1 standard deviation (T1-SD) (i.e. more heterogenous), compared to those with high mean T1 and low T1-STD; suggesting that a combination of mean native T1 measurements with standard deviation, as a measure of native T1 heterogeneity, may be a useful novel predictor of LV reverse remodelling in those patients assessed without Gadolinium contrast. (167)

PREDICT-HF aimed to investigate the role of CMR biomarkers at the time of diagnosis in predicting response to HF therapy and left ventricular reverse remodelling in a cohort of patients hospitalised with a new diagnosis of HF.

4.2 Methods – Reverse Remodelling Analysis

Full PREDICT-HF study methods are detailed in **section 3.3.**

Hypothesis 2: Increased Left Ventricular Focal (LGE) and diffuse fibrosis (T1 values and ECV) identified by CMR at baseline is negatively associated with response and beneficial reverse remodelling to Heart Failure therapies, in patients hospitalised with a new diagnosis of Heart Failure.

Only the PREDICT-HF participants with Heart Failure with reduced Ejection Fraction (HFrEF) and LVEF <40% on their baseline echocardiography were included in this analysis.

As previously discussed, there is no accepted standardised definition of Left Ventricular Reverse Remodelling.

For this study, "Responders" to guideline directed HFrEF therapy were defined as those participants who had an **absolute increase in Left Ventricular Ejection Fraction of ≥10 points on Transthoracic Echocardiogram (TTE) to a value of LVEF ≥40%** from their baseline to latest follow up echocardiogram. Participants not reaching these criteria were deemed "Non-Responders".

Participants were treated according to international ESC HF guidelines (2016) (21) and underwent clinical reviews, assessment and repeat transthoracic echocardiography at 6, 12-18 and 24-30 months. Best practice HF therapy consisted of "three pillars" medical therapy (ACE-I, BB, MRA) and consideration of Cardiac Resynchronisation Therapy +/- Defibrillator therapy after at least 3 months of Optimum Medical Therapy. *The PREDICT-HF cohort predated the inclusion of ARNI (sacubitril/valsartan) and SLGT2 inhibitors to HF management guidelines.*

Baseline CMR parameters including LV, RV and atrial volumes, LV and RV function, presence of Late Gadolinium Enhancement (LGE), LGE pattern and quantification as % LV mass, septal (ROI) and whole heart T1 and ECV values were compared between Responder and Non-Responder groups.

4.3 Results

4.3.1 Baseline Characteristics

A total of 47 participants were recruited to PREDICT-HF between April 2018 and April 2019. Three participants met exclusion criteria and 1 withdrew consent. Two participants were diagnosed as HFpEF and were excluded from this analysis.

One participant passed away before their first follow up echocardiogram. Four participants were diagnosed, treated and followed up as HFrEF on the basis of clinical presentation and baseline CMR LV Ejection Fraction. Their LV Ejection Fractions on baseline TTE were however, reported as LVEF >40%. These participants were treated appropriately with HF therapy in what is now recognised as HF with mildly reduced ejection fraction, but for the purposes of comparing response to therapy, LV reverse remodelling and LVEF improvement, were excluded from this analysis.

A total of 36 participants met criteria for this analysis and were included. Median follow up period was 26 months. 27 (75%) were male and mean age was 65±12 years. The majority (72%) had a diagnosis of Non-Ischaemic Cardiomyopathy. Overall median NTproBNP at baseline was 5783 (3000-7641) ng/L.

There were no significant differences in baseline clinical, biochemical characteristics or NYHA functional class between Responder and Non-Responder groups. There was very high uptake of HFrEF medical therapy in both groups with 100% of participants on an ACEI/ARB and Beta Blocker and 86% on MRA. A total of 10 (28%) participants had Cardiac Resynchronisation Therapy (CRT) during the study period with no difference between Responder vs. Non-Responder groups. (26% vs 33%; p=0.686). **(Table 4.1)**

	All (n=36)	Responder (n=27)	Non-Responder (n=9)	p Value
Clinical parameters				
Age (years)	65±12	65±13	65±11	0.994
Male, n (%)	27 (75%)	20 (74%)	7 (78%)	1.000
BMI (kg/m2)	27.9±4.6	27.3±4.1	29.8±5.8	0.179
SBP (mmHg)	125±19	126±20	121±13	0.524
DBP (mmHg)	79±14	79±15	78±10	0.830
HR (beats/min)	91 (70-116)	90 (68-118)	91 (69-100)	0.674
NICM, n (%)	26 (72%)	21 (78%)	5 (56%)	0.226
ICM, n (%)	10 (28%)	6 (22%)	4 (44%)	0.226
MAGGIC score	20±6	19±7	20±6	0.880
MAGGIC 1 year risk (%)	11±6	11±6	11±6	0.988
MAGGIC 3 year risk (%)	26±13	26±13	26±12	0.970
NYHA functional class				
I, n (%)	0	0	0	
II, n (%)	21 (58%)	16 (59%)	5 (56%)	1.000
III, n (%)	15 (42%)	11 (41%)	4 (44%)	1.000
IV, n (%)	0	0	0	
Comorbidity				
Hypertension, n (%)	17 (47%)	13 (48%)	4 (44%)	1.000
Diabetes, n (%)	10 (28%)	7 (26%)	3 (33%)	0.686
IHD, n (%)	10 (28%)	6 (22%)	4 (44%)	0.226
Atrial Fibrillation, n (%)	13 (36%)	10 (37%)	3 (33%)	1.000
Current smoking, n (%)	8 (22%)	6 (22%)	2 (22%)	1.000
Laboratory data				
NTproBNP (ng/L)	5783 (3000-7641)	5492 (2967-7281)	6075 (2318-11290)	0.701
Haemoglobin (g/L)	137±17	135±18	144±15	0.170
Urea (mmol/L)	7.6±3.0	7.7±2.8	9.5±3.2	0.099
Creatinine (umol/L)	93±26	90±22	107±34	0.081
Iron (nmol/L)	11 (7-20)	10 (8-20)	13 (6-16)	0.982

HFrEF Therapy				
ACEI/ARB, n(%)	36 (100%)	27 (100%)	9 (100%)	
Beta Blocker, n (%)	36 (100%)	27 (100%)	9 (100%)	
MRA, n (%)	31 (86%)	23 (85%)	8 (89%)	1.000
Loop Diuretics, n (%)	31 (86%)	23 (85%)	8 (89%)	1.000
CRT Therapy	10 (28%)	7 (26%)	3 (33%)	0.686

Table 4.1 Baseline characteristics for all participants, Responder group vs. Non-Responder group

BMI=Body Mass Index, SBP= Systolic Blood Pressure, DBP= Diastolic Blood Pressure, NICM= Non-Ischaemic Cardiomyopathy, ICM= Ischaemic Cardiomyopathy, HFpEF= Heart Failure with preserved Ejection Fraction, MAGGIC= Meta-Analysis Global Group in Chronic Heart Failure, NYHA= New York Heart Failure Association functional classification, IHD=Ischaemic Heart Disease, ACEI/ARB=ACE-inhibitors/Angiotensin II Receptor Blockers, MRA= Mineralocorticoid Receptor Antagonists.

4.3.2 LV Ejection Fraction on Transthoracic Echocardiography

27 (75%) participants were "Responders" to HF therapy and had increased their LVEF by ≥10 points to an LVEF ≥40% between baseline and latest follow up TTE. Nine (25%) participants did not. Median LV Ejection Fractions on Transthoracic Echocardiography (TTE) at each assessment timepoint for All, Responder and Non-Responder groups are below. **(Table 4.2)**

Timepoint	All (n=36)	Responder (n=27)	Non-Responder (n=9)	*p* Value
Baseline LVEF (%)	18 (15-29)	15 (10-20)	25 (20-25)	**0.009**
6 month LVEF (%)	45 (30-55)	48 (32-55)	35 (29-43)	0.065
12-18 month LVEF (%)	45 (30-55)	50 (40-55)	35 (35-39)	**0.003**
24-30 month LVEF (%)	50 (40-55)	50 (47-59)	30 (25-40)	**<0.001**

Table 4.2 Median LV Ejection Fraction (%) as measured by Transthoracic Echocardiography at each assessment timepoint for All, Responder and Non-Responder groups.

The Responder group had a lower median LVEF on echocardiography at baseline 15% (10-20%) vs 25% (20-25%); p=0.009 compared to the Non-Responder group. The significant increase in median LVEF in the Responder group occurred within the first 6 months of HFrEF therapy from 15% (10-20%) to 48% (35-55%); p<0.001 and remained sustained throughout the study period**. (Figure 4.1)**

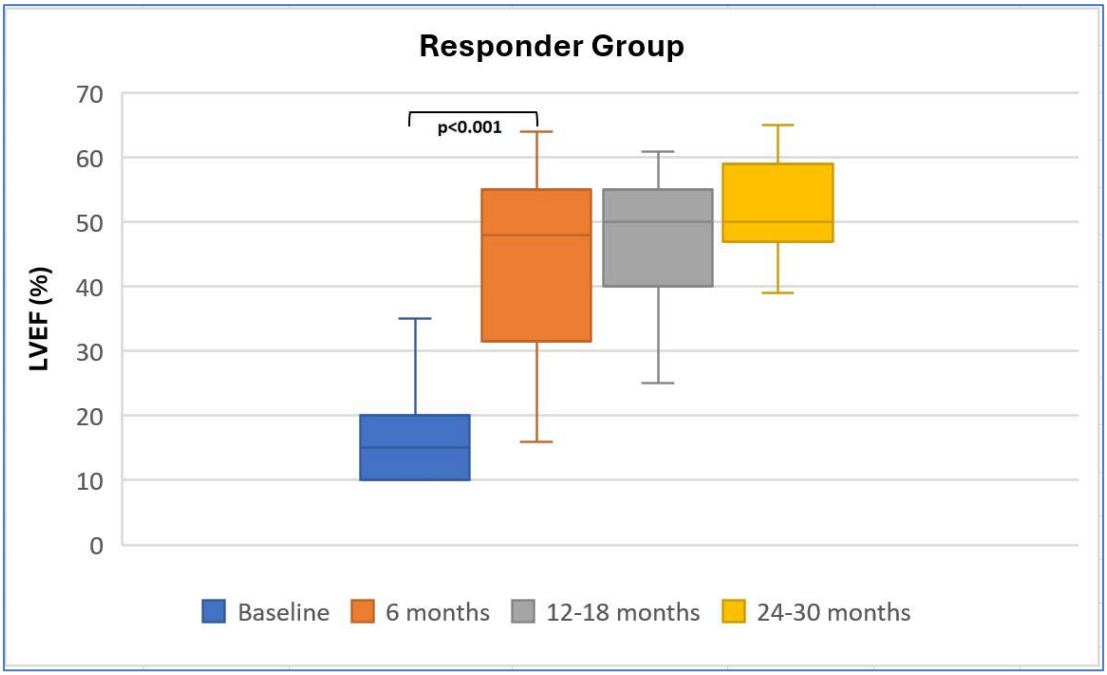

Figure 4.1 Median LVEF (%) on Transthoracic Echocardiography in Responder Group across time.

There was still a statistically significant difference between baseline median LVEF (%) and subsequent follow up median LVEF (%) across time for the Non-Responder Group (p=0.001).

Post-hoc analysis with Wilcoxon signed-rank test was conducted with Bonferroni correction applied resulting in a new level of significance set at p <0.017 (accounting for multiple comparisons).

Median LVEF (%) increase was statistically significant only between Baseline LVEF [25% (20-25%)] and at 12-18 months [35% (35-39%); p=0.012]. The improved median LVEF however remained **below** the defined cut-off of LVEF >40% for Reverse Remodelling and response to HFrEF therapy. **(Figure 4.2)**

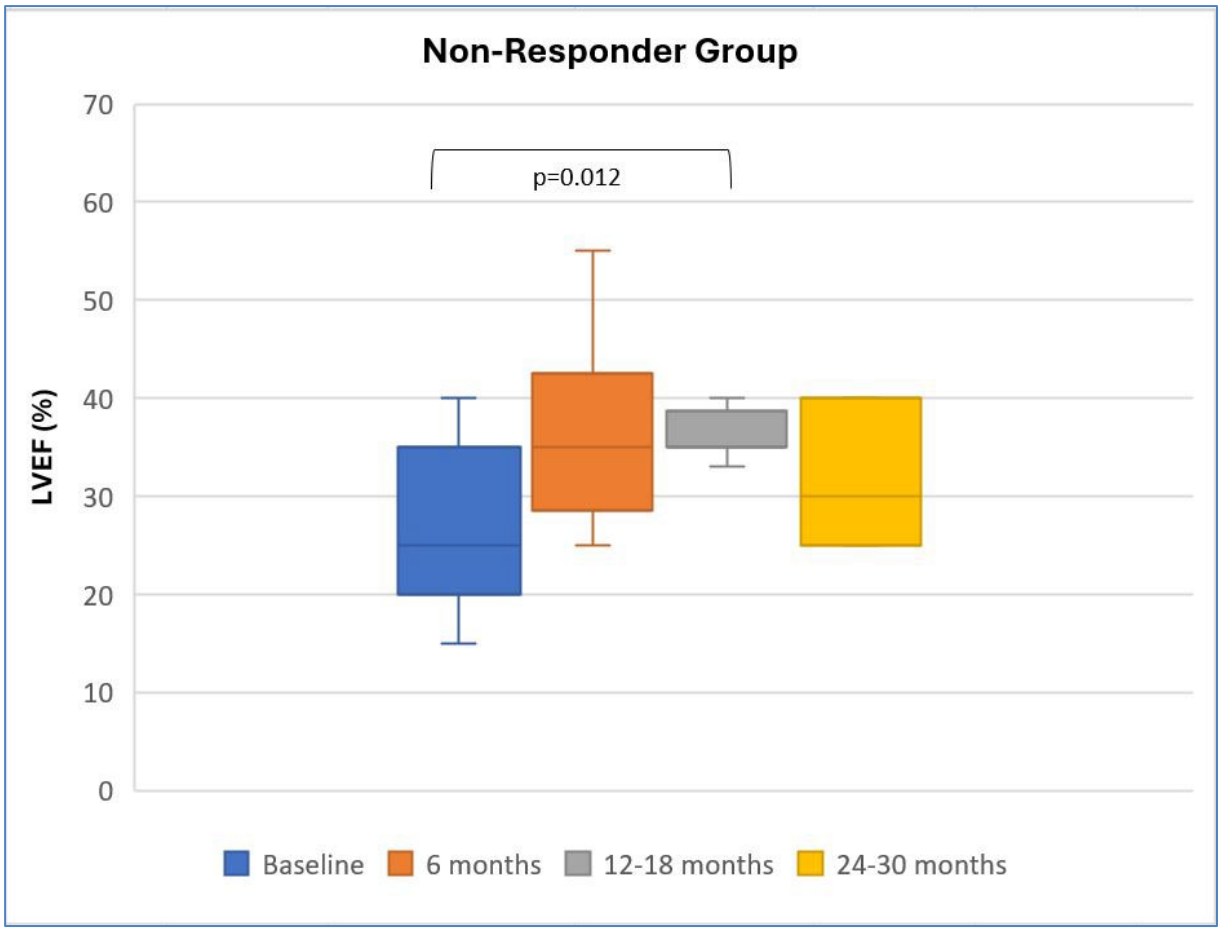

Figure 4.2 Median LVEF (%) change on Echocardiography in Non-Responder Group across time. Median LVEF remained <40% throughout.

4.3.3 Cardiac Magnetic Resonance (CMR) Parameters

Baseline CMR LV and RV volumetric, function and LV tissue characteristic parameters for all participants, Responder and Non-Responder groups are reported below. **(Table 4.3)**

The majority of the cohort, 25 (69%) had Left Ventricular focal fibrosis present, detected as Late Gadolinium Enhancement (LGE).

There was no difference found in the proportion of participants with LGE present between Responder and Non-Responder groups (74% vs. 56%; p=0.409). There was a higher proportion of participants with a non-ischaemic LGE pattern in the Responder group compared to Non-Responder group (48% vs 11%; p=0.053).

Median LGE mass, manually quantified as % LV mass, was also not significantly different between Responder and Non-Responder groups; 9% (0-15%) vs 14% (2-24%); p=0.233.

There was no significant difference found between median septal (ROI) or mean whole heart native T1 values between Responder and Non-Responder groups; 1003ms (968-1019ms) vs 974ms (968-1051ms); p=0.812 and 1015±38 ms vs 1026±46 ms; p=0.502 respectively.

There was no significant difference found between mean septal (ROI) ECV values between Responder and Non-Responder groups; 28±5% vs. 30±5%; p=0.312. There was a trend towards lower whole heart ECV values in the Responder group; 29% (27-32%) vs. 35% (29-38%); p=0.06 but this did not reach statistical significance. **(Figure 4.3)**

There was no difference between baseline indexed LVEDV, LV Mass, RVEDV, or Left Atrial Volume between Responder and Non-Responder groups. The median baseline LVEF and mean RVEF as measured on CMR were not statistically different between Responder vs Non-Responder groups.

CMR parameter	All (n=36)	Responder (n=27)	Non-Responder (n=9)	p Value
LVEDVi (ml/m2)	106±29	109±30	100±27	0.436
LVESVi (ml/m2)	81±28	83±28	73±25	0.341
LV Massi (g/m2)	89±20	88 (82-96)	86 (60-106)	0.298
LVEF (%)	23 (20-29)	22 (19-29)	26 (21-35)	0.129
RVEDVi (ml/m2)	72±26	74±26	68±24	0.584
RVESVi (ml/m2)	49±23	50±24	44±21	0.479
RVEF (%)	35±13	35±13	37±13	0.650
LAVi (ml/m2)	57±20	60±21	50±15	0.181
LGE presence, n (%)	25 (69%)	20 (74%)	5 (56%)	0.409
Ischaemic LGE, n (%)	11 (31%)	7 (26%)	4 (44%)	0.261
Non-Ischaemic LGE, n (%)	14 (39%)	13 (48%)	1 (11%)	**0.053**
LGE mass (% LV mass)	10 (2-16)	9 (0-15)	14 (2-24)	0.233

ROI Native T1 (ms)	1003±42	1003 (968-1019)	974 (968-1051)	0.812
ROI Post Contrast T1 (ms)	425±51	428±54	415±44	0.525
ROI ECV (%)	29±5	28±5	30±5	0.312
Whole Heart Native T1 (ms)	1018±40	1015±38	1026±46	0.502
Whole Heart Post Contrast T1 (ms)	407±60	402 (376-445)	410 (351-445)	0.784
Whole Heart ECV (%)	31±4	29 (27-32)	35 (29-38)	0.060

Table 4.3 Baseline CMR parameters for all participants, Responder group vs. Non-Responder group

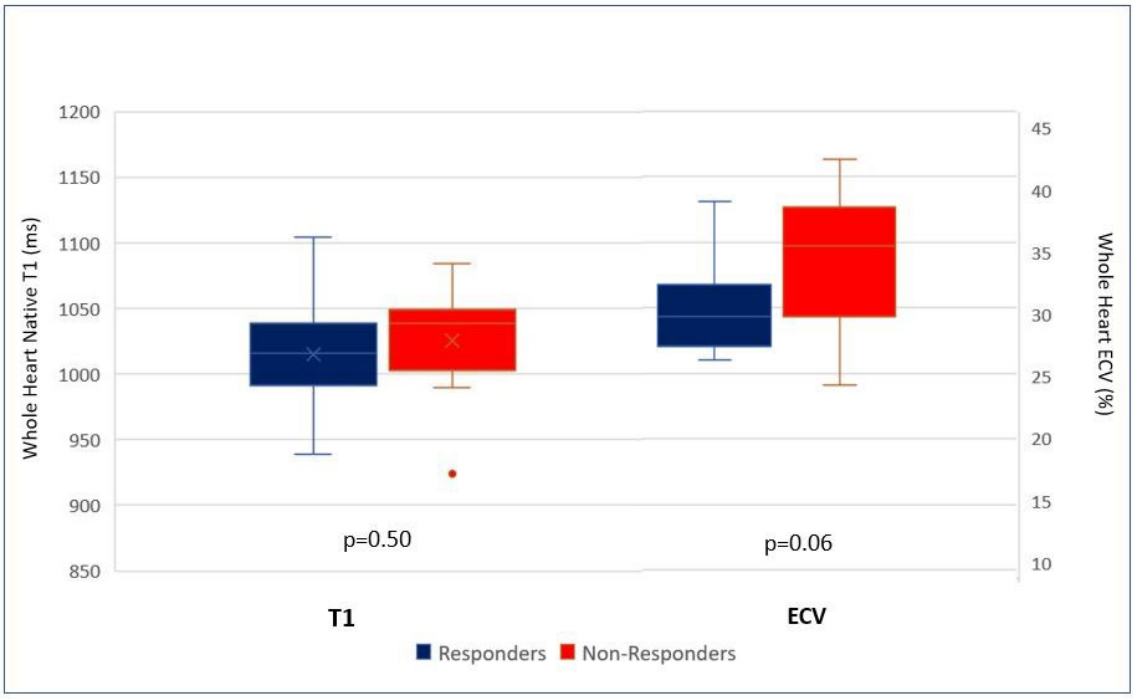

Figure 4.3 Whole heart native T1 (ms) of responder vs. non-responder groups and whole heart ECV (%) of responder vs. non-responder groups.

4.4 Discussion

In this sub-analysis of PREDICT-HF participants with HFrEF, the majority responded to HF therapies and demonstrated reverse remodelling (defined as increased LVEF by ≥10 points to an EF >40%) within the first 6 months, with sustained improved function at 26 months.

Those who responded to HFrEF therapy and demonstrated reverse remodelling had a lower baseline LVEF on baseline Transthoracic Echocardiography (TTE), supporting the findings of other echocardiographic studies that patients with lower LVEF at baseline appear to gain more benefit with HF treatment and achieve greater reverse remodelling effect. (168) This was, however, not the case when comparing the LVEF at baseline as measured on CMR between groups, highlighting the variations in LVEF assessment between differing imaging modalities.

Baseline CMR tissue characteristic assessment of both focal fibrosis (LGE presence and manual LGE quantification as % LV mass) and diffuse fibrosis (Native T1 values and ECV) of the Left Ventricle were not found to be predictors of response to HFrEF therapy in this cohort.

There was, however, a higher proportion of Non-Ischaemic LGE scar pattern present in the Responder group compared to Non-Responder group. This supports previous published data that patients with non-ischaemic aetiology of cardiomyopathy, or lack of myocardial infarction are more prone to improvement to LVEF and recovery. (169)

The predictive value of LGE absence in particular, or lower burden of LGE have been shown in multiple studies to be strong predictors of reverse remodelling in dilated non-ischaemic cardiomyopathy. (153) Our study was a unique real world all-comer cohort of both non-ischaemic and ischaemic aetiologies, the limitations of which are noted below.

Although not reaching statistical significance, whole heart Extracellular Volume (ECV) (%) representing whole heart fibrosis appeared to be trending higher in the Non-Responder group. Our original hypothesis was that higher levels of fibrosis whether it be focal or diffuse would result in a lower chance of response to HFrEF therapy and reverse remodelling. Whole heart T1 mapping and ECV assessment technique as previously discussed is recognised as an emerging technique but not yet widely used, and would be an interesting area to develop and investigate in larger studies.

4.5 Limitations

The main limitation of this sub-analysis was the small study size. As an original proof of concept study, and further sub-selection of the HFrEF cohort within, the small sample size contributed to insufficient statistical significance and power.

The study design was one of all-comer, new HF diagnosis regardless of LVEF and aetiology. Whereas it has been interesting to study the outcomes of this real-world cohort as a whole, future larger recruitment would allow more meaningful sub-analysis of outcomes between ischaemic and non-ischaemic aetiologies.

4.6 Conclusion

In this cohort of study participants hospitalised with a new HFrEF diagnosis, the majority demonstrated reverse remodelling in response to HFrEF therapy within 6 months and sustained at 26 months. Whole heart ECV (%) as a surrogate marker for fibrosis calculated by whole heart T1 mapping may play a role in understanding which patients are likely to respond to HF therapy, but further larger studies are required.

Chapter 5 RESULTS 3: T1MES phantom - T1 measurement stability over time on 1.5T Siemens Sola Cardiovascular Magnetic Resonance (CMR) Scanner at University Hospital Southampton

5.1 Acknowledgement

This work was carried out with Dr Geoffrey Payne from the University of Southampton MRI physics department, who performed the T1MES phantom scanning and generated the T1 data sets in 2018 and 2022.

5.2 Introduction

Tissue characterisation by CMR T1 mapping and ECV are key to the studies in this thesis.

T1 measures the longitudinal relaxation time for the protons to re-equilibrate their spins after excitation by a radiofrequency pulse. T1 values vary depending on the magnet field strength, differences in acquisition schemes e.g. pulse sequence used and phase of cardiac cycle, and post-processing methods. Comparisons of T1 values must therefore always include the T1 mapping technique that was used, and the normal reference range specific to the scanning site. (170)

The ENVI study described in **Chapter 7** compares Native and Post-Contrast myocardial T1 values before and after 6 months of optimised HFrEF treatment. The calculated ECV (%) incorporates native and post-contrast blood pool T1 values at baseline and at 6 months. To obtain meaningful results to compare over time, it was important to confirm there was no drift or variability in T1 measurements, and that the measurement system (CMR scanner) was stable over time.

Development of the “T1MES: The T1 mapping and ECV Standardisation Program” phantom Quality Assurance (QA system) has allowed accurate and reproducible verification of T1 measurements over time for any individual CMR scanner. (171) The reported variability (%

change) of the T1MES phantom T1 values from multicentre testing over 2 years at 1.5T was 1.95±1.29%. (172)

We hypothesised that there would be no significant variability in the T1 values measured by the 1.5T Siemens Sola CMR scanner over time, using the T1MES phantom.

5.3 Methods

The T1MES phantom is an agarose gel-based phantom using nickel chloride as the paramagnetic relaxation modifier. Each bottle contains 9 different agarose tubes with different agarose gel/beads matrix composition. (171) **(Figure 5.1)**

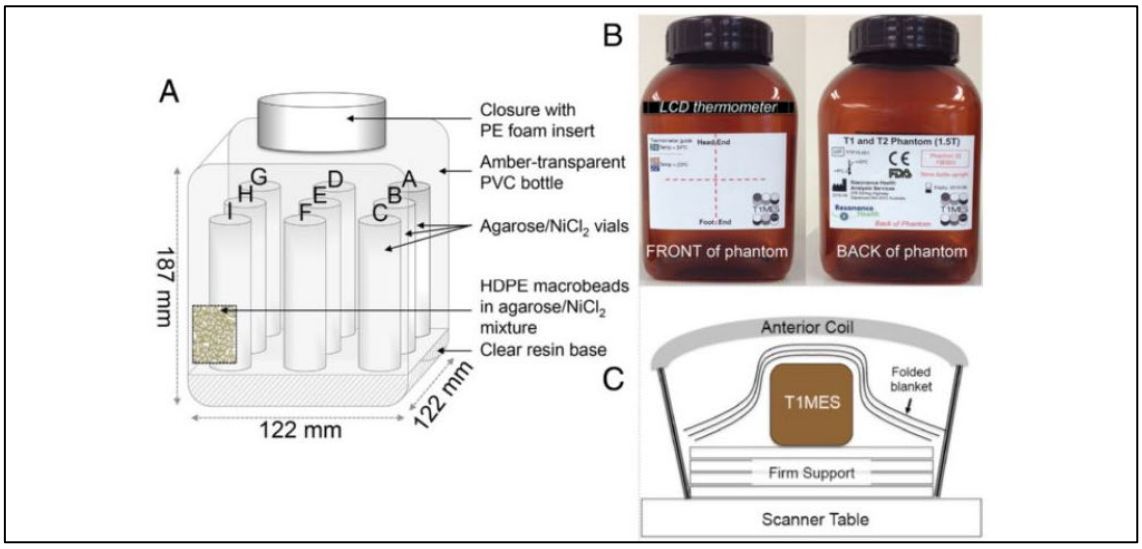

Figure 5.1 T1MES phantom structure. A – Internal 9 tubes, B – External bottle, C – Recommended positioning on scanner table. PE= Polyethylene, PVC = Polyvinyl Chloride, NiCl2 = Nickel Chloride, LCD = Liquid Crystal Display, HDPE = High Density Polyethylene. Reproduced from Captur et al. (171)

The CMR scanner used for The ENVI study participants was a 1.5T Siemens Sola magnet at University Hospital Southampton (UHS). A T1MES phantom T1 dataset from this scanner had been measured by our research group in 2018, in a project investigating variability between CMR scanners within the Trust. (148)

In October 2022, three sets of T1 measurements were acquired using the validated Modified Look-Locker Inversion recovery (MOLLI) 5(3)3 sequence, and gated using a synthetic ECG trace, as detailed in the T1MES user manual. (See **Appendix**)

The temperature of the T1MES phantom bottle was checked using the LCD temperature strip and ensured that the bottle temperature remained within controlled levels.

Three separate sets of T1 values for each of the 9 tubes within the T1MES phantom were generated. A Region of Interest (ROI) was drawn on each tube as per the T1MES protocol and analysed using the Siemens Syngo®.via analysis package.

The T1 value mean±SD of the 3 data sets was calculated for each tube 1-9 and compared to the 2018 data set which was obtained using identical methodology, with the same operator on the same scanner. The percentage difference between mean values across time was calculated with the following equation:

% Difference = (Mean T1 (ms) 2018 – Mean T1(ms) 2022)/Mean T1(ms) 2018 x 100

The p value was calculated using Paired t-test on IBM® SPSS® software package version 27 to compare the means of the 2018 and 2022 groups.

5.4 Results

The results for the T1MES phantom T1 mean values for 2018 and 2022 are displayed in **Table 5.1** and **Figure 5.2**.

The largest discrepancy (%) difference was 1.25% in Bottle 9 (1561.95±1.32 ms vs 1542.50±1.93ms); p=0.009 followed by 1.20% in Bottle 8 (1291.75±1.00ms vs 1276.23±0.60ms); p=0.001. There was a <1% difference found in all other bottles.

Paired t-test comparing the means of both groups showed statistically significant differences between bottles 1,4,5,6,8 and 9 however the absolute % differences were minimal.

T1MES Phantom Bottle	Mean T1±SD (ms) 2018	Mean T1±SD (ms) 2022	% Difference	p Value
1	263.50±0.41	262.10±0.36	0.53	**0.004**
2	293.83±0.48	292.80±0.70	0.35	0.118
3	417.68±1.32	416.97±2.24	0.17	0.876
4	476.50±1.20	473.90±0.83	0.55	**0.017**
5	541.80±1.98	539.60±0.73	0.41	**0.013**
6	776.70±2.18	771.37±2.25	0.69	**0.028**
7	1050.48±2.36	1044.20±8.94	0.60	0.529
8	1291.75±2.36	1276.23±0.60	1.20	**0.001**
9	1561.95±1.32	1542.50±1.93	1.25	**0.009**

Table 5.1 Comparison of mean±SD T1 values from T1MES phantom tubes 1-9 between 2018 and 2022.

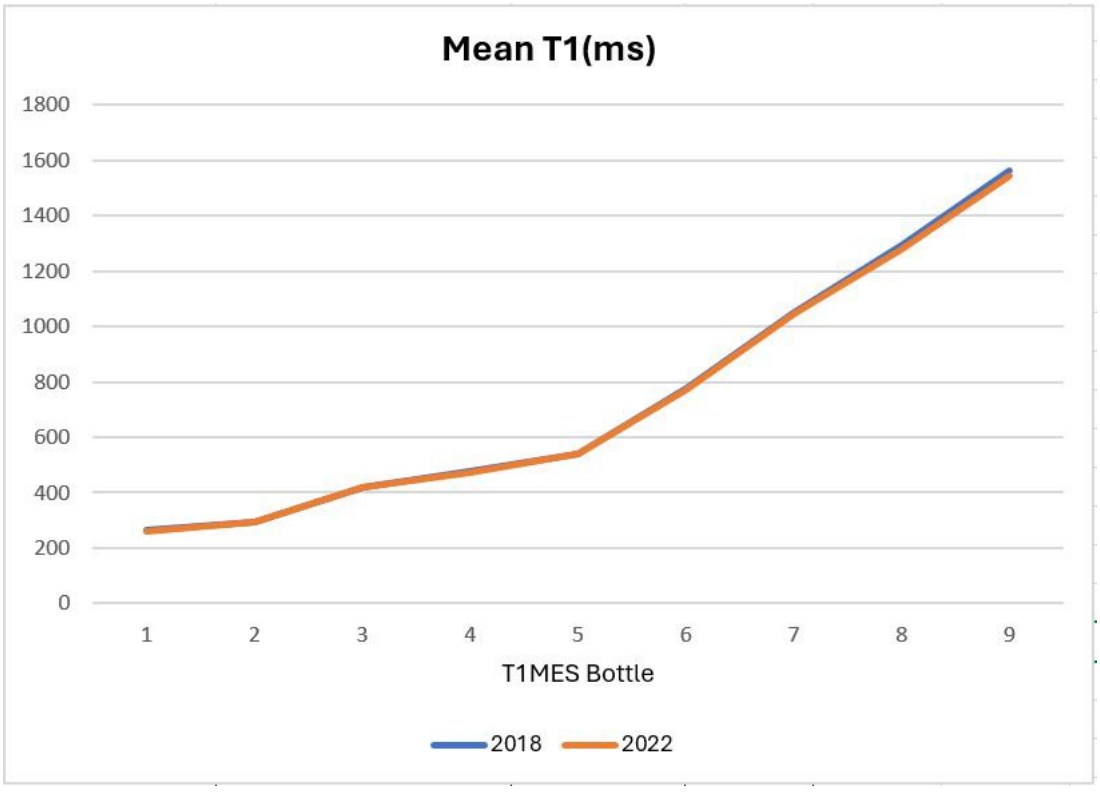

Figure 5.2 Mean T1 values of the T1MES phantom (Bottle 1-9) from 2018 (blue) and 2022 (orange).

5.5 Discussion

Although there were some statistically significant differences found between the mean T1 values of the T1MES phantom, the largest discrepancy was only 1.25% and most were <1% over a 4-year period.

Our findings were far less than the cited reference in the T1MES performance and repeatability paper, which quoted a difference of 1.95±1.39% at 1.5T as stable compared to baseline over a 2-year period. (172)

The multiple factors that affect T1 value measurements such as manufacturer hardware, pulse sequence and acquisition, post-processing and analysis software are well recognised. These factors present challenges in interpreting and comparing meaningful T1 data in clinical practice, and the need for local reference ranges specific to the site, scanner and scanning technique has been previously discussed.

Further work into developing techniques for standardisation, with validated Quality Assurance (QA) systems such as the T1MES phantom is therefore important towards developing a "T1 standard" and ultimately negating the requirement for local reference ranges and allowing multicentre studies in the future. (172)

5.6 Conclusion

Scanning the T1MES phantom in the Siemens 1.5T Sola CMR scanner at University Hospital Southampton twice over a 4-year period (2018 to 2022) confirmed that there was negligible difference between mean T1 measurements.

Our scanner demonstrated no significant variation or drift in T1 measurements over a 4-year period. The ENVI study and comparison of tissue characterisation in **Chapter 7** compared two scans for each participant over a 6-month period only.

We have demonstrated that the T1 differences reported in The ENVI study are genuine and due to the study intervention (optimisation of HFrEF therapy) and not due to any inherent variation of the CMR scanner.

Chapter 6 RESULTS 4: Effects of optimisation to contemporary HFrEF medical therapy with sacubitril/valsartan (Entresto) and dapagliflozin on left Ventricular reverse remodelling as demonstrated by Cardiac Magnetic Resonance (CMR) Imaging: *The ENVI Study* – Cardiac Remodelling Analysis

A version of this chapter has been published in Open Heart, BMJ.

Zheng A, Adam R, Peebles C, Harden S, Shambrook J, Abbas A, Vedwan K, Adam G, Haydock P, Cowburn P, Young C, Long J, Walkden M, Smith S, Greenwood E, Olden P, Flett A. Effect of optimisation to contemporary HFrEF medical therapy with sacubitril/valsartan (Entresto) and dapagliflozin on left Ventricular reverse remodelling as demonstrated by cardiac magnetic resonance (CMR) Imaging: the ENVI study. Open Heart. 2024 Dec 2;11(2):e002933

6.1 Introduction

Since the landmark PARADIGM-HF (20) and DAPA-HF (26) trials, HFrEF guidelines have been updated to incorporate the angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril/valsartan and SGLT2 inhibitors. Contemporary therapy now consists of “four pillars”, with ARNI replacing conventional ACE-inhibitor or Angiotensin Receptor Blocker (ARB) therapy, beta blockers, mineralocorticoid receptor antagonists (MRA) and SGLT2-inihibitors.

If LVEF remains ≤35% after 3 months of “optimum medical therapy”, and depending on QRS duration, complex device therapy in the form of primary prevention Implantable Cardioverter-Defibrillator (ICD) or Cardiac Resynchronisation Therapy (CRT-D/P) should be considered. (1)

Morbidity and mortality in HFrEF result from complex processes and is unlikely to be predicted by any single parameter, however cardiac and in particular left ventricular, reverse remodelling has been studied as a surrogate marker for efficacy of HFrEF treatments. Favourable features of LV reverse remodelling are associated with reduced mortality risk. (111)

The clinical benefit for HFrEF therapies is well evidenced, however relatively few studies have described associated reverse remodelling processes and relation to outcome. The current evidence base on HFrEF therapies and reverse remodelling been discussed in **Section 1.3.4**.

The exact mechanism by which sacubitril/valsartan achieves its profound clinical benefit is still not fully understood. Echocardiographic studies have shown that switching to sacubitril/valsartan results in LVEF improvement and reduction in left ventricular and atrial volumes, as well as improvement in mitral regurgitation degree and reduction in NTproBNP.(124,135,173,174) There are no Cardiac Magnetic Resonance imaging (CMR) studies on the effects of sacubitril/valsartan treatment.

Studies on the remodelling effects of SGLT2 inhibitors are also limited, but reduction in left ventricular and atrial volumes, as well as NTproBNP have been reported.(175,176)

6.2 The ENVI Study Methods

6.2.1 Study Rationale

At the time of updated Heart Failure guidelines recommending ARNI switchover, a level of clinical equipoise existed between Heart Failure clinicians regarding the timing of complex device implantation. “Three months of optimal medical therapy” was not clearly defined and open to interpretation, with clinicians considering complex device therapy at different points along the treatment timeline in relation to switchover to sacubitril/valsartan and uptitration.

We aimed to conduct the first study to examine the effects of optimisation to contemporary HFrEF medical therapy on cardiac reverse remodelling as evaluated by CMR in HFrEF patients and how this would affect eligibility for complex device prescription.

6.2.2 Study Hypotheses

1. Optimisation to contemporary HFrEF medical therapy as per updated HF guidelines results in beneficial reverse remodelling, improvement in LV volumes and LVEF as measured by CMR imaging.

2. Beneficial reverse remodelling effects at 6 months will result in a proportion of HFrEF patients no longer meeting criteria for complex device implantation in clinical practice.

6.2.3 Study Sample Size

A sample size of 45 patients was required by power calculation, to achieve 80% power to detect a 5% (SD 8%) change in LVEF, at a significance level of 5% (two sided). (177)

Patients were screened and recruited from the existing waiting list for the sacubitril/valsartan (Entresto) switchover clinic.

6.2.4 Inclusion and Exclusion Criteria

Inclusion criteria:

- Age ≥18 years
- Symptomatic (NYHA II-III) HFrEF diagnosis
- LVEF ≤35%, despite established treatment with ACE-Inhibitor/Angiotensin Receptor Blocker (ARB), beta blocker and Mineralocorticoid Receptor Antagonist (MRA) referred for sacubitril/valsartan (Entresto) initiation
- LVEF ≤35% for inclusion was determined by Transthoracic Echocardiography (TTE)
- Able and willing to provide informed consent
- Able to under CMR

Exclusion criteria:

- Pre-existing implanted device
- Symptomatic hypotension (Systolic BP <95mmHg) (PARADIGM-HF exclusion)
- Severe renal failure (eGFR <30ml/min/1.73m^2)
- Hyperkalaemia (K > 5.4mmol/L)
- Diagnosis of amyloidosis, sarcoidosis or hypertrophic cardiomyopathy
- History of angioedema
- Myocardial infarction or revascularisation within the last 40 days
- Valve disease expected to require surgery
- Life expectancy <2 years secondary to any other cause e.g. malignancy
- Pregnancy

6.2.5 Study Design

The ENVI study was a prospective, single centre, single-arm cohort study at a tertiary centre (University Hospital Southampton NHS Foundation Trust, UK) of patients with symptomatic heart failure and severe left ventricular systolic dysfunction (LVEF ≤35%), already established on at least 3 months of "conventional" HFrEF therapy.

6.2.6 Ethics and Registration

The study was approved by National Research Ethics Committee (21/WM/0073) and approved by University of Southampton NHS Foundation Trust Research and Development department.

The study was registered with ClinicalTrials.gov (ID: NCT05348226).

6.2.7 Study Procedures

Patients were recruited from the waiting list for sacubitril/valsartan (Entresto) switchover clinic or from Heart Failure outpatient clinics. All provided written informed consent after receiving a full explanation of the study, a Participant Information Sheet, and sufficient time for consideration.

All patients had assessment at baseline including clinical and medication history, cardiovascular examination, 12-lead electrocardiogram (ECG), blood tests, quality of life (QOL) assessments in the form of KCCQ-12 questionnaire and 6 Minute Walk Test and a cardiomyopathy protocol Cardiac Magnetic Resonance (CMR) scan. (See Chapter 2)

Sacubitril/valsartan (Entresto) initiation

If already established on an ACE-Inhibitor, this was discontinued for at least 36 hours prior to the initiation of sacubitril/valsartan (Entresto) as per usual practice. Where patients were taking Angiotensin Receptor Blocker therapy, no such wash out period was required, the ARB was discontinued, and sacubitril/valsartan started the following day.

Sacubitril/valsartan was uptitrated to target doses as per British National Formulary (BNF) recommendation as standard of care. Patients were started initially on 49/51 mg twice daily for 2–4 weeks and increased if tolerated to 97/103 mg twice daily. A lower starting dose of 24/26 mg was considered if starting systolic blood pressure less than 110 mmHg.

At 2 weeks, a clinical review took place where brief history, examination, blood pressure and routine blood test (including renal function) were taken before increasing sacubitril/valsartan to the target or maximum tolerated dose.

Blood Tests

The following blood tests were taken at baseline prior to initiation of sacubitril/valsartan and at the 6 month review prior to their follow up CMR scan.

- Full blood count
- Renal function (Creatinine, urea, estimates eGFR) and electrolytes (Na+, K+)
- Liver function tests (ALT, ALP, Albumin, Bilirubin)
- N-terminal pro B type Natriuretic Peptide (NTproBNP)

Renal function was checked prior to CMR scan and 2-weekly following initiation or increase in Entresto dosage.

Dapagliflozin 10mg was added following establishment of sacubitril/valsartan if there were no contraindications. HbA1c was tested prior to dapagliflozin initiation.

At 3 months, TTE was repeated to assess LV Ejection Fraction. If LVEF remained ≤35%, the responsible HF clinician decided whether to recommend complex device implantation at that point, reflecting guideline indicated practice.

If the participant was added to the device waiting list, repeat CMR was scheduled to occur prior to complex device implantation. Otherwise, follow-up CMR scan was performed 6 months after optimisation to maximum tolerated dose of sacubitril/valsartan+/-dapagliflozin. Blood tests including NTproBNP, ECG and QOL assessments were repeated at follow up. **(Figure 6.1)**

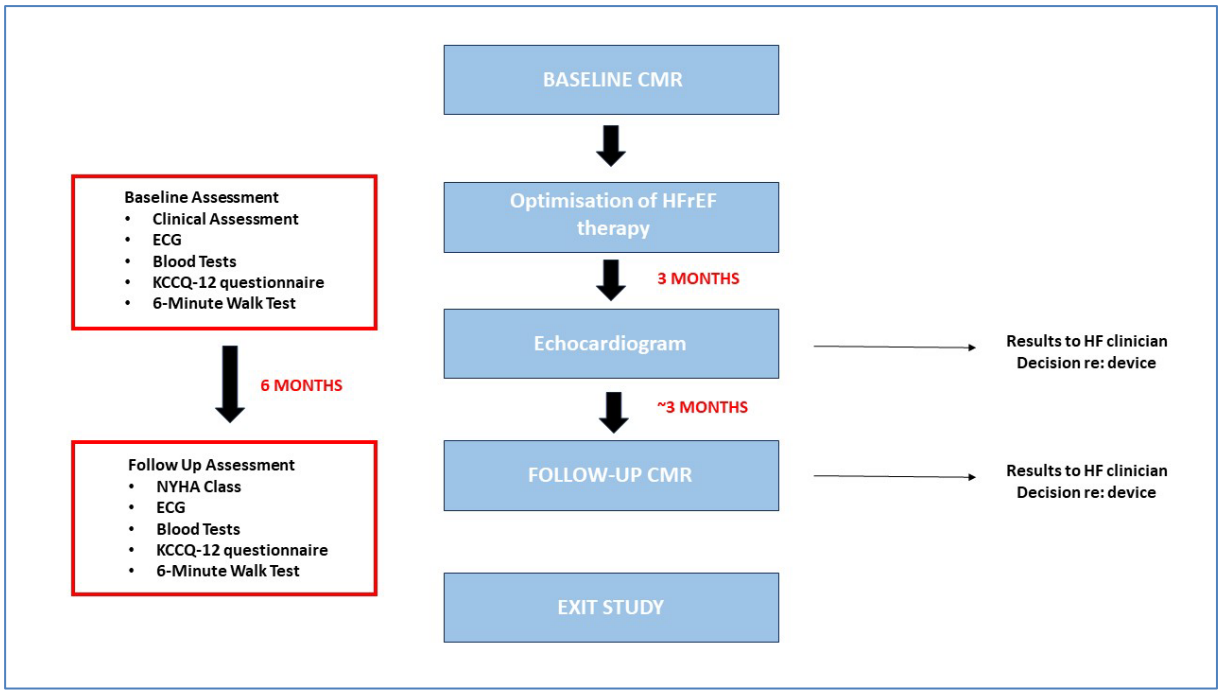

Figure 6.1 The ENVI Study schema. Reproduced from study protocol.

6.2.8 CMR Methods and Analysis

CMR scans were performed at baseline and follow up on 1.5 Tesla Siemens Sola scanner with a standardised cardiomyopathy protocol including cines, late gadolinium enhancement, T1 and T2 mapping. All scans were anonymised; baseline and follow up CMR scans were analysed independently.

All analysis was performed using CVI42® (Circle) software. Volumetric and function data were compared between baseline and follow up CMR scans. Full methods for volumetric analysis have been described in **General Methods section 2.1.2 and 2.1.3.**

Clinical outcome data including death and HF hospitalisation was obtained for the 6 month follow up period from hospital electronic patient records.

6.2.9 Statistical Analyses

All statistical tests were performed using IBM® SPSS® software package version 27.

All variables for each data set were tested for normality using Shapiro-Wilk test, correlated with visual histogram assessment.

For continuous variables, results are reported as mean±standard deviation (SD) for normally distributed (parametric) data and median (interquartile range IQR) for non-parametric data.

Categorical variables are reported as number and percentage frequencies.

Paired T-test was used to compare paired data sets of normally distributed (parametric) continuous variables. Wilcoxon signed ranks test was used to compare paired data sets of non-parametric continuous variables. A p value of ≤0.05 was considered statistically significant.

6.3 Results

6.3.1 Study Population

A total of 49 participants were recruited between June 2021 and August 2022. The majority, 39 (80%) were male and the mean age was 63±14 years. Most participants, 35 (71%) had a diagnosis of non-ischaemic cardiomyopathy (NICM) and 14 (29%) had a diagnosis of ischaemic cardiomyopathy.

Among clinical characteristics, 23 (47%) had hypertension, 14 (29%) had Type 2 Diabetes, and 20 (41%) had Atrial Fibrillation. At baseline, 35 participants (71%) were NYHA Class II.

All participants were already receiving optimised conventional HFrEF therapy at time of recruitment, with 49 (100%) on ACEI/ARB, 47 (96%) on beta blocker and 48 (98%) on MRA therapy at baseline. 28 participants (57%) were already on an SGLT2 inhibitor (dapagliflozin). **(Table 6.1)**

At baseline, the median left ventricular Ejection Fraction (LVEF) as measured by CMR was 31% (21-35) and the median NTproBNP was 883ng/L (293-2043).

Clinical Characteristic	**n=49**
Age (years)	63±14
Male Sex n (%)	39 (80%)
Body Mass Index (kg/m^2)	29.5±6.1
Aetiology	
Non-ischaemic Cardiomyopathy n (%)	35 (71%)
Ischaemic Cardiomyopathy n (%)	14 (29%)

Functional Classification	
NYHA Class II n (%)	35 (71%)
NYHA Class III n (%)	14 (29%)
Comorbidities	
Hypertension n (%)	23 (47%)
Ischaemic Heart Disease n (%)	21 (43%)
Type 2 Diabetes n (%)	14 (29%)
History of Atrial Fibrillation n (%)	20 (41%)
Chronic Kidney Disease n (%)	9 (18%)
Peripheral Vascular Disease n (%)	2 (4%)
Cerebrovascular Disease n (%)	2 (4%)
Chronic Obstructive Pulmonary Disease n (%)	3 (6%)
Physiology	
Mean Systolic Blood Pressure (mmHg)	129±16
Mean Diastolic Blood Pressure (mmHg)	76±11
Mean Heart Rate (bpm)	75±12
Sinus Rhythm - Baseline ECG	34 (69%)
Left Bundle Branch Block – Baseline ECG n (%)	5 (10%)
Right Bundle Branch Block – Baseline ECG n (%)	3 (6%)
Laboratory	
Mean Haemoglobin (g/L)	140±14
Median Urea (umol/L)	8.3 (6.3-9.4)
Mean Creatinine (umol/L)	96±25
Mean Potassium (mmol/L)	4.3±0.4
Median NTproBNP (ng/L)	883 (293-2043)
HFrEF Medical Therapy	
ACE-Inhibitor/Angiotensin Receptor Blocker n (%)	49 (100%)
Beta Blockers n (%)	47 (96%)
Mineralocorticoid Receptor Antagonist (MRA) n (%)	48 (98%)
SGLT2 Inhibitor n (%)	28 (57%)

Table 6.1 Clinical and Biochemical Characteristics of all participants at baseline.

6.3.2 Follow Up and Clinical Outcomes

At follow-up, all participants had been optimised to maximally tolerated dose of sacubitril/valsartan and 38 (78%) were taking dapagliflozin.

Two (4%) participants died (Out of Hospital cardiac arrest) during the study period. Both died within 40 days of recruitment; one of whom had previously been offered a CRT-D but had declined.

The remaining 47 participants were followed up for a median period of 7.4 (6.7-7.9) months. There were no Heart Failure hospitalisations during the study period.

Median NTproBNP reduced from 883 ng/L (293-2043) to 429 ng/L (171-1421) [p<0.001] between baseline and follow-up.

6.3.3 Cardiac Reverse Remodelling Outcomes

At three months, 44 participants attended for transthoracic echocardiogram (TTE). 26 (59%) participants still had an LVEF of ≤35% at this point. At 6 months, 29 (59%) participants had demonstrated an improvement on follow-up CMR scan to an LVEF >35%.

There was no apparent difference between remodelling observed by aetiology: 21(60%) of the 35 participants with Non-ischaemic Cardiomyopathy and 8 (57%) of the 14 participants with Ischaemic Cardiomyopathy demonstrated LVEF improvement to >35%. Of the 39 male participants, 22 (56%) remodelled; of the 10 female, 7 (70%) remodelled. The sample size was however too small to perform formal subgroup analysis.

12 (24%) participants who had severe LVEF ≤35% on TTE at 3 months went on to remodel further to an improved LVEF >35% on follow-up CMR. 13 (27%) participants had a normalised LVEF >50% at follow up.

Volumetric comparisons between baseline and follow up CMR scans, indexed to body surface area (BSA) are shown in **Table 6.2** and **Figure 6.2**.

At follow up, there were significant reductions in median indexed Left Ventricular End Diastolic volume (LVEDVi) from 109ml/m^2 (74-125) to 76 ml/m^2 (58-102) [p<0.001] and median indexed Left Ventricular End Systolic Volume (LVESVi) from 74ml/m^2 (50-92) to 43ml/m^2 (27-58) [p<0.001].

The median indexed Left Ventricular Stroke Volume (LVSVi) increased from 30ml/m^2 (21-38) to 32 ml/m^2 (25-39) [p=0.033] and the median Left Ventricular Ejection Fraction (LVEF) increased from 31% (21-35) to 43% (26-50) [p<0.001].

The median indexed Left Atrial volume (LAVi) reduced from 54ml/m^2 (41-72) to 39ml/m^2 (30-60) [p<0.001] and the mean indexed Left Ventricular Mass (LV Massi) reduced from 72±13g/m^2 to 62±13g/m^2 (p<0.001).

	Baseline (n=49)	**Follow Up (n=47)**	**p Value**
Left Ventricle			
LV EDV i (ml/m^2)	109 (74-125)	76 (58-102)	<0.001
LV ESV i (ml/m^2)	74 (50-92)	43 (27-58)	<0.001
LV SV i (ml/m^2)	30 (21-38)	32 (25-39)	0.033
LV EF (%)	31 (21-35)	43 (26-50)	<0.001
LV Mass i (g/m^2)	72±13	62±13	<0.001
Septal Thickness (mm)	9 (8-11)	10 (8-12)	0.307
Left Atrium			
LA Volume i (ml/m^2)	54 (41-72)	39 (30-60)	<0.001
LA Diameter (mm)	43±9	40±8	0.001

Table 6.2 Comparison of Left Ventricular and Left Atrial CMR parameters reported as mean ± Standard Deviation or median (Inter Quartile Range) between Baseline and Follow Up scans.

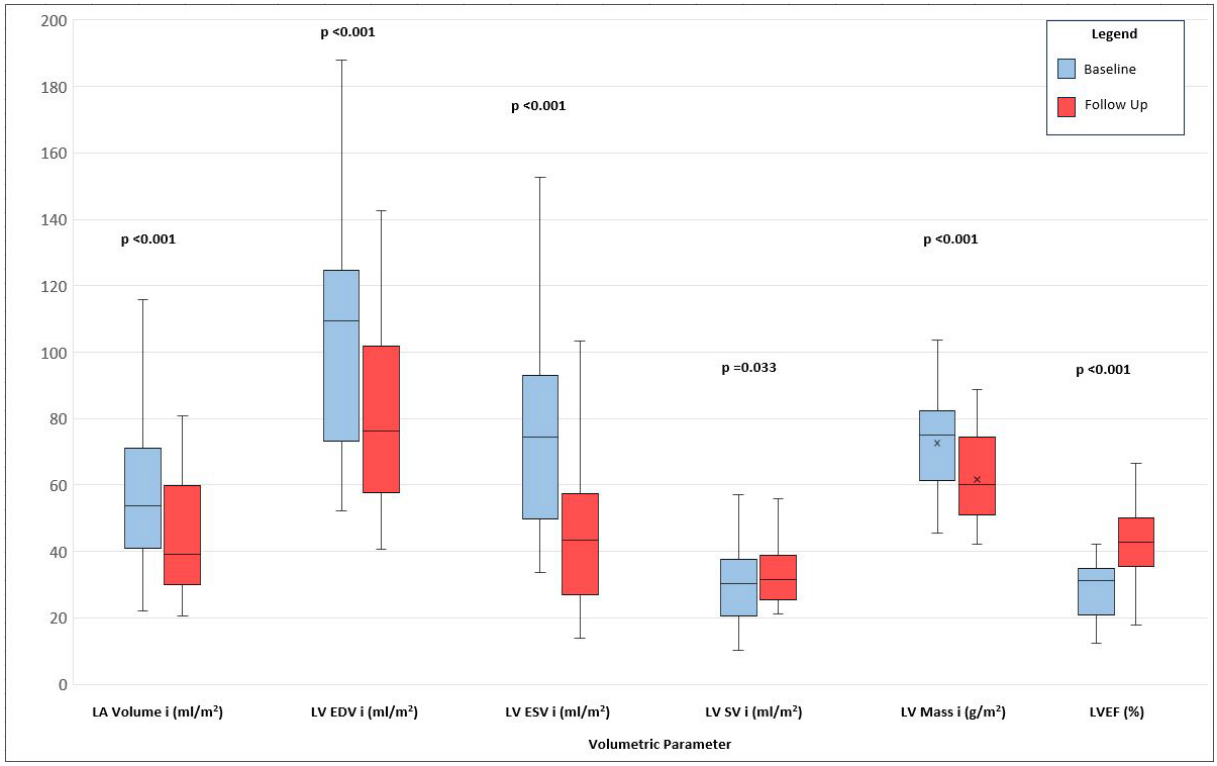

Figure 6.2 Comparison of indexed volumetric parameters and LVEF between Baseline and 6-month Follow Up CMR scans following optimisation to contemporary HFrEF medical therapy

6.3.4 LVEF Improvement and Complex Device Therapy

44 participants attended for TTE at three months, of which 26 had a reported LVEF ≤35%. After individual assessments by their responsible HF clinician, six participants were offered a complex device (ICD or CRT-D/P) at that point.

One participant had a CRT-D implanted within the month, and had their follow-up CMR brought forwards. The remainder were listed for a device, but due to standard NHS waiting times, their allocated device implant date occurred after their follow-up CMR.

At the end of the study period, a total of nine (18%) participants received a complex device, as they had not positively remodelled on their follow-up CMR. After shared decision making processes, four declined a device and three were still undecided.

At baseline, eight participants had a bundle branch block on ECG (3 with Right Bundle Branch Block, 5 with Left Bundle Branch Block). At follow-up, four participants no longer met criteria for Cardiac Resynchronisation Therapy as their LVEF had improved, and one no longer had a Left Bundle Branch Block.

No participants developed a new Bundle Branch Block over the study period. The median QRS duration decreased from 110ms (104-125) at baseline to 106ms (98-119) at follow-up (p=0.01).

Over half the cohort, 29 (59%) participants had demonstrated beneficial reverse remodelling after optimisation to contemporary HFrEF therapy, with improved LVEF >35% on follow-up CMR, whereby a complex device was no longer indicated.

6.3.5 Quality of Life Outcomes

A total of 40 (85%) participants completed 6 Minute Walk Tests both at baseline and at follow up (some unable to complete due mobility/pain).

There was significant improvement in mean 6MWT distance walked (361±133m vs 393±115m; p=0.03) for the participants who had improved LVEF to >35% after 6 months of optimised HFrEF therapy. There was no difference in the group who had not beneficially remodelled and still had LVEF ≤35% (323±69m vs 321±94m; p=0.96).

The comparison of QOL assessments between baseline and follow-up are shown in **Table 6.3**.

6MWT	**Baseline (metres)**	**Follow Up (metres)**	**p Value**
All participants (n= 40)	348±117	370±113	0.09
LVEF >35% at FU (n= 27)	361±133	393±115	***0.03**
LVEF ≤35% at FU (n=13)	323±69	321±94	0.96
KCCQ-12	**Baseline Score**	**Follow Up Score**	**p Value**
All participants (n= 47)	75 (46-90)	78 (50-94)	0.07
LVEF >35% at FU (n= 29)	73 (44-92)	78 (43-96)	0.09
LVEF ≤35% at FU (n=18)	75 (56-81)	78 (52-90)	0.42

Table 6.3 Comparison of Quality of Life (QOL) parameters at Baseline and Follow-up. 6 Minute Walk Test (6MWT) and Kansas City Cardiomyopathy Questionnaire (KCCQ-12) scores are shown for all participants; participants who had improved LVEF >35% at Follow Up, and those with LVEF remaining ≤35% at Follow Up.

At baseline, 35 (71%) of participants were NYHA Class II and 14 (29%) were NYHA III. After 6 months, 13 (28%) of participants reported being asymptomatic (NYHA I). The proportion of participants reporting both NYHA II and III symptoms at follow up reduced to 53% and 19% respectively. **(Table 6.4)**

NYHA Functional Class	Baseline (n=49)	Follow Up (n=47)
NYHA I, n (%)	0	13 (28%)
NYHA II, n (%)	35 (71%)	25 (53%)
NYHA III, n (%)	14 (29%)	9 (19%)
NYHA IV, n (%)	0	0

Table 6.4 Comparison of NYHA Classification of Functional Status between Baseline and Follow Up.

6.4 Discussion

After 6 months of optimised contemporary HFrEF medical therapy, there was significant beneficial left ventricular and left atrial reverse remodelling, resulting in an improvement in median LVEF of 12 points.

Adverse cardiac remodelling is intrinsic to the progression of HFrEF. Compensatory mechanisms triggered by myocardial injury and stress result in molecular, cellular and interstitial changes of the myocardium. As left ventricular dysfunction progresses, cardiac dimensions, volumes and mass increase and the heart's geometry changes from an elliptical to spherical shape, causing secondary mitral regurgitation, exacerbating preload and further dilatation. (101)

6.4.1 Sacubitril/Valsartan and Reverse Remodelling

Potential beneficial effects of sacubitril/valsartan on cardiac reverse remodelling have thus far all been assessed by echocardiography.

EVALUATE-HF found a reduction from baseline in the sacubitril/valsartan group of LVEDVi, LVESVi and LAVi, as well as improved diastolic function, compared to enalapril observed at 12 weeks. They did not however, demonstrate a difference in LVEF. (128)

PRIME found, in patients with left ventricular dysfunction and chronic secondary Mitral Regurgitation, a significant decrease in effective regurgitant orifice area and regurgitant volume, as well as reduction in LVEDVi in the sacubitril/valsartan group at 12 months, compared to valsartan.(178)

PROVE-HF found that magnitude and speed of reduction of NTproBNP concentration correlated with improvement of cardiac volume and function at 12 months. They reported a mean increase of 9 points in LVEF at 12 months from 28% to 37%; as well as improvements in LVEDVi, LVESVi, LAVi, and E/E' ratio. (124)

A study that focused on association of reverse remodelling of patients treated with sacubitril/valsartan found that those who demonstrated LV reverse remodelling (EF >45% or LVESV volume reduction by >15%) had a significantly improved prognosis compared to those who did not respond. (179)

6.4.2 SGLT2 Inhibitors and Reverse Remodelling

There is limited but emerging data on the effects of SGLT2 inhibitors on cardiac remodelling. A meta-analysis of 9 SGLT2 inhibitor trials in HF reported reductions in absolute LV volumes (LVEDV, LVESV) and indexed LV mass, and an increase in mean LVEF of +2% (p=0.003), particularly in HFrEF patients. The majority of trials included were Empagliflozin and Canagliflozin. The only included trial evaluating Dapagliflozin (REFORM) found no significant changes in cardiac remodelling parameters on CMR in patients with diabetes and HFrEF. (176,180) The DAPA-MODA study which included patients with HF regardless of LVEF treated with Dapagliflozin and evaluated cardiac remodelling parameters with echocardiography, found global reductions in indexed left ventricular volumes, mass and indexed left atrial volume at 180 days. There was also significant reduction in NTproBNP at 180 days. (175)

6.4.3 Contemporary HFrEF Therapy Effects on Reverse Remodelling and Function on CMR

This study was the first to report the effects of optimisation to contemporary HFrEF therapy on cardiac reverse remodelling in a cohort of symptomatic patients who had not demonstrated improvement despite established conventional therapy using CMR.

SGLT2 inhibitors became included in international HF guidelines during the recruitment period and so the study reflects real world practice.

57% of the cohort were already on Dapagliflozin at baseline, which increased to 78% at follow-up. The predominant intervention to optimise HFrEF therapy was switchover to maximum tolerated dose of sacubitril/valsartan, in all participants.

There was a 30% decrease in median LVEDVi and a 42% decrease in median LVESVi; as well as an absolute increase of 12 points in median LVEF after 6 months. The data complements previously published echocardiographic remodelling studies and show beneficial improvement in LV geometry and improvement in function as demonstrated by CMR, a key mechanism in achieving the prognostic benefits in these HFrEF patients.

6.4.4 Left Atrial Volume and Left Ventricular Mass

Other putative mechanisms for improved prognostic outcomes include reductions in indexed left atrial volumes and left ventricular mass.

Left atrial enlargement and dysfunction are established markers of both systolic and diastolic dysfunction and predictors of poor cardiovascular outcome including stroke, Atrial Fibrillation, heart failure and mortality. (181)

Increased left ventricular mass is an independent risk factor for adverse cardiovascular events including myocardial infarction, stroke, heart failure hospitalisation and death. (182,183)

This study showed a 28% reduction in median LAVi and a 14% reduction in mean indexed LV mass following 6 months of optimised HFrEF medical therapy.

Figure 6.3 shows an example of CMR 4-Chamber cine still captures in diastole and systole, before and after optimisation of HFrEF therapy.

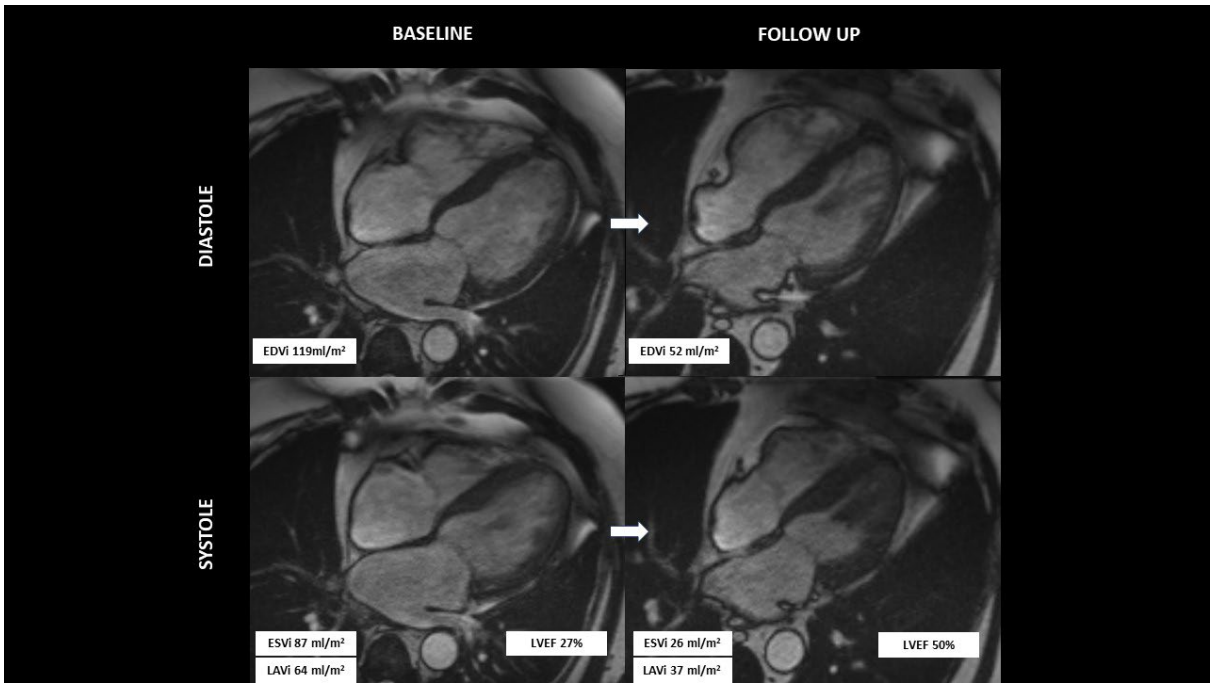

Figure 6.3 CMR 4-Chamber cine still captures in diastole and systole demonstrating beneficial left ventricular and left atrial reverse remodelling after 6 months of optimisation to contemporary HFrEF therapy.

6.4.5 Reverse Remodelling and Complex Devices

Current ESC guidelines recommend consideration of complex device implantation (ICD or CRT-P/D) for patients with symptomatic HFrEF and LVEF ≤35% after at least 3 months of optimum medical therapy, to prevent sudden cardiac death or to optimise dyssynchrony in the case of CRT. (1)

At baseline, all participants in our study had LVEF ≤35% despite establishment on conventional HF therapy of ACEI/beta blocker/MRA and thus were all complex device candidates.

At 3 months after optimisation, 47% had improved LVEF >35% on echocardiography. By 6 months, 59% had an LVEF >35% on follow-up CMR and no longer qualified for a complex device. This included one participant who no longer had a LBBB on ECG.

The PROVE-HF investigators also found that among the cohort of patients who met eligibility for an ICD at baseline, 32% had improved their LVEF to >35% by 6 months and 62% to >35% by 12 months, after initiation of sacubitril/valsartan. The risk of sudden cardiac death was 2% within 6 months for PARAGIM-HF and <1% at 1 year for PROVE-HF. (184)

Analysis into the modes of death in PARADIGM-HF showed that 44.8% (n=561) of deaths were classed as “sudden death” and a 20% reduction in risk was observed in the sacubitril/valsartan group, compared with enalapril (HR 0.80; 95% CI 0.68-0.94; p=0.008). (132) An anti-arrhythmic effect has been described in two prospective studies of HFrEF patents with ICD/CRT-Ds in situ and remote monitoring. Following switchover from ACE-I/ARB to sacubitril/valsartan, episodes of non-sustained ventricular tachycardia (NSVT), sustained VT and appropriate ICD shocks were significantly decreased. (133,134)

In 2021, the American College Cardiology (ACC) published updated consensus stating that LV re-assessment to determine device decision should occur between 3 and 6 months following optimisation of medical therapy, with a shorter period for those at “higher risk e.g. EF <30%, evidence of ventricular ectopy or ischaemic cardiomyopathy” and 6 months for those at “lower risk”. (185)

This data which includes patients all established on sacubitril/valsartan and most on dapagliflozin, found an even higher proportion improving LVEF to >35% at 6 months. It suggests that a longer period before re-assessment such as 6 months, would mean a significant number of HFrEF patients may avoid the need, and the associated complications of complex device implantation. This could also mean significant cost reduction to the healthcare system.

It is however, not known whether transitioning from an LVEF ≤35% to >35% means that a complex device would not benefit a patient, either in terms of sudden cardiac death risk reduction, or reduction in HF symptoms in the case of CRT. The current LVEF cut-off values for recommendation of complex devices are derived from the inclusion criteria of landmark device trials. More recently, DANISH (32) demonstrated no overall benefit in all-cause mortality of primary prevention ICDs in Non-Ischaemic Cardiomyopathy with LVEF ≤35%.

Conversely, the presence of mid-wall LGE has been shown to be associated with a nine-fold increase in sudden cardiac death/aborted sudden cardiac death in patients with non-ischaemic cardiomyopathy and an LVEF >40%. (186)

There is growing evidence that using LVEF cut-off as the sole arbiter of ICD recommendation is insufficient. The aetiology of cardiomyopathy and other factors e.g. genetics, LGE and family history are likely to play significant roles. Further research to guide a more multiparametric risk assessment of patients with cardiomyopathy is required moving forward. (187)

6.5 Limitations

The main limitations of this study were the relatively small sample size and the single-arm nature, without control. Given the proven prognostic benefits of ARNI and SGLT2 Inhibitors in this population, a control arm would not have been ethically possible.

The majority (80%) of our study population was male. This is similar to the proportion of males in both PARADIGM-HF (78%) (20)and DAPA-HF (77%) (26). Women are unfortunately consistently underrepresented in clinical trials, and this is a recognised limitation when interpreting our conclusions. (188)

6.6 Conclusion

After 6 months of optimisation to contemporary medical therapy for HFrEF patients, to include maximum tolerated dose of sacubitril/valsartan and dapagliflozin, there were significant improvements to both left ventricular and left atrial remodelling parameters as demonstrated by CMR imaging in both non-ischaemic and ischaemic aetiologies.

There were reductions in indexed left ventricular volumes and mass, indexed left atrial volume and a significant increase of median Left Ventricular Ejection by 12 points. There was also a significant reduction in median NTproBNP concentration.

59% of this cohort, all of whom had LVEF ≤35% at baseline, demonstrated beneficial left ventricular reverse remodelling by 6 months, and no longer met criteria for complex device implantation.

Chapter 7 RESULTS 5: Effects of optimisation to contemporary HFrEF medical therapy with sacubitril/valsartan (Entresto) and dapagliflozin on left Ventricular reverse remodelling as demonstrated by Cardiac Magnetic Resonance (CMR) Imaging*: The ENVI Study* – Tissue Characterisation Analyses

7.1 Introduction

As previously discussed in detail, CMR offers the marked benefits of greater contrast resolution, reproducibility and information on myocardial tissue composition; with Late Gadolinium Enhancement (LGE) allowing assessment of focal scar and fibrosis, and T1 mapping techniques allowing assessment of diffuse myocardial fibrosis, oedema and Extracellular Volume (ECV).

The known evidence base so far on CMR tissue characterisation data and its relationship to response to HFrEF therapy and beneficial cardiac reverse remodelling was introduced in **Chapter 4.1**.

To recap, there have been a number of relatively small studies published, almost exclusively in small cohorts of patients with Non-Ischaemic Cardiomyopathy (NICM). The absence, or the lower percentage mass, of LGE present on baseline CMR have been shown to be predictive of greater Reverse Remodelling effects and greater improvements in follow up LVEF (accepting that multiple different definitions of Reverse Remodelling exist). (155,156,159,189)

The evidence for parametric T1 mapping and its relationship to Reverse Remodelling is far more limited, with a few small studies producing mixed results, within NICM cohorts.

Lower ECV (%) at baseline has been shown to predict Reverse Remodelling and improvement in LVEF in NICM in two fairly recent single centre studies in Japan and China. (165,166)

Multivariate analysis however, found only a lower baseline LVEF and the absence of LGE were significant independent predictors of Reverse Remodelling. (166) There was no significant correlation found between change in LVEF and baseline native or post-contrast T1 values in the Japanese study. (165) Another small CMR study of 34 patients with NICM however, found that baseline LGE presence and extent, native T1, and basal or mid ECV (%) were not significantly associated with Reverse Remodelling. (190)

In the Chinese study of 157 patients with NICM, 48 (31%) demonstrated Reverse Remodelling: defined as "an absolute increase in LVEF of >10% to a final value of ≥35% and a relative decrease in indexed LVEDV of >10%" with "Guideline Directed Medical Therapy (GDMT)". The Remodelled group were shown to have significant reductions in native myocardial T1, "absolute indexed cellular volume" and "absolute indexed matrix volume" between first and second CMR (median interval 13.8 months), but no change in percentage ECV. The study was published in 2021, with GDMT stated as "ACEI/ARB, MRA, Beta blockers, diuretics Digoxin and Warfarin" within the Methods. (166)

The limited studies on reverse remodelling cited above were all with patients established on what is now considered "conventional" HFrEF therapy, i.e. prior to the inclusion of sacubitril/valsartan (Entresto) and SGLT2 inhibitors as the third and fourth pillars of HFrEF therapy. They also almost exclusively studied patients with dilated, Non-Ischaemic Cardiomyopathy.

There have been to date, no published studies describing the effects on CMR tissue characterisation before and after treatment of HFrEF patients with sacubitril/valsartan (Entresto) and dapagliflozin.

7.2 Methods

7.2.1 Study Rationale

The ENVI Study was the first study to examine how optimisation to contemporary HFrEF medical therapy for 6 months affected Cardiac Magnetic Resonance (CMR) Tissue Characterisation parameters e.g. T1 mapping, ECV and LGE in HFrEF patients with *both* non-ischaemic and ischaemic aetiologies.

The cardiac reverse remodelling effects of optimisation to contemporary HFrEF medical therapy have been described in **Chapter 6**.

We also aimed to investigate whether there were differences in baseline Tissue Characterisation parameters between those participants that demonstrated beneficial cardiac reverse remodelling, and those who did not.

7.2.2 Hypotheses

1. Optimisation to contemporary HFrEF medical therapy as per updated HF guidelines for 6 months results in a reduction in diffuse cardiac fibrosis as measured by T1 mapping and ECV (%) on CMR.
2. Lower native T1 and ECV (%) values (reflecting less diffuse cardiac fibrosis) at baseline is associated with beneficial reverse remodelling in response to optimisation to contemporary HFrEF medical therapy.

7.2.3 The ENVI Study Methods

The ENVI study full methods, inclusion and exclusion criteria and study design are detailed in **section 6.2.**

7.2.4 CMR Tissue Characterisation Analysis

CMR scans were performed at baseline and 6 months follow up on 1.5 Tesla Siemens Sola scanner with a standardised cardiomyopathy protocol. All scans were anonymised; baseline and follow up CMR scans were analysed independently.

Full T1 mapping acquisition and analysis methods and ECV calculations have been previously described in **General Methods section 2.1.5.**

In short, T1 mapping was performed at basal and mid-myocardium levels (12 AHA segments). Analysis was performed using Circle CVI42® software. Septal Region of Interest (ROI), segmental and blood Native and Post-Contrast T1 values were used to calculate ROI and "whole heart" Global Extracellular Volume (ECV %).

The process was then repeated excluding any myocardial segments with Late Gadolinium Enhancement (LGE) present to give Global Native and Post-Contrast T1 values *excluding* LGE, and Global ECV *excluding* LGE (%).

The presence and pattern of LGE was noted for each scan and manually quantified as a % of LV mass as described in **section 2.1.4.**

Septal ROI, Global and Global *excluding* LGE Native and Post-Contrast T1 (ms) and calculated ECV (%) values were compared between baseline and follow-up CMR scans.

Myocardial ECV calculated from T1 mapping values and Haematocrit as described above is a volume fraction. It can therefore change as a result of not only changes in the extracellular matrix compartment, but also the intracellular volume. A reduction in extracellular matrix alone results in a reduction in ECV (%), reduction in intracellular volume alone results in an increase in ECV (%) and a proportional reduction in *both* compartments would result in an unchanged ECV (%). (191)

Absolute indexed LV Matrix and Cell Volumes were therefore calculated, using the following calculations (whereby 1.05 g/ml represents the specific gravity of myocardium) and indexed to Body Surface Area (BSA):

LV Matrix Volume = (LV Mass / 1.05g/ml) x ECV

LV Cell Volume = (LV Mass/1.05g/ml) x (1-ECV) (166,191)

Calculated indexed LV Matrix and LV Cell volumes were compared between baseline and follow up CMRs. The ECV value used in these calculations was septal ROI ECV as recommended by EACVI and SCMR consensus statement. (192)

7.2.5 Tissue Characterisation Analysis - Responder vs. Non-Responder

For The ENVI Study, the criterion for "Responder" was different to PREDICT-HF study. **(Chapter 4)**

Participants who had demonstrated Reverse Remodelling on follow up CMR at 6 months, to an improved LVEF value of >35% no longer qualified for complex device procedure prescription as discussed in **Chapter 6.**

This same cut-off value was therefore used to separate the participants into "Responders" and "Non-Responders" after 6 months of optimisation to contemporary HFrEF therapy to include sacubitril/valsartan (Entresto) +/- Dapagliflozin.

Baseline septal ROI, Global and Global *excluding* LGE Native and Post-Contrast T1 (ms), calculated ECV (%), indexed LV Matrix volume and indexed LV Cell volumes were compared between Responder and Non-Responder groups.

The proportion of participants with LGE present n (%), pattern of scar (non-ischaemic or ischaemic) and % mass of manually quantified LGE at baseline were also compared between Responder and Non-Responder groups.

7.2.6 Statistics

Statistical tests used for The ENVI study are previously described in **section 6.2.9.**

Paired T-test (parametric) and Wilcoxon signed ranks test (non-parametric) were used to compare paired data sets i.e. baseline vs. follow-up results.

For the Responder vs. Non-Responder analysis, independent 2 sample t-test was used to compare continuous parametric variables and Mann-Whitney U test for continuous non-parametric variables.

Fisher's exact test was used to compare categorical variables between groups as study sample size was small and >20% expected counts were <5.

7.3 Results

7.3.1 Study Population

Between June 2021 and August 2022, a total of 49 participants were recruited. 39 (80%) participants were male, and the mean age was 63±14 years. Most participants (71%) had a diagnosis of non-ischaemic cardiomyopathy. The clinical baseline characteristics are listed in **Table 6.1.** and described in **section 6.3.1.**

At baseline, there was excellent uptake of conventional HFrEF medical therapy. All participants were switched from ACEI/ARB to sacubitril/valsartan (Entresto) as per study protocol. 28 (57%) participants were already on Dapagliflozin at baseline and at follow up, this number increased to 38 (78%).

Two (4%) participants died within 40 days of recruitment and 47 were followed up for 6 months.

There were reductions in both mean systolic and diastolic Blood Pressures of 10mmHg and 7mmHg respectively, at follow up (129±16mmHg vs 119±16mmHg; p=0.003 and 76±11mmHg vs 69±11mmHg; p=0.003).

There was no significant change in renal function but mean Haemoglobin (140±14g/L vs. 148±14g/L; p<0.001) and mean Haematocrit (0.41±0.04L/L vs. 0.44±0.04L/L; p<0.001) were higher at follow-up compared to baseline.

Median NTproBNP reduced from 883 ng/L (IQR 293-2043) to 429 ng/L (IQR 171-1421) (p<0.001).

Follow-up physiological and biochemical (laboratory) characteristics at 6 months follow up, compared to baseline are displayed in **Table 7.1**.

Clinical Characteristic	**Baseline n=49**	**Follow Up n=47**	**p Value**
Age (years)	63±14		
Male Sex n (%)	39 (80%)		
Aetiology			
Non-ischaemic Cardiomyopathy n (%)	35 (71%)		
Ischaemic Cardiomyopathy n (%)	14 (29%)		
Comorbidities			
Hypertension n (%)	23 (47%)		
Ischaemic Heart Disease n (%)	21 (43%)		
Type 2 Diabetes n (%)	14 (29%)		
History of Atrial Fibrillation n (%)	20 (41%)		
Chronic Kidney Disease n (%)	9 (18%)		
Peripheral Vascular Disease n (%)	2 (4%)		
Cerebrovascular Disease n (%)	2 (4%)		
HFrEF Medical Therapy			
ACE-Inhibitor/ARB n (%)	49 (100%)		
Beta Blockers n (%)	47 (96%)		
MRA n (%)	48 (98%)		
SGLT2 Inhibitor n (%)	28 (57%)		
Physiology			
Body Mass Index (kg/m^2)	30 ±6	31±7	**0.007**
Mean Systolic Blood Pressure (mmHg)	129±16	119±16	**0.003**
Mean Diastolic Blood Pressure (mmHg)	76±11	69±11	**0.003**
Mean Heart Rate (bpm)	75±12	72±10	0.067

Laboratory			
Mean Haemoglobin (g/L)	140±14	148±14	**<0.001**
Mean Haematocrit (L/L)	0.41±0.04	0.44±0.04	**<0.001**
Median Urea (umol/L)	8.3 (6.3-9.4)	7.2 (6.1-9.1)	0.163
Mean Creatinine (umol/L)	96±25	97±25	0.216
Mean Potassium (mmol/L)	4.3±0.4	4.5±0.3	**0.004**
Median NTproBNP (ng/L)	883 (293-2043)	429 (171-1421)	**<0.001**

Table 7.1 Clinical and biochemical characteristics of participants at Baseline and Follow Up.

7.3.2 Tissue Characterisation Following Optimisation of HFrEF Therapy

All native and post-contrast T1 values were found to be normally distributed. There were significant reductions found in mean T1 values at 6 months follow up, compared to baseline in all categories compared.

Septal Region of Interest (ROI) analysis (sampled away from LGE) demonstrated a reduction in mean native T1 from 1040±48ms to 1020±48ms (p=0.003) and a reduction in mean post-contrast T1 from 430±55ms to 398±49ms (p=0.001).

“Whole heart” Global Native T1 analysis demonstrated a reduction in mean native T1 from 1036±54ms to 1017±41ms (p=0.001) and a reduction in mean post-contrast T1 from 427±53ms to 388±49ms (p<0.001).

“Whole heart” Global *excluding* LGE analysis demonstrated a reduction in mean native T1 from 1027±52ms to 1012±43ms (p=0.034) and a reduction in mean post-contrast T1 from 436±52ms to 398±43ms (p<0.001). Results are displayed in **Table 7.2** and **Figure 7.1.**

ECV (%) values were not normally distributed and there were no significant differences found when comparing baseline and follow up median ECV (%) values between groups.

Median septal ROI ECV was 29% (IQR 26-33) at baseline and 28% (25-32) at follow up; p=0.159. Median “whole heart” Global ECV was 29% (IQR 27-32) at baseline and 30% (IQR 27-32) at follow up; p=0.629. Median “whole heart” Global *excluding* LGE ECV was 28% (IQR 26-30) at baseline and 28% (IQR 26-31) at follow up; p=0.694. **Table 7.2** and **Figure 7.2.**

Calculated mean indexed LV Matrix and indexed LV Cell Volumes however, demonstrated significant reductions from 21±5 ml/m^2 to 16±6 ml/m^2; p<0.001 and from 49±10 ml/m^2 to 40±12

ml/m^2; p<0.001 respectively from baseline to follow up, associated with a significant reduction in indexed LV mass. Results are shown in **Table 7.3** and **Figure 7.3.**

There was no difference found in Left Ventricular median LGE (% mass) between baseline 5% (IQR 1-12) and at follow-up 4% (IQR 1-13); p=0.863.

CMR Tissue Characterisation	Baseline (n=49)	Follow Up (n=47)	p Value
Septal ROI Native T1 (ms)	1040±48	1020±48	**0.003**
Septal ROI Post-Contrast T1 (ms)	430±55	398±49	**0.001**
Septal ROI ECV (%)	29 (26-33)	28 (25-32)	0.159
Global Native T1 (ms)	1036±54	1017±41	**0.001**
Global Post-Contrast T1 (ms)	427±53	388±49	**<0.001**
Global ECV (%)	29 (27-32)	30 (27-32)	0.629
Global *excluding* LGE Native T1 (ms)	1027±52	1012±43	**0.034**
Global *excluding* LGE Post-Contrast T1 (ms)	436±52	398±43	**<0.001**
Global *excluding* LGE ECV (%)	28 (26-30)	28 (26-31)	0.694

Table 7.2 Comparison of Tissue Characterisation parameters reported as mean±SD and median (IQR) between Baseline and Follow Up at 6 months.

	Baseline (n=49)	Follow Up (n=47)	p Value
Indexed LV Matrix Volume (ml/m^2)	21±5	16±6	**<0.001**
Indexed LV Cell Volume (ml/m^2)	49±10	40±12	**<0.001**
LV Mass i (g/m^2)	72±13	62±13	**<0.001**

Table 7.3 Comparison of mean indexed LV Matrix and Cell Volumes and indexed LV Mass between Baseline and Follow Up at 6 months.

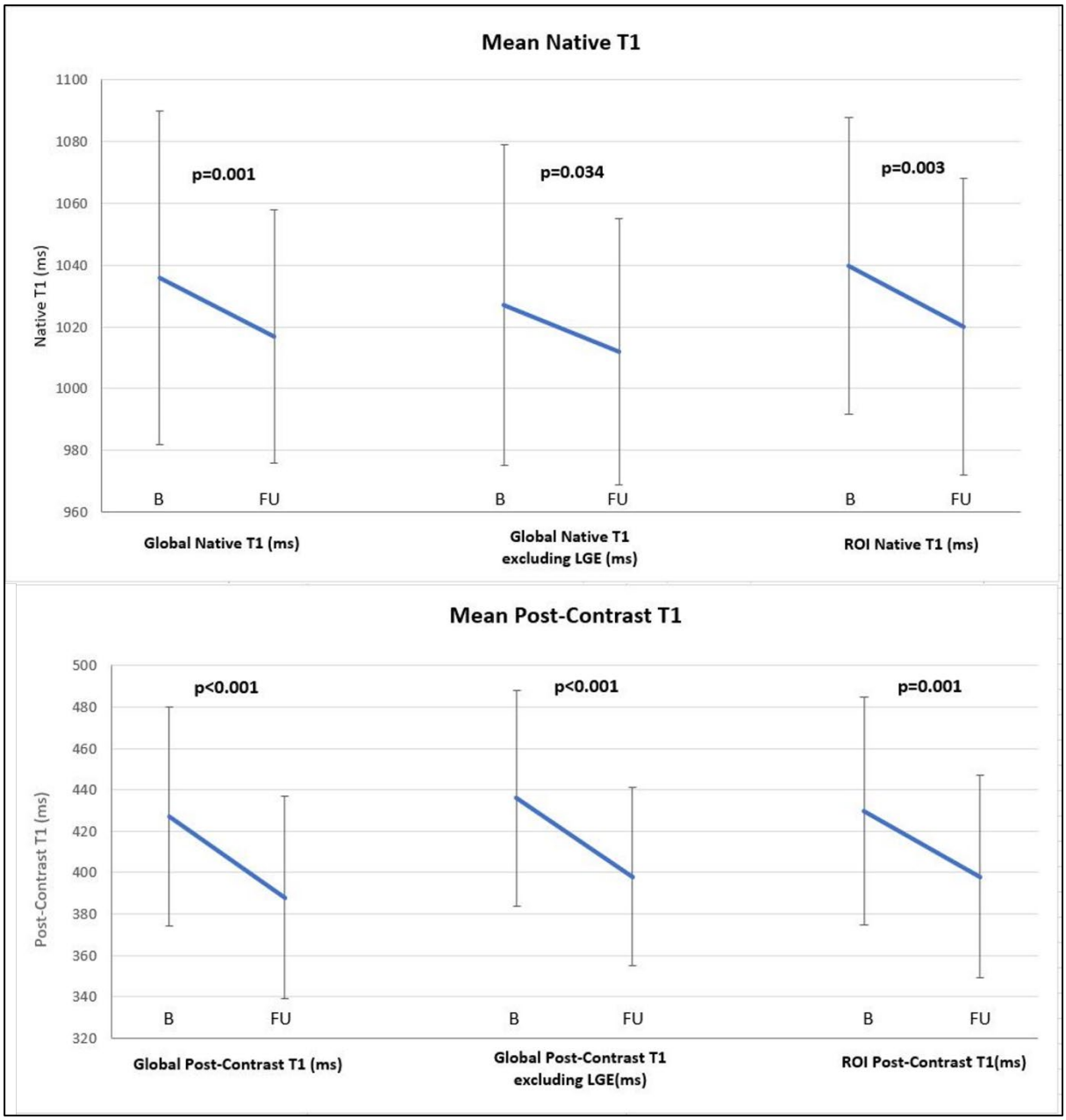

Figure 7.1 Comparison of mean (+/-SD) Global, Global excluding LGE and septal ROI Native and Post-Contrast T1 values between Baseline and Follow Up at 6 months.

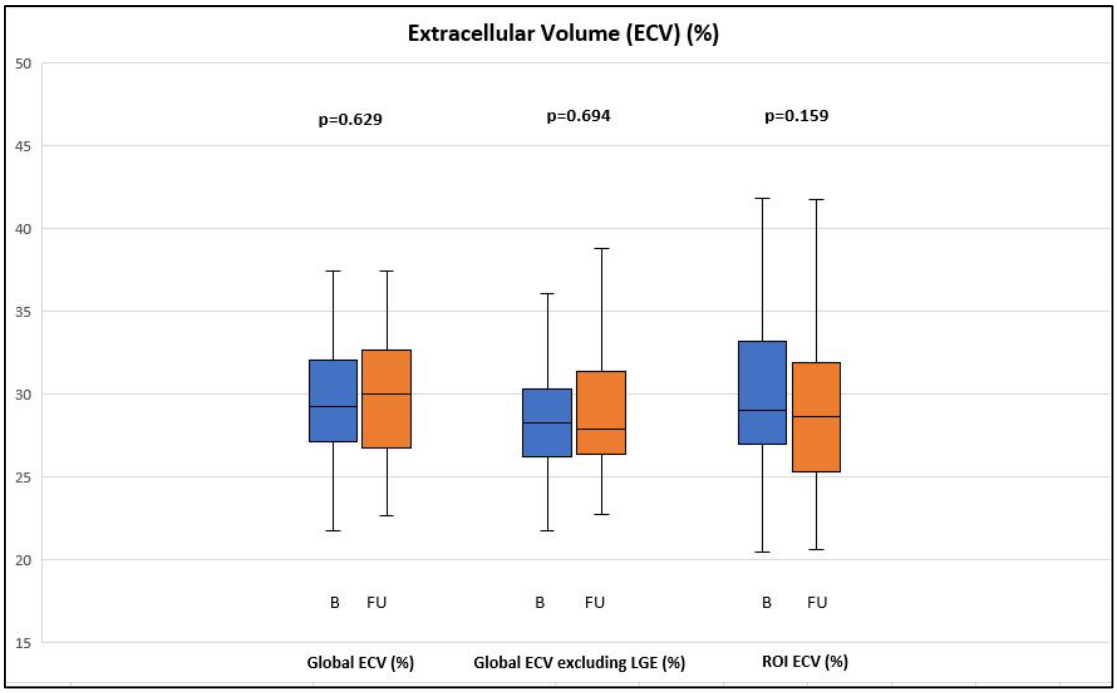

Figure 7.2 Comparison of median Global, Global excluding LGE and septal ROI ECV (%) between Baseline and Follow Up at 6 months.

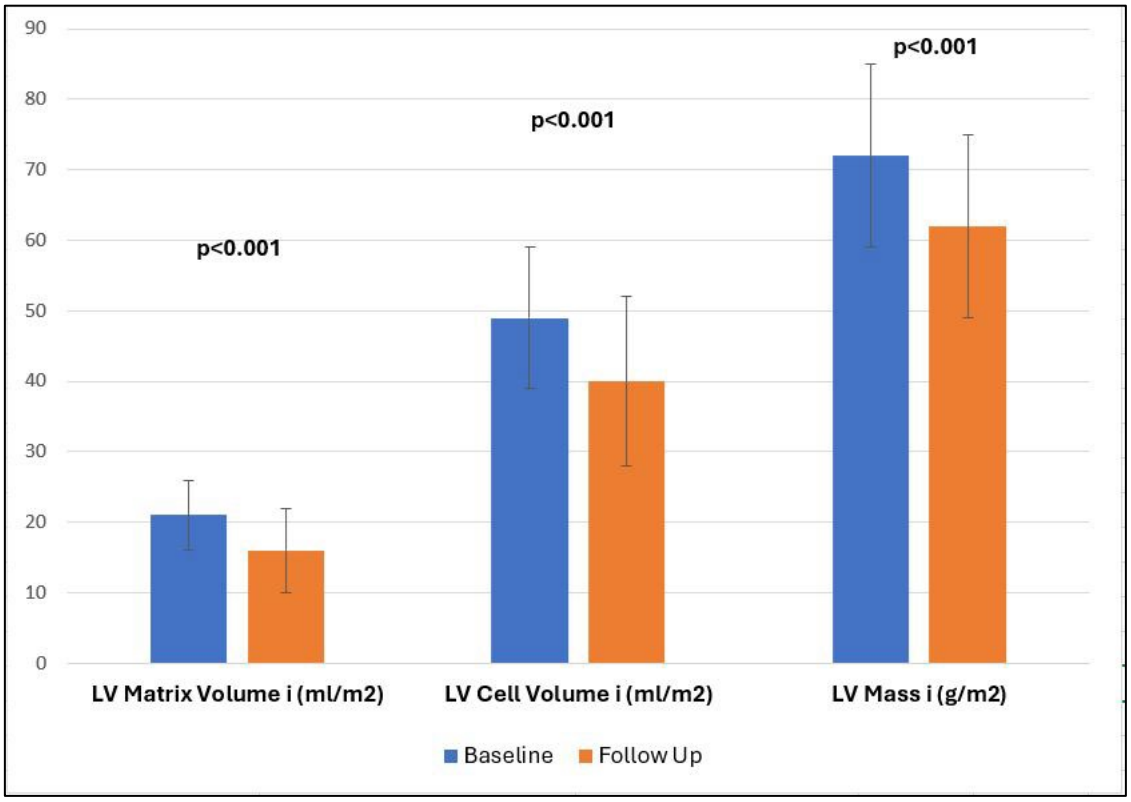

Figure 7.3 /Comparison of mean indexed LV Matrix Volume, LV Cell Volume and LV Mass between Baseline and Follow Up at 6 months.

7.3.3 Responder vs. Non-Responder Tissue Characterisation Analysis

"Responders" in this sub-analysis were defined as those participants who had beneficially remodelled to an **improved LVEF >35%** on their follow-up CMR after 6 months of optimisation to contemporary HFrEF therapy to include sacubitril/valsartan (Entresto) +/- Dapagliflozin.

29 (59%) participants were classified as "Responders" at 6 months, and no longer met criteria for complex device therapy. 18 (37%) participants were classified as "Non-Responders" and still had LVEF ≤35% at 6 months.

The Responder group had a significantly lower median septal (ROI) native T1 (ms) on baseline CMR compared to the Non-Responder group; 1019 (IQR 996-1061) ms vs 1048 (IQR 1028-1075) ms, p=0.039. (**Table 7.4** and **Figure 7.4**)

There were no statistical differences found between baseline "whole heart" Global Native T1 (ms) or "whole heart" Global *excluding* LGE Native T1 (ms) median values between Responder and Non-Responder groups.

There was no difference found between baseline septal ROI, Global or Global *excluding* LGE post-contrast T1 (ms), or calculated ECV (%) values between Responder and Non-Responder groups.

Baseline CMR Parameter	All (n=49)	Responder (n=29)	Non-Responder (n=18)	p Value
Septal ROI Native T1 (ms)	1040±48	1019 (996-1061)	1048 (1028-1075)	**0.039**
Septal ROI Post-Contrast T1 (ms)	430±55	429 (383-461)	409 (397-481)	0.768
Septal ROI ECV (%)	29 (26-33)	29±5	31±4	0.317
Global Native T1 (ms)	1036±54	1014 (993-1055)	1029 (1013-1081)	0.358
Global Post-Contrast T1 (ms)	427±53	425±560.	431±47	0.704
Global ECV (%)	29 (27-32)	29 (27-31)	30 (27-34)	0.187

Global *excluding* LGE Native T1 (ms)	1027±52	1013 (989-1041)	1025 (1010-1062)	0.229
Global *excluding* LGE Post-Contrast T1 (ms)	436±52	433±54	442±50	0.596
Global *excluding* LGE ECV (%)	28 (26-30)	28 (26-30)	29 (26-32)	0.328

Table 7.4 Comparison of baseline CMR Tissue Characterisation parameters reported as median (IQR) and mean±SD between Responder and Non-Responder groups.

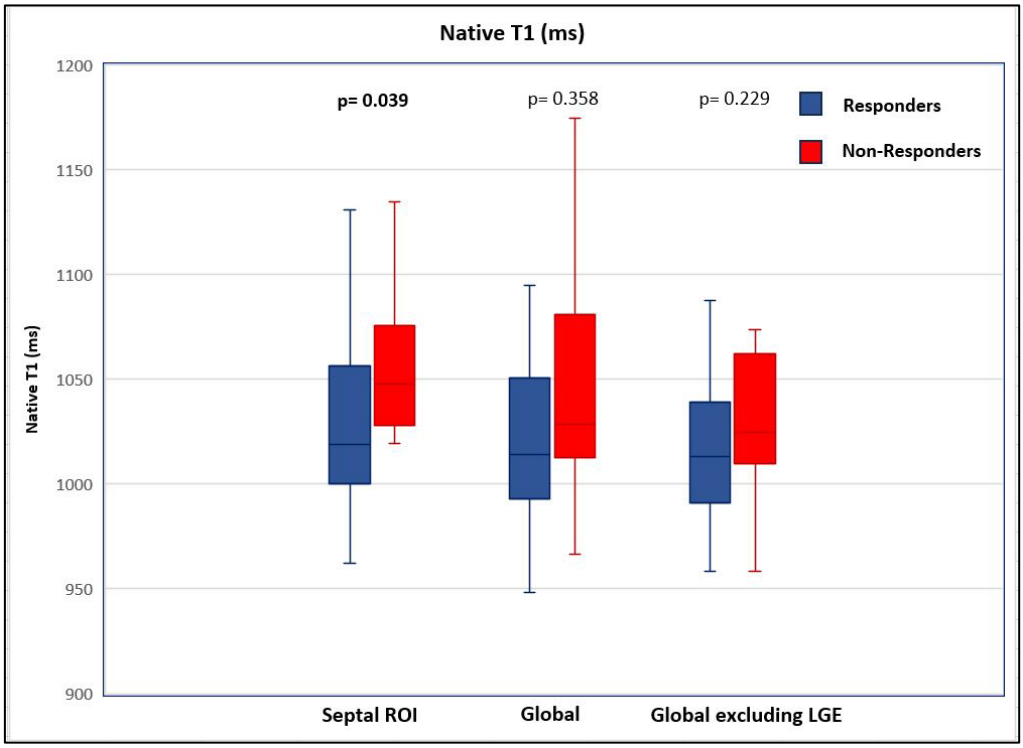

Figure 7.4 Comparison of baseline median Septal (ROI), Global and Global excluding LGE Native T1 (ms) between Responder and Non-Responder groups.

When comparing the baseline absolute indexed LV matrix and cell volumes, the Responder group had significantly lower values compared to the Non-Responder group; 19±5 ml/m^2 vs 23±4 ml/m^2, p=0.005 and 46±10 ml/m^2 vs 52±9 ml/m^2, p=0.04 respectively. The Responder group also had lower mean indexed LV mass at baseline, 68±14 g/m^2 vs 79±12 g/m^2, p=0.008 at baseline. (**Table 7.5** and **Figure 7.5)**

	Responder (n=29)	Non-Responder (n=18)	p Value
Indexed LV Matrix Volume (ml/m^2)	19±5	23±4	**0.005**
Indexed LV Cell Volume (ml/m^2)	46±10	52±9	**0.040**
LV Mass i (g/m^2)	68±14	79±12	**0.008**

Table 7.5 Comparison of mean indexed LV Matrix and Cell Volumes (ml/m^2) and indexed LV Mass between Responder and Non-Responder groups.

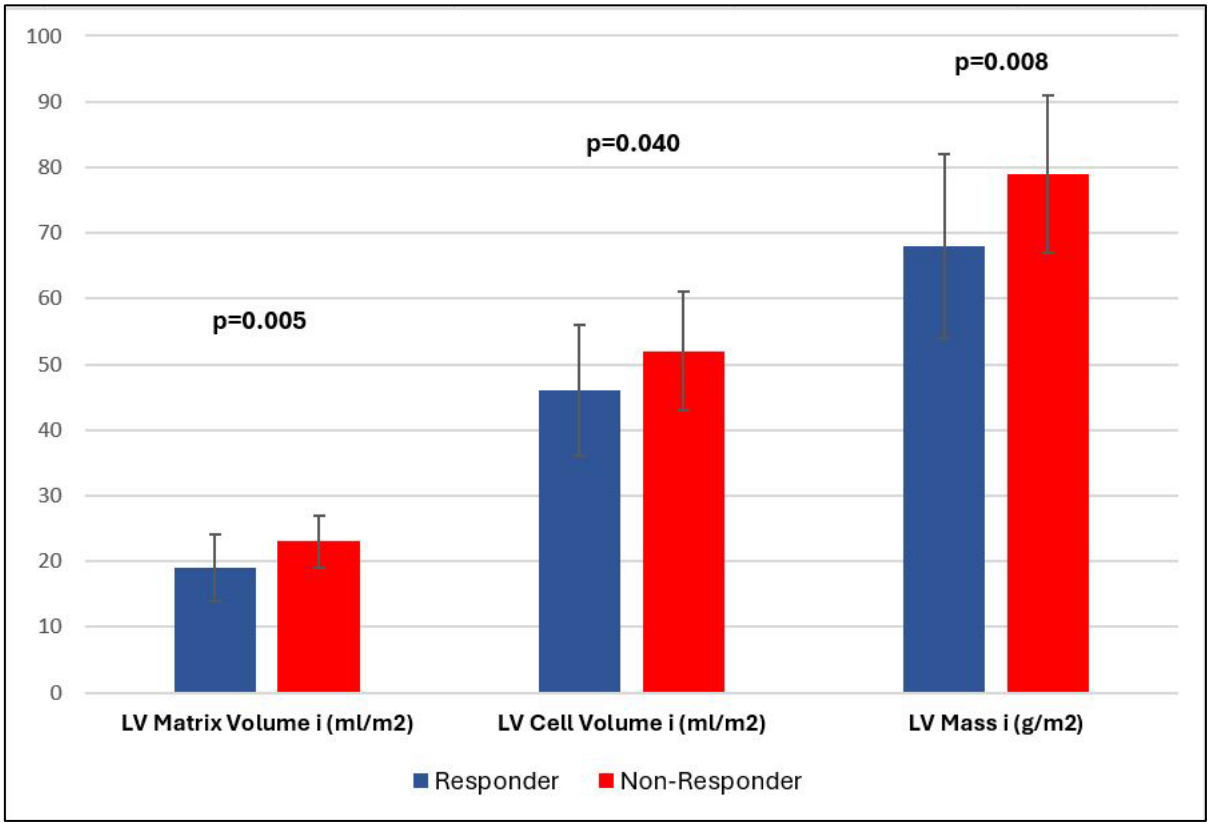

Figure 7.5 Comparison of mean indexed LV Matrix Volume, LV Cell Volume and LV Mass between Responder and Non-Responder groups.

A total of 37 (76%) participants had LGE present on their baseline CMR. Of these, 21 (57% of LGE group) were Responders and 16 (43% of LGE group) did not respond. Of the 12 (24%) participants who did not have LGE present on their baseline CMR, 8 (67% of No LGE group) were Responders and 4 (33% of No LGE group) did not respond. There was no statistical difference found between the presence or absence of LGE on baseline CMR in this cohort, and response to optimisation of HFrEF therapy (p=0.543).

There was no difference in the proportion of participants with LGE present on their baseline CMR between the Responder and Non-Responder groups; 72% vs 78%, p=0.744. There were also no differences found when LGE scar pattern distribution and quantified median LGE (% mass) were compared between groups. (**Table 7.6**.)

Baseline CMR Parameter	All (n=49)	Responder (n=29)	Non-Responder (n=18)	p Value
LGE present, n (%)	37 (76%)	21 (72%)	14 (78%)	0.744
Ischaemic LGE, n (%)	18 (37%)	11 (38%)	6 (33%)	1.000
Non-Ischaemic LGE, n (%)	19 (38%)	10 (34%)	8 (44%)	0.548
LGE (% mass)	7 (4-19)	4 (0-11)	6 (4-13)	0.179

Table 7.6 Comparison of baseline LGE characteristics reported as n (%) and median (IQR) between Responder and Non-Responder groups.

7.4 Discussion

7.4.1 Tissue Characterisation in Optimised Contemporary HFrEF Therapy

Th ENVI study was the first to investigate the effects of optimisation to contemporary HFrEF therapy on CMR tissue characterisation parameters. 100% of participants were transitioned to sacubitril/valsartan (Entresto) and 78% were taking Dapagliflozin by the time of follow up. As previously discussed, ESC HF guidelines were updated part way through the study period, and therefore this reflected real-world practice.

This study was novel in that all patients recruited had *not* remodelled on conventional HFrEF therapy of ACE-i or ARB/BB/MRA for a minimum of 3 months, and still had symptomatic HF with LVEF <35%, qualifying for sacubitril/valsartan (Entresto) switchover at baseline.

Secondly, contrary to previous remodelling studies, participants with both non-ischaemic and ischaemic aetiologies were included.

After 6 months of optimised HFrEF therapy, there were significant reductions in both Native and Post-Contrast T1 mapping parameters in all analysed categories: septal T1 (ms), “whole heart” Global Native T1 (ms) and “whole heart” Global Native T1 (ms) *excluding* LGE.

These findings support our original hypothesis that optimisation of HFrEF treatment would result in reductions in T1 mapping values. The significant reduction seen in native septal T1 as a response to optimised therapy is consistent with the findings of the previously cited study of DCM patients who had remodelled with conventional GDMT. (166)

Our original hypothesis was that ECV (%) would reduce across time as well, reflecting a reduction in diffuse myocardial fibrosis (extracellular compartment) but this was found not to be the case. Calculated ECV (%) both from septal ROI and “whole heart” global analysis was unchanged between baseline and follow up, despite the significant decreases in T1 mapping values and indexed LV mass.

As previously discussed, should the intracellular compartment of the myocardium also reduce with optimisation of HFrEF therapy, then ECV which is a volume fraction, may appear unchanged. Other studies have described this concept and have utilised separate calculations to derive an absolute intracellular LV cell volume and extracellular LV matrix volume in order to help facilitate a greater understanding into the potential mechanisms of reverse remodelling. (166,191)

Using these calculations to compare the separate intracellular and extracellular compartments, our cohort demonstrated significantly lower absolute LV matrix and cell volumes at follow-up compared to baseline. This reflects changes in both extracellular and intracellular compartments in response to optimised medical therapy, and was associated with significant reduction in LV mass, and improvement in LV function.

There was no change (reduction) in the quantified LGE extent (% mass) in our cohort following optimisation of HFrEF therapy and this is consistent with other published findings. Any increase in LGE extent over time has been associated with worse LV dysfunction. (189)

7.4.2 Responder vs. Non-Responder Analysis

A large proportion of participants (59%) experienced beneficial remodelling after the introduction of sacubitril/valsartan (Entresto) and Dapagliflozin, and had an improvement in LVEF to >35%. These patients no longer met criteria for complex device implantation. Full Reverse Remodelling analysis has been discussed in **Chapter 6**.

As discussed, evidence so far on the relationship between T1 mapping and Reverse Remodelling is scarce and with mixed results. We hypothesised lower baseline T1 values would result in more beneficial LV remodelling and have found in our cohort that native septal (ROI) T1 values were significantly lower in the Responder group compared to Non-Responder group. There was no difference however between "whole heart" Global T1 values.

Although lower ECV (%) has been found in other studies to be a predictor of LV reverse remodelling, we did not find a significant difference in baseline ECV (%) between our Responder and Non-Responder groups. This could be due to relatively small sample size once the cohort was divided into the sub-groups. The Responder group was found however, to have lower absolute indexed LV matrix and cell volumes and lower indexed LV mass at baseline compared to the Non-Responder group.

Despite LGE presence/extent being a recognised predictor of reverse remodelling, we did not find a significant difference between our Responder and Non-Responder groups. This could be partly due to sample size and also because the majority (76%) of the cohort had LGE present on baseline CMR, with mixed aetiologies.

7.4.3 Role of "Whole Heart" Global T1 Mapping

Our study goes beyond the analysis of septal ROI T1 values, to include reported differences in relatively novel "whole heart" Global T1 assessment, with and without the inclusion of LGE segments.

The latest consensus statement for T1, T2 and T2* and ECV on CMR, endorsed by the European Association of Cardiovascular Imaging (EACVI) and Society for Cardiovascular Magnetic Resonance (SCMR), recommend a single ROI to be selected for T1 and ECV analysis on a mid-cavity short-axis slice avoiding artefact, adjacent blood pool and LGE (although inclusion of non-ischaemic LGE is acceptable). This consensus statement recognises the potential of whole heart T1 mapping as an emerging future technique. (192)

A group in Germany have recently investigated global and regional reproducibility of T1 mapping in 50 healthy volunteers. They quantified the LV into three short-axis slices and found “good” reproducibility of global T1 mapping overall. They found some regional variability with “good” reproducibility of T1 values in apical and basal short axis slices whereas reproducibility of T1 values for the midventricular slice was “excellent”. Reproducibility of T1 mapping values was highest in the septum compared to anterior, lateral and inferior walls. (193) Other groups have recently published their myocardial Global native T1 reference ranges at 3T CMR in healthy volunteers (China) and in patients with aortic stenosis (Monaco). (194,195)

7.5 Limitations

The main limitation of the ENVI study is the relatively small sample size and the absence of control group as discussed in section 6.5**.** Due to the sample size, it was not possible to separate the groups into ischaemic and non-ischaemic aetiologies, or sex-based sub-analysis for example.

The study sample size was originally powered to detect a 5% (SD 8%) change in LVEF. Once the group was further divided into Responder vs. Non-Responder sub-analysis, we recognise the sample size would be too small to draw meaningful conclusion but feel our data is still relevant as an addition to this emerging field.

Lastly, for Global T1 mapping analysis, only two short axis slices representing 12 AHA myocardial segments were acquired, and the values extrapolated to represent “whole heart” T1 and ECV. This could potentially underestimate T1 and ECV in those individuals with significant apical fibrosis.

7.6 Conclusion

In this cohort of HFrEF patients with both non-ischaemic and ischaemic aetiologies, optimised to contemporary HFrEF therapy with sacubitril/valsartan (Entresto) and Dapagliflozin for 6 months, there were significant reductions in Native and Post-Contrast T1 values.

There was no detected change in ECV (%) however there were reductions in absolute indexed LV matrix and indexed LV cell volumes, and a reduction in indexed LV mass reflecting changes in myocardial tissue composition.

Patients who experienced beneficial reverse remodelling to an LVEF of >35% had lower native septal T1 (ms), lower indexed LV matrix and cell volumes, and lower indexed LV mass at baseline compared to those who did not respond.

There was no difference in quantified LGE (% mass) or ECV (%) between these groups. Larger studies over a longer follow up will help further our understanding in this area.

Chapter 8 CONCLUSIONS

8.1 Background and Hypothesis

Non-invasive tissue characterisation of the myocardium using CMR to assess aetiology of cardiomyopathy by LGE scar distribution is a well-established practice in the diagnosis and management of Heart Failure patients. Assessment of myocardial diffuse fibrosis and oedema with parametric T1 mapping is emerging as a key tool and now also becoming standard practice in CMR centres.

The potential for CMR tissue characterisation as a biomarker for risk stratification, predicting prognosis and monitoring response to therapy in Heart Failure is an expanding field.

The aim of this thesis was two-fold:

1) To investigate the changes in CMR tissue characterisation and volumetric parameters before and after 6 months of optimisation to contemporary HFrEF therapy, in patients who had not demonstrated reverse remodelling with conventional HFrEF therapy.
2) To investigate the association between baseline CMR tissue characterisation parameters and adverse outcome, or response to HFrEF therapy, in two discrete Heart Failure cohorts.

8.2 Novel Clinical Insights – Reverse Remodelling

In this thesis, we describe for the first time using CMR, the effects of optimisation to contemporary HFrEF therapy with sacubitril/valsartan (Entresto) +/- dapagliflozin.

We have demonstrated significant beneficial reverse remodelling, with reductions in left ventricular and atrial volumetric parameters, as well as left ventricular mass.

We found a 30% decrease in median LVEDVi and a 42% decrease in median LVESVi; resulting in a significant increase in median LVEF with 59% of the cohort no longer meeting criteria for implantation of a complex device by 6 months.

This supports an emerging consensus that perhaps, the current recommendations of LVEF re-assessment at 3 months of medical therapy, to decide on complex device implantation, should be lengthened.

We also report novel CMR tissue characterisation data in this cohort. We have found significant reductions in both septal and global native and post-contrast T1 values, along with significant reductions in both intracellular (LV cell volume) and extracellular (LV matrix volume) components, resulting in an apparently unchanged ECV (%) over the 6 month period.

Cardiac adverse remodelling results from a complex interplay of pathophysiological processes including neurohormonal, immune-mediated and inflammatory pathways resulting in activation of fibroblasts, hypertrophy-signalling pathways and myocyte apoptosis. Within the extracellular matrix, increases in metalloproteinase activity results in extracellular composition changes, leading to dilatation and altered geometry, increased myocardial stiffness with abnormal collagen deposition and increased fibrosis.

The capability of the heart to undergo reverse remodelling, attenuate and ultimately reverse the consequences of these maladaptive mechanisms with optimum medical and device therapy has been described in the literature. The exact mechanisms of how this is achieved from a genetic, biochemical, cellular and ultimately functional level is however, not yet fully understood. As discussed, at present even a standardised definition of Reverse Remodelling is lacking, with the most common criterion being “LVESV reduction by ≥15%”.

Our findings complement prior echocardiographic remodelling studies and support the use of CMR tissue characterisation in increasing our understanding into the mechanisms by which sacubitril/valsartan (Entresto) +/- dapagliflozin achieve their beneficial effects in HFrEF. We have found reductions in both myocardial intracellular and matrix volumes as well as mass, suggesting that regressions in both myocyte mass and extracellular diffuse fibrosis play a role.

8.3 CMR Tissue Characterisation and Prediction of Outcome

In this thesis, we investigated the association between baseline CMR tissue characterisation parameters and clinical outcomes in two very different cohorts of Heart Failure patients.

PREDICT-HF pre-dated the introduction of sacubitril/valsartan (Entresto) and dapagliflozin into HF guidelines and was a proof of concept pilot study of all-comer patients hospitalised with a new diagnosis of HF (both HFrEF and HFpEF), initiated on therapy and followed up over 24 months.

The ENVI study were patients with ongoing symptomatic HF and severe LVEF <35% despite being established on 3 months of conventional HF therapy, hence qualifying for switchover to sacubitril/valsartan (Entresto). Both studies included HF patients with both non-ischaemic and ischaemic aetiologies.

In PREDICT-HF over 2 years, we found that higher native septal T1 values and an ischaemic pattern of LGE at baseline (i.e. at time of HF diagnosis) were significantly associated with worse outcome (all-cause mortality or HF hospitalisation).

We did not however find any significant differences in baseline T1 or ECV (%) values between the participants who "responded" to therapy, and those who did not. There was a trend towards lower whole heart ECV (%) in the Responder group but this did not meet statistical significance.

The inclusion of the HFpEF population in PREDICT-HF, within a relatively small cohort to start, was a limitation to studying LV reverse remodelling endpoints over time by reducing the sample size further and likely affecting statistical power.

In The ENVI Study, we found that participants who experienced beneficial reverse remodelling (to an LVEF >35%) after 6 months of optimisation to contemporary HFrEF therapy had lower baseline septal native T1 values, LV mass, cell and matrix volumes, compared to those who did not. This supports the concept that a lower baseline of adverse remodelling i.e. lower LV mass and cell hypertrophy, with less baseline diffuse fibrosis is beneficial, and more likely to attenuate and improve with medical therapy.

Although the criterion of increase in LVEF to a final LVEF >35% is not commonly used in the Reverse Remodelling literature, this cut-off was selected to separate Responders from Non-Responders, due to the clinical significance of an LVEF 35% cut-off when prescribing complex device implantation according to current HFrEF guidelines. The exact change in risk to a patient when transitioning from an LVEF ≤35% to >35% is not known, and there is an increasing body of evidence that using LVEF as the sole arbiter of ICD recommendation is insufficient.

The definitions for beneficial reverse remodelling and subsequent analyses of "Responder" vs "Non-Responder" groups in both studies were binary i.e. did LVEF improve to the defined cut-off at follow-up, or not. This method has its limitations, particularly when investigating predictors of outcome. Binary classification simplifies a continuum and does not account for degree of LV improvement.

Further analyses of the existing study data sets could study continuous measures of LV reverse remodelling such as change in LVEF, in association with outcome. Performing time-to-event modelling for clinical outcomes and regression modelling for LVEF as a continuous variable may add statistical power.

While we recognise the limitations of relatively small sample sizes of the studies, our findings add to the growing body of evidence in the potential role of tissue characterisation and T1 mapping as a prognostic biomarker in heart failure patients.

8.4 CMR and T1 Measurement Stability

Using the validated T1MES phantom, we demonstrated that T1 measurements on the 1.5T Siemens Sola CMR scanner at UHS remained stable over a four year period, with no significant drift in acquired T1 values over time.

We can therefore be confident that the significant T1 value reductions reported in The ENVI Study were due to the study intervention and not discrepancies within the CMR scanner.

8.5 Future Research

We have reported the Left Ventricular volumetric and tissue characterisation data before and after 6 months of optimisation to contemporary HFrEF therapy in The ENVI Study. Future analysis of the study dataset is planned and will investigate:

- Effects on Right Ventricular volumetrics and function
- Effects on Left Ventricular Strain on CMR

Larger studies would be required in order to allow separate sub-analyses of response to therapy by Heart Failure aetiology or sex, for example.

Improvement in LV function with optimised HFrEF therapy represents what can be thought of as “remission” and ultimately “recovery” in some patients but larger scale studies over longer periods of time are required in order to understand which patients have sustained long-term recovery, and which patients worsen again or “relapse” in the future.

Future, larger studies would also allow for more meaningful interpretation of the association between T1 and ECV values and clinical outcomes in Heart Failure.

We have seen in our data, that studying change in calculated ECV alone may not reflect the true picture, as changes in the myocardial intracellular compartment affects the percentage ECV fraction. Is there a role therefore for T1 mapping, ECV *and* calculated absolute LV cell and matrix volumes in monitoring regression of left ventricular hypertrophy and diffuse fibrosis in response to therapies in patients with heart failure and other cardiac conditions?

The technique of Global or Whole Heart T1 mapping and ECV calculation, has been used in this thesis. Its feasibility as a technique has been described by our group previously, and other groups have since published their reference ranges of Global T1 in healthy subjects. It is now recognised as an emerging technique by SCMR/EACVI. Large scale studies are required to evaluate whether Global T1 and ECV could be used to study associations with clinical outcomes in heart failure patients, or whether it could have potential to monitor response to therapy.

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Appendix – T1MES Phantom User Manual

THE T1MES PHANTOM USER MANUAL

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T1MES
cmr
T1 Mapping and ECV Standardisation
Improving patient care through CMR phantoms

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ADDITIONAL MATERIALS NEEDED TO SCAN THE PHANTOM

1. A **firm support** to elevate the T1MES bottle to isocenter (for approximate heights please see the specific **Siemens/Philips/General Electric (GE) Appendix** scanner instructions but these may vary depending on couch options).
2. A **double folded blanket** to separate the phantom from the anterior coil.
3. **For GE centers only** – a 'Chicken Heart' ECG Simulator.

Written and produced by Gatehouse P, Captur G, Moon JC, Pang W, Royet C.
Every effort shall be made to keep this manual as relevant and up-to-date as possible – so it is subject to change without notification. Version 15 September 2015.

Regulatory information – Medical Device classification:

Europe	USA
Class I non-sterile and non-measuring CE	Class I FDA Establishment Registration #3005450718

TABLE OF CONTENTS

ABBREVIATIONS LIST

AP = antero-posterior
ECG = electrocardiogram
FOV = field of view
GE = General Electric
HF = head-foot
ID = phantom identity number
LCD = liquid crystal display
$NiCl_2$ = nickel chloride
PMU = physiologic monitoring unit
P(P)NS = predicted peripheral nerve stimulation
RL = right-left
SAR = specific absorption rate
T = tesla
T1MES = T1 Mapping and ECV Standardisation

INTRODUCTION TO THE T1MES USER MANUAL

Above all, the aim is consistency each time the phantom is setup and measured. These instructions mainly attempt to keep everything the same every time: phantom orientation and position, coil setup, heart rate, factors affecting scanner calibrations such as the "shim" volume, shim methods, etc. Please try to keep this basic aim in mind. Although running the B_0 "shim" is arguably undesirable please note this is specified and should be operated in the same mode with the same receiver coils for it, and the same calculation or fitting volume used each time.

The arrangement of tubes in the phantom is not random: it avoids placing long-T1 tubes in the corner positions where B_0 and B_1 distortions associated with the phantom are greatest. Alignment of tubes with the B_0 direction and scanning halfway along them, not towards their ends, are also important factors in avoiding measurements in regions using distorted fields.

Please do not add "loading" phantoms – the phantom has been tested without these on all systems.

The suggested R-R interval 900ms (heart-rate 67bpm) requires explanation. For good reasons known in the literature, some T1-mapping methods on some scanners run for a fixed period of seconds, fitting in however many images they can, at one per cardiac-cycle in the prescribed time. However, a phantom scan using a simulator resulting in an exact "fit" of cycles into the prescribed delay, could result in a variable number of images caused by small simulator timing differences on repeated scans. The R-R at 900ms is an attempt to avoid this problem in the most common case (Siemens 5s[3s]3s and 4s[1s]3s[1s]2s). Depending on your T1-mapping sequence, an R-R of 800ms or 1000ms may still run repeatably reliably. Provided that the SAME R-R value is used for each session this would be acceptable if 900ms cannot easily be obtained (but if possible please use 900ms).

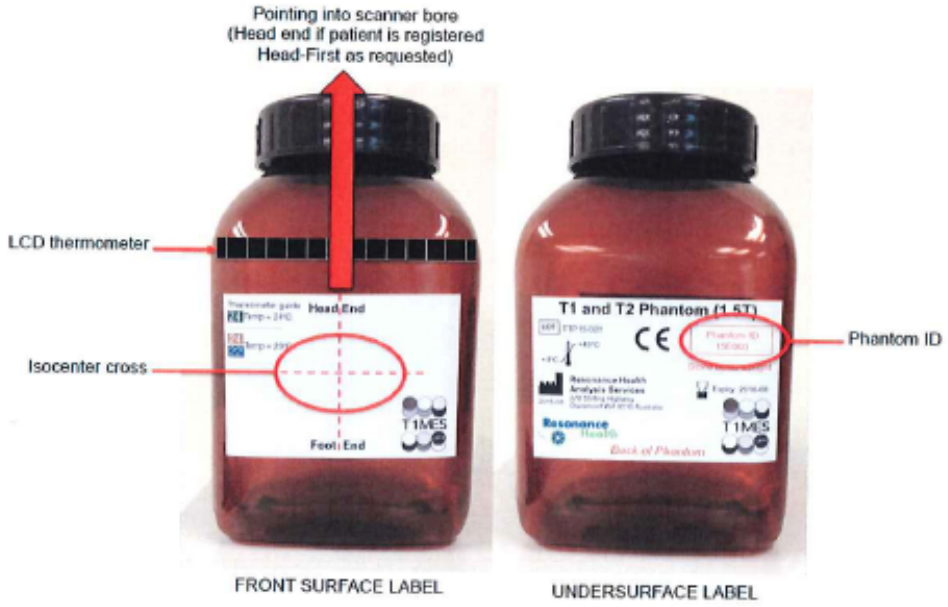
1 | PHANTOM OVERVIEW

1. The phantom consists of an amber plastic bottle sealed by a tight black cap.

   △ NEVER OPEN THE CAP

2. Inside the bcttle is an agar/nickel chloride ($NiCl_2$)/high-density plastic bead fill containing a 3 X 3 array of plastic tubes filled with the T1/T2 mixtures. The tubes rest on a resin layer at the base (**Figure 1**).
3. There is a label with a red isocenter cross on the front surface of the bottle to aid positioning in the scanner.
4. There is another label on the back of the bottle that contains the unique 6-digit phantom identity number (ID) - e.g. 15E001 or 30E008. The first 2 numbers ('15' | '30') indicate whether this is a 1.5T or 3T phantom. 'E' indicates the model, and the last three digits are the unique serial number.
5. Please use the Phantom ID for all data entry.
6. Along the top of the bottle's front surface, is a liquid crystal display (LCD) thermometer strip.

Figure 1. External features of the phantom.



2 | PHANTOM CARE

1. On receiving the phantom, unpack and inspect it. Take photos if it appears damaged and upload these onto REDCap (see 6.1). Use REDCap to log a description of the fault.
2. Please be gentle when moving the phantom around - do not drop or shake it.
3. Do not place heavy objects on top of or strongly against the phantom at any time (the phantom outer bottle is quite flexible).
4. In between research scans, store the phantom upright in your scanner room for temperature consistency with scanning, and in the same protected area each time.

△ STORE THE PHANTOM VERTICALLY UPRIGHT

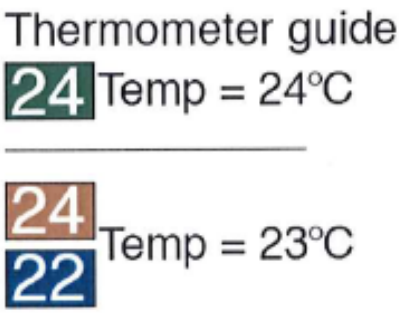
3 | INSTRUCTIONS FOR PHANTOM SETUP

3.1 | TEMPERATURE

1. There is a self-adhesive LCD temperature strip with temperature range 10°C to 40°C along the upper surface of the phantom (**Figure 2**). Temperature markers appear at an interval of 2°C, but the **resolution of the strip is actually 1°C**.
2. Take note of phantom temperature **before** starting each new scan.
3. If there is a bright GREEN cell, this marks the exact phantom temperature (it will be an even number).
4. If there is no green cell but adjacent BLUE and TAN cells, then exact phantom temperature is the odd number **in between** (**Figure 3**).
5. Phantom temperature must be added to the <Patient Name> when **registering the new scan** on your MRI scanner (see 4.1).

Figure 2. Temperature strip

Figure 3. If **GREEN** cell = take this value;
If adjacent **TAN/BLUE** cells = take middle value.



3.2 | ORIENTATION

△AIM TO POSITION THE PHANTOM AT ISOCENTER USING THE SAME SUPPORTING MATERIALS IN EACH SCANNING SESSION
(+/-1cm across [*x*] and along [*z*] the bed; +/-3cm for height [*y*])

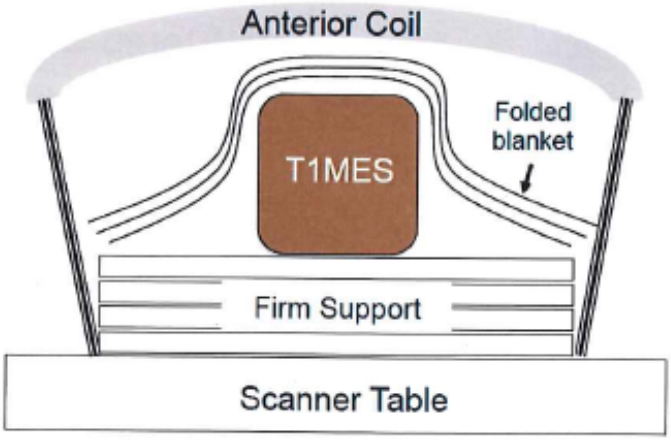
1. Set up and scan the phantom at the isocenter position and in exactly the same way each time for repeat scans.
2. If you notice something unspecified while handling/scanning the phantom, please feedback on what it was.
3. Read your manufacturer-specific instruction in the **Appendix** for where along the table to place the phantom, i.e. in the *z* direction (for Siemens see A8.1.1; for Philips see A8.2.1; for GE see A8.3.1).
4. Do not place the phantom directly onto the spine or bed coil. To bring it up to isocenter you must elevate the phantom bottle above the spine or bed coil by using a firm support.
5. This height depends on your scanner model and MRI table options. (For Siemens see A8.1.1; for Philips see A8.2.1; for GE see A8.3.1). Test the height of the firm support to find one that will lift your phantom to isocenter (see **Figure 4**).

△USE THIS SAME FIRM SUPPORT FOR ALL SUBSEQUENT SCANS.

6. The firm support must be **FIRM**. It cannot be so soft that it will deform erratically and prevent consistent phantom positioning (i.e. avoid ordinary pillows and blankets for this application).
7. Suggested materials to use as firm support include:
   a. A stack of glued (not stapled) spine journals.
   b. A firm supporting (foam plastic) slab that may come with your scanner equipment.
8. Once you configure the correct firm support STORE it in the scanner room with the phantom.
9. Lay the T1MES phantom onto the firm support as in **Figure 4**.

△ STORE AND ALWAYS USE THE SAME FIRM SUPPORT FOR EACH SCAN

Figure 4. Phantom setup on the table (the 'M' of T1MES in the figure below is at isocenter).



10. Consistent elevation will optimise the height of T1MES isocenter so that you obtain repeated T1MES data with CONSISTENT tube position and orientation over time.

11. Place the firm support in the middle of the table's receiver coil relative to *x*-axis and between the correct table markers for where you would usually position the patient's heart.
12. The **black bottle cap** (equivalent to the 'Head') for the specified head-first registration of patient orientation must point into the bore. The isocenter cross sticker must be on the upper surface of the bottle.
13. ***Before doing anything else***, move the table and shine the laser target markers onto the phantom arrangement till the laser markers are aligned with the red isocenter cross. The pair of *x*-lines and the pair of *z*-lines should overlap.
14. **Memorize phantom temperature now and before introducing bottle into the bore.**
15. Obtain a thick blanket, folded over into a generous rectangular shape and drape this over the top of the phantom. Do this ***after*** having isocentered with lights, ***but before*** applying the surface coil.
16. If possible, use the same anterior cardiac coil for all subsequent phantom experiments.
17. During the subsequent steps, note that the phantom may accidentally be shifted or twisted, and this **should be avoided**.
18. Place the anterior coil onto the blanket that is overlying the phantom with laser target marker still turned on. Adjust the position of the anterior coil manually (do not move the table nor inadvertently slide the phantom) till the ***isocenter cross of the coil*** is aligned with the laser target markers.
19. Strap the anterior coil into place to prevent it slipping off the phantom arrangement. Tighten the straps to secure the blanket around the T1MES bottle.
20. While unlikely to matter, please use consistent air-flow settings for repeated scans (e.g. **set the patient fan in the scanner to medium** each session).
21. Once you configure the correct firm support, STORE it in the scanner room ready for repeated use with the phantom.

4 | PHANTOM SCANNING

4.1 | SCAN SETUP

1. Register the phantom on your MRI scanner using the Phantom ID. For Siemens see A8.1.2; for Philips see A8.2.2; for GE see A8.3.2.
2. **FOR THE MAJORITY OF CENTERS** that are scanning **one phantom on just one magnet** serially for one year please register the phantom as follows:

   Enter **Temperature after** the <Phantom ID> and **before** the <Date> (DDMMYYYY) separated by underscores.

   E.g. if the bottle is 15E001 and its temperature is 22°C at the start of the scan conducted on 31st January 2015, then log scan as:

   15E001_22_31012015

3. **FOR THE MINORITY OF CENTERS** that are scanning **one phantom on more than one magnet** serially for 1 year please register the phantom as follows:

   After the <Phantom ID> enter the '3-letter' <**Magnet Denomination**> that we will provide for each of the magnets you intend to use. Enter **temperature after** the <Magnet Denomination> and **before** the <Date> (DDMMYYYY) separated by underscores.

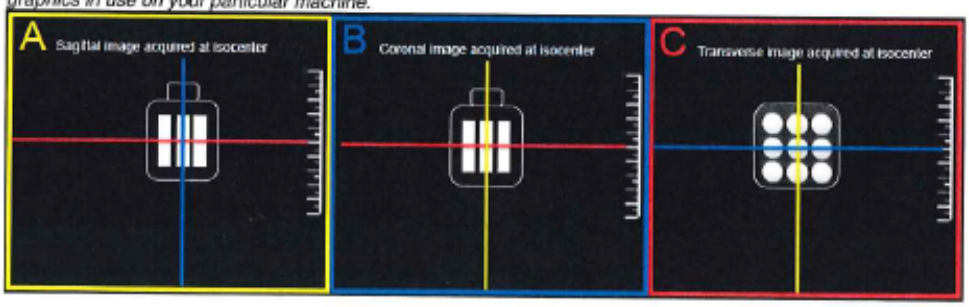
E.g. if the bottle is 15E001 and its temperature is 22°C at the start of the scan conducted on 31st January 2015 on the 1.5T Philips Achieva XR, then log scan as:
15E001axr_22_31012015

AND

E.g. if the same bottle 15E001 is of temperature 23°C at the start of the scan conducted on 3rd February 2015 on the 1.5T GE Signa HDx, then log scan as:
15E001sdx_23_03022015

4. Set up the simulated electrocardiographic (ECG) signal. Please see the note in the <Introduction> explaining the 900ms advised and when, if necessary, other R-R intervals could be used. For Siemens see A8.1.3; for Philips see A8.2.3; for GE see A8.3.3.
5. Before starting the scans make sure **all relevant coils are switched on.**
6. Start with scout or localizer imaging. For simplicity it is best if these localisers are all **acquired at isocenter with no image-plane or field of view (FOV) offsets away from isocenter**. Note that: **preset localiser protocols often contain such FOV-shifts or offsets** as typically suiting average patient morphology in the registered patient orientation. It may therefore be easier if you **TURN OFF/UNCHECK** any such FOV-shifts/offsets before running the scout.
7. Check that the physical positioning of the T1MES phantom is correct (along all three directions) as follows and that the phantom is not tilted or twisted (for system specific instructions on this see Appendix).
8. Isocentering the T1MES phantom along the head-foot (HF) direction (red lines in **Panels A** and **B** in **Figure 5**) should simply be governed by the laser marker. Similarly, isocentering the bottle along the supine patient right-left (RL) direction (yellow lines in **Panels B** and **C** in **Figure 5**) should again simply be governed by the laser marker.
9. Using the firm support, the T1MES phantom should be at the correct **height** such that the isocenter is halfway up the central tube, and at the level of the blue line in **Panels A** and **C**, **Figure 5**.
10. In **Panel C** (**Figure 5**) along the yellow line (i.e. height [*y*]), if the isocenter is further than **3cm** from the center of the middle tube, then **positioning is not acceptable**. Please pull out the table, ***change the height of the firm support*** and try again. Once you obtain the correct support for your scanner/phantom arrangement remember this and if possible **store the materials used with the phantom**, so that repeated scanning is less painful!
11. In the other two directions (along the patient bed [*z*] and across the patient bed [*x*]) the center of the middle tube should be **≤1cm** from isocenter. This should be easy to achieve using the laser guidelines and isocenter cross.
12. Please check that the phantom is not tilted or rotated in any axis beyond 10 degrees.

Figure 5. Achieving perfect isocenter position of T1MES phantom.
Note that this does not depict any particular scanning software and is for guidance in interpreting the isocenter graphics in use on your particular machine.



5 | SHIM SETTINGS AND SHIM VOLUME[1]

△ BE CAREFUL TO SET THE SHIM VOLUME AS SPECIFIED IN THIS MANUAL

1. Before running any T1 mapping sequence you must select the correct shimming method and specify a particular shim volume over the T1MES phantom. Please follow the manufacturer-specific instructions for these steps (see the Appendix).
2. Apply the same shim volume before starting each set of experiments in a reproducible manner.
3. The shim volume should be positioned at isocenter.
4. **Remember to wait at least 10 seconds with no scanner activity whatsoever before running the first T1 map on your phantom bottle.**
5. Now run your T1 mapping sequence positioned transversely and positioned with FOV centered exactly at isocenter in all three directions.
6. **Remember to wait at least 10 seconds with no scanner activity whatsoever before running any further T1 map on your phantom bottle.**
7. If multiple T1 sequences are run, please try to apply them in the same order each time. This is simply to help us with data processing not for physics reasons. A typical site would run just 1 or 2 versions each time the bottle is scanned (e.g. a MOLLI and a ShMOLLI). Running several repetitions of a T1 sequence each time would also be welcome for some indication of any short-term scatter (or serious drift issues!). Please tell us if you change these sequences during the repeated supply of T1MES data by completing a REDCap module.
8. If you have access to both the <pre-GAD> and <post-GAD> versions of a particular T1 mapping sequence, we would be grateful if you could run both on the phantom each time, with suitable definite scanner inactivity before each (10 seconds if in doubt!). Running both <pre> and <post-GAD> T1 mapping sequences is **not** obligatory - we leave it up to each center to provide what they can repeatedly over the 1-year period.
9. Do not modify the FOV or any other parameters of your chosen protocolled T1 mapping during the period of supplying T1MES repeat scans – stick to a fixed protocol (as specified in the JCMR Guidelines for T1/ECV). If you deviate from a protocol for any given reason or are forced to change sequence please you will need to complete a REDCap module for that scan date.

[1] *N.B. 'Shim Volume' = shorthand for adjustments volume, adjust region, shim region, shim box. See manufacturer-specific Appendix for more details.*

6 | ONLINE DATA TRANSFER

6.1 | REDCap Module

1. Near shipping time you will have received a further REDCap survey from us, collecting more detailed site-specific information.
2. You will then receive an email with account details to be able to access the REDCap online **T1MES_Project** database. You may wish to write down login details here:

   USERNAME _____

   PASSWORD_____

3. To access REDCap enter this URL in your browser:

   https://redcaphh.c-cloudservices.net/

4. Click on <My Projects> to find the T1MES_Project.
5. Having opened the Project by clicking on the project title, hit <Record Status Dashboard> on the LEFT panel to locate your 1.5T/3T phantom by ID number from the list of buttons.
6. If your center has received **more than one** phantom, please search for both IDs.
7. If your center plans to serially scan a particular phantom **on more than one magnet** for the 1-year period (e.g. you plan to scan your phantom '15E001' on both a 1.5T Philips **and** 1.5T GE) then please search for Phantom ID plus the Magnet Denomination (e.g. 15E001axr and 15E001sdx).
8. At first login, you will be asked to fill in more magnet-specific data. This first module is called <Enrolment> and it is launched by hitting the first 'Button' on the dashboard, nearest to your Phantom ID.
9. Some fields inside the <Enrolment> module **will be pre-filled** based on information you had previously submitted to us. Please check that all this information is still correct.
10. If your center has received more than one phantom or if you are scanning your phantom on more than one magnet, then please verify and complete the separate <Enrolment> pages that we have prepared for you.
11. If scanner hardware/software items change over the course of the year, or you undergo an upgrade or a service you will have a chance to refresh this information by entering it into the corresponding repeating forms for each of the serial scans.
12. Once you have completed a module select <COMPLETE> at the bottom of the form and then <SAVE>.
    a. <COMPLETE> turns button for that module GREEN.
    b. <INCOMPLETE> turns button for that module RED.
    c. <UNVERIFIED> turns button for that module YELLOW (e.g. If you need to check on a sequence detail/scanner date and enter that information later etc).
    d. An empty module, containing no data will appear GREY.
13. To the right of the <Enrolment> button, are many other GREY buttons called <SCAN_1> all the way to <SCAN_30>. As we hope that you will be scanning the T1MES phantom every fortnight for about a year, 30 repeating modules have been empirically created for your device.
14. Please note REDCap is NOT where you upload the scan DICOMs (see 6.2).
15. We shall however be uploading your phantom analysis results onto REDCap ourselves, inside each of your modules for your device sequentially.

16. After filling in the one-off <Enrolment> module at the start, you **WILL NOT** need to access REDCap for any data input after each repeat scan **UNLESS** it is to:
    a. report a software/hardware change/update
    b. report that you are having to make a change to the baseline T1 mapping sequence/s that you had previously been using (please avoid this as much as possible)
    c. report an issue with the phantom or any other aspect of our infrastructure
    d. download copies of your phantom's results or review pooled data
17. As you will already have entered <Temperature> and <Scan_Date> information per scan directly into the Phantom Registration ID, there is **NO NEED** to repeat this data entry procedure inside REDCap as well.
18. Therefore, provided none of the criteria in **16a-d** apply, **YOUR ONLY TASK** after phantom scanning will be to submit DICOMs through the SFTP portal, as outlined next in 6.2.

6.2 | DICOM PORTAL

1. You will have received an email and a separate instruction manual for how to download and install Filezilla SFTP to be able to access the **T1MES_DICOM_PORTAL**.
2. Once you click on the folder 'T1MES_DICOM_PORTAL' you will find a collection of >80 subfolders inside named according to Phantom ID and in some cases with an additional Magnet Denomination. Locate the subfolder/s for your phantom/s ID +/- magnet.
3. Each phantom subfolder then contains 30 further subfolders labeled SCAN_1 to SCAN_30 (matching the REDCap modules).
4. At the end of each fortnightly scan export all the DICOMS pertaining to the T1MES scan that has just been performed. Please make sure that you **do** export ***ALL*** the DICOMS (i.e. T1 maps but also any scouts, MOCO if on, T1 T1* residual etc).
5. **There is NO NEED to anonymise this data.**
6. Transfer the DICOMS into the correct Phantom ID and sequential SCAN subfolder (SCAN_1 > SCAN_2 > SCAN_3 etc.) so that we may start your analysis in a timely fashion.
7. Once we have processed the data pertinent to your latest submission (e.g. SCAN_1), we will be responsible for changing that subfolder's name in your DICOM_PORTAL to: "**x**SCAN_1".
8. Thus, you will easily know next time, to transfer DICOMS straight into SCAN_2 subfolder located at the top of your list.

7 | RESULTS

1. We will be providing prompt analyses of site data and displaying these graphically as well as providing stability data and potentially in future looking at conversion equations to generate standard T1 values.
2. We want to provide anonymised multisite data to show broad stabilities. These interfaces will be built once we have multisite data to look at.

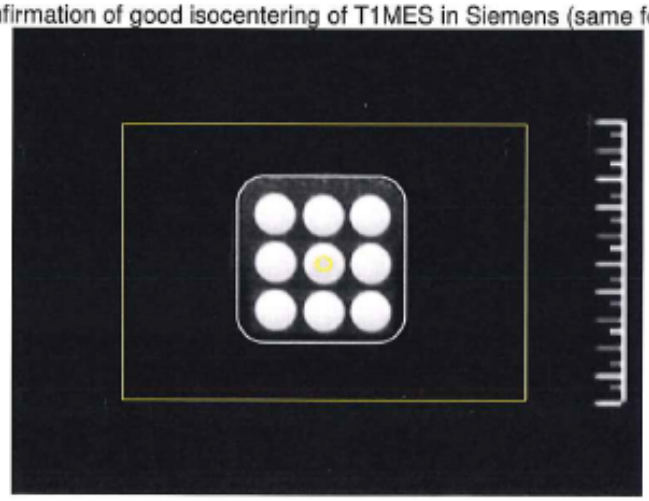
8 | APPENDIX

A8.1 | SIEMENS-specific instructions

A8.1.1 | Table positioning of phantom for SIEMENS

1. For Siemens the bottle should be positioned between **S1 and S2 marker levels** (or if using the 32-channel posterior array consistently center on that array). This is not essential but we ask as this is easily replicated on each session in case of any unforeseen sources of variability (e.g. there is some metal in the patient table which is known to affect some sequences).
2. Our tests on a 3T Siemens Skyra with a detachable couch have suggested that a firm support of height 7.5cm provides the right height to achieve T1MES isocenter positioning along the *y* axis.
3. The height for your particular Siemens machine, table and couch settings ***may vary*** so please test firm support height to find your ideal setup (then remember it and if possible store it with phantom!).
4. If your firm support height is correct and isocentering by laser target markers was done carefully, you should expect to see transverse (axial) images similar to those in **Figure A1** when you open your T1 mapping sequence after running the scouts.
5. Aim for the middle of the T1MES phantom to be within +/-1cm of isocenter across the bed and within +/-3cm for height (but consistent to within +/-1cm each repeated session).

Figure A1. Confirmation of good isocentering of T1MES in Siemens (same for Philips).



A8.1.2 | Register the phantom for SIEMENS

1. <Surname> enter your unique Phantom ID_Temp_Date of scan (with date as DDMMYYYY). (15E032)
   e.g. **15E001_22_31012015** if temperature 22 degrees or
   e.g. **30E004_23_31012015** if temperature 23 degrees
   (**ONLY** for centers scanning **one phantom on more than one magnet**: remember to add the 3-letter <Magnet Denomination> after <Phantom ID> and before <Temperature>. Eg. for Siemens 3T Prisma Fit register as: **30E004pft_23_31012015**).
2. <Name> Copy paste same content as <Surname> (1) above.

3. <ID> Copy paste same content as <Surname> (1) above.
4. <DOB> 1/1/1980.
5. <Sex> Male.
6. <Height> 1.8 (m) or 180 (cm).
7. <Weight> 80 (kg).
8. <Patient position> select <Head first – supine>.
9. <Region being scanned> select <Heart> as this can affect specific absorption rate (SAR) modeling.
10. **Enable** <First-level SAR> and <First-level PNS "SP"> (predicted peripheral nerve stimulation) either during registration or if the scanner asks about these during phantom scanning. This is essential in case the T1 mapping sequence parameters are modified to lower these by "helpful" scanner software.

A8.1.3 | Setting up simulated ECG for SIEMENS

1. You will need the Advanced User mode (password is typically <meduser1> for Siemens).
2. Start with <Ctrl-Esc> to launch the <Windows Start> menu.
3. Chose <Run> option.
4. Type: ideacmdtool
5. <Enter>
6. Type: 1
7. <Enter> to Start PMU (physiologic monitoring unit) control.
8. Type: 1 (or '4 on >VD-level software)
9. <Enter> to start ECG simulation.
10. For <ECG period in ms [1000]:>
11. Type: **900**
12. For <RESP period in ms [3000]:>
13. <Enter>
14. For <PULSE period in ms [1000]:>
15. Type: **900**
16. For <EXT period in ms [2000]:>
17. <Enter>
18. Check that the ECG waveform parameters generated are HR=**67**bpm and RR period =900ms.
19. You may now close the black "ideacmdtool" window (you do not need to remember to turn off the simulated ECG settings by using <ideacmdtool> again after the end of your phantom scans to allow the resumption of normal clinical scans, as a new <Patient Registration> will automatically clear it).

△ FOR SIMULATED ECG PLEASE ALLOW TIME FOR SOFTWARE-"AVERAGED" HEART RATE (if your system uses it) **TO SETTLE, BEFORE STARTING T1MAPPING**

A8.1.4 | Shim settings for SIEMENS

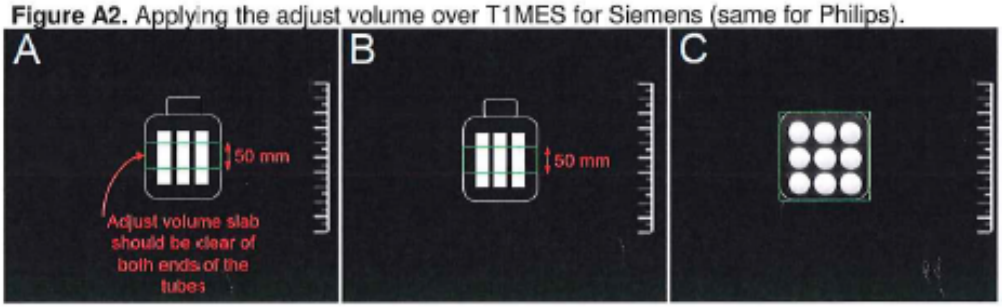
1. Navigate to <System>
2. <Adjustments>
3. Next to <B0 Shim mode> choose the option <Cardiac>
4. If you do not have the option <Cardiac> available on your Siemens system, then choose <Standard>
5. Make sure that the option <Adjust with body coil> is **ticked**.

A8.1.5 | Adjust volume for SIEMENS

1. Go to <System> and then to <Adjust Volume>.

2. Next to <! Pos tion> select from dropdown list <Isocenter>.
3. Please apply the shim volume tightly around the phantom bottle as shown in **Figure A2**. It should be set 5cm thick in the HF direction and it should follow (+/-2cm) the size of the T1MES bottle in the RL and antero-posterior (AP) directions. Adjust the size of the green volume as follows:
    a. Set AP to **120** (mm)
    b. Set RL to **120** (mm)
    c. Set HF **thickness** of the shim slab to **50** (mm).
4. Prescribe the size of the volume in the 3 orthogonal planes to ensure consistent adjustments of B_0 and scanner reference frequency over the phantom each time you scan it.
5. Acquire the T1 mapping sequence at isocenter with the T1MES phantom right in the middle of the adjust volume.

Figure A2. Applying the adjust volume over T1MES for Siemens (same for Philips).



A8.2 | PHILIPS-specific instructions

A8.2.1 | Table positioning of phantom for PHILIPS

1. The T1MES isocenter cross should be placed at the level of the MIDDLE side marker on the Philips table (there are side markers denoting the top, middle and bottom of the elements encased in the coil base).
2. Our tests on a 3T Philips Achieva have suggested that a firm support of height **8cm** provides the right height to achieve T1MES isocenter positioning along the *y* axis.
3. The height for your particular Philips machine, table and couch configuration ***may vary*** so please test firm support height to find your ideal setup (then remember it and if possible store it with phantom!).
4. If your firm support height is correct and isocentering by laser target markers was done carefully, you should expect to see images similar to those in **Figure A1** (in previous **section A8.1.1**) when you open your T1 mapping sequence after running the scouts.

A8.2.2 | Register the phantom for PHILIPS

1. Select <Patient> on the main menu bar.
2. Select <New exam>.
3. Patient name: enter your unique Phantom ID_Temp_Date of scan (with date as DDMMYYYY).
   e.g. **15E001_22_31012015** if temperature 22 degrees or
   e.g. **30E004_23_31012015** if temperature 23 degrees.
   (**ONLY** for centers scanning **one phantom on more than one magnet**: remember to add the 3-letter <Magnet Denomination> after <Phantom ID> and before <Temperature>. Eg. for Philips 1.5T Achieva XR register as: **15E001axr_22_31012015**).

4. Registration number (also called Registration ID): Copy + Paste same content as <Patient Name> (1) above.
5. Patient birth cate: 01/01/1980.
6. Patient's sex: Male.
7. Weight: 80 (kg).
8. Referring physician: Phantom.
9. Comments: leave blank.
10. <Enter>.
11. Click <Proceed> at the bottom of the panel.

A8.2.3 | Setting up simulated ECG for PHILIPS

1. Right click the main window and select <Control Parameter Editor>.
2. Select <General Tab>.
3. Select <Physiology Simulation>.
4. Select <Yes>.
5. Set the number of RR intervals = 1
6. Set RR interval (in ms) = **900**
7. Click <Apply>.
8. Remember to turn off the simulated ECG settings after the end of your phantom scans to allow the resumption of normal clinical scans.

Δ FOR SIMULATED ECG PLEASE ALLOW TIME FOR SOFTWARE-"AVERAGED" HEART RATE (if your system uses it) **TO SETTLE, BEFORE STARTING T1MAPPING**

A8.2.4 | Before running a T1 Map that involves SENSE in PHILIPS

1. Before setting up your mapping protocol it is your responsibility to check the control parameters of your Philips platform.
2. Ensure control parameters on Philips are set to DEFAULT VALUES.
3. Ensure no "patches" that could impact scanner behaviour unexpectedly are installed, except of course the patch to run your T1 mapping sequence if you need this.
4. Allow the scanner to perform the SENSE/CLEAR reference scans if using a T1 mapping sequence with parallel imaging (as the vast majority do).
5. If it asks about **PPNS** and **SAR** allow 1st Level.

A8.2.5 | Shim settings for PHILIPS

1. To set shim mode on Philips select <Contrast> tab.
2. Locate <Shim> in the column of parameters on the left.
3. Select option <volume>. **CAUTION** - please do not use other "shim" options and if in doubt please ask for advice.
4. Next adjust the green volume slab: Please apply the shim volume tightly around the phantom bottle as shown in **Figure A2** (in previous **section A8.1.5**). It should be set 50mm thick in the HF direction and it should follow (+/-2cm) the size of the T1MES bottle in the RL and AP directions.
5. Go to the tab <offc/ang>.
6. Under <Shim Size> adjust the size of the green volume as follows:
    a. Set AP to **120** (mm)
    b. Set RL to **120** (mm)
    c. Set HF **thickness** of the shim slab to **50** (mm).
7. Prescribe the size of the volume in the 3 orthogonal planes to ensure consistent shim and reference frequency estimation over the phantom each time you scan it.

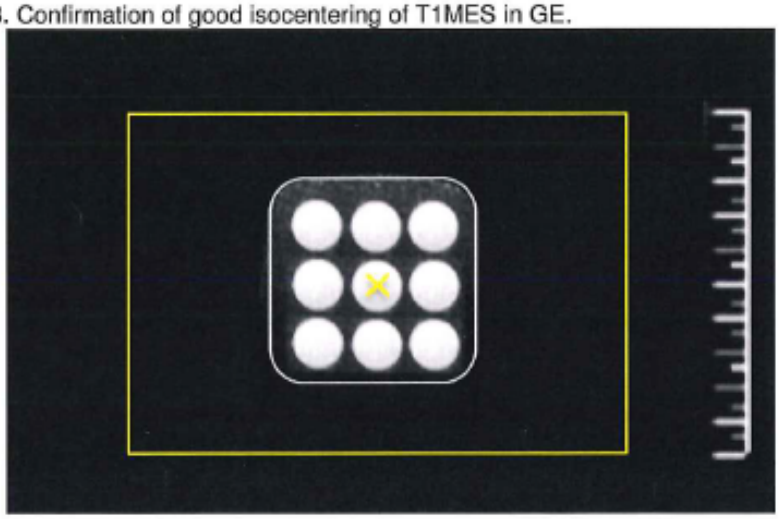
8. Acquire the T1 mapping sequence at isocenter with the T1MES phantom right in the middle of the adjust volume.

A8.3 | GE-specific instructions

A8.3.1 | Table positioning of phantom for GE

1. Our tests on a 3T GE 750 have suggested that a firm support of height **3cm** provides the right height to achieve T1MES isocenter positioning along the *y* axis.
2. The height for your particular GE machine, table and couch configuration ***may vary*** so please test firm support height to find your ideal setup (then remember it and if possible store it with phantom!).
3. If your firm support height is correct and isocentering by laser target markers was done carefully, you should expect to see images similar to those in **Figure A3** when you open your T1 mapping sequence after running the scouts.
4. Aim for the middle of the T1MES phantom to be within +/-1cm of isocenter. If it's perfectly correct you will see an <X> mark in the middle tube on the GE scanning software. A +/-3cm offset on the vertical (*y*) axis is acceptable but whatever height is achieved should be replicated each session to within +/-1cm. Both horizontal directions (across [*x*] and along [*z*] the patient bed) should be easily within +/-1cm using the laser guides and isocenter cross sticker.

Figure A3. Confirmation of good isocentering of T1MES in GE.



A8.3.2 | Register the phantom for GE

1. Select <Scan> desktop icon.
2. Click <New Pt> from the Patient Register window.
3. Patient ID: enter your unique Phantom ID_Temp_Date of scan (with date as DDMMYYYY).
   e.g. **15E001_22_31012015** if temperature 22 degrees or
   e.g. **30E004_23_31012015** if temperature 23 degrees.
   (**ONLY** for centers scanning **one phantom on more than one magnet**: remember to add the 3-letter <Magnet Denomination> after <Phantom ID> and before <Temperature>. Eg. for GE 1.5T Signa HDx register as: **15E001sdx_23_03022015**).
4. Patient name: Copy + Paste same content as 'Patient ID' (3).

5. Birth date: 01/01/1980.
6. Sex: Male.
7. Weight: 80 (kg).

A8.3.3 | Setting up simulated ECG for GE

1. **OUR PREFERENCE** is that you use (or purchase, if you do not already have one) **a basic 'ECG simulator' (also known as 'Chicken Heart')**. Work with CAUTION this ECG simulator may be dangerous in the magnet room.
2. Set heart rate on the device to **67bpm**.
3. Please position the ECG simulator a safe distance from the bore and follow the manufacturer's instructions.
4. The **less preferred** alternative is to use the command window to set the ECG Simulator on GE to 80bpm.
5. Go to <Tools> menu (this is the icon at the top left showing a spanner/hammer).
6. Click on the icon's arrow to reveal the drop down.
7. Select <Command Window>.
8. Type: rlogin scp
9. <Enter>
10. Login: scp
11. Password: scpservice
12. Type: SCP_LX->EmulatePac
13. <Enter>
14. This sets a simulated ECG with rate 100bpm (this heart rate is too fast for the T1 mapping planned for T1MES. Siemens and Philips users will be using a simulated ECG of 67bpm).
15. To slow down the heart rate (imperfectly) go to back to <Tools> menu and hit the actual button.
16. Select <Oper Gating Control Window>.
17. <Waveform display> (select all).
18. By setting <Trigger Lead> to <PG> heart rate will slow from 100bpm to 80bpm – it is still imperfect as the heart rate of 67bpm cannot be achieved; hence why we recommend the 'Chicken Heart'. Either way, please use the same heart rate for all sessions!
19. If you have set the simulated ECG using the command window in GE, please allow time for any software-"averaged" heart rate (if your system uses it) to settle, before starting T1 mapping work.
20. If you have set the simulated ECG using the command window in GE, remember to disable it when done scanning to permit resumption of routine clinical scans. To disable simulated ECG: hit <Tools> icon.
21. Select <Go to Service Desktop Manager> and hit <TPS Reset> to REMOVE the simulated ECG and reset the gating.

A8.3.4 | Before running a T1 Map that involves SENSE in GE

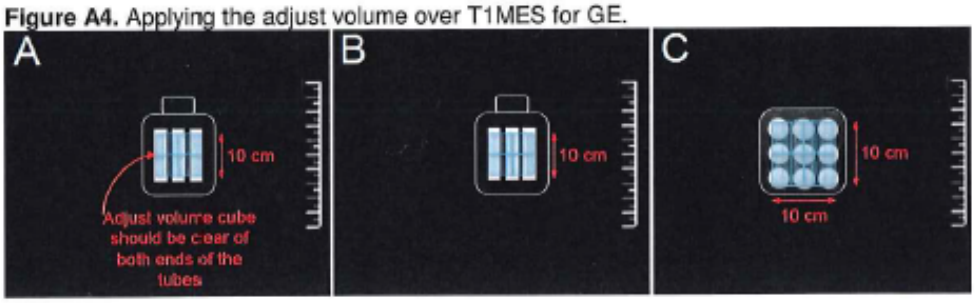
1. Select to run <**First Level Mode**> if prompted.

A8.3.5 | Shim for GE

1. Shim volume in GE is shaped by default as an obligatory cube.
2. To adjust its size go to <Graphic Rx Toolbar> (if you do not immediately see the Toolbar, hit the <GRx> tab).
3. Click <Shim>.

4. Uncheck the <Hide Shim> option to reveal the shim cube (it will look like a green/yellow hashed cube).
5. Next to <FOV> enter <10> to set the size of the cube to 10 X 10 X 10cm.
6. Move the cube so that it covers the middle lengths of the tubes and try to avoid the edges at either end as in **Figure A4**.

Figure A4. Applying the adjust volume over T1MES for GE.



Thank you