Dilated Cardiomyopathy: Remodelling, Risk Stratification and Personalising Therapy

Thesis submitted for the degree of *Doctor of Philosophy*

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Statement of Originality

I declare that this thesis represents my own work except where referenced or acknowledged otherwise.

Copyright Declaration

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Personal Contribution to Work

I was appointed as a Research Fellow in the Cardiovascular Research Centre at Royal Brompton Hospital in October 2015 under the supervision of Dr Sanjay Prasad and Professor John Cleland. Under their guidance, I designed and conducted the work in this thesis.

Along with Dr Prasad, I formulated the hypotheses and designed the studies in Chapters 2-5. I collected and assimilated the data for the registry of 881 patients with dilated cardiomyopathy described in Chapters 2-5. Of the patients in the final registry, data on 472 scanned between 2000 and 2008 had previously been gathered by Dr Ankur Gulati. I led the updating of this follow-up information and the gathering of all follow-up data for the remaining patients scanned between 2008 and 2011. I was assisted by 2 junior doctors and a medical student in this task. I personally assimilated all of the data and populated the database. I subsequently chaired an independent expert panel, who adjudicated all outcome events. I collated late gadolinium images from each patient and chaired sessions with a senior expert operator who adjudicated the presence, location and pattern of late enhancement on each scan. I planned and formulated all of the statistical analyses. I performed analyses of baseline characteristics and basic survival modelling in Chapters 2-5. These were confirmed by a medical statistician, Mr Simon Newsome, who also performed more complex analyses including the inverse probability weighting analysis described in Chapter 3. The figures presented in Chapters 3-5 were produced by Mr Simon Newsome. I drafted the three manuscripts relating to the work in Chapters 3-5 and have been listed as first author on each.

Together with Dr Prasad and Professor Cleland, I formulated the hypothesis and designed the TRED-HF study. Under their guidance, I wrote the grant application for the trial to the British Heart Foundation, completed the applications to the Ethics Committee and Medicines and

Healthcare Products Regulatory Agency and drafted the study protocol. I met with the Trust's Research Coordinator and Patient Advisory Group in order to harness patient opinion on the study protocol. I attended the Research Ethics Committee meeting to answer questions on the study prior to gaining formal approval. With the assistance of Dr Prasad, I set up collaborations with colleagues from nearby hospitals that acted as participant identification centres. I also met and liaised with staff from Cardiomyopathy UK and Pumping Marvellous in order to provide their members with information on the trial. With the assistance of a research nurse, I recruited and enrolled all of the patients into the study and performed randomisation. I carried out all patient screening, 16 week and 6 month trial visits. With only a few exceptions, I completed all interval patient visits and supervised all CMR scans and exercise tests. I was in charge of data input into the patient notes and the trial database and chaired all trial monitoring visits and the meetings with our Independent Trial Safety Advisor. I led the recording of adverse events and protocol deviations in the trial management file. I blinded all CMR scans that were subsequently analysed by independent operators in the Core Lab and led independent expert panels who adjudicated the aetiology of original diagnoses and the presence of late enhancement on CMR. I formulated, planned and performed all statistical analyses described and presented in Chapters 6-8, with guidance from Dr Prasad, Professor Cleland and Mr Simon Newsome (Medical Statistician).

Funding

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My primary supervisor, Dr Sanjay Prasad has shaped and championed my academic development over the last 3 years. He has provided me with perpetual support, encouragement and mentorship. He has focused, not only on achieving academic objectives but also equally importantly, on my personal development as a future independent academic clinician. His door is always open and his enthusiasm in discussing the latest results or future possible projects is enormously appreciated.

I wish to thank my co-supervisor, Professor John Cleland for his inspiration, wisdom and guidance. I have hugely appreciated the time he has dedicated to discussing the work in this thesis and beyond; this has been central to my development as a researcher. His passion for producing meaningful research is inspirational and his intellect and pragmatism have been fundamental to the success of this work.

I also wish to thank Professor Dudley Pennell for his support and advice. This work would not have been possible without the support of the Cardiovascular Research Centre and the Cardiovascular Magnetic Resonance Unit. I owe a huge amount of thanks to Mrs Rebecca Wassall, our research nurse specialist. Her patience, cheerfulness and knowledge have been instrumental to the running of the clinical trial. The trial would not have been possible without her help, coordinating and helping to carry out patient visits. I have learnt a huge amount from her about the regulatory aspects of clinical trials. I also wish to thank previous Fellows, particularly Dr Ankur Gulati and Dr Aamir Ali and the Cardiovascular Research Nurses who have previously worked tirelessly to recruit patients to the database.

As outlined above, Mr Simon Newsome and Dr John Gregson have provided important statistical input. I have learnt an enormous amount regarding statistical methods from discussions with them. Their expertise in refining statistical methods has been critical during peer review of manuscripts.

My research colleagues have provided support throughout. They have also helped with analysis of scans and adjudication of outcome events, in particular Dr Amrit Lota, Dr Zohya Khalique and Dr Vassilis Vassiliou. Dr John Baksi and Dr Francisco Alpendurada have also provided important guidance throughout and dedicated time and effort to the adjudication of events and scan results. I also wish to thank Mr Rick Wage, Dr Gillian Smith, Ms Tsveta Rahneva, Mr Robert Jackson and Dr Lucia Venneri who have given up a large amount of their time to perform scans and tests for the studies.

I wish to give particular thanks to the patients who took part in the studies, especially those who took part in the randomised trial. This would not have been possible without their dedication and desire to improve the treatment of future patients who find themselves in similar positions.

Finally, I thank my family for their love and unwavering support, especially my partner, Arad and my father and mother. My father, Henry has shown me it is possible to achieve major academic goals and combine this with clinical work and family life; he continues to provide me with the inspiration and motivation for my chosen path.

Abbreviations

ACEI – Angiotensin converting enzyme inhibitor

AF – Atrial fibrillation

ARB – Angiotensin II receptor blocker

ARVC – Arrhythmogenic right ventricular cardiomyopathy

ATP – Antitachycardia pacing

BSA – Body surface area

BNP – Brain natriuretic peptide

CAD – Coronary artery disease

CI – Confidence intervals

CMR – Cardiovascular magnetic resonance

CPET – Cardiopulmonary exercise testing

CRT – Cardiac resynchronisation therapy

DCM – Dilated cardiomyopathy

DENSE – Density encoding with stimulated echoes

ECG - Electrocardiogram

ECV – Extracellular volume

HASTE – Half-Fourier acquisition single short turbo spin echo (HASTE) imaging

HCM – Hypertrophic cardiomyopathy

HF-REF – Heart failure with reduced ejection fraction

HF – Heart failure

HR – Hazard ratio

ICD – Implantable cardioverter defibrillator

IHD – Ischaemic heart disease

IQR – Interquartile range

KCCQ – Kansas City Cardiomyopathy Questionnaire

LA – Left atrial

LAVi – Left atrial volume indexed to body surface area

LBBB – Left bundle branch block

LGE – Late gadolinium enhancement

LV – Left ventricular

LVEDVi - Left ventricular end diastolic volume indexed to body surface area

LVEDD – Left ventricular end diastolic dimension

LVEF – Left ventricular ejection fraction

MIBG – ^{123}Metaiodobenzylguanidine

MOLLI – Modified Look-Locker inversion recovery sequence

MR – Magnetic resonance

MRA – Mineralocorticoid receptor antagonist

MTWA – Microvolt T wave alternans

NSVT – Non-sustained ventricular tachycardia

NT-pro-BNP - N-terminal pro-peptide of BNP

NYHA – New York Heart Association

OMT – Optimal medical therapy

RAAS – Renin-angiotensin-aldosterone system

RVEF – Right ventricular ejection fraction

SAQ – Symptom Assessment Questionnaire

SCD – Sudden cardiac death

SD – Standard deviation

SSFP – Steady state free precession imaging

SV – Stroke volume

VF – Ventricular fibrillation

VT – ventricular tachycardia

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Abstract

Introduction: Dilated cardiomyopathy (DCM) is a common heterogeneous disease with variable outcomes. Unmet needs include the improvement of risk stratification, particularly in patients with mild and moderately reduced left ventricular ejection fraction (LVEF). It is also unclear whether DCM patients with improved LVEF simply have remission of disease or have permanently recovered. The benefit of continued therapy is unclear.

Methods & Results: We investigated the use of late gadolinium enhancement cardiovascular magnetic resonance (LGE-CMR) in the risk stratification of patients with DCM in a large registry. The presence of mid-wall LGE was associated with a nine-fold increase in the risk of SCD events in patients with mild and moderately reduced LVEF. In a study, including patients of all disease severities, the presence of septal LGE was most strongly associated with all-cause mortality whilst septal and left ventricular free-wall enhancement was associated with the greatest risk of SCD events. For both end-points, even small degrees of LGE were associated with large increases in risk. We also demonstrated that women with DCM have markers of less severe disease and reduced adjusted all-cause mortality compared to men with the disease. In addition, the safety and feasibility of heart failure therapy withdrawal in DCM patients with improved LVEF, normal left ventricular cavity size and low natriuretic peptide concentration was investigated in a randomised controlled trial. The preliminary results of the first 35 patients enrolled demonstrated that 41.2% of patients suffered a relapse within 6 months of starting therapy withdrawal compared to none of the patients in the control arm.

Conclusions: LGE-CMR can identify patients at risk of SCD. Women with DCM have better outcomes compared to men. At least a proportion of patients with improved LVEF continue to benefit from therapy. Routine withdrawal of therapy in this group is unwise.

Chapter 1

Background

1 Dilated Cardiomyopathy: Current Understanding and Therapeutic Challenges

Extracts from this chapter are based on my own work which has been published or accepted for publication.

Halliday BP, Cleland JGF, Goldberger JJ, Prasad SK. Personalising risk stratification for sudden cardiac death in dilated cardiomyopathy: The Past, Present and Future. Circulation 2017;136:215-231.

Halliday BP, Tayal U, Prasad SK. Role of Cardiovascular Magnetic Resonance in Dilated Cardiomyopathy. In: Manning WJ, Pennell DJ ed. Cardiovascular Magnetic Resonance, 3rd edition. Elsevier, 32-1-32-8. In press.

Elsevier and Wolters Kluwer confirm that they are happy for extracts to be reproduced for the purpose of this thesis (*Appendix*)

1.1 Definition and Epidemiology

Dilated cardiomyopathy (DCM) is a disease of the myocardium characterised by a reduction in left ventricular (LV) systolic function and LV dilatation, that cannot be explained by abnormal loading or ischaemic injury (Pinto *et al*, 2016a). The true prevalence is debated due to a lack of large contemporary epidemiological studies. The Olmsted County Study, a population-wide screening study performed in Minnesota, USA between 1975 and 1984, estimated the prevalence to be around 1 in 2,700 (Codd *et al*, 1989). In this study, DCM was twice as prevalent as hypertrophic cardiomyopathy (HCM). However, this study was performed when experience with echocardiography was still limited. The sensitivity of the technique for the diagnosis of DCM and HCM may therefore have been poor. This is supported by the observation that the predicted prevalence of HCM in the study has since been shown to be an under-estimate (Maron *et al*, 1995).

More recent studies have calculated the prevalence of DCM in the Western World to be greater (Hershberger *et al*, 2013). It has recently been estimated that 6 million people suffer from heart failure (HF) in the USA (Go *et al*, 2013), of whom around half have LV systolic dysfunction (Redfield *et al*, 2003). Extrapolating from clinical trial data, around 30-50% of patients with left ventricular systolic dysfunction have a non-ischaemic aetiology (McMurray *et al*, 2014; Zannad *et al*, 2011). Amongst patients with non-ischaemic cardiomyopathy in a recent large trial, 76% were labelled as having idiopathic disease (Kober *et al*, 2016). Based on these estimates, the prevalence of idiopathic DCM amongst the 300 million people in the USA is around 1 in 400. This is consistent with more recent population studies which have estimated the prevalence of HCM to be 1 in 500 individuals (Maron *et al*, 1995).

Nevertheless, DCM is a commonly encountered condition and contributes towards a large proportion of cardiovascular morbidity and mortality. It is the second most common cause of HF worldwide, the most common indication for cardiac transplantation and a frequent cause of sudden cardiac death (SCD) (Bagnall *et al*, 2016; Lund *et al*, 2017). It affects men more often than women, with a 2:1 male predominance and is diagnosed in patients of all ages, (McNamara *et al*, 2011). The median age of diagnosis from large registries is 45-55 years of age (Gulati *et al*, 2013c; McNamara *et al*, 2011; Merlo *et al*, 2011).

Despite advances in therapy, outcome varies amongst patients. While the disease runs a benign course in many, up to 1 in 5 patients die within 5 years (Gulati *et al*, 2013c; Kober *et al*, 2016). Around a half of cardiac deaths in DCM are secondary to pump failure and a half due to SCD (Bardy *et al*, 2005; Gulati *et al*, 2013c; Kober *et al*, 2016). The predominant cause of SCD is thought to be ventricular arrhythmia, although a proportion will be related to bradycardia and unrelated cerebral or aortic events. Current management focuses on contemporary HF therapy, including pharmacological therapy and cardiac resynchronisation therapy (CRT) and the selection of patients at high-risk of SCD for implantable cardioverter defibrillators (ICDs). Given the heterogeneity in outcome, improvements in therapy and the selection of patients for specific therapies remain major unmet needs.

1.2 The Genetic and Environmental Aetiology of DCM

DCM represents a common morphological phenotype which is manifest in a heterogeneous group of individuals due to a diverse combination of environmental insults and underlying genetic susceptibility (*Figure 1.1*). A large number of environmental insults and genetic

variants have been implicated in the aetiology of the disease *(Hershberger et al, 2013; Pinto et al, 2016a)*.

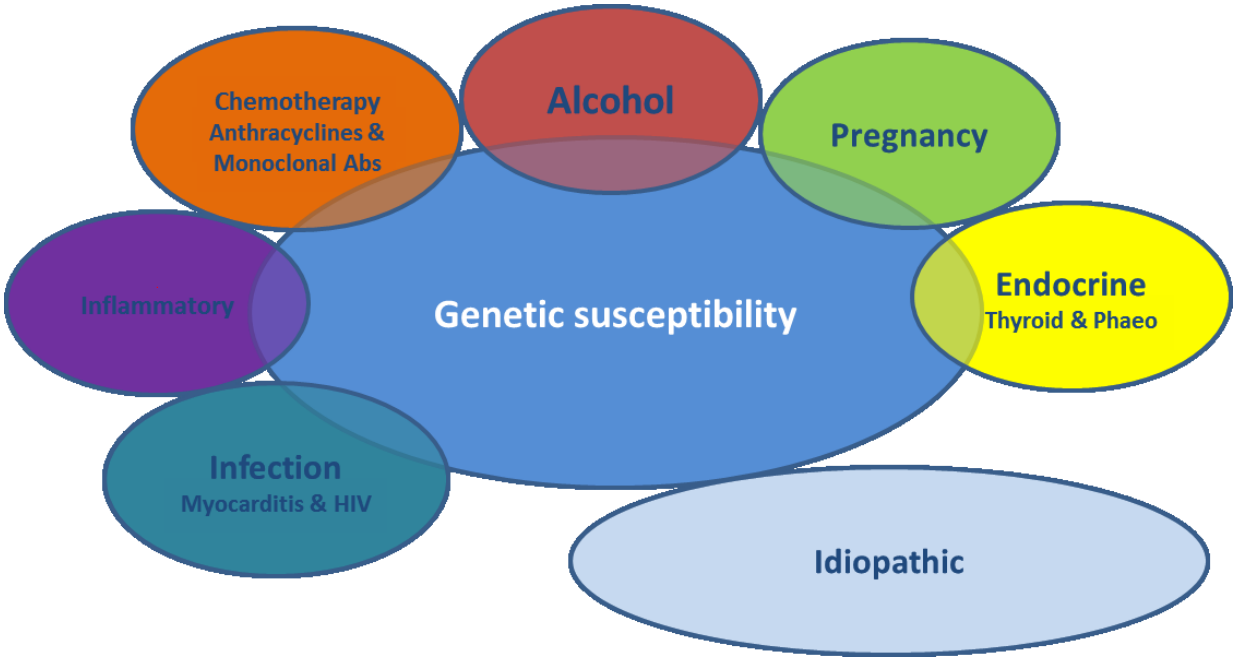

Figure 1.1. The acquired and genetic insults implicated in dilated cardiomyopathy. Reproduced with permission from (Halliday *et al*, 2017)**.**

Familial disease is defined as DCM in at least 2 closely related relatives and is thought to represent around 25-50% of cases *(Hershberger et al, 2013; Pinto et al, 2016a)*. As a result of advances in sequencing, a likely pathogenic genetic variant *(Table 1.1*) can be identified in up to 30-40% of familial cases and 15-20% of all cases (Hershberger *et al*, 2013; Hershberger *et al*, 2011; McNally *et al*, 2013). Most variants occur in autosomal genes and are unique to the family in which they are identified. Inheritance has traditionally been considered as Mendelian, implying that a single potent rare variant causes the disease with segregation in family members that are also carriers. However, reduced penetrance and variable expression are frequent and demonstrate the importance of environmental triggers and genetic modifiers (Hershberger *et al*, 2013).

Genetic Variants in Dilated Cardiomyopathy	
Sarcomeric	**Cytoskeleton**
TTN (25%, Titin)	*DMD* (N/A, Dystrophin)*
MYH6 (4%, α-myosin heavy chain)	*DES* (<1%, Desmin)
MYH 7 (4%, β-myosin heavy chain)	**Spliceosomal**
MYPN (3-4%, Myopalladin)	*RBM20* (2%, RNA-binding protein 20)
TNNT 2 (3%, Troponin T)	**Ion Channels**
TNNC1 (<1%, Troponin C)	*SCN5A* (2-3%, Sodium channel protein type 5 subunit)
TNNI3 (<1%, Troponin I)	**Mitochondrial**
FLNC (NA, Filamin C)	*TAZ* (NA, Tafazzin)*
Nuclear Envelope	**Sarcoplasmic reticulum**
LMNA (6%, Lamin A/C)	*PLN* (<1%, Phospholamban)

Table 1.1. Genetic variants implicated in the aetiology of dilated cardiomyopathy.
(Gene listed, followed by prevalence and the protein encoded; *denotes X-linked gene)

More rapid and cheaper genetic sequencing has led to an exponential increase in the literature on the genetics of DCM and has facilitated the introduction of the technique into clinical practice where it is primarily used for cascade family screening. A huge number of rare variants associated with the disease have been identified, most commonly affecting genes encoding sarcomeric proteins and also those related to the nuclear envelope, the cytoskeleton, potassium channels and Z-band proteins (McNally *et al*, 2013). In contrast to other cardiomyopathies, the affected genes encode proteins that carry out a wide range of cellular functions, exhibiting diverse ontology. The vast number and range of genes that are affected create a huge challenge in interpreting the pathogenic significance of variants. The sequencing of large numbers of the general population, as part of international projects, has helped with variant interpretation and highlighted cases where the interpretation of variants as disease-causing is likely to have been inaccurate (Bezzina *et al*, 2015; Lek *et al*, 2016).

Truncating variants of the large titin gene, *TTN*, are the most common pathogenic variants identified in patients with DCM. Titin is the largest protein in the human body, spanning the length of the sarcomere and acts to generate and regulate contractile force (Horowits *et al*, 1986; Liversage *et al*, 2001; Muhle-Goll *et al*, 2001). Large cohorts have identified truncating variants in *TTN* (*TTNtv*) in 25% cases of familial DCM, 18% of sporadic cases and <1% of healthy controls (Roberts *et al*, 2015a). Even within healthy controls, *TTNtv* are associated with sub-clinical eccentric remodelling with a significant increase in absolute LV volumes and a trend towards lower LV ejection fraction (LVEF) (Schafer *et al*, 2016). *TTN*, therefore, appears to have an important role in modulating responses to insults and loads and truncating mutations appear to result in a susceptibility to developing contractile impairment.

It has been established that there is a similar incidence and pattern of rare genetic variants in patients with peripartum cardiomyopathy, a disease traditionally viewed as being acquired, compared to those with idiopathic cardiomyopathy (Ware *et al*, 2016). This suggests that a common genetic susceptibility may exist across the diverse spectrum of DCM (*Figure 1.1*), that is simply uncovered to varying extents by different environmental insults and epigenetic modifiers. The findings support a 'two-hit' hypothesis whereby the disease is unmasked in susceptible individuals following a challenge, such as exposure to a toxic insult or a haemodynamic load. Therefore, whilst it may be convenient to label the condition as the result of a single acquired environmental or genetic insult, there may be considerable overlap between what have been traditionally viewed as separate acquired and inherited diseases.

1.3 Pathology

1.3.1 Morphology

DCM is characterised by adverse ventricular remodeling with LV dilatation and reduced LV systolic function. There is a change in LV geometry from an elliptical to spherical shape. Coexistent right ventricular (RV) systolic dysfunction and dilatation occur in around 35% of cases as a result of intrinsic myocardial dysfunction and increased afterload related to increased pulmonary vascular resistance (Gulati *et al*, 2013a; Pueschner *et al*, 2017). Increases in ventricular pressure as a result of contractile impairment lead to atrial dilatation. Annular dilatation and leaflet tethering secondary to ventricular remodelling may result in functional mitral regurgitation. Valvular structure is otherwise normal and epicardial coronary arteries are typically free of obstructive disease.

1.3.2 Pathophysiology of Heart Failure

As the disease progresses and contractile impairment advances, the characteristic HF syndrome develops. Rising ventricular filling pressures and, later in the disease, reduction in stroke volume and cardiac output, activate neurohormonal networks which trigger increased sympathetic activity, a rise in catecholamines, increased natriuretic peptide production and activation of the renin-angiotensin-aldosterone system. This results in fluid retention, tachycardia and increased cardiac preload and afterload. This increases LV wall stress and myocardial oxygen demand, driving a cycle of deteriorating cardiac performance (*Figure 1.2*). Adverse cardiac remodelling is characterised by increasing ventricular volumes, worsening systolic and diastolic function and wall thinning.

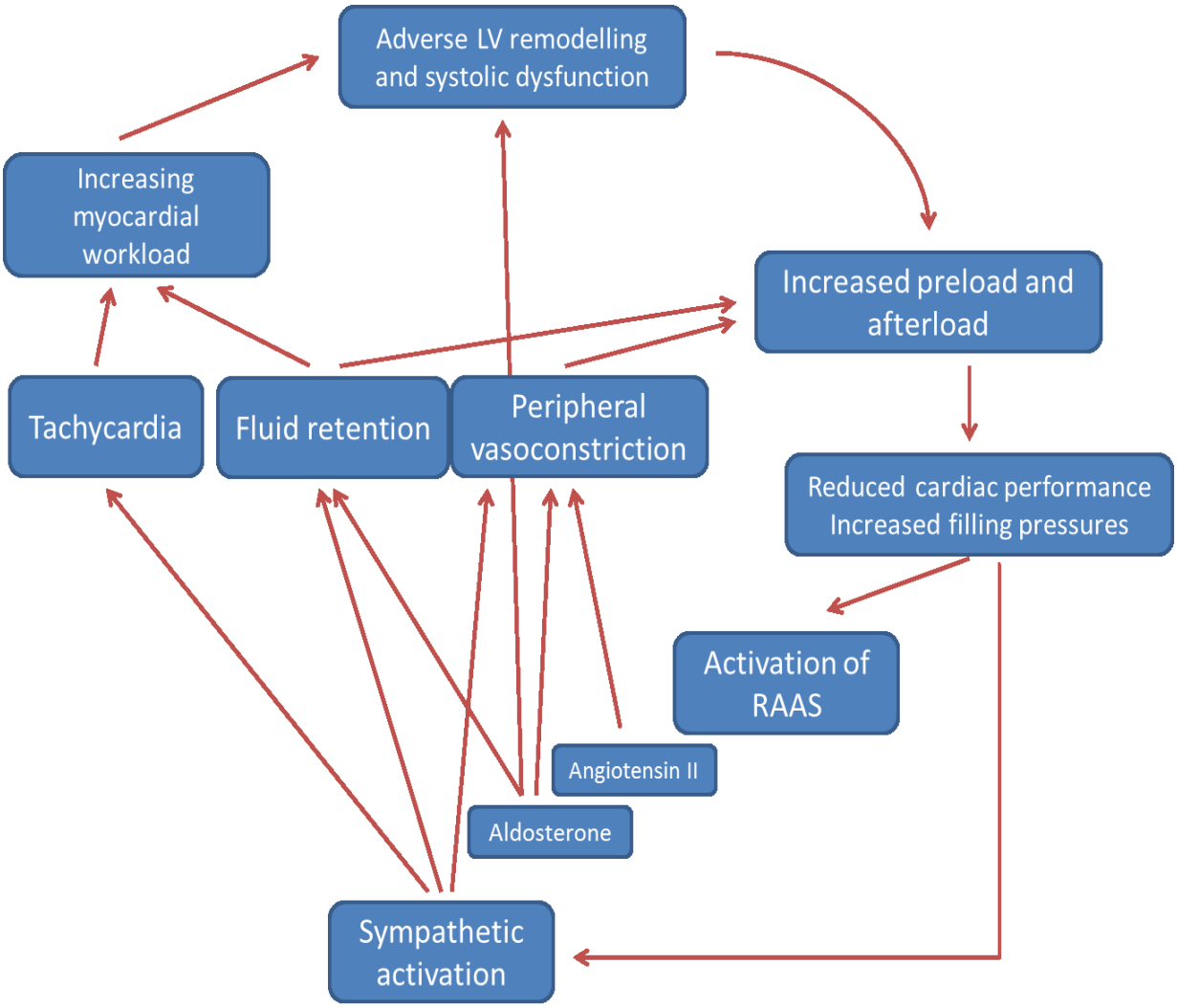

Figure 1.2. Pathophysiology of heart failure

Neurohormonal cascade that is activated as a result of deteriorating cardiac performance and results in the characteristic features of the heart failure syndrome.

1.3.3 Histological Changes

The histological features of DCM include myocyte hypertrophy, cell death and interstitial and replacement fibrosis (Beltrami *et al*, 1995). Interstitial fibrosis describes an increase in the collagen volume fraction with expansion of the extracellular matrix in the absence of cell death, while replacement fibrosis describes discrete areas of scar which result from collagen deposition following myocyte cell death (*Figure 1.3*). Fibrosis is promoted through activation of the renin-angiotensin-aldosterone and the beta-adrenergic axes (Mewton *et al*, 2011). Injurious stimuli and toxins also play an important role by activating inflammatory cascades leading to the production of reactive oxygen species (Mewton *et al*, 2011). These pathways result in activation of myofibroblasts, with upregulation of transforming growth factor β, altered activity in matrix metalloproteinases and, ultimately, the production of collagen (Beltrami *et al*, 1995; Mewton *et al*, 2011).

Myocardial fibrosis is associated with adverse ventricular remodelling in DCM, including worsening systolic and diastolic dysfunction. Fibrosis is thought to play an important role in the generation of ventricular tachycardia (VT) by causing conduction block, creating electrical heterogeneity and hence providing the substrate for re-entrant circuits (Bogun *et al*, 2009; Disertori *et al*, 2017; Steinberg *et al*, 2017). Interstitial or patchy areas of fibrosis may lead to conduction slowing and provide triggers for ectopy which may be important for the initiation of focal tachycardias (Disertori *et al*, 2017; Steinberg *et al*, 2017). Activation of the sympathetic and renin-angiotensin-aldosterone axes and autonomic dysfunction also create heterogeneity in conduction velocities, generating a pro-arrhythmic environment (Goldberger *et al*, 2015).

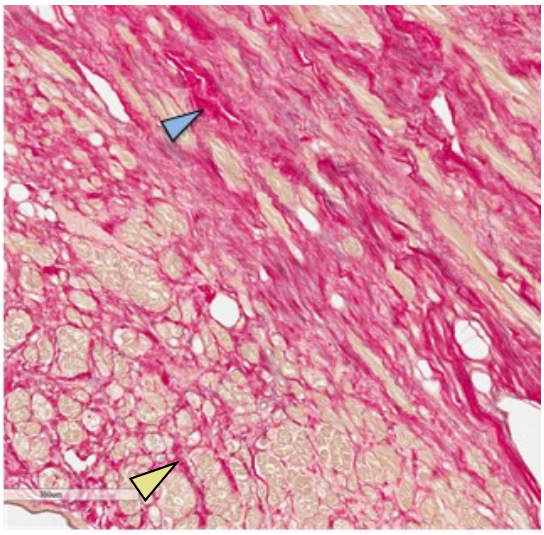

Figure 1.3. Replacement and interstitial fibrosis. Microscopic examination of tissue from the septum of an explanted heart with DCM. Blue arrow demonstrates replacement fibrosis while the yellow arrow demonstrates pericellular interstitial fibrosis. Reproduced with permission from (Halliday *et al*, 2017)

1.4 Diagnosis

The diagnosis of DCM involves the confirmation of both LV systolic dysfunction and dilatation and the exclusion of other causes, including ischaemic heart disease (IHD) and abnormal loading. It is recommended that systolic dysfunction, defined by an abnormal LVEF, should ideally be demonstrated using two different imaging modalities or the same technique on two separate occasions (Pinto *et al*, 2016a). Diagnosis therefore relies on detailed assessment of LV morphology and function. Echocardiography is the first-line imaging investigation in the work-up of most patients with DCM due to its relatively low cost and widespread availability. Echocardiography also enables the accurate assessment of functional valvular pathology and the evaluation of right ventricular size and function.

An ischaemic cause has traditionally been excluded using coronary angiography and defined by the presence of ≥75% stenosis in the left main stem, proximal left anterior descending artery, or 2 or more epicardial coronary arteries (Felker *et al*, 2000). However, given the prevalence of coronary disease with advancing years, ventricular dysfunction due to concomitant non-ischaemic and ischaemic pathology is well recognised. It has also been demonstrated that up

to 13% of patients labelled as having DCM following the finding of unobstructed coronary arteries on angiography, have in fact had prior myocardial infarction, presumably secondary to plaque rupture with recanalisation or an embolic event (McCrohon *et al*, 2003). Comprehensive tissue characterisation using cardiovascular magnetic resonance (CMR) enables the detection of sub-clinical infarction, demonstrating the value of this modality in confirming the diagnosis of DCM. This will be discussed further below.

A 12-lead electrocardiogram (ECG) is another important aspect of the diagnostic work-up in suspected DCM. Non-specific ST and T wave changes are often present and may be the first suggestion of possible underlying pathology in asymptomatic individuals. A narrow QRS complex is associated with increased chances of reverse remodelling with appropriate therapy (Sze *et al*, 2018) whilst prolonged QRS duration identifies patients who may benefit from cardiac resynchronization therapy (CRT).

Laboratory testing should include skeletal muscle isoforms of creatine kinase, which may be elevated in neuromuscular diseases; serum iron and ferritin, which will be markedly elevated in haemochromatosis; thyroid function tests, which will be abnormal in hypo- and hyperthyroidism and calcium and phosphate, which will be abnormal in diseases of calcium and phosphate metabolism. An autoimmune screen may be performed if there is co-existing rheumatological disease or an inflammatory aetiology is suspected. In individual cases, phaeochromocytoma and Cushing's disease may be ruled out by measuring urinary and serum cathecholamine and cortisol levels. Testing for human immunodeficiency virus may also be considered, however viral serology for other cardiotropic viruses is not routinely performed due to lack of correlation with myocardial infection and a high-rate of seropositivity in healthy individuals.

Genetic testing is recommended in cases of familial DCM or in those with clinical features which suggest a specific genetic diagnosis. For example, genetic testing for rare variants in *LMNA* may be considered in those with premature conduction disease or a high burden of ventricular arrhythmia. Family screening with imaging and a 12-lead ECG is recommended for first-degree relatives of the proband (Pinto *et al*, 2016a).

Endomyocardial biopsy may be performed in cases where an inflammatory, metabolic or infiltrative cause is suspected. In cases with ongoing myocardial inflammation, viral persistence may be confirmed using immunohistology and polymerase chain reaction, although the pathological significance of these findings is controversial. Given the invasive nature of the procedure and the risk of complications, biopsy is usually reserved for cases of progressive HF when an inflammatory cause is suspected. In such cases, a biopsy-confirmed diagnosis of lymphocytic or giant cell myocarditis may alter management by guiding the use of specific immunosuppressive therapy.

Given the complex heterogeneous nature of cardiomyopathy, a diagnostic classification, has been proposed to fully describe the multiple aetiological facets that have variable roles in individual patients (*Table 1.2*) *(*Arbustini *et al, 2014)*. An approach which, in addition, incorporates the factors that currently inform therapy decisions, such as LVEF and QRS duration may have added advantages. Including current therapy in a final category may also be worthwhile.

1.4.1 Natriuretic Peptides

Current guidelines recommend the use of brain natriuretic peptide (BNP) and N-terminal pro-peptide of BNP (NT-pro-BNP) to exclude a diagnosis of HF when suspected (Ponikowski *et*

al, 2016). BNP is released from the atrial and ventricular myocardium in response to increased wall stress. Following release it initiates protective mechanisms such as vasodilation and natriuresis. BNP is released from the myocardium following the cleavage of pre-propeptide BNP. Cleavage of pre-propeptide BNP also leads to the production of NT-pro-BNP. BNP is cleared by the membrane bound natriuretic peptide receptor C and degraded by an endopeptidase, neprilysin while NT-pro-BNP is predominantly excreted via the kidneys (Daniels *et al*, 2007).

Both biomarkers have excellent negative predictive value for the diagnosis of HF in patients presenting with breathlessness and are also powerful independent predictors of all-cause mortality and SCD (Maisel *et al*, 2008). BNP and NT-pro-BNP cut-offs of 100pg/ml and <300ng/l, respectively, have been reported to have a negative predictive value for the diagnosis of HF of between 0.94-0.98 amongst older people with HF of mixed aetiology (Roberts *et al*, 2015b). ESC Guidelines suggest a plasma concentration of NT-proBNP <125ng/L excludes a diagnosis of HF (Ponikowski *et al*, 2016; Zaphiriou *et al*, 2005). Natriuretic peptides are therefore frequently used to diagnose and monitor HF in patients with DCM and also provide important prognostic information.

However, whilst these thresholds may be useful for excluding HF as a cause of symptoms and signs, they may not indicate an absence of disease. Natriuretic peptides are markers of both cardiac and renal function and as such their plasma concentration rises with age as renal and cardiac performance decline and are also higher in women compared to men (Costello-Boerrigter *et al*, 2006; Galasko *et al*, 2005; McDonagh *et al*, 2004). An NT-proBNP of 100ng/L in an asymptomatic 40-year old man with normal renal function may therefore be abnormal and indicate underlying myocardial disease. The use of age- and sex-specific normal values is therefore important.

Categories	M Morpho-functional phenotype	O Organ system involvement	G Genetic inheritance pattern	E Etiology	S Stage
Features	Cardiomyopathy diagnosis	Extracardiac involvement	Genetic and clinical family screening to determine inheritance	Acquired, genetic or mixed aetiology	Functional status as determined by ACC/AHA and NYHA class
Notations	**D – Dilated** H -Hypertrophic A - ARVC R - Restrictive NC - LVNC	**H** – Heart *LV – left ventricle* *RV – right ventricle* *RLV – biventricular* **M** – Muscle **N** – Nervous **C** – Cutaneous **E** – Eye **A** – Auditory **K** – Kidney **G** – Gastrointestinal **Li** – Liver **Lu** – Lung **S** – Skeletal **O** – phenotype negative	**N** – no family history **U** – family history unknown **AD** – autosomal dominant **AR** – autosomal recessive **XLD** – X-linked dominant **XLR** – X-linked recessive **XL** – X-linked **M** – Matrinlineal **O** – Family history not investigated **Undet** – undetermined **S** – phenotypically sporadic	**G** – genetic cause **OC** – obligate carrier **ONC** – obligate non-carrier **Neg** – genetic test negative for family mutation **N** – no genetic defect identified **O** – no genetic test **M** – myocarditis **AI** – autoimmune **I** – infectious **T** – toxicity **Eo** - hypereosinophilic	ACC/AHA stage **A, B, C, D** NYHA class **I, II, III, IV**

Table 1.2. The MOGES classification of cardiomyopathy.

As described by Arbustini and colleagues (Arbustini *et al*, 2014).

1.5 Assessment using Cardiovascular Magnetic Resonance

Although echocardiography is the most commonly used first-line investigation in patients with suspected DCM, CMR is considered the gold-standard non-invasive technique due to its unique ability to accurately and reproducibly quantify ventricular volumes and function and perform detailed tissue characterisation in a single test without ionising radiation. Geographical variation in availability and relatively greater cost limits its use in some areas.

1.5.1 Basic Physics

CMR generates magnetic resonance (MR) signal by using radiofrequency energy to excite hydrogen nuclei within a static magnetic field (B_0). In the body, hydrogen nuclei are abundant within fat and water. In the scanner, the nuclei align with or against the magnetic field, rotating or precessing around B_0 (*Figure 1.4*). At rest, there is a small excess of hydrogen nuclei aligning with B_0, producing a small net magnetisation (M_0) in the longitudinal 'z' direction (*Figure 1.4)*.

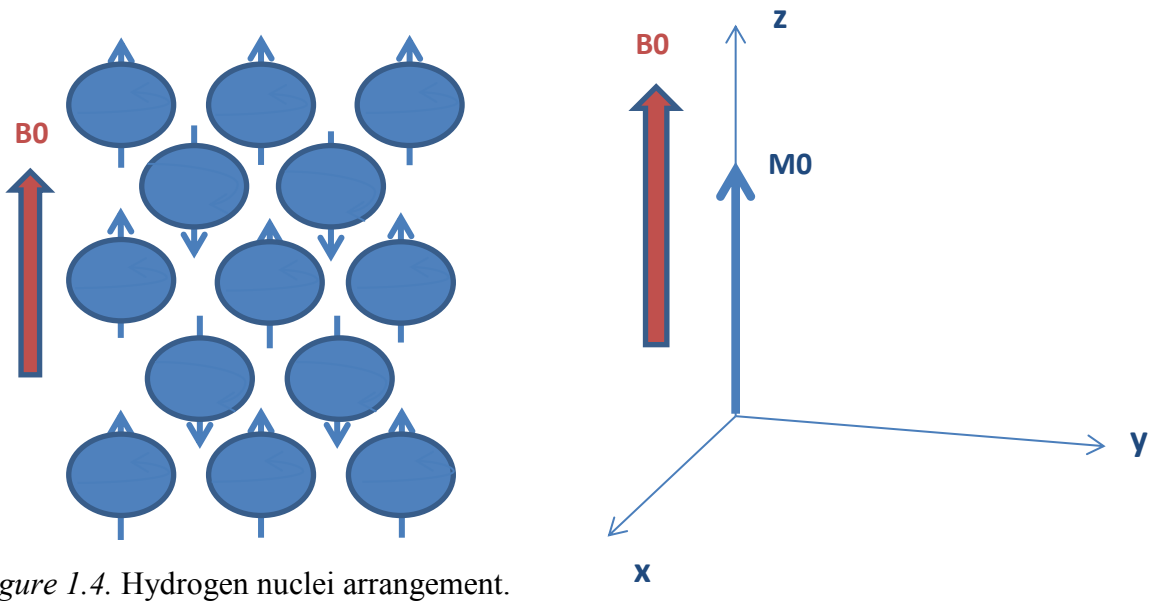

Figure 1.4. Hydrogen nuclei arrangement.
A. Hydrogen nuclei alignment in a magnetic field (B_0). *B.* At equilibrium, there is a small net magnetisation in the longitudinal z direction.

Radiofrequency energy is used to excite the nuclei, flipping the net magnetisation vector away from the z direction into the 'xy' plane. Following excitation, the hydrogen nuclei return to their original equilibrium, in a process known as relaxation. During relaxation the nuclei emit energy as radio signal that is picked up by receiver coils next to the patient. This signal is converted into an image by the Fourier transformation.

Tissue Characterisation

The process of relaxation that generates the MR signal is made of two components relating to the longitudinal (z) and transverse components (xy) of magnetisation. Longitudinal relaxation, also known as T1 relaxation, refers to the recovery of magnetisation in the z direction. Transverse relaxation is responsible for the decay of magnetisation in the transverse (xy) direction, causing a loss of observed signal. The decay of transverse magnetisation is influenced by T2 relaxation. The T1 and T2 relaxation times of hydrogen nuclei are influenced by the surrounding molecular environment. Hydrogen nuclei in water, for example, have long T1 and T2 relaxation times, while those in muscle and fat have short T1 and T2 values.

An imaging sequence is composed of a series of radiofrequency pulses which create signal. The extent to which the signal relies on T1 or T2 relaxation can be manipulated by the properties of the sequence used. Images may therefore be weighted to the T1 or T2 properties of the tissues examined. Given the different T1 and T2 values of hydrogen nuclei in different tissues, different image contrasts may be produced by specific sequences.

There are two key components to CMR in the assessment of DCM: 1) high spatial resolution cine imaging involving rapid serial assessment throughout the cardiac cycle to assess cardiac morphology and function and 2) images taken at a single time point to characterise the myocardium, before and after the administration of gadolinium.

1.5.2 Assessment of Morphology and Function

CMR allows accurate, reproducible assessment of LV volume, mass and ejection fraction without geometrical assumptions using high spatial resolution imaging and is therefore considered gold standard (*Figure 1.5)* (Buser *et al*, 1989; Maceira *et al*, 2006a). Regional function and myocardial strain can be assessed using tissue tagging, or density encoding with stimulated echoes (DENSE) (Buss *et al*, 2015; Chen *et al*, 2016; Shehata *et al*, 2009).

CMR also enables accurate, non-invasive assessment of RV size and function due to its unique ability to image in multiple planes without anatomical restriction (Globits *et al*, 1995; Maceira *et al*, 2006b). Accurate assessment can be challenging using other forms of imaging, such as echocardiography, due to its complex and variable shape. Reduced RV ejection fraction on CMR has been shown to be an independent predictor of all-cause mortality and adverse HF outcomes in DCM (Gulati *et al*, 2013a).

Left atrial (LA) volume can be calculated using the biplane area-length method (*Figure 1.5*) (Lang *et al*, 2005). This compares favourably against other modalities, where imaging planes are restricted by anatomical borders and remains robust in atrial fibrillation (AF) (Anderson *et al*, 2005; Pritchett *et al*, 2005; Therkelsen *et al*, 2005; Whitlock *et al*, 2010). LA size is increased in DCM due to pressure overload related to LV systolic and diastolic impairment, functional mitral regurgitation and AF. LA size is thought to act as an accurate barometer of LV filling pressures, sensitive to both changes in LV systolic and diastolic dysfunction (Pellicori *et al*, 2015; Pritchett *et al*, 2005). It has been demonstrated that a LA volume $<72ml/m^2$ predicts cardiac transplant-free survival in DCM (Gulati *et al*, 2013b).

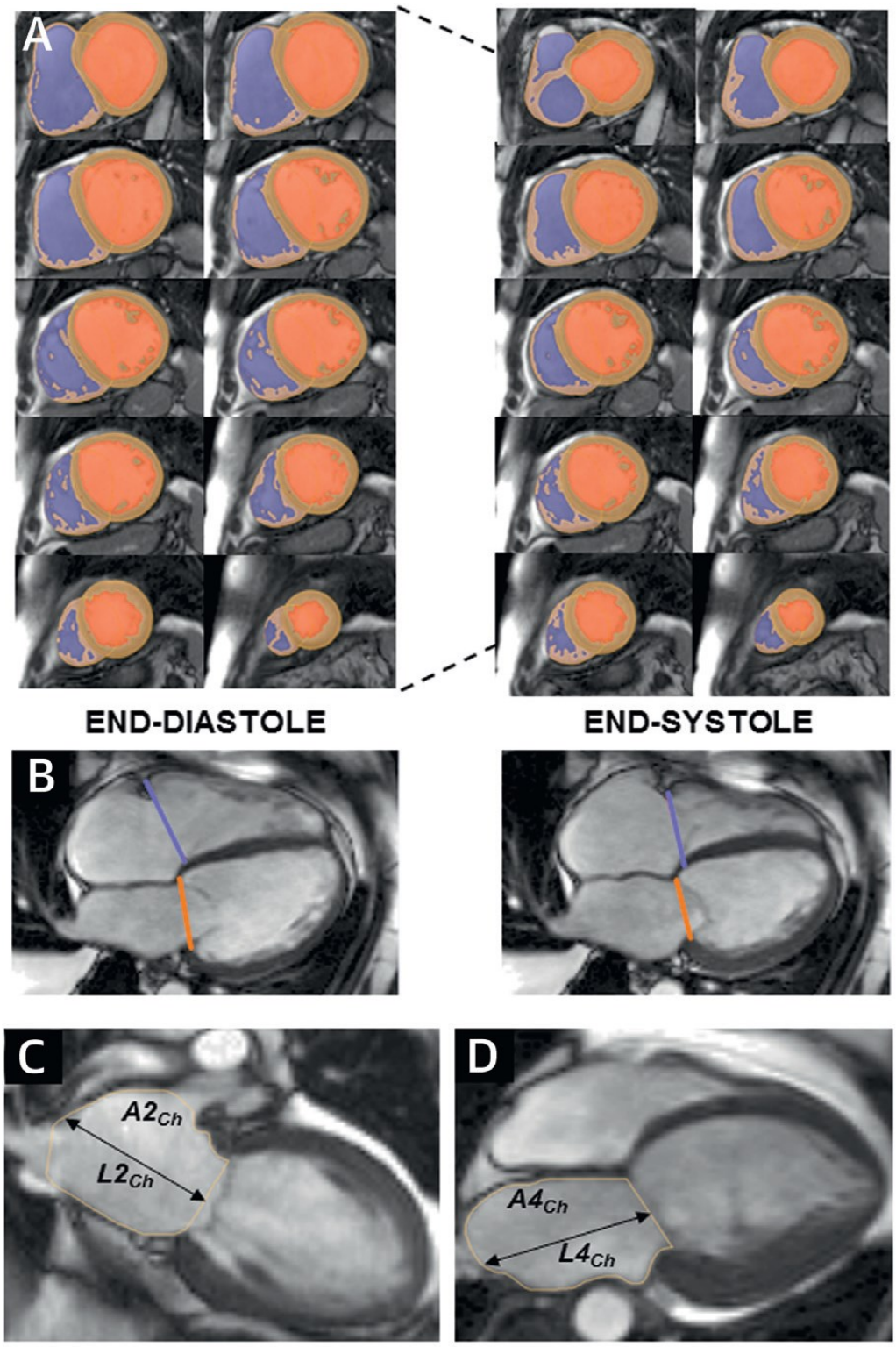

Figure 1.5. Volumetric assessments using cardiovascular magnetic resonance.

A&B: Measurement of left and right ventricular volumes and ejection fraction. C&D: Measurement of left atrial volume using the biplane area length method in end-systole. Reproduced with permission from (Japp *et al*, 2016).

Other common features of DCM accurately assessed by CMR include functional mitral regurgitation. An assessment of the individual leaflet scallops, chordae and papillary muscles can be performed using cine imaging and regurgitant volume can be calculated by subtracting the aortic forward flow volume from the total LV stroke volume (Chan *et al*, 2008). Assessment of functional mitral regurgitation has been shown to provide independent prognostic information in DCM (Stolfo *et al*, 2015).

Given the accuracy and reproducibility of volumetric and functional assessment, CMR is considered the gold standard for follow-up following pharmacologic and surgical intervention (Bocchi *et al*, 1994; Doherty *et al*, 1992). Considering this, the use of CMR in clinical trials may reduce the sample size required, reducing the overall cost and time of research (Bellenger *et al*, 2000).

1.5.3 Late Gadolinium Enhancement Imaging

Tissue characterisation forms another important facet of DCM assessment. Image contrast can be generated by manipulating T1 relaxation times using gadolinium contrast agents. Gadolinium is an extracellular contrast agent that dramatically shortens T1 recovery and therefore creates a strong signal on T1 weighted images. It is unable to cross intact cell membranes and therefore has a low concentration in areas of healthy myocardium at steady state. Gadolinium accumulates in areas of myocardium with an expanded extracellular space and adequate blood supply. The most frequent cause of extracellular expansion is the presence of myocardial fibrosis. Similarly, there will be a high concentration of gadolinium in areas of acute myocardial injury, associated with the disruption of the myocyte cell membrane (*Figure 1.6*).

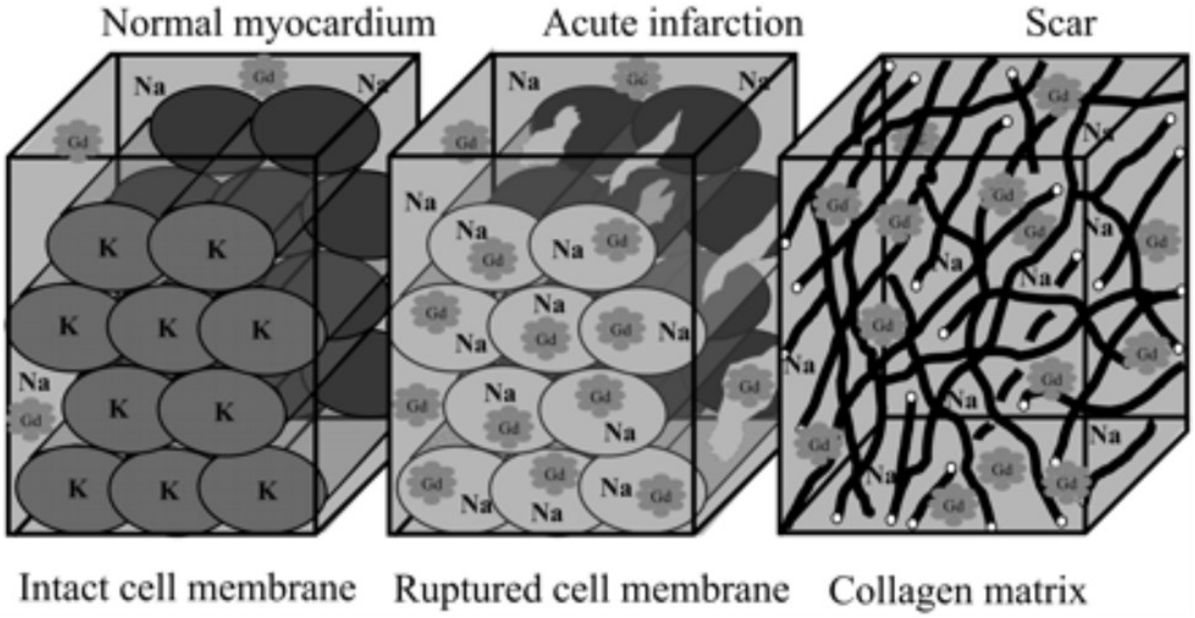

Figure 1.6. Late gadolinium enhancement.
High concentrations of gadolinium in areas acute or chronic myocardial injury. Reproduced with permission from (Mahrholdt *et al*, 2005).

Late gadolinium enhancement (LGE) imaging is performed 10-15 minutes after the administration of 0.1mmol/kg of contrast using an inversion recovery sequence. This is a T1 weighted sequence that uses a radiofrequency pulse to flip the net magnetization 180° from M0. T1 relaxation and recovery of M0 take place rapidly in tissues with extracellular expansion or disrupted cell membranes, where gadolinium has accumulated and more slowly in healthy myocardium. The aim is to perform LGE imaging when the longitudinal magnetisation of the healthy tissue is close to zero (*Figure 1.7; green line)*. The time interval between the radiofrequency pulse and the read-out is known as the inversion time (TI). At the optimal inversion time, healthy tissue will be 'nulled', producing no signal and appearing black. Given the more rapid recovery of longitudinal magnetisation in the presence of gadolinium, at the same point, there will be a strong signal from diseased tissues and these areas appear bright (*Figure 1.7; red line)*. These principles form the basis of LGE imaging and the detection of myocardial infarction and myocardial replacement fibrosis.

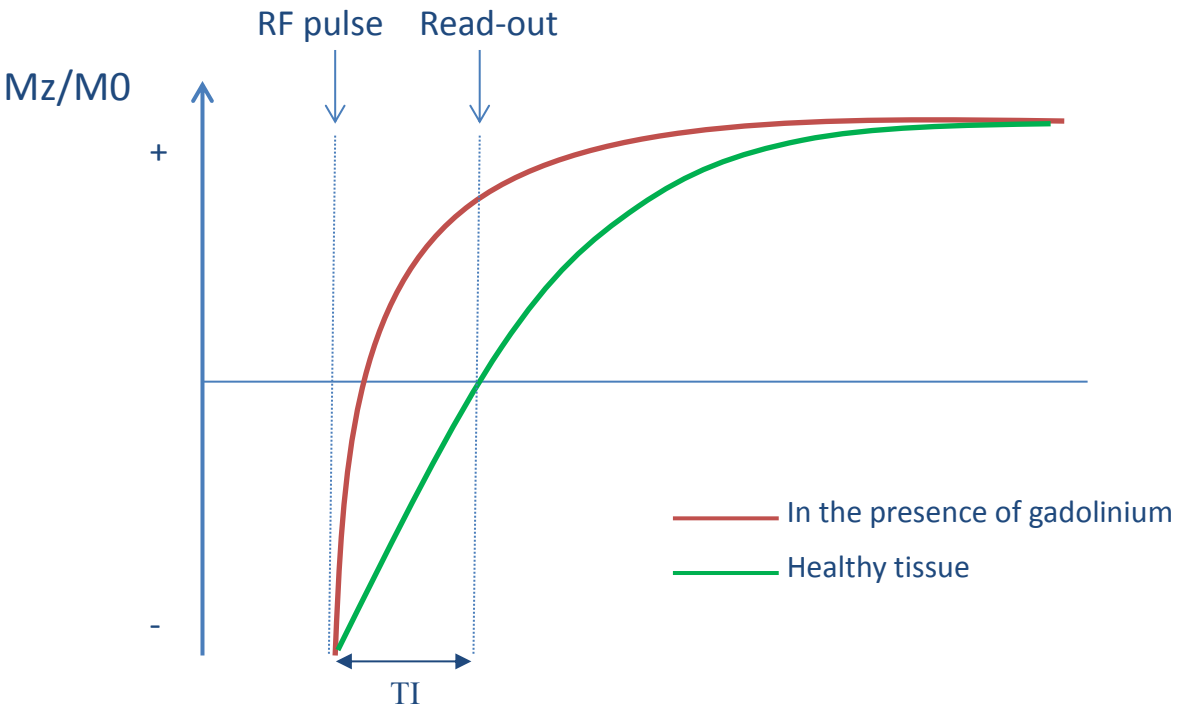

Figure 1.7. Pulse sequence used in late gadolinium imaging.

Late Gadolinium Enhancement in Dilated Cardiomyopathy

LGE-CMR detects the presence of non-ischaemic mid-wall enhancement in 30-40% of patients with DCM (*Figure 1.8*) (Disertori *et al*, 2016; Gulati *et al*, 2013c). Histological correlation has demonstrated that this represents areas of replacement myocardial fibrosis. Non-ischaemic LGE in DCM most frequently occurs within the LV septum in a mid-wall distribution (*Figure 1.8A*), although LV free-wall enhancement and those occurring in focal or sub-epicardial distributions (*Figure 1.8B*) are also recognised. It is possible that different aetiological insults result in non-ischaemic LGE in different locations and patterns. Importantly, non-ischaemic LGE spares the subendocardium allowing reliable differentiation from LGE seen following myocardial infarction.

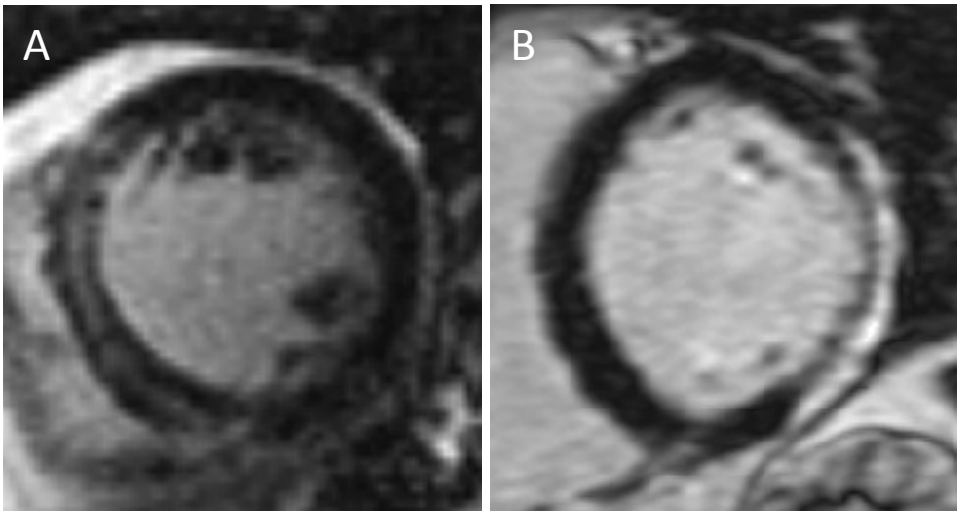

Figure 1.8. Late gadolinium enhancement in dilated cardiomyopathy.
A: Septal mid-wall late enhancement. B: sub-epicardial enhancement in the lateral wall.

The mass of LGE can be quantified using semi-automated software. The most commonly used techniques to quantify LGE are the full-width at half maximum and the >2 standard deviation approach (>2SD) (Neilan *et al*, 2013). The full-width at half maximum method quantifies regions of myocardium with a signal intensity >50% of the maximally enhanced region while the >2SD approach includes regions with a signal intensity >2SD above that of a reference area of normal myocardium. As we will discuss, mid-wall LGE is associated with a range of adverse outcomes. There is therefore interest in using LGE-CMR to identify patients with DCM at high-risk of adverse outcomes who may benefit from specific therapies.

Exclusion of an Ischaemic Aetiology using LGE-CMR

As discussed, LGE-CMR also plays an important role in the exclusion of an ischaemic cause in patients presenting with suspected DCM. In one study, 13% of patients with suspected DCM, had subendocardial enhancement on LGE-CMR, indicative of previous myocardial infarction

(McCrohon *et al*, 2003). It is recognized that a proportion of patients with unobstructed coronary arteries on angiography have had asymptomatic myocardial infarction due to recanalization of the vessel or an embolic mechanism. This study emphasised that a conventional diagnostic approach without LGE-CMR may misdiagnose a significant proportion of patients. Given the different clinical courses and management strategies, accurate diagnosis is crucial. A further study demonstrated that LGE-CMR had 97% accuracy for the determination of aetiology in new-onset HF compared to 95% based on coronary angiography (Assomull *et al*, 2011). These findings suggest an important role for CMR in determining the aetiology of disease in new-onset HF.

1.5.4 Parametric Mapping

Parametric mapping is a contemporary CMR technique that directly quantifies the T1 or T2 relaxation time of each voxel within an image. A visual map can be constructed where each voxel's signal intensity corresponds to the specific T1 or T2 time (*Figure 1.9)*. The myocardial extracellular volume (ECV) can be calculated from pre- and post-contrast T1 maps, by estimating the amount of contrast in the extracellular compartment relative to the blood pool at steady state (Flett *et al*, 2010). Native (pre-contrast) T1 times and ECV fraction have been shown to correlate well with the degree of interstitial fibrosis in a range of diseases including DCM (aus dem Siepen *et al*, 2015; Flett *et al*, 2010). This has led to the possibility of estimating the degree of interstitial fibrosis using a non-invasive technique. T1-mapping therefore has advantages over LGE which relies on a reference area of normal myocardium and has the potential to miss global myocardial disease and *interstitial* fibrosis.

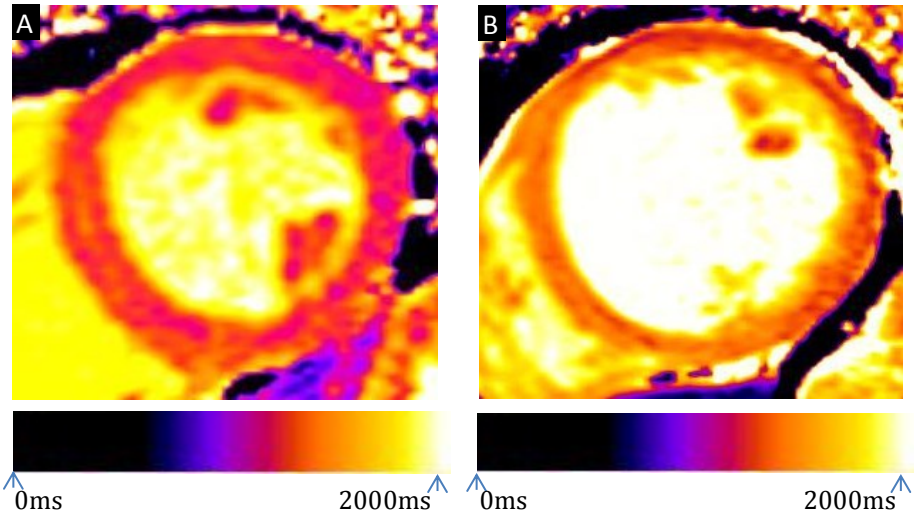

Figure 1.9. Parametric mapping.
Pre-contrast native T1 mapping performed at 3T (Siemens, Skyra) on a healthy control (A) and a patient with advanced dilated cardiomyopathy. Reproduced from (Halliday *et al*, 2017)

Nakamori and colleagues have recently demonstrated good correlation between native T1 times (r=0.77) and ECV (r=0.66) and collagen volume fraction on myocardial biopsy in 36 patients with advanced DCM (Nakamori *et al*, 2017). Aus dem Siepen et al demonstrated good correlation between ECV and the collagen volume fraction on biopsy in patients with varying severities of DCM (r=0.85) (aus dem Siepen *et al*, 2015). Another study demonstrated strong correlation between ECV on pre-transplant CMR and collagen volume fraction on 96 post-transplant tissue samples taken from 16 segments of 6 explanted hearts (r=0.75) (Miller *et al*, 2013). Additionally, the authors demonstrated higher ECV in segments free of LGE in patients pre-transplant compared to healthy controls (41.4 +/- 5.0% vs 25.5% +/- 2.6%; $p<0.001$) (Miller *et al*, 2013).

Although existing studies are small and susceptible to publication bias, current data introduce the possibility of using non-invasive markers of interstitial fibrosis to risk stratify patients. Considering interstitial fibrosis may be reversible, parametric mapping may be used to select patients who benefit from novel anti-fibrotic therapies.

1.6 Pharmacological Treatment – Current Guidelines

Current pharmacological treatment of DCM focuses on HF therapies which modulate the detrimental neurohormonal networks that are activated as a consequence of reduced cardiac performance in the setting of LV systolic dysfunction. Pharmacological therapy of HF has progressed significantly over the last 20 years with a marked improvement in outcomes and better quality of life for many patients with the disease (Shen *et al*, 2017). These therapies are not specific to the underlying cause of DCM and are used for both ischaemic and non-ischaemic causes of HF with reduced ejection fraction (HF-REF). HF-REF is defined as a LVEF <40%, regardless of aetiology (Ponikowski *et al*, 2016; Yancy *et al*, 2013). The following studies, which form the basis of guideline recommendations, include patients with both ischaemic and non-ischaemic HF, unless otherwise stated.

1.6.1 Angiotensin-converting Enzyme Inhibitors

Angiotensin-converting enzyme inhibitors (ACEI) and beta-blockers are recommended for patients with HF-REF to reduce mortality and HF hospitalisation rates (CIBIS-II Investigators and Committees, 1999; Consensus Trial Study Group, 1987; Packer *et al*, 1996; Packer *et al*, 2001; Ponikowski *et al*, 2016; Yusuf *et al*, 1991). The landmark Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), published in 1987, demonstrated that enalapril (2.5 to 40mg per day) reduced all-cause mortality by 40% compared to placebo in 253 patients with severe symptomatic (New York Heart Association [NYHA] class IV) HF-REF over an average follow-up of only 188 days ($p<0.003$) (Consensus Trial Study Group, 1987). The mortality rate in the placebo group over this short follow-up period was 44%, demonstrating the very poor prognosis of the disease without therapy. The Studies of Left Ventricular Dysfunction (SOLVD) trial later demonstrated a reduction in mortality with

enalapril (2.5 to 20mg per day) compared to placebo in HF-REF patients with NYHA class II-III symptoms (HR 0.84; 95% CI: 0.74-0.95; p=0.004) (Yusuf *et al*, 1991). ACEI and beta-blockers are also recommended for those with asymptomatic reductions in LVEF below 40% to prevent the onset of HF (Ponikowski *et al*, 2016). The SOLVD investigators confirmed that enalapril compared to placebo reduced a composite of death and HF hospitalization in patients with reduced LVEF who were labelled as asymptomatic (HR 0.80; 95%CI 0.7-0.91; p<0.001) (Yusuf *et al*, 1992). Subsequent 12-year follow-up of patients in both SOLVD studies suggested sustained improvement in survival beyond the end of the original studies (Jong *et al*, 2003).

1.6.2 Beta-Blockers

Following the introduction of ACEI, Packer and colleagues established that carvedilol was associated with a reduction in mortality over a median follow-up of 6.5 months in patients with HF-REF (HR 0.35; 95%CI 0.2-0.61; p<0.001) (Packer *et al*, 1996). The majority of patients had NYHA class II-III symptoms and 95% were prescribed an ACEI. This was followed by a series of confirmatory studies demonstrating mortality benefit with bisoprolol, controlled release metoprolol and carvedilol in patients with HF-REF and NYHA II-IV symptoms (CIBIS-II Investigators and Committees, 1999; MERIT-HF Study Group, 1999; Packer *et al*, 2002; Poole-Wilson *et al*, 2003). A recent individual patient data meta-analysis, including 11 trials investigating the use beta-blockers in HF, demonstrated that beta-blockers were associated with improvement in all-cause and cardiovascular (CV) mortality in patients who were in sinus rhythm with a LVEF <50% (Cleland *et al*, 2017a). Whilst beta-blockers were associated with an improvement in LVEF in patients with atrial fibrillation, there was no associated improvement in outcome (Cleland *et al*, 2017a).

1.6.3 Mineralocorticoid Receptor Antagonists

Current guidelines advocate the use of mineralocorticoid receptor antagonists (MRA) for patients with HF-REF who have ongoing symptoms despite treatment with ACEI and beta-blockers (Ponikowski *et al*, 2016). Spironolactone has been shown to reduce all-cause mortality in patients with HF-REF (HR 0.70; 95% CI 0.60:0.82; p<0.001). In this study, most patients were in NYHA class III or IV, 95% were taking an ACEI but only 11% were prescribed beta-blockers (Pitt *et al*, 1999). The Eplerenone in Mild Patients Hospitalization and Survival Study in HF (EMPHASIS) established that this medication reduced all-cause mortality (HR 0.76; 95% CI 0.62-0.93; p=0.008) in patients with mildly symptomatic HF-REF (NYHA II), who were prescribed an ACEI and beta-blocker (Zannad *et al*, 2011).

1.6.4 Loop Diuretics

Current guidelines suggest loop diuretics should only be used to improve signs and symptoms of fluid congestion and at the lowest possible dose to maintain euvolaemia (Ponikowski *et al*, 2016). The effect of diuretics on mortality and morbidity has not been studied in randomised controlled trials although withholding diuretics from a congested patient is likely to be fatal.

1.6.5 Additional Treatments

The combination of valsartan and sacubitril, a neprilysin inhibitor, has recently been recommended for patients with HF-REF who remain symptomatic despite treatment with ACEI, beta-blocker and MRA (Ponikowski *et al*, 2016). The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF) demonstrated that this combination was superior to enalapril in reducing

mortality and HF hospitalisation in patients with symptomatic HF-REF and elevated natriuretic peptides (HR 0.84; 95% CI 0.76-0.93; P<0.001) (McMurray *et al*, 2014). Some concern exists, however, around the risk of symptomatic hypotension in unstable patients. Treatment with angiotensin receptor blockers (ARB) is recommended for those patients who are unable to tolerate ACEI. Candesartan has been shown to reduce CV mortality in patients with HF-REF unable to tolerate ACEI (HR 0.80; 95% CI 0.66-0.96; p=0.02) (Granger *et al*, 2003). Ivabradine and the combination of hydralazine and nitrates have also been shown to have benefits in specific subsets of patients with HF-REF who remain symptomatic despite ACEI and beta-blockers, particularly when heart rates remain elevated or in those unable to tolerate conventional therapy, respectively (Swedberg *et al*, 2010; Taylor *et al*, 2004).

1.7 Device Therapy - Current Guidelines

1.7.1 Implantable Cardioverter Defibrillators

ICDs can promptly recognize and treat ventricular arrhythmias and thus form a cornerstone of SCD prevention in high-risk patients. They are recommended to reduce the risk of SCD and all-cause mortality in patients with a life expectancy >1 year, who have recovered from a ventricular arrhythmia causing haemodynamic instability or in those with symptomatic HF with a LVEF ≤35% who have been on optimal medical therapy (OMT) for at least 3 months (Ponikowski *et al*, 2016; Yancy *et al*, 2013). While the use of ICDs for secondary prevention appears robust (AVID Investigators, 1997; Connolly *et al*, 2000), the recent DANISH trial has cast doubt about the benefit of ICDs for the primary prevention of SCD in patients with DCM and HF-REF (Kober *et al*, 2016).

Five trials have investigated the benefit of ICD therapy in DCM patients without a history of haemodynamically unstable ventricular arrhythmia (*Table 1.3)* (Bansch *et al*, 2002; Bardy *et al*, 2005; Kadish *et al*, 2004; Kober *et al*, 2016; Strickberger *et al*, 2003). The Cardiomyopathy Trial (CAT) and the Amiodarone vs Implantable Cardioverter-Defibrillator (AMIOVIRT) trial were stopped early due to a low event rate and lack of power (Bansch *et al*, 2002; Strickberger *et al*, 2003). The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) investigated ICD implantation in patients with both ischaemic and non-ischaemic HF-REF, LVEF <35% and NYHA class II-III symptoms (Bardy *et al*, 2005). ICD therapy was associated with a reduction in overall mortality across both aetiologies (HR 0.77; 97.5% CI: 0.62-0.96; p=0.007). The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) study evaluated ICD implantation in patients with DCM, HF-REF, a LVEF ≤35% and non-sustained ventricular arrhythmia (Kadish *et al*, 2004). A reduction in SCD was observed (HR 0.20; 95%CI 0.06-0.71; p=0.006) however all-cause mortality was not significantly different with ICD therapy, possibly because the study was underpowered (HR 0.65; 95%CI 0.40-1.1; p=0.08).

Current guidelines are based on a meta-analysis of these four trials, which demonstrated a reduction in all-cause mortality associated with ICD therapy (HR 0.74, p=0.02) (Desai *et al*, 2004; Ponikowski *et al*, 2016; Priori *et al*, 2015). Published after the most recent guidelines, the Danish Study to Assess the Efficacy of ICDs in Patients with Non-Ischemic Systolic Heat Failure on Mortality (DANISH) compared ICD therapy with optimal HF management in patients with non-ischemic cardiomyopathy HF, a LVEF <35% and NT-pro-BNP >200pg/ml (Kober *et al*, 2016). This included patients with hypertensive heart disease and previous valve disease. Similar to DEFINITE, ICD therapy did not reduce all-cause mortality (HR 0.87; 95% CI: 0.68-1.12; p=0.28) despite reducing SCD (HR 0.50; 95% CI: 0.31-0.82; p=0.005). The

annual mortality rate was less than 5% and only 1/3 of the deaths in the control arm were sudden, demonstrating the major impact of contemporary HF therapy, in this relatively sick group of patients. Notably, the number treated with optimal HF therapy was higher than previous trials; 97% were prescribed ACEIs or ARBs and 92% were on beta-blockers. Additionally, 58% received cardiac resynchronisation therapy (CRT), including 93% of patients with LBBB and a QRS >150ms. Updated meta-analyses, including DANISH, has since demonstrated a 23% reduction in all-cause mortality with ICD therapy compared to medical therapy (HR 0.77; 95% CI 0.64-0.91) (Golwala *et al*, 2017; Shun-Shin *et al*, 2017). However, of those included in these analyses, only patients enrolled in the DANISH trial were taking contemporary HF therapy which has dramatically changed the rate and mode of SCD in HF-REF (Shen *et al*, 2017).

Study	N	Inclusion criteria	Intervention	Follow-up (median)	All-cause mortality	SCD
CAT (Bansch *et al*, 2002)	104	LVEF<30% NYHA 2-3	ICD vs OMT	23 months	Terminated early	
AMIOVIRT (Strickberger *et al*, 2003)	103	LVEF≤35% NYHA 1-3 NSVT	ICD vs amio	24 months	Terminated early	
SCDHeFT (DCM cohort) (Bardy *et al*, 2005)	1211	LVEF<35% NYHA 2-3	ICD vs OMT vs amio	46 months	I: 21.4%, C: 27.9% (5 yrs) HR 0.73; 95% CI 0.50-1.07 p=0.06	
DEFINITE (Kadish *et al*, 2004)	458	LVEF<36% NYHA 1-3 NSVT or PVCs	ICD vs OMT	29 months	I: 12.2%, C: 17.4% HR 0.65; 95% CI 0.40-1.06 p=0.08	I: 1.3%, C:6.1% HR 0.20; 95% CI 0.06-0.71 P=0.006
DANISH (Kober *et al*, 2016)	1116	LVEF<35% NYHA 2-3 (4 if CRT) NT-pro-BNP>200pg/ml	ICD vs OMT	68 months	I: 21.6%, C: 23.4% HR 0.87; 95% CI 0.68-1.12 p=0.28	I: 4.3%, C: 8.2% HR 0.50; 95% CI 0.31-0.82 p=0.005

Table 1.3. Randomised trials of implantable cardioverter defibrillators.

Randomised trials investigating effect of implantable cardioverter defibrillators in patients with dilated cardiomyopathy without a history of haemodynamically unstable ventricular arrhythmia. Reproduced with permission from (Halliday *et al*, 2017)

(amio: amiodarone, C: optimal medical therapy arm, CI confidence interval, HR – hazard ratio, I: implantable cardioverter defibrillator therapy arm, NSVT – non-sustained ventricular tachycardia, PVCs – premature ventricular complexes, OMT – optimal medical therapy)

1.7.2 Cardiac Resynchronisation Therapy

CRT is the treatment of cardiac dyssynchrony with atrio-biventricular pacing. It has been shown to improve HF symptoms, quality of life, morbidity and mortality in patients with prolonged QRS duration and symptomatic HF-REF in sinus rhythm (Cleland *et al*, 2013; Cleland *et al*, 2005). The main mechanism responsible for the improvement in outcomes is thought to be beneficial reverse remodelling characterised by an improvement in LVEF and a reduction in ventricular size that results in reduced neurohormonal activation. Prevention of fatal bradycardia may also play a role in reducing SCD. The landmark Cardiac Resynchronisation in Heart Failure (CARE-HF) study demonstrated reduced all-cause mortality with CRT in patients with symptomatic HF-REF and a QRS duration greater than 120ms on OMT (HR 0.64; 95% CI 0.48-0.85; p=0.002) (Cleland *et al*, 2005). A subsequent individual patient data meta-analysis has demonstrated that the magnitude of the effect is directly proportional to the QRS duration with greater benefit at longer QRS durations (Cleland *et al*, 2013).

CRT is associated with greater reverse remodelling in patients with non-ischaemic HF compared to those with ischaemic HF (Bleeker *et al*, 2006). However, the effect of CRT on prognosis appears to be similar in both sub-groups following adjustment for QRS duration (Cleland *et al*, 2008; Cleland *et al*, 2013). Current guidelines recommend CRT for patients with symptomatic HF and a QRS duration of >150msec and state that it may be considered for those with a QRS duration of between 130-149msec (Ponikowski *et al*, 2016).

1.8 The Unmet Needs: Improving the Selection of Patients for Implantable Cardioverter Defibrillators

As highlighted above, DCM is a heterogeneous disease affecting a diverse group of people. A disease with such complexity requires contemporary, personalised and precise algorithms to guide management, ensuring the selection of patients most likely to gain benefit from specific therapies. Current guidelines which centre on LVEF, as determined by echocardiography and NYHA class, lack the precision needed to make therapeutic decisions about a heterogeneous disease (Ponikowski *et al*, 2016; Yancy *et al*, 2013). The current approach dichotomises patients into groups based on single measurements of subjective, dynamic variables and is widely regarded as sub-optimal.

An important area where the precision of current guidelines needs to be improved is the selection of patients for ICDs for the primary prevention of SCD. The uncertainty about whether patients with DCM benefit from such devices may reflect a weak overall impact or that an ICD only benefits sub-groups who are at increased risk of SCD or at low risk of other competing modes of death. It is well established that the sensitivity of the current approach for the selection of patients for ICD therapy is poor (Huikuri *et al*, 2001). Several studies have demonstrated that the majority of SCD occurs in patients without severely reduced LVEF (de Vreede-Swagemakers *et al*, 1997; Gorgels *et al*, 2003; Huikuri *et al*, 2001; Stecker *et al*, 2006; Wellens *et al*, 2014). In one sudden death registry, of those cases who underwent pre-mortem echocardiography, only 20-30% had a low enough LVEF to meet conventional criteria for an ICD (Gorgels *et al*, 2003; Stecker *et al*, 2006). DCM registries have confirmed that, although the overall risk of SCD may be higher in those with severely reduced LVEF, there are many more patients with mild or moderate reductions in LVEF, who still have a substantial risk

(Grimm *et al*, 2003a). Importantly, they are likely to be exposed to this risk for a longer period of time, due to better life expectancy. Their cumulative life-time SCD risk may therefore be greater than those with more severe HF (*Figure 1.10*). They are also less likely to have limiting symptoms and the likelihood of gaining quality life from successful ICD therapy may be greater. The risk of SCD from ventricular arrhythmia is affected by many factors including structural substrate such as myocardial fibrosis, autonomic dysfunction, electrical instability and genetic predisposition. An approach incorporating multiple factors in addition to LVEF may be required (*Figure 1.10*).

Equally, the available trials also uncover the poor specificity of an approach based on LVEF; only 11.5% of patients with an ICD in the DANISH trial received an appropriate shock over a median follow-up of 5.6 years (Kober *et al*, 2016). This finding may be partially explained by the improved outcome for many patients with optimal HF therapy (Merlo *et al*, 2011). Another explanation may be a high incidence of death from competing non-sudden causes. It is well recognised that as the risk of death from HF rises, the chances of gaining longevity from an ICD rapidly reduces, regardless of SCD risk.

When reflecting on the level of precision that is required from selection criteria, it is also important to consider the complications and costs associated with ICD implantation. Inappropriate shocks lead to morbidity and reduce quality of life (Kadish *et al*, 2004; Kober *et al*, 2016; Poole *et al*, 2008). Device infection complicated 4.9% of device implants in the DANISH trial and early procedure-related complications, such as pneumothorax, pocket haematomas or lead displacement occur in up to 4% of cases (Kober *et al*, 2016; Poole *et al*, 2010). Complications also add significant costs to the huge expenditure associated with ICDs.

In conclusion, current guidelines on ICD therapy for the primary prevention of SCD in DCM patients fail to provide the necessary level of precision. Areas of unmet need include the

identification of patients with mild or moderate reduction in LVEF at high-risk of SCD who may benefit from ICD therapy. Equally important is the identification of individuals who are unlikely to benefit from ICD therapy despite a significant risk of SCD, due to a high risk of death from competing non-sudden causes. Several techniques, including LGE-CMR, offer hope in the pursuit of predicting the risk of SCD and non-sudden death (*Figure 1.10*).

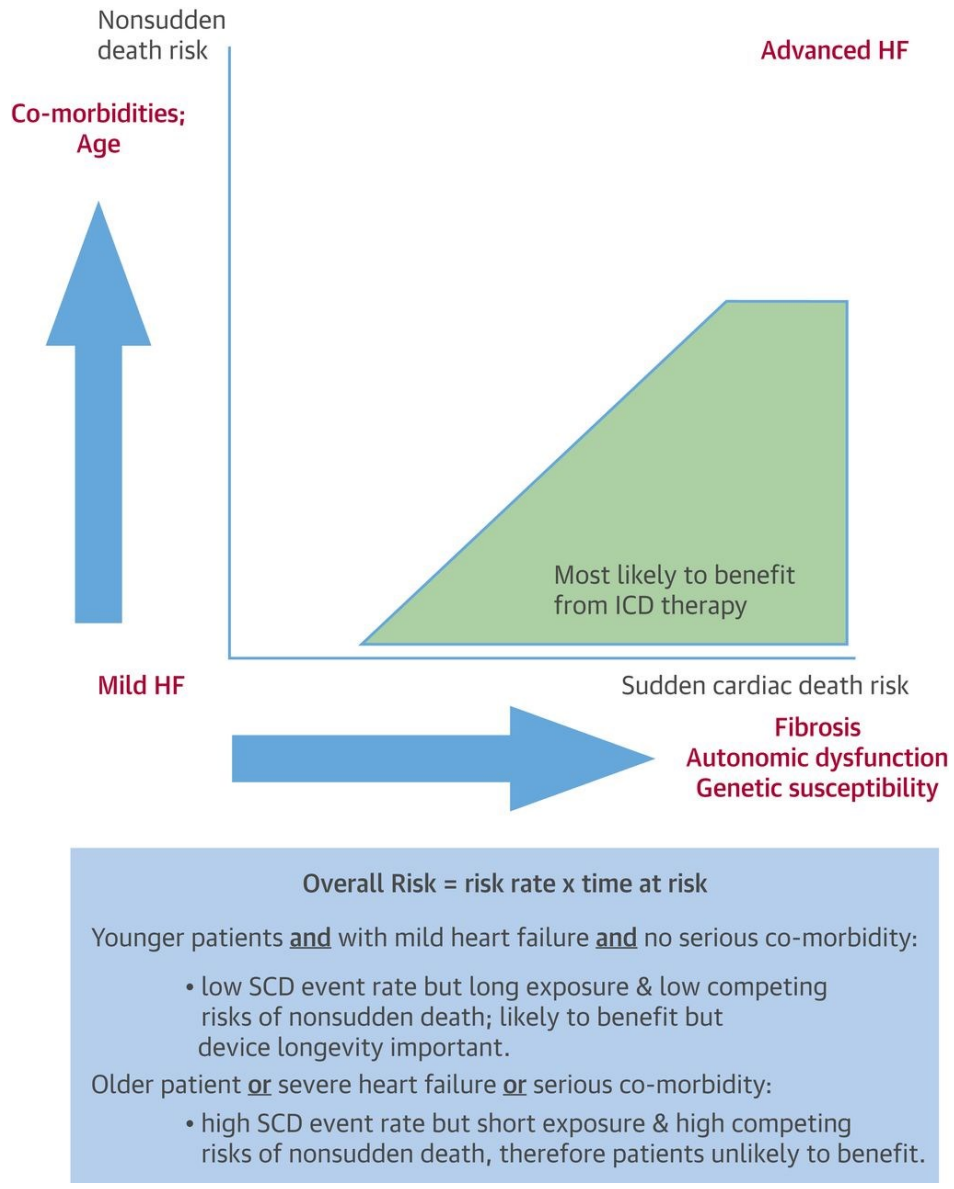

Figure 1.10. Selecting patients for implantable cardioverter defibrillators

Factors to consider during the selection of patients with DCM for ICDs for the primary prevention of sudden cardiac death. Reproduced with permission from (Cleland *et al*, 2017b).

1.8.1 Stratifying Sudden Death Risk using Late Gadolinium Enhancement Imaging

Multiple studies and large meta-analyses have demonstrated an association between the presence of non-ischaemic LGE and SCD events in patients with DCM (Assomull *et al*, 2006; Cheong *et al*, 2009; Di Marco *et al*, 2016; Disertori *et al*, 2016; Gao *et al*, 2012; Gulati *et al*, 2013c; Klem *et al*, 2012; Kuruvilla *et al*, 2014; Lehrke *et al*, 2011; Leyva *et al*, 2012; Leyva *et al*, 2017; Masci *et al*, 2014; Muller *et al*, 2013; Neilan *et al*, 2013; Perazzolo Marra *et al*, 2014; Piers *et al*, 2015). These are supported by mechanistic studies linking the presence of replacement fibrosis with the inducibility of VT (Bogun *et al*, 2009) and conduction abnormalities, known to play a role in ventricular arrhythmogenesis (de Bakker *et al*, 1996; Hsia *et al*, 2002). Studies focusing on the prediction of SCD events and major arrhythmic events are summarised in *Table 1.4*.

Gulati and colleagues performed a prospective study of 472 patients with DCM of all severities (Gulati *et al*, 2013c). Over a median follow-up of 5.3 years, 29.6% of patients with non-ischaemic LGE suffered SCD or aborted SCD compared to just 7.0% of those without (HR 5.24; 95% CI 3.15-8.72; $p<0.001$). After adjustment, the presence of LGE predicted the composite SCD end-point (HR 4.61; 95% CI 2.75-7.74; $p<0.001$) as well as all-cause mortality (HR 2.43; 95% CI 1.50-3.92; $p<0.001$) and a composite HF end-point (HR 1.62; 95% CI 1.00-2.61; $p=0.049$). The addition of LGE to a model including LVEF improved the net re-classification index, correctly re-classifying 29% of patients. Although, LGE predicted the occurrence of all 3 end-points, the hazard ratio for SCD was greatest. This suggests that LGE may be able to discriminate between SCD risk and the risk of death from competing causes.

Authors	N (LGE)	Inclusion criteria	Arrhythmic end-point	Follow-up (median)	Occurrence of end-point as per presence of LGE
Gulati et al (2013)	472 (142)	Consecutive patients referred for CMR	SCD* and aborted SCD† (excluding ATP)	64	Total events 65 Event rate: LGE: 29.6%; no LGE 7.0% HR 5.24 (95% CI 3.15-8.72; p<0.001)
Assomull et al (2006)	101 (35)	Consecutive patients referred for CMR	SCD* and sustained VT	22	Total events: 7 Event rate: LGE: 14.3%; no LGE 3.3% HR 5.2 (95% CI 1.0-26.9; p=0.03)
Neilan et al (2013)	162 (81)	Consecutive patients referred for CMR	SCD* and aborted SCD† (including ATP)	29	Total events: 37 Event rate: LGE: 41.9%; no LGE 3.7% HR 14.0 (95%CI 4.39:45.65; p<0.0001)
Masci et al (2014)	228 (61)	Patients with DCM without a history of HF	Aborted SCD† (including ATP)	23	Total events: 8 Event rate: LGE: 9.8%; no LGE 1.2% HR 8.31 (95%CI 1.66:41.55; p=0.01)
Perazzolo-Marra et al (2014)	137 (76)	Consecutive patients	SCD* and aborted SCD† (including ATP)	36	Total events: 22 Event rate: LGE: 22.3%; no LGE 8.2% HR 4.17 (95% CI 1.56-11.2; p=0.005)
Leyva et al (2012)	97 (25)	Patients referred for CRT	SCD*	35	Total events: 3 Event rate: LGE: 15.0%; no LGE 0% HR 31.0 (95% CI 1.5-627.8; p=0.013)

Table 1.4. Late gadolinium enhancement and outcome in dilated cardiomyopathy.

Studies investigating the association between non-ischaemic late gadolinium enhancement and major arrhythmic outcomes in dilated cardiomyopathy. Reproduced with permission from (Halliday *et al*, 2017)

(*witnessed cardiac arrest, death within 1 hour after onset of symptoms or unexpected, unwitnessed death in a patient known to have been well 24 hours previously; †sustained VT, resuscitated cardiac arrest, appropriate ICD intervention; ATP – antitachycardia pacing, CI - confidence interval, HR – hazard ratio, PVCs – premature ventricular complexes, OMT – optimal medical therapy)

More recently, Leyva et al followed 252 patients with DCM following CRT. Mid-wall LGE on CMR prior to implant was an independent predictor of SCD (HR 3.75; 95% CI 1.26:11.2) and all-cause mortality (HR 2.31; 95% CI 1.32:3.09) over a median follow-up of 3.8 years (Leyva *et al*, 2017). Importantly, mortality was lower in patients with mid-wall LGE who received CRT-D compared to those who received CRT-P (HR 0.23; 95% CI 0.07:0.75) but not different amongst patients without LGE who received either device.

Neilan and colleagues followed 162 DCM patients with DCM prior to scheduled ICD implantation (Neilan *et al*, 2013). Following adjustment, LGE presence predicted a composite of CV death and major arrhythmic events (HR 6.21; 95% CI 1.73-22.2; $p<0.0004$) and the secondary end-point of SCD and appropriate ICD intervention (HR 14.0; 95% CI 4.39-45.65; $p<0.0001$). This study established that LGE quantification was reproducible between operators. LGE occupying >6.1% of the myocardium by the >2 SD method or >4.4% by the full width at half maximum method provided the highest sensitivity and specificity for the primary end-point.

Data on the optimal cut-offs of LGE extent for the prediction of SCD events are yet to be published. Whether LGE cut-offs remain consistent between datasets from different centres remains uncertain. Moreover, although both studies reported an association between the extent of LGE and outcome, the exact nature and linearity of the relationship remains uncertain. In this context, the most reliable form of LGE risk stratification currently appears to be based on the presence or absence of LGE. Whether the risk associated with LGE is dependent on the location and pattern of enhancement is also uncertain. Two studies in patients with acute myocarditis have demonstrated a greater incidence of adverse events in patients with septal LGE compared to those with LGE in the LV free-wall (Aquaro *et al*, 2017; Grani *et al*, 2017). Whether this holds true in DCM is unclear.

Another important unanswered question is whether LGE-CMR is able to identify those patients with a LVEF >35% who are at high-risk of SCD events and do not currently meet criteria for ICD therapy. In a meta-analysis of 2948 DCM patients, Di Marco and colleagues, demonstrated an association between LGE and a composite end-point of SCD, sustained ventricular arrhythmia and appropriate ICD therapy in studies where the mean LVEF was >35% (OR 5.2; 95% CI 3.4-7.9; p<0.001). This requires confirmation in further studies. Finally, whether LGE-CMR can ultimately identify patients who benefit from ICD therapy can only be answered from randomised controlled trials.

Parametric mapping

Given the correlation between native T1 and ECV values and interstitial fibrosis and the role the latter may play in the generation of ventricular arrhythmias triggered by focal mechanisms, there has been interest in the possibility of using parametric mapping in SCD risk stratification. Puntmann and colleagues investigated 637 patients with DCM who had undergone parametric mapping and demonstrated an association between all-cause mortality and native T1 values (Puntmann *et al*, 2016). Studies investigating SCD end-points in DCM patients are required to determine whether mapping provides incremental value to LGE.

1.8.2 Additional Methods to Stratify Sudden Death Risk

Electrical markers

Several studies have focused on the utility of electrical measurements in the prediction of SCD risk in DCM, including features on surface electrocardiograms such as the presence of microvolt T wave alternans (MTWA) or left bundle branch block (LBBB), markers of autonomic tone and the presence of ventricular arrhythmia on Holter monitoring or during

programmed stimulation in the catheter laboratory (Calo *et al*, 2011; Chan *et al*, 2010; Cheema *et al*, 2010; Daubert *et al*, 2009; De Ferrari *et al*, 2009; Goldberger *et al*, 2014; Grimm *et al*, 2005; Grimm *et al*, 1998; Grimm *et al*, 2003b; Gupta *et al*, 2012; Hohnloser *et al*, 2012; Hohnloser *et al*, 2003; Merchant *et al*, 2012; Pezawas *et al*, 2014; Rankovic *et al*, 2002; Verrier *et al*, 2011; Zecchin *et al*, 2008). The results of these studies have been inconsistent, possibly due to the heterogeneity and small size of these patient cohorts (Goldberger *et al*, 2014). Goldberger and colleagues performed a meta-analysis to summarise the data (Goldberger *et al*, 2014). They demonstrated that reproducibility was poor for the majority of the variables measured but concluded that the presence of MTWA (OR 4.66; 95% CI 2.55-8.53; $p<0.001$) and QRS fragmentation (OR 6.73; 95% CI 3.85-11.76; $p<0.001$) were the most promising for the prediction of SCD events. The potential of MTWA has been reinforced by several large studies and meta-analyses (Calo *et al*, 2011; Chan *et al*, 2010; De Ferrari *et al*, 2009; Gupta *et al*, 2012; Merchant *et al*, 2012). It has been suggested that this may be a stronger predictor of major arrhythmic events in patients taking beta-blockers (patients on beta-blockers: HR 5.39; 95% CI 2.68-10.84 $p<0.001$; entire population: HR 1.95; 95% CI 1.29-2.96; $p=0.002$) (Chan *et al*, 2010). Other authors have emphasised the negative predictive value of the test and suggested that it may be used to identify those patients who are unlikely to benefit from ICD therapy (Hohnloser *et al*, 2012). However, it has been noted that in populations with a low event rate, even a coin toss has a good negative predictive value (Goldberger, 2010).

Cardiac MIBG

Autonomic dysregulation predisposes to ventricular arrhythmia by producing heterogeneous sympathetic activation of the myocardium and creating variability in conduction velocities and refractory periods. Although measures of baroreflex sensitivity, heart rate turbulence and heart rate variation have been inconsistent in predicting arrhythmic events (Grimm *et al*, 2005;

Grimm *et al*, 2003b), the detection of autonomic dysfunction using 123-metaiodobenzylguanidine (MIBG) scintigraphy has been more promising (Boogers *et al*, 2010; Jacobson *et al*, 2010; Kioka *et al*, 2007; Merlet *et al*, 1999; Sood *et al*, 2013; Tamaki *et al*, 2009).

Elevated tracer washout rates, abnormal ratio of uptake between the heart and the mediastinum and extensive myocardial tracer defects can be used to detect autonomic dysregulation. One study, performed in patients with DCM, demonstrated that low heart/mediastinum uptake ratio predicted SCD (Merlet *et al*, 1999). The larger AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) study, performed in patients with both ischaemic and non-ischaemic HF, demonstrated that a heart/mediastinum ratio of ≥1.6 was associated with a lower risk of major arrhythmic events. However, survival modelling of those patients without an ICD at baseline suggested that heart/mediastinum ratio did not identify those patients who would benefit from ICD implantation (Hachamovitch *et al*, 2015). A low ratio may therefore simply indicate sicker myocardium which is associated with a higher mortality. Some patients who were soon to die of HF may have had this pre-empted by SCD. An ICD would not usefully prolong life in these patients.

Genetics

Despite recent advances in sequencing, there are currently only a few circumstances when the results of genetic screening guide the management of patients. The most commonly encountered scenario is the finding of a pathogenic variant in *LMNA,* a gene which encodes the Lamin A and C proteins, part of the nuclear envelope (McNally *et al*, 2013). Lamin cardiomyopathy is characterised by progressive disease with early onset atrial and ventricular arrhythmias, atrioventricular block and the development of advanced HF. By 50 years of age, penetrance approaches 100% in gene carriers and mortality at 5 years in those with a positive

phenotype is as high as 40% (Pasotti *et al*, 2008; van Rijsingen *et al*, 2012). Current consensus supports a lower threshold for ICD therapy in individuals with a pathogenic variant and in all those requiring permanent pacing for a bradycardia indication (Pasotti *et al*, 2008; van Rijsingen *et al*, 2012).

A specific deletion in *PLN,* which encodes phospholamban, an important protein in calcium handling has been associated with a high incidence of malignant arrhythmias and SCD events in patients with DCM and also those without identifiable structural phenotypes (van Rijsingen *et al*, 2014). Truncating mutations in *FLNC* which produces filamin, an important cytoskeletal protein, has been linked with an arrhythmogenic cardiomyopathy characterised by extensive fibrofatty infiltration and a high incidence of SCD (Ortiz-Genga *et al*, 2016). In contrast, a recent study has demonstrated that truncating variants of *TTN* are associated with a similar incidence of adverse events compared to patients with idiopathic cardiomyopathy (Tayal *et al*, 2017).

1.8.3 Predicting the Competing Risks of Death from Non-Sudden Causes

As discussed, the DANISH trial demonstrated that ICD therapy did not reduce all-cause mortality in patients with non-ischaemic HF and a LVEF <35% despite reducing the incidence of SCD (Kober *et al*, 2016). This suggests that ICD therapy simply changed the mode of death from SCD to non-sudden death and emphasises the importance of selecting patients with low risks of death from competing causes (*Figure 1.11*). Current guidelines do not recommend ICD therapy for patients with a life expectancy <1 year or those in NYHA Class IV unless cardiac transplantation is planned (Ponikowski *et al*, 2016; Yancy *et al*, 2013). However, a large

number of patients at high-risk of death from non-sudden causes still receive ICDs. Less subjective and more precise measures are required.

Pre-planned sub-group analysis of the DANISH trial demonstrated that patients <59 years of age gained mortality benefit from ICD therapy, suggesting a role for this simple, universally available variable (Kober *et al*, 2016). The exact explanation for this finding is not clear. A higher rate of death from competing causes later in life may dilute the benefit of ICD therapy. It is also possible that those presenting later in life have a lower incidence of ventricular arrhythmias or that patients who are more arrhythmia-prone are less likely to survive to an older age. Indeed, Maron and colleagues demonstrated a lower incidence of adverse arrhythmic events in patients diagnosed with HCM after the age of 60 years (Maron *et al*, 2013). Examining the rates of death from non-sudden and sudden causes in DCM according to age could help direct management strategy.

Biomarkers such as NT-pro-BNP, measures of renal function and prognostic HF scores may also play a role in stratifying competing risks of death. Those patients with a NT-pro-BNP level < 1177pg/ml in the DANISH trial gained mortality benefit from ICD therapy. A meta-analysis of ICD trials in patients with ischaemic and non-ischaemic HF established a reduction in mortality benefit in patients with reduced estimated glomerular filtration rate (Pun *et al*, 2014). Prognostic scores such as the Seattle Heart Failure Model also offer huge potential in quantifying the predicted risk of HF death (Levy *et al*, 2006). Patients with a score of 3 or 4 have a relative risk of HF death of 38.4 and 87.6 and a relative risk of SCD of 6.5 and 6.5, compared to those patients with a score of 0, respectively (Mozaffarian *et al*, 2007). This demonstrates that as the severity of HF increases, the risk of HF death rises much more rapidly than the risk of SCD, reducing the chances of gaining longevity from ICD therapy.

Data from HF studies suggest that women have better survival compared to men with the condition (Martinez-Selles *et al*, 2012). Whether this relates to a higher proportion of non-ischaemic HF in women is debated (Hsich *et al*, 2009). Sex differences in adverse remodelling have been demonstrated across several conditions and it is possible that women remodel more favourably than men (Cocker *et al*, 2009; Treibel *et al*, 2017). The impact of sex on the risk of non-sudden death and SCD in DCM remains unexplored. This simple, universally available variable deserves consideration with respect to risk stratification.

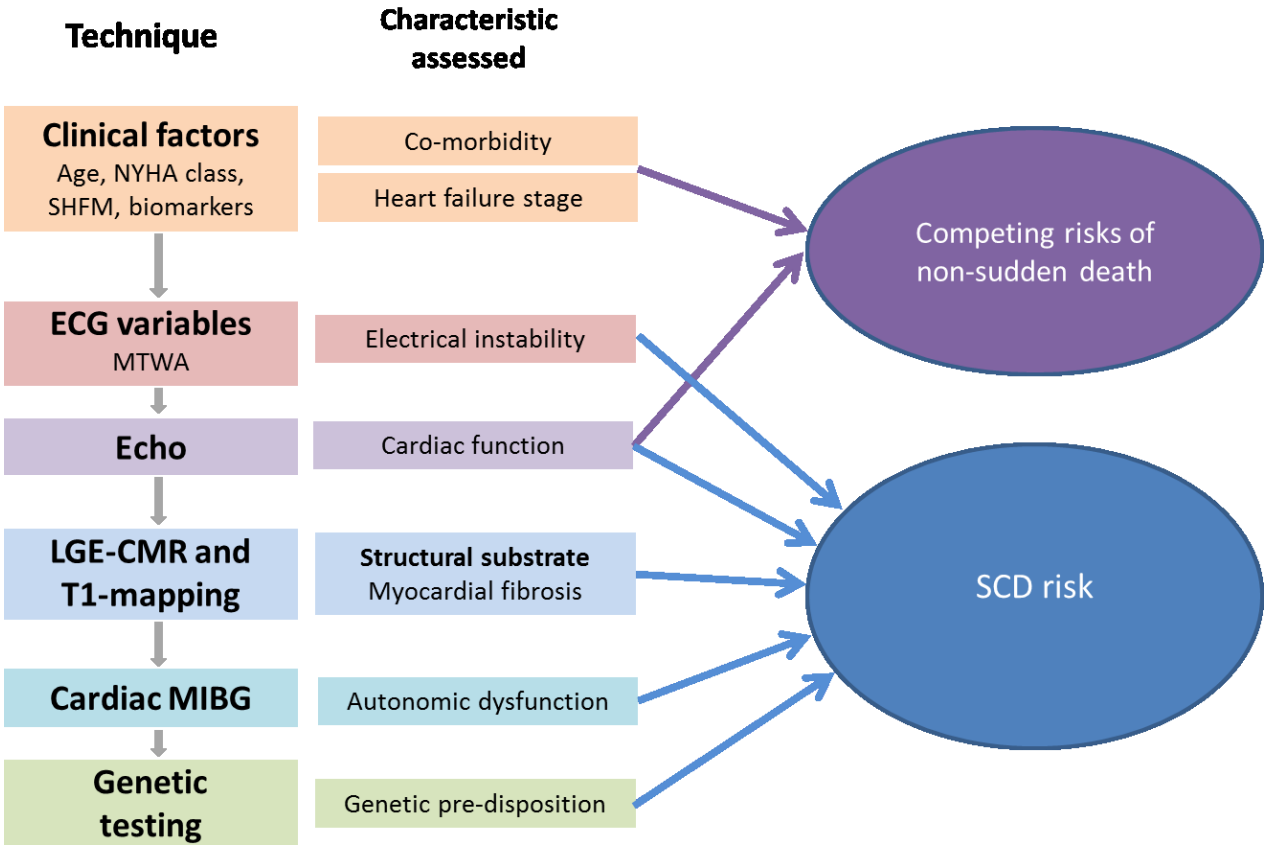

Figure 1.11. Prediction of the risk of sudden and non-sudden death.
Techniques that may be used to predict the risk of SCD and non-sudden cardiac death in the selection of patients most likely to benefit from ICDs for primary prevention purposes. Reproduced with permission from (Halliday *et al*, 2017)

Given the unmet needs in the risk stratification of DCM outlined above, we set out to perform a series of studies investigating the following specific hypotheses.

1.9 Hypotheses (Part 1) – Outcomes in Dilated Cardiomyopathy

1. ***The presence of non-ischaemic late gadolinium enhancement identifies patients with dilated cardiomyopathy and a left ventricular ejection fraction >40% at high-risk of sudden cardiac death events***

2. ***The extent of late gadolinium enhancement is associated with adverse outcomes in a linear dose-dependent manner***

3. ***Mid-wall late gadolinium enhancement in the septum is associated with a higher rate of adverse outcomes compared to late gadolinium enhancement in the free-wall of the left ventricle***

4. ***The all-cause mortality rate and the rate of death from non-sudden causes rises with advancing age in patients with dilated cardiomyopathy, while the rate of sudden cardiac death increases less steeply and declines as a proportion of overall deaths***

5. ***There is no difference in outcome between men and women with dilated cardiomyopathy***

1.10 The Unmet Needs: The Management of Patients with Recovered Dilated Cardiomyopathy

1.10.1 Left Ventricular Reverse Remodelling: Remission or Cure?

Left ventricular reverse remodelling is defined as an improvement in LVEF and a reduction in LV size (Basuray *et al*, 2014; Doughty *et al*, 1997; Konstam *et al*, 1992; McNamara *et al*, 2011; Merlo *et al*, 2015; Punnoose *et al*, 2011; Wilcox *et al*, 2012). Contemporary HF therapy is associated with reverse remodelling in up to 40% of patients with DCM and this is associated with an excellent short and medium-term prognosis (Basuray *et al*, 2014; Doughty *et al*, 1997; Konstam *et al*, 1992; McNamara *et al*, 2011; Merlo *et al*, 2015; Punnoose *et al*, 2011; Wilcox *et al*, 2012). Reverse remodelling is more common in in DCM compared to HF-REF due to IHD, women, younger patients, those with fewer co-morbidities, narrow QRS complex, smaller LV and LA volumes and those with less severe degrees of LV impairment (Doughty *et al*, 1997; Konstam *et al*, 1992; McNamara *et al*, 2011; Merlo *et al*, 2015; Punnoose *et al*, 2011; Sze *et al*, 2018).

A new HF phenotype has been proposed for patients with a previous diagnosis of HF-REF, in whom the LVEF has subsequently improved: 'HF with recovered ejection fraction' (Basuray *et al*, 2014; Kalogeropoulos *et al*, 2016). Basuray and colleagues studied 1821 HF patients from a prospective registry and classified 10% as HF with recovered LVEF (LVEF <50% at baseline with improvement to >50%) (Basuray *et al*, 2014). Similar to other studies, this population was distinct from those with HF-REF, with a greater proportion of women and non-ischaemic HF and a lower prevalence of co-morbidities. Those with recovered LVEF had improved long-term outcomes compared to those with HF-REF. However, most had persisting symptoms; only 28% of the cohort was in NYHA Class 1. Additionally, circulating biomarker

profiles, including natriuretic peptide and troponin, remained abnormal in a proportion suggesting ongoing myocyte stretch and stress. Other retrospective studies using a variety of cut-offs for recovered LVEF (from 40% to 50%) have demonstrated similar findings (de Groote *et al*, 2014; Merlo *et al*, 2011; Punnoose *et al*, 2011). These studies demonstrate that at least a proportion of patients with HF and improved LVEF have ongoing evidence of myocardial dysfunction.

Another well described group of patients who demonstrate reverse remodelling are those who receive a left ventricular assist device as a bridge to recovery and demonstrate improvement in function after a period of mechanical unloading (Madigan *et al*, 2001; Ruwald *et al*, 2014). Although, many beneficial changes in gene expression, myocyte metabolism and extracellular matrix have been demonstrated in these patients, some differences persist compared to healthy controls (Kim *et al*, 2017).

Current studies defining reverse remodelling on the basis of an increase in LVEF therefore include a heterogeneous group of ischaemic and non-ischaemic patients with a spectrum of improvement (*Figure 1.12*). A proportion of patients have ongoing clinical or sub-clinical myocardial dysfunction. Others, particularly those with non-ischaemic aetiology, demonstrate more complete myocardial recovery with resolution of symptoms and normalisation of circulating biomarkers. Given the heterogeneity of the population, it has been suggested that the terminology, 'HF with improved LVEF' may be appropriate than 'HF with recovered LVEF' (Stevenson, 2014).

Universal definitions of reverse remodelling and myocardial recovery incorporating clinical, biochemical and imaging assessments of HF status are therefore required to reduce heterogeneity and enable targeted and relevant research in the correct patient groups. From the available evidence, those with improved LVEF but persistent mild abnormalities may be

considered to have remission of HF. Whether those with DCM and the most marked improvement have remission of disease or whether their underlying cardiomyopathy has permanently recovered and is 'cured' remains uncertain.

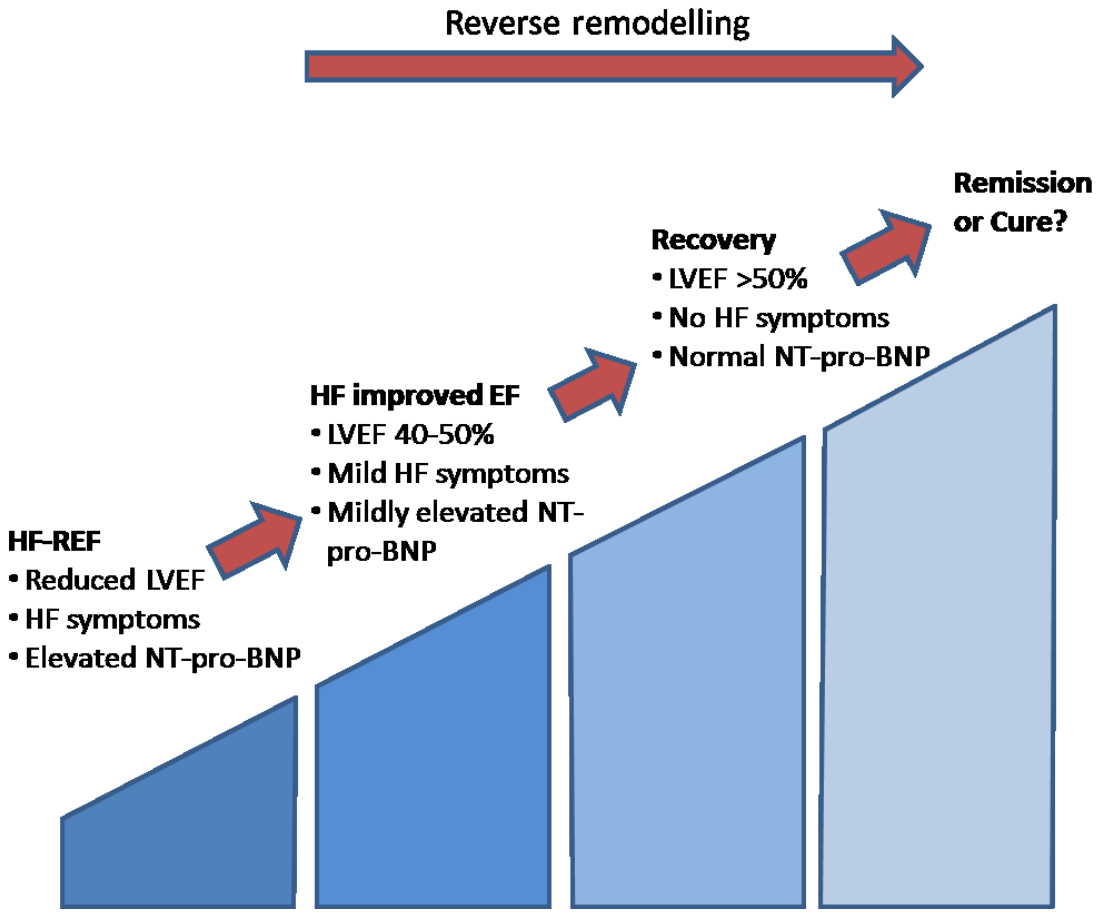

Figure 1.12. Left ventricular reverse remodelling.
A proposed scheme to demonstrate the spectrum of left ventricular reverse remodelling from improvement in ejection fraction to myocardial recovery.

1.10.2 Therapy Withdrawal in Recovered Dilated Cardiomyopathy

Given the increasing incidence of reverse remodelling with the use of contemporary HF therapy, a frequently encountered question is the optimal management of DCM patients with improved LVEF. It is common to consult patients with improved clinical status asking whether they can reduce or stop their pharmacological therapy, years after initial presentation. There is

little evidence on which to base these decisions. Available studies examining withdrawal of therapy have been performed in heterogeneous populations of patients, some also including patients with IHD and most including those with ongoing clinical evidence of HF and reduced LVEF. With little evidence on which to base decisions, the current management of DCM patients with improved LVEF varies amongst clinicians.

Studies Investigating the Withdrawal of Pharmacological Therapies

Three small studies have examined beta-blocker withdrawal in patients with ongoing mild-to-moderate HF and reduced LVEF (Morimoto *et al*, 1999; Swedberg *et al*, 1980; Waagstein *et al*, 1989). Swedberg and colleagues investigated 15 patients, with LV dilatation (left ventricular end diastolic diameter [LVEDD] >60mm) and reduced LVEF (range of LVEF 32-64%) (Swedberg *et al*, 1980). Following beta-blocker withdrawal, 6 patients developed worsening HF and one patient died suddenly. Similarly Waagstein *et al* examined withdrawal of metoprolol in 24 patients with a diagnosis of DCM (Waagstein *et al*, 1989). At the time of withdrawal the mean LVEF and LVEDD was 41% and 6.5cm respectively and most patients had mild or moderate symptoms of HF. Following withdrawal, 12 patients developed worsening HF, 4 patients died suddenly and 8 patients remained clinically stable. Morimoto and colleagues investigated 13 patients taking metoprolol following the diagnosis of DCM. At the start of the study, mean LVEF and LVEDD was 38% and 6.0cm respectively. Following beta-blocker cessation, 3 patients suffered relapses of HF and 4 died; 2 from worsening HF and 2 suddenly. Of note, there was a high prevalence of preceding ventricular arrhythmia within the cohort, with the majority of patients taking additional class I and III anti-arrhythmic agents at baseline.

Studies have also examined the impact of ACEI withdrawal in similar populations of patients with ongoing features of HF. Initial studies focused on the immediate haemodynamic and

neurohormonal effects in patients with HF-REF secondary to CAD (Maslowski *et al*, 1981; Nicholls *et al*, 1982). Captopril withdrawal was associated with increases in heart rate, arterial pressure, angiotensin II and aldosterone and a reduction in plasma renin (Maslowski *et al*, 1981; Nicholls *et al*, 1982). Subsequent studies investigated the clinical impact of ACEI withdrawal (Pflugfelder *et al*, 1993). Pflugfelder and colleagues performed a double-blind randomised trial of quinapril withdrawal in 224 patients with HF-REF (LVEF<35% and NYHA II-III) (Pflugfelder *et al*, 1993). Patients received a 10 week run-in of quinapril titrated to blood pressure. Following this, they were randomised to placebo or continuation of maximum tolerated therapy. Patients on placebo had a significant and gradual deterioration in exercise tolerance that began 4-6 weeks after randomisation. Moreover, 15.7% of those in the placebo arm were withdrawn from the study due to worsening HF, compared to 4.5% in the treatment arm.

More contemporary studies have attempted to examine the effects of therapy withdrawal in those with a previous diagnosis of non-ischaemic HF who have demonstrated at least partial reverse remodelling. The only prospective study investigated withdrawal of ACEI and beta-blockers in 20 patients with a previous diagnosis of chemotherapy-induced left ventricular dysfunction with improvement in LVEF to >50% (Fadol *et al*, 2016). Twelve patients completed 6-months of therapy withdrawal and none developed recurrent HF. Two patients had beta-blocker therapy re-introduced for self-reported palpitation and a further two had therapy re-established after slight reduction in LVEF (50% to 48% and 60% to 51%). Four patients dropped out for non-clinical reasons.

Two further retrospective studies have been performed in patients with previous diagnoses of peripartum cardiomyopathy and DCM who had demonstrated reverse remodelling on therapy (Amos *et al*, 2006; Moon *et al*, 2009). Amos and colleagues studied 22 patients with peripartum

cardiomyopathy and improvement in LVEF to >50% on therapy (Amos *et al*, 2006). Fifteen patients subsequently stopped ACEI or beta-blocker and 5 stopped both medications. Over a mean follow-up of 29 months, none of the patients exhibited deterioration in LVEF. Another group examined 42 patients with idiopathic DCM and partial reverse remodelling, defined as improvement in LVEF to >40% (Moon *et al*, 2009). Seven patients discontinued medications and 5 subsequently suffered deterioration in LVEF, at a median time of 32 months from medication withdrawal. Of note, the majority of patients who demonstrated a reduction in LVEF had mid-range LVEF (40-49%) and LV dilatation at the point of withdrawal. No information was provided on symptom or natriuretic peptide status at the time of therapy withdrawal.

Trials of diuretic withdrawal are also limited by relatively small numbers of patients, most of whom had ongoing evidence of HF and/or reduced LVEF (Braunschweig *et al*, 2002; Damman *et al*, 2011; Galve *et al*, 2005; Grinstead *et al*, 1994; Richardson *et al*, 1987; van Kraaij *et al*, 2003; Walma *et al*, 1997). In each study there was a high rate of diuretic re-introduction following the development of symptoms. Diuretic withdrawal was least successful in those with severely reduced LVEF or a recent episode of decompensation.

In conclusion, withdrawal of beta-blockers, ACEIs and diuretics is associated with adverse events in patients with ongoing evidence of HF and reduced LVEF. There is a limited amount of evidence on the withdrawal of these agents in well-characterised DCM patients with clinical, biochemical and imaging features of myocardial recovery. It appears likely that future management will rely on precise phenotyping and the discrimination of patients who demonstrate partial reverse remodelling, who may benefit from continued therapy and those with 'recovered' DCM, who may be able to discontinue therapy without deterioration. Prospective studies of therapy withdrawal in well-characterised patients with improvement in

LVEF, complete resolution of symptoms and absence of biochemical evidence of HF are required to further inform practice.

Withdrawal of Device Therapy

A growing area of interest is the management of patients who have demonstrated improvement in LVEF and require generator replacement following the implantation of an ICD for the primary prevention of SCD (Kramer *et al*, 2012). As discussed, there are substantial risks associated with ICDs, including the risk of inappropriate shocks and device infection (Poole *et al*, 2010; Poole *et al*, 2008). The benefits of downgrading defibrillator generators to simple pacing devices, removing the risks of inappropriate shocks and complications associated with defibrillator leads may outweigh the benefits of continued therapy in sub-groups. This is most relevant to patients who have a reduced risk of major ventricular arrhythmias as a result of improved cardiac function and have never received an appropriate device therapy. Indeed, 75-80% of patients with a primary prevention ICD are free of appropriate ICD therapies at the time of their first generator change (Kremers *et al*, 2013; Madhavan *et al*, 2016; Qiu *et al*, 2005). This is particularly relevant in patients with CRT devices who demonstrate positive remodelling following resynchronisation (Chatterjee *et al*, 2015; Manfredi *et al*, 2013; Ruwald *et al*, 2014). Several studies have reported a low incidence of appropriate therapies in patients with improved LVEF following the implantation of ICDs or CRT defibrillators (CRT-Ds) (Chatterjee *et al*, 2015; Manfredi *et al*, 2013; Ruwald *et al*, 2014). Unsurprisingly, this is most marked in those with a non-ischaemic aetiology and those who have the most complete recovery.

Ruwald and colleagues followed up 752 patients randomised to CRT as part of the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronisation (MADIT-CRT)

(Ruwald *et al*, 2014). Patients were divided into three groups based on LVEF at 12 months (<35%, 36-50%, >50%). Of the 55 patients with a LVEF>50%, over a median of 2.2 years, only 1 had a ventricular arrhythmia >200 beats per minute that was terminated by anti-tachycardia pacing. Importantly 7% of those with a LVEF>50% had an inappropriate shock.

A meta-analysis including 6 studies (n=1,740) investigating the incidence of appropriate device therapies following CRT-D implantation corroborated the results (Chatterjee *et al*, 2015). In patients with a LVEF >35% and LVEF >45% (for a mixture of primary and secondary prevention indications), the incidence of appropriate therapies was 5.4 and 2.3 per 100 person-years respectively. In those with a primary prevention indication and a LVEF >35%, the incidence dropped further to 0.4 per 100 person years. Given the doubt over the incremental benefit of CRT-D over CRT pacemakers (CRT-P) in DCM and the risks associated with defibrillators, these data raise the question of whether those most likely to recover should receive CRT-P at baseline.

Two groups have reported outcomes of patients undergoing generator replacement following implantation of ICDs for primary prevention indications (Kini *et al*, 2014; Madhavan *et al*, 2016). In those patients no longer meeting criteria, the rate of appropriate therapies was between 2.8 and 5% per year and significantly lower than those patients who continued to meet criteria. Schliamser and colleagues followed up patients in the DEFINITE trial (Schliamser *et al*, 2013). The authors classified patients based on the change in LVEF rather than the latest LVEF; therefore some patients classified as 'recovered' may still have significantly reduced LVEF. Out of the 96 patients with an improvement in LVEF >5%, 17.3% received appropriate shocks over a follow-up of around 2.5 years.

A small number of studies have investigated withdrawal of CRT in patients who had responded to initial therapy but still had reduced LVEF. Unsurprisingly withdrawal of CRT was

associated with fairly rapid deterioration in LVEF, a rise in left atrial volumes and the development of worsening HF (Knappe *et al*, 2013; Ypenburg *et al*, 2008; Yu *et al*, 2002).

Given the paucity of evidence and lack of consensus regarding the management of patients with improved cardiac function, we designed two studies to investigate the following specific hypotheses.

1.11 Hypotheses (Part 2) – Therapy Withdrawal in Recovered Dilated Cardiomyopathy

6. ***Patients with dilated cardiomyopathy and improved left ventricular ejection fraction will have fewer co-morbidities compared to those with dilated cardiomyopathy and reduced left ventricular ejection fraction.***

7. ***Patients with a previous diagnosis of dilated cardiomyopathy who have demonstrated improvement in left ventricular ejection fraction to >50% with normal indexed left ventricular end-diastolic volume will have:***

    a. ***Normal plasma concentration of NT-pro-BNP***

    b. ***Normal peak oxygen consumption on maximal treadmill exercise based on age and sex-specific normal ranges***

    c. ***Similar native T1 and global strain values on cardiovascular magnetic resonance compared to healthy volunteers***

    d. ***No evidence of late gadolinium enhancement on cardiovascular magnetic resonance***

8. ***Withdrawal of pharmacological therapy for heart failure is safe in asymptomatic patients with a previous diagnosis of dilated cardiomyopathy who now have (a) normal indexed left ventricular end-diastolic volume, (b) a left ventricular ejection fraction >50% and (c) a plasma NT-pro-BNP <250ng/L.***

9. ***(a) Changes in left ventricular size and left ventricular ejection fraction, (b) quality of life scores, (c) exercise capacity and (d) NT-pro-BNP levels will be similar in***

patients with recovered DCM undergoing therapy withdrawal compared to those who remain on therapy.

10. ***The following variables will be associated with the likelihood of relapse in patients with recovered DCM:***

    a. ***Late gadolinium enhancement***

    b. ***Native T1 values and extracellular volume fractions***

    c. ***Left atrial volumes as determined by cardiovascular magnetic resonance***

    d. ***Plasma concentration of NT-pro-BNP***

    e. ***Peak oxygen consumption on maximal treadmill exercise at baseline***

Chapter 2

2 Common Methods – (Part 1) - Outcomes in Dilated Cardiomyopathy

2.1 Dilated Cardiomyopathy Registry

Consecutive patients with suspected DCM referred to Royal Brompton Hospital for evaluation in the Cardiomyopathy Clinic or for CMR between January 2000 and December 2011 were screened. The inclusion criterion was a diagnosis of DCM which was confirmed by an independent clinician who had access to the CMR imaging and clinical history. The definition of DCM proposed by the European Society of Cardiology Working Group on Myocardial and Pericardial disease was used: '*Left ventricular or biventricular systolic dysfunction and dilatation that are not explained by abnormal loading conditions or coronary artery disease*'. Within this, it is recommended that systolic dysfunction is defined by abnormal ejection fraction (Pinto *et al*, 2016a). Reduced LVEF and elevated left ventricular end-diastolic volume indexed to body surface area (BSA) (LVEDVi) were defined by published age- and sex-specific reference values (Maceira *et al*, 2006a; Maceira *et al*, 2006b). Patients entered into the registry provided informed consent and the study was approved by the National Research Ethics Committee (07/H0708/83 & 09/H0504/104).

2.1.1 Exclusion Criteria

Patients with significant CAD were excluded. This was defined as a stenosis of >50% in a major coronary artery coronary on angiography, evidence of inducible myocardial ischaemia on nuclear, CMR or echocardiography stress imaging or patterns of LGE on CMR characteristic of previous myocardial infarction. Patients with clinical or CMR evidence of acute myocarditis, as defined by International Consensus Criteria were also excluded (Friedrich *et al*, 2009). In addition, those with hypertensive heart disease, primary valvular disease, arrhythmogenic right ventricular cardiomyopathy (ARVC), athletic remodelling, hypertrophic cardiomyopathy, left ventricular non-compaction, congenital heart disease, myocardial iron

overload, infiltrative disease such as cardiac sarcoidosis or amyloidosis and vasculitis were also excluded. Athletic remodelling was defined as LV dilatation with reduced LVEF and high LV stroke volume, in the context of regular high-intensity athletic activity. Primary valvular heart disease was defined as moderate or severe valve stenosis or regurgitation with the exception of functional mitral regurgitation. This was defined as mitral regurgitation secondary to mal-coaptation of the valve leaflets because of LV remodelling with otherwise normal valve structure. ARVC was defined using Modified Task Force Criteria (Marcus *et al*, 2010).

2.2 Cardiovascular Magnetic Resonance Protocol

CMR was performed using a standardised protocol on 1.5 Tesla scanners (*Sonata/Avanto, Siemens, Erlangen, Germany*). Localiser images were acquired in transaxial, coronal and sagittal planes with half-Fourier acquisition single short turbo spin echo (HASTE) imaging (*Figure 2.1*A). Following this, cine images were taken using breath-hold steady-state free precession (SSFP) imaging. Using the localiser images as landmarks, an image in the vertical long-axis plane was acquired (*Figure 2.1*B). Following this, a short-axis scout image, perpendicular to the vertical long-axis image, at the level of the left ventricular outflow tract was acquired (*Figure 2.1*C). Two, three and four-chamber cine images were taken using the short-axis scout and vertical long-axis image as landmarks (*Figure 2.1*D). Contiguous 10 millimetre short-axis cine images extending from the mitral valve annulus to the apex were then acquired (*Figure 2.1*E). Retrospective gating was used unless the R-R interval was markedly variable due to arrhythmia, in which case prospective triggering was used. LGE imaging was performed 10 minutes after the intravenous injection of gadopentate dimeglumine or gadobutrol (*Bayer*) at a dose of 0.1mmol/kg. Images were acquired using an inversion-recovery gradient echo sequence in identical two-, three- and four-chamber long-axis planes

and consecutive short axis slices (8mm thickness, 2mm gap). This was repeated in the opposite phase-encoding direction. Inversion times were selected to null the myocardium.

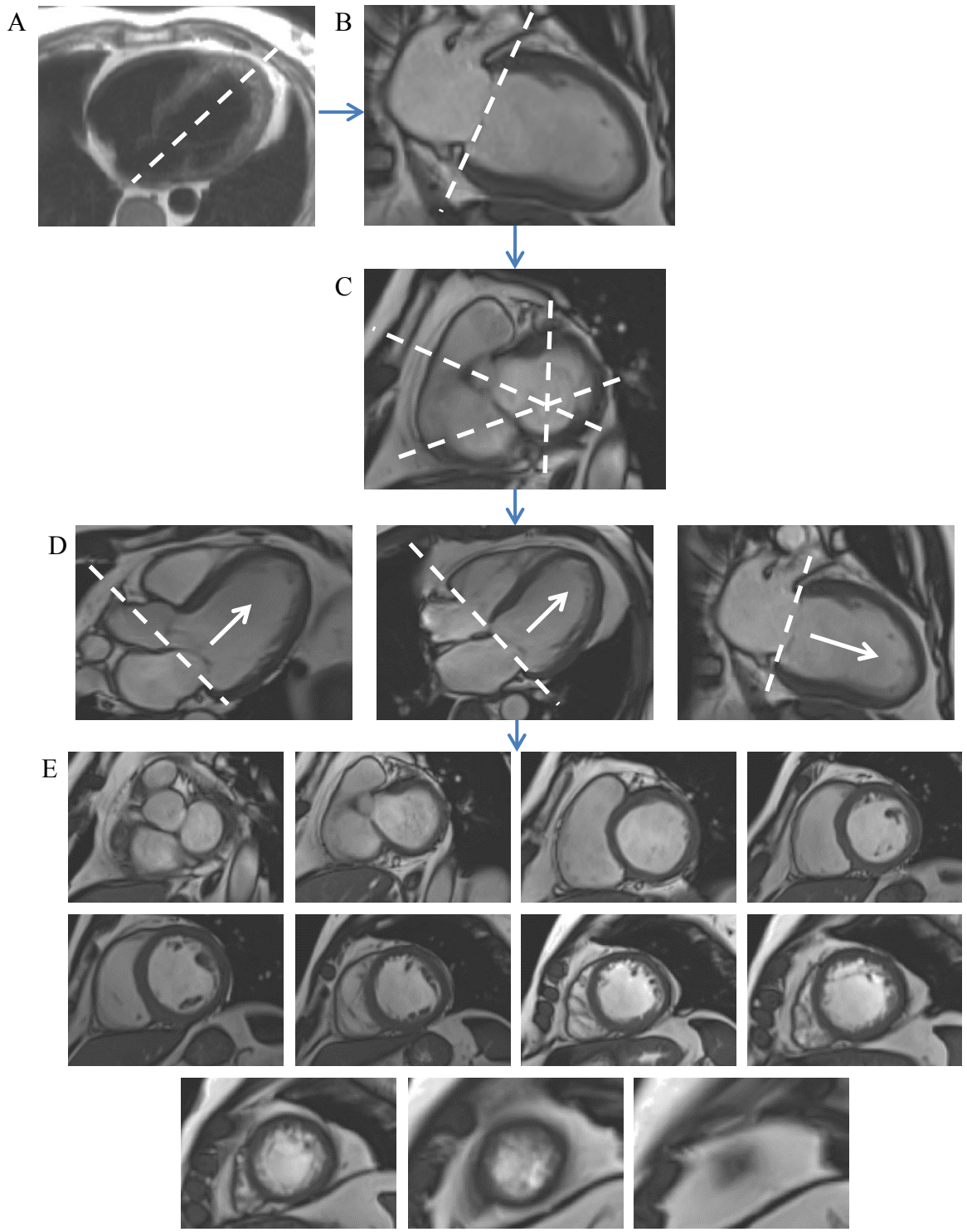

Figure 2.1. Acquisition of cine images for volumetric analysis.

2.3 Image Analysis

Volumetric chamber analysis was performed by independent operators who were blinded to patient outcomes, as illustrated in *Figure 1.5*, using CMR Tools (*Cardiovascular Imaging Solutions, London).* For the left ventricle, endocardial and epicardial contours were traced in end-systole and end-diastole for each short-axis slice. For the right ventricle, the endocardial contours were delineated in end-systole and end-diastole for each short-axis slice. Exclusion of the papillary muscles and trabeculae was performed using a semi-automated threshold technique. Valve planes were identified throughout each phase of the cardiac cycle in order to exclude atrial and arterial blood from the ventricular analyses. From the final models, ventricular end-diastolic and end-systolic volumes were estimated, enabling calculation of stroke volume (SV; SV = end-diastolic volume [EDV] – end systolic volume) and ejection fraction (EF; EF = LVSV/LVEDV x 100). LV myocardial mass was estimated by calculating the estimated myocardial volume from each short-axis slice and multiplying the total volume by the estimated density of myocardial tissue (1.05g/ml).

The LA area on 2-chamber and 4-chamber images was calculated by tracing the endocardial border of the left atrium in end-systole, immediately before mitral valve opening. The LA appendage and the pulmonary veins were excluded from the planimetred area. The distance from the centre of the mitral valve leaflet to the back of the left atrium was then calculated to estimate the LA length.LA volumes were then calculated from these measurements using the biplane area-length method [LA volume = 8 x (LA area from 2 chamber) x (LA area from 4 chamber) / (3π LA length)] (Lang *et al*, 2005).

The presence of LGE was determined by two independent senior operators who were blinded to patient outcomes. A third operator provided the final decision in cases of disagreement. LGE was judged to be present if seen in two orthogonal planes and in two-phase encoding directions. LGE localised only to the ventricular insertion areas was considered a normal variant and was not included. A further senior operator, blinded to patient outcomes, determined the location and pattern of LGE. The location of LGE was categorised as septal, free-wall (anterior, anterolateral, inferolateral or inferior wall) or as occurring in both locations concomitantly. The pattern of LGE was classified as linear mid-wall, sub-epicardial, focal or multiple patterns.

The quantity of LGE was calculated by two independent operators on semi-automated software (*Circle Cardiovascular Imaging, Calgary, Canada*) using the full-width at half maximum technique. This technique involves defining an area of maximally enhanced myocardium. The software then defines all areas of myocardium with a signal intensity above 50% of the reference area as enhanced and estimates the mass of this enhanced myocardium (in grams) (*Figure 2.2*).

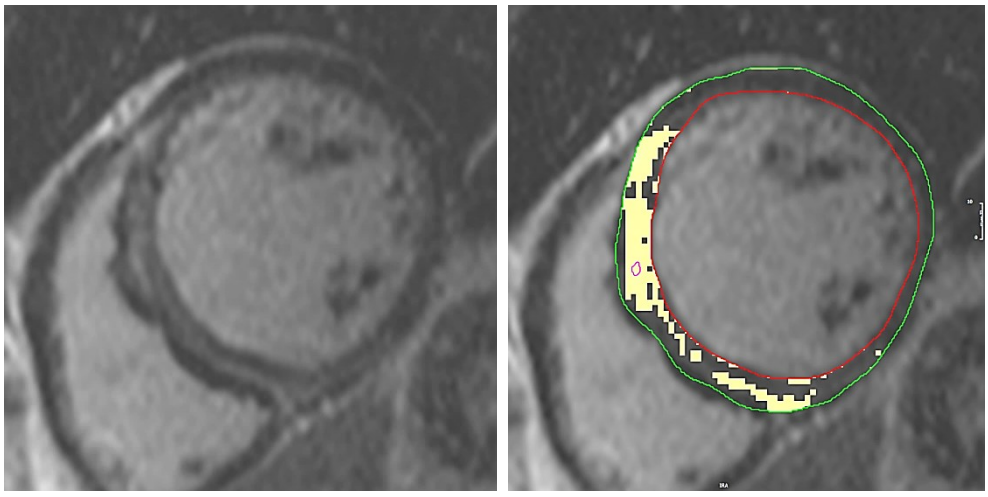

Figure 2.2. Late gadolinium enhancement quantification
A mid-ventricular, short-axis, late gadolinium enhancement image with enhancement quantification using the full width at half maximum method (Circle Cardiovascular Imaging, Calgary, Canada).

2.4 Patient Follow-up & Outcome Events

Patients were followed up from the date of their baseline CMR scan. Patients were sent postal questionnaires to gather information about current symptom status and the occurrence of key outcome events such as unplanned hospitalisations, medical or surgical procedures or device therapies. If the patient did not respond to two consecutive questionnaires, a telephone interview was attempted. In addition, summary care records, clinic letters, hospital discharge summaries and cardiac investigation reports were gathered from the patients' general practitioners and cardiologists. When necessary, hospital records and device electrograms were collected to confirm the occurrence of outcome events. Deaths were also identified using the United Kingdom Health and Social Care Information Service, to ensure none were missed.

Follow-up duration was calculated from the date of the baseline CMR scan until the occurrence of an event or last patient contact. An adjudication committee of at least 3 independent cardiologists, who were blinded to all CMR data, was assembled at the end of follow-up. The committee established the cause of death from medical records, death certificates and when available, post-mortem reports. All other outcome events including unplanned CV hospitalisations, appropriate ICD therapies and documented new-onset sustained arrhythmias were also confirmed by the committee.

End-points included all-cause mortality, CV death, SCD, non-sudden death, a composite of SCD and aborted SCD and a composite including HF death, unplanned HF hospitalisation and cardiac transplantation. Definitions for events, including cause of death were taken from published guidance (Buxton *et al*, 2006; Greenberg *et al*, 2004; Hicks *et al*, 2015). CV death included those secondary to HF, SCD, thromboembolism or cerebrovascular events. HF death was defined as one preceded by progressive deterioration in signs and symptoms in HF. SCD

was defined '*as unexpected death either within 1 hour of the onset of cardiac symptoms in the absence of progressive cardiac deterioration; during sleep; or within 24 hours of last being seen alive' (Hicks et al, 2015)*. Aborted SCD included appropriate ICD shocks for episodes of ventricular arrhythmia, sustained VT resulting in haemodynamic instability and requiring cardioversion and successful resuscitation from cardiac arrest resulting from VT or VF (Buxton *et al*, 2006). Episodes of sustained VT without haemodynamic compromise and those terminated with appropriate anti-tachycardia pacing from implanted devices were not included in this end-point, given the potential that these episodes were not life threatening and may have terminated spontaneously without treatment.

2.5 Derivation of the Registry

Derivation of the final registry is illustrated in *Figure 2.3*. Of 1352 patients screened, 171 were excluded due to alternative diagnoses, most commonly significant CAD. A further 249 patients were excluded due to failure to meet diagnostic criteria on the basis of a normal LVEF or LVEDVi. A further 42 did not provide informed consent and 9 moved abroad.

Overall 881 patients were included in the final cohort. In addition to LGE-CMR, which is accurate in the diagnosis of the aetiology of LV dysfunction (Assomull *et al*, 2011), 691 patients underwent coronary angiography to exclude CAD. An additional 63 underwent stress imaging without evidence of inducible ischaemia. Of the remaining 129 patients, none had angina, all were considered to have a low-risk of CAD by their cardiologist and the majority (n=82) were under 40 years of age. None of these patients suffered an acute coronary syndrome or underwent coronary revascularisation during follow-up.

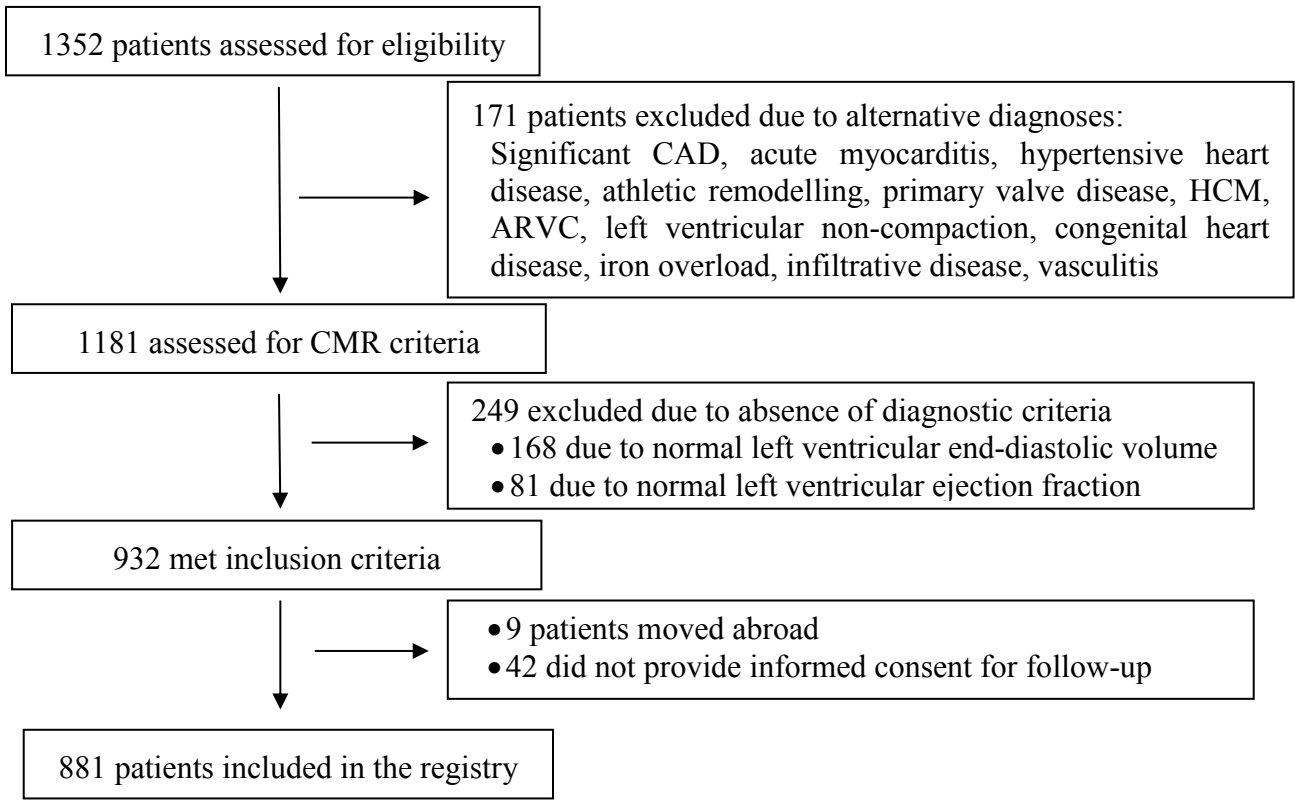

Figure 2.3. Derivation of the cohort for outcome analyses.

2.6 Outcome Analysis

The specific statistical analyses performed are described in detail within chapters. In brief, baseline characteristics are presented as mean with standard deviation for continuous variables and integers with percentages for categorical variables. Continuous variables were compared between two groups using the Mann-Whitney test and between multiple groups using the Kruskal-Wallis Rank test. Categorical data were compared between groups using the Fisher's Exact test. To examine survival, Kaplan-Meier curves were generated and compared using the log-rank test. Proportional hazard modelling was used to investigate the association between end-points and variables of interest. Results are presented as HR with 95% CI. A p value of <0.05 was taken as significant. Analyses were performed using SPSS (Version 24, SPSS, Chicago, USA) and Stata (Version 14, StatCorp, College Station, USA).

Chapter 3

3 Prediction of Sudden Cardiac Death for Patients with Dilated Cardiomyopathy and Mild and Moderate Left Ventricular Systolic Dysfunction

This chapter includes the following work published under a Creative Commons Attribution License (Appendix):

Halliday BP, Gulati A, Ali A et al. Association between mid-wall late gadolinium enhancement and sudden cardiac death in patients with dilated cardiomyopathy and mild and moderate left ventricular systolic dysfunction. Circulation 2017;135:2106-2115.

3.1 Hypothesis

1. ***The presence of non-ischaemic late gadolinium enhancement identifies patients with dilated cardiomyopathy and a left ventricular ejection fraction >40% at high-risk of sudden cardiac death events***

3.2 Abstract

Background: Current guidelines only recommend the use of an ICD in patients with DCM for the primary prevention of SCD in those with a LVEF<35%. However, registries of out-of-hospital cardiac arrests demonstrate that 70-80% of such patients have a LVEF>35%. Patients with a LVEF>35% also have low competing risks of death from non-sudden causes. Therefore, those at high-risk of SCD may gain longevity from successful ICD therapy.

Methods: We investigated the association between mid-wall LGE and the primary composite outcome of SCD or aborted SCD amongst referrals with DCM and a LVEF≥40% to our center between January 2000 and December 2011, who did not have a pre-existing indication for ICD implantation.

Results: Of 399 patients (145 women, median age 50 years, median LVEF 50%, 25.3% with LGE) followed for a median of 4.6 years, 18 of 101 (17.8%) patients with LGE reached the pre-specified end-point, compared to 7 of 298 (2.3%) without (HR 9.2; 95% CI 3.9-21.8; p<0.0001). Nine patients (8.9%) with LGE compared to 6 (2.0%) without (HR 4.9; 95% CI 1.8-13.5; p=0.002) died suddenly, whilst 10 patients (9.9%) with LGE compared to 1 patient (0.3%) without (HR 34.8; 95% CI 4.6-266.6; p<0.001) had aborted SCD. Following adjustment, LGE predicted the composite end-point (HR 9.3; 95% CI 3.9-22.3; p<0.0001), SCD (HR 4.8; 95% CI 1.7-13.8; p=0.003) and aborted SCD (HR 35.9; 95% CI 4.8-271.4; p<0.001). Estimated HRs for the primary end-point for patients with a LGE extent of 0-2.5%, 2.5-5% and >5% compared to those without LGE were 10.6 (95%CI 3.9-29.4), 4.9 (95% CI 1.3-18.9) and 11.8 (95% CI 4.3-32.3) respectively.

Conclusions: Mid-wall LGE identifies a group of patients with DCM and LVEF≥40% at increased risk of SCD and low-risk of non-sudden death who may benefit from ICD implantation.

3.3 Background

Guidelines only recommend the use of ICDs in patients with DCM for the primary prevention of SCD in those with a LVEF <35% (Ponikowski *et al*, 2016; Priori *et al*, 2015; Russo *et al*, 2013; Yancy *et al*, 2013). However, registries of out-of-hospital cardiac arrests demonstrate that 70-80% of such patients have a LVEF >35% indicating that, in fact, the major burden of SCD occurs in patients with less severe degrees of LV impairment (Gorgels *et al*, 2003; Stecker *et al*, 2006). The need to identify the sub-group of patients with mild and moderate reductions in LVEF at high risk of SCD has been highlighted by guidelines and statements from the American Heart Association, American College of Cardiology, European Society of Cardiology and Heart Rhythm Societies (Fishman *et al*, 2010; Goldberger *et al*, 2008; Priori *et al*, 2015; Zipes *et al*, 2006). Importantly, such patients are likely to have a lower risk of death from competing causes and fewer symptoms compared to patients with lower LVEF and may potentially have more to gain in terms of quality-adjusted life years from successful ICD therapy. This is particularly pertinent following the DANISH trial, which highlighted the importance of selecting patients with a low risk of death from other causes (Kober *et al*, 2016).

LGE-CMR has shown that approximately 30% of patients with DCM have mid-wall LGE which represents replacement fibrosis and that this provides incremental prognostic information to LVEF (Assomull *et al*, 2006; Disertori *et al*, 2016; Gao *et al*, 2012; Gulati *et al*, 2013c; Klem *et al*, 2012; Kuruvilla *et al*, 2014; Lehrke *et al*, 2011; Muller *et al*, 2013; Neilan *et al*, 2013). Whether mid-wall LGE also identifies a high-risk of SCD in patients with DCM and less severe reductions in LVEF, who might consequently benefit from an ICD, is unknown (Bilchick, 2016). Accordingly, we investigated whether mid-wall LGE is associated with SCD and aborted SCD in a large cohort of patients with DCM and LVEF≥40%. A LVEF cut-off of ≥40% on CMR was chosen as this approximates to an LVEF of 35% on echocardiography, the

current arbiter of primary prevention ICD implantation (Hoffmann *et al*, 2005; Malm *et al*, 2004; Ponikowski *et al*, 2016; Priori *et al*, 2015; Russo *et al*, 2013).

3.4 Methods

3.4.1 Patient Cohort

Patients with suspected DCM and a LVEF ≥40% referred to our centre for CMR or evaluation in the Cardiomyopathy Clinic between January 2000 and December 2011 were screened. Of 424 patients who met the inclusion criteria, 6 moved abroad and 19 did not provide informed consent. The final analysis included 399 patients.

Details of the inclusion and exclusion criteria have been described in Section 2.1**.** In addition, for the purpose of this study, patients with a history of sustained VT, VF or syncope were excluded given a potential pre-existing secondary prevention indication for ICD implantation. No patients had a pre-existing indication for ICD implantation on the basis of primary prevention of SCD, given the inclusion criterion based on LVEF.

In line with guidelines, an ischaemic aetiology was considered in all patients and excluded as follows (Ponikowski *et al*, 2016). All patients underwent LGE-CMR and those with infarct-patterns of enhancement were excluded (Assomull *et al*, 2011). In addition, of the final 399 patients, 268 (67.1%) patients underwent invasive or computed tomography coronary angiography and a further 41 (10.3%) had perfusion imaging (nuclear or CMR) or stress echocardiography with no provocation of ischaemia. Of the remaining, 60 (15.0%) were ≤40 years of age without a history of angina or a family history of premature CAD and further investigation was deemed unnecessary. All of the remaining 30 (7.5%) patients were free of

angina and considered to have a low risk of CAD and in the absence of a class 1 indication, this was not performed. Importantly, none of the patients underwent coronary revascularisation or suffered an acute coronary syndrome during the follow-up period.

3.4.2 CMR Protocol & Image Analysis

All patients underwent CMR using the standardised protocol detailed in Section 2.2**.** Volumetric analysis (Section 2.3**)** was performed by independent operators blinded to outcomes. The presence of mid-wall LGE was assessed by two independent expert operators blinded to outcomes, with a third providing adjudication if necessary. LGE was considered present if mid-myocardial or sub-epicardial and visible in two phase-encoding directions and two orthogonal planes. The mass of LGE (grams) was quantified by a blinded operator using the full-width at half-maximum technique (*CMR42, Circle Cardiovascular Imaging Inc, Calgary, Canada*) and indexed as a percentage of LV mass.

3.4.3 End-points

The *primary end-point* was a composite of SCD or aborted SCD. A committee of cardiologists blinded to CMR data adjudicated all outcome events including the cause of death, in line with guidance (Buxton *et al*, 2006; Hicks *et al*, 2015). SCD was defined as unexpected death either within 1 hour of the onset of cardiac symptoms in the absence of progressive cardiac deterioration; during sleep; or within 24 hours of last being seen alive (Hicks *et al*, 2015). Aborted SCD was defined as an appropriate ICD shock for ventricular arrhythmia, successful resuscitation following VF or sustained VT causing haemodynamic compromise and requiring cardioversion (Buxton *et al*, 2006). Aborted SCD was confirmed from records including ICD electrograms when necessary. The principal secondary end-point was all-cause mortality.

Additional secondary end-points were: (i) a composite of CV mortality (SCD, HF, stroke or thromboembolism), CV hospitalisation or cardiac transplantation; and (ii) a HF composite of HF death, unplanned HF hospitalisation or cardiac transplantation. Death was attributed to HF if preceded by deterioration in symptoms and signs. HF hospitalisation was defined as an admission with new or worsening signs and symptoms of HF requiring intensification of HF-specific treatment (Hicks *et al*, 2015).

3.4.4 Patient Follow-up

Patients were followed-up as detailed in Section 2.4. The duration of follow-up was calculated from the baseline scan until an end-point occurred or last patient contact. Specifically, for the primary end-point, any patients meeting the pre-specified criteria for an event were censored from that date.

3.4.5 Statistical Analysis

Patients were dichotomised based on the presence or absence of LGE and baseline characteristics between the groups were compared using the Mann-Whitney test for continuous data and Fisher's exact test for categorical data. Survival times were calculated from the time of the baseline scan for a maximum of 8 years and compared for those with and without LGE using the log-rank test. Events after 8 years were not included due to the small number of patients remaining at this time point. Kaplan Meier curves were generated.

The associations between the end-points and the presence of LGE were examined using proportional hazard modelling. Multivariable models were adjusted for LVEF, NYHA class and age. In addition, a propensity score was constructed to model the likelihood of an individual having LGE based on 13 baseline co-variates. A model was then adjusted using inverse-

probability weighting by the propensity score, to examine whether the results were sensitive to the choice of variables used in the model. The following co-variates were used in the propensity score: LVEF, age, sex, left atrial volume indexed to BSA (LAVi), LVEDVi, RVEF, NYHA class, heart rate, prescription of ACEI and beta-blocker, diabetes mellitus, presenting indication and the implantation of ICD or CRT as a time-varying covariate.

To establish the relationship between LGE extent and outcome, patients with LGE were divided into 3 groups depending on the mass of LGE: 1) 0-2.5% of overall mass, 2) 2.5-5% and 3) >5%. The cut-offs were chosen to produce 3 approximately equal-sized groups. The association with the primary end-point was examined within each group and amongst those without LGE using univariable proportional hazard models. Given the non-linear relationship between LGE extent and outcome, the estimated risk of the primary end-point per percentage increase in LGE extent was not reported. The LGE extent with the greatest c-statistic for the prediction of the primary end-point was estimated from 1000 bootstrap samples. The c-statistic measures the ability of a model to discriminate between cases and controls, producing values from 0.5 to 1.0, with larger values establishing better discrimination.

In addition, the 5-year predicted risk of the primary end-point was estimated using a proportional hazard model, which included 5 categories of LVEF (40-43%, 44-47%, 48-51%, 52-55% and 56-59%) and the presence or absence of LGE.

Results are presented as HRs with 95% CIs. A p value of <0.05 was taken as significant. The cohort was estimated to have >90% power to detect a difference in the incidence of SCD and aborted SCD if the HR between those with and without LGE was at least 3.

3.5 Results

3.5.1 Baseline Characteristics

Of 399 patients, 145 were women, the median LVEF was 50% (IQR:46-54%) and mid-wall LGE was present in 25.3%. There was disagreement on the presence of LGE in 8 cases, requiring adjudication by a third reviewer. Median follow-up until an event or last contact was 4.6 years (IQR: 3.5 – 7.0) years.

Baseline characteristics are presented in *Table 3.1*. Patients with mid-wall LGE were older (mean 53.0 vs 48.9 years; p=0.03), more likely to be men (78.2% vs 58.7%; p<0.001), to have diabetes mellitus (11.9% vs 4.4%; p=0.015), and to receive loop diuretics (32.7% vs 19.5%; p=0.009). They also had lower heart rates (mean 67.3bpm vs 70.7bpm; p=0.02) and diastolic blood pressure (mean 71.0 mmHg vs 73.5mmHg; p=0.02).

The most common clinical presentation was with signs or symptoms of HF (n= 176; 44.1%). An additional 69 (17.2%) patients presented with symptoms of palpitation secondary to atrial arrhythmia or ventricular ectopy, 7 (1.8%) with symptoms of light-headedness or pre-syncope and 3 (0.8%) with 1st degree AV block or a blunted chronotropic response. A further 39 (9.8%) patients were diagnosed following referral for family screening. Common indications classified as 'Other' included diagnostic uncertainty or an abnormal electrocardiogram such as the finding of LBBB. There was no difference in presenting indication between those patients with LGE compared to those without.

		Midwall LGE		
	All Patients (n=399)	**No (n=298)**	**Yes (n=101)**	**p**
Mean Age (SD), yrs	49.9 (15.3)	48.9 (15.5)	53.0 (14.2)	0.030
Men, n (%)	254 (63.7)	175 (58.7)	79 (78.2)	<0.001
Body surface area, m^2	1.96 (0.24)	1.95 (0.24)	1.98 (0.22)	0.11
Heart rate, bpm	69.8 (13.0)	70.7 (13.3)	67.3 (11.8)	0.020
Systolic blood pressure, mmHg	122.7 (16.3)	123.4 (16.5)	120.8 (15.5)	0.22
Diastolic blood pressure, mmHg	72.9 (9.9)	73.5 (9.8)	71.0 (10.2)	0.018
Atrial Fibrillation / Flutter, n (%)	64 (16.0)	49 (16.4)	15 (14.9)	0.76
Hypertension, n (%)	81 (20.3)	56 (18.8)	25 (24.8)	0.20
Diabetes mellitus, n (%)	25 (6.3)	13 (4.4)	12 (11.9)	0.015
Moderate Alcohol Excess n (%)	33 (8.3)	25 (8.4)	8 (7.9)	1.00
Family History of DCM, n (%)	51 (12.8)	35 (11.7)	16 (15.8)	0.30
Family History of SCD, n (%)	36 (9.0)	26 (8.7)	10 (9.9)	0.69
Left bundle branch block, n (%)	103 (25.8)	81 (27.2)	22 (21.8)	0.36
Medications				
Beta-blocker, n (%)	259 (64.9)	187 (62.8)	72 (71.3)	0.15
ACE Inhibitor, n (%)	268 (67.2)	193 (64.8)	75 (74.3)	0.087
ARB, n (%)	80 (20.1)	61 (20.5)	19 (18.8)	0.78
Loop Diuretic, n (%)	91 (22.8)	58 (19.5)	33 (32.7)	0.009
MRA, n (%)	78 (19.6)	58 (19.5)	20 (19.8)	1.00
Scan indication				
HF, n (%)	176 (44.1)	132 (44.3)	44 (43.6)	0.50
Palpitation or presyncope, n (%)	79 (19.8)	54 (18.1)	25 (24.8)	
Family Screening, n (%)	39 (9.8)	30 (10.1)	9 (8.9)	
Other, n (%)	105 (26.3)	82 (27.5)	23 (22.8)	
NYHA				
I, n (%)	228 (57.3)	170 (57.2)	58 (57.4)	0.36
II, n (%)	144 (36.2)	110 (37.0)	34 (33.7)	
III, n (%)	25 (6.3)	17 (5.7)	8 (7.9)	
IV, n (%)	1 (0.3)	0 (0.0)	1 (1.0)	
CMR parameters				
LVEDVi, ml/m^2	111.1 (19.4)	110.0 (18.2)	114.2 (22.4)	0.16
LVEF (%)	49.6 (4.9)	49.9 (4.9)	49.0 (4.9)	0.11
LV Mass Index (g/m^2)	86.0 (22.5)	85.0 (24.0)	89.0 (17.2)	0.007
RVEDVi, ml/m^2	88.6 (20.3)	87.7 (20.1)	91.0 (20.8)	0.15
RVEF (%)	57.4 (9.4)	57.8 (9.2)	56.1 (9.7)	0.15
LAVi, ml/m^2	58.3 (22.6)	57.3 (22.3)	61.1 (23.4)	0.079

Table 3.1. Baseline characteristics of the cohort.

Mann-Whitney Test used to compare continuous data; Fisher's Exact for categorical data.

3.5.2 Primary End-Point

During follow-up, 18 of 101 patients (17.8%) with LGE reached the primary end-point compared to 7 of 299 patients (2.3%) without (HR 9.2; 95% CI 3.9-21.8; P<0.0001) (*Figure 3.1* & *Figure 3.2.* Diagram indicating the occurrence of events by patient groups.*Figure 3.2*).

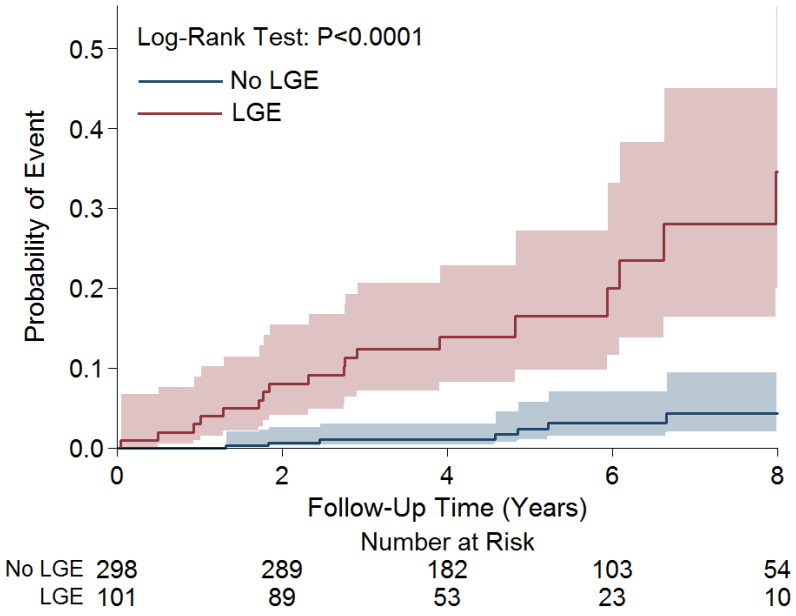

Figure 3.1. Kaplan-Meier curve for the primary end-point.
Kaplan-Meier curve of the time to first event for the primary end-point by presence (red-line) or absence (blue line) of mid-wall LGE.

After adjusting for LVEF, NYHA class and age, the presence of LGE predicted SCD and aborted SCD (HR 9.3; 95%CI 3.9-22.2; p<0.0001) (*Table 3.2)*. Overall, 9 of 101 patients (8.9%) with LGE and 6 of 299 (2.0%) without died suddenly (HR 4.9; 95% CI 1.8-13.5; p=0.002). Correspondingly, 10 of 101 patients (9.9%) with LGE compared to 1 out of 299 patients (0.3%) without (HR 34.8; 95% CI 4.6-266.6; p<0.0001) suffered aborted SCD. One patient with LGE had an aborted SCD and later suffered SCD. After adjusting for LVEF, NYHA class and age, the presence of LGE predicted SCD (HR 4.8; 95% CI 1.7-13.8; p=0.003) and aborted SCD (HR 35.9; 95% CI 4.8-271.4; p<0.001) when analysed individually (*Table 3.2)*.

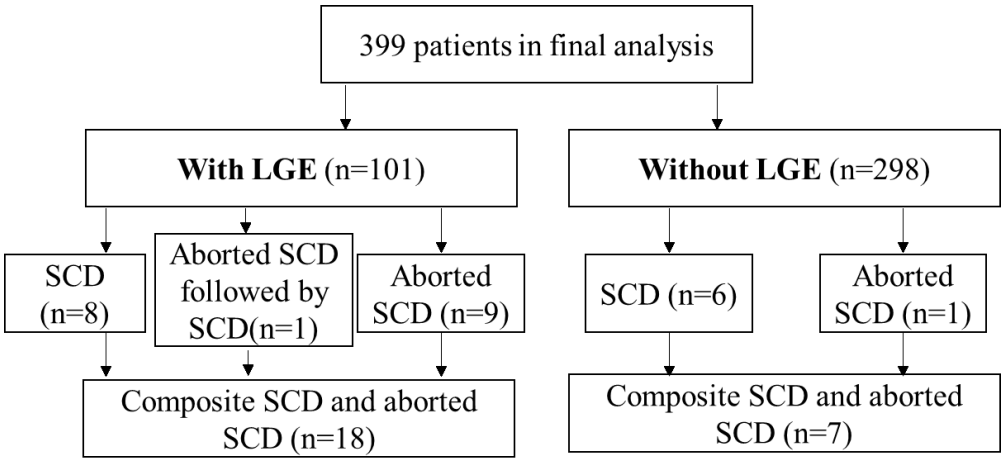

Figure 3.2. Diagram indicating the occurrence of events by patient groups.

Outcome	LGE status	Events n (%)	Univariable		Multivariable*	
			HR (95% CI)	P Value	HR (95% CI)	P Value
SCD or Aborted SCD	LGE -	7 (2.3)	9.2 (3.9, 21.8)	<0.0001	9.3 (3.9, 22.3)	<0.0001
	LGE +	18 (17.8)				
SCD	LGE -	6 (2.0)	4.9 (1.8, 13.5)	0.002	4.8 (1.7, 13.8)	0.003
	LGE +	9 (8.9)				
Aborted SCD	LGE -	1 (0.3)	34.8 (4.6, 266.6)	<0.0001	35.9 (4.8, 271.4)	<0.001
	LGE +	10 (9.9)				

Table 3.2. Proportional hazard modelling for the primary end-point.

*Adjusted for LVEF, NYHA class and age

The results were qualitatively the same following adjustment based on the propensity score (*Table 3.3*). Details of the propensity score model are included in the Appendix.

Outcome	LGE Status	Events n (%)	IPW Estimate*	
			HR (95% CI)	P Value
SCD or Aborted SCD	LGE -	7 (2.3)	8.0 (3.3, 19.5)	<0.0001
	LGE +	18 (17.8)		
SCD	LGE-	6 (2.0)	4.6 (1.6, 13.1)	0.005
	LGE+	9 (8.9)		
Aborted SCD	LGE-	1 (0.3)	32.9 (4.3, 249.9)	<0.001
	LGE+	10 (9.9)		

Table 3.3. Inverse probability weighting analyses for the primary end-point.

*Adjusted using a propensity score

There was little evidence of a dose-response relationship between LGE extent and the primary end-point. Estimated HRs for patients with a LGE extent of 0-2.5%, 2.5-5% and>5% were 10.6 (95%CI 3.9-29.4), 4.9 (95% CI 1.3-18.9) and 11.8 (95% CI 4.3-32.3) respectively. In keeping with this relationship, the cut-off percentage extent of LGE that provided the largest c-statistic was >0% (95% CI: 0.0-8.5; c-statistic: 0.72).

The predicted 5-year risk of the primary end-point using a model including both LGE and LVEF was markedly different to a model using LVEF alone (*Figure 3.3*). For example, a patient with a LVEF of 45% had a 5-year predicted risk of 7.8% on the basis of LVEF alone, which fell to 3.2% in the absence of LGE but increased to 20.2% if LGE was present.

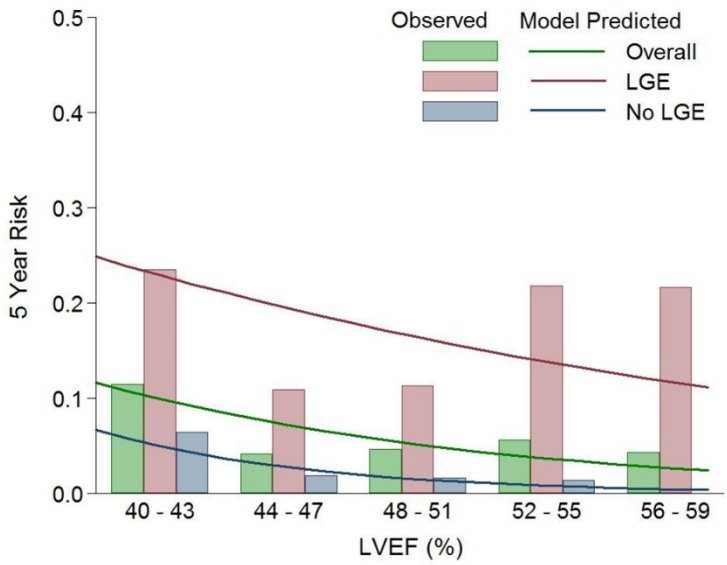

Figure 3.3. 5-year risk estimates for the primary end-point.
5-year risk estimates for the primary end-point based on LVEF alone (green line) and mid-wall LGE status in addition to LVEF (red line – presence of LGE, blue line – absence of LGE)

ICD Implantation during Follow-up

During follow-up, 32 patients (9.0%) had an ICD implanted before the occurrence of the primary end-point, 17 of whom also received CRT. Eighteen patients received ICDs in line with primary prevention guideline recommendations following deterioration in LVEF from baseline, 2 following new episodes of sustained VT without haemodynamic compromise and 12 outside of conventional guideline recommendations following review at multidisciplinary meetings (Ponikowski *et al*, 2016; Priori *et al*, 2015; Russo *et al*, 2013; Yancy *et al*, 2013). Out of the latter 12 patients, one had a pathogenic Lamin A/C mutation, two had a pacing indication with non-sustained VT (NSVT), three had NSVT and a family history of SCD, four had a history of NSVT alone and two presented with worsening HF and LBBB and had CRT with a defibrillator. Of 32 patients who received an ICD system, four patients (23.5%) with and none without LGE had aborted sudden deaths. Of 367 patients without an ICD system, 9 patients (10.7%) with and 6 patients (2.1%) without LGE died suddenly.

3.5.3 Secondary End-points

All-Cause Mortality

During follow-up, there were 32 deaths, of which 19 were CV and 13 were not (cancer, end-stage lung-disease, sepsis and acute small bowel obstruction). The overall mortality rate was higher in patients with LGE (12.9% vs 6.4%; HR 2.3; 95% CI 1.1-4.6; p=0.02) (*Figure 3.4)*. Following adjustment for LVEF, NYHA class and age, a trend towards higher mortality in those patients with LGE was noted, however this did not reach statistical significance (HR 2.0; 95%CI 1.0-4.1; p=0.056).

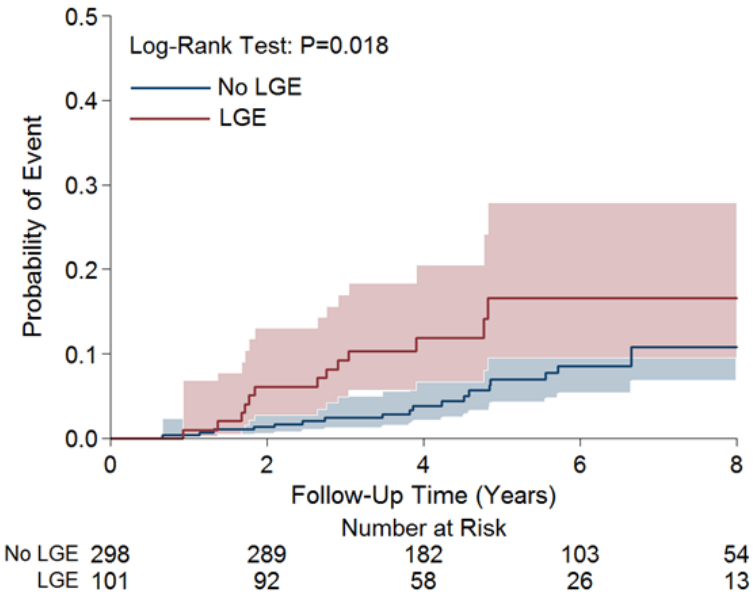

Figure 3.4. Kaplan-Meier curves for all-cause mortality.
Curves demonstrate time to first event by presence (red-line) or absence (blue line) of LGE. Survival compared using Log-rank test.

Cardiovascular Death, Hospitalisation and Transplantation

There were 19 CV deaths (including 15 SCDs and 3 HF deaths) and 42 unplanned CV hospitalisations. Two patients underwent cardiac transplantation, one of whom had full histopathological examination of the explanted heart. The gross and microscopic examinations correlated with LGE-CMR images (*Figure 3.5Figure 3.5*).

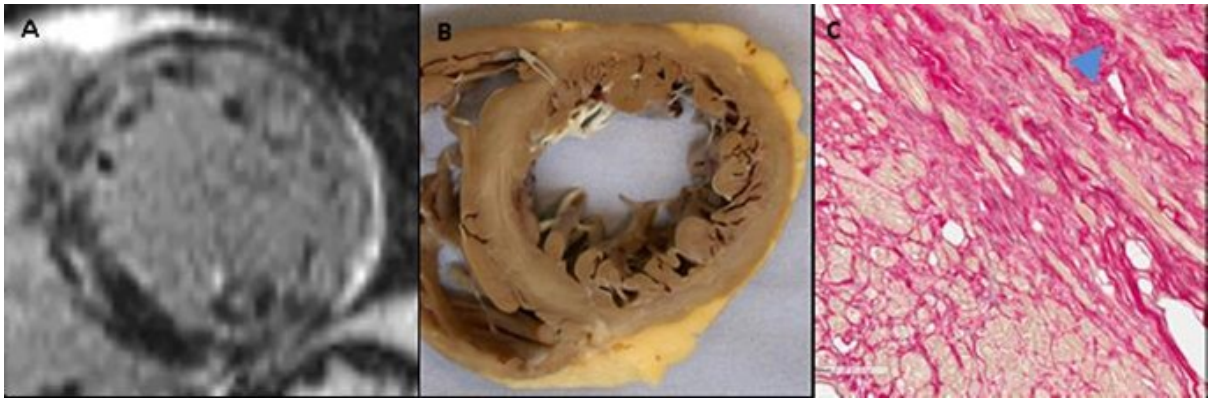

Figure 3.5. Correlation between LGE images and gross and microscopic histopathology. *A:* Pre-transplant LGE-CMR demonstrating extensive mid-wall and sub-epicardial LGE, including the septum at mid-ventricular level. *B:* Post-transplant gross examination of a short-axis slice at mid-ventricular level confirming extensive mid-wall replacement fibrosis. *C:* Post-transplant micrscopic examination of a specimen from the septum of the explanted left ventricle, at x300 magnification, confirming replacement (arrow) and pericellular fibrosis.

Overall, this composite end-point was more common in patients with LGE compared to those without (30.7% vs 10.7%; HR 3.6; 95% CI 2.2-5.8; p<0.0001) (*Figure 3.6).* After adjusting for LVEF, NYHA class and age, the presence of LGE remained an independent predictor of the CV composite end-point (HR 3.2; 95%CI 1.9-5.4; p<0.0001).

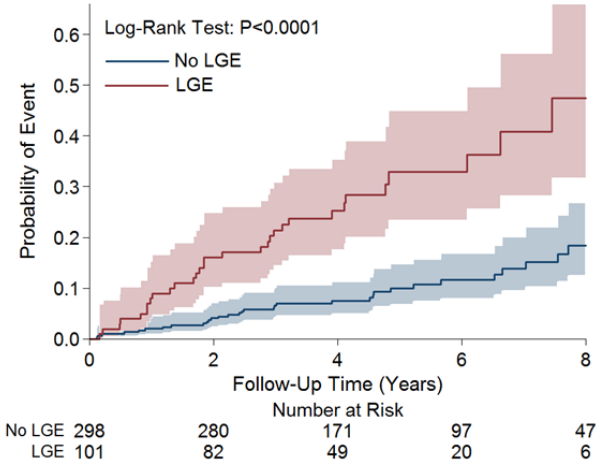

Figure 3.6. Kaplan-Meier curves for the composite cardiovascular end-point.
Curves demonstrate time to first event by presence (red line) or absence (blue line) of LGE. Survival compared using Log-rank test.

Heart failure death, heart failure hospitalisation and transplantation

There were 3 deaths secondary to HF and 18 unplanned HF admissions. The incidence of this composite end-point was nominally more common in those with LGE compared to those without, although the difference was not statistically significant (7.9% vs 4.4%; HR 1.9; 95% CI 0.8-4.6; p=0.15) (*Figure 3.7*). This remained the case following adjustment for LVEF, NYHA class and age (HR 1.7; 95% CI 0.7-4.2; p=0.27).

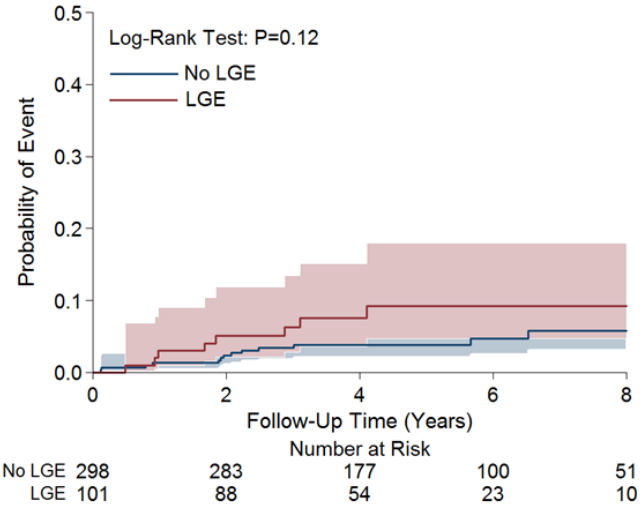

Figure 3.7. Kaplan-Meier curves for the composite heart failure end-point.
Curves demonstrate time to first event by presence (red-line) or absence (blue line) of LGE. Survival compared using Log-rank test.

3.6 Discussion

This large study in a population of well-treated and well-characterised DCM patients with mild or moderate LV impairment is the first investigation to demonstrate that mid-wall LGE on CMR is associated with a nine-fold increased risk of SCD and aborted SCD in this select sub-group. Importantly, none of the patients within the cohort had a pre-existing indication for ICD implantation at baseline, demonstrating the incremental value of LGE-CMR in risk

stratification in this population. This focused investigation emphasises the importance of extending risk stratification beyond LVEF assessment and demonstrates the potential utility of LGE-CMR in identifying a high-risk sub-group of patients who do not currently meet guideline criteria for ICD implantation. Our study extends prior observations in HF populations including both ischaemic and non-ischaemic aetiologies which demonstrated adverse risk associated with LGE in patients with a spectrum of LVEF (Cheong *et al*, 2009; Klem *et al*, 2012). In our study, prediction of SCD and aborted SCD was independent of established prognostic variables, including LVEF, NYHA class and age and qualitatively the same following adjustment for a large number of covariates based on a propensity score.

International guidelines and statements have highlighted the need to identify those patients with an LVEF>35% at highest risk of SCD because the major burden of SCD lies within this sub-group and this is currently not accounted for by primary prevention ICD guidelines (Fishman *et al*, 2010; Goldberger *et al*, 2008; Gorgels *et al*, 2003; Stecker *et al*, 2006; Zipes *et al*, 2006). Furthermore, as we move to an era of precision medicine, there is an expanding cohort of patients identified with milder reductions in LVEF in whom optimal therapy remains unclear (Pinto *et al*, 2016a). The DANISH trial has re-emphasised the need to refine our current approaches to risk stratification (Kober *et al*, 2016). Although, the trial demonstrated a reduction in SCD in patients with severely reduced LVEF randomised to ICD implantation, this was not associated with a significant reduction in all-cause mortality because of high rates of non-sudden cardiac death and non-cardiac death (Kober *et al*, 2016). In other words, in this population of sick patients, ICD therapy simply changed the mode of death but not the overall mortality rate. This illustrates the importance of selecting patients with a high-risk of SCD and low-risk of non-sudden death who will be exposed to longer periods at risk of arrhythmias and may therefore have the most to gain from ICD therapy. Indeed in sub-group analysis of the

DANISH trial, patients most likely to benefit from ICD therapy were those at low risk of non-sudden death, specifically patients <59 years of age and those with a NT-pro-BNP<1177pg/ml (Kober *et al*, 2016). Patients with mild or moderate reductions in LVEF, not only have a low risk of non-sudden death, but are also less likely to have limiting HF symptoms compared to those with more severe LV impairment and may therefore have the potential to gain a greater number of quality-adjusted life years following an aborted SCD. Our new data suggest a role for LGE-CMR in the identification of patients with less severe LV impairment who are at high risk of SCD, low risk of non-sudden death and who may therefore benefit from ICD implantation.

In patients with a LVEF≥40%, over a median follow-up of 4.6 years, the risk of the primary end-point in those with mid-wall LGE was 17.8%. In a similarly-designed study with marginally longer follow-up (median 5.3 years), the risk of SCD and aborted SCD in all-comer DCM patients with an LVEF≤35% was 17.9%, increasing to 27.9% in the subgroup with LGE, but dropping to only 11.1% in those without LGE (Gulati *et al*, 2013c). We have therefore observed an approximately equivalent rate of SCD events in patients with an LVEF≥40% and LGE compared to all those with an LVEF≤35%. This observation provides support for the CMR-Guide (NCT01918215) randomised trial which aims to evaluate the benefit of ICD therapy in patients with LVEF 36-50% and LGE.

The greatest increment in SCD risk occurred between patients with no LGE and those with the smallest extent (0-2.5%). This was confirmed by analysis of Harrell's C Statistic which demonstrated a LGE extent cut-off of >0% as the best discriminator of event-free survival time. The lack of a linear dose-response relationship between the extent of LGE and the primary end-point is novel and suggests that binary risk models based on the presence or absence of LGE may be the most optimal. This emphasises the need for further work, in larger numbers of

patients, investigating the exact relationship between LGE extent and outcome. Whether risk varies depending on the location and pattern of non-ischaemic LGE is also uncertain. These questions form the basis of Chapter 4 of this thesis.

Myocardial fibrosis is a widely accepted substrate for ventricular arrhythmia, supporting the biological plausibility of the findings. An electro-mapping study in patients with DCM demonstrated LGE in all patients with inducible VT or a history of sustained VT and mapped the arrhythmia to the corresponding location (Bogun *et al*, 2009). Additionally, areas of fibrosis interacting with channels of healthy myocardium in the peripheral 'heterogeneous zone' of the scar have been associated with re-entry wavefronts and targeting of these at catheter ablation reduces VT (de Bakker *et al*, 1990; Estner *et al*, 2011; Hsia *et al*, 2002; Perez-David *et al*, 2011). It is therefore conceivable that the surface area of the 'gray-zone' between scar and healthy tissue determines the risk of VT, rather than the mass of the scar, explaining the lack of a dose-dependent association between LGE extent and SCD events in our study (Bilchick, 2016; Disertori *et al*, 2016). Heterogeneity within areas of scar is likely to be an important factor determining pro-arrhythmia.

3.6.1 Limitations

This study was performed in a single, large-volume, experienced centre. While this enables the use of a standardised protocol and scan interpretation from the same independent operators, it introduces the possibility of referral bias. We do, however, report similar baseline characteristics to other registries (Kuruvilla *et al*, 2014; Merlo *et al*, 2015). Moreover, the referral base is broad, from specialist and non-specialist centres and we report a range of common indications for the scan. Data from 193 of 399 patients were included in an earlier investigation on 'all-comers' with DCM (Gulati *et al*, 2013c). These patients had extended follow-up in this study which is unique in examining a focused clinical question in a targeted

population using an alternative pre-specified primary end-point in order to address an unmet clinical need.

We also recognise the modest number of events in the study. We specified strict criteria for the primary end-point, excluding appropriate ATP, in order to generate the most clinically meaningful data. Within this large study, we have identified a strong predictor of clinically important events responsible for a major burden of SCD in the DCM population. Based on the event rates in this study, a randomised trial of defibrillator therapy versus medical therapy in patients with a LVEF>40% and mid-wall LGE followed-up for 5 years would require 971 patients to have 80% power to detect a difference in all-cause mortality, at a significance level of 5%, assuming a 60% reduction in SCD with the intervention. This is comparable to the sample size of other large device trials (Kober *et al*, 2016).

In this study, CAD was not excluded in all cases by coronary angiography. However, LGE-CMR has been shown to be as accurate in the diagnosis of the aetiology of HF (Assomull *et al*, 2011). In addition, the majority of patients who did not undergo coronary angiography were ≤40 years of age without a history of angina or a family history of premature CAD. Only 30 patients, all without a history of angina, were aged over 40 and had no additional investigations to exclude CAD. None of the patients suffered an acute coronary syndrome or had coronary revascularisation during the study. Whilst we accept that CAD cannot be definitively excluded in this small group, significant CAD is nevertheless unlikely. The small size of this group means that this is unlikely to have biased the data to a significant extent.

ICD implantation was more frequent in patients with LGE; however our results were consistent after adjusting for this as part of the propensity score analysis. Whilst it is possible that the higher rate of ICD implantation reflects selection bias, the presence of LGE was not cited as an indication for implantation in any case. Amongst patients who had an ICD implanted, the

rate of aborted SCD was higher in those with LGE compared to those without. Furthermore, despite the higher rate of ICD implantation in those with LGE, these patients had a higher rate of SCD. We acknowledge the limitations of aborted SCD as an end-point and recognise that a proportion of arrhythmias resulting in appropriate shocks may have terminated spontaneously. However, our data on the association with SCD adds robustness. We also recognise that a proportion of SCDs may relate to aneurysmal rupture and cerebral haemorrhage, however, in the absence of a biologically plausible link between LGE and these events, the effect of this would be to dilute the association between LGE and SCD rather than to enhance it. ICD programming was at the discretion of the individual units.

We did not routinely measure B-type natriuretic peptide but we have included alternative variables which strongly predict prognosis in HF, such as LAVi and NYHA class. Contemporary CMR techniques such as T1-mapping were not available at the outset. Whilst associations between native T1 values and all-cause mortality and HF end-points have been demonstrated in DCM, there is a lack of current data investigating hard SCD end-points (Puntmann *et al*, 2016). Given the possible link between interstitial fibrosis and ventricular arrhythmia, specifically those with focal mechanisms, we eagerly await the result of future studies. An important question will be whether this technique can add incremental value to LGE, which already forms part of a routine scan protocol. In our study, the event rate in patients without LGE was only 2.3% over a median follow-up of 4.6 years. Significant overlap in native T1 values also exists in patients with DCM without LGE and healthy controls (Liu *et al*, 2017).

3.7 Conclusion

For the first time, we demonstrate that in patients with DCM and mild or moderate LV systolic impairment, who do not meet conventional criteria for an ICD, the presence of mid-wall LGE identifies a sub-group at high-risk of SCD. The risk of SCD in this sub-group was comparable to that seen in all-comer patients with a LVEF<35%, and importantly their risk of non-sudden cardiac death was low, suggesting that ICD therapy may have the potential to reduce all-cause mortality and extend 'quality life'. Whether ICD therapy can accomplish this goal and increase longevity for patients with LGE and mild or moderate LV systolic impairment can only be definitively answered in randomised controlled trials.

Chapter 4

4 Outcome in Dilated Cardiomyopathy Related to the Extent, Location and Pattern of Late Gadolinium Enhancement

Halliday BP, Baksi AJ, Gulati A et al. Outcome in Dilated Cardiomyopathy Related to the Extent, Location and Pattern of Late Gadolinium Enhancement.

4.1 Hypothesis

2. ***The extent of late gadolinium enhancement is associated with adverse outcomes in a linear dose-dependent manner***

3. ***Mid-wall late gadolinium enhancement in the septum is associated with a higher rate of adverse outcomes compared to late gadolinium enhancement in the free-wall of the left ventricle***

4.2 Abstract

Background: The relationship between the extent, pattern and location of LGE and prognosis in DCM is incompletely understood. More precise phenotypic characterisation may enable more personalised therapy.

Methods: We examined the association between the extent, location and pattern of LGE and all-cause mortality and a SCD composite in DCM patients referred to our centre between January 2000 and December 2011.

Results: Of 874 patients (588 men, median age 52 years; median LVEF 39%) followed for a median of 4.9 years, 300 (34.3%) had non-ischaemic LGE (septum only: 142, free-wall only: 42, septum & free-wall: 116; median extent 3.8%, IQR 2.0:6.7%). Estimated adjusted HRs for patients with an LGE extent of 0-2.5%, 2.5-5% and >5% respectively, were 1.47 (95% CI 0.90-2.40), 1.76 (1.10-2.82) and 2.19 (1.43-3.36) for all-cause mortality and 2.65 (95% CI 1.31-5.37), 4.11 (2.19-7.70) and 5.05 (95% CI 2.87-8.91) for the SCD end-point. There was a marked non-linear relationship between LGE extent and outcome such that even small amounts of LGE predicted a substantial increase in risk. The presence of septal LGE was associated with increased mortality, but SCD was most associated with the combined presence of septal and free-wall LGE. Predictive models using LGE presence and location were superior to models based on LGE extent or pattern.

Conclusions: In DCM, the presence of septal LGE is associated with a large increase in the risk of death and SCD events, even when the extent is small. SCD risk is greatest with concomitant septal and free wall LGE. The incremental value of LGE extent beyond small amounts, and LGE pattern is limited.

4.3 Background

Despite advances in therapy, outcomes in DCM remain poor (Gulati *et al*, 2013c). DCM is a heterogeneous disease affecting a diverse group of patients and response to therapy is varied (McNamara *et al*, 2011). Precise phenotyping, enabling targeted and personalised management to improve outcomes and avoid unnecessary interventions remains a long-term therapeutic goal.

LGE-CMR detects non-ischaemic LGE in approximately 30% of patients, which correlates with replacement fibrosis on histology (Gulati *et al*, 2013c). LGE provides incremental value, in addition to LVEF, for predicting all-cause mortality and SCD events and therefore has the potential to guide therapy such as the selection of patients for ICD implantation (Gulati *et al*, 2013c).

Non-ischaemic LGE most often occurs in a linear pattern in the mid-wall of the septum, however sub-epicardial patterns and LGE occurring in the free-wall of the left ventricle are also recognised (Mahrholdt *et al*, 2005). It is possible that areas of scar in different locations are the result of different pathological processes, have different microstructure and varying degrees of heterogeneity. Geographical location may also impact upon the effect on cardiac performance and the probability of creating re-entry circuits. The nature of the dose-response relationship between LGE and outcome is also poorly understood. Data examining the association between the extent, location and pattern of LGE and specific clinical outcomes are lacking. Identifying an amount, location or pattern of LGE that provides the optimal mode of risk stratification will help guide the use of this technique in clinical practice.

4.4 Methods

4.4.1 Patient Cohort

Patients with suspected DCM referred to our centre for CMR or evaluation in the Cardiomyopathy Clinic between January 2000 and December 2011 were screened.

Details of the inclusion and exclusion criteria have been described in Section 2.1. Of 925 patients who met the inclusion criteria, 9 moved abroad and 42 did not provide informed consent. For the purpose of this study, a further 7 patients were excluded as LGE quantification was unable to be performed on available images. The final analysis therefore included 874 patients.

An ischaemic aetiology was considered in all cases and excluded as follows. All those with infarct patterns of LGE were excluded (Assomull *et al*, 2011). Additionally, 681 (77.9%) underwent coronary angiography and 63 (7.2%) had perfusion imaging or stress echocardiography without provocation of ischaemia. All of the remaining patients (n=130) were free of angina and considered to have a low risk of IHD by their attending cardiologists; the majority (n=82) were ≤40 years of age. In the absence of a class 1 indication, coronary angiography was not performed (Ponikowski *et al*, 2016; Yancy *et al*, 2013). None of these patients underwent coronary revascularisation or suffered an acute coronary syndrome during follow-up.

4.4.2 CMR Protocol & Image Analysis

All patients underwent CMR using the standardised protocol detailed in Section 2.2. Volumetric analysis (Section 2.3) was performed by independent operators blinded to

outcomes. The presence of non-ischaemic LGE was determined by two independent operators, with a third providing adjudication if necessary. LGE was considered present if seen in both long- and short-axis planes, in two phase-encoding directions and extending beyond the localised ventricular insertion areas. A senior operator categorised the location and pattern of LGE. The location was classified as septal, LV free-wall or as occurring in both locations. LGE occurring in the anterior, anterolateral, inferolateral or inferior walls was categorising as occurring in the free-wall. The pattern was classified as linear mid-wall, sub-epicardial, focal or as occurring in multiple patterns. LGE quantification was performed by two senior operators using the full width at half maximum method (CMR42, Circle Cardiovascular Imaging Inc, Calgary, Canada).

4.4.3 End-points

The primary outcome of interest was all-cause mortality. Deaths were confirmed using the UK Health and Social Care Information Service to ensure none were missed. The cause of death was confirmed by an independent adjudication committee of cardiologists, blinded to CMR data, using a combination of medical records, death certification and post-mortem results in line with ACC/AHA guidance (Buxton *et al*, 2006; Hicks *et al*, 2015).

The secondary end-point was a composite of SCD or aborted SCD. SCD was defined as unexpected death either within 1 hour of the onset of cardiac symptoms in the absence of progressive cardiac deterioration; during sleep; or within 24 hours of last being seen alive (Hicks *et al*, 2015). Aborted SCD was defined as an appropriate ICD shock for ventricular arrhythmia, successful resuscitation following VF or sustained VT causing hemodynamic compromise and requiring cardioversion (Buxton *et al*, 2006; Greenberg *et al*, 2004).

4.4.4 Patient Follow-up

Patients were followed-up as detailed in Section 2.4. The duration of follow-up was calculated from the baseline scan until an end-point occurred or last patient contact.

4.4.5 Statistical Analysis

To establish the relationship between the extent of LGE and outcome, patients with LGE were divided into three groups depending on the mass of LGE: 1) 0-2.5% of overall myocardial mass, 2) 2.5-5% and 3) >5%. The cut-offs were chosen to produce 3 approximately equal-sized groups of patients with increasing extents of LGE. Differences in baseline characteristics between those with and without LGE were examined using the Kruskal-Wallis Rank Test for continuous data and Fisher's Exact Test for categorical data. Proportional hazard modelling was used to establish the associations between the extent, location and pattern of LGE and the primary and secondary end-points. Multivariable models were adjusted for LVEF, age and sex given the potential that these variables would confound the associations between the outcomes and LGE. As part of a sensitivity analysis, the models were also adjusted for LVEF, age, sex, RVEF, NYHA class, LVEDVi, LV mass index and LAVi. To illustrate the relationship between LGE extent and outcome, a cubic spline curve was fitted to the observed data. The LGE extent with the greatest c-statistic for the prediction of the outcomes was estimated from 1000 bootstrap samples. Event times were measured from the baseline scan date for a maximum of 10 years. Results are presented as HRs with 95% CIs. A p value of <0.05 was taken as significant.

In addition, the Akaike information criterion (AIC) was used to examine whether models based on the presence, extent, location or pattern of LGE were most effective in predicting the end-

points (May *et al*, 2004). This test allows comparison of nested and non-nested models and reduces the likelihood of over-fitting the data. Smaller values indicate the most effective model.

To examine the interobserver variability in LGE quantification, a random sample of 60 patients, including 20 from each group based on varying extents had analysis performed by 2 independent operators. The intraclass correlation coefficient (ICC) was calculated for percentage extent and the Kappa coefficient was calculated based on the LGE group in which patients were categorised based on the overall percentage extent of LGE calculated by each operator. A Bland-Altmann plot was produced to illustrate the difference in LGE quantification between the operators.

4.5 Results

4.5.1 Baseline Characteristics

Of the 874 patients, 588 (67.3%) were men, the median LVEF was 39% (IQR: 29-50%) and non-ischaemic LGE was present in 300 (34.3%). LGE was present only in the septum in 142 (16.2%) cases, only in the LV free-wall in 42 (4.8%) and in both locations in 116 (13.3%) (*Figure 4.1*). LGE was categorised as linear mid-wall in 185 (21.1%) cases, sub-epicardial in 25 (2.9%), focal in 22 (2.5%) and as occurring in multiple patterns in a further 68 (7.8%) (*Figure 4.1*). LGE occupied 0-2.5% of total myocardial mass in 97 (11.1%) patients, between 2.5-5% in a further 99 (11.3%) and >5% in 104 (11.9%).

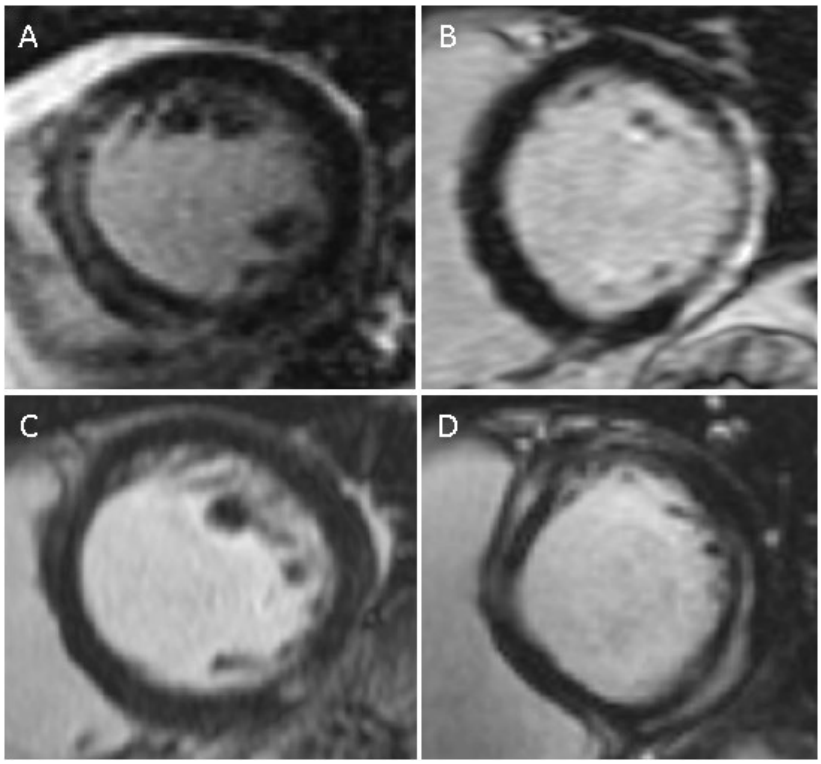

Figure 4.1. Patterns of LGE in DCM.
LGE images demonstrating A) linear mid-wall enhancement in the septum, B) sub-epicardial enhancement in the lateral wall, C) focal enhancement of the inferior wall and D) mid-wall enhancement of the septum, lateral and inferior wall.

Baseline characteristics are presented in *Table 4.1*. Patients with LGE were older ($p=0.02$), more likely to be men ($p<0.0001$), prescribed loop diuretics ($p<0.0001$) or MRAs ($p=0.007$), had lower systolic ($p=0.013$) and diastolic blood pressures ($p=0.024$), worse NYHA class ($p=0.007$), lower LVEF ($p<0.0001$) and greater LVEDVi ($p<0.0001$).

	LGE				
	No (n=574)	**0-2.5% (n=97)**	**2.5-5% (n=99)**	**>5% (n=104)**	***P***
Mean Age (SD), yrs	51.0 (15.1)	52.9 (14.4)	53.4 (14.7)	56.3 (14.5)	0.020
Men, n (%)	352 (61.3)	79 (81.4)	74 (74.7)	83 (79.8)	<0.0001
BSA, m^2	1.95 (0.24)	2.04 (0.25)	1.97 (0.21)	1.93 (0.21)	0.005
Heart Rate, bpm	73.3 (13.9)	74.5 (15.3)	73.7 (16.2)	70.8 (14.2)	0.28
Systolic blood pressure, mmHg	121.5 (17.6)	120.2 (16.3)	117.3 (17.9)	116.3 (17.1)	0.013
Diastolic blood pressure, mmHg	73.2 (11.0)	72.3 (9.8)	71.0 (10.6)	70.1 (10.9)	0.024
Atrial fibrillation/flutter, n (%)	108 (18.8)	23 (23.7)	19 (19.2)	19 (18.3)	0.70
Hypertension , n (%)	117 (20.4)	24 (24.7)	26 (26.3)	23 (22.1)	0.48
Diabetes, n (%)	43 (7.5)	16 (16.5)	9 (9.1)	11 (10.6)	0.044
Family History of DCM, n (%)	52 (9.1)	15 (15.5)	11 (11.2)	8 (7.7)	0.22
LBBB, n (%)	170 (29.7)	28 (28.9)	33 (33.3)	25 (24.3)	0.56
Moderate Alcohol Excess, n (%)	64 (11.1)	10 (9.7)	14 (14.1)	12 (11.5)	0.83
Previous Chemotherapy, n (%)	35 (6.1)	4 (4.1)	4 (4.0)	2 (1.9)	0.29
Peripartum diagnosis, n (%)	15 (2.6)	2 (2.1)	0 (0)	1 (1.0)	0.4
Neuromuscular disease, n (%)	7 (1.2)	0 (0)	0 (0)	1 (1.0)	0.74
Medications					
Beta Blocker, n (%)	407 (71.0)	74 (76.3)	74 (74.7)	82 (78.8)	0.32
ACE Inhibitor, n (%)	409 (71.3)	71 (73.2)	72 (72.7)	73 (70.2)	0.96
ARB, n (%)	117 (20.5)	18 (18.6)	20 (20.2)	25 (24.0)	0.79
Loop Diuretic, n (%)	209 (36.4)	60 (61.9)	57 (57.6)	61 (58.7)	<0.0001
MRA, n (%)	173 (30.2)	38 (39.2)	44 (44.4)	43 (41.3)	0.007
NYHA					
I, n (%)	254 (44.4)	33 (34.7)	32 (32.3)	35 (34.0)	0.007
II, n (%)	229 (40.0)	45 (47.4)	38 (38.4)	42 (40.8)	
III / IV, n (%)	89 (15.6)	17 (17.9)	29 (29.3)	26 (25.2)	
CMR Measurements					
LVEF (%)	40.6 (12.1)	34.5 (13.5)	35.0 (13.1)	35.5 (12.1)	<0.0001
LVEDVi (ml/m^2)	126.3 (36.6)	147.2 (45.8)	145.6 (50.0)	134.0 (37.4)	<0.0001
LV Mass Index (g/m^2)	93.0 (27.7)	108.2 (26.6)	101.5 (23.5)	95.2 (25.4)	<0.0001
RVEF (%)	52.4 (13.6)	48.7 (16.6)	47.3 (15.5)	50.7 (13.6)	0.028
RVEDVi (ml/m^2)	87.9 (24.5)	93.6 (25.1)	96.0 (30.4)	85.6 (27.8)	0.002
LAVi (ml/m^2)	63.6 (25.0)	74.5 (29.7)	69.8 (26.2)	68.0 (26.7)	<0.0001

Table 4.1. Baseline characteristics.

Mann-Whitney Test used to compare continuous data; Fisher's Exact for categorical data.

4.5.2 Reproducibility of LGE Detection and Quantification

There was agreement between two operators on the presence of LGE in 94.7% of cases (n=828). There was an absolute mean difference of 0.87% between operators in the quantification of the extent of LGE (ICC - 0.87) (*Table 4.2* & *Figure 4.2*). Additionally, there was 86.7% agreement in categorising the LGE extent within three groups (0-2.5%, 2.5-5%, >5%) (Kappa coefficient - 0.80) *(Table 4.3)*.

Observer 1 Mean (SD)	Observer 2 Mean (SD)	Absolute Mean Difference (SD)	ICC (95% CI)
4.10 (2.91)	4.38 (3.46)	0.87 (1.43)	0.87 (0.79, 0.92)

Table 4.2. Interobserver reproducibility in LGE quantification
Mean quantity of LGE calculated by two operators and the intraclass correlation coefficient

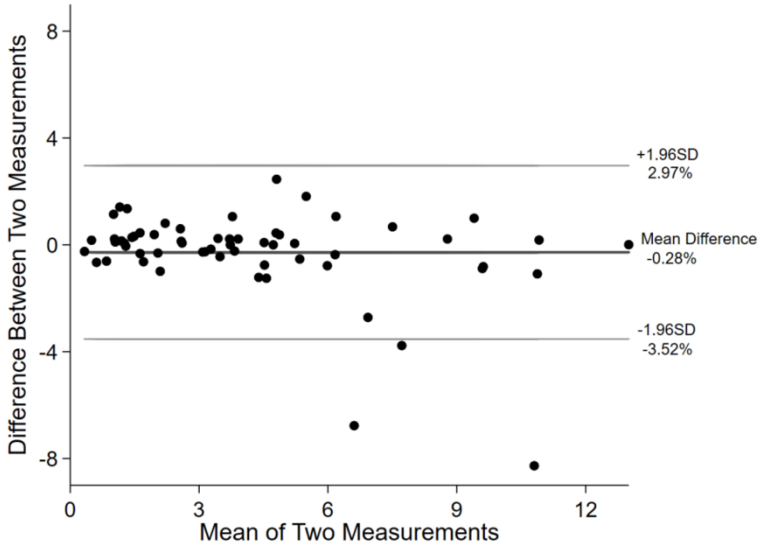

Figure 4.2. Interobserver reproducibility in LGE quantification
Bland-Altmann plot illustrating the difference between two operators in the quantification of late gadolinium enhancement, with the mean of the two measurements on the x-axis and the difference between the two measurements on the y-axis.

		Observer 2		
	Group	1	2	3
Observer 1	1	19	1	0
	2	2	17	2
	3	0	3	16

86.7% Agreement Kappa = 0.80

Table 4.3. Interobserver reproducibility in classifying LGE mass within three categories
Classification of the quantity of LGE within three groups by two operators and the Kappa coefficient of variation

4.5.3 All-Cause Mortality

Over a median follow-up of 4.9 years (IQR 3.5-7.0), 150 patients (17.2%) died including 77 (25.7%) with LGE and 73 (12.7%) without. In univariable analysis, the presence of LGE was associated with greater all-cause mortality (HR 2.39; 95% CI 1.73:3.29; p<0.001) (*Figure 4.3*). Following adjustment for LVEF, age and sex, the strength of the association was similar (HR 1.81; 95% CI 1.30:2.52; p<0.001). The results were qualitatively the same when adjusting for LVEF, age, sex, RVEF, NYHA class, LVEDVi, LV mass index, LAVi as part of a sensitivity analysis (HR 1.70; 95% CI 1.21:2.39; p=0.002).

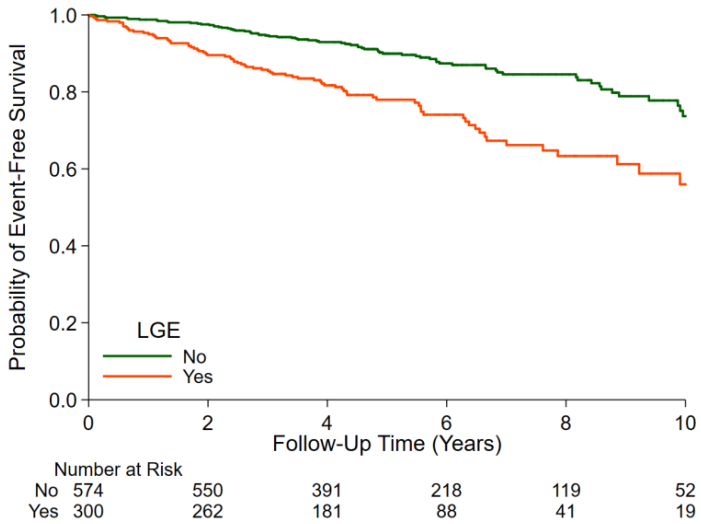

Figure 4.3. Kaplan-Meier curve for the primary end-point.
Kaplan-Meier curve of the time to first event for the primary end-point by presence (orange line) or absence (green line) of mid-wall LGE.

Extent of LGE: Estimated adjusted HRs for patients with LGE extents of 0-2.5%, 2.5-5% and >5% were 1.47 (95% CI 0.90-2.40; p=0.12), 1.76 (1.10-2.82; p=0.018) and 2.19 (1.43-3.36; p<0.001) compared to those without LGE (*Figure 4.4A, Figure 4.5)*. Modelling LGE as a linear measure, per percentage increase in extent, underestimated risk in most patients while overestimating risk in the small proportion of patients with the largest extent (*Figure 4.4B).* The percentage extent of LGE giving the largest c-statistic was 1.29% (c-statistic 0.70).

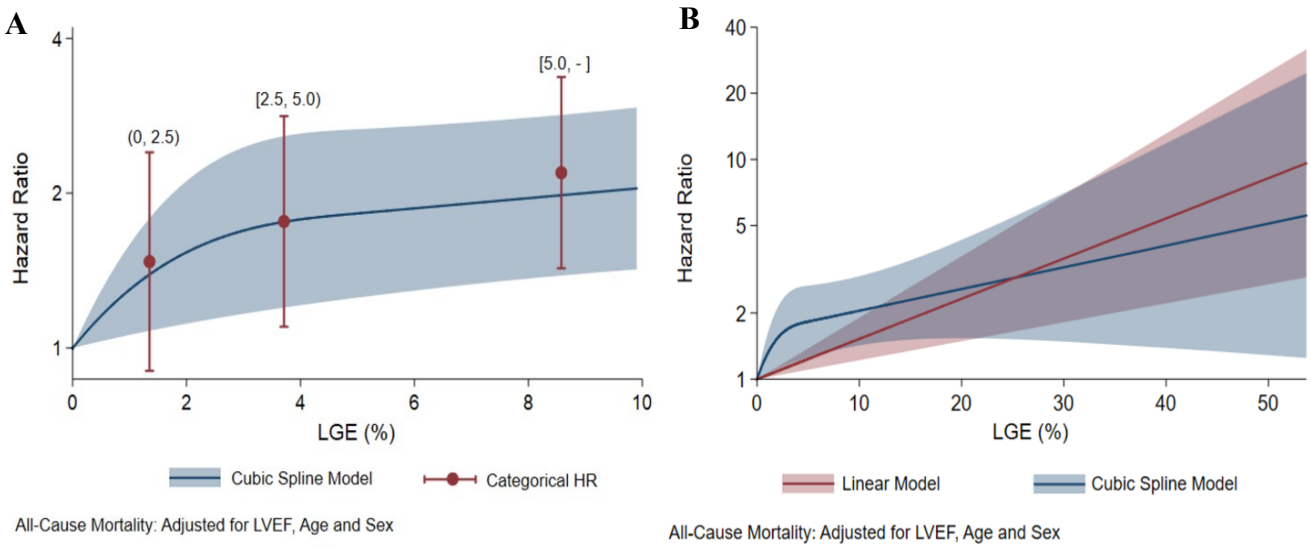

Figure 4.4. Association between LGE extent and all-cause mortality.
(A) Estimated adjusted HRs with 95% CIs (red lines) for all-cause mortality, per patient group based on increasing extent of LGE (0-2.5%, 2.5-5%, >5%). HRs are positioned at the median LGE extent within each category. A cubic spline model (blue line) has been fitted to the observed data. (B) The cubic spline curve has been modelled for greater extents of LGE (blue line). The data was also modelled based on a linear relationship, per percent increase in extent (red line), demonstrating over-prediction of risk at the largest extents.

Location of LGE: Patients with LGE only in the septum, only in the free-wall and in both locations had adjusted HRs for the primary end-point of 1.96 (95% CI: 1.32:2.92; p<0.001), 0.77 (95% CI: 0.28:2.12; p=0.77) and 1.99 (95% CI: 1.30:3.04; p=0.002), compared to those

without LGE (*Figure 4.5*). A simplified model demonstrated that those patients with septal LGE had an estimated adjusted HR of 2.00 (95% CI: 1.43:2.81; p<0.0001) compared to those without septal LGE (*Figure 4.5*).

Pattern of LGE: Estimated adjusted HRs for patients with linear mid-wall, sub-epicardial, focal and multiple patterns of enhancement were 1.70 (95% CI: 1.17:2.49; p=0.006), 1.29 (95% CI: 0.47:3.57; p=0.62), 2.85 (95%CI: 1.30; 6.23; p=0.009) and 2.00 (95% CI: 1.20:3.34; p=0.008) compared to those patients without LGE (*Figure 4.5*).

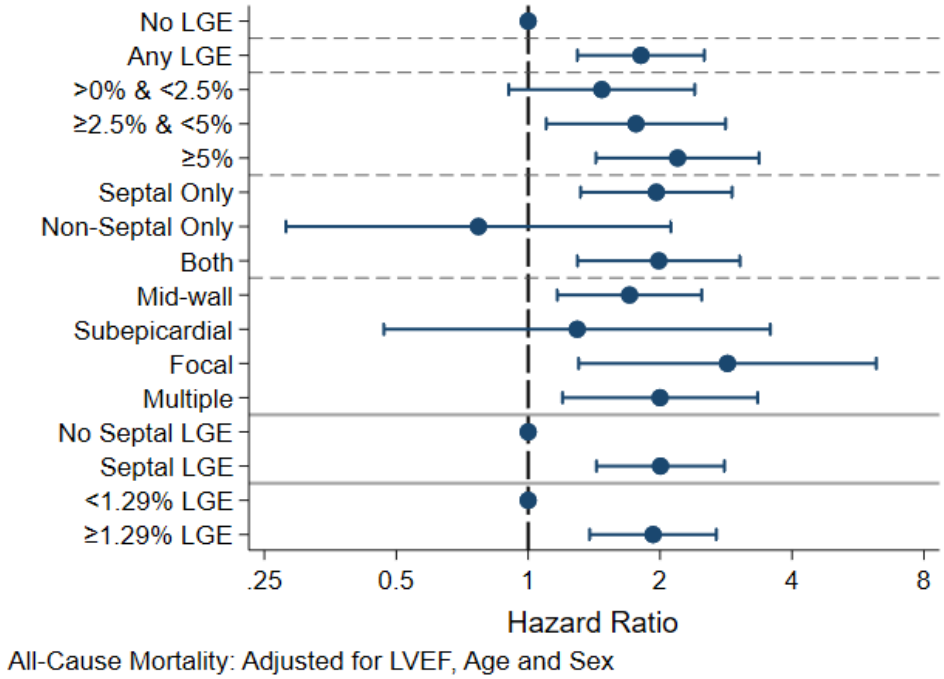

Figure 4.5. All-cause mortality related to the extent, location and pattern of LGE.
A Forrest plot demonstrating the estimated adjusted HRs for all-cause mortality per patient group based on LGE extent, location and pattern.

The model with the smallest AIC and the most effective for the prediction of the primary end-point was based on the presence of septal LGE (*Table 4.4).* This was superior to those based on extent or pattern of LGE and the LGE cut-off with the largest c-statistic for the prediction of the primary end-point.

			Mortality	Adjusted for LVEF, sex & age			
			n (%)	HR (95% CI)	Individual P	Overall P	AIC
Presence & Extent	**A:** LGE (Binary) [Any]	0%	73 (12.7)	1.00	-	<0.001	1790.1
		>0%	77 (25.7)	1.81 (1.30, 2.52)	<0.001		
	B: LGE (Binary) [Cut-off]	<1.29%	81 (13.1)	1.00	-	<0.0001	1787.6
		≥1.29%	69 (26.8)	1.93 (1.38, 2.69)	<0.001		
	C: LGE (4 Groups)	0%	73 (12.7)	1.00	-	<0.001	1792.0
		>0% & <2.5%	22 (22.7)	1.47 (0.90, 2.40)	0.12		
		≥2.5% & <5%	24 (24.2)	1.76 (1.10, 2.82)	0.018		
		≥5%	31 (29.8)	2.19 (1.43, 3.36)	<0.001		
Location & Pattern	**D**: LGE (by Location)	Absent	73 (12.7)	1.00	-	<0.001	1789.7
		Septal Only	41 (28.9)	1.96 (1.32, 2.92)	<0.001		
		Free-wall Only	4 (9.5)	0.77 (0.28, 2.12)	0.61		
		Both	32 (27.6)	1.99 (1.30, 3.04)	0.002		
	E: LGE (Septal)	**No**	**77 (12.5)**	**1.00**	**-**	**<0.0001**	**1786.0**
		Yes	**73 (28.3)**	**2.00 (1.43, 2.81)**	**<0.001**		
	F: LGE (by Pattern)	Absent	73 (12.7)	1.00	-	0.005	1794.0
		Mid-wall	47 (25.4)	1.70 (1.17, 2.49)	0.006		
		Subepicardial	4 (16.0)	1.29 (0.47, 3.57)	0.62		
		Focal	7 (31.8)	2.85 (1.30, 6.23)	0.009		
		Multiple	19 (27.9)	2.00 (1.20, 3.34)	0.008		

Table 4.4. Models demonstrating the association between all-cause mortality and LGE

The association between all-cause mortality and (A) the presence of LGE; (B) the extent of LGE with the largest c-statistic; (C) the extent of LGE (as per 3 categories); (D) the location of LGE; (E) the presence of septal LGE; (F) the pattern of LGE. P values are quoted for each model overall and for the individual components. The model with the smallest Akaike information criterion and the most optimal was (E).

4.5.4 Sudden Cardiac Death and Aborted Sudden Cardiac Death

Overall, 84 patients (9.6%) suffered SCD or aborted SCD, including 55 patients (18.3%) with LGE and 29 (5.1%) without. In univariable analysis, the presence or absence of LGE was associated with the SCD end-point (HR 4.12; 95% CI 2.64:6.45; p<0.001) (*Figure 4.6)*. Following adjustment for LVEF, age, sex the strength of the association remained similar (HR 3.96; 95% CI 2.41:6.52; p<0.001). The results were also similar following adjustment LVEF, age, sex, RVEF, NYHA class, LVEDVi, LV mass index, LAVi as part of a sensitivity analysis (HR 3.99; 95% CI 2.37-6.69; p<0.0001).

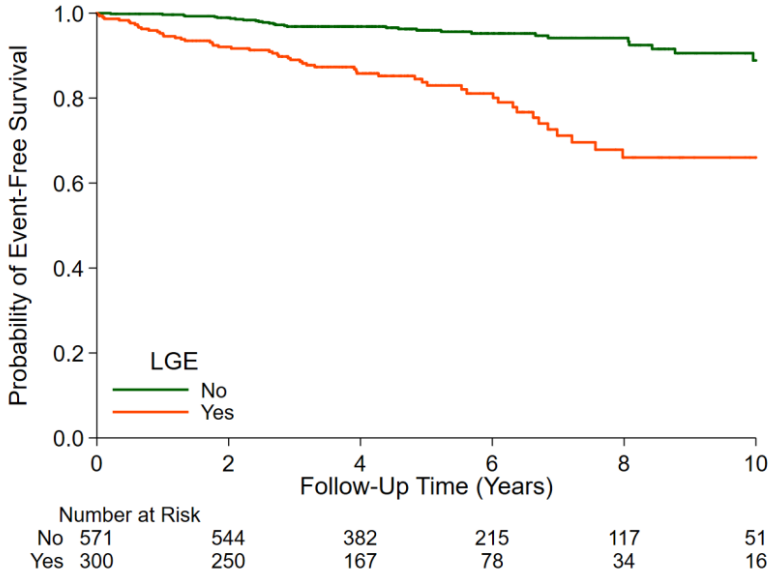

Figure 4.6. Kaplan-Meier curve for the SCD end-point.
Kaplan-Meier curve of the time to first event for the SCD composite end-point by presence (orange line) or absence (green line) of mid-wall LGE.

Extent of LGE: Estimated adjusted HRs for patients with LGE extents of 0-2.5%, 2.5-5% and >5%, respectively, were 2.65 (95% CI 1.31-5.37; p=0.007), 4.11 (2.19-7.70; p<0.0001) and 5.05 (95% CI 2.87-8.91; p<0.0001), compared to patients without LGE (*Figure 4.7A* & *Figure 4.8*). Modelling LGE as a linear measure, per percentage increase in extent, underestimated

risk in most patients while overestimating risk in the proportion of patients with the largest extent (*Figure 4.7B)*. The percentage extent of LGE giving the largest c-statistic for the prediction of the arrhythmic end-point was 0.71% (c-statistic 0.70).

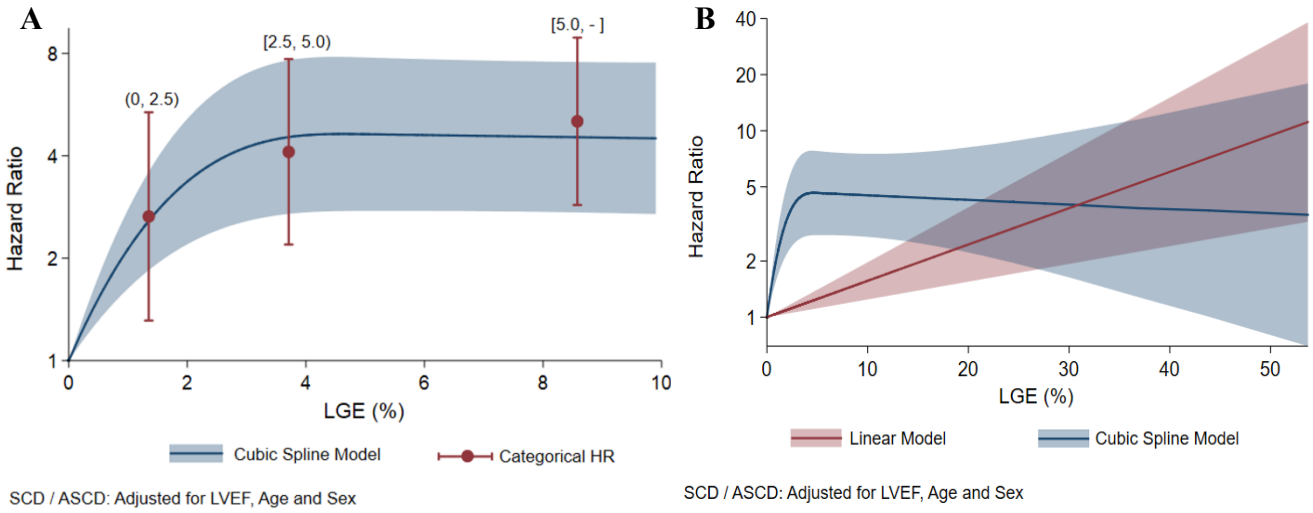

Figure 4.7. Association between the SCD end-point and LGE extent.
(A) Estimated adjusted HRs with 95% CIs (red lines) for SCD events, per patient group based on increasing extent of LGE (0-2.5%, 2.5-5%, >5%). The HRs are positioned at the median LGE extent within each category. A cubic spline model (blue line) has been fitted to the observed data. (B) The cubic spline curve has been modelled for greater extents of LGE (blue line). The data was also modelled based on a linear relationship, per percent increase in extent (red line), demonstrating over-prediction of risk at the largest extents.

Location of LGE: Patients with LGE in the septum (HR 3.13; 95% CI 1.68:5.81; p<0.001) and in both the septum and free-wall (HR 5.82; 95% CI: 3.30:10.27; p<0.0001) had greater incidence of the SCD end-point compared to patients without LGE. Whilst there was a weaker trend towards increased events in patients with LGE only occurring in the free-wall, this did not reach statistical significance (HR 2.19; 95% CIs 0.76:6.31; p=0.15) (*Figure 4.8)*.

Pattern of LGE: Estimated adjusted HRs for patients with linear mid-wall, sub-epicardial, focal and multiple patterns of enhancement were 3.21 (95% CI: 1.82:5.66; p<0.0001), 5.54 (95% CI: 2.18:14.08; p<0.001), 3.16 (95% CI: 0.91:10.97; p=0.070) and 5.72 (95% CI: 3.06:10.69; p<0.0001) compared to those patients without LGE (*Figure 4.8)*.

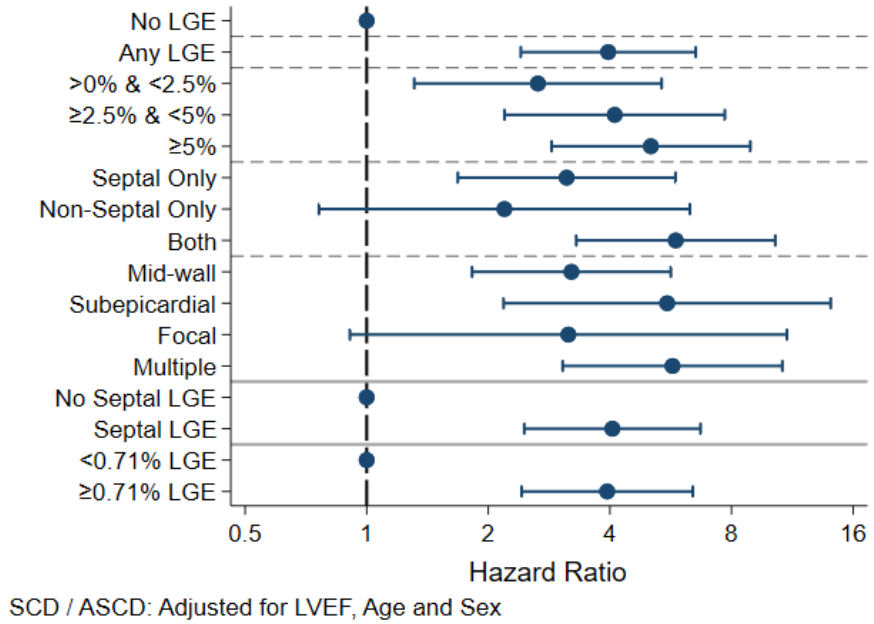

Figure 4.8. SCD events related to the extent, location and pattern of LGE.
A Forrest plot demonstrating the estimated adjusted hazard ratios for the SCD end-point per patient group based on late gadolinium enhancement extent, location and pattern.

Overall, the model with the smallest AIC that best predicted the SCD end-point was based on the presence and location of LGE within the septum, the free-wall or in both locations (*Table 4.5*). This was superior to models based on extent and pattern of LGE.

			SCD/ASCD	Adjusted for LVEF, sex & age			
			n (%)	HR (95% CI)	Individual P	Overall P	AIC
Presence & Extent	**A**: LGE (Binary) [Any]	0%	29 (5.1)	1.00	-	<0.0001	1027.6
		>0%	55 (18.3)	3.96 (2.41, 6.52)	<0.0001		
	B: LGE (Binary) [Cut-off]	<1.29%	30 (5.2)	1.00	-	<0.0001	1027.6
		≥1.29%	54 (18.6)	3.94 (2.42, 6.41)	<0.0001		
	C: LGE (4 Groups)	0%	29 (5.1)	1.00	-	<0.0001	1027.9
		>0% & <2.5%	13 (13.4)	2.65 (1.31, 5.37)	0.007		
		≥2.5% & <5%	18 (18.2)	4.11 (2.19, 7.70)	<0.0001		
		≥5%	24 (23.1)	5.05 (2.87, 8.91)	<0.0001		
Location & Pattern	**D: LGE (by Location)**	**Absent**	**29 (5.1)**	**1.00**	**-**	**<0.0001**	**1024.8**
		Septal Only	**21 (14.8)**	**3.13 (1.68, 5.81)**	**<0.001**		
		Free-wall Only	**4 (9.5)**	**2.19 (0.76, 6.31)**	**0.15**		
		Both	**30 (25.9)**	**5.82 (3.30, 10.27)**	**<0.0001**		
	E: LGE (Septal)	**No**	33 (5.4)	1.00	-	<0.0001	1027.4
		Yes	51 (19.8)	4.06 (2.46, 6.71)	<0.0001		
	F: LGE (by Pattern)	Absent	29 (5.1)	1.00	-	<0.0001	1029.5
		Mid-wall	29 (15.7)	3.21 (1.82, 5.66)	<0.0001		
		Subepicardial	5 (20.0)	5.54 (2.18, 14.08)	<0.001		
		Focal	3 (13.6)	3.16 (0.91, 10.97)	0.070		
		Multiple	18 (26.5)	5.72 (3.06, 10.69)	<0.0001		

Table 4.5. Models demonstrating the association between SCD end-points and LGE

The association between SCD end-points and (A) the presence of LGE; (B) the extent of LGE with the largest c-statistic; (C) the extent of LGE (as per 3 categories); (D) the location of LGE; (E) the presence of septal LGE; (F) the pattern of LGE. P values are quoted for each model overall and for the individual components. The model with the smallest Akaike information criterion and the most optimal was (D).

4.6 Discussion

This is the largest study to date to examine the association between the extent, location and pattern of LGE and outcome in a large, well-phenotyped DCM cohort. We demonstrate the superiority of models based on the presence and location of LGE for the prediction of all-cause mortality and SCD events, over those based on the extent and pattern of LGE. Our data establish a non-linear association between LGE extent and all-cause mortality and SCD events with a large increase in risk with small degrees of LGE and less marked increases with greater extents thereafter. The increase in risk with small amounts of LGE was most marked for SCD events (*Figure 3*).

Previous studies have demonstrated that non-ischaemic LGE is associated with an increased risk of death and arrhythmic events (Disertori *et al*, 2016; Gulati *et al*, 2013c). It has been proposed that LGE-CMR may be able to improve the selection of patients who benefit from ICD implantation (Arbustini *et al*, 2017). However, up until now there has been a paucity of data examining the relationship between LGE extent, location and pattern and specific outcomes.

Our data suggest that measures based on LGE location are better than those based on extent for risk prediction. We demonstrate that patients with septal LGE were at highest risk of death whilst those with free-wall LGE were at similar risk to those without LGE. Accordingly, a model based on the presence of septal LGE best predicted all-cause mortality. While septal LGE was also associated with increased SCD events, the greatest risk was seen with concomitant septal and free-wall LGE. A model accounting for the greater risk associated with concomitant LGE in the septum and free-wall was most effective for SCD. Additionally, sub-epicardial or multiple patterns of LGE were associated with a high-risk of SCD events. These

data add important new information on how to best to use LGE-CMR in risk stratification, an area of unmet need (Arbustini *et al*, 2017; Kober *et al*, 2016).

Similar to our results, septal LGE has been associated with worse prognosis in myocarditis (Grani *et al*, 2017). The variation in risk based on location may be explained by differences in aetiological substrate, scar microstructure and geographical effects. Idiopathic DCM is most commonly associated with septal mid-wall LGE whilst a previous episode of myocarditis, the cause of a third of DCM, is often associated with free-wall LGE (Mahrholdt *et al*, 2006). Different insults may create fibrosis with different microstructures and varying levels of risk. Septal LGE also has a greater effect on the right ventricle and is more likely to involve the proximal conduction system. It may therefore be more likely to result in worsening HF and conduction disease.

Inherited cardiomyopathies may have contributed to the increased risk of SCD events associated with sub-epicardial or multiple patterns of LGE and concomitant LGE in the septum and free-wall. For example, lamin cardiomyopathies are characterised by mid-wall and sub-epicardial LGE in multiple locations and are associated with malignant arrhythmias (Pasotti *et al*, 2008; Pinto *et al*, 2016a). It is recognised that left ventricular forms of arrhythmogenic cardiomyopathy constitute part of the DCM spectrum (Pinto *et al*, 2016a; Pinto *et al*, 2016b). While cases of suspected ARVC were excluded, it is possible that our cohort included left-dominant disease, characterised by sub-epicardial fibrofatty replacement. This reflects 'real-world' clinical populations. Genetic substrate and fatty infiltration are likely to predispose to arrhythmias in this group. Interestingly, sub-epicardial LGE was associated with a marked increase in the risk of SCD events without a similar increase in all-cause mortality. This suggests a relatively low-risk of death from competing causes and a high likelihood that these patients may gain longevity from ICD therapy (Cleland *et al*, 2017b).

We also demonstrate a non-linear relationship between LGE extent and outcome, such that small degrees of fibrosis were associated with a large increase in risk, particularly with regards to SCD events. Similar to previous studies, we confirm good reproducibility between operators in LGE quantification (Mikami *et al*, 2014; Neilan *et al*, 2013). The non-linear relationship may be explained by the multifactorial disease process. Replacement fibrosis is one of several processes contributing to ventricular arrhythmogenesis. It is likely that the synergistic presence of multiple features leads to ventricular arrhythmia rather than one factor in a linear dose-dependent manner. In addition, it appears that risk is influenced by fibrosis microstructure and heterogeneity, not simply mass. Areas of scar with the greatest heterogeneity will cause the largest variation in conduction velocities and the greatest chance of creating re-entrant arrhythmia. Computational modelling of scar microstructure and its effect on electrical propagation offers the potential to provide further insights into the arrhythmic risk associated with specific regions of scar (Arevalo *et al*, 2016).

Localised LGE at the ventricular insertion areas is common, even in healthy volunteers. What this represents and its significance is uncertain. Examining this was beyond the scope of this study; therefore, localised LGE at the ventricular insertion areas was not included. Quantifying the 'gray-zone' surrounding an area of replacement fibrosis was proposed in the context of myocardial infarction (Yan *et al*, 2006). There is a lack of histological correlation examining this concept in DCM. Given the ambiguity over what this technique measures in DCM, we chose not to include it in our analysis.

4.6.1 Limitations

Single center studies are susceptible to selection bias. However, our registry includes patients with a complete spectrum of disease severity referred from secondary and tertiary centres with

a comprehensive range of common indications. In addition, the baseline characteristics are similar to other studies (McNamara *et al*, 2011). Whilst data from a proportion of patients have been presented in a previous study (Gulati *et al*, 2013c), patients in this larger cohort had extended follow-up for the purpose of this investigation. The large number of patients and events affords greater statistical power and enables the investigation of multiple statistical models. The smaller number of patients in sub-groups such as those with focal or sub-epicardial LGE does, however, limit the interpretation of this specific data.

We acknowledge that the use of different contrast agents has the potential to impact upon the quantification of LGE. However, there was no difference in the quantity, pattern or location of LGE for those patients scanned with gadobutrol compared to gadopentetate dimeglumine (*Appendix*). In addition, the associations between LGE and outcome remain similar when patients are divided based on contrast agent administered and there is no difference in the estimated effect of LGE on outcome between groups (*Appendix*).

Parametric mapping was not available at the outset of the current study and was therefore not included in the current analysis. This technique has the advantage of identifying diffuse global myocardial changes which LGE imaging may not detect. Previous work has demonstrated associations between native T1 values and mortality and HF outcomes in DCM (Puntmann *et al*, 2016). Given the possible role of diffuse interstitial fibrosis in arrhythmia generation, parametric mapping offers hope in the identification of those at risk of SCD. We eagerly await further data examining the incremental value of parametric mapping in addition to LGE. Our data suggest the need to examine the incremental value of this technique in addition to the presence of septal LGE.

4.7 Conclusion

We demonstrate a large increase in all-cause mortality and SCD risk with small amounts of LGE. The incremental value of LGE extent is therefore limited. In addition, we demonstrate that septal LGE is associated with all-cause mortality and concomitant LGE in the septum and free-wall is associated with the greatest risk of SCD events.

Chapter 5

5 Sex and Age-Based Differences in the Natural History and Outcome of Dilated Cardiomyopathy

Halliday BP, Gulati A, Ali A et al. Sex and Age-Based Differences in the Natural History and Outcome of Dilated Cardiomyopathy. Eur J Heart Fail. 2018 Jun 3. doi: 10.1002/ejhf.1216. [Epub ahead of print]

5.1 Hypotheses

4. ***The all-cause mortality rate and the rate of death from non-sudden causes rises with advancing age in patients with dilated cardiomyopathy, while the rate of sudden cardiac death increases less steeply and declines as a proportion of overall deaths***

5. ***There is no difference in outcome between men and women with dilated cardiomyopathy***

5.2 Abstract

Background: The relationship between sex, age and the natural history of DCM is poorly understood. Defining these associations may improve understanding of the disease and help personalise management.

Methods: We used proportional hazard modelling to examine the association between sex, age and all-cause mortality, CV, sudden and non-sudden death in patients with DCM referred for investigation from 2000 to 2011.

Results: Overall, 881 patients (290 women, median age 52 years) were followed for a median of 4.9 years. Women were more likely to present with HF (64.0% vs 54.5%; p=0.007) and had more severe symptoms (p<0.001) compared to men. Women had smaller LVEDVi (125ml/m^2 vs 135ml/m^2, p<0.001), higher LVEF (40.2% vs 37.9%, p=0.019) and were less likely to have mid-wall LGE (23.0% vs 38.9%, p<0.0001). During follow-up 149 (16.9%) patients died, including 41 (4.7%) who died suddenly. After adjustment, all-cause mortality (HR 0.61; 95%CI 0.41:0.92; p=0.018) was lower in women, with similar trends for cardiovascular (HR 0.60; 95%CI 0.35-1.05 ;p=0.07), non-sudden (HR 0.63; 95%CI 0.39-1.02; p=0.06) and sudden death (HR 0.70, 95%CI 0.30:1.63; p=0.41). All-cause mortality (per 10 yrs: HR 1.36, 95%CI 1.20-1.55; p<0.00001) and non-sudden death (per 10 yrs: HR 1.51, 95%CI 1.26 – 1.82; p<0.00001) increased with age. Cumulative incidence curves confirmed increased all-cause mortality driven by non-sudden death in patients >60 years of age that was less marked in women.

Conclusion: Women with DCM have better survival compared to men, which may partly be due to less severe LV dysfunction and a smaller scar burden. There is increased mortality driven by non-sudden death in patients >60 years of age that is less marked in women. Outcomes with contemporary treatment were favourable, with a low incidence of SCD.

5.3 Background

DCM is a heterogeneous condition manifest in a diverse group of patients due to a combination of underlying genetic susceptibility and environmental insults (Japp *et al*, 2016). The prognosis of many patients with DCM remains poor and more precise risk stratification and personalised therapy may considerably improve outcomes. Sex and age are two simple, universally available patient characteristics that deserve consideration.

Data from large registries suggest that women with HF have better transplant-free survival compared to men (Martinez-Selles *et al*, 2012). Whether this relates to a higher proportion of non-ischaemic HF in women or whether this is independent of aetiology remains controversial (Hsich *et al*, 2009). DCM is known to affect men more commonly than women (McNamara *et al*, 2011), however detailed data comparing differences in disease phenotype, severity and outcome between sexes are lacking.

The DANISH study found that implantation of an ICD did not reduce overall mortality; the authors emphasised the need for more precise selection of patients with DCM for ICD implantation (Kober *et al*, 2016). Sub-group analysis demonstrated a mortality benefit with ICD implantation in patients aged <59 years and a trend towards worse outcomes in those >68 years. The explanation for these findings is unclear but a higher rate of death from competing causes later in life may dilute the benefit of an ICD. It is also possible that those presenting later in life have a lower incidence of ventricular arrhythmias or that patients who are more arrhythmia-prone are less likely to survive to an older age. Examining the rates of death from non-sudden and sudden causes according to sex and age could help inform management strategy.

5.4 Methods

5.4.1 Patient Cohort

Patients with suspected DCM referred to our centre for CMR or evaluation in the Cardiomyopathy Clinic between January 2000 and December 2011 were screened.

Details of the inclusion and exclusion criteria have been described in Section 2.1**.** Of 925 patients who met the inclusion criteria, 9 moved abroad and 42 failed to provide informed consent. The final analysis included 881 patients.

An ischaemic aetiology was considered in all cases and excluded as follows. All those with infarct patterns of LGE were excluded (Assomull *et al*, 2011). In addition, CAD was excluded by invasive coronary angiography in 78.4%. A further 7.1% had functional imaging without evidence of inducible ischemia. Of the remaining patients (of whom 41.1% women), none had angina, all were considered to be at low-risk of CAD by their attending physicians and the majority (n=82; 9.2%) were aged <40 years; accordingly, coronary angiography was not performed (Ponikowski *et al*, 2016). None of these patients underwent coronary revascularisation or suffered an acute coronary syndrome during follow-up.

5.4.2 CMR Protocol & Image Analysis

All patients underwent CMR using the standardised protocol detailed in Section 2.2**.** Volumetric analysis (Section 2.3**)** was performed by independent operators blinded to outcomes.

5.4.3 End-points

The primary outcome of interest was all-cause mortality. Secondary end-points were cardiovascular, non-sudden and sudden cardiac death. Deaths were confirmed using the UK Health and Social Care Information Service to ensure none were missed. The cause of death was confirmed by an independent adjudication committee of cardiologists, blinded to CMR data, using a combination of medical records, death certification and post-mortem results in line with ACC/AHA guidance (Buxton *et al*, 2006; Hicks *et al*, 2015). SCD was defined as unexpected death either within 1 hour of the onset of cardiac symptoms in the absence of progressive cardiac deterioration; during sleep; or within 24 hours of last being seen alive (Hicks *et al*, 2015).

5.4.4 Patient Follow-up

Patients were followed-up as detailed in Section 2.4. The duration of follow-up was calculated from the baseline scan until an end-point occurred or last patient contact.

5.4.5 Statistical Analysis

Differences in baseline characteristics amongst men and women and between those below and above the age of 60 years were examined using the Mann-Whitney test for continuous data and the Fisher's Exact test for categorical data. Proportional hazard modelling was used to analyse the association between age (as a continuous variable) and sex and each end-point. Multivariable models were adjusted for age, sex, LVEF, NYHA symptoms class, LBBB, AF, smoking status, the presence of LGE on CMR and the use of device therapy (as a time-varying covariate) given the potential for these factors to confound the association. Cumulative

incidence curves were produced for the end-points for men and women and those over and under the age of 60 years. Event times were measured from the baseline CMR date for a maximum of 10 years. Results are presented as HRs with 95% CIs. A p value of <0.05 was taken as significant.

5.5 Results

The study population included 881 patients. The median age was 52 (IQR: 42-63) years, the median LVEF was 39% and 290 (32.9%) were women. The proportion of women recruited did not change based on the year of the baseline scan (p=0.86) (*Figure 5.1)*.

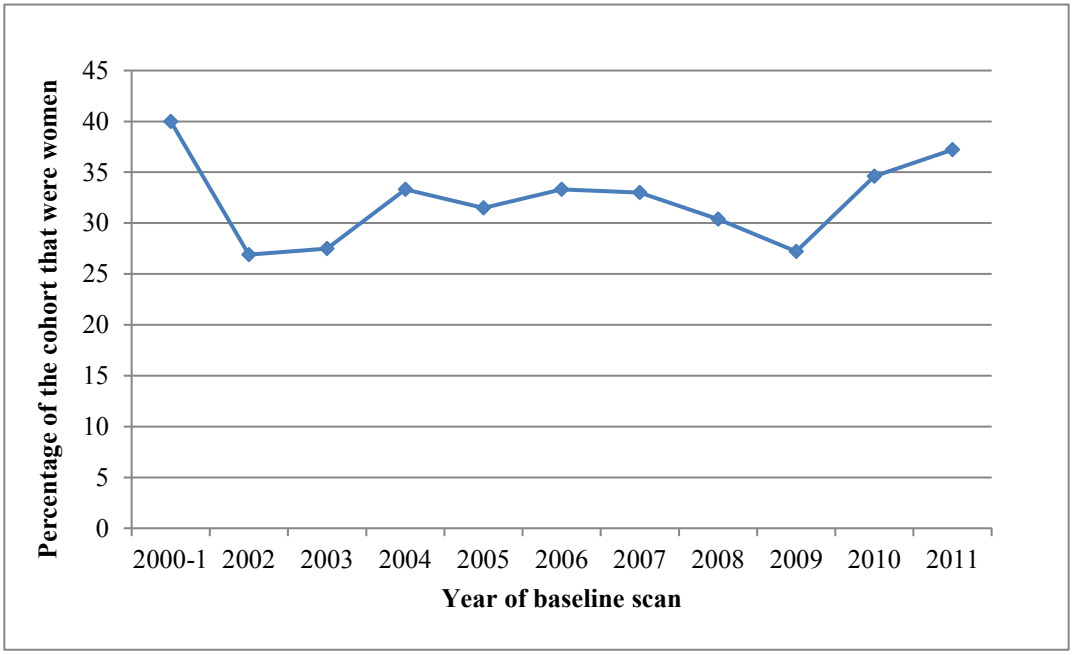

Figure 5.1. Percentage of women recruited based on the year of baseline scan.

5.5.1 Baseline Characteristics

Sex-Based Differences in Baseline Characteristics

Baseline characteristics are presented in *Table 5.1*. Women were less likely to have a history of AF ($p<0.001$) and moderate alcohol excess ($p<0.001$) and more likely to have LBBB ($p<0.001$) compared to men. HF was more likely to be the presenting indication in women compared to men (64.0 vs 54.5%; $p=0.007$) whilst a greater proportion of men (22.0% vs 13.8%) were referred after presenting with arrhythmia ($p=0.004$). In keeping with this, NYHA class was worse in women compared to men ($p<0.001$). However, on CMR, women had smaller LVEDVi ($p<0.006$), indexed right ventricular end-diastolic volumes ($p<0.001$) and LAVi ($p<0.001$), lower LVEF ($p=0.005$) and right ventricular ejection fraction ($p<0.001$) and a lower prevalence of mid-wall LGE ($p<0.001$). The results remained qualitatively the same after indexing values using height rather than body surface area.

Apart from a higher prescription rate of ARBs in women compared to men ($p=0.04$), pharmacological therapies for HF were similar between sexes.

Age-Based Differences in Baseline Characteristics

Patients aged >60 years had worse NYHA class ($p=0.001$), were more likely to be prescribed loop diuretics ($p=0.001$) and had higher systolic blood pressures ($p<0.001$); they were more likely to have a history of AF ($p<0.001$), hypertension ($p<0.001$) and LBBB ($p<0.001$) but less likely to have a family history of DCM ($p=0.015$) or to be referred in the context of family screening ($p<0.001$). On CMR, those aged >60 years had lower LVEF ($p<0.001$) and greater LAVi ($p<0.001$).

	Sex			Age		
	Men (n=591)	**Women (n=290)**	***P****	**<60 (n=597)**	**≥60 (n=284)**	***P****
Mean Age (SD), yrs	52 (14.8)	53 (15.1)	0.099	44 (10.8)	69 (6.1)	-
Men, n (%)	-	-	-	418 (70.0)	173 (60.9)	0.009
Body surface area, m^2	2.05 (0.20)	1.77 (0.19)	<0.001	1.97 (0.24)	1.92 (0.22)	0.006
Heart rate, bpm	72.7 (14.4)	74.0 (14.2)	0.079	73.1 (14.4)	73.1 (14.4)	0.96
Systolic blood pressure, mmHg	120.2 (17.3)	120.2 (18.0)	0.89	118.3 (17.3)	124.2 (17.4)	<0.001
Diastolic blood pressure, mmHg	72.9 (10.9)	71.4 (10.4)	0.041	71.9 (11.0)	73.4 (10.4)	0.072
Smoker, n (%)	117 (19.8)	32 (11.0)	0.001	122 (20.4)	27 (9.5)	<0.001
Moderate Alcohol Excess, n (%)	97 (16.4)	5 (1.7)	<0.001	76 (12.7)	26 (9.2)	0.14
Atrial fibrillation, n (%)	140 (23.7)	28 (10.0)	<0.001	86 (14.4)	82 (27.9)	<0.001
Hypertension, n (%)	123 (20.8)	68 (23.4)	0.38	99 (16.6)	92 (32.4)	<0.001
Diabetes mellitus, n (%)	50 (8.5)	27 (9.3)	0.70	44 (7.4)	33 (11.6)	0.041
Hypercholesterolaemia, n (%)	124 (21.0)	55 (19.0)	0.53	92 (15.4)	87 (30.6)	<0.001
Cerebrovascular accident, n (%)	8 (1.3)	3 (1.1)	1.00	6 (1.0)	5 (1.7)	0.52
Family History of DCM, n (%)	50 (8.5)	37 (12.8)	0.054	73 (12.3)	14 (4.9)	<0.001
Family History of SCD, n (%)	39 (6.6)	24 (8.3)	0.40	48 (8.1)	15 (5.3)	0.16
Left bundle branch block, n (%)	134 (22.7)	124 (42.9)	<0.001	140 (23.5)	118 (41.8)	<0.001
Medications						
Beta Blocker, n (%)	433 (73.4)	209 (72.1)	0.69	435 (72.9)	207 (73.1)	1.00
ACE Inhibitor, n (%)	433 (73.4)	198 (68.3)	0.13	429 (71.9)	202 (71.1)	0.87
ARB, n (%)	109 (18.5)	71 (24.5)	0.041	113 (19.0)	67 (23.7)	0.11
Loop Diuretic, n (%)	262 (44.3)	125 (43.1)	0.77	233 (39.0)	154 (54.2)	<0.001
MRA, n (%)	195 (33.0)	108 (37.4)	0.20	208 (34.9)	95 (33.5)	0.70
NYHA						
I, n (%)	267 (45.3)	88 (30.8)	<0.001	263 (44.1)	92 (32.9)	0.001
II, n (%)	231 (39.2)	125 (43.7)		219 (36.7)	137 (48.9)	
III / IV, n (%)	92 (15.6)	73 (25.5)		114 (19.1)	51 (18.2)	
Indications						
Heart Failure, n (%)	322 (54.5)	186 (64.1)	0.007	346 (57.9)	162 (57.0)	0.83
Arrhythmic, n (%)	130 (22.0)	40 (13.8)	0.004	116 (19.4)	54 (19.0)	0.93
Family screening, n (%)	25 (4.2)	15 (3.4)	0.61	38 (6.3)	2 (0.7)	<0.001
Other , n (%)	114 (19.2)	49 (16.9)	0.41	120 (20.1)	43 (15.1)	0.08
CMR Measurements						
$LVEDVi^{BSA}$ (ml/m^2)	135.4 (43.3)	125.3 (35.2)	<0.001	132.2 (42.1)	131.8 (39.0)	0.81
$LVEDVi^{Height}$ (ml/m)	154.9 (50.3)	135.4 (38.1)	<0.001	149.9 (50.2)	145.6 (41.4)	0.54
LVEF (%)	37.9 (12.9)	40.2 (12.0)	0.019	39.1 (13.0)	37.5 (11.8)	0.025
LV Mass $Index^{BSA}$ (g/m^2)	100.1 (27.9)	87.9 (25.6)	<0.001	95.6 (27.9)	97.2 (27.3)	0.33
LV Mass $Index^{Height}$ (g/m)	115.1 (34.2)	95.2 (28.2)	<0.001	109.0 (35.1)	107.9 (30.6)	0.91
$RVEDVi^{BSA}$ (ml/m^2)	94.5 (27.0)	79.1 (21.1)	<0.001	92.5 (26.0)	83.2 (25.7)	<0.001
$RVEDVi^{Height}$ (ml/m)	108.2 (31.0)	86.3 (24.6)	<0.001	105.0 (30.9)	92.8 (29.1)	<0.001
RVEF (%)	48.9 (13.6)	55.4 (14.9)	<0.001	50.0 (14.4)	53.3 (13.9)	0.003
$LAVi^{BSA}$ (ml/m^2)	68.6 (26.9)	61.0 (24.0)	<0.001	64.1 (24.3)	70.3 (29.5)	0.001
$LAVi^{Height}$ (ml/m)	78.6 (31.1)	65.9 (25.6)	<0.001	72.7 (28.2)	78.4 (33.3)	0.014
LGE (presence)	229 (38.9)	66 (23.0)	<0.001	189 (31.9)	106 (37.5)	0.11

Table 5.1. Baseline Characteristics

Mann-Whitney Test used to compare continuous data; Fisher's Exact for categorical data.

5.5.2 Primary and Secondary End-points

During follow-up, 149 (16.9%) patients died, 99 (11.2%) due to CV causes (including 50 HF and 41 SCDs) and a further 50 (5.7%) due to non-cardiovascular causes (including cancer, sepsis, lung disease, gastrointestinal haemorrhage, massive haemoptysis and small bowel obstruction). Rate of events per 100 patient years by sex and age are included in (*Table 5.2*).

	Rate per 100 patient years (95% CI)			
	Men (N=591)	**Women (N=290)**	**<60 (N=597)**	**≥60 (N=284)**
All-Cause Mortality	3.6 (3.0, 4.3)	2.3 (1.7, 3.2)	2.4 (1.9, 3.0)	4.9 (3.9, 6.2)
Cardiovascular	2.5 (2.0, 3.1)	1.4 (0.9, 2.1)	1.8 (1.4, 2.3)	2.8 (2.1, 3.8)
Non-Sudden Death	2.6 (2.1, 3.2)	1.7 (1.2, 2.5)	1.5 (1.2, 2.0)	4.1 (3.2, 5.3)
Sudden Cardiac Death	1.0 (0.7, 1.4)	0.6 (0.3, 1.1)	0.9 (0.6, 1.3)	0.8 (0.5, 1.5)

Table 5.2. End-point events per 100 patient years by sex and age-group.

5.5.3 Association between Sex and Outcome

All-cause mortality (HR 0.64; 95% CI 0.44-0.94; p=0.020) and CV death (HR 0.58; 95% CI 0.36-0.93; p=0.025) were lower in women compared to men with similar trends for non-sudden (HR 0.68, 95% CI 0.44-1.05; p=0.088) and SCD (HR 0.58, 95% CI 0.28-1.22; p=0.15) (*Figure 5.2 & Table 5.3)*. Following adjustment for age, LVEF, NYHA class, AF, LBBB, smoking status, LGE and CRT or ICD implantation, all cause-mortality (HR 0.61; 95% CI 0.41:0.92; p=0.018) was lower in women compared to men with similar trends for CV (HR 0.60; 95% CI 0.35-1.05; p=0.07) and non-sudden death (HR 0.63; 95% CI 0.39-1.02; p=0.06) (*Figure 5.2 & Table 5.3*).

During follow-up, of those with a LVEF≤35% at baseline, 32 (32.3%) women and 99 (38.8%) men underwent ICD implantation (p=0.27). Of those with a LVEF ≤35% and LBBB at baseline, 37 (74.0%) women and 43 (59.7%) men received CRT (p=0.12). Women with LBBB

had lower mortality compared to men with LBBB (HR 0.39; 95% CI 0.20-0.78; p=0.008). This was not significantly different from the HR for women without LBBB compared to men without LBBB (HR 0.81, 95% CI 0.52-1.26, p=0.35; heterogeneity p=0.086). Of those with an ICD, the rate of appropriate shocks was similar for women and men (HR 0.94; 95%CI: 0.47-1.89; p=0.86). Of those without an ICD, women tended to be less prone to SCD than men but this did not achieve statistical significance (HR 0.60; 95%CI: 0.29-1.27; p=0.18).

5.5.4 Association between Age and Outcome

All-cause mortality increased with age (per 10 years: HR 1.32, 95% CI 1.17-1.48; p<0.00001), largely driven by a rise in the rate of death from non-sudden causes (per 10 years: HR 1.51, 95% CI 1.29 – 1.78; p<0.00001) (*Figure 5.2 & Table 5.3*). Death from CV (HR 1.12; 95% CI 0.95-1.31; p=0.18) and sudden causes (per 10 years: HR 0.92, 95% CI 0.73– 1.15; p=0.47) did not significantly change with advancing age. Results were similar in univariable and multivariable analyses (*Figure 5.2 & Table 5.3*).

During follow-up, of those with a LVEF≤35% at baseline, 86 (39.1%) of those <60 years of age and 45 (36.3%) of those older underwent ICD implantation (p=0.91). Of those with a LVEF ≤35% and LBBB at baseline, 46 (70.8%) of those <60 years of age underwent CRT compared to 34 (59.6%) of those older (p=0.25). Of those with an ICD, there was no difference in the rate of appropriate shocks with advancing age (per 10 years: HR 0.89; 95%CI: 0.71-1.11; p=0.30). Of those without an ICD, there was no difference in the rate of SCD with advancing age (per 10 years: HR 0.90; 95%CI: 0.72-1.12; p=0.35).

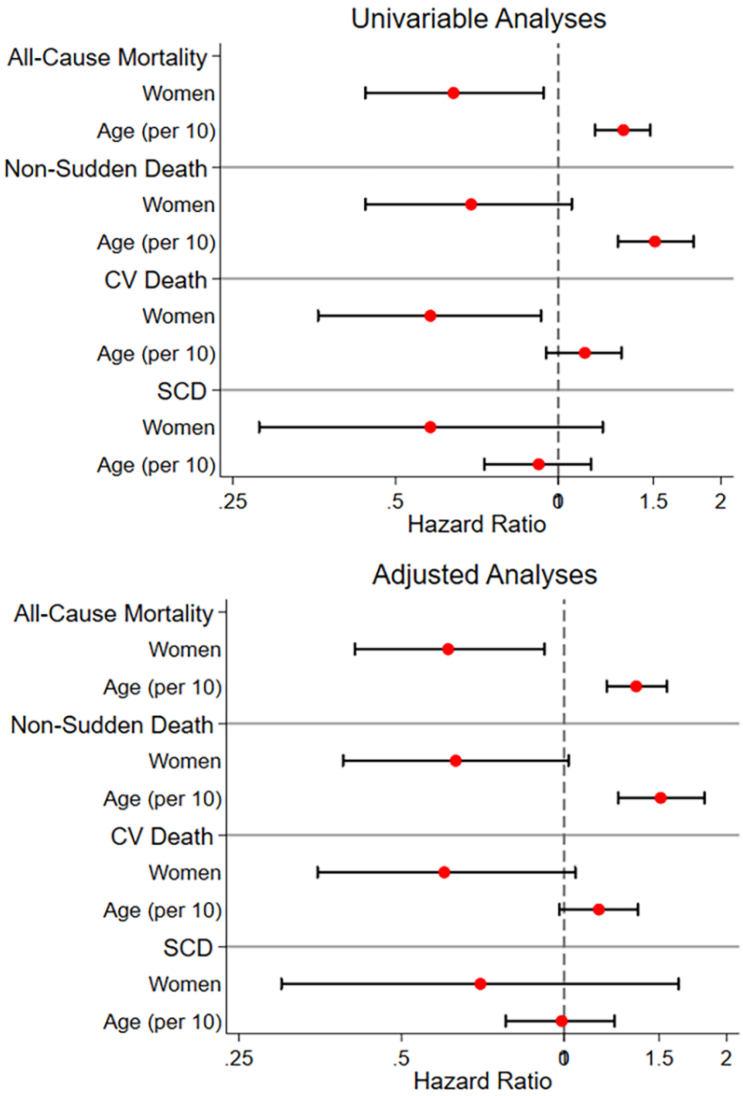

Figure 5.2. Hazard ratios for the end-points by sex and age.

Forrest plots demonstrating unadjusted and adjusted hazard ratios for the primary and secondary end-points stratified by sex and age.

In keeping with the proportional hazard analysis, cumulative incidence curves demonstrated increased all-cause mortality in patients over 60 years of age compared to those younger that was driven by death from non-sudden causes, without a similar rise in SCD (*Figure 5.3*). The rise in all-cause mortality and non-sudden death was less marked in women compared to men. In women under the age of 60 years, 5-year mortality estimates from Kaplan-Meier curves was 6.7% (95% CI 3.7:11.8) compared to 11.9% (95% CI 6.7:21.0) in those older. In men under the age of 60 years, 5-year mortality estimates from Kaplan-Meier curves was 13.5% (95% CI 10.3:17.5) compared to 24.4% (95% CI 18.3:32.2) in those older.

HR for Women vs Men	All-Cause Mortality		CV Death		Non-Sudden Death		SCD	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Univariable	0.64 (0.44, 0.94)	0.020	0.58 (0.36, 0.93)	0.025	0.68 (0.44, 1.05)	0.088	0.58 (0.28, 1.21)	0.15
Multivariable*	0.61 (0.41, 0.92)	0.018	0.60 (0.35, 1.05)	0.074	0.63 (0.39, 1.02)	0.060	0.70 (0.30, 1.63)	0.41
HR based on Age (per 10 years increase)	**All-Cause Mortality**		**CV Death**		**Non-Sudden Death**		**SCD**	
	HR (95% CI)	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
Univariable	1.32 (1.17, 1.48)	<0.00001	1.12 (0.95, 1.31)	0.18	1.51 (1.29, 1.78)	<0.00001	0.92 (0.73, 1.15)	0.47
Multivariable†	1.36 (1.20, 1.55)	<0.0001	1.16 (0.98, 1.37)	0.078	1.51 (1.26, 1.82)	<0.00001	0.99 (0.78, 1.24)	0.90

Table 5.3. Hazard modelling for primary and secondary end-points

*adjusted for LVEF, NYHA class, AF, LBBB, smoking, the presence of LGE, age and the presence of an ICD or CRT as time varying co-variates

† adjusted for LVEF, NYHA class, AF, LBBB, smoking, the presence of LGE, sex and the presence of an ICD or CRT as time varying co-variates

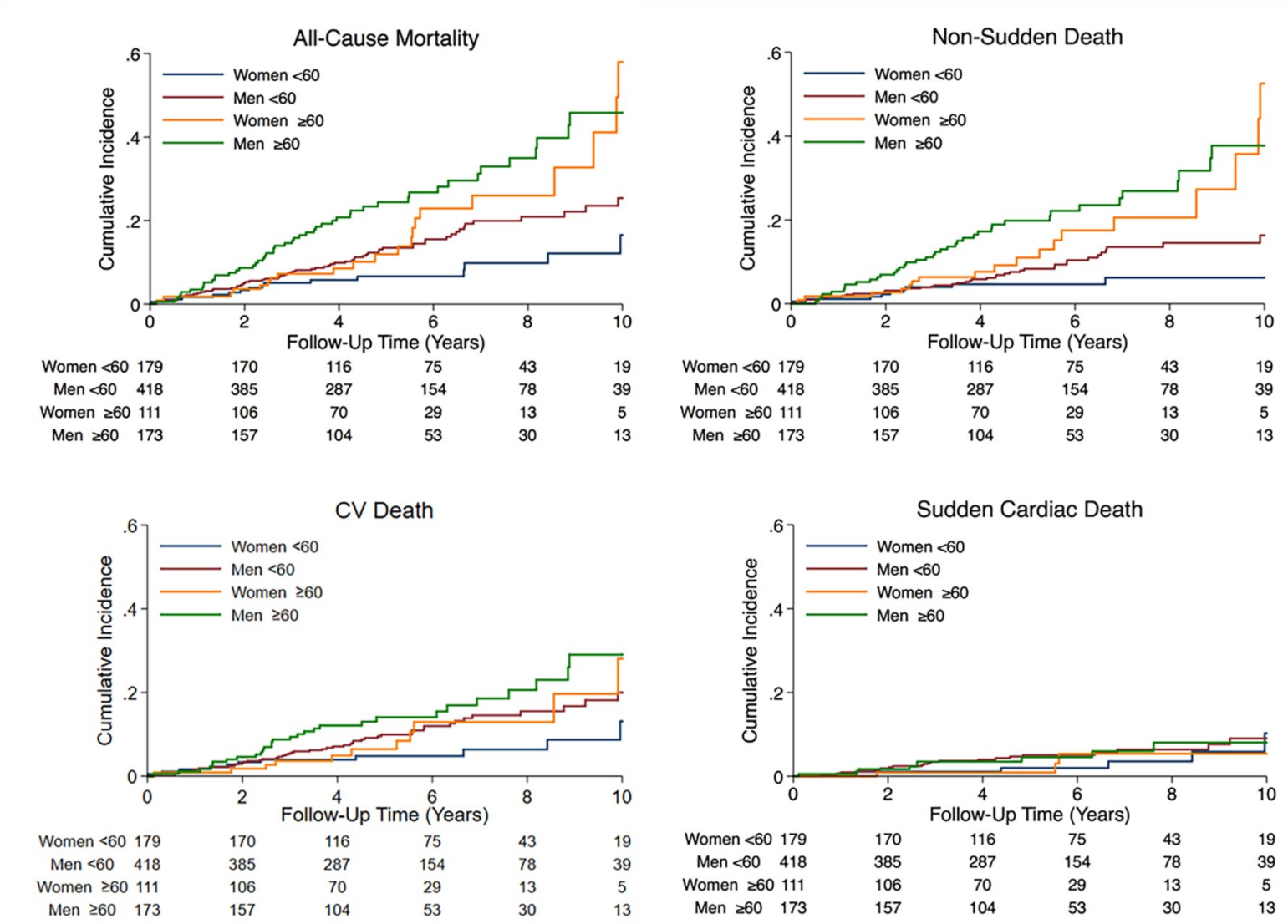

Figure 5.3. Cumulative incidence curves based on the age and sex of patients.

Cumulative incidence curves of the time to first event for men and women aged less than 60 years and greater than 60 years.

5.6 Discussion

This is the first study to specifically examine the impact of sex and age on the phenotype and outcome of DCM in a well-characterised population. Women with DCM had a lower mortality than men even after adjusting for several key prognostic variables, including implanted devices. The slightly higher rate of CRT amongst women, reflecting the higher prevalence of LBBB, did not account for the differences in outcome. Interestingly, women had more severe symptoms despite having less severe cardiac dysfunction, a lower burden of scar and similar pharmacological therapy compared to men. Our data show that mortality is higher in patients over 60 years of age and that this is predominantly driven by death from non-sudden causes rather than SCD. The proportion of deaths that were sudden reduced with advancing age. Overall outcomes with contemporary treatment were favourable. For example, women under the age of 60 years had a 5-year mortality rate of only 6.7%. Sudden death accounted for only 27.5% of overall mortality, in keeping with recent data from Shen and colleagues demonstrating a reduction in this mode of death with current HF therapy (Shen *et al*, 2017).

A detailed description of differences in the outcome of men and women in a broad well-characterised DCM population has been lacking until now. For patients with HF of mixed aetiology, several studies have reported a lower mortality amongst women compared to men but this may reflect the higher prevalence of CAD amongst men, which carries a worse prognosis (Hsich *et al*, 2009). Studies in patients with DCM secondary to specific genetic mutations also suggest that men have a worse prognosis than women, however, it has been unclear whether this is genotype-specific (Herman *et al*, 2012; van Rijsingen *et al*, 2012). Our study in patients with well-characterised DCM is not confounded by CAD or specific to small sub-groups with specific genetic causes.

This study offers several possible explanations for the better prognosis amongst women with DCM including less severe cardiac dysfunction and lower scar burden. Similar to previous multi-centre registries (McNamara *et al*, 2011) there was a predominance of men in our study, making up almost 70% of the cohort. A greater susceptibility to developing ventricular impairment in men may explain this disparity. Truncating mutations in *TTN* are thought to make individuals susceptible to developing contractile impairment and men with such variants have been shown to have worse outcome than women (Herman *et al*, 2012). Protection from CV disease in pre-menopausal women has been linked with sex hormones, including estradiol (Payne *et al*, 2004). In patients with arrhythmogenic cardiomyopathy estradiol appears to have a protective and testosterone a detrimental effect across both sexes (Akdis *et al*, 2017). In the same study, increased levels of estradiol reduced myocyte apoptosis in an in vitro model of arrhythmogenic cardiomyopathy, while increased testosterone levels potentiated it. Myocyte death is central to the development of replacement fibrosis and it is possible that the different impact of these sex hormones on myocyte survival contributes to a higher prevalence of replacement fibrosis in men. A sex disparity in the prevalence of replacement fibrosis in DCM is consistent with other studies and has also been demonstrated in acute myocarditis and aortic stenosis (Cocker *et al*, 2009; Elming *et al*, 2017; Treibel *et al*, 2017). Other studies have demonstrated sex differences in gene expression in patients presenting with heart failure secondary to DCM and these may be responsible for differences in phenotype and outcome (Heidecker *et al*, 2010).

In our cohort, a greater percentage of women were referred following a presentation with HF whilst an arrhythmic presentation was more common in men. In keeping with this and similar to previous studies in patients with HF, women reported more severe functional limitation compared to men (Martinez-Selles *et al*, 2012). Whether the greater HF symptom burden in

women is explained by differences in pathophysiology, symptom reporting or perception is unclear. HF secondary to diastolic dysfunction is more common in women (Hsich *et al*, 2009) but in our cohort, LAVi, a useful marker of chronically elevated filling pressure, was smaller in women. Other markers of diastolic function, exercise performance and natriuretic peptides were not available for the current analysis but would provide interesting insights.

LBBB was more common in women compared to men. This observation is particularly interesting as LBBB is often attributed to more advanced disease; however, in our study women had other markers of less severe disease. Previous work in patients receiving CRT demonstrated that LBBB is associated with better survival in women compared to men, even when controlling for co-morbidities (Loring *et al*, 2013). Our data also demonstrated greater survival in women with LBBB compared to men with LBBB, despite similar rates of CRT. The mechanism explaining the greater incidence of LBBB in women and whether the prognostic significance of LBBB differs between sexes merits further research.

Our study also suggests that caution should be exercised with regards to the implantation of ICDs in patients over 60 years of age due to an increased risk of death from competing causes, lending support to the recent DANISH trial that demonstrated an absence of overall survival benefit with ICD therapy in patients aged >59 years (Kober *et al*, 2016). These data suggest that the lack of survival benefit with ICD therapy in older patients is because a higher proportion of deaths are non-sudden rather than a lower risk of arrhythmic death.

5.6.1 Limitations

This cohort, although large, was enrolled in a single center, introducing the possibility of selection bias. However, our referral base is broad and the baseline characteristics of the population are similar to other large cohorts (Merlo *et al*, 2015). The referral characteristics

and specifically the proportion of men and women referred remain stable over the study period. This approach also enables detailed CMR phenotyping using well-established protocols generating a well-characterised population.

For some secondary end-points, we had fewer events, limiting statistical power. Differences in disease characteristics between men and women may reflect differences in the time taken to seek medical attention after the onset of symptoms. However, the difference in all-cause mortality persisted following adjustment for indicators of disease severity at referral. Information on sex-specific variables including obstetric history, use of hormone replacement therapy or an oral contraceptive, age of menopause and previous gynaecological surgery was not available.

Finally, whilst the study demonstrates novel associations between outcome and sex and age, it does not define the cause of the difference in the outcomes. Further animal or cell-based work may provide novel insights into mechanisms.

5.7 Conclusion

The prognosis of women with DCM is, on average, better than for men. This may be partly attributed to a disease course characterised by less severe ventricular dysfunction and a smaller scar burden. The chance of death due to causes other than arrhythmias increases with age, rendering ICDs less effective in reducing all-cause mortality. Our data emphasise the importance of developing sex- and age-specific risk stratification and management approaches.

Chapter 6

6 Comprehensive Phenotyping of Patients with Dilated Cardiomyopathy and Improved Left Ventricular Ejection Fraction

6.1 Hypotheses

6. ***Patients with dilated cardiomyopathy and improved left ventricular ejection fraction will have fewer co-morbidities compared to those with dilated cardiomyopathy and reduced left ventricular ejection fraction.***

7. ***Patients with a previous diagnosis of dilated cardiomyopathy who have demonstrated improvement in left ventricular ejection fraction to >50% with normal indexed left ventricular end-diastolic volume and without symptoms of heart failure will have:***

    a. ***Normal concentrations of plasma NT-pro-BNP***

    b. ***Normal peak oxygen consumption on maximal treadmill exercise based on age and sex-specific normal ranges***

    c. ***Similar native T1 and global strain values on cardiovascular magnetic resonance compared to healthy volunteers***

    d. ***No evidence of late gadolinium enhancement on cardiovascular magnetic resonance***

6.2 Abstract

Background: Left ventricular reverse remodelling is common in patients with DCM. Whether this represents remission or recovery is unclear.

Methods: Patients with a prior diagnosis of DCM and LVEF <40%, who have subsequently demonstrated improvement in LVEF to ≥50% with a normal LVEDVi underwent comprehensive evaluation using CMR, cardiopulmonary exercise testing (CPET) and plasma NT-pro-BNP measurement. To explore the characteristics of those who reverse remodel, baseline characteristics were compared with a cohort of DCM patients who had LVEF<40%. In order to establish whether there was evidence of persistent subclinical myocardial dysfunction in those with improved LVEF, CMR, CPET and natriuretic peptide data were compared against values derived from healthy volunteers or published reference values from healthy populations.

Results: Patients with DCM and improved LVEF were less likely to have LBBB, LGE or a history of hypertension and had lower heart rate and higher systolic and diastolic blood pressure compared to patients with DCM and LVEF<40%. Overall, 35.2% of patients with improved LVEF had LGE and 53.7% had a NT-pro-BNP level above age- and sex-specific normal values (median 75.5ng/L, IQR: 43.0-134.3). Patients with DCM and improved LVEF also had lower than predicted peak VO_2 (mean percentage of the predicted VO_2: 92.6%, 95% CIs 88.3:97.0) compared to healthy reference values and 28.8% had a VE/VCO_2 slope >34. In addition, they had lower global radial (0.28 vs 0.57; p<0.0001) and circumferential strain (-0.15 vs -0.17; p=0.009) compared to healthy volunteers.

Conclusion: Patients with DCM and improved LVEF are distinct from patients with DCM and LVEF<40%. Despite improvement in LVEF, some patients have biochemical, functional and structural markers of persistent myocardial disease.

6.3 Background

LV reverse remodelling, defined as an improvement in LVEF and a reduction in LV size, is observed in 40% of well-treated DCM patients and is associated with favourable outcomes (Merlo *et al*, 2015). However, it is recognised, from studies in DCM and IHD, that there is a spectrum of improvement amongst patients who positively remodel (Basuray *et al*, 2014; Florea *et al*, 2016; Punnoose *et al*, 2011). Whilst reverse remodelling is usually defined by an increase in LVEF, it may be preferable to define *recovery* using a more comprehensive approach including functional, biochemical and imaging assessments of HF status.

Several techniques may enable better characterisation of this population. Cardiopulmonary exercise testing (CPET) enables the detection of impaired exercise performance. Low peak VO_2 and a VE/VCO_2 ratio of >34 are associated with adverse outcomes (Arena *et al*, 2004; Mancini *et al*, 1991; Ukkonen *et al*, 2008). CMR can detect persistent functional and structural abnormalities by calculating myocardial strain and assessing the presence of myocardial fibrosis. (Budge *et al*, 2012; Nakamori *et al*, 2017). Abnormal strain, elevated native T1 values and LGE are associated with adverse outcomes (Puntmann *et al*, 2016; Romano *et al*, 2018). Natriuretic peptides provide important prognostic information and enable the detection of subclinical myocardial stretch (Maisel *et al*, 2008; Ponikowski *et al*, 2016; Zaphiriou *et al*, 2005). Age- and sex-specific normal ranges have been derived from large studies of well-characterised normal subjects without signs of CV disease (McDonagh *et al*, 2004).

Comprehensive, prospective evaluation of DCM patients with improved LVEF has not been reported. Whether improvement in LVEF reflects true recovery or simply remission of disease with persistent subtle sub-clinical abnormalities is unknown. This has important therapeutic implications and may inform the risk of future relapse.

6.4 Methods

6.4.1 Patient Cohort

Patients with a prior diagnosis of DCM with a LVEF<40% and who subsequently demonstrated improvement in LVEF to >50% with a normal LVEDVi were recruited from our pre-existing registry (as described in Section 2.1), cardiomyopathy clinic and clinical CMR lists at the Royal Brompton Hospital. Additionally, patients were referred from a network of collaborating hospitals that agreed to act as Participant Identification Centres. A summary of the study was also included in patient newsletters and on the websites of Cardiomyopathy UK and Pumping Marvellous. Patients interested in taking part in the study subsequently contacted us and if suitable, a study visit was arranged. All patients gave written informed consent. The study was approved by the National Research Ethics Committee (Reference: 16/LO/0065).

6.4.2 Inclusion and Exclusion Criteria

Inclusion criteria included: 1) A prior diagnosis of DCM with LVEF <40%, 2) Current treatment with at least 1 of the following: loop diuretic, beta-blocker, ACE inhibitor, ARB or MRA, 3) A current LVEF ≥ 50% and a normal LVEDVi, 4) Absence of symptoms of HF (NYHA class I).

Exclusion criteria included an estimated glomerular filtration rate<30mls/min, pregnancy, more than moderate valve disease, angina and age <16 years.

6.4.3 Comprehensive Evaluation of Disease Phenotype

Patients underwent comprehensive CMR assessment and maximal CPET using treadmill ergometry and ramp protocols (section 6.4.4 and section 6.4.5). Blood was drawn for plasma NT-pro-BNP. Age- and sex-specific reference ranges for NT-pro-BNP from population studies were used (McDonagh *et al*, 2004).

6.4.4 Cardiovascular Magnetic Resonance Baseline Assessment

CMR was performed using a standardised protocol on a 3 Tesla scanner (*Skyra, Siemens, Erlangen, Germany*) (*Figure 6.1*). Localiser images were acquired using HASTE imaging. Following this resting long- and short-axis cine images were taken using breath-hold SSFP imaging, as described in Section 2.2.

In order to measure circumferential, radial and longitudinal myocardial strain, images were acquired using displacement encoding with stimulated echoes (DENSE) in 2-chamber and 4-chamber planes and in a short-axis plane at mid-ventricular level (Aletras *et al*, 1999; Budge *et al*, 2012).

Native T1 maps were also acquired at basal- and mid-ventricular level in short-axis planes, using a breath-hold 5-3-3 modified Look-Locker inversion recovery (MOLLI) sequence. Two maps were acquired in each plane. Post-contrast T1 maps were also acquired, 15 minutes after the administration of gadolinium, in identical locations to the pre-contrast maps, using the same breath-hold 5-3-3 MOLLI sequence. Pixel-wise maps were automatically generated by the sequence (*Figure 6.2*).

Immediately before and after the acquisition of post-contrast T1 maps, LGE imaging was performed, starting around 10 minutes after the intravenous administration of gadobutrol

(0.1mmol/kg), as described in Section 2.2. Images were acquired in identical short- and long-axis planes to cine imaging.

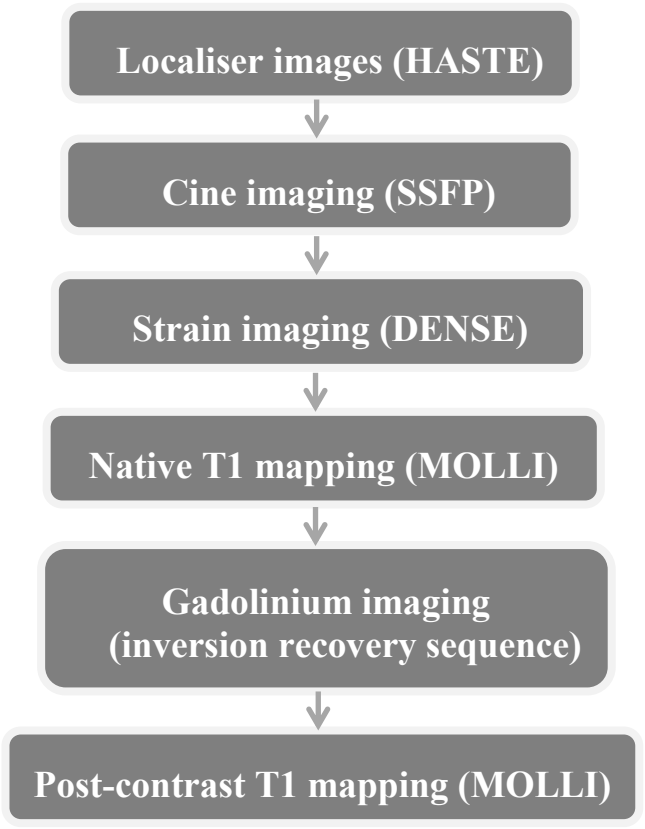

Figure 6.1. Protocol for cardiovascular magnetic resonance assessment.

Image Analysis

Volumetric analysis was carried out using CMR Tools (*Cardiovascular Imaging Solutions, London)* as described in Section 2.3.

T1 maps were analysed using CMR Tools (*Cardiovascular Imaging Solutions, London).* Raw images were initially inspected for artefact secondary to cardiac or respiratory motion. Those deemed satisfactory were analysed by drawing a crescent-shaped region of interest in the middle third of the septum, in order to avoid contamination of the myocardial signal with that

of the blood pool (*Figure 6.2*). On the same image, an additional circular region of interest was drawn in the blood pool, avoiding trabeculae and papillary muscles. The software was then used to calculate the T1 values from the specified regions.

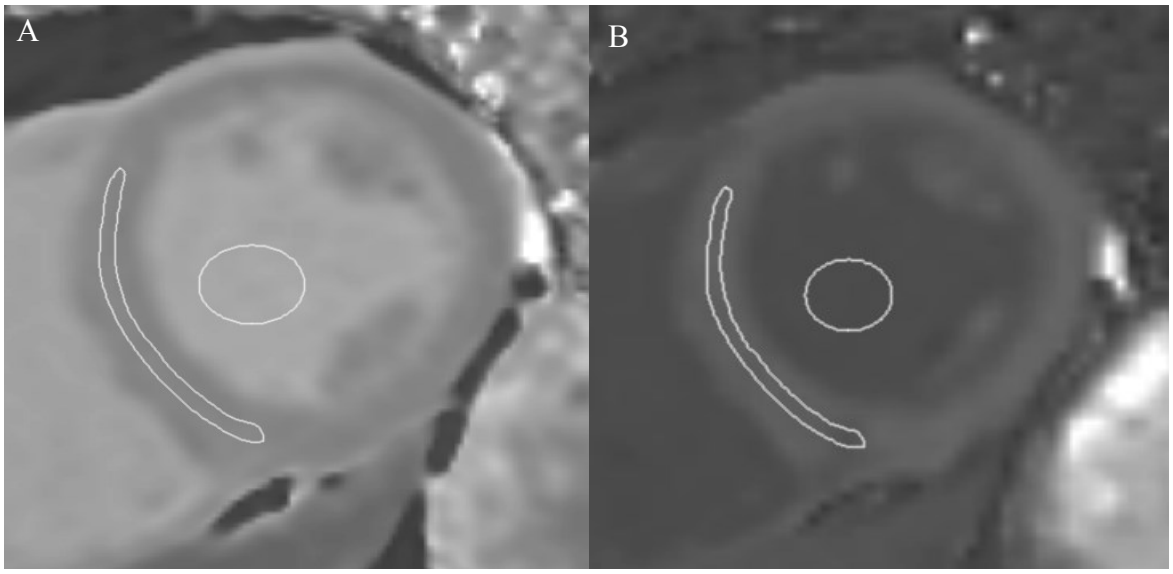

Figure 6.2. Native and post-contrast T1 maps
A: Native T1 map in a basal short-axis slice of the left ventricle. **B:** Post-contrast T1 map in the corresponding short-axis slice.

Using the native and post-contrast T1 values and the haematocrit value, measured immediately prior to the scan, the extracellular volume (ECV) fraction was calculated, using the following formula (Flett *et al*, 2010):

$$ECV - (1 - \text{haematocrit}) \times \frac{\left(\frac{1}{T1\ \text{myo post}} - \frac{1}{T1\ \text{myo pre}}\right)}{\left(\frac{1}{T1\ \text{blood post}} - \frac{1}{T1\ \text{blood pre}}\right)}$$

Myocardial strain was calculated from DENSE data using semi-automated software on Matlab (*Mathworks, Natick, USA*), developed by the University of Virginia (Suever *et al*, 2014). For long-axis images, a contour was placed in the mid-myocardium of the left ventricle in peak systole or diastole. For short-axis images, a region of interest, including the endocardial and epicardial borders of the LV, was defined. The contours were then propagated to the remaining phases of the cardiac cycle using motion-guided segmentation. Those phases with significant artefact were discarded and minor manual adjustments were made when necessary. Regional polar strain time curves were generated for radial and circumferential strain and contour strain/time curves for longitudinal strain. From this data, global longitudinal, circumferential and radial strain were calculated.

The presence of LGE was determined by an independent operator and judged to be present if seen in two orthogonal planes and in two-phase encoding directions.

6.4.5 Cardiopulmonary Exercise Test

Patients underwent CPET using maximal treadmill ergometry and dedicated ramp protocols (low, intermediate and high), under the direction of a specialist exercise physiologist. The exercise protocols were specifically designed for the study, with guidance from Professor Jonathan Myers (*Stanford University, USA*) and Professor Chip Lavie (*University of Queensland, Australia*) (*Appendix*). The protocols were designed to accommodate patients with a range of exercise capacities with the overall aim of getting each patient to achieve a total exercise time of 8-12 minutes, as previously described (Myers *et al*, 1994). Before the test, the Veteran Specific Activity Questionnaire was used to estimate the patient's current exercise capacity. The eventual protocol was chosen based on the estimated pre-test exercise tolerance. The total exercise time, resting and maximum heart rates, peak oxygen consumption (VO_2),

the percentage of predicted peak VO_2 achieved, VO_2 at the anaerobic threshold and minute ventilation/carbon dioxide production slope (VE/VCO_2) were calculated and recorded.

The predicted peak VO_2 was calculated using equations from Wasserman (Wasserman, 2012). These equations are based on data from large healthy populations who underwent maximal cycle ergometry. Sex, age, height and ideal body weight are the primary factors used to calculate the predicted VO_2 with adjustments made based on the difference between the ideal and actual body weight. A further adjustment is made based on the observed difference between peak VO_2 during cycle as compared with treadmill ergometry (Wasserman, 2012). Studies have demonstrated that peak VO_2 on cycling is approximately 90% of that observed during treadmill exercise (Faulkner *et al*, 1971; Hermansen *et al*, 1969; Wasserman, 2012).

6.4.6 Statistical Analysis

To examine the characteristics of those with improved LVEF, baseline features were compared between DCM patients with improved LVEF and DCM patients with LVEF <40% (as described in Section 2.1). The latter group were matched to the former so that the overall time since index diagnosis was similar. To explore differences within DCM patients with improved LVEF based on final LVEF, the cohort was divided into two groups based on LVEF (50-59% and >60%).

To establish the presence of subclinical myocardial dysfunction in those with improved LVEF, global radial strain (GRS), global longitudinal strain (GLS) and global circumferential strain (GCS) and native T1 values were compared between patients and healthy volunteers (HVOLs). Differences between groups were examined using the Mann-Whitney test for continuous data and the Fisher's Exact Test for categorical data. These data are presented as median and

interquartile range (IQR). The percentage of the predicted peak VO_2 achieved by patients with DCM and improved LVEF was calculated using equations described by Wasserman (Wasserman, 2012). Normality of the data was tested using the Shapiro-Wilk test. The mean, SD and 95% CIs are presented for CPET data. Analyses were performed using SPSS (V 23, *IBM, Chicago, Illinois).* A $p < 0.05$ was taken as significant.

6.5 Results

Overall 54 patients with DCM and improved LVEF met all of the inclusion criteria and none of the exclusion criteria and were included in the study (*Figure 6.3*).

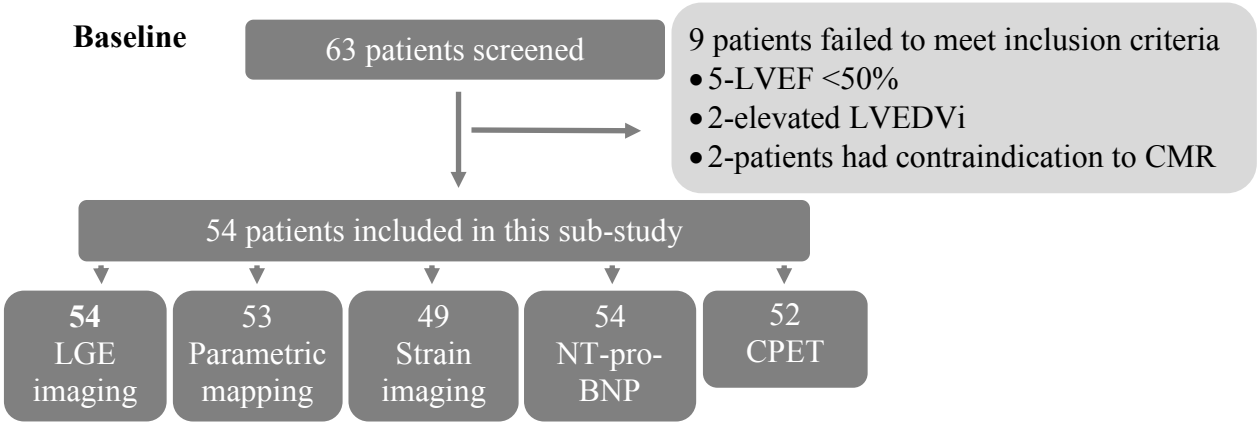

Figure 6.3. Derivation of the study cohort.

6.5.1 Baseline Characteristics

Baseline characteristics of DCM patients with and without improved LVEF are included in *Table 6.1.* The median time since original diagnosis was similar between groups. DCM patients with improved LVEF had lower heart rate, higher blood pressure and were less likely to be prescribed loop diuretics, have LBBB, LGE or a history of hypertension. Treatment with beta-blockers was nominally lower in those with LVEF<40%.

	DCM with improved LVEF (n=54)	**DCM with LVEF<40%** (n=100)	**p**
Median Age (IQR), yrs	55.5 (45.8, 64.0)	56.5 (56.5, 66.3)	0.92
Men, n (%)	35 (64.8)	71 (71.0)	0.45
Body surface area, m^2	2.03 (1.79, 2.38)	1.93 (1.74, 2.14)	0.15
Heart rate, bpm	67.0 (59.0, 73.3)	75.0 (65.0, 85.0)	<0.001
Systolic blood pressure, mmHg	124.5 (118.0, 134.3)	119.0 (105.0, 130.0)	<0.001
Diastolic blood pressure, mmHg	75.0 (69.0, 80.0)	70.0 (63.0, 80.0)	0.016
Smoker, n (%)	3 (5.6)	12 (12.0)	0.26
Moderate Alcohol Excess, n (%)	11 (20.4)	13 (13.0)	0.25
Previous atrial fibrillation, n (%)	12 (22.2)	31 (31.0)	0.27
Hypertension, n (%)	4 (7.4)	22 (22.0)	0.02
Diabetes mellitus, n (%)	1 (1.9)	11 (11.0)	0.06
Family History of DCM, n (%)	12 (22.2)	11 (11.0)	0.10
LBBB, n (%)	9 (16.7)	41(41.0)	0.002
Time from index diagnosis (days)	1737 (756, 2882)	1703 (802, 2655)	0.87
Medications			
Beta-Blocker, n (%)	48 (89.0)	76 (76.0)	0.06
ACEI/ARB, n (%)	52 (96.3)	95 (95.0)	1
MRA, n (%)	25 (46.3)	51 (51.0)	0.62
Loop Diuretic, n (%)	6 (11.1)	76 (76.0)	<0.001
CMR variables			
LVEDVi, ml/m^2	82.5 (74.5, 89.3)	144.0 (119.3, 193.0)	<0.001
LVEF, %	61.0 (55.8, 64.0)	28.5 (22.3, 35.0)	<0.001
LV Mass Index, g/m^2	71.5 (61.5, 78.0)	106.0 (88.3, 131.5)	<0.001
RVEDVi, ml/m^2	77.0 (70.0, 88.8)	78.0 (61.3, 102.5)	0.69
RVEF, %	58.0 (55.0, 63.3)	50.0 (35.3, 58.8)	<0.001
LAVi, ml/m^2	41.6 (34.0, 45.6)	71.3 (54.0, 88.7)	<0.001
LGE, presence	19 (35.2)	53 (53.0)	0.04

Table 6.1. Baseline characteristics for DCM patients with improved LVEF and LVEF <40%. Mann-Whitney Test used to compared continuous data; Fisher's Exact for categorical data.

Of those with improved LVEF, patients with LVEF 50-59% were more likely to have LGE and had worse GRS, GLS and GCS compared to those with LVEF>60% (*Table 6.2*).

	DCM with improved LVEF		
	LVEF 50-59%	**LVEF ≥60** (n=31)	**p**
Median Age (IQR), yrs	62.0 (46.0, 66.0)	52.0 (45.0, 61.0)	0.12
Men, n (%)	15 (65.2)	20 (64.5)	0.59
Body surface area, m^2	1.99 (1.77, 2.12)	2.05 (1.80, 2.31)	0.11
Heart rate, bpm	70.0 (60.0, 75.0)	62.0 (56.0, 72.0)	0.17
Systolic blood pressure, mmHg	124.0 (111.0, 132.0)	125.9 (120.0, 136.0)	0.18
Diastolic blood pressure, mmHg	71.0 (67.0, 80.0)	77.0 (70.0, 80.0)	0.09
Smoker, n (%)	2 (8.7)	1 (3.2)	0.39
Moderate Alcohol Excess, n (%)	6 (26.1)	5 (16.1)	0.29
Previous atrial fibrillation, n (%)	3 (13.0)	9 (29.0)	0.14
Hypertension, n (%)	1 (4.3)	3 (9.7)	0.43
Diabetes mellitus, n (%)	1 (4.3)	0 (0)	0.43
Family history of DCM, n (%)	7 (30.4)	5 (16.1)	0.18
LBBB, n (%)	4 (17.4)	5 (16.1)	0.59
History of Recovery			
LVEF at diagnosis, %	24.9 (8.9)	26.3 (9.1)	0.56
LVEF improvement, %	30.1 (10.6)	31.1 (9.4)	0.81
Time recovered, months	31.2 (24.5)	22.5 (17.9)	0.27
Medications			
Beta-Blocker, n (%)	19 (82.6)	29 (93.5)	0.20
ACEI/ARB, n (%)	22 (95.7)	30 (96.8)	0.68
MRA, n (%)	12 (52.2)	13 (41.9)	0.32
Loop Diuretic, n (%)	3 (13.0)	3 (9.7)	0.51
CMR variables			
LVEDVi, ml/m^2	83.0 (76.0, 88.0)	81.0 (73.0, 90.0)	0.74
LVEF, %	54.0 (52.0, 57.0)	63.0 (62.0, 78.0)	<0.001
LV Mass, g/m^2	73.0 (64.0, 78.0)	69.0 (57.0, 78.0)	0.61
RVEDVi, ml/m^2	74.0 (63.0, 81.0)	81.0 (73.0, 95.0)	0.04
RVEF, %	58.0 (55.0, 61.0)	61.0 (56.0, 65.0)	0.18
LAVi, ml/m^2	39.9 (33.1, 44.5)	46.5 (37.6, 46.4)	0.22
LGE, presence	12 (52.1)	7 (29.2)	0.03
Native T1, ms	1293 (1279, 1313)	1285 (1264, 1315)	0.29
ECV, %	26.2 (24.1, 28.0)	25.5 (23.8, 27.7)	0.55
Global radial strain	0.23 (0.18, 0.26)	0.30 (0.21, 0.40)	0.04
Global circumferential strain	-0.14 (-0.15, -0.12)	-0.17 (-0.19, -0.15)	<0.001
Global longitudinal strain	-0.13 (-0.15, -0.11)	-0.14 (-0.16, -0.13)	0.04
Other			
NT-pro-BNP, ng/L	82.0 (32.0, 135.0)	75.0 (43.0, 120.0)	0.88
Peak VO2, ml/kg/min	25.6 (22.0, 31.0)	25.6 (20.8, 33.5)	0.89
% of predicted peak VO2	95.2 (82.0, 107.7)	90.8 (83.1, 99.1)	0.47

Table 6.2. Comparison of patients with DCM and improved LVEF based on final LVEF. Mann-Whitney Test used to compared continuous data; Fisher's Exact for categorical data.

6.5.2 Natriuretic peptides

The median NT-pro-BNP of patients with DCM and improved LVEF was 75.5ng/L (IQR: 43.0-134.3). Overall 29 (53.7%) patients had a level above the 95th centile of age- and sex- specific reference values (*Table 6.3*). One patient had a NT-pro-BNP of 2486ng/L.

		< 70years			>70years		
		n	DCM & improved LVEF	95th Centile	n	DCM & improved LVEF	95th Centile
NT-pro-BNP (ng/L)	Men	34	64.5 (38.3, 115.8)	49	1	173	67
	Women	18	78.5 (63.3, 135.0)	88	1	76	123

Table 6.3. NT-pro-BNP in DCM with improved LVEF.
NT-pro-BNP levels (ng/L) in DCM with improved LVEF compared to the 95th centile of age- and sex-specific normal values (McDonagh *et al*, 2004). Median and (IQR).

6.5.3 Cardiopulmonary Exercise Testing

Of 54 patients with DCM and improved LVEF, 52 completed maximal CPET using treadmill ergometry. Two patients were unable to complete CPET testing due to musculoskeletal problems. One patient performed the test using the low intensity protocol, 32 using the intermediate intensity protocol and 19 using the high intensity protocol. The mean exercise time was 580 seconds (SD: 79 seconds). Results are presented in *Table 6.4*.

	Peak$V0_2$ (ml/kg/min)	Anaerobic threshold (ml/kg/min)	VE/VCO_2 slope	RER	% predicted max. HR (bpm)
Mean (SD)	26.8 (6.7)	20.5 (4.4)	32.2 (5.9)	1.2 (0.1)	94.7 (25.3)

Table 6.4. CPET in patients with DCM and improved LVEF.
RER – respiratory exchange ratio

Only 16 (30.8%) patients achieved 100% or greater of the predicted peak VO_2 (*Figure 6.4*). For the overall population, the peak VO_2 was less than that predicted (mean percentage predicted VO_2: 92.6%, 95% CIs 88.3:97.0) and 15 (28.8%) patients had a VE/CO_2 slope >34.

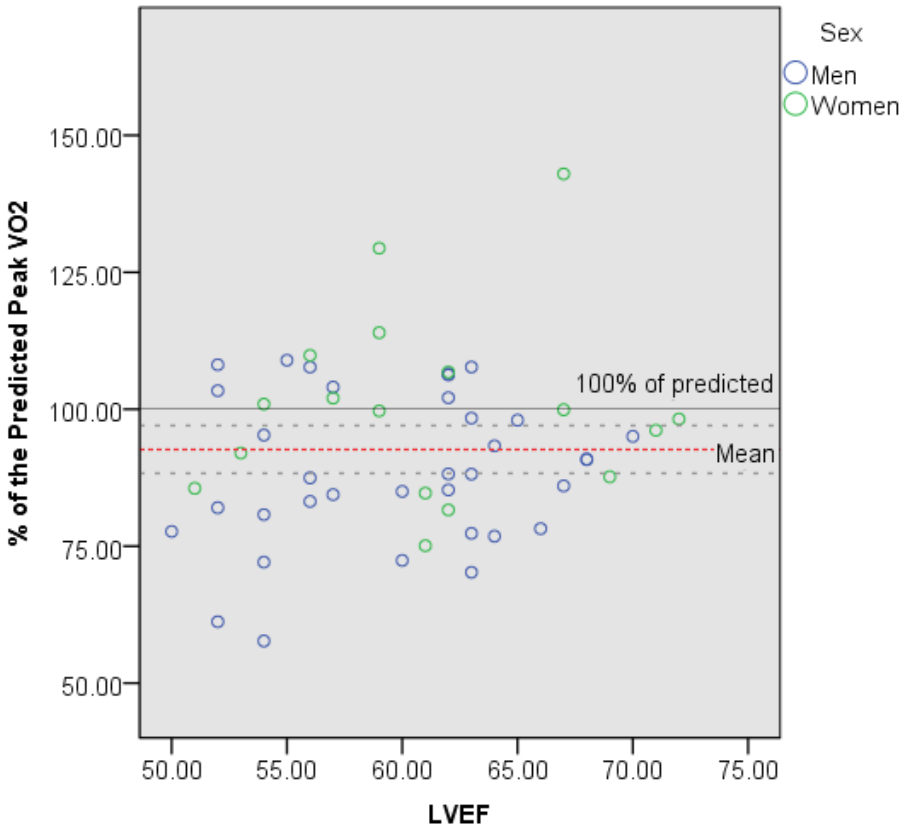

Figure 6.4. Peak VO_2 in DCM patients with improved LVEF.

Percentage of the predicted VO_2 in patients with DCM and improved LVEF, based on LVEF and sex. (Shapiro-Wilk test of normality – p=0.24)

(..... mean percentage of the predicted peak VO_2, ------ 95% confidence intervals of the percentage of the predicted peak VO_2, ——100% of the predicted peak VO_2)

6.5.4 CMR phenotyping

In total, 53 DCM patients with improved LVEF and 20 healthy volunteers (HVOLs) underwent native T1 mapping. The median age of the HVOLs was 34 (31-38) years and 13 (65.0%) were men. In addition 49 DCM patients with improved LVEF and 24 HVOLs underwent strain assessment. The median age of the HVOLs was 44 (34-59) years and 12 (50.0%) were men. The results are presented in *Table 6.5 & Figure 6.5*. Native T1 values were not different between patients and HVOLs. Patients with DCM and improved LVEF had worse GRS (p<0.001) and GLS (p=0.009) compared to HVOLs. The group of patients with a LVEF >60% had lower GRS compared to HVOLs (p<0.001).

	n	DCM & improved LVEF	n	HVOLs	p
Median **Native T1** (IQR), ms	53	1291 (1272, 1314)	20	1284 (1247, 1321)	0.79
GRS	48	0.25 (0.21, 0.36)	24	0.55 (-0.47, 0.72)	<0.001
GCS	48	-0.15 (-0.18, -0.14)	24	-0.17 (-0.18, -0.16)	0.009
GLS	49	-0.14 (-0.15, -0.12)	15	-0.14 (-0.15, -0.13)	0.47

	n	DCM & improved LVEF>60%	n	HVOLs	p
Median **Native T1** (IQR), ms	30	1285 (1263, 1314)	20	1284 (1247, 1321)	0.91
GRS	29	0.31 (0.22, 0.40)	24	0.55 (-0.47, 0.72)	<0.001
GCS	29	-0.17 (-0.19, -0.14)	24	-0.17 (-0.18, -0.16)	0.62
GLS	30	-0.14 (-0.16, -0.13)	15	-0.14 (-0.15, -0.13)	0.90

Table 6.5. CMR characterisation of DCM patients with improved LVEF
Comparison of global strain and native T1 values between DCM patients with improved LVEF and HVOLs using Mann-Whitney Test.

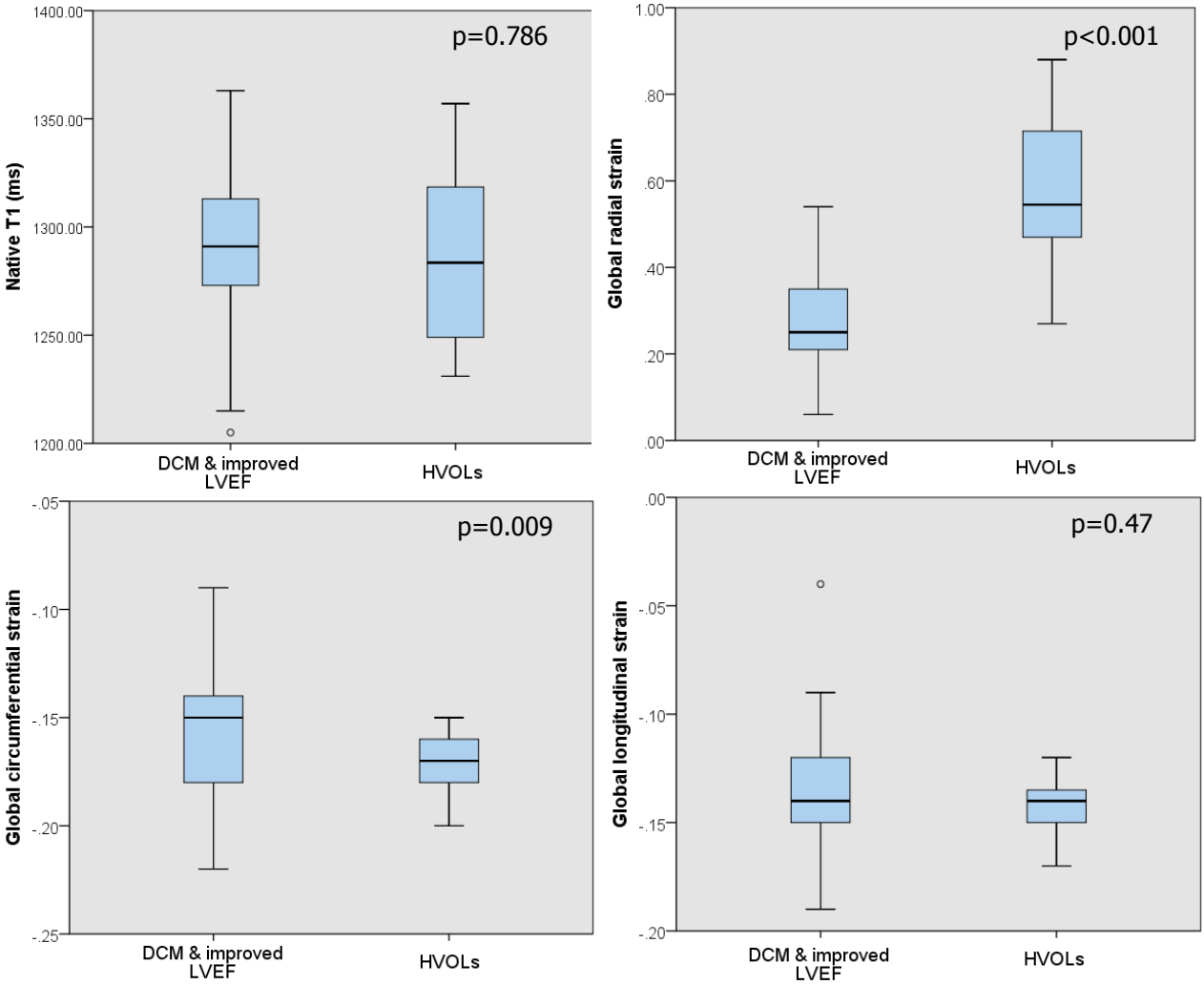

Figure 6.5. Global strain and native T1 values
Box plots demonstrating differences in strain and native T1 values between DCM patients with improved LVEF and HVOLs.

6.6 Discussion

This is the first study to comprehensively phenotype a cohort of patients with DCM who have demonstrated evidence of reverse remodelling, on the basis of improved LVEF (>50%) and normalisation of LVEDVi. The data demonstrate that at least a proportion of patients with DCM and improved LVEF have ongoing biochemical and functional evidence of myocardial dysfunction and imaging evidence of structural changes such as myocardial fibrosis.

Consistent with previous studies, there were differences in baseline characteristics between patients with improved LVEF and those with reduced LVEF (Basuray *et al*, 2014; Florea *et al*, 2016). Our data demonstrated that patients with improved LVEF were less likely to have a history of hypertension and had higher current systolic and diastolic blood pressures compared to DCM patients with a LVEF <40%. In addition, LBBB and LGE were less common in those with improved LVEF. This is consistent with recent research that demonstrated a lower rate of reverse remodelling in patients with these characteristics (Kubanek *et al*, 2013; Sze *et al*, 2018). Patients with DCM and improved LVEF also had lower heart rates compared to the patients with reduced LVEF and treatment with beta-blockers was nominally more common. It is well established that lower heart rates are associated with favourable prognosis in HF patients (Bohm *et al*, 2010).

Interestingly, patients with improved LVEF had a nominally higher rate of a family history of DCM compared to patients with lower LVEF. It is well established that the most common genetic cause of DCM are truncating variants in *TTN,* occurring in up to 25% of patients (Herman *et al*, 2012). Jansweijer and colleagues have recently reported a high rate of reverse remodelling in patients with such mutations, with improvements in cardiac function occurring in up to 46.9% (Jansweijer *et al*, 2016). Recovery in cardiac function in patients with TTN-

associated DCM has also been reported by others (Felkin *et al*, 2016; Luk *et al*, 2017). The overall findings suggest that this form of DCM may be particularly responsive to pharmacological off-loading and this may help to explain the differences observed in family history amongst the populations in this study.

CPET testing demonstrated lower peak VO_2 in patients with DCM and improved LVEF compared to large cohorts of healthy individuals. Consistent with this, around a half of patients had at least mild elevations in NT-pro-BNP and GRS and GCS values were lower in patients compared to HVOLs. GRS remained significantly lower in patients with LVEF>60% compared to HVOLs. This suggests that there are persistent subclinical abnormalities in cardiac function despite improvement and even normalisation of LVEF.

CMR also demonstrated that over a third of patients had LGE on CMR, representing areas of replacement fibrosis. This was less than the prevalence of LGE amongst patients with reduced LVEF. The presence of replacement fibrosis in patients with DCM and improved LVEF demonstrates the persistence of structural changes despite improvement in function. Native T1 values were not significantly different between patients with DCM and improved LVEF and HVOLs. Native T1 values correlate with the degree of interstitial fibrosis in many conditions, including DCM (Flett *et al*, 2010; Nakamori *et al*, 2017). Aus dem Siepen and colleagues have demonstrated differences in native T1 values between patients with mild DCM and controls (aus dem Siepen *et al*, 2015). Our findings suggest that there was not a large difference in the degree of interstitial fibrosis between patients with DCM and improved LVEF and HVOLs. This raises the possibility that interstitial fibrosis may have reversed with appropriate therapy and positive remodelling (Stuckey *et al*, 2014).

Overall, our data suggest that assessment of myocardial recovery based on solely on the assessment of LVEF is sub-optimal. Additional biochemical, structural and functional markers of recovery may provide more comprehensive evaluation.

6.6.1 Limitations

Our cohort of patients with DCM and improved LVEF is small and therefore the power to detect differences in some characteristics may be limited. The HVOLs used to derive the reference ranges for global strain and native T1 values were also younger compared to the patients. Previous studies investigating the measurement of global strain using DENSE and native T1 values using the same sequence at 3T have demonstrated that age only has a small effect on overall values (Mangion *et al*, 2016; Rauhalammi *et al*, 2016). It therefore appears that the discrepancy in age will have had minimal impact on the results. It is not possible to definitively conclude that native T1 values reduce in the context of reverse remodelling given the absence of serial testing in patients from the time of the original diagnosis to the point of improvement in LVEF.

6.7 Conclusion

Patients with DCM and improved LVEF are less likely to have co-morbidities compared to patients with reduced LVEF. Despite improvement in LVEF, biochemical, functional and structural markers of myocardial disease persist in at least a proportion of patients. Assessment of the degree of myocardial recovery should incorporate a comprehensive assessment of disease, beyond the simple measurement of LVEF, including measurement of natriuretic peptides, global myocardial strain, peak oxygen consumption on exercise and detection of replacement myocardial fibrosis using CMR.

Chapter 7

7 Methods – (Part 2) – The Design of a Randomised Crossover Trial of Therapy Withdrawal in Recovered Dilated Cardiomyopathy: the TRED-HF study

7.1 Overall Study Design

An open-label, cross-over, randomised controlled trial was designed to examine the safety and feasibility of short-to-medium term pharmacological HF therapy withdrawal in patients with a previous diagnosis of DCM, who had improvement in LVEF and complete remission of HF symptoms. The study protocol was approved by the National Research Ethics Committee (Reference: 16/LO/0065) and the Medicines and Healthcare Products Regulatory Agency and sponsored by Royal Brompton & Harefield NHS Foundation Trust. The study was funded by a British Heart Foundation Clinical Research Training Fellowship (FS/15/29/31492). The Royal Brompton and Harefield NHS Foundation Trust Cardiovascular Patient Advisory Group were consulted on the study rationale and design and their opinions were considered in the drafting of the following protocol.

7.1.1 Inclusion Criteria

The inclusion criteria for the study for the study were as follows:

1. A prior diagnosis of DCM with LVEF <40% as agreed by an independent clinician based on clinical details and previous imaging (echocardiography or CMR).
2. Current treatment with at least 1 of the following medications: loop diuretic, beta-blocker, ACEI, ARB or MRA.
3. Evidence of left ventricular reverse remodelling following the initial diagnosis with subsequent improvement in ejection fraction to ≥50% with normal LVEDVi on CMR (or echocardiography if a contraindication to CMR exists).
4. Absence of symptoms of HF (NYHA Class 1).
5. Plasma NT-pro-BNP concentration < 250 ng/L.

7.1.2 Exclusion Criteria

The following were exclusion criteria:

1. Uncontrolled hypertension (clinic blood pressure >160/100mmHg)
2. More than moderate valvular disease
3. Estimated glomerular filtration rate <30mls/min
4. Atrial/supraventricular/ventricular arrhythmia requiring beta-blockade.
5. Pregnancy
6. Angina.
7. Age <16 years.

7.2 Baseline Assessment

Potential participants were invited to attend a screening visit. All patients provided full written informed consent. To confirm eligibility and as part of baseline assessments, a full medical history was taken. This was followed by a physical examination, measurement of resting blood pressure and a 12-lead ECG. Patients completed a questionnaire in order to confirm the absence of contraindications for magnetic resonance imaging. Females of child-bearing age also underwent a pregnancy test. Those without contraindication underwent comprehensive CMR assessment (as detailed in section 6.4.4) and all others underwent 3-dimensional echocardiography (section 7.2.1). Blood samples were taken for routine haematology and biochemistry tests including measurement of plasma NT-pro-BNP. To enable the storage of serum, plasma and whole blood samples, 5 millilitres (mls) of blood was drawn into serum separator tubes and lithium heparin tubes with a further 8mls in a ethylenediaminetetraacetic acid (EDTA) tube. These samples were allowed to stand for 20 minutes before the blood taken

for the serum and plasma samples was centrifuged for 15 minutes, at 3000 revolutions per minute and 4°C. The serum and plasma layers of the centrifuged samples as well as the whole blood were then pipetted into 0.5ml aliquots and stored at -80°C.

Patients subsequently underwent a CPET using a dedicated ramp protocol (as detailed in section 6.4.5) and completed the Kansas City Cardiomyopathy Questionnaire (KCCQ) and Symptom Assessment Questionnaire (SAQ) (*Appendix*). Lower scores on KCCQ and higher scores on the SAQ indicate a greater symptom burden.

7.2.1 Echocardiography Assessment

The following protocol was drafted together with Dr Lucia Venneri. Patients unable to undergo CMR due to contraindications, such as previous device implantation, underwent comprehensive echocardiographic assessment. Studies were performed by the same operator using a commercially available system (iE33, Philips Healthcare, Best, The Netherlands) with a 3.5 MHz transducer for 2D study and with a X5-1 transducer for 3D study. Measurements were made according to current guidelines (Lang *et al*, 2015; Lang *et al*, 2005). LV volumes were traced manually at end-diastole and end-systole in apical 4- and 2-chamber views. LVEF was calculated using the modified Simpson's biplane method. LV mass was calculated using the corrected American Society of Echocardiography method. LA volume was measured using the biplane method in 4- and 2-chamber. To assess LV diastolic function, E/A ratio and deceleration time were calculated. In addition, tissue Doppler indices were measured in the apical 4-chamber view. Peak systolic (S'), early diastolic (E') medial and lateral mitral annular velocities were measured and medial and lateral E/E' ratio were calculated (Lang *et al*, 2015). Full-volume multi-beat acquisitions from 4- and 2-chamber views were obtained for the assessment of 3D LV volumes and EF according to current guidelines using the cardiac 3

dimensional Quantification Advanced software (3DQ Advanced). TAPSE and S' velocity values were recorded as measures of RV function (Rudski *et al*, 2010). Speckle tracking was used to calculate global longitudinal strain using aCMQ software (QLAB 10.0, iE33, Philips Healthcare, Best, The Netherlands) (Mor-Avi *et al*, 2011). Sector size and depth were adjusted for each patient to achieve optimal visualization at the highest possible frame rate.

7.3 Randomisation

Patients fulfilling all inclusion criteria and meeting none of the exclusion criteria were randomised to step-wise ***therapy withdrawal*** or ***continued therapy*** using an online service, delivered by Sealed Envelope Ltd. The randomisation service used a method based on random permuted blocks to produce a final allocation ratio of 1:1. Randomisation was stratified by tertiles of NT-pro-BNP level (0-50ng/l, 50-125ng/l and 125-250ng/l). Forced randomisation was not allowed. A randomisation log is included in the *Appendix*.

Patients were informed of the randomisation result and their general practitioner and cardiologist were notified. Labelled medications were prescribed for patients in both arms of the study for the duration of the study via the hospital pharmacy.

7.4 Treatment Withdrawal

Patients randomised to therapy withdrawal underwent supervised, step-wise reduction in pharmacological HF therapy over 16 weeks (*Figure 7.1*). Changes to medications were made every 2 weeks. Before making a change to medications the patient was assessed by the research team, either in clinic or by telephone, to ensure it was safe to do so. During withdrawal of

therapy, if the patient was stable without symptoms, clinic assessments occurred every 4 weeks with interval assessments taking place *via* telephone. During clinic assessment a history was taken followed by clinical examination, blood pressure measurement and an ECG. NT-pro-BNP was measured every 4 weeks during therapy withdrawal. If a patient demonstrated signs of possible deterioration, more regular clinic review was arranged. Patients were educated on the signs and symptoms of HF, advised to weigh themselves daily and contact the team if their weight increased by more than 2kg on 3 consecutive days.

Patients stopped or reduced the dose of their loop diuretic, followed by MRA, beta-blocker and finally ACEI or ARB. Diuretics were withdrawn first to ensure the patient did not develop fluid congestion before withdrawal of further therapies. If the patient was taking greater than the equivalent of 40mg of Frusemide or 50mg of Spironolactone, the dose was initially reduced by 50% before being stopped 2 weeks later. Patients taking 25% or less of the guideline recommended dose of beta-blocker or ACEI/ARB stopped the medication, otherwise the dose was reduced by 50% every two weeks.

7.5 Continued Therapy

Patients in the continued therapy arm remained on pre-existing medical therapy for the first 6 months of the study. Patients attended a clinic visit at 8 weeks which included history and clinical examination, blood pressure and NT-pro-BNP measurement and an ECG. Patients in the control arm were also educated on the signs and symptoms of HF, advised to weigh themselves daily and contact the team if their weight increased by more than 2kg on three consecutive days. Those who demonstrated signs of possible deterioration had more regular clinic review arranged, as deemed appropriate by the trial team.

7.6 16 Week Assessment

After 16 weeks, patients in both arms of the trial underwent an identical clinic review which included history and clinical examination, blood pressure and NT-pro-BNP measurement and an ECG. A short CMR scan was also performed which included cine imaging in long- and short-axis planes, in order to perform volumetric analysis (as described in Section 2.2**)** and native T1 mapping, as described in section 6.4.4.

7.7 6 Month Assessment

After 6 months, patients in both arms of the trial attended an identical clinic review which included history and clinical examination, blood pressure and NT-pro-BNP measurement and an ECG. All patients also underwent a CMR scan which included SSFP cine imaging in long- and short-axis planes, DENSE imaging enabling the calculation of myocardial strain, native and post-contrast T1 mapping and LGE imaging (as described in section 6.4.4). A repeat CPET was also performed. The same CPET protocol was used for each patient at baseline and 6 month visits. The patients also repeated the KCCQ and SAQ.

7.8 End-points

7.8.1 Primary End-point

The primary endpoint was a relapse of DCM, defined as one of the following:

1. A reduction in LVEF by >10% and to below 50%
2. An increase in LVEDV by >10% and to above the normal range
3. A two-fold rise in baseline NT-pro-BNP concentration and to >400ng/L

4. Clinical evidence of HF, based on signs and symptoms as agreed by the research team.

Test results and progress of patients in the trial were reviewed at regular meetings by an adjudication panel led by a Consultant Cardiologist. Therapies were re-established if patients fulfilled any of the criteria for the primary end-point. Decisions to re-establish therapy were made by the panel. The ongoing management of patients with adverse events, such as episodes of confirmed arrhythmia was discussed by the panel together with their usual clinical teams. Decisions on re-establishing therapy based on episodes of arrhythmia were made on an individual case basis. Regular meetings were held with an independent expert who acted as a Trial Safety Advisor and reviewed the progress of patients in the study and the decisions made by the trial team.

CMR analysis was performed as described in section 6.4.4. LV volumetric analysis for baseline, 16 week and 6 month assessments was performed by a blinded Core Lab. Serial scans from each patient were analysed by the same operator who was blinded to the treatment arm and stage. NT-pro-BNP was performed using the same immunoassay throughout the study (*Roche, Basel, Switzerland).*

7.8.2 Secondary End-points

Secondary endpoints were included to gather information on the safety of therapy withdrawal and collect pilot data into possible effect sizes for future work. A composite safety end-point included CV mortality, major adverse CV events and unplanned CV hospitalisation. Other end-points included the occurrence of sustained arrhythmias, changes in exercise performance based on CPET, changes in symptom severity and quality of life as assessed by the questionnaires and changes in LVEF, LVEDVi, NT-pro-BNP, LAVi, heart rate and blood pressure.

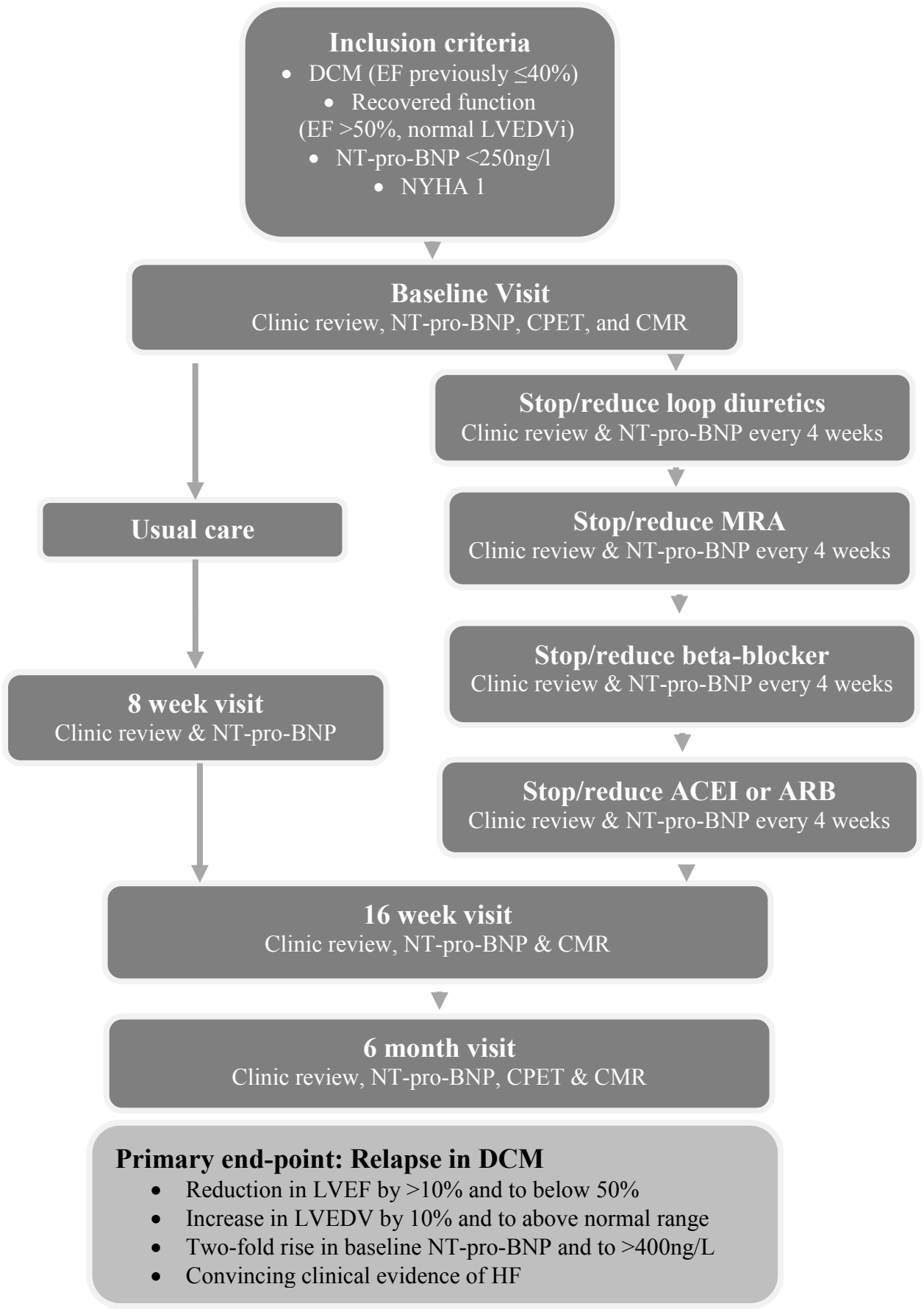

Figure 7.1. Flow chart demonstrating the study protocol.

7.9 Study Cohort Identification

Patients were identified from our pre-existing registry (as described in Section 2.1), cardiomyopathy clinic and clinical CMR lists at the Royal Brompton Hospital. Additionally, suitable patients were referred from a network of collaborating hospitals that agreed to act as Participant Identification Centres. These sites included Guy's and St Thomas' NHS Foundation Trust, King's College Hospital NHS Foundation Trust, St George's NHS Foundation Trust, London Northwest NHS Healthcare Trust, Epsom and St Helier University Hospitals, Milton Keynes University Hospital and Basildon and Thurrock University Hospitals. A summary of the study was also included in patient newsletters and on the websites of Cardiomyopathy UK and Pumping Marvellous. Patients interested in taking part in the study subsequently contacted us and if suitable, a baseline screening visit was arranged.

Of 63 patients who attended baseline screening visits between 21st April 2016 and 22nd August 2017, 51 met inclusion criteria and all were randomised into the study. Of the 12 who were screened but not randomised, 3 had NT-pro-BNP concentration >250ng/L, 5 had a LVEF<50% and 2 had elevated LVEDVi. In addition one patient had a short self-terminating episode of paroxysmal AF at peak exercise during CPET whilst another was subsequently diagnosed with prostate cancer and a radical prostatectomy was planned.

Chapter 8

8 A Randomised Controlled Crossover Trial of Therapy Withdrawal in Recovered Dilated Cardiomyopathy

The TRED-HF study

Preliminary Results of the First 35 Patients

8.1 Hypotheses

8. ***Withdrawal of pharmacological therapy for heart failure is safe in asymptomatic patients with a previous diagnosis of dilated cardiomyopathy who now have (a) normal indexed left ventricular end-diastolic volume, (b) a left ventricular ejection fraction >50% and (c) a plasma NT-pro-BNP <250ng/L.***

9. ***(a) Changes in left ventricular size and left ventricular ejection fraction, (b) quality of life scores, (c) exercise capacity and (d) NT-pro-BNP levels will be similar in patients with recovered DCM undergoing therapy withdrawal compared to those who remain on therapy.***

10. ***The following variables will be associated with the likelihood of relapse in patients with recovered DCM:***

    a. ***Late gadolinium enhancement***

    b. ***Native T1 values, extracellular volume fractions and strain values***

    c. ***Left atrial volumes as determined by CMR***

    d. ***Plasma concentration of NT-pro-BNP***

    e. ***Peak oxygen consumption on maximal treadmill exercise at baseline***

8.2 Abstract

Background: The benefit of therapy in asymptomatic DCM patients with improved LVEF is unclear. No prospective randomised controlled trial has investigated withdrawal of HF therapies in well-characterised DCM patients with improved LVEF.

Methods: Patients with a previous diagnosis of DCM (LVEF<40%), who had demonstrated LV reverse remodelling (improvement in LVEF to ≥50%, normal LVEDVi and NT-pro-BNP <250ng/L) were randomised to gradual, staged withdrawal of HF therapies or to continue usual therapy over 6 months. After 6 months, those in the control arm then had treatment withdrawn in the same fashion. The primary end-point was a relapse of their condition defined by 1) a reduction in LVEF>10% and to below 50%, 2) an increase in LVEDV by >10% and to above normal range, 3) a two-fold rise in baseline NT-pro-BNP and to >400ng/L or 4) convincing clinical evidence of HF.

Results: Of the first 35 patients enrolled, 18 were randomised to therapy withdrawal and 17 to the control arm. Relapse occurred in 8 (44.4%) patients originally randomised to therapy withdrawal and none of the patients in the control arm (p<0.001). Sixteen of 17 patients initially assigned to the control arm subsequently crossed over to have therapy withdrawn after 6 months; six (37.5%) of these patients relapsed with therapy withdrawal. Therefore 14 of 34 patients (41.4%) relapsed after therapy withdrawal. Those initially assigned to therapy withdrawal had a reduction in LVEF (median: -10.0%; IQR: -14.5:-0.25) and elevations in heart rate (19.0; 15.0:21.0), systolic (10.0; 0.0, 20.0) and diastolic blood pressure (8.0; -2.5:12.5) compared to those in the control arm (LVEF -1; -6.0:3.5; p=0.009, heart rate -2.0; -10.0:5.0; p<0.001, systolic blood pressure -4.0; -10.5:8.0; p=0.024, diastolic blood pressure 0.0; -6.0:4.0; p=0.024).

Conclusion: Relapse was observed in 41.2% of patients with DCM and improved LVEF after withdrawing HF therapies compared to none of those who remained on therapy.

8.3 Background

LV reverse remodelling, defined as improvement in LVEF and reduction in LV size is observed in up to 40% of patients with DCM on HF therapy (Merlo *et al*, 2011). Patients with improved ejection fraction have favourable outcomes and are distinct from those with HF-REF (Basuray *et al*, 2014; Florea *et al*, 2016; Merlo *et al*, 2015; Punnoose *et al*, 2011). However, there is a paucity of evidence on whether these patients continue to derive benefit from HF therapies.

Following the resolution of HF symptoms, many patients ask whether therapies are still necessary and ask to stop them due to concern regarding side effects. These patients are typically young with little co-morbidity and are often reluctant to take multiple medications without firm evidence of benefit. Reducing the number of medications a patient takes might improve their overall well-being. Whether patients with structural, biochemical and functional markers of recovery in cardiac function still gain benefit from HF therapies is unknown. Some patients with these features may have achieved permanent recovery of myocardial function rendering continuation of therapies unnecessary. For other patients, relapse may occur if therapy is withdrawn.

There are a lack of prospective data examining the safety and feasibility of therapy withdrawal in patients with well-characterised DCM patients with structural, functional and biochemical markers of recovery. Consequently, there is a lack of consensus amongst experts on how to manage such patients and no recommendations in most recent guidelines (Ponikowski *et al*, 2016). We set out to perform a prospective randomised controlled trial to examine the safety and feasibility of therapy withdrawal in patients with structural, biochemical and clinical markers of recovery.

8.4 Methods

The methods have been described in detail in Chapter 6. A brief summary is given below.

8.4.1 Patient Cohort

Patients with a previous diagnosis of DCM and LVEF<40%, who subsequently demonstrated improvement in LVEF to >50% and who were free of symptoms of HF were invited for a screening visit. All patients provided full written informed consent. The study was approved by the National Research Ethics Committee (16/LO/0065) and was authorised by the Medicines and Healthcare Products Regulatory Agency. The study was sponsored by Royal Brompton and Harefield NHS Foundation Trust (ClinicalTrials.gov: NCT02859311).

8.4.2 Baseline Assessments

At baseline, all patients underwent comprehensive CMR assessment using the standardised protocol detailed in section 6.4.4**.** Blood was drawn for routine laboratory tests including plasma NT-pro-BNP. Patients underwent maximal treadmill CPET using dedicated ramp protocols (section 6.4.5 & *Appendix***)** and completed the KCCQ and SAQ.

8.4.3 Inclusion and Exclusion Criteria

Inclusion criteria included: 1) A prior diagnosis of DCM with LVEF ≤ 40%, 2) Current treatment with at least 1 of the following: loop diuretic, beta-blocker, ACE inhibitor, ARB or MRA, 3) A current LVEF ≥ 50% and a LVEDVi within normal range, 4) Absence of symptoms of HF (NYHA class I) and 5) Plasma NT-pro-BNP <250ng/L.

Exclusion criteria included: 1) uncontrolled hypertension (clinic blood pressure >160/100mmHg), 2) more than moderate valvular disease, 3) estimated glomerular filtration rate <30mls/minute, 4) atrial, supraventricular or ventricular arrhythmia requiring beta-blockade, 5) pregnancy, 6) angina and 7) age <16 years.

Those meeting all inclusion criteria and none of the exclusion criteria were randomised to supervised step-wise therapy withdrawal or continued therapy, stratified by tertiles of NT-pro-BNP (0-50ng/l, 50-125ng/l, 125-250ng/l).

8.4.4 Intervention and Follow-up

Patients randomised to therapy withdrawal underwent supervised, step-wise reduction in pharmacological therapy over a maximum of 16 weeks. Changes to medication were made every 2 weeks. Prior to this, each patient was reviewed in clinic or via telephone. Clinic visits and NT-pro-BNP measurement occurred at least every 4 weeks during therapy withdrawal. Patients initially stopped or reduced the dose of loop diuretic, followed by MRA, beta-blocker and finally ACEI or ARB. If the patient was taking more than the equivalent of 40mg of frusemide or 50mg of spironolactone, or more than 25% of the maximum recommended dose of beta-blocker or ACEI/ARB, the dose was reduced by 50% in a stepwise manner, otherwise the treatment was stopped. Patients in the control arm underwent clinic review with NT-pro-BNP measurement after 8 weeks.

At 16 weeks, all patients underwent a review which included NT-pro-BNP measurement and a limited CMR scan to calculate LV size and function. After 6 months, patients had a further clinic review which included a CMR scan, NT-pro-BNP measurement, a CPET, using the same protocol as the baseline visit, and the KCCQ and SAQ. Patients in the control arm subsequently crossed-over and had treatment withdrawn in the same fashion as above.

8.4.5 End-points

The primary endpoint was a relapse of DCM within 6 months, defined as one of the following: 1) A reduction in LVEF by >10% and to below 50%, 2) An increase in LVEDV by >10% and to above the normal range, 3) A two-fold rise in baseline NT-pro-BNP concentration and to >400ng/L or 4) Clinical evidence of HF, based on signs and symptoms as agreed by the research team. Therapies were restarted if patients fulfilled any criteria for relapse. LV volumetric analysis was performed by a Core Lab. The operators were blinded to the treatment arm and stage. Serial scans from each patient were analysed by the same operator. NT-pro-BNP was performed using the same immunoassay throughout the study (*Roche, Basel, Switzerland).*

Secondary end-points included :1) a composite safety end-point (CV mortality, major adverse CV events and unplanned CV hospitalisation), 2) the occurrence of sustained atrial or ventricular arrhythmias and 3) changes between baseline and follow-up, in (a) LVEF, (b) LVEDVi, (c) NT-pro-BNP, (d) LAVi, (e) quality of life as assessed by the symptom questionnaires and (f) exercise performance as determined by exercise time and peak oxygen consumption on CPET, (g) heart rate and (h) blood pressure. Lower scores on KCCQ and higher scores on the SAQ indicate a greater symptom burden.

8.4.6 Statistical Analysis

Baseline characteristics are presented for all patients enrolled to date (n=51) as well as the first 35 patients enrolled in the study, based on assignment at randomisation.

Event-free survival from the primary end-point was modelled in the first 35 patients, on the basis of time to event or the end of the study using Kaplan-Meier curves. Event-free survival

was compared between those randomised to the therapy withdrawal and control arms using the log-rank test. Patients who withdrew from the study or restarted therapy without meeting the primary end-point were included and were censored from the date of withdrawal or re-initiation of therapy. It was not possible to perform proportional hazard modelling due to the absence of events in one arm.

Differences in secondary end-point variables between baseline and follow-up were compared based on assigned treatment arm. In addition, variables were compared between arms at baseline. Data are presented in dot plots. Data from patients randomised to the control arm who, after 6 months, had therapy withdrawn were not included in the therapy withdrawal component of these primary and secondary end-point analyses in order to maintain independence between groups.

Variables were also compared between baseline and follow-up for all patients who had therapy withdrawn (n=33), including those who 'crossed-over' from the control arm after 6 months. The patient who withdrew from the study was excluded from secondary analyses due to the absence of follow-up data.

Differences in baseline characteristics were examined using the Mann-Whitney (independent data) and Wilcoxon signed-rank test (paired data) for continuous data and the Fisher's Exact Test for categorical data. Data are presented as median and IQR.

Cox regression analysis was performed for those who underwent therapy withdrawal in order to examine association of variables with the primary end-point. Variables associated with the end-point on univariable analysis were carried forward into a multivariable model. Statistical analyses were performed using SPSS Version 23 (*IBM, Chicago, Illinois).* A p value of <0.05 was taken as significant.

8.5 Results

Derivation of the entire study population is outlined in *Figure 8.1*. Between 11th April 2016 and 16th August 2017, 63 patients were screened, 51 of whom were enrolled and randomised. Overall, 26 were randomised to the continued therapy arm and 25 to the therapy withdrawal arm.

At the time of writing, the first 35 patients enrolled in the study had completed follow-up. The preliminary results from this sub-group are presented for the purpose of this thesis. Of this group, 18 were randomised to therapy withdrawal and 17 to the control arm. One patient assigned to the control arm did not have therapy withdrawn after 6 months due to symptoms suspicious of paroxysmal AF. Therefore, 16 of 17 patients in the control arm had therapy withdrawn arm after 6 months. Overall, 34 of 35 patients began therapy withdrawal.

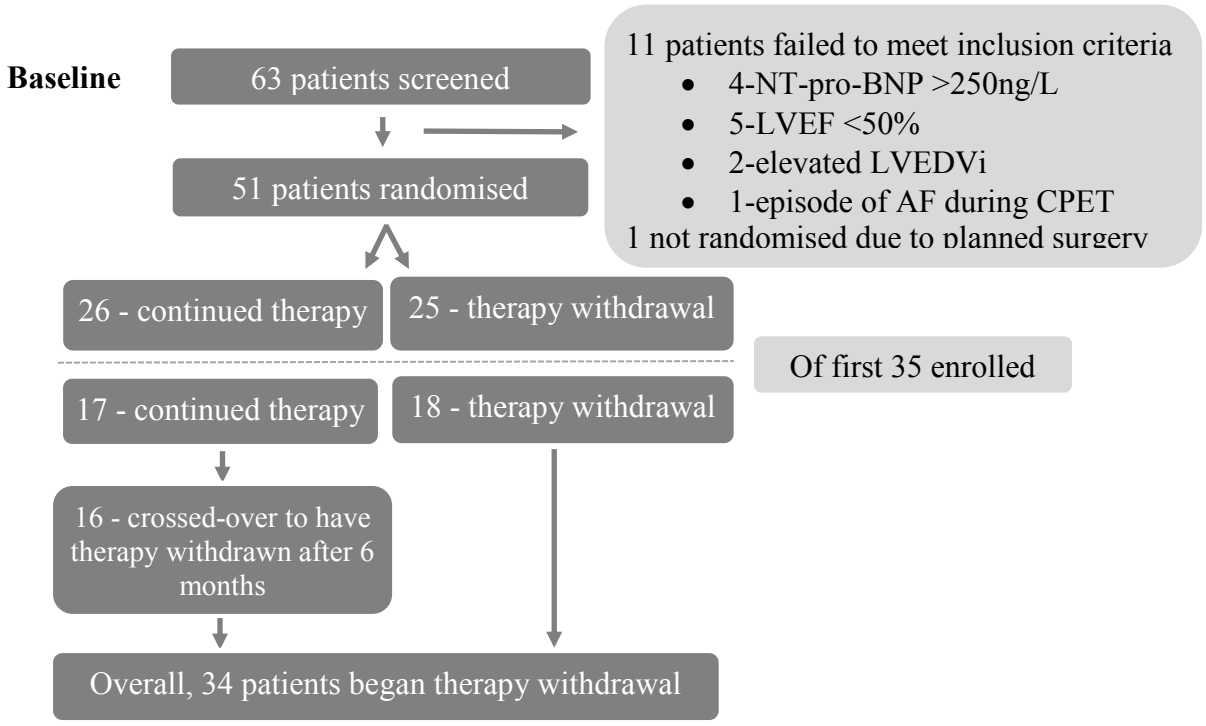

Figure 8.1. Derivation of the final study cohort.

8.5.1 Baseline Characteristics of the Entire Cohort

Of the 51 patients randomised, 34 (66.7%) were men, the median age was 55.0 (45.5-63.5) years and LVEF 61% (55-63). The median LVEF at original diagnosis was 29.5% (24.0-35.8) and the median time since improvement in LVEF to >50% was 24 (8-42) months. Baseline characteristics, including prescribed medical therapies and perceived aetiology of disease, were well matched between treatment arms (*Table 8.1*).

8.5.2 Baseline Characteristics of the First 35 Patients in the Study

Of the first 35 patients enrolled, 23 (65.7%) were men, the median age was 56.0 (46.0-64.0) years and LVEF 60% (55-64). The median LVEF at original diagnosis was 28.0% (19.0-35.0) and the median time since improvement in LVEF to >50% was 28 (14-49) months. Baseline characteristics, including prescribed medical therapies and perceived aetiology of disease, were well matched between treatment arms (*Table 8.2*).

	Control n=26	**Therapy Withdrawal** n=25	**p value**
Median Age (IQR), yrs	56.0 (44.5, 64.0)	54.0 (45.5, 63.5)	0.84
Men, n (%)	18 (69.2)	16 (64)	0.77
Body surface area, m2	2.08 (1.80, 2.21)	2.08 (1.73, 2.28)	0.76
Heart rate, bpm	70.0 (60.0, 74.8)	62.0 (57.5, 74.0)	0.17
Systolic blood pressure, mmHg	127 (117, 134)	123 (117, 133)	0.39
Diastolic blood pressure, mmHg	76.0 (70.0, 80.0)	72.0 (67.5, 80.0)	0.44
LBBB, n (%)	4 (15.4)	3 (12.0)	1
QRS duration (ms)	94.0 (88.0, 110.5)	98.4 (19.9)	0.78
Study baseline NT-pro-BNP	75.0 (37.3, 132.8)	72.0 (43.5, 147.0)	0.85
Medical history			
Smoker, n (%)	3 (11.5)	0 (0)	0.24
Moderate Alcohol Excess, n (%)	6 (23.1)	6 (24.0)	1
Atrial fibrillation, n (%)	4 (15.4)	8 (32.0)	0.2
Hypertension, n (%)	3 (11.5)	1 (4.0)	0.61
Diabetes mellitus, n (%)	1 (3.8)	0 (0)	1
Family History of DCM, n (%)	3 (11.5)	3 (12.0)	1
Previous HF admission, n (%)	14 (53.8)	18 (72.0)	0.25
LVEF at DCM diagnosis (%)	25.0 (19.0, 32.9)	28.0 (20.0, 33.0)	0.84
Improvement in LVEF (%)	29.8 (24.8, 38.3)	29.0 (23.0, 37.8)	0.76
Time recovered (months)	19.5 (6.0, 44.0)	28.0 (8.0, 45.0)	0.66
Aetiology			
Idiopathic n (%)	15 (57.7)	20 (80.0)	0.20
Familial/genetic n (%)	4 (15.4)	3 (12.0)	
External insult, n (%)	7 (26.9)	2 (8.0)	
Medications			
Beta-Blocker, n (%)	24 (92.3)	21 (84.0)	0.42
ACEI/ARB, n (%)	26 (100)	25 (100)	1
MRA, n (%)	12 (46.2)	12 (48.0)	1
Loop Diuretic, n (%)	3 (11.5)	3 (12.0)	1
CMR variables			
LVEDVi, ml/m^2	82.0 (70.8, 90.3)	83.0 (73.0, 88.5)	0.62
LVEF, %	59.5 (55.8, 62.3)	62.0 (54.0, 65.5)	0.38
LV Mass Index, g/m^2	71.0 (64.5, 80.0)	72.0 (56.0, 81.0)	0.50
RVEDVi, ml/m^2	75.0 (66.5, 89.5)	78.0 (70.8, 92.5)	0.54
RVEF, %	58.0 (54.5, 63.5)	58.0 (56.0, 62.8)	0.91
LAVi, ml/m^2	41.8 (33.4, 45.0)	41.3 (35.0, 45.8)	0.92
LGE, presence	10 (40.0)	10 (42.7)	1
CPET variables			
Peak VO2 (ml/kg/min)	25.6 (22.2, 31.1)	29.1 (22.0, 31.6)	0.62
Percentage of predicted peak VO2 (%)	89.5 (80.6, 106.8)	95.3 (85.3, 102.1)	0.63

Table 8.1. Baseline characteristics based on assigned group.

Mann-Whitney Test and Fisher's Exact Test used to compare continuous and categorical data respectively.

	Control n=17	**Therapy Withdrawal** n=18	**p value**
Median Age (IQR), yrs	56.0 (44.5, 63.0)	58.5 (46.3, 64.3)	0.53
Men, n (%)	12 (70.6)	11 (61.1)	0.73
Body surface area, m2	2.09 (1.80, 2.27)	1.97 (1.71, 2.24)	0.66
Heart rate, bpm	69.0 (59.5, 78.5)	62.5 (59.0, 71.3)	0.37
Systolic blood pressure, mmHg	130 (120, 134)	124 (115, 132)	0.35
Diastolic blood pressure, mmHg	78.0 (70.0, 80.0)	71.5 (68.0, 77.8)	0.25
LBBB, n (%)	2 (11.8)	2 (11.1)	1
QRS duration (ms)	96.0 (85.0, 106.0)	99.0 (85.5, 104.5)	0.96
Study baseline NT-pro-BNP	90.0 (41.0, 132.0)	77.0 (43.8, 141.0)	0.94
Medical history			
Smoker, n (%)	3 (17.6)	0 (0)	0.1
Moderate Alcohol Excess, n (%)	6 (35.3)	4 (22.2)	0.47
Atrial fibrillation, n (%)	2 (11.8)	5 (27.8)	0.4
Hypertension, n (%)	1 (5.9)	0 (0)	0.49
Diabetes mellitus, n (%)	0 (0)	0 (0)	n/a
Family History of DCM, n (%)	3 (17.6)	3 (16.7)	1
Previous unplanned HF admission, n	10 (58.8)	13 (72.2)	0.49
Baseline LVEF (%)	25.0 (19.0, 35.0)	30.5 (19.8, 33.5)	0.73
Improvement in LVEF (%)	31.0 (22.8, 38.5)	25.5 (19.9,35.0)	0.42
Time recovered (months)	26.0 (9.5, 54.5)	28.5 (15.5, 49.3)	0.88
Aetiology			
Idiopathic n (%)	10 (58.8)	13 (72.2)	0.70
Familial/genetic n (%)	3 (17.6)	3 (16.7)	
External insult, n (%)	4 (23.5)	2 (11.1)	
Medications			
Beta-Blocker, n (%)	15 (88.2)	14 (77.8)	0.66
ACEI/ARB, n (%)	17 (100)	18 (100)	n/a
MRA, n (%)	7 (41.2)	10 (55.6)	0.51
Loop Diuretic, n (%)	3 (17.6)	3 (16.7)	1
CMR variables			
LVEDVi, ml/m^2	76.0 (68.5, 88.0)	86.0 (67.5, 90.0)	0.41
LVEF, %	60.0 (55.0, 63.5)	59.0 (54.8, 64.0)	0.83
LV Mass Index, g/m^2	67.0 (58.0, 74.0)	63.5 (51.8, 72.5)	0.53
RVEDVi, ml/m^2	74.0 (62.0, 95.0)	79.0 (66.5, 93.0)	0.69
RVEF, %	57.0 (50.5.61.0)	63.0 (59.0, 64.5)	0.03
LAVi, ml/m^2	41.8 (33.4, 43.7)	41.3 (37.2, 45.1)	0.72
LGE, presence	6 (35.3)	6 (33.3)	1
CPET variables			
Peak VO2 (ml/kg/min)	23.4 (19.9, 30.3)	24.5 (21.0, 31.8)	0.61
Percentage of predicted peak VO2 (%)	87.4 (79.5, 93.5)	95.3 (84.9, 102.1)	0.15

Table 8.2. Baseline characteristics of the first 35 patients based on assigned group. Mann-Whitney Test and Fisher's Exact Test used to compare continuous and categorical data respectively.

8.5.3 Primary End-point

Of the 18 patients randomised to therapy withdrawal, 8 (44.4%) met the criteria for relapse over 6 months compared to none in the control arm (p<0.001; Chi-square 14.6; event rates at 6 months: 44.4% vs 0%) (*Figure 8.2*). Of the 16 patients who subsequently had therapy withdrawn arm after completing 6 months in the control arm, 6 (37.5%) met the criteria for relapse over the following 6 months. Therefore, of the 34 patients who underwent therapy withdrawal, 14 (41.4%) relapsed over the study period. In addition, of all those who underwent therapy withdrawal, one patient dropped out of the study shortly after enrolment and 2 were restarted on therapy for resistant hypertension and AF without meeting the primary end-point. Therefore, 17 (50.0%) patients successfully completed the pre-specified follow-up period following therapy withdrawal without meeting the primary end-point.

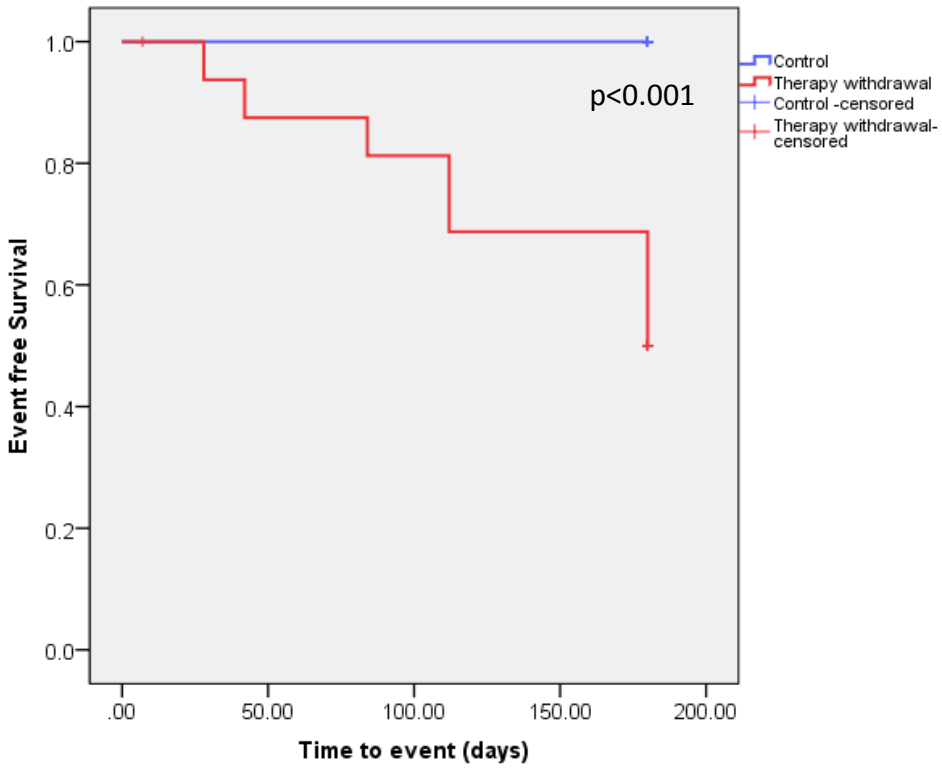

Figure 8.2.Kaplan-Meier curves for the primary end-point

Kaplan-curves comparing event-free survival for patients randomised to the control (n=17) and therapy withdrawal arms (n=18). Log-rank test used to compare arms.

Of those who met the primary end-point, nine met the LVEF criterion for relapse, eight the LVEDVi criterion, seven the NT-pro-BNP criterion and one developed peripheral oedema (*Figure 8.3*). All those who fulfilled only 1 end-point criterion also had deterioration in at least one other variable that did not reach the pre-specified threshold.

There were no CV deaths, unplanned CV hospitalisations, major adverse CV events or serious adverse events in either randomised group. Two patients in the therapy withdrawal arm developed AF, 1 of whom met the primary end-point based on elevation in NT-pro-BNP.

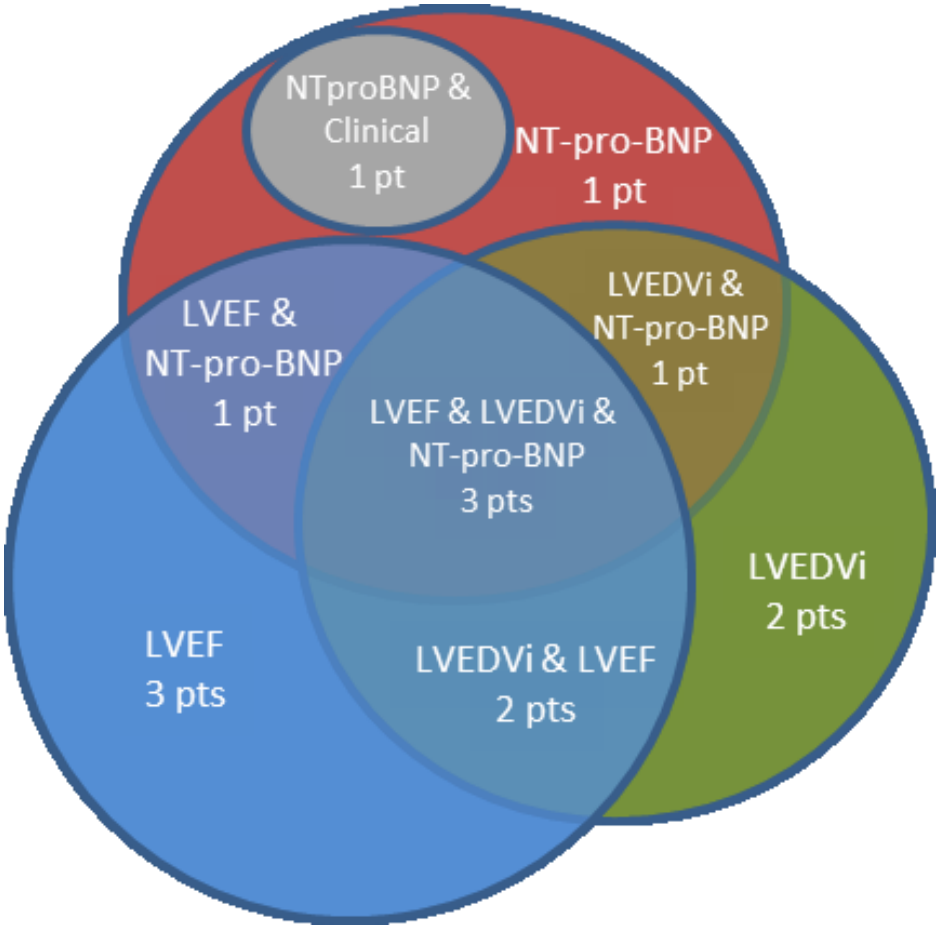

Figure 8.3. Venn diagram illustrating the primary end-point criteria fulfilled by patients.

8.5.4 Secondary End-points

LVEF, LVEDVi, NT-pro-BNP, LAVi, exercise time, peak oxygen consumption, heart rate, systolic and diastolic blood pressures, KCCQ and SAQ score were similar at baseline for those assigned to the control (n=17) and therapy withdrawal (n=17) arms *(Table 8.3)*. There was a reduction in LVEF and increase in heart rate, systolic and diastolic blood pressures between baseline and follow-up in patients assigned to the therapy withdrawal arm and this was greater than the change observed in patients in the control arm (*Table 8.4* & *Figure 8.4*). The changes in LVEDVi and NT-pro-BNP were nominally greater in the therapy withdrawal arm, although this did not reach statistical significance. The changes in exercise time, peak VO_2, symptom status, and LAVi between baseline and follow-up were not different between arms (*Table 8.4*, *Figure 8.5* & *Figure 8.6*).

	n	**Control Baseline** (n=17)	**n**	**Therapy Withdrawal Baseline** (n=17)	**p value**
LVEF, %	17	60.0 (55.5, 63.5)	17	58.5 (54.3, 63.0)	0.92
LVEDVi, ml/m^2	17	76.0 (68.5, 88.0)	17	76.0 (64.3, 84.5)	0.52
NT-pro-BNP, ng/L	17	90.0 (41.0, 132.0)	17	87.5 (40.0, 125.8)	0.97
LAVi, ml/m^2	17	41.8 (33.4, 43.7)	17	41.9 (30.7, 48.2)	0.81
KCCQ, n	17	93.8 (90.4, 99.0)	17	94.8 (88.0, 98.2)	0.11
SAQ, n	17	10.1 (5.1, 16.7)	17	11.8 (4.6, 22.7)	0.54
Exercise Time, seconds	17	571 (545, 636)	16	593 (554, 631)	0.79
Peak oxygen consumption, ml/kg/min	17	23.4 (19.9, 30.3)	16	23.9 (19.8, 31.5)	0.61
Heart rate (bpm)	17	69.0 (59.5, 78.5)	17	63.0 (60.0, 72.5)	0.47
Systolic blood pressure (mmHg)	17	130 (120, 134)	17	124 (117, 137)	0.63
Diastolic blood pressure (mmHg)	17	78.0 (70.0,80.0)	17	72.0 (68.5, 80.0)	0.47

Table 8.3. Secondary end-point variables at baseline based on assigned treatment arm. Mann-Whitney Test used to compare groups.

	n	**Control** (n=17)	n	**Therapy withdrawal** (n=17)	**p value**
LVEF, %	17	-1.0 (-6.0, 3.5)	17	-10 (-14.5, -0.25)	0.009
LVEDVi, ml/m^2	17	-1.0 (-5.5, 5.5)	17	7 (-5.8, 18.0)	0.15
NT-pro-BNP, ng/L	17	-7.0 (-17.5, 34.5)	17	18.0 (-16.5, 289)	0.17
LAVi, ml/m^2	17	2.3 (-5.7, 4.3)	16	1.6 (-3.4, 6.0)	0.68
KCCQ, n	16	0 (-3.1, 3.0)	17	-1.1 (-7.6, 0.5)	0.17
SAQ, n	16	1.5 (-1.8, 6.1)	17	0.3 (-0.8, 4.8)	0.9
Exercise Time, seconds	16	-6.5, (-44.8, 41.0)	15	1 (-30.0, 29.0)	0.57
Peak oxygen consumption, ml/kg/min	16	-0.8 (-2.3, 0.93)	15	-1.5 (-4.8, 0.3)	0.34
Heart rate (bpm)	17	-2.0 (-10.0, 5.0)	17	19.0 (15.0, 21.0)	<0.001
Systolic blood pressure (mmHg)	17	-4.0 (-10.5, 8.0)	17	10.0 (0.0, 20.0)	0.024
Diastolic blood pressure (mmHg)	17	0.0 (-6.0, 4.0)	17	8.0 (-2.5, 12.5)	0.024

Table 8.4. Differences in secondary end-point variables between baseline and follow-up based on assigned treatment arm.

Mann-Whitney Test used to compare groups.

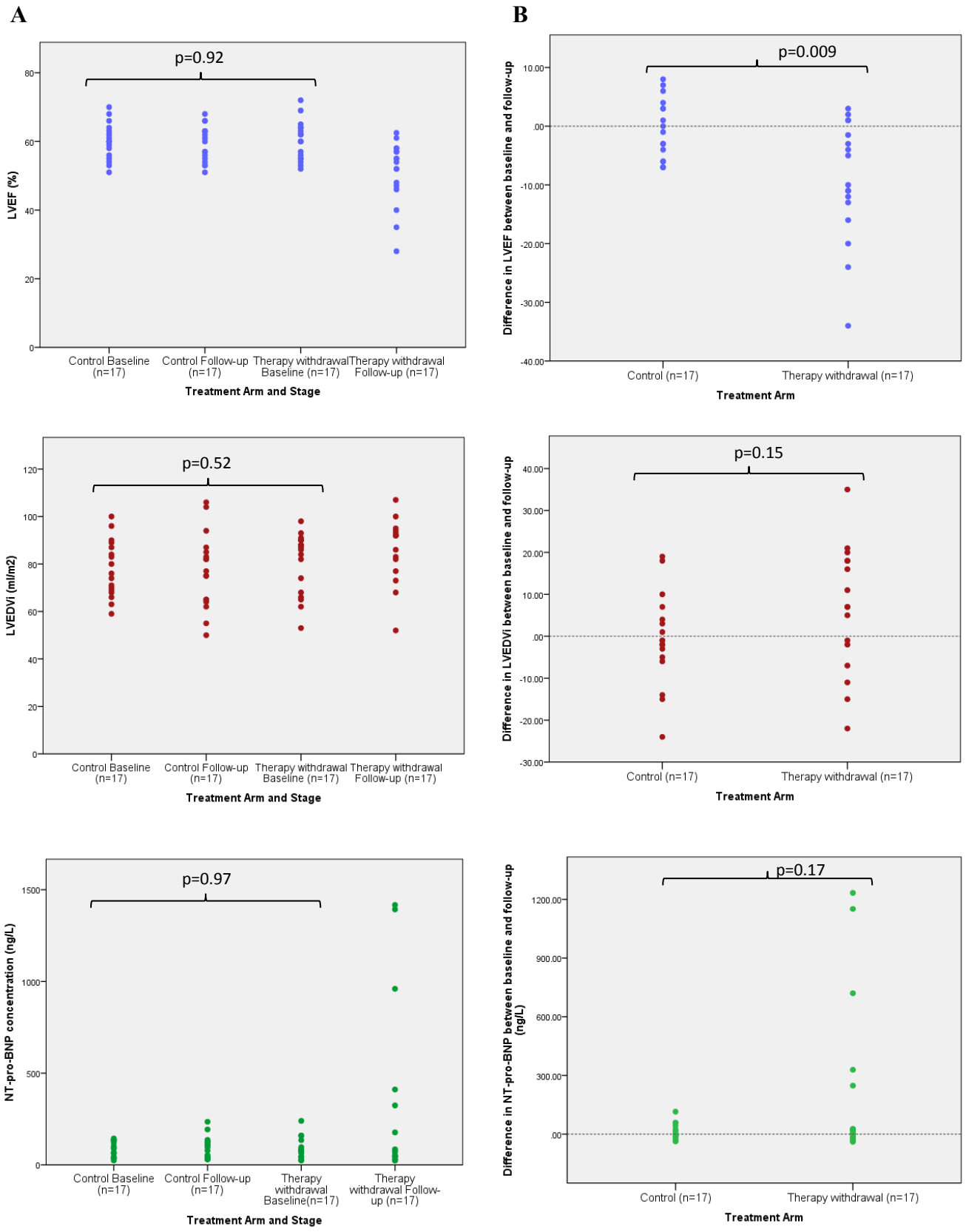

Figure 8.4. Changes in LVEF, LVEDVi and NT-pro-BNP between baseline and follow-up. A – absolute values for each variable at specific time points; p values stated for comparison between arms at baseline. B – difference in variables between baseline and follow-up.

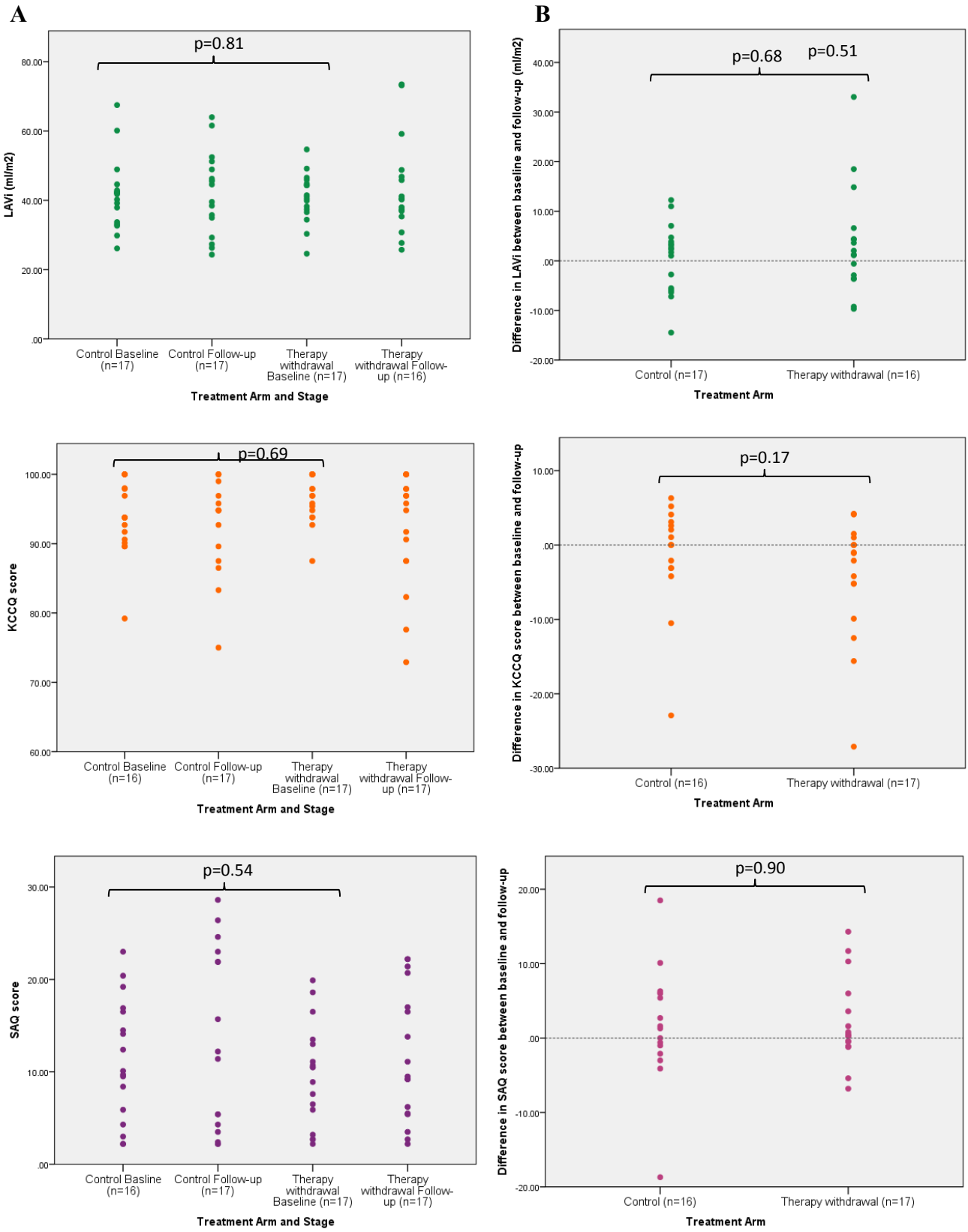

Figure 8.5. Changes in LAVi, KCCQ and SAQ score between baseline and follow-up. A – absolute values for each variable at different time points; p values included for comparison between arms at baseline. B – difference in variables between baseline and follow-up.

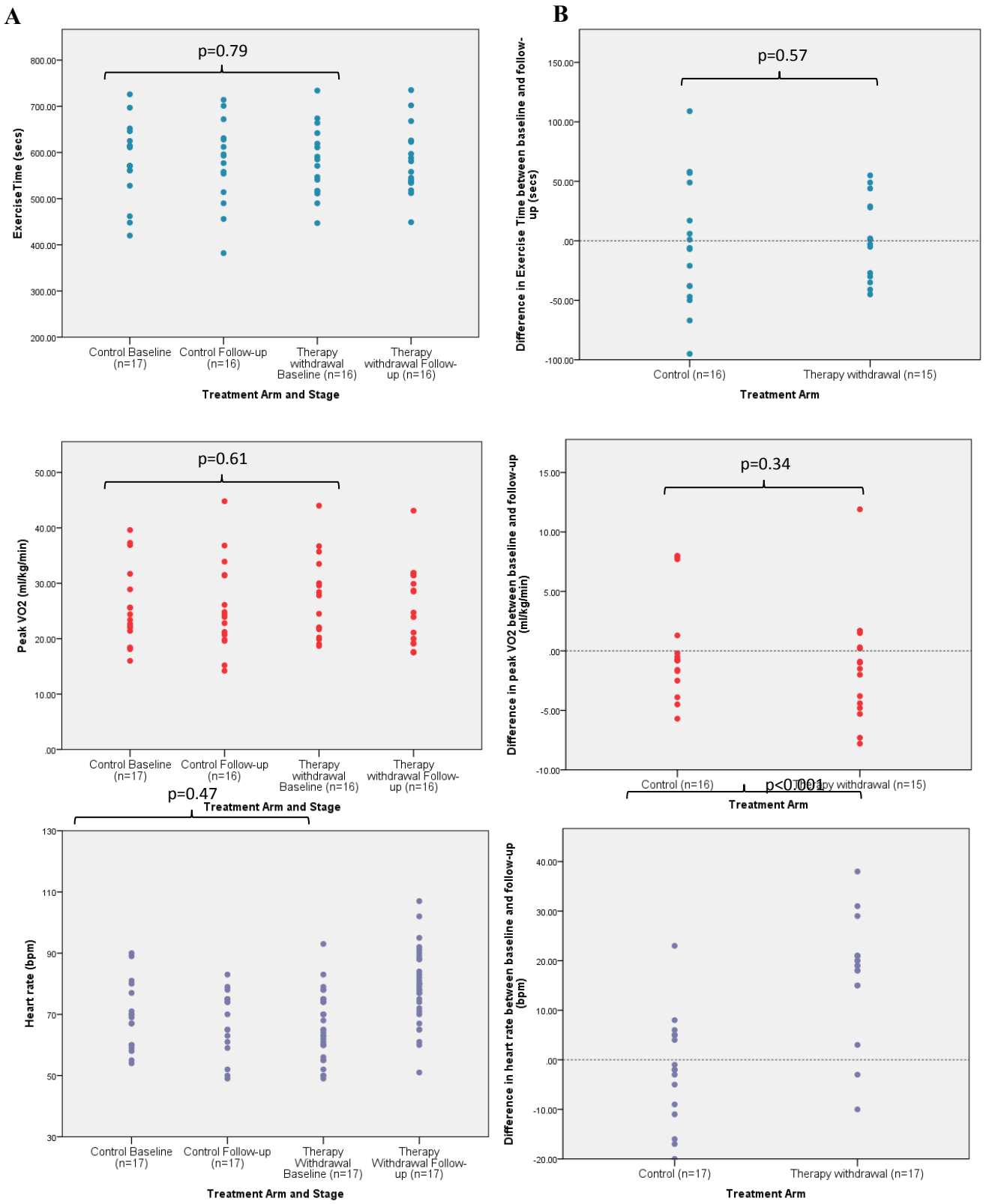

Figure 8.6. Changes in exercise time, peak oxygen consumption and heart rate between baseline and follow-up.

A – absolute values for each variable at different time points; p values included for comparison between arms at baseline. B – difference in variables between baseline and follow-up.

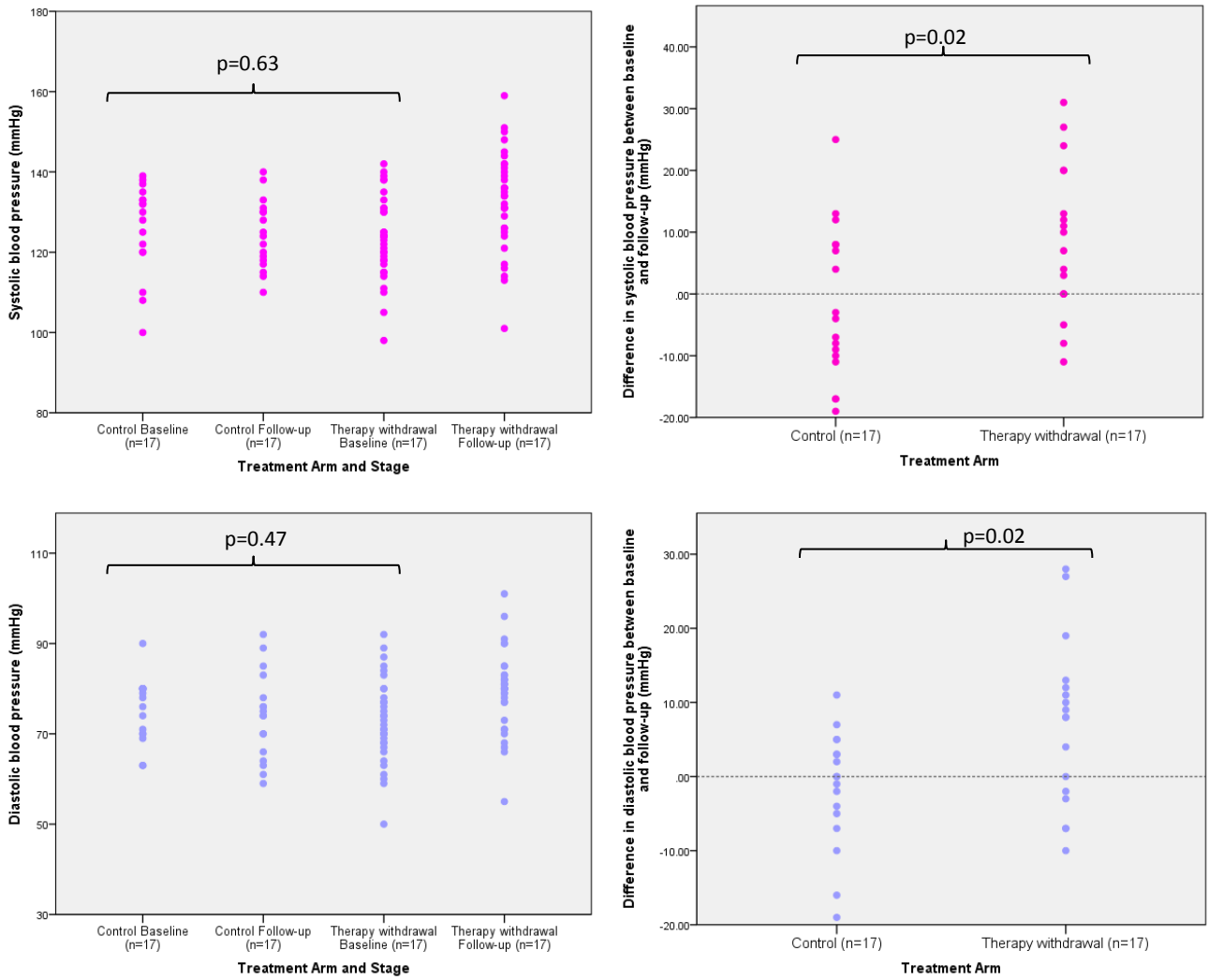

Figure 8.7. Changes in blood pressure between baseline and follow-up.
A – absolute values for each variable at different time points; p values included for comparison between arms at baseline. B – difference in variables between baseline and follow-up.

8.5.5 Differences between Baseline and Follow-up with Therapy Withdrawal

Amongst the 33 patients who underwent therapy withdrawal and completed planned investigations (17 patients assigned to therapy withdrawal and 16 who 'crossed-over' after 6 months), LVEF was lower at follow-up compared to the start of therapy withdrawal, while LVEDVi, NT-pro-BNP, heart rate, systolic and diastolic blood pressure were higher (*Table 8.5*).

	n	**Baseline** (n=33)	n	**Follow-up** (n=33)	**p value**
LVEF, %	33	60.0 (55.0, 63.5)	33	54.0 (48.0, 57.0)	<0.001
LVEDVi, ml/m^2	33	82.0 (65.0, 88.0)	33	86.0 (80.0, 94.0)	0.001
NT-pro-BNP, ng/L	33	78.0 (41.0, 125.5)	33	78.0 (43.0, 266.0)	0.006
LAVi, ml/m^2	33	41.1 (35.4, 46.1)	31	41.1 (36.9, 47.6)	0.46
KCCQ, n	33	95.4 (92.7, 100.0)	33	96.9 (87.5, 100.0)	0.38
SAQ, n	33	10.5 (4.9, 17.6)	33	12.2 (5.5, 16.8)	0.93
Exercise Time, seconds	31	585 (517, 631)	27	585 (526, 632)	0.93
Peak oxygen consumption, ml/kg/min	31	24.4 (20.2, 31.5)	27	24.5 (19.4, 31.0)	0.15
Heart rate (bpm)	33	65.0 (60.0, 75.0)	33	79.0 (71.5, 88.0)	<0.001
Systolic blood pressure (mmHg)	33	124 (118, 131)	33	134 (126, 142)	0.001
Diastolic blood pressure (mmHg)	33	72.0 (67.5, 79.0)	33	80.0 (75.0, 83.0)	0.003

Table 8.5. Baseline and follow-up values for secondary end-point variables for all patients who underwent therapy withdrawal.
Wilcoxon signed-rank test used to compare data.

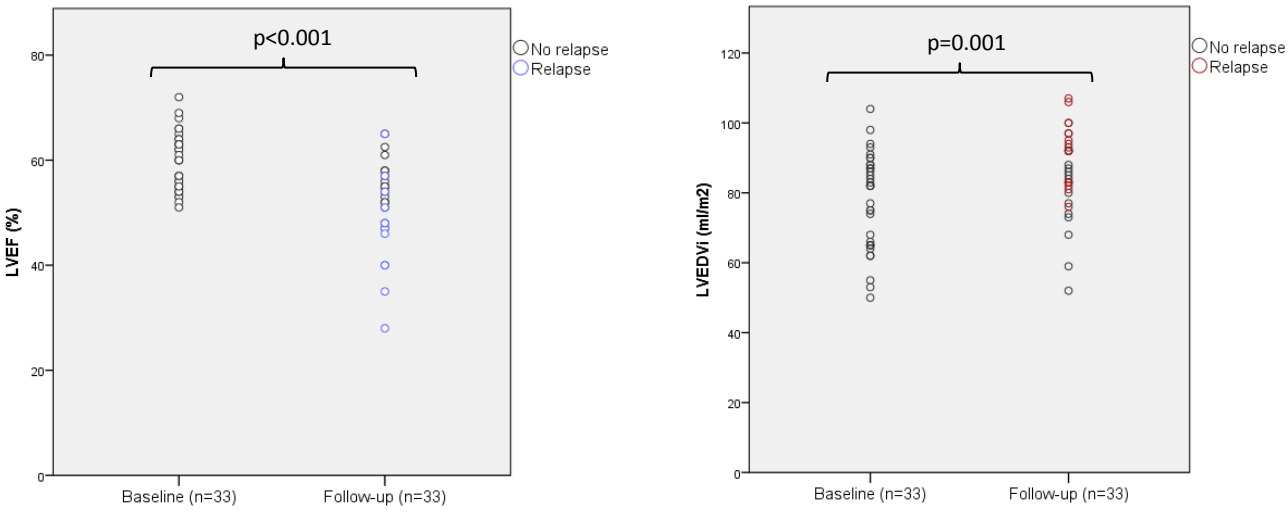

Figure 8.8. Baseline and follow-up values for secondary end-points amongst patients who had therapy withdrawn.

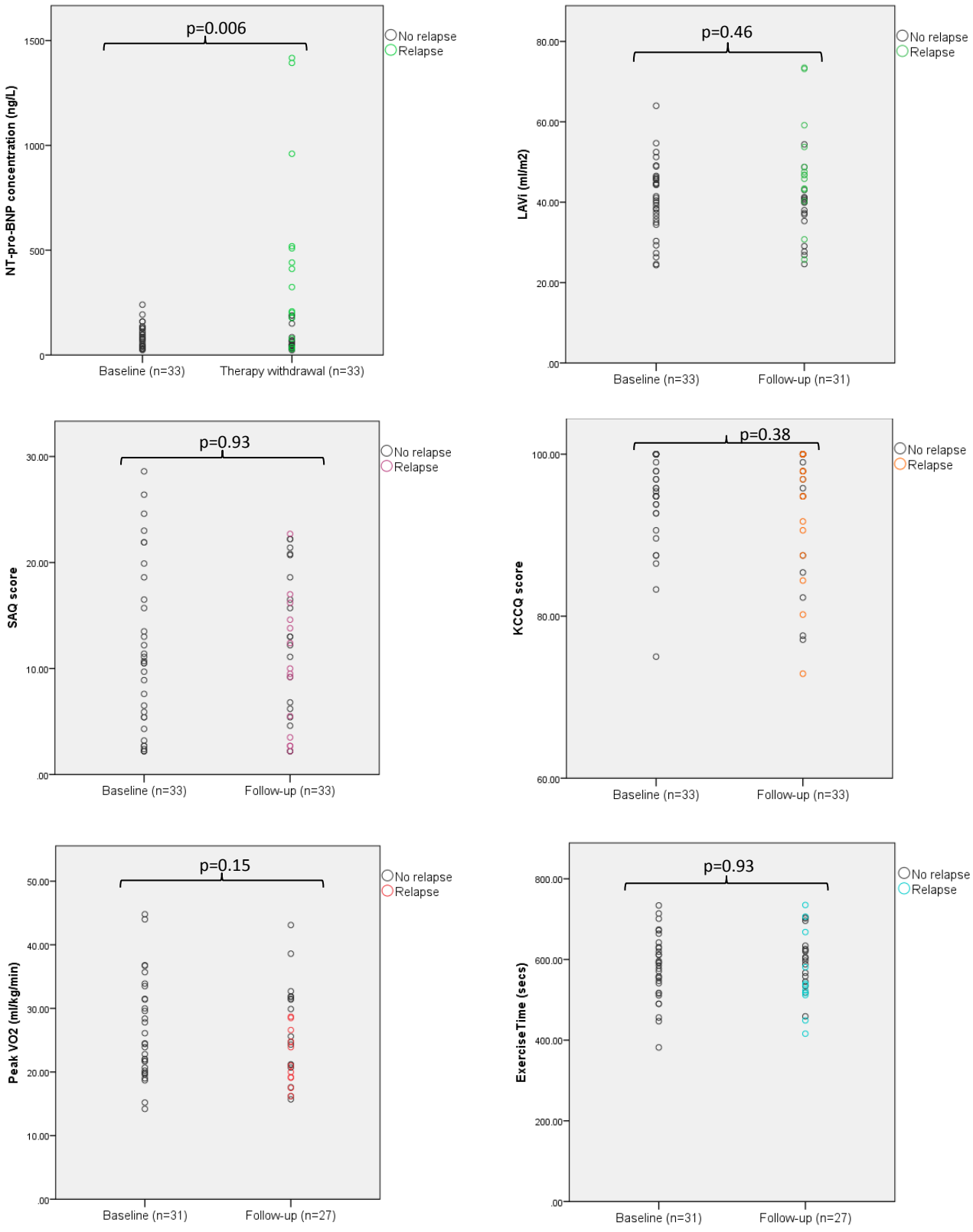

Figure 8.8. Baseline and follow-up values for secondary end-points amongst patients who had therapy withdrawn.

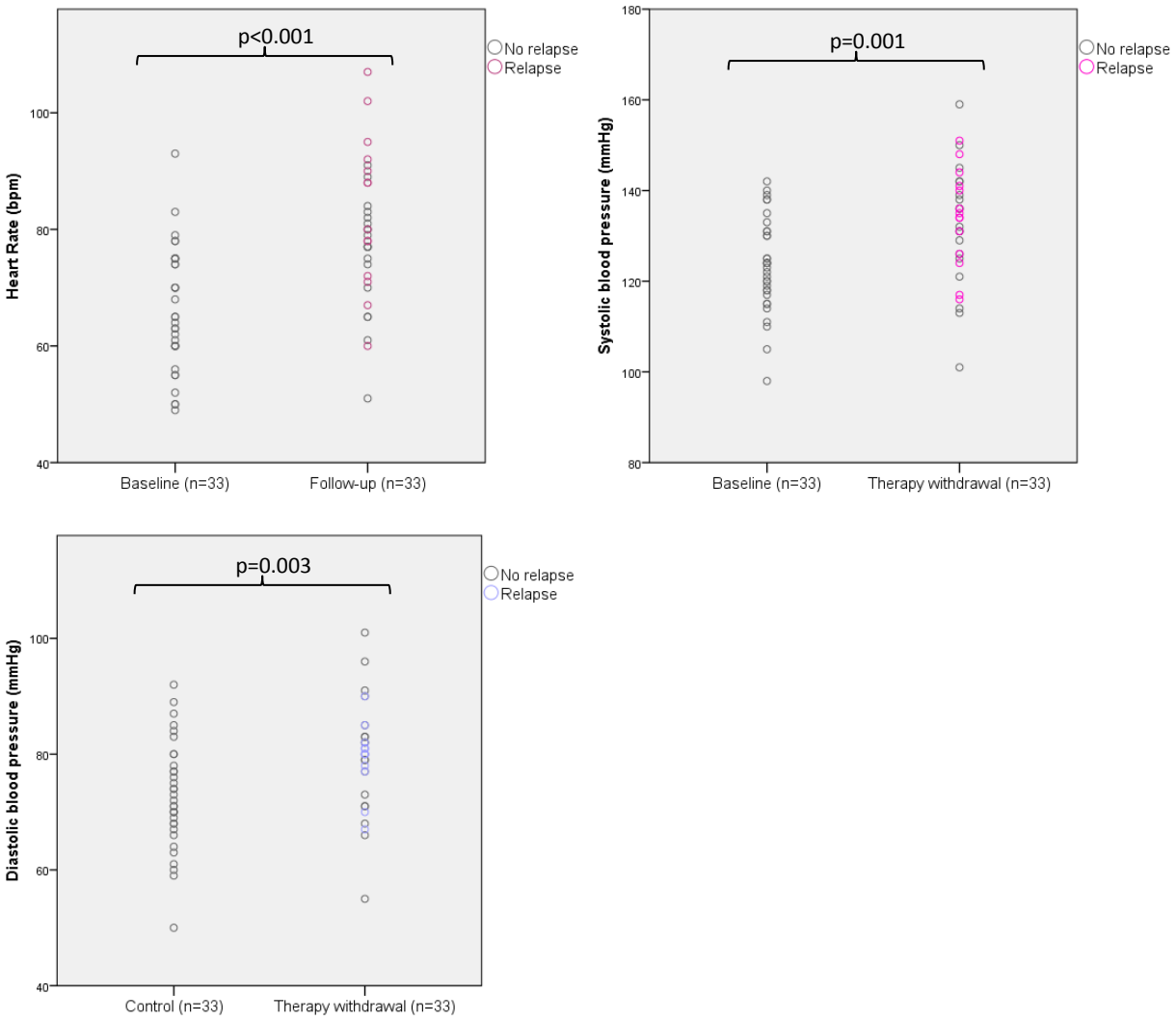

Figure 8.8. Baseline and follow-up values for secondary end-points amongst patients who had therapy withdrawn.

8.5.6 Baseline Variables Associated with Relapse

Age, baseline NT-pro-BNP and baseline global radial strain were associated with the risk of relapse on univariable analysis amongst those who underwent therapy withdrawal (*Table 8.6*). In a multivariable model, including these three variables, only global radial strain was associated with the outcome (*Table 8.7*).

	HR (95% CI)	p value
Clinical variables		
Age (per 5yrs)	1.26 (1.03, 1.56)	**.027**
Sex (men)	0.79 (0.49, 1.27)	.33
LVEF at DCM diagnosis (per %)	0.99 (0.91, 1.07)	.26
LVEF improvement (per %)	1.01 (0.97, 1.06)	.54
Time recovered (per month)	1.00 (0.98, 1.02)	.78
Idiopathic aetiology	1.23 (0.38, 3.94)	.72
Family history of DCM	1.17 (0.26, 5.25)	.83
Unplanned HF admission	1.10 (0.68, 1.78)	.70
Heart rate (per bpm)	1.00 (0.96, 1.05)	.82
LBBB (presence)	0.80 (0.43, 1.50)	.49
NT-pro-BNP (per 20ng/L)	1.22 (1.06, 1.40)	**.006**
CMR variables		
LVEF (per %)	0.99 (0.91, 1.07)	.74
LVEDVi (per 5ml/m^2)	1.00 (0.98, 1.03)	.79
RVEF (per %)	0.99 (0.97, 1.02)	.64
LAVi (per 5 ml/m^2)	0.98 (0.73, 1.30)	.86
LGE (presence)	1.38 (0.43, 4.41)	.58
Native T1 (per 10ms)	0.96 (0.83, 1.11)	.58
ECV (per %)	0.98 (0.85, 1.14)	.79
GRS (per 0.05)	0.72 (0.55, 0.96)	**.024**
GCS (per -.02)	1.26 (0.87, 1.82)	.23
GLS (per -.02)	1.28 (0.81, 2.03)	.30
CPET variables		
Percentage predicted VO2 (per %)	1.03 (0.98, 1.07)	.25
Peak VO2 (per ml/kg/min)	0.96 (0.89, 1.04)	.34
VE/VCO2 (per unit)	1.01 (0.94, 1.08)	.76

Table 8.6. Association between variables and relapse on univariable regression analysis.

	HR (95% CI)	p value
Age (per 5yrs)	1.06 (0.88, 1.28)	.12
NT-pro-BNP (per 20ng/L)	1.06 (0.88, 1.28)	.56
GRS (per 0.05)	0.74 (0.55, 0.99)	**.045**

Table 8.7. Association between variables and relapse on multivariable regression analysis. Variables associated with the end-point on univariable analysis were carried into multivariable model.

8.6 Discussion

We report the preliminary findings of the first randomised controlled trial of pharmacological HF therapy withdrawal in asymptomatic patients with a prior diagnosis of DCM, recovered LVEF, normal LVEDVi and low plasma NT-pro-BNP. Initial results suggest that around 40% of such patients relapse within 6 months of starting therapy withdrawal. This suggests that for, at least a proportion of patients, the improvement in cardiac function following the initial diagnosis represents remission of their cardiomyopathy rather than a permanent cure and that they require at least some of their therapy to be maintained.

Previous retrospective observational studies examining the impact of therapy withdrawal in patients with DCM and improved LVEF have provided conflicting results. Moon and colleagues studied 42 patients with idiopathic DCM whose LVEF had improved to above 40% (Moon *et al*, 2009). Seven patients subsequently discontinued therapy, 5 of whom demonstrated a reduction in LVEF at a median time of 32 months. However, most of the patients who suffered subsequent deterioration had mid-range reduced LVEF and LV dilatation prior to medication discontinuation. Conversely, Amos and colleagues studied 22 patients with peripartum cardiomyopathy whose LVEF had improved to greater than 50% (Amos *et al*, 2006). Fifteen subsequently stopped either ACEI or beta-blocker, 5 of whom stopped both medications. None of the patients demonstrated deterioration in LVEF over a median follow-

up of 29 months. Whilst, it may be hypothesised that the difference in findings is the results of different pathophysiological drivers in each cohort, it has recently been demonstrated that idiopathic and peripartum DCM often share common genetic backgrounds (Ware *et al*, 2016). The preliminary results, from this first prospective study investigating this topic, suggest that therapy withdrawal is associated with deterioration of cardiac function in a large proportion of patients. In this small sample, there was no obvious difference in the rate of relapse depending on the perceived aetiology of the disease.

Importantly, in the first 35 patients, there were no MACE, unplanned HF hospitalisations or serious adverse events. Moreover, none of the patients developed marked symptoms of HF and only one developed mild peripheral oedema associated with a rise in NT-pro-BNP. This suggests that intensive monitoring can detect changes in cardiac function, allowing the re-introduction of therapy before the development of symptoms or serious complications. However, this level of monitoring may not be practical in clinical practice. Routine therapy withdrawal in such patients therefore appears to be imprudent.

Whether it is possible to distinguish between patients who have complete recovery as opposed to disease remission is unclear. Baseline global radial strain was the only variable associated with the risk of relapse in exploratory multivariable analysis within this small sample. However, whether this is reproducible and able to distinguish reliably between recovery and remission in large numbers of patients is unclear.

At the time of writing, the randomised phase of the trial is complete but 7 patients remain in follow-up after having treatment withdrawn after 6 months. The trial team and the Independent Trial Safety Advisor believe it is important to complete the study as planned given the small number of patients and the desire to determine the relapse rate with the greatest precision. The

absence of MACE and unplanned HF hospitalisations to date supports this decision. Given the results to date, these patients continue under regular review with more intensive observation if any clinical concern arises. Patients in the study are also aware of the intermediate probability of requiring therapy re-initiation based on the results to date.

8.6.1 Limitations

The study has a small sample size with single centre enrolment. Whilst this ensures standardised approaches to patient visits and investigations, it may make the study susceptible to selection bias. However, patients have been referred from a network of 7 collaborating hospital trusts covering a broad referral population. The final cohort includes patients of all ages, with a range of disease chronicities and aetiologies. It therefore encompasses the heterogeneity of the wider population encountered in clinical practice. The power to examine baseline variables associated with the primary end-point is limited given the small sample size. Nevertheless, we felt it was important to perform exploratory analyses to guide future research.

8.7 Conclusion

The preliminary results of the TRED-HF study suggest that around 40% of asymptomatic patients with DCM, recovered LVEF, normal LVEDVi and low concentrations of natriuretic peptide will experience relapse within 6 months of withdrawing HF therapy. This is much greater than the rate of relapse in patients who remain on therapy. Routine withdrawal of therapy in such patients as part of clinical practice appears unwise.

Chapter 9

9 General Discussion and Future Work

9.1 Overview of Thesis

The aim of this thesis was to explore important unmet needs in the contemporary management of patients with DCM; specifically, improving risk stratification for SCD and the selection of patients for ICD implantation and also the treatment of patients with DCM and improved LVEF. The risk stratification theme was explored in observational studies based on a large registry of patients, whilst the safety and feasibility of HF therapy withdrawal in patients with DCM and improved LVEF was investigated in an open-label, cross-over randomised controlled trial.

9.1.1 Improving Risk Stratification Approaches in DCM

At the outset of the research, the DANISH trial emphasised the importance of developing novel approaches for the risk stratification of patients with DCM (Kober *et al*, 2016). The current approach used to guide the selection of patients for primary prevention ICD implantation lacks both sensitivity and specificity. We demonstrate that LGE-CMR offers the potential to improve both metrics. The presence of mid-wall LGE identifies a sub-group of patients with mild and moderate degrees of LV impairment, who do not currently meet guideline criteria for ICD implantation but who are at nine-fold increased risk of SCD compared to those without LGE. DCM patients with LGE in the septum or occurring concomitantly in the septum and LV free-wall were found to be at the highest risk of SCD. Conversely, those patients with reduced LVEF and without LGE were found to be at relatively low risk of SCD events.

We also demonstrate that men with DCM have features of more severe disease on CMR and higher adjusted mortality compared to women. Whilst studies have suggested that men with HF have worse outcome compared to women, it has previously been suggested that this may

be driven by a higher proportion of ischaemic HF in men (Hsich *et al*, 2009; Martinez-Selles *et al*, 2003). Our study confirms that the difference in outcome between men and women is independent of aetiology. This may, in part, be explained by sex-dependent differences in ventricular remodelling. A more marked fibrotic response is observed in men compared to women in several diseases (Cocker *et al*, 2009; Treibel *et al*, 2017). If it is possible to unravel the mechanisms driving the differences in outcome, novel therapeutic approaches may be uncovered.

9.1.2 Therapy Withdrawal in DCM with Improved LVEF

We report the preliminary results of the first randomised controlled trial examining the safety and feasibility of therapy withdrawal in asymptomatic patients with DCM, improved LVEF and low plasma natriuretic peptide concentrations. The preliminary results suggest that around 40% of such patients relapse within 6 months of starting gradual therapy withdrawal. In addition, those patients who underwent therapy withdrawal had more marked reductions in LVEF over follow-up compared to those in the control arm. The results indicate that the risk of early deterioration in cardiac function following therapy withdrawal is substantial. This suggests that therapy should not routinely be withdrawn from patients who exhibit left ventricular reverse remodelling even if LVEF and NT-pro-BNP are within the normal range. If patients elect to have a trial of therapy discontinuation, in the knowledge of these risks, this should be performed with regular imaging and biomarker follow-up.

9.1.3 Personalising therapy in patients with DCM

In conclusion, a number of variables investigated in this thesis, such as the presence of LGE, sex and age may improve the risk stratification and prognostication of patients with DCM. This may enable a more personalised approach to management by selecting patients who are most likely to gain benefit from certain therapies. For example, the presence of LGE may be used to identify patients at high-risk of SCD who may be most likely to gain longevity from ICD implantation. Conversely, age may be a useful indicator of the risk of dying from non-sudden causes and used to identify patients unlikely to gain benefit from such a device. It is foreseeable that these characteristics and features could be built into management algorithms leading to personalised selection for therapy, improved patient outcomes and more cost-effective use of resources. Randomised controlled trials examining the use of such variables in guiding management are required in order to confirm that this more personalised approach improves patient outcomes.

The TRED-HF study has yielded novel data in the unique group of patients with DCM and improved LVEF. Features which identify the sub-group of patients within this cohort who have true myocardial recovery and who may be able to successfully withdraw or reduce therapy are required to further personalise care. An approach integrating imaging techniques such as myocardial strain analysis, proteomics and metabolomics appears promising.

9.2 Future Work

9.2.1 Improving the Selection of Patients for ICDs for the Primary Prevention of SCD

It is clear that the identification of DCM patients who are most likely to gain longevity from ICD implantation requires a more sophisticated approach than that recommended in current guidelines (Ponikowski *et al*, 2016; Yancy *et al*, 2013). A model that balances an individual's risk of SCD and their risk of dying from competing non-sudden causes is crucial. Patients with a high mortality risk from non-sudden causes will, on average, obtain less benefit from ICD therapy. Fatal arrhythmias in this sub-group may simply be a sign of advanced disease that would soon otherwise end in death secondary to pump failure. Those most likely to gain longevity following an aborted SCD are those with a low risk of dying from competing causes. Evidence supports a substantial benefit of ICDs only in young patients with mild symptoms of HF and reduced LVEF. It is possible that a multivariable risk score, including mid-wall LGE, that balances an individual's risk of SCD and non-sudden death will provide a sensitive and specific approach to this challenge in the future.

We plan to model the risk of SCD and non-sudden death in our DCM registry cohort on the basis of age, NYHA class, LVEF and the presence of mid-wall LGE. We will aim to establish the characteristics of patients with at least a moderate risk of SCD as well as a low risk of dying from non-sudden causes. Large randomised trials are then required to confirm mortality benefit from ICD implantation in such patients.

9.2.2 The Management of Patients with DCM and Improved LVEF

Based on the preliminary results of the TRED-HF study, it appears that routine withdrawal of therapy in patients with DCM and improved LVEF is unwise. The statistical power to identify

markers that predict successful therapy withdrawal within the final study cohort appears limited. Furthermore, it appears unlikely to be ethical to perform a larger trial of therapy withdrawal in a similar population to more definitively establish these variables, given the associated risks. Future work should therefore aim to precisely phenotype the population of patients with improved LVEF and aim to establish markers of true myocardial recovery.

It appears likely that there is a final common pathway driving recurrence of contractile impairment in this heterogeneous population following withdrawal of therapies. One hypothesis is that mitochondrial dysfunction and abnormal myocardial energetics are the central common features amongst those who deteriorate following therapy withdrawal. Evaluating cardiac energetics using ^{31}phosphorus magnetic resonance spectroscopy or biomarkers of mitochondrial function may enable more accurate assessment of the degree of myocardial recovery (Neubauer *et al*, 1997). We plan to track changes in the circulating proteome of patients in TRED-HF by analysing stored serum samples using a high throughput immunoassay panel and stored urine using untargeted mass spectrometry. This may provide insight into particular pathways which play important roles in ventricular remodelling.

Chapter 10

10 References

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With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. *Circulation* 114:e385-484.

Prizes, Publications & Abstracts Relating to this Thesis

Prizes

1. Winner of the **European Society of Cardiology Heart Failure Association Young Investigator Award** at **Heart Failure 2018.**
2. Winner of the **British Society of Heart Failure Young Investigator Award** 2016
3. Finalist in **British Society of Cardiovascular Magnetic Resonance Young Investigator Award**, 2017
4. Finalist in the **British Heart Foundation Fellows Abstract Prize** at the Annual Fellows Meeting, 2017
5. Graded as one of the **'Top 3 Abstracts'** in Cardiovascular Magnetic Resonance at the European Society of Cardiology Congress, 2016

Original Research Peer-Reviewed Publications

1. **Halliday BP**, Gulati A, Ali A, Newsome SJ, Arzanauskaite M, Izgi C, Lota AS, Tayal U, Vassiliou VS, Krishnathasan K, Singhal A, Chiew K, Gregson J, Frenneaux MP, Cook SA, Pennell DJ, Collins P, Cleland JG, Prasad SK. Sex and age-based differences in the natural history and outcome of dilated cardiomyopathy. **Eur J Heart Fail**. 2018 Jun 3. doi: 10.1002/ejhf.1216. [Epub ahead of print]

2. **Halliday BP**, Gulati A, Ali A, Guha K, Newsome SJ, Arzanauskaite M, Vassiliou VS, Lota AS, Izgi C, Tayal U, Khalique Z, Stirrat C, Auger D, Pareek N, Ismail TF, Rosen SD, Vazir A, Alpendurada F, Gregson J, Frenneaux MP, Cowie MR, Cleland JG, Cook SA, Pennell DJ, Prasad SK. Association between mid-wall late gadolinium enhancement and sudden cardiac death in patients with dilated cardiomyopathy and mild and moderate left ventricular systolic dysfunction. **Circulation** 2017;135:2106-2115.

3. Tayal U, Newsome S, Buchan R, Whiffin N, **Halliday BP** et al. Integrated analysis of the phenotype and clinical outcome of titin cardiomyopathy. **J Am Coll Cardiol** 2017; 70: 2264-2274.

4. Vassiliou VS, Perperoglou A, Raphael CE, Joshi S, Malley T, Everett R, **Halliday B**, Dweck MR, Prasad SK. Midwall fibrosis and 5-year outcome in moderate and severe aortic stenosis. **J Am Coll Cardiol** 2017;69:1755-56.

Peer-Reviewed Review Articles

1. **Halliday BP,** Cleland JGF, Goldberger JJ, Prasad SK. Personalizing sudden cardiac death risk stratification in dilated cardiomyopathy. **Circulation** 2017;136:215-231.

Peer-Reviewed Editorials

1. Cleland JGF, **Halliday BP**, Prasad SK. Selecting patients with nonischemic dilated cardiomyopathy for ICDs. Myocardial function, fibrosis and what's attached. **J Am Coll Cardiol** 2017;70:1228-1231.

2. Lota AS, **Halliday BP,** Vassiliou VS**.** Iatrogenic myocarditis – biomarkers, cardiovascular MRI and the need for early diagnosis. **Oxf Med Case Reports** 2018;1:15-17

Book Chapters

1. **Halliday BP**, Tayal U, Prasad SK. Role of Cardiovascular Magnetic Resonance in Dilated Cardiomyopathy. In: Manning WJ, Pennell DJ ed. Cardiovascular Magnetic Resonance, 3rd edition. Elsevier, 32-1-32-8. *In press*.

Invited Talks

1. Cardiovascular Magnetic Resonance 2018 Congress; Barcelona, Spain
   'The role of CMR in risk stratification: a myth or enough evidence?'
   A joint session with the Heart Failure Society of America, 'Current and Future Final Perspectives to Improve Patient Care in Heart Failure'

2. Cardiovascular Magnetic Resonance 2018 Congress; Barcelona, Spain
   'Cardiomyopathy' *Part of the Non-Cardiologists Course, 'Pathophysiology'*

1st Author Oral Abstract Presentations

1. American College of Cardiology Annual Congress 2018; Orlando, USA

   Halliday BP, Baksi AJ, Gulati A et al. Defining the relationship between the extent of mid-wall late gadolinium enhancement and adverse heart failure events in patients with dilated cardiomyopathy.

2. British Society of Cardiovascular Magnetic Resonance Annual Meeting 2017; Manchester, UK

   Halliday BP, Gulati A, Ali A et al. Sudden death risk stratification in patients with mild dilated cardiomyopathy.

   Finalist in Young Investigator Award

3. Society of Cardiovascular Magnetic Resonance – 20th Annual Scientific Sessions 2017; Washington DC, USA

   Halliday BP, Gulati A, Ali A et al. Prediction of adverse cardiovascular outcomes in patients with mild dilated cardiomyopathy.

4. Society of Cardiovascular Magnetic Resonance – 20th Annual Scientific Sessions 2017; Washington DC, USA

   Halliday BP, Khalique Z, Scott AD et al. Insights from T1-mapping into left ventricular reverse remodelling in dilated cardiomyopathy.

5. British Society of Heart Failure Annual Autumn Meeting 2016; Young Investigator Award, London

   Halliday BP**,** Gulati A, Ali A et al. Prediction of sudden death risk in patients with dilated cardiomyopathy and mild or moderate reductions in left ventricular ejection fraction.

   Winner of the Young Investigator Award

6. ESC Congress, Rome August 2016; Advances in Science Session

   Halliday BP**,** Gulati A, Ali A et al. Risk stratification of mild-to-moderate phenotypes of dilated cardiomyopathy**.**

   Top 3 Abstracts in CMR

1st Author Poster Abstract Presentations

1. American College of Cardiology Annual Congress 2018; Orlando, USA

   Halliday BP, Gulati A, Ali A et al. Sex difference in the natural history and outcome of dilated cardiomyopathy.

2. Cardiovascular Magnetic Resonance 2018 Congress; Barcelona, Spain

   Halliday BP, Baksi AJ, Izgi C et al. Defining the association between the extent and location of mid-wall late gadolinium enhancement and outcome in dilated cardiomyopathy.

3. British Heart Foundation, Fellows Meeting, 2017; Cambridge, UK

   Halliday BP, Gulati A, Ali A et al. Sudden cardiac death risk stratification in patients with dilated cardiomyopathy and mild left ventricular dysfunction.

   Finalist in Fellows' Abstract Prize

4. European Society of Cardiology Heart Failure Association Annual Congress 2017; Paris, France

   Halliday BP, Chiew K, Newsome S. Incremental prognostic value of cardiopulmonary exercise testing in non-ischemic dilated cardiomyopathy.

5. Society of Cardiovascular Magnetic Resonance – 20th Annual Scientific Sessions 2017; Washington DC, USA

   Halliday BP, Ali A, Gulati A et al. Gender differences in dilated cardiomyopathy phenotype as determined by cardiovascular magnetic resonance.

6. ESC Working Group for Myocardial and Pericardial disease, Rostock, October 2016

   Halliday BP, Gulati A, Ali A et al. Prediction of sudden death risk in patients with dilated cardiomyopathy and mild and moderately impaired ejection fraction.

7. ESC Congress, Rome, August 2016

   Halliday BP**,** Ali A, Gulati A et al. The natural history of non-ischaemic dilated cardiomyopathy diagnosed after the age of 65 years of age.

8. ESC Congress, Rome, August 2016

   Halliday BP**,** Ali A, Gulati A et al. Gender differences in the natural history and outcome of dilated cardiomyopathy.

Appendix

Propensity Score Model – Chapter 3

	OR (95% CI)	p
LVEF (per 10)	0.94 (0.54, 1.62)	0.82
Age (per 10)	1.14 (0.94, 1.37)	0.18
Male	2.46 (1.34, 4.49)	0.003
LAVi (per 10)	1.01 (0.89, 1.15)	0.83
NYHA II	0.97 (0.54, 1.73)	0.55
NYHA III / IV	1.74 (0.61, 4.97)	
LVEDVi (per 10)	1.06 (0.90, 1.24)	0.50
RVEF (per 10)	0.94 (0.66, 1.33)	0.72
ACE Inhibitor	1.30 (0.74, 2.30)	0.36
Beta Blocker	1.34 (0.75, 2.37)	0.32
Diabetes mellitus	2.65 (1.06, 6.62)	0.037
HR (per 10)	0.89 (0.72, 1.09)	0.26
Scan Indication		
Heart Failure	1.00	0.24
Palpitation / Presyncope	1.29 (0.68, 2.45)	
Family Screening	1.50 (0.61, 3.68)	
Other	0.68 (0.35, 1.32)	
ICD Implant (time-varying)	3.31 (1.67, 6.58)	<0.001

Appendix Table 1. Covariates included in the propensity score model in Chapter 3.
The model was used to adjust for confounding variables in the hazard analysis examining the association between LGE and SCD in DCM patients with mild-to-moderate LV impairment.

LGE characteristics based on contrast agent administered – Chapter 4

	Gadopentetate dimeglumine (n=303)	Gadobutrol (n=571)	*P**
LGE	93 (30.7)	207 (36.3)	0.12
LGE (%)	1.80 (4.65)	2.03 (4.71)	0.084
LGE Pattern			
Mid-wall	57 (18.8)	128 (22.4)	0.61
Sub-Epicardial	7 (2.3)	18 (3.2)	
Focal	7 (2.3)	15 (2.6)	
Multiple	22 (7.3)	46 (8.1)	
LGE Location			
Septal Only	43 (14.2)	99 (17.3)	0.43
Free-wall Only	14 (4.6)	28 (4.9)	
Both	36 (11.9)	80 (14.0)	

Association between LGE and all-cause mortality based on contrast agent used – Chapter 4

		Gadopentetate dimeglumine			Gadobutrol			Interaction P
		Mortality n (%)	HR (95% CI)	P	Mortality n (%)	HR (95% CI)	P	
A: LGE (Binary) [Any]	0%	39 (18.6)	1.00	-	34 (9.3)	1.00	-	0.94
	>0%	36 (38.7)	2.42 (1.54, 3.81)	<0.001	41 (19.8)	2.37 (1.50, 3.73)	<0.001	
B: LGE (Binary) [Best]	<1.29%	46 (20.3)	1.00	-	35 (9.0)	1.00	-	0.54
	≥1.29%	29 (38.2)	2.28 (1.43, 3.64)	<0.001	40 (22.1)	2.79 (1.77, 4.39)	<0.0001	
C: LGE (4 Groups)	0%	39 (18.6)	1.00	-	34 (9.3)	1.00	-	0.92
	>0% & <2.5%	13 (38.2)	2.20 (1.17, 4.12)	0.001	9 (14.3)	1.77 (0.85, 3.70)	0.002	
	≥2.5% & <5%	8 (30.8)	2.12 (0.99, 4.54)		16 (21.9)	2.57 (1.42, 4.66)		
	≥5%	15 (45.5)	2.90 (1.60, 5.26)		16 (22.5)	2.66 (1.47, 4.82)		
D: LGE (by Location)	Absent	39 (18.6)	1.00	-	34 (9.3)	1.00	-	0.54
	Septal Only	16 (17.2)	2.54 (1.42, 4.56)	<0.0001	25 (25.3)	2.94 (1.76, 4.93)	<0.001	
	Free-wall Only	2 (14.3)	0.61 (0.15, 2.54)		2 (7.1)	0.95 (0.23, 3.95)		
	Both	18 (50.0)	3.41 (1.95, 5.97)		14 (17.5)	2.09 (1.12, 3.89)		
E: LGE (Septal)	No	41 (18.3)	1.00	-	36 (9.2)	1.00	-	0.62
	Yes	34 (43.0)	3.03 (1.92, 4.78)	<0.0001	39 (21.8)	2.57 (1.64, 4.05)	<0.0001	
F: LGE (by Pattern)	Absent	39 (18.6)	1.00	-	34 (9.3)	1.00	-	0.69
	Mid-wall	20 (35.1)	2.25 (1.31, 3.86)	0.002	27 (21.1)	2.39 (1.44, 3.97)	0.002	
	Sub-EpiCardial	3 (42.9)	2.59 (0.80, 8.38)		1 (5.6)	0.72 (0.10, 5.26)		
	Focal	4 (57.1)	4.74 (1.69, 13.27)		3 (20.0)	2.50 (0.77, 8.16)		
	Multiple	9 (40.9)	2.28 (1.10, 4.70)		10 (21.7)	2.90 (1.43, 5.88)		

Kansas City Cardiomyopathy Questionnaire – Chapter 6

Kansas City Cardiomyopathy Questionnaire (KCCQ-12)

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Activity	**Extremely** Limited	**Quite a bit** Limited	**Moderately** Limited	**Slightly** Limited	**Not at all** Limited	Limited for other reasons or did not do the activity
a. Showering/bathing	O	O	O	O	O	O
b. Walking 1 block on level ground	O	O	O	O	O	O
c. Hurrying or jogging (as if to catch a bus)	O	O	O	O	O	O
	1	2	3	4	5	6

2. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
O	O	O	O	O
1	2	3	4	5

3. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
O	O	O	O	O	O	O
1	2	3	4	5	6	7

4. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
O	O	O	O	O	O	O
1	2	3	4	5	6	7

5. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
O	O	O	O	O
1	2	3	4	5

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6. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
O	O	O	O	O
1	2	3	4	5

7. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
O	O	O	O	O
1	2	3	4	5

8. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Activity	**Severely** Limited	Limited **quite a bit**	**Moderately** limited	**Slightly** limited	**Did not** limit at all	Does not apply or did not do for other reasons
a. Hobbies, recreational activities	O	O	O	O	O	O
b. Working or doing household chores	O	O	O	O	O	O
c. Visiting family or friends out of your home	O	O	O	O	O	O
	1	2	3	4	5	6

Symptom Assessment Questionnaire – Chapter 6

Symptoms Score using any number between 0 and 9 With 0 meaning no problem or none, 5 meaning troublesome and 9 being severe	
Breathlessness	
Running (score 9 if you don't run because it makes you very breathless)	
On moderate exertion (eg:- walking quickly, climbing 2-3 flights of stairs)	
On mild exertion (eg:- walking slowly or doing light housework)	
On slight exertion (washing or dressing)	
Is walking impaired due to joint, nerve or muscle problems?	
Sitting at rest	
Do you get breathless lying flat?	
Other Symptoms	
Swelling of Ankles	
Swelling of Legs Above Ankles	
Are you troubled by tiredness during the day?	
Do you suffer much from anxiety?	
Do you feel depressed?	
Chest Pain on Exertion	
Dizziness	
Palpitations	
Muscle Aches & Pains	
Cough and/or Wheeze	
Other Symptom or Problem (Name)	
Other Symptom or Problem (Name)	
Quality of Life (with 1 = very good, 5 = average, 9 = very bad)	
How do you rate your health?	
How do you rate your overall quality of life?	
Please also answer these questions "Yes" or "No" or Give a Number	
How many pillows do you sleep with?	
Do you sometimes wake in the night fighting for breath?	
If so, how many nights in the last two months?	
Have you had any falls?	
If so, how many in the last two months?	
Have you had any blackouts?	
If so, how many in the last two months?	

CPET protocols – Chapter 6

Exercise	Time	Speed (mph)	Speed (kph)	Gradient
Stage 1	00:15	1	1.6	0
Stage 2	00:15	1.1	1.8	0.1
Stage 3	00:15	1.2	1.9	0.3
Stage 4	00:15	1.3	2.1	0.5
Stage 5	00:15	1.4	2.3	0.7
Stage 6	00:15	1.5	2.4	0.9
Stage 7	00:15	1.6	2.6	1
Stage 8	00:15	1.7	2.7	1.1
Stage 9	00:15	1.8	2.9	1.3
Stage 10	00:15	1.9	3.1	1.5
Stage 11	00:15	2	3.2	1.7
Stage 12	00:15	2.1	3.4	1.9
Stage 13	00:15	2.1	3.4	2
Stage 14	00:15	2.2	3.5	2.1
Stage 15	00:15	2.3	3.7	2.3
Stage 16	00:15	2.3	3.7	2.5
Stage 17	00:15	2.3	3.7	2.7
Stage 18	00:15	2.4	3.9	2.9
Stage 19	00:15	2.4	3.9	3
Stage 20	00:15	2.5	4.0	3.1
Stage 21	00:15	2.5	4.0	3.1
Stage 22	00:15	2.6	4.2	3.5
Stage 23	00:15	2.6	4.2	3.7
Stage 24	00:15	2.7	4.3	3.9
Stage 25	00:15	2.7	4.3	4
Stage 26	00:15	2.8	4.5	4.1
Stage 27	00:15	2.8	4.5	4.3
Stage 28	00:15	2.9	4.7	4.5
Stage 29	00:15	2.9	4.7	4.7
Stage 30	00:15	3	4.8	4.9
Stage 31	00:15	3	4.8	5
Stage 32	00:15	3.1	5.0	5.1
Stage 33	00:15	3.1	5.0	5.2
Stage 34	00:15	3.2	5.1	5.5
Stage 35	00:15	3.2	5.1	5.7
Stage 36	00:15	3.3	5.3	5.9
Stage 37	00:15	3.3	5.3	6
Stage 38	00:15	3.4	5.5	6.1
Stage 39	00:15	3.4	5.5	6.3
Stage 40	00:15	3.5	5.6	6.5
Stage 41	00:15	3.5	5.6	6.7
Stage 42	00:15	3.6	5.8	6.9
Stage 43	00:15	3.6	5.8	7
Stage 44	00:15	3.7	6.0	7.1
Stage 45	00:15	3.7	6.0	7.3
Stage 46	00:15	3.8	6.1	7.5

Appendix Table 2. Low-intensity treadmill ergometry protocol detailing the incremental stages of exercise.

Exercise	Time	Speed (mph)	Speed (kph)	Gradient
Stage 1	00:15	1	1.6	0
Stage 2	00:15	1.1	1.8	0.2
Stage 3	00:15	1.2	1.9	0.5
Stage 4	00:15	1.3	2.1	0.7
Stage 5	00:15	1.4	2.3	1
Stage 6	00:15	1.5	2.4	1.2
Stage 7	00:15	1.5	2.4	1.5
Stage 8	00:15	1.6	2.6	1.7
Stage 9	00:15	1.7	2.7	2
Stage 10	00:15	1.8	2.9	2.1
Stage 11	00:15	1.9	3.1	2.3
Stage 12	00:15	2	3.2	2.5
Stage 13	00:15	2	3.2	2.7
Stage 14	00:15	2.1	3.4	3
Stage 15	00:15	2.2	3.5	3.1
Stage 16	00:15	2.3	3.7	3.3
Stage 17	00:15	2.4	3.9	3.5
Stage 18	00:15	2.5	4.0	3.7
Stage 19	00:15	2.5	4.0	3.9
Stage 20	00:15	2.6	4.2	4
Stage 21	00:15	2.7	4.3	4.1
Stage 22	00:15	2.8	4.5	4.3
Stage 23	00:15	2.9	4.7	4.5
Stage 24	00:15	3	4.8	4.7
Stage 25	00:15	3	4.8	4.9
Stage 26	00:15	3.1	5.0	5
Stage 27	00:15	3.2	5.1	5.1
Stage 28	00:15	3.3	5.3	5.3
Stage 29	00:15	3.4	5.5	5.5
Stage 30	00:15	3.5	5.6	5.7
Stage 31	00:15	3.5	5.6	5.9
Stage 32	00:15	3.6	5.8	6
Stage 33	00:15	3.7	6.0	6.3
Stage 34	00:15	3.8	6.1	6.7
Stage 35	00:15	3.9	6.3	7
Stage 36	00:15	4	6.4	7.3
Stage 37	00:15	4.1	6.6	7.7
Stage 38	00:15	4.2	6.8	8
Stage 39	00:15	4.3	6.9	8.3
Stage 40	00:15	4.4	7.1	8.7
Stage 41	00:15	4.5	7.2	9
Stage 42	00:15	4.6	7.4	9.3
Stage 43	00:15	4.7	7.6	9.7
Stage 44	00:15	4.8	7.7	10
Stage 45	00:15	4.9	7.9	10.3
Stage 46	00:15	5	8.0	10.7
Stage 47	00:15	5.1	8.2	11
Stage 48	00:15	5.2	8.4	11.3
Stage 49	00:15	5.3	8.5	11.7

Appendix Table 3. Intermediate-intensity treadmill ergometry protocol detailing the incremental stages of exercise.

Exercise	Time	Speed (mph)	Speed (kph)	Gradient
Stage 1	00:15	1	1.6	0
Stage 2	00:15	1.1	1.8	0.5
Stage 3	00:15	1.2	1.9	1
Stage 4	00:15	1.3	2.1	1.5
Stage 5	00:15	1.4	2.3	2
Stage 6	00:15	1.5	2.4	2.5
Stage 7	00:15	1.6	2.6	3
Stage 8	00:15	1.8	2.9	4
Stage 9	00:15	1.9	3.1	4.5
Stage 10	00:15	2	3.2	5
Stage 11	00:15	2.1	3.4	5.5
Stage 12	00:15	2.2	3.5	6
Stage 13	00:15	2.3	3.7	6.5
Stage 14	00:15	2.4	3.9	7
Stage 15	00:15	2.5	4.0	7.5
Stage 16	00:15	2.6	4.2	8
Stage 17	00:15	2.7	4.3	8.5
Stage 18	00:15	2.8	4.5	9
Stage 19	00:15	2.9	4.7	9.5
Stage 20	00:15	3	4.8	10
Stage 21	00:15	3.1	5.0	10.5
Stage 22	00:15	3.2	5.1	11
Stage 23	00:15	3.3	5.3	11.5
Stage 24	00:15	3.4	5.5	12
Stage 25	00:15	3.5	5.6	12.5
Stage 26	00:15	3.6	5.8	13
Stage 27	00:15	3.8	6.1	14
Stage 28	00:15	3.9	6.3	14.5
Stage 29	00:15	4	6.4	15
Stage 30	00:15	4.1	6.6	15.5
Stage 31	00:15	4.2	6.8	16
Stage 32	00:15	4.3	6.9	16.5
Stage 33	00:15	4.4	7.1	17
Stage 34	00:15	4.5	7.2	18
Stage 35	00:15	5	8.0	18
Stage 36	00:15	5.1	8.2	18.5
Stage 37	00:15	5.2	8.4	19
Stage 38	00:15	5.3	8.5	19.5
Stage 39	00:15	5.4	8.7	20
Stage 40	00:15	5.5	8.8	20.5
Stage 41	00:15	5.6	9.0	21
Stage 42	00:15	5.7	9.2	21.5
Stage 43	00:15	5.8	9.3	22
Stage 44	00:15	5.9	9.5	22.5
Stage 45	00:15	6	9.7	23
Stage 46	00:15	6.1	9.8	23.5
Stage 47	00:15	6.2	10.0	24
Stage 48	00:15	6.3	10.1	24.5
Stage 49	00:15	6.4	10.3	25

Appendix Table 4. High-intensity treadmill ergometry protocol detailing the incremental stages of exercise.

Randomisation Log – Chapters 6-8

Subject ID	Screening ID	Date of entry	Randomised group	Date of birth	NTpro-BNP level
1-001	TRED02	21/04/2016	Control	14/07/1969	0 to less than 50 (ng/ml)
1-002	TRED03	21/04/2016	Treatment withdrawal	17/12/1947	0 to less than 50 (ng/ml)
1-003	TRED04	22/04/2016	Treatment withdrawal	03/07/1950	50 to less than 125 (ng/ml)
1-004	TRED05	03/05/2016	Control	15/12/1973	50 to less than 125 (ng/ml)
1-005	TRED08	17/05/2016	Control	08/02/1990	50 to less than 125 (ng/ml)
1-006	TRED09	17/05/2016	Treatment withdrawal	25/11/1971	50 to less than 125 (ng/ml)
1-007	TRED07	17/05/2016	Treatment withdrawal	30/01/1966	50 to less than 125 (ng/ml)
1-008	TRED10	24/05/2016	Control	26/05/1952	125 to less than 250 (ng/ml)
1-009	TRED11	31/05/2016	Control	31/12/1973	0 to less than 50 (ng/ml)
1-010	TRED12	23/06/2016	Control	27/01/1951	50 to less than 125 (ng/ml)
1-011	TRED13	23/06/2016	Treatment withdrawal	01/04/1938	50 to less than 125 (ng/ml)
1-012	TRED15	13/07/2016	Control	30/03/1954	50 to less than 125 (ng/ml)
1-013	TRED16	13/07/2016	Treatment withdrawal	15/06/1953	0 to less than 50 (ng/ml)
1-014	TRED17	21/07/2016	Treatment withdrawal	24/03/1969	125 to less than 250 (ng/ml)
1-015	TRED18	03/08/2016	Control	12/11/1969	0 to less than 50 (ng/ml)
1-016	TRED19	03/08/2016	Treatment withdrawal	08/08/1952	50 to less than 125 (ng/ml)
1-017	TRED20	18/08/2016	Control	24/04/1960	125 to less than 250 (ng/ml)
1-018	TRED21	18/08/2016	Control	15/09/1968	50 to less than 125 (ng/ml)
1-019	TRED24	02/09/2016	Treatment withdrawal	23/12/1971	0 to less than 50 (ng/ml)
1-020	TRED22	13/09/2016	Treatment withdrawal	15/04/1948	125 to less than 250 (ng/ml)
1-021	TRED25	18/10/2016	Treatment withdrawal	30/04/1955	125 to less than 250 (ng/ml)
1-022	TRED26	18/10/2016	Control	05/06/1954	0 to less than 50 (ng/ml)
1-023	TRED27	01/11/2016	Control	21/03/1973	0 to less than 50 (ng/ml)
1-024	TRED28	01/11/2016	Control	10/02/1955	50 to less than 125 (ng/ml)
1-025	TRED29	01/11/2016	Control	14/07/1950	125 to less than 250 (ng/ml)
1-026	TRED30	08/11/2016	Treatment withdrawal	27/03/1964	50 to less than 125 (ng/ml)
1-027	TRED31	29/11/2016	Treatment withdrawal	19/01/1969	0 to less than 50 (ng/ml)
1-028	TRED34	20/01/2017	Control	27/12/1949	125 to less than 250 (ng/ml)
1-029	TRED36	31/01/2017	Treatment withdrawal	03/12/1978	50 to less than 125 (ng/ml)
1-030	TRED37	22/02/2017	Control	20/01/1961	50 to less than 125 (ng/ml)
1-031	TRED38	22/02/2017	Control	09/03/1963	125 to less than 250 (ng/ml)
1-032	TRED39	07/03/2017	Treatment withdrawal	12/08/1955	125 to less than 250 (ng/ml)
1-033	TRED41	07/03/2017	Treatment withdrawal	26/06/1960	0 to less than 50 (ng/ml)
1-034	TRED40	20/03/2017	Treatment withdrawal	01/01/1954	125 to less than 250 (ng/ml)
1-035	TRED42	24/03/2017	Treatment withdrawal	24/04/1974	0 to less than 50 (ng/ml)
1-036	TRED43	18/04/2017	Treatment withdrawal	12/08/1975	0 to less than 50 (ng/ml)
1-037	TRED45	16/05/2017	Treatment withdrawal	18/08/1947	125 to less than 250 (ng/ml)
1-038	TRED46	18/05/2017	Control	28/10/1954	125 to less than 250 (ng/ml)
1-039	TRED47	24/05/2017	Control	30/07/1966	0 to less than 50 (ng/ml)
1-040	TRED48	24/05/2017	Control	15/06/1960	0 to less than 50 (ng/ml)

1-041	TRED49	24/05/2017	Control	20/09/1950	50 to less than 125 (ng/ml)
1-042	TRED51	27/06/2017	Treatment withdrawal	02/12/1971	0 to less than 50 (ng/ml)
1-043	TRED52	17/07/2017	Control	16/02/1947	125 to less than 250 (ng/ml)
1-044	TRED53	17/07/2017	Control	25/08/1994	0 to less than 50 (ng/ml)
1-045	TRED54	21/07/2017	Treatment withdrawal	02/03/1971	50 to less than 125 (ng/ml)
1-046	TRED56	31/07/2017	Control	16/10/1982	50 to less than 125 (ng/ml)
1-047	TRED57	31/07/2017	Treatment withdrawal	24/01/1962	0 to less than 50 (ng/ml)
1-048	TRED58	03/08/2017	Control	06/12/1971	0 to less than 50 (ng/ml)
1-049	TRED61	11/08/2017	Treatment withdrawal	01/12/1962	125 to less than 250 (ng/ml)
1-050	TRED62	14/08/2017	Treatment withdrawal	19/12/1967	50 to less than 125 (ng/ml)
1-051	TRED63	22/08/2017	Control	21/01/1953	125 to less than 250 (ng/ml)

Appendix Table 5. Randomisation log of all patients enrolled in the TRED-HF study.

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Chapter No.	Type of work:	My own work	Source of work	Copyright holder and contact	permission requested on	I have permission yes /no	Permission note
1	Extracts	Yes	Halliday BP, Tayal U, Prasad SK. Role of Cardiovascular Magnetic Resonance in Dilated Cardiomyopathy. In: Manning WJ, Pennell DJ ed. Cardiovascular Magnetic Resonance, 3rd edition. Elsevier, 32-1-32-8. In press.	© Elsevier	20.04.18	yes	Written permission & Contributor agreement
1 Figure 1.1, 1.6, 1.9, 1.11	Extracts and Figures	Yes	Halliday BP, Cleland JGF, Goldberger JJ, Prasad SK. Personalising risk stratification for sudden cardiac death in dilated cardiomyopathy: The Past, Present and Future. Circulation 2017;136:215-231.	© Wolters Kluwer/AHA	06.04.15	yes	Permission granted via Copyright Clearance Center
1 Figure 1.6	Figure		Mahrholdt H, Wagner A, Judd RM, Sechtem U, Kim RJ. (2005) Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. *Eur Heart J* 26:1461-74.	© OUP	29.03.15	yes	Permission granted via Copyright Clearance Center
1 Figure 1.5	Figure		Japp AG, Gulati A, Cook SA, Cowie MR, Prasad SK. (2016) The Diagnosis and Evaluation of Dilated Cardiomyopathy. *J Am Coll Cardiol* 67:2996-3010.	© Elsevier	29.03.15	yes	Permission granted via Copyright Clearance Center
1 Figure 1.10	Figure	Yes	Cleland JGF, Halliday BP, Prasad SK. (2017b) Selecting Patients With Nonischemic Dilated Cardiomyopathy for ICDs: Myocardial Function, Fibrosis, and What's Attached? *J Am Coll Cardiol* 70:1228-1231.	© Elsevier	29.03.15	yes	Permission granted via Copyright Clearance Center
1 Table 1.4	Table		Goldberger JJ, Subacius H, Patel T, Cunnane R, Kadish AH. (2014) Sudden cardiac death risk stratification in patients with nonischemic dilated cardiomyopathy. *J Am Coll Cardiol* 63:1879-89.	© Elsevier	29.03.15	yes	Permission granted via Copyright Clearance Center
3	Extracts	Yes	Halliday BP, Gulati A, Ali A et al. Association between mid-wall late gadolinium enhancement and sudden cardiac death in patients with dilated cardiomyopathy and mild and moderate left ventricular systolic dysfunction. Circulation 2017;135:2106-2115.	© 2017 The Authors		yes	Published via Creative Commons Attribution License (CC-BY)
4	Extracts	Yes	Halliday BP, Gulati A, Ali A et al. Sex- and age-based differences in the natural history and outcome of dilated	© 2018 The Authors		yes	Published via Creative Commons

			cardiomyopathy. Eur J Heart Fail. 2018 Jun 3. doi: 10.1002/ejhf.1216.				Attribution License (CC-BY)
5	Extracts	Yes	Halliday BP, Baksi AJ, Gulati A et al. Outcome in dilated cardiomyopathy related to the extent, location, and pattern of late gadolinium enhancement. *In press with JACC Cardiovasc Imaging.*	© 2018 The Authors		Yes	To be published under Creative Commons Attribution License (CC-BY)

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2. Halliday BP, Gulati A, Ali A et al. Sex- and age-based differences in the natural history and outcome of dilated cardiomyopathy. Eur J Heart Fail. 2018 Jun 3. doi: 10.1002/ejhf.1216.
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