RISK-STRATIFICATION IN NON-ISCHEMIC CARDIOMYOPATHY BASED ON CORROBORATIVE EVIDENCE FROM CHARACTERIZATION OF THE PHENOTYPE AND CARDIAC SCAR

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To family, teachers, friends, and

patients who were subjects for this project

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DECLARATION

I hereby declare that the work undertaken in this thesis has been conducted by me alone. I conducted this work between March 2019 and November 2023, during which period I was a PhD student at the Australian National University.

This thesis, in whole or any part of it, has not been submitted to this or any other university for a degree. This thesis is submitted as a *Thesis by Compilation,* in accordance with relevant ANU policies. Of the 7 chapters, 3 chapters are published in peer reviewed journals and are reproduced for the purpose of dissertation with the required permissions from the publishers. One chapter has been submitted for consideration for publication to a peer-reviewed journal and is reproduced in the same form.

I have made significant contribution to each of these chapters, journal articles and have written the text of the papers myself, under the guidance of my supervisors.

Deep Chandh Raja Soundararajan

19th November, 2023

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IMPACT OF COVID-19

My PhD research program with the ANU started in March 2019. Exactly a year into my research, we encountered a unique unheard-of scenario in name of COVID-19. This was the exactly the time we had got all our ethics committee approvals and were planning to initiate the prospective projects. For the whole rest of my tenure at the ANU, the COVID-19 situation continued. With so many uncertainties around, the situation did affect our research. The recruitment of subjects for the prospective project could not proceed as per plan due to frequent lockdowns. Also, due to less than expected recruitment in the prospective studies, we could not proceed with other planned prospective studies.

Nevertheless, as a team we utilised whatever time and opportunities we had, to perform our systematic review and retrospective studies. The Australian National University was very supportive in these tough times by providing online access to many learning materials. Dr Rajeev Pathak and Canberra Heart Rhythm Foundation was also very supportive by providing premises and access to software for conducting research activities.

THESIS OUTLINE

Chapter 1 is a literature review on sudden cardiac death (SCD) in nonischemic cardiomyopathy (NICM). The DANISH study clearly exposed the current lacunae in guideline recommendations in identifying the right candidates who would benefit from implantable cardioverter defibrillators (ICD). Risk-stratification tools in NICM need to look beyond left ventricular ejection fraction (LVEF). Several tools like genetics, biomarkers, ECG variables, echocardiography variables, electroanatomical mapping information, cardiac MRI (CMR) have shown to yield valuable information to suggest increased risk of SCD in NICM. These parameters need to be explored and refined so that they can be incorporated into future risk-stratification models. This literature review lists out a few grey zones in literature, based on which 4 research questions have been formulated. These research questions form the basis of the projects conducted for the Thesis.

Condensed abstract of Chapter 2

A *systematic review and metanalysis* with data from 18 eligible large-scale studies including 126,239 patients was conducted, to compare all-cause and cause-specific mortality in patients with heart failure mid-range ejection fraction (HFmrEF) compared to heart failure reduced ejection fraction (HFrEF) and heart failure preserved ejection fraction (HFpEF).

Patients with HFmrEF had a lower risk of all-cause death and cardiovascular (CV) deaths than those with HFrEF. Subgroup analysis showed that studies recruiting >50% of males had higher risk of deaths with HFrEF. When compared with HFpEF, patients with HFmrEF had comparable risk of all-cause death. Similarly, there were no differences in the 1-, 2-, and 3-year deaths; CV and non-CV deaths were insignificant between HFmrEF and HFpEF.

The study concludes that HFmrEF has better prognosis than HFrEF but similar prognosis when compared with HFpEF. Gender disparity between studies seems to influence the results between HFmrEF and HFrEF. Transition in left ventricular ejection fraction (LVEF), which could not be addressed in the study, may play a decisive role in determining outcomes.

Condensed abstract of Chapter 3

In a *single center observational cohort* of 526 patients with a mean follow-up 8.7±3.5 years, there were 42.5% patients with ischemic cardiomyopathy (ICM), 26.9% with non-ischemic cardiomyopathy (NICM) and 30.6% with 'mixed' cardiomyopathy. Mixed cardiomyopathy is a phenotype with overlapping clinical features of ischemic and nonischemic cardiomyopathy. In our study, the cohort of mixed cardiomyopathy had elderly population with higher incidence of comorbidities. The prognosis, in terms of device shocks and all-cause mortality, in patients with mixed cardiomyopathy is similar to ischemic and worse than nonischemic cardiomyopathy. With this knowledge it is worthwhile to explore the pathophysiological substrate in this entity.

Condensed abstract of Chapter 4

A *prospective analysis* of high density endocardial electro-anatomical mapping characteristics of the left ventricle in 43 patients of NICM revealed better correlation for unipolar EGM variables, with baseline LVEF, than bipolar EGM variables: unipolar voltage, peak negative unipolar voltage, peak positive unipolar voltage, and percentage area of unipolar LVZ. Extent of unipolar low voltage zone (LVZ) and LVEF≤35% had significant association with VT. ROC-curve analysis revealed cut-off of an extent of >3 segments of unipolar LVZ and >33% area of unipolar LVZ to predict VT with good diagnostic accuracy. Future search for non-invasive surrogate tools for endocardial unipolar voltage can be useful risk-stratification markers for NICM.

Condensed abstract of Chapter 5

Nineteen consecutive CMRs of patients with electroanatomic mapping were analysed offline by CMR-feature tracking strain. There was significant correlation between combined percentage circumferential and longitudinal (CS+LS) abnormality with percentage unipolar low voltage zone (LVZ). Per-unit increase in CS increased the percentage area of unipolar LVZ by 2.09 and per-unit increase in LS increased percentage area of unipolar LVZ by 2.5. The concordance rates between CS and LS to localize segments with bipolar/unipolar LVZ was 79%

and 95% compared to 63% with late gadolinium enhancement (LGE). Myocardial strain picked up by CMR-feature tracking has good correlation with unipolar low voltage zones. The strain parameters can also be used to detect the segmental abnormalities with concordance rates better than LGE.

Chapter 6 discusses the future directions with specific reference to risk-stratification models for prediction of SCD in NICM. The inadequacies of the contemporary risk-models are that none of them are inclusive of all the known risk-stratification markers. We have proposed the variables to be included in a risk-model so that the tool is comprehensive. The challenges in utilising artificial intelligence in this regard is also discussed.

Chapter 7 summarises the findings arising out of the thesis. These findings have become the basis of ongoing research being conducted by our research team. The ongoing projects are listed in the chapter.

PUBLICATIONS AND COMMUNICATIONS TO LEARNED SOCIETIES

Original articles in peer-reviewed journals arising out of Thesis

1. **Raja DC**, Samarawickrema I, Das S, Mehta A, Tuan L, Jain S, Dixit S, Marchlinski F, Abhayaratna WP, Sanders P, Pathak RK. Long-term mortality in heart failure with mid-range ejection fraction: systematic review and meta-analysis. ESC Heart Fail. 2022 Dec;9(6):4088-4099.

2. **Raja DC**, Samarawickrema I, Menon SK, Singh R, Mehta A, Tuan LQ, Pandurangi U, Jain S, Callans DJ, Marchlinski FE, Abhayaratna WP, Sanders P, Pathak RK. Characteristics of the phenotype of mixed cardiomyopathy in patients with implantable cardioverter-defibrillators. J Interv Card Electrophysiol. 2023 Jun 5.

3. **Raja DC**, Samarawickrema I, Srinivasan JR, Menon S, Das SK, Jain S, Tuan LQ, Desjardins B, Marchlinski FE, Abhayaratna WP, Sanders P, Pathak RK. Correlation of myocardial strain by CMR-feature tracking with substrate abnormalities detected by electro-anatomical mapping in patients with nonischemic cardiomyopathy. J Interv Card Electrophysiol. 2023 May 2.

4. **Raja DC**, Shroff J, Nair A, Abhilash SP, Tuan LQ, Mehta A, Abhayaratna WP, Sanders P, Frankel DS, Marchlinski FE, Pathak RK. Correlation of extent of left ventricular endocardial unipolar low-voltage zones with ventricular tachycardia in nonischemic cardiomyopathy. Heart Rhythm. 2024 Apr 16:S1547-5271(24)02392-0.

Original articles in peer-reviewed journals during tenure at ANU

1. Kistler PM, Chieng D, Sugumar H, Ling LH, Segan L, Azzopardi S, Al-Kaisey A, Parameswaran R, Anderson RD, Hawson J, Prabhu S, Voskoboinik A, Wong G, Morton JB, Pathik B, McLellan AJ, Lee G, Wong M, Finch S, Pathak RK, **Raja DC**, Sanders Prashanthan, Sterns Laurence, Ginks Matthew, Reid Christopher M, Kalman Jonathan M, Kistler Peter, Catheter Ablation for Persistent Atrial Fibrillation: a **Multicentre Randomised Trial** of Pulmonary Vein Isolation (PVI) versus PVI with Posterior Left Atrial Wall Isolation (PWI) - the CAPLA Study, American Heart Journal, **http://dx.doi.org/10.1016/j.ahj.2021.09.015**.

2. Chieng David, Sugumar Hariharan, Ling Liang-Han, Segan Louise, Azzopardi Sonia, Prabhu Sandeep, Al-Kaisey Ahmed, Voskoboinik Aleksandr, Parameswaran Ramanathan, Morton Joseph B, Pathik Bhupesh, McLellan Alex J, Lee Geoffrey, Wong Michael, Finch Sue, Pathak Rajeev K, **Raja DC**, Sanders Prashanthan, Sterns Laurence, Ginks Matthew, Reid Christopher M, Kalman Jonathan M, Kistler Peter, Catheter Ablation for Persistent Atrial Fibrillation: a **Multicentre Randomised Trial** of Pulmonary Vein Isolation (PVI) versus PVI with Posterior Left Atrial Wall Isolation (PWI) - the CAPLA Study, American Heart Journal, **http://dx.doi.org/10.1016/j.ahj.2021.09.015**.

3. Abhilash SP, **Raja DC**, Stolcman S, Yi DS, Rahman M, Tan R, Mahajan A, Lau DH, Abhayaratna WP, Sanders P, Pathak RK. Computerized tomography image correlation of His bundle/deep septal pacing location and outcomes: an analysis from the Canberra HIs bundle/deep septal Pacing Study (CHIPS). J Interv Card Electrophysiol. 2022 Jan 27.

Review articles, Case reports in peer-reviewed journals

during tenure at Australian National University

1. **Deep Chandh Raja**, Prashanthan Sanders, Rajeev Kumar Pathak. Utility of Intracardiac Echocardiography to Guide Transseptal Catheterization for Different Electrophysiology Procedures. Cardiac Electrophysiology Clinics, Volume 13, Issue 2, 293 – 301. https://doi.org/10.1016/j.ccep.2021.02.003

2. **Deep Chandh Raja**, Vickram Vignesh Rangaswamy, Sreevilasam Pushpangadhan Abhilash, Kieran King, Rajeev K Pathak. Electrophysiological Substrates in Papillary Muscle Arrhythmias – Implications for Catheter Ablation. European Journal of Arrhythmia & Electrophysiology. 2020;6(1):32–8.

3. **Deep Chandh Raja**, Prashanthan Sanders, Rajeev Pathak. How much is enough? An appraisal of high-power short-duration radiofrequency ablation for pulmonary vein isolation. J Cardiovasc Electrophysiol. 2019; 1– 4.

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(May, 2020 ebooks.cardiotextpublishing.com)

5. Craig J McCallum, **Deep Chandh Raja**, Rajeev K Pathak. Aust Prescr 2019;42:186–91.

Abstract presentations arising out of Thesis

Cardiology Society of ANZ 2021, Adelaide

- Survival characteristics in 566 patients receiving ICD: Real-world data from The Canberra Hospital device (TCH-ICD) registry
- Characteristics of patients and the device therapies: Real world-data from The Canberra Hospital device (TCH-ICD) registry

Indian Heart Rhythm Society 2023, India

- Defining cut-offs for endocardial unipolar voltage abnormalities in non-ischemic cardiomyopathy presented under **'Young Investigator award' category**

Heart Rhythm Society 2024, Boston, USA

- Risk prediction of ventricular tachyarrhythmias in non-ischemic cardiomyopathy using unipolar low voltage zones in the left ventricle

Abstract presentations during tenure at Australian National University

Cardiology Society of ANZ 2021, Adelaide

- 3-D electro-anatomical mapping guided lead placement in CRT **(Heart Rhythm Prize finalist- oral presentation)**
- Prophylactic Radio-Frequency Ablation (RFA) before an Implantable Cardioverter Defibrillator (ICD): a case series **(Poster Prize Finalist)**

Heart-Rhythm Society (HRS) 2019, San Franscico

- Para-Hisian pacing by RV-coil in lieu of CRT-D
- Pacing from atrial-dipole for optimisation of positioning of the DX-ICD lead
- Co-existence of concealed epicardial (left) and endocardial (right) accessory pathway: Illustration and mechanisms

Chapter 1: Literature review on sudden cardiac death in nonischemic cardiomyopathy, existing risk-prediction tools, knowledge gaps and formulation of research questions

Cardiomyopathy is a disease of the heart muscle. The causes of cardiomyopathy are diverse, but broadly can be divided into ischemic cardiomyopathy (ICM) and non-ischemic cardiomyopathy (NICM).[1] NICM encompasses a wide phenotype of heart muscle diseases. Certain categories of NICM have been extensively studied like hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, cardiac sarcoidosis, and genetic cardiomyopathy. Idiopathic NICM is a terminology used to categorise a group of NICM patients in whom a possible aetiology may not be attributed. Dilated cardiomyopathy (DCM) is used to describe a subset of cardiomyopathy patients who have a dilated heart and depressed left ventricular ejection fraction (LVEF).[2]

The reason behind cardiovascular deaths (CVD) in NICM is either due to heart-failure related deaths or sudden cardiac deaths (SCD).[3] Advances in medical therapy have helped reduce all-cause mortality due to pump-failure. However, the proportion of SCD continues to be as high as 7%, even with current guideline-directed medical treatment (GDMT) and in the absence of any intervention like implantable cardioverter-defibrillator (ICD) therapy.[4] In the adult age group, DCM is the second leading cause of SCD next to coronary artery disease (CAD), with an annual incidence of 2-4%.[5]

Around one-third of all deaths in NICM is due to SCD. ICD intervention should potentially be able to mitigate the risk of SCD, by appropriately detecting and terminating the ventricular tachyarrhythmias (VAs). There is a large lacuna in understanding the risk for SCD in NICM. Only if the right risk-stratification tools are in place, then there could be benefit for advocating ICD for purpose of SCD risk reduction to the patient subgroup destined to have high risk of VAs.

This chapter is a literature review, which discusses the current evidence behind guideline recommendations for primary prevention of SCD in NICM and the utility of contemporary risk-stratification tools. The chapter also explores the knowledge gaps with regards to risk-stratification in NICM. Based on a few compelling questions in this regard, we would then frame our research questions to address risk-stratification in NICM.

1.1 ICD for Primary Prevention of SCD in NICM

Contemporary guidelines from international societies suggest use of ICD for reduction in mortality in NICM patients with symptomatic NYHA Class II-III heart failure and left ventricular ejection fraction (LVEF) ≤35% despite ≥3 months of optimal medical therapy.[6,7] However, the two major societies, namely the American Heart Association and European Heart Association, give conflicting classes of recommendation for use of ICD in NICM. While one of the societies[6] relies on evidence from meta-analyses and gives Class 1 recommendation for the group of patients as mentioned above, another society[7] gives Class 2A recommendation primarily based on recent evidence from large RCTs.

Meta-analyses and data from large, randomised control trials (RCTs) meant to address the benefit of ICD in patients with NICM can be reasonably divided into studies before and after the DANISH-era. In the pre-DANISH era, guidelines were based on evidence from pooled analysis of 7 trials of ICD use in primary prevention trial in NICM patients. This meta-analysis demonstrated a statistically significant 31% overall reduction in mortality with ICD therapy (RR 0.69; 95% CI, 0.56-0.86).[8] The Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischaemic Heart Failure on Mortality (DANISH) study was the first RCT to specifically address the mortality reduction of ICD in NICM population. The DANISH study did not show significant reduction in all-cause mortality in patients receiving ICD. Though the DANISH study did not show significant mortality reduction with ICD in NICM, the study did show significant reduction in SCD in these patients (risk reduction 0.50; 95% CI 0.31-0.82) and a significant mortality reduction was observed in age group<59 years (risk reduction 0.51; 95% CI 0.29-0.92).[9]

1.2 Prominent Knowledge Gaps in Risk-Assessment in NICM

1.2.1 Waiting period of 3 months

The waiting time of 3 months before considering a patient for primary prevention is based on the recruitment criteria in the large RCTs. However, the PROLONG study, which included 167 patients of recent onset heart failure and left ventricular ejection fraction (LVEF) ≤35%, the incidence of VAs was 9%.[10]

1.2.2 LV ejection fraction may not be the lone risk-stratification marker

The yardstick of all the trials for advocating use of ICD in NICM has been LVEF≤35%. Using LVEF as a risk-stratification tool has resulted in mixed results. With the current guideline recommendations, only 20-25% patients with ICD have found to receive an appropriate shock.[8] In the very recent DANISH study with contemporary medical therapies, in the ICD patients with LVEF≤35%, 88.5% patients did not receive any device shock and 82.6% patients did not receive any device therapy at all and moreover SCD was observed in 4.3%.[9]

It is also known that there is a significant proportion of patients with LVEF>35% with ongoing risk for VAs and SCD. Certain subsets of NICM, such as cardiac sarcoidosis, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and certain genetic mutations have significant risks of VAs despite LVEF>35%. The inadequacy of LVEF in prediction of SCD was highlighted in a study involving large number of community participants. A SCD risk prediction model that was developed from two very large community cohorts showed that SCD was observed in a significant proportion of patients with preserved LVEF during the 10-year follow-up.[11] In the DANISH study, a large proportion of SD occurred in patients with LVEF>30%.[9]

1.2.3 Heart failure with mid-range ejection fraction– a grey zone

Previous studies have focussed on heart failure patients with reduced ejection fraction (HFrEF, LVEF <35-40%) and heart failure patients with preserved ejection fraction (HFpEF, LVEF>50%). However, there was a gap of knowledge in patients comprising of LVEF between 40 and 49%. This category of heart failure with midrange ejection fraction (HFmrEF) was introduced in 2016.[12] Studies are shifting their focus on the lesser explored phenotype of HFmrEF, as this is a grey zone with no clear distinction and overlap of features between HFrEF and HFpEF. This phenotype is prevalent in 10-20% of HF patients.[13] There is still a large gap in evidence regarding phenotype characteristics, long-term prognosis and optimal therpies for these patients. Cardiovascular events are highest in the HFrEF. However, it is not known if the cardiovascular events are any more in the HFmrEF category compared to HFpEF.

Research Question 1: What is the long-term all-cause mortality, and cause-specific mortality in HFmrEF compared to HFrEF and HFpEF?

This question has been addressed in chapter 2 in the form of a systematic review and meta-analysis of studies reporting long term outcomes in each of the three categories of heart failure.

Hypothesis: Prognosis, in terms of all-cause mortality and cardiac mortality, in HFmrEF is worse than HFpEF and better than HFrEF.

1.2.4 Influence of Coronary artery disease in NICM– the 'Mixed' phenotype

Historically, cardiomyopathies are classified into ischemic and non-ischemic cardiomyopathies based on a cut-off of 75% epicardial stenosis in one or more of the coronary epicardial arteries, detected by a coronary angiogram.[1] In NICM patients, though CAD may not be sufficient enough to cause global systolic dysfunction, the influence of bystander CAD cannot be underestimated. In a prospective study of 139 patients with NICM, CAD burden was studied and was found to be a significant predictor of adverse cardiovascular events.[14] Dilated cardiomyopathy patients have concomitant CAD.[15] This phenotype of 'mixed' ischemic and nonischemic substrate is novel and is largely unexplored.[16]

Research Question 2: What are the clinical characteristics and prognosis in 'mixed' cardiomyopathy? This question is addressed in chapter 3, by means of a large retrospective analysis of ICD recipients. The patients were categorised into ICM, NICM and mixed cardiomyopathy based on coronary angiogram findings and the differences among the three groups were studied.

Hypothesis: The phenotype of mixed cardiomyopathy is similar to ischemic cardiomyopathy. All-cause and cardiac mortaliy in mixed cardiomyopathy patients is similar to ischemic cardiomyopathy and worse than patients with nonischemic cardiomypathy.

1.3 Risk-Stratification Tools for SCD Risk Assessment in DCM:

Tools to explore these additional risks of VAs are being extensively studied. These tools are listed in Table 1.

Table 1-1: Risk-stratification tools for prediction of ventricular tachyarrhythmias and sudden cardiac death in nonischemic cardiomyopathy

Risk marker	Parameters	References
Biomarkers	CRP, IL-6, BNP, NT-BNP, Troponin	[17-20]
Genetic mutations	LAMIN A/C, Desmosomal variants, Phospholamban	[21-24]
ECG	PVC, NSVT, Heart rate variability, QT dispersion,	[25,26]
Echocardiography	LVEF, Global longitudinal strain, Mechanical dispersion	[27-30]
Cardiac MRI	LGE, T1 mapping, ECV estimation, Myocardial strain	[31-35]
Electroanatomical mapping	Bipolar voltage, Unipolar voltage	[36-52]
ECG- Electrocardiography; CRP- C-reactive protein; IL-6- Interleukin-6; BNP- Brain natriuretic peptide; PVC- premature ventricular complex, NSVT- nonsustained ventricular tachycardia; LVEF- left ventricular ejection fraction; LGE- late gadolinium enhancement; ECV- extracellular volume		

1.3.1 Biomarkers for SCD assessment

Biomarkers can predict ventricular arrhythmias and SCD in heart failure patients. They can be broadly classified into “Conventional” and “Novel” biomarkers. The conventional blood biomarkers encompass three main pathophysiological mechanisms– markers of inflammation, neurohumoral activation, myocardial injury.[17-20] Novel biomarkers have gained momentum.

Markers of inflammation: Acute phase reactants are primarily secreted by the liver during acute and chronic inflammation. Interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-alpha), and C-reactive protein have been extensively studied in acute and chronic heart failure states. Even in the absence of CAD, these biomarkers have been linked to all-cause mortality, ventricular arrhythmias and SCD. IL-6 is a cytokine released during acute inflammation before release of CRP. In patients receiving ICD, and with follow-up arrhythmic events have noted to have high serum levels of IL-6. Patients with arrhythmogenic cardiomyopathy have shown to have higher levels of CRP, thus suggesting a link between inflammation and arrhythmias. Low grade inflammation is better detected with high-sensitive assays of CRP– hsCRP. There also seems to be an association between hsCRP and heart failure hospitalisations, all-cause mortality. Also, BNP and hsCRP were found to be significantly elevated in patients experiencing a ventricular arrhythmic storm.[20]

Brain natriuretic peptides (BNP): Under circumstances of myocardial stretch, both BNP and NT-proBNP are released by the cardiac myocardial as a compensatory response to maintain neuro-humoral homeostasis. NT-proBNP stays in the blood for a longer period of time and is also influenced by renal functions. However, NT-proBNP is more easily measurable

than BNP. In a meta-analysis of studies reporting association of BNP with ventricular arrhythmias, BNP had significant high relative risk (3.68; 95% CI 1.9-7.1) in 3543 patients without ICD and in 1047 patients (2.54; 95% CI 1.8-3.4) with ICD. The cut-offs for interpreting high NT-proBNP might vary depending on age and kidney disease.[18]

Markers of cardiac injury: Cardiac troponins (cTn-I and cTn-T) are specific to myocardial tissues. Their levels signal the necrosis of myocardial cells subsequent to damage due to inflammation. Strong associations between cTn-I and cTn-T have been detected with mortality, occurrence of ventricular arrhythmias and SCD. High sensitive assays of cTn-T have been studied in dilated cardiomyopathy and hypertrophic cardiomyopathy and have found to be a better predictor than cTn-T of cardiovascular events, especially sustained VT.[20]

Multi bio-marker approach: In the Prospective Observational Study of Implantable Cardioverter Defibrillators (PROSe-ICD), 1189 patients with ICD implantation for primary prevention of SCD for chronic heart failure were enrolled. While IL-6 levels had strong association for appropriate ICD shocks, CRP, IL-6, TNF-alpha, pro-BNP, and cTnT showed significant trends for all-cause mortality. Combination of these 5 biomarkers had better predictive power for all-cause mortality than for appropriate shocks. Thus, a multi biomarker approach might help to identify patients who are unlikely to benefit from ICD.[17]

*Novel biomarker*s: A biomarker which is objectively measured should aid in prognosis and more so prediction of adverse cardiac events especially ventricular arrhythmias and sudden cardiac death. Cardiac biomarkers are products specific to cardiac musculature which get releases into the blood stream either due to myocardial necrosis or increased production at times of myocardial stress. In recent times, a few biomarkers in addition to the above discussed conventional markers, have shown promise for prognostication in heart failure. *Soluble ST-2 (sST-2)* is a marker that is released parallelly as of NT-proBNP in heart failure. It is a marker of neuro-humoral axis dysfunction. High levels of sST-2 have been found to be predictive of increased ventricular arrhythmic events in patients with ICD. *Galectin-3* is an other marker that could be the link between inflammation and fibrosis. Their levels have been found to be elevated in heart failure and is associated with high mortality and sudden cardiac death. *Cystatin-C* is a marker of both kidney damage and is raised in heart failure. Investigations are on to study the risk prediction potential of this novel biomarker, especially in the setting of cardiorenal dysfunction. Other similar biomarkers that hold promise for SCD prediction are *uric acid, fibrinogen, free fatty acids and matrix mettaloproteinase.*[20]

1.3.2 Genetic markers for SCD prediction

Inherited cardiomyopathies and congenital channelopathies are known to cause sudden cardiac death. Cardiac structural alterations lead to cardiomyopathies. These cardiac changes are a result of genetic mutations which could be either inherited or acquired during life. Genetic mutations can lead to dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic cardiomyopathy, and noncompaction cardiomyopathy. The yield for genetic screening in hypertrophic cardiomyopathy is 60% in familial and 30% in sporadic forms. Autosomal dominant pattern of inheritance is usually seen in hypertrophic cardiomyopathy. The main genes include sarcomere proteins, namely: MYBPC3 (cardiac myosin binding protein), MYH7 (β-myosin heavy chain), TPM (tropomyosin), TNNT2 (cardiac troponin T), MYL2 (myosin regulatory light chain), and MYH6 (α- myosin heavy chain). [21] Troponin-T mutations have been associated with SCD through changes in calcium equilibrium in the cardiac tissues.[23] Sarcomeric mutations bear higher risk for SCD than non-sarcomeric mutations. Certain genetic mutations result in a phenotype resembling hypertrophic cardiomyopathy, namely: Fabry disease, Pompe disease, Danon disease (LAMP2 mutation), familial amyloidosis (TTR mutation) and left ventricular hypertrophy with Wolff–Parkinson–White syndrome (PRKAG2 mutation). In arrhythmogenic cardiomyopathy, familial forms account for nearly 60% cases. Most common mutations involve the desmosomal genes, namely the plakophilin-2, plakoglobin, and desmoplakin.[21] Desmosome mutations affect sodium channel functions and cause conduction system slowing.[23] In addition, Cavelolin gene mutations have been implicated in various forms of cardiomyopathy.[21]

Familial dilated cardiomyopathy accounts for 20% cases of idiopathic cases and has strong linkage with genetic mutations. The yield for genetic testing in dilated cardiomyopathy is around 20%. The most common genetic mutations are due to involvement of sarcomere proteins, namely Titin. Phospholamban and Lamin A/C mutations have found to be particularly implicated in sudden cardiac death in dilated cardiomyopathy.[21] In a study involving 487 patients with dilated cardiomyopathy, association of mutations with all-cause mortality, sudden cardiac death, occurrence of ventricular arrhythmias and heart transplantation was studied. Pathogenic/likely pathogenic variants were found in 178 patients (37%). The identified mutations were Titin 54 (11%); Lamin A/C (LMNA) 19 (4%); desmosomal genes 16 (3.5%); sarcomeric genes 46 (9.5%). The highest rate of SCD was in carriers of

desmosomal and LMNA variants and this finding was independent of the left ventricular ejection fraction.[22] Filamin-C and RBM20 gene mutations are also implicated to have high arrhythmic risk and SCD. Phenotypes with Lamin A/C mutations have strong associations with conduction system diseases.[23] Double gene mutations have profound impact on the phenotype and have been associated with aggressive manifestations such as higher risk of ventricular arrhythmias and SCD.[21]

The sensitivity and diagnostic yield of genetic testing has increased with the advent of Next-Generation Sequencing. Instead of testing a targeted gene, Next-Generation Sequencing focusses on a set of genes implicated in the disease subset. This has helped unearth unknown variants of significance. With proven disease association, these variants are reclassified into pathogenic or likely pathogenic mutations. Single Nucleotide Polymorphisms (SNPs) can be unearthed by Genome-Wide Association studies, and this can give new insights into the genetic causes of cardiac electrical instabilities.[23]

1.3.3 ECG markers of SCD

In a study involving 162 patients, the Selvester ECG derived QRS-score was applied in patients with LVEF<35%. This study included both patients with ischemic and non-ischemic cardiomyopathy. All of these patients had a cardiac MRI scan. The ECG-estimated scar was compared to the CMR-derived scar. Each QRS-point was equal to 3% of scar in the LV. In patients of NICM, the QRS-score was correctly able to identify CMR-scar in 51% patients. There was a good agreement between QRS-score and extent of CMR-LGE scar ($r=0.60$, $P<0.0001$) and in assessing the presence or absence of scar (ROC=0.81; 95% CI 0.70-0.91). Though localisation of scar was difficult, the correlation was better with anteroseptal scar in the LV. In logistic analysis, including LV ejection fraction, the QRS score ($P=0.006$) was the only significant predictor of inducible ventricular tachycardia. Each 3-point increase in QRS-score was associated with 2.2 times higher odds for inducing monomorphic ventricular tachycardia.[25] It was hypothesised that false negative cardiac MRI and possible overestimation with QRS score could be reason for mismatches between ECG-score and CMR-scar in NICM.

T wave alternans (TWA) represents beat-to-beat variability in shape, amplitude of the T wave, usually measured in a 24-hour ambulatory ECG. It was found to have high negative predictive value for SCD in dilated cardiomyopathy. Premature ventricular complexes (PVCs) and non-sustained VT is frequently seen in patients with NICM. High PVC burden has not been

associated with SCD. However, non-sustained VT has better predictive value for occurrence of ventricular arrhythmias and SCD in NICM. Single averaged electrocardiography (SAECG) can detect areas of slow conduction in the myocardium. Signals are revealed in the μV range after removal of noise. Criteria have been laid to suggest positivity: (1) filtered QRS> 114 ms; (2) potentials <40μV within the last portion of the QRS (3) Duration of more than 40ms of the terminal QRS with low potentials <20μV. In a metanalysis of 10 studies, the odds ratio for SCD was 2.1 for abnormal SAECG. Repolarisation indices like QT interval and QT dispersion, though are prolonged in dilated cardiomyopathy patients, have poor predictive value for detection of SCD. Heart rate variability (HRV) is estimated in a 24-h Holter recording usually by deriving the standard deviation of all normal RR intervals (SDNN). Though HRV is reduced in NICM, it has not been able to predict worse arrhythmic outcomes. While none of the above parameters can serve as stand-alone risk stratification tools, a composite of these ECG-derived variables might have good diagnostic accuracies in prediction of SCD in NICM.[26]

1.3.4 Echocardiographic variables for prediction of SCD in NICM

In two large community-based studies, the baseline echocardiographic parameters were studied for association with SCD, in the follow-up. The significant predictors of SCD were reduced left ventricular ejection fraction- 3.07 (2.29–4.11); 1 SD increase in left atrial diameter- 1.15 (1.02–1.30); mitral annular calcification- 1.85 (1.36–2.52); 1 SD increase in left ventricular mass- 1.30 (1.15–1.48); mitral E/A >1.5- 1.64 (1.07–2.51); and mitral E/A <0.7- 1.52 (1.14–2.02).[27] Moreover, addition of these echocardiographic variables improved the C-statistic for prediction of SCD in comparison to the conventional Framingham risk score variables. Thus, the prognostic value of echocardiographic markers was proven.

In the last decade, advanced cardiac imaging parameters like myocardial deformation imaging for prediction of SCD are being evaluated. In a study involving more than 900 patients, global longitudinal strain in all the 16 segments of the LV was computed and the mechanical dispersion noted. Mechanical dispersion >75ms was shown to have a strong association with SCD and ventricular arrhythmic events in a follow-up of nearly 10 years, irrespective of the ejection fraction. Also, the strain parameter ruled out any SCD if normal.[29]

Exploring the link between abnormal strain and SCD, a study involving 50 patients of NICM analysed the correlation between longitudinal strain derived by speckle tracking and SCD. The study did show a strong correlation between abnormal longitudinal strain and an underlying substrate for ventricular tachycardia. Also, the study proposed that localisation of myocardial abnormalities was possible with segmental strain abnormalities. Bipolar scar was identified by endocardial strain, unipolar scar correlated well with mid-myocardial strain and epicardial strain. As the correlation of regional and global longitudinal strain and scar percentage was linear, it was hypothesised that suggesting that scar burden may be quantifiable using echocardiographic strain analysis.[30]

1.3.5 Cardiac MRI for SCD risk-assessment in DCM

Cardiac MRI can reveal myocardial abnormalities. There are various tools of Cardiac MRI to detect these structural changes in the myocardium. The most studied modality is late gadolinium enhancement (LGE). The other tools of CMR are T1 mapping, ECV estimation and myocardial strain measurement. LGE can be detected in around 30% patients of DCM. Mere presence of LGE even in patients with LVEF>35% has been shown to be associated with increased risk of VA and SCD.[35]

In the largest study of 1165 patients of DCM with a median follow-up of 36 months, LGE was an independent and strong predictor of VAs (hazard ratio: 9.7), across all ranges of LVEF.[31] An algorithm combining LGE and LVEF superseded LVEF and could reclassify 36% patients of DCM with true arrhythmic risk. The largest metanalysis in NICM patients including a total of 46 studies and 10,548 NICM patients has shown 4.6 times increased risk of VAs and SCD and 2.9 times increase in mortality in patients with LGE.[34]

T1 mapping and ECV estimation can provide incremental value to LGE for prognostication. This was shown in a study of 659 patients of DCM, wherein even in LGE negative patients, T1 mapping and ECV estimation had strong association with cardiac-mortality.[55] Tools like CMR-derived myocardial strain have also shown to have prognostic implications in heart failure. In a study of 1169 chronic heart failure patients, global circumferential and longitudinal strain based on fast-SENC acquisitions could subclinical LV dysfunction and such patients had strong association with all-cause mortality.[33]

With the advent of registration of cardiac MRI modalities to electroanatomical mapping softwares, studies analysed the correlation of cardiac MRI-derived LGE with the

ventricular low voltage zones. In first of such studies, in 10 patients of NICM, it was shown that endocardial bipolar LVZ was dependent of endocardial core detected by LGE. Whereas, more extensive distribution of scar beyond the endocardium into the deeper mid myocardium and epicardium seems to influence the endocardial unipolar LVZ, than the bipolar LVZ.[42] There is significant variability in detection of true myocardial scar by LGE detected by cardiac MRI.

The inadequacies of LGE detected by conventional methods by cardiac MRI was exposed in a study on 90 patients on NICM, where 36% of these patients had discordance between low endocardial voltage detected and no LGE. All the discordant segments had low endocardial unipolar voltage. In these patients of discordance, a significant proportion of patients had VT arising from these discordant segments. However, the concordance rates could be improved by lowering the threshold for detection of LGE to signal intensity >2 standard deviations, rather than the conventional 5 standard deviations.[44] The importance of relying on unipolar low voltage zones in NICM was reiterated in an other study, wherein the authors showed poor agreement between bipolar LVZ and LGE detected by cardiac MRI. With the advent of parametric imaging with cardiac MRI, there are attempts to improve upon the agreement rates with low voltage zones detected by electroanatomical mapping. In an elegant study on 51 patients undergoing VT ablation with no LGE, shorter post contrast T1 mapping values correlated well with VT recurrence. A significant inverse relation was noted between T1 values and both unipolar and bipolar LVZ.[48] It is possible that diffuse fibrosis in NICM is better depicted by parametric mapping rather than LGE.

Research Question 3: What is the correlation of cardiac MRI-derived myocardial strain compared to conventional LGE with the endocardial unipolar voltage abnormalities? Chapter 5 addresses this question. The patients in the prospective cohort who had undergone both CMR and EAM were analysed for various CMR-derived strain and LGE measurements and the correlation with LVEF and endocardial unipolar low voltage zones were analysed. The classification agreements between LGE and CMR-strain to detect abnormal low voltage zones were analysed.

Hypothesis: Cardiac MRI-derived circumferential, longitudinal and radial strain has good correlation with LV ejection fraction and LV endocardial unipolar and bipolar voltage. The

classification rate of Cardiac MRI-derived strain parameters is better than LGE-detected scar for detection of LV endocardial unipolar and bipolar low voltage zones.

1.3.6 Electro-anatomical mapping (EAM) as a tool for risk-stratification

NICM is characterised by a heterogenous, and patchy distribution of scar primarily confined to the deeper myocardial layers namely the mid-myocardium and the epicardium.[53] This distribution of scar in myocardium can be best studied in-vivo by directly measuring the endocardial electrical properties by means of invasive electroanatomical mapping (EAM).[43] In an elegant study on 22 patients of NICM with VT, the authors clearly showed greater distribution of abnormal electrograms and low voltage areas in the LV epicardium. These abnormal signals were fractionated >80ms or late potentials or split potentials. The abnormal zones were predominantly located in the basal lateral region of the LV. The low voltage zones in the epicardium measured <1.0mV.[37] Subsequently in 11 patients of NICM, endocardial unipolar voltages were studied for their correlation with epicardial low bipolar voltage zones. This study concluded that endocardial unipolar voltage abnormalities were found to correspond to the epicardial bipolar voltage abnormalities.[40] Thus, the intramural substrate of NICM can be picked up by measuring endocardial unipolar voltages. This study introduced a cut-off of <8.27mV for endocardial unipolar voltage to pick up epicardial scars. Epicardial substrate of NICM is best represented by patients of arrhythmogenic right ventricular cardiomyopathy (ARVC). In this subset of patients, endocardial unipolar voltage <5.5mV was shown to correlate with epicardial VT substrate.[46] In an other study on 20 patients with RV epicardial VT, endocardial unipolar voltage <1.66mV was found to correlate well with dense epicardial scar.[50] The study also highlighted that endocardial bipolar voltage could not predict epicardial VT substrate. The study also showed that a cut-off of endocardial unipolar voltage <4.4mV was shown to correlate better with epicardial VT substrate in the RV.

Septal substrate in isolation can be found in around 12% cases of NICM. Such patients with VT can be difficult to treat by conventional radiofrequency ablation because of the deep located mid myocardial substrates. These septal substrates are more often distributed basally.[39] However, septal substrate along with lateral LV involvement can be found in 80% patients with NICM. At a cut-off of <4.8mV of LV endocardial unipolar voltage, delayed enhancement can be noted in cardiac MRI in the same locations.[49] Further studies were

undertaken to analyse the prognostic significance of endocardial unipolar voltages in NICM. A study showed that distribution of endocardial unipolar low voltage of >32% correlated with irreversibility of LV functions.[41] In 55 patients of NICM who underwent VT ablation, unipolar low voltage area of >54% correlated with VT recurrence and >145 cm^2 was a strong predictor of cardiac death. Thus, it was shown that the extent of the endocardial unipolar LVZ can predict cardiac mortality in NICM.[51]

A cut-off of <8.3mV of endocardial unipolar voltage in the left ventricle and <5.5mV in the right ventricular interventricular septum was shown to correlate with LGE detected by cardiac MRI.[39,41,46] Though the definition of these voltage cut-offs were made with low density mapping points derived with 3d EAM, these cut-offs have served as standard points of reference to define voltage abnormalities. There are attempts to redefine these voltage cut-offs with current high density mapping systems.[54] High density mapping systems and correlation with cardiac MRI abnormalities detected by T1 mapping have been shown to correlate with epicardial scar at lower cut-off of 3.8mV, instead of the conventional 5.5mV.[54]

Hypothesis: LV Endocardial unipolar voltage has better correlation than bipolar electrogram characteristics with LV ejection fraction and for prediction of VT substrate.

Research Question 4: What is the cut-off for the extent of abnormal endocardial unipolar low voltage that can reliably correlate with the substrate causing ventricular tachycardia?

To address this question in Chapter 4, a prospective study was designed to analyse the various endocardial derived electrogram characteristics. The correlation of these electrogram variables were studied against LVEF and for association with VT. Cut-offs with best diagnostic accuracies were then derived.

Chapter 2: Prognosis of patients with Heart Failure with mid-range ejection fraction compared to Heart Failure with reduced ejection fraction and Heart Failure with preserved ejection fraction

2.1 Preface to This Chapter

The newer international society guidelines have advocated classification of heart failure patients based on left ventricular ejection fraction (LVEF). This is meant to give more clarity on the phenotype of patients in each category. Henceforth, the heart failure patients are grouped into one of the three categories: Heart Failure with reduced Ejection Fraction (HFrEF, LVEF<40%), Heart Failure with mid-range Ejection Fraction (HFmrEF, LVEF 40-49%) and Heart Failure with preserved Ejection Fraction (HFpEF, LVEF>49%).

The long-term prognosis with regards to annual mortality, all-cause mortality, cause-specific mortality like cardiovascular deaths, sudden cardiac deaths in each of these categories with respect to the other has not been studied adequately, primarily because the classification scheme has been recent.

We set out to conduct the largest systematic review and meta-analysis of studies to analyse the long-term mortality in patients with HFmrEF compared to HFrEF and HFpEF. This will give important insights on the prognosis of the phenotype of HFmrEF and will unearth pertinent knowledge gaps that would help future research.

Hypothesis: Prognosis, in terms of all-cause mortality and cardiac mortality, in HFmrEF is worse than HFpEF and better than HFrEF.

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ORIGINAL ARTICLE

Long-term mortality in heart failure with mid-range ejection fraction: systematic review and meta-analysis

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Abstract

Aims Heart failure patients with mid-range ejection fraction (HFmrEF) have overlapping clinical features, compared with patients with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF). We aim to perform a meta-analysis of studies reporting long-term outcomes in HFmrEF compared with HFrEF and HFpEF.

Methods and results Data from 18 eligible large-scale studies including 126 239 patients were pooled. Patients with HFmrEF had a lower risk of all-cause death than those with HFrEF [risk ratio (RR) = 0.92; 95% CI = 0.85–0.98; $P < 0.001$]. This significant difference was seen in the follow-up at 1, 2, and 3 years. Patients with HFmrEF had significantly lower risk of cardiovascular (CV) deaths than HFrEF (RR = 0.77; 95% CI = 0.65–0.92; $P < 0.001$). Subgroup analysis showed that studies recruiting >50% of males had higher risk of deaths with HFrEF (RR = 1.15; 95% CI = 1.04–1.26; $P = 0.006$). When compared with HFpEF, patients with HFmrEF had comparable risk of all-cause death (RR = 1.02; 95% CI = 0.96–1.09; $P = 0.53$). Similarly, there were no differ- ences in the 1, 2, and 3 year deaths; CV and non-CV deaths were insignificant between HFmrEF and HFpEF.

Conclusions The results of the study support that HFmrEF has better prognosis than HFrEF but similar prognosis when com- pared with HFpEF. Gender disparity between studies seems to influence the results between HFmrEF and HFrEF. Transition in left ventricular ejection fraction (LVEF), which could not be addressed in the study, may play a decisive role in determining outcomes. PROSPERO review registration number CRD42021277107.

Keywords Systematic review; Meta-analysis; Heart failure; Mid-range ejection fraction; Mortality; Gender differences

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2.2 Introduction

Mortality in patients with symptomatic chronic heart failure varies from 25%-80% at 5 years, depending on the stage of heart failure.[56] Left ventricular ejection fraction (LVEF) is an important prognostic indicator for the risk of all-cause mortality as well as sudden cardiac death in chronic heart failure patients.[57] Since the introduction of categories of chronic heart failure based on LVEF, heart failure with mid-range (borderline) ejection fraction (HFmrEF) is recognised as an entity with overlapping clinical, treatment and outcome characteristics compared to heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).[58]

Large scale registries, multi-centre and single-centre studies have reported their observations on prognosis in each of these categories of heart failure.[59-76] However, only a few meta-analyses have been carried out comparing the prognosis of HFmrEF with HFrEF and HFpEF.[77-79] Moreover, these meta-analyses did not then have studies adequately powered to examine the annual mortality risk in the follow-up between these groups. Additionally, none of the meta-analyses have explored the difference in outcomes according to certain important subgroups which could be important moderators influencing the results. To explore these gaps in knowledge, we proposed a systematic review and meta-analysis to determine the long-term cumulative and annual mortality risk, cardiovascular and non- cardiovascular deaths in patients with HFmrEF compared with those with HFrEF and HFpEF.

2.3 Methods

2.4 Objectives

The primary objective was to determine the effect size of long-term cumulative mortality risk and all-cause mortality risk at 1-year, 2-years, 3-years, 4-years, 5-years, and 10-years; in persons with HFmrEF compared to HFrEF and HFpEF. Our secondary objectives were to 1) explore the long-term cause-specific mortality risk for deaths from cardiovascular, non-cardiovascular, heart failure, and sudden cardiac deaths in persons with HFmrEF compared with HFrEF and HFpEF; 2) identify clinical variables influencing the long-term mortality risk estimates.

2.4.1 Search strategy and eligibility criteria

We followed the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines in conducting this systematic review and the meta-analysis.[80] We searched MEDLINE, PubMed, EMBASE, Web of Science and Cochrane Library from inception to September 30, 2021, for studies reporting mortality outcomes between persons with heart failure with mid-range/ borderline ejection fraction (40-49%, HFmrEF) compared with reduced (<40%, HFrEF) or preserved ejection fraction (≥50%, HFpEF). The key search terms used were "ejection-fraction", "heart-failure", "death*", "mortality*", and "hazard-ratio*". The detailed search strategy is in ***Supplementary Table 1***. To identify additional studies, we manually searched the reference lists of the included studies. This study is registered at the PROSPERO review database (CRD42021277107).

The inclusion criteria were full-text peer reviewed papers in English, randomised controlled trials, cohort studies, observational studies with consecutive recruitment of patients with heart failure; standard case definition of heart failure, studies defining HFmrEF or borderline heart failure ejection fraction as 40-49%, HFrEF as <40% and HFpEF as ≥50% in adults aged 18 years and above; reporting cumulative all-cause deaths in HFmrEF and HFrEF/ HFpEF/ both along with annual all-cause, cardiovascular, non-cardiovascular, heart failure deaths or sudden cardiac deaths; follow-up ≥1-year; the sample size ≥100 with HFmrEF and the total sample size of heart failure patients ≥1000 when the power of the study was not listed. When there were ≧ 2 articles on the same group of patients, we selected the newest study best representing the cohort and the inclusion criteria.

The exclusion criteria were study protocols, brief reports, case studies, abstracts, theses, reviews, duplicate studies, incomplete and unpublished studies, studies of pregnant women, participants with a specific disease or a health condition in addition to heart failure and duplicate studies reporting outcomes from the same study population.

2.4.2 Data extraction

Retrieved studies were exported to Covidence^{R}. IS (Indira Samarawickrema) and DR (Deep Raja) screened the titles and the abstracts independently in Covidence^{R} for eligibility. RP (Rajeev Pathak) was the third independent reviewer. IS and DR independently extracted data from the eligible full-text studies into the custom designed data extraction tables in

Covidence[R]. Corresponding authors of studies without data on mortality outcomes were contacted. We analysed for consensus to ensure reliability of the data. Inter-rater agreement in data extraction was calculated. We had meetings to come to a consensus to resolve any discrepancies.

The data collated comprised study design, dataset, study period, study population, definitions of mid-range or borderline, reduced and preserved ejection fraction in heart failure, mean follow-up and standard deviation, study power, sample size, mean age and standard deviation, proportion of males, number of patients at baseline, number of cumulative, cardiovascular, non-cardiovascular and sudden cardiac deaths and all-cause deaths at 1-year intervals up to 10-years.

2.4.3 Quality appraisal

IS and DR independently assessed the quality of eligible used Newcastle-Ottawa quality assessment scale (NOS) for cohort studies and Cochrane Risk of Bias tool for randomised clinical trials (RoB 2).[80] We calculated inter-rater agreement for quality assessment and consensus reached following discussions for the disagreements. The third independent reviewer was RP. The objective of the quality appraisal was to exclude low quality studies, i.e. NOS score <7 and RoB 2 score <2. This study did not have patient or public involvement.

2.4.4 Statistical analysis

Pooled data of mortality and survival data for HFmrEF were compared with HFrEF and HFpEF for cumulative, cardiovascular, non-cardiovascular, heart failure and sudden cardiac deaths; and cumulative deaths at 1-year, 2-years, 3-years, 4-years, 5-years and 10-years; to determine the effect size (risk ratio (RR)) for the risk of death in the meta-analysis. To minimise potential of biases, each meta-analysis required ≥2 studies. Heterogeneity was calculated as I^2 and the cut-off for low heterogeneity was I^2 <30%. We used random effects maximum likelihood model for I^2 ≥30% and fixed effect model with inverse-variance for I^2 <30%. We reported exponentiated effect sizes from the log risk ratios. The effect size for death was determined as a risk ratio with 95% confidence intervals in the meta-analysis.

We explored heterogeneity between studies due to publication bias with visual inspection of funnel plots and Egger's linear regression test for the influence from small

studies. Sensitivity analysis excluding one study at a time was also performed to examine the influence of individual study on the effect size. We examined potential factors for between-study heterogeneity with clinically and epidemiologically relevant covariates (moderators) in the subgroup analysis and in the random-effects meta-regression. The covariates included were the proportion of men below or above 50%, mean age of the participants below or above 50 years, studies recruiting outpatients vs hospitalised patients, studies recruiting de novo vs chronic heart failure patients, single vs multi-centre studies, and follow-up period ≤2 vs >2 years. We conducted statistical analyses with Stata 17.0 (STATA Corporation, Texas, USA).

2.5 Results

The search process is outlined in ***Figure 2-1*** and the search strategy is listed in ***Supplementary Table 1***. Eighteen eligible studies were included in the meta-analysis of the mortality outcomes between HFmrEF and HFrEF, and seventeen eligible studies were included in meta-analysis of the mortality outcomes between HFmrEF and HFpEF. All studies were follow-up of patient cohorts from observational studies and there were no eligible randomised controlled trials. Inter-rater reliability in data extraction was 0.91 and Cohen's Kappa was 0.39. The quality of evidence of each selected study is listed in ***Supplementary Table 2***. Inter-rater reliability in quality appraisal was 0.84 and Cohen's Kappa was 0.67.

2.5.1 Study and patient characteristics (Table 2-1)

There were 14 prospective and four retrospective cohort studies; 13 including hospitalised patients; three including outpatients; 14 multi-centre and four single-centre studies; 13 studies with enrolments before 2010 and five studies with enrolments during or after 2010. The participant follow-up ranged from 1 to 10 years. The noteworthy large-scale studies were the 1-year and 5-year data from the Get With The Guidelines–Heart failure (GWTG-HF) registry, 3-year data from the Swedish Heart Failure Registry, and 1-year data from the ESC Heart Failure long-term registry.[60,63,70,74] Choi KH, et al. reported outcomes for both de novo-heart failure and acute decompensated chronic heart failure patients and was hence considered as two separate studies.[64]

The included studies had 126,239 heart failure patients inclusive of; 64,779 patients with HFrEF (51.3%); 20,301 patients with HFmrEF (16.1%); and 41,159 patients with HFpEF (32.6%). The average age of the patients was 71.9 years. The proportion of men in the overall

cohort was 60.6% with 60.5% in HFrEF, 69% in HFmrEF and 40.4% in HFpEF. The HFmrEF group had significantly reduced proportion of patients with hypertension, diabetes mellitus, kidney disease, atrial fibrillation, and coronary artery disease (9.7%, 5.2%, 3.2%, 7%, 8.1% respectively) than both HFrEF (29%, 17%, 11%, 19%, 27% respectively) and HFpEF groups (23%, 11%, 8.5%, 14.6%, 12.2% respectively). (***Supplementary Table 3***)

2.5.2 Risk of all-cause mortality (Figure 2, 3)

Patients with HFmrEF had a significantly lower risk of all-cause death than those with HFrEF (Risk Ratio (RR)= 0.92; 95% C.I= 0.85-0.98; p<0.001), using the random-effects model (***Figure 2-2***). Subgroup analysis (***Figure 2-3***) revealed that studies recruiting >50% of men had a lower risk ratio for HFmrEF vs HFrEF (RR= 0.87; 95% C.I= 0.79-0.96; p=0.006). This translated into a higher risk of deaths with HFrEF in studies recruiting >50% of males (RR= 1.15; 95% C.I= 1.04-1.26; p=0.006). However, studies ≤50% of men had insignificant differences in the risks of deaths (HFmrEF Vs HFrEF: RR= 1.00; 95% C.I= 0.99-1.03; p=0.63). Subgroup analysis also revealed that studies including only outpatients had lesser risk of death with HFmrEF (RR= 0.78; 95% C.I= 0.65-0.93; p=0.006) than studies including only hospitalised patients (RR= 0.97; 95% C.I= 0.94-1.01; p=0.13).

Patients with HFmrEF had comparable risk of all-cause death with HFpEF (pooled RR= 1.02; 95% C.I= 0.96-1.09; p=0.53) using the random-effects model (***Figure 2-2***). Subgroup analysis (***Figure 2-3***) revealed higher risk of deaths in HFmrEF, than HFpEF, in single-centre studies (RR= 1.13; 95% C.I= 1.03-1.24; p=0.008) compared to multi-centre studies (RR= 1.00; 95% C.I= 0.92-1.07; p=0.91).

There was high level of heterogeneity between the included studies for HFmrEF Vs HFrEF (I^2= 87%) as well as for HFmrEF Vs HFpEF (I^2= 80.2%). To assess publication bias, a sensitivity analysis was conducted by exclusion of individual studies and the smaller studies, and this was found to not affect the results. Meta-regression analysis for between-study variance in overall mortality risk ratio between HFmrEF and HFrEF identified that studies on hospitalised patients and multi-centre studies contributed to 98.6% variance (p=0.0001). Meta-regression analysis for between-study variance in overall mortality risk ratio between HFmrEF and HFpEF identified that multi-centre studies attribute to 53.7% of variance (p=0.005).

2.5.3 Annual all-cause mortality in the follow-up (Figure 2-3)

Analysis of studies with annual all-cause deaths showed that patients with HFmrEF had a significantly lower risk of all-cause death than those with HFrEF at 1-year (7 studies; pooled RR= 0.84; 95% C.I= 0.74-0.95; p= 0.03; I^2=54%), 2-years (4 studies; pooled RR= 0.86; 95% C.I= 0.75-0.98; I^2=34%) and 3-years (2 studies; pooled RR= 0.38; 95% C.I= 0.32-0.44; I^2=88%). The differences were insignificant at 5-years (4 studies) and 10-years (2 studies). In contrast, patients with HFmrEF had comparable risk of all-cause death with HFpEF at all the specified years. (***Figure 2-4***)

2.5.4 Cardiovascular, non-cardiovascular deaths, heart-failure and sudden cardiac deaths (Figure 2-4, 2-6, 2-7, 2-8)

Patients with HFmrEF had significantly lower risk of cardiovascular deaths than HFrEF (pooled RR= 0.77; 95% C.I= 0.65-0.92; p<0.001; I^2= 76%). Patients with HFmrEF had significantly lower risk of SCD than in HFrEF (pooled RR= 0.59; 95% C.I= 0.41-0.85; p<0.001; I^2=0). Patients with HFmrEF had trends of lower risk of heart-failure related deaths than in HFrEF (pooled RR= 0.72; 95% C.I= 0.43-1.21; p=0.21; I^2= 86%). However, the risk of non-cardiovascular deaths was comparable (pooled RR= 1.20; 95% C.I= 1.05-1.37; p=0.15; I^2=12.7%) between HFmrEF and HFrEF groups.

In contrast, patients with HFmrEF and HFpEF had comparable risks of cardiovascular deaths (pooled RR= 1.10; 95% C.I= 0.99-1.21; p=0.38; I^2=6%), heart failure deaths (pooled RR= 0.93; 95% C.I= 0.70-1.24; p=0.62; I^2=44%), SCD (pooled RR= 1.33; 95% C.I= 0.85-2.09; p=0.27; I^2=23%) and non-cardiovascular deaths (pooled RR= 1.05; 95% C.I= 0.77-1.44; p=0.76; I^2=77%).

2.6 Discussion

The salient features of our meta-analysis are: 1) The risk of long-term all-cause mortality is reduced in patients with HFmrEF compared to HFrEF at 1-year, 2-years and 3-years; beyond which the differences in mortality risk are insignificant; 2) The risk ratios for all-cause deaths between HFmrEF and HFrEF are different when accounting for gender disparity– while studies recruiting > 50% men show a higher risk of deaths in the HFrEF category compared to HFmrEF, the risk ratios are indifferent in studies recruiting higher proportion of

women; 3) The risk of long-term all-cause mortality, cardiovascular and non-cardiovascular deaths is similar between patients with HFmrEF and HFpEF.

Our study is the largest meta-analysis of large-scale studies reporting long-term mortality outcomes in HFmrEF compared to HFrEF and HFpEF. The last meta-analysis on this topic included studies till end of April 2019 and had evaluated only the adjusted mortality ratios between these groups.[78] While two of the previous meta-analyses reported both short-term and long-term mortality ratios between the groups, only one meta-analysis reported the 1-year mortality ratios.[77,79] The results of our study on the cumulative all-cause mortality outcomes between HFmrEF and HFrEF as well as HFpEF groups are consistent with the earlier meta-analyses.[77,81] While HFmrEF bears a better long-term prognosis compared to HFrEF, the outcomes seem to be similar compared to HFpEF.

Our study, in addition, explores the annual mortality outcomes in the follow-up. Beyond 3 years, the risk differences seem to level out between HFmrEF and HFrEF. This observation could be due to either transition in LVEF from one group to the other in the follow-up, or inadequate power of the very long-term studies to detect differences in the deaths between the two groups. Transition of patients from one group to the other has not been reported uniformly in the registries. In a seminal study involving 4942 patients, among those patients with HFmrEF, 37% patients had worsened to HFrEF and 25% patients improved to HFpEF category. Also, 21% patients of HFpEF had progressive failing of LV function and shifted to HFmrEF category and 16% patients of HFrEF improved to the HFmrEF category.[82] This shows that HFmrEF is likely a heterogenous entity comprising of patients with improved ejection fraction, stable left ventricular functions, and progressive LV dysfunction. Though LVEF helps to categorise these patients, the dynamic change in LVEF is an important consideration to keep in mind while interpreting the long-term outcomes.

Gender disparity between studies and its influence on the outcomes is revealed in our analysis. Studies with more proportions of women had comparable risk of deaths between HFmrEF and HFrEF, while those with more proportion of men had higher risk of deaths in HFrEF. Studies on gender differences in incidence and prognosis of heart failure show higher risk of HFrEF, incident heart failure and deaths in men compared to higher incidence of HFpEF amongst women.[83] Hospitalisation is an important event in the natural history of HF that portends poor prognosis.[84] In our analysis, the studies including only outpatients had reported lesser all-cause mortality rates ranging from 7.6% to 28% in HFmrEF group compared to

mortality rates ranging from 18% to 75% in the studies including only hospitalised patients. Predictably, our subgroup analysis showed a significantly reduced deaths in the HFmrEF compared to HFrEF only amongst the studies reporting outpatients.

An individual patient data meta-analysis showed no differences in the risks of all-cause mortality as well as cardiovascular deaths at LVEF $\geq$ 40%.[81] Our observation also shows no differences in absolute mortality, cardiovascular, non-cardiovascular and sudden cardiac deaths, between the HFmrEF and HFpEF groups. Thus, this group is a large cluster of heart failure patients, wherein LVEF fails to dictate prognosis. This underlines the need to look for additional non-cardiac and cardiac prognostic indicators like associated comorbidities, cardiac MRI, arrhythmia burden and henceforth. Cardiac specific investigations need to be considered beyond the conventional echocardiogram in this subset. Recent large-scale studies have shown that cardiac MRI could identify subtle myocardial abnormalities in this subset that may portend a poor prognosis both in terms of worsening myocardial dysfunction and increase in risk of arrhythmias.[85]

2.7 Limitations

1) In spite of application of strict eligibility criteria, our meta-analysis does bear a high level of heterogeneity between the included studies. This heterogeneity was adequately addressed statistically with appropriate sensitivity, subgroup and meta-regression analysis. The results seem to be unaffected by any of the included studies. 2) The lack of a standard reporting protocol of long-term outcomes in registries was evident during our systematic review, such as: variable period of follow-up; gender disparity; variable age groups; variable outcomes in single and multi-centre studies; inclusion of both hospitalised and outpatients in a few studies; inclusion of both denovo and chronic heart failure patients in a few registers; and representation of more valvular heart diseases and myocardial infarction in a few registries. We have attempted to address this heterogeneity arising due to clinical variables in our subgroup analysis. 3) Medical therapy has improved enormously with regards to heart failure. However, due to considerable heterogeneity in the reporting of medical therapy in the included studies, we could not address this in the subgroup analysis. 4) It is possible that, the recruited studies did not have adequate power to detect significant differences in risk-ratios in heart failure deaths and very long-term (beyond 3 years) deaths between HFmrEF and

HFrEF groups. Similarly, the single-centre studies may not have sufficient power to detect enough deaths in the HFpEF group.

2.8 Future Directives

1) Adoption of a standard reporting guideline on long-term outcomes with respect to the clinically relevant confounders could reduce the level of heterogeneity between studies; 2) Transition in LVEF needs to be considered while analysing the outcomes in chronic heart failure; 3) Additional risk-stratification tools should be aggressively sought to understand better the similarities and differences between HFmrEF and HFpEF.

2.9 Conclusion

Our meta-analysis concludes that risk of long-term all-cause mortality is less in patients with HFmrEF compared to HFrEF till 3-years; beyond which the differences in mortality risk were insignificant, for which transition in LVEF could play an important role. The insignificant differences in the risk-ratio between HFmrEF and HFrEF while considering studies representing greater proportion of women, suggests that gender disparity may play a divisive role in determining outcomes. The differences in risk of long-term all-cause mortality were comparable between patients with HFmrEF compared to HFpEF, thus suggesting the need to explore the mortality risks with tools other than LVEF.

2.10 Figure Legends

- **Figure 2-1:** Flow chart of search process and results
- **Figure 2-2:** Forest plots demonstrating all-cause deaths in (A) HFmrEF and HFrEF, and (B) HFmrEF and HFpEF; HFmrEF- heart failure with mid-range (borderline) ejection fraction, HFrEF- heart failure with reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction
- **Figure 2-3:** Forest plots of sub-group analysis of long-term all-cause mortality in (A) HFmrEF and HFrEF, and (B) HFmrEF and HFpEF; HFmrEF- heart failure with mid-range (borderline) ejection fraction, HFrEF- heart failure with reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction
- **Figure 2-4:** Forest plots demonstrating annual all-cause deaths in (A) HFmrEF and HFrEF, and (B) HFmrEF and HFpEF; HFmrEF- heart failure with mid-range (borderline)

ejection fraction, HFrEF- heart failure with reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction

- **Figure 2-5:** Forest plots demonstrating cardiovascular deaths in (A) HFmrEF and HFrEF, and (B) HFmrEF and HFpEF; HFmrEF- heart failure with mid-range (borderline) ejection fraction, HFrEF- heart failure with reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction

Table 2-1: Characteristics of the included studies

Source #	Study design	Country	Study period	Follow-up in years	Age* (years) (mean± SD/ median± IQR)	Total sample size	Number of patients					
							HFrEF (<40%)		HFmrEF (40-49%)		HFpEF (≥50%)	
							No.	Male %	No.	Male %	No.	Male %
Bonsu, et al., 2017	Retrospective single hospital registry	Ghana	Jan 2009 - Dec 2013	5	60.8±14.6	1488	345	48.1	265	50.2	878	43.3
Cheng, et al., 2014	Prospective multi-hospital registry	U.S.A	Jan 2005- Dec 2011	1	80±74-86	40239	15716	60	5626	49.5	18897	32.7
Chioncel, et al., 2017	Prospective multi-hospital registry	Europe and Mediterranean countries	May 2011 - Apr 2013	1	68.6±13.7	9134	5460	78.4	2212	68.5	1462	52.1
Choi, et al., 2018 de novo	Prospective multi-hospital registry	South Korea	Mar 2011 - Feb 2014	4	71.7±14.5	2867	1631	61.8	492	50	744	42.3
Choi, et al., 2018 ADHF	Prospective multi-hospital registry	South Korea	Mar 2011 - Feb 2014	4	72.6±12.0	2547	1551	60.7	383	43.9	613	33.8
Coles, et al., 2014[+]	Prospective multi-hospital registry	U.S.A.	1995, 2000, 2002, 2004	4	76.5 ±11.9	3604	1479	56.5	346	45.4	1779	33.4
Farre, et al., 2017	Prospective multi-hospital registry	Spain	Aug 2001 - Jun 2015	10	73.5±11.4	3580	2232	75.7	504	66.9	844	44
Ganapathi, et al., 2020	Retrospective single hospital registry	India	Jan 2001 - Dec 2010	10	48.8±14.7	1502	404	78.2	231	74.5	867	51.7
Gomez-Otero, et al., 2017	Prospective multi-hospital registry	Spain	Oct 2013 - Dec 2014	1	72.5±11.1	1420	583	76.7	227	67	610	46.7
Guisado-Espartero, et al., 2018	Prospective multi-hospital registry	Spain	Feb 2008 - Feb 2009	1	81±76–86	2753	808	62.5	281	58	1664	37.4
Hamatani, et al., 2018	Prospective multi-hospital registry	Japan	Jun 2005 - Apr 2016	5	77±11	1792	860	71.2	318	64.5	614	47.4
Koh, et al., 2017	Retrospective multi-hospital registry	Sweden	Jan 2000 - Dec 2012	3	77±11	42061	23402	71.2	9019	60.8	9640	45.4
Lam, et al., 2018	Prospective multi-hospital registry	New Zealand, Singapore	Mar 2010 - Aug 2014	2	71.5±11.8	2039	1209	83.5	256	69.9	574	52.3
Liu, et al., 2021[+]	Retrospective single hospital registry	Germany	Jul 2009 - Dec 2017	8	69±13	2018	1067	76.3	951	74.2	--	--
Pascual-Figal, et al., 2017	Prospective multi-hospital registry	Spain	Apr 2003 - Jan 2011	4	72.1±12.2	3446	2351	76.8	460	73	635	42.8
Shah, et al., 2017	Prospective multi-hospital registry	U.S.A.	Jan 2005 - 30 Dec 2009	5	82±75-87	39982	18398	59	3285	48.5	18299	32.4
Shiga, et al., 2019	Retrospective multi-hospital registry	Japan	Apr 2013 - Mar 2014	2	81±72-87	1156	412	68.2	248	53.2	496	39.5
Vergaro, et al., 2019[+]	Prospective single hospital registry	Italy	Jan 2000 – Dec 2016	5	71±12	2791	1539	76.3	623	71.6	629	4.5

studies have been mentioned in order of first author followed by year of publication; aditionally these studies had defined HFmrEF as 41-49%, remainder of the studies defined HFmrEF as 40-49%; * average age is presented as mean and 95% standard deviation or median with 25th and 75th interquartile ranges; HFrEF- heart failure with reduced ejection fraction; HFmrEF- heart failure with mid-range ejection fraction; HFpEF- heart failure with preserved ejection fraction; ADHF- acute decompensated heart failure patients; U.S.A- United States of America

Figure 2-1: Flow chart of search process and results

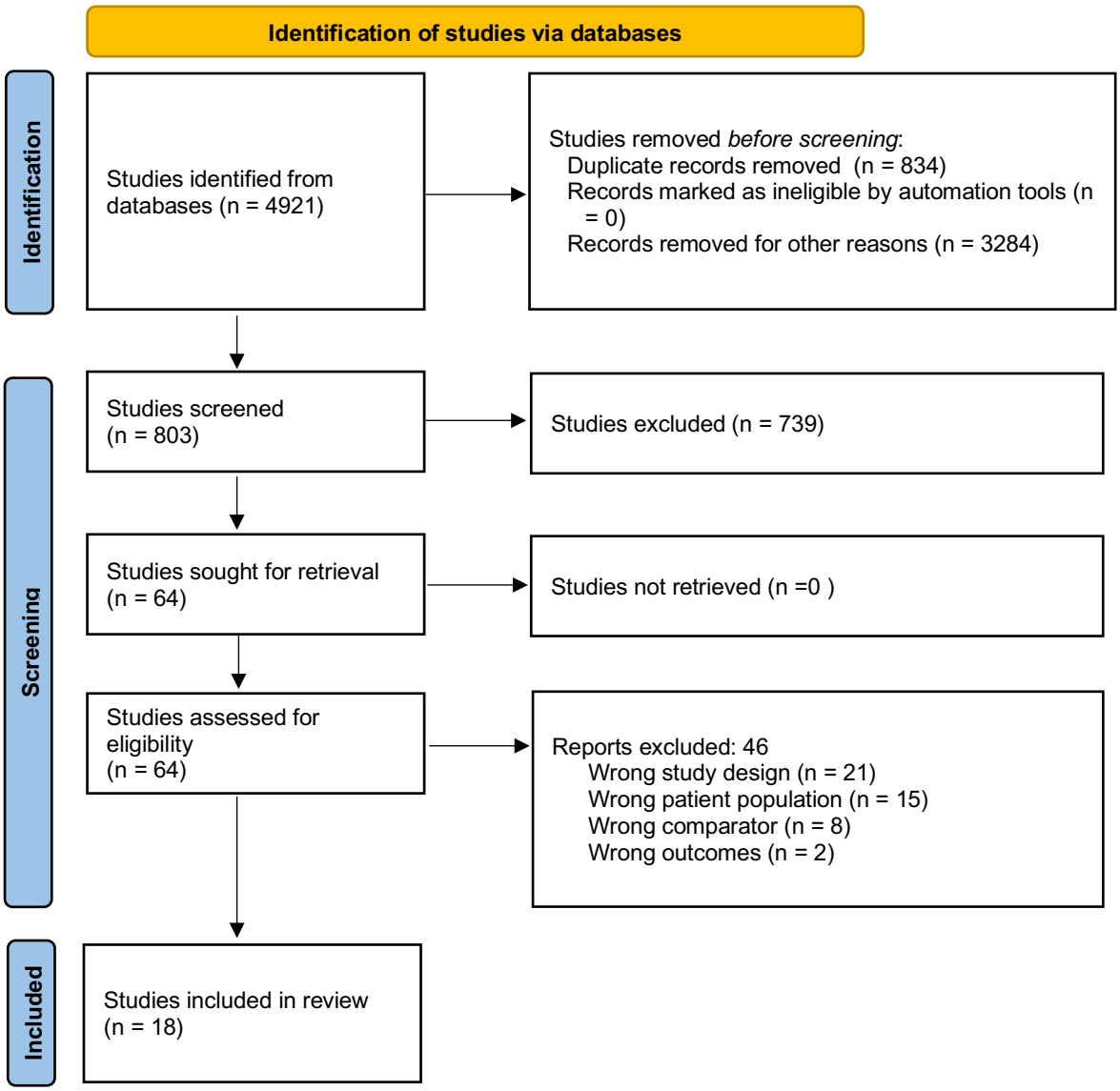
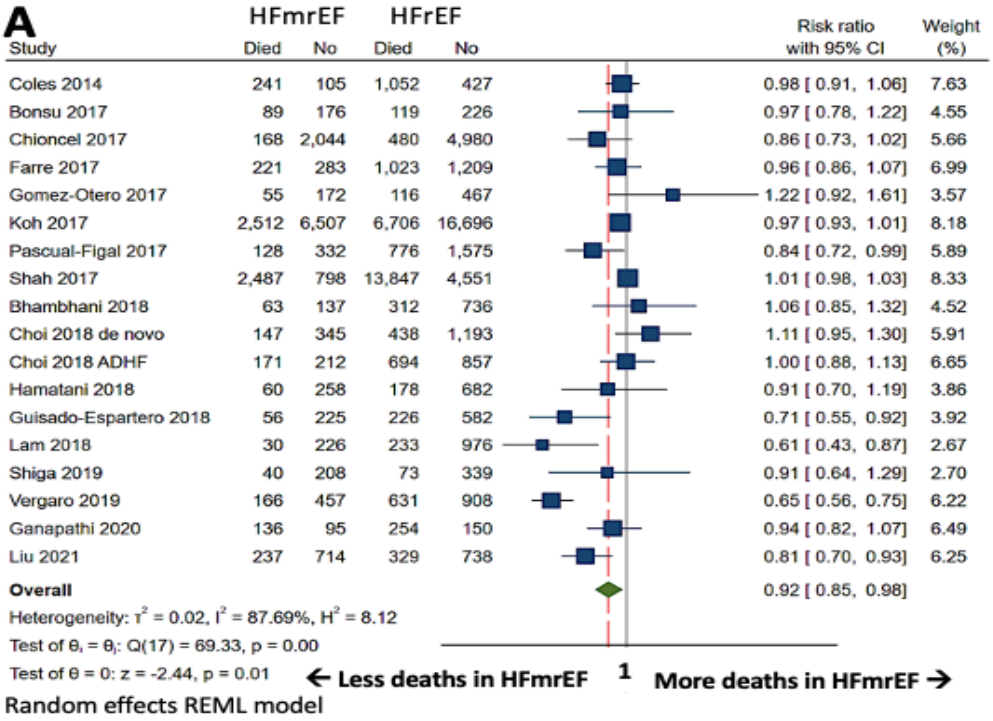


Figure 2-2: Forest plots demonstrating all-cause deaths in (A) HFmrEF and HFrEF, and (B) HFmrEF and HFpEF; HFmrEF- heart failure with mid-range (borderline) ejection fraction, HFrEF- heart failure with reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction



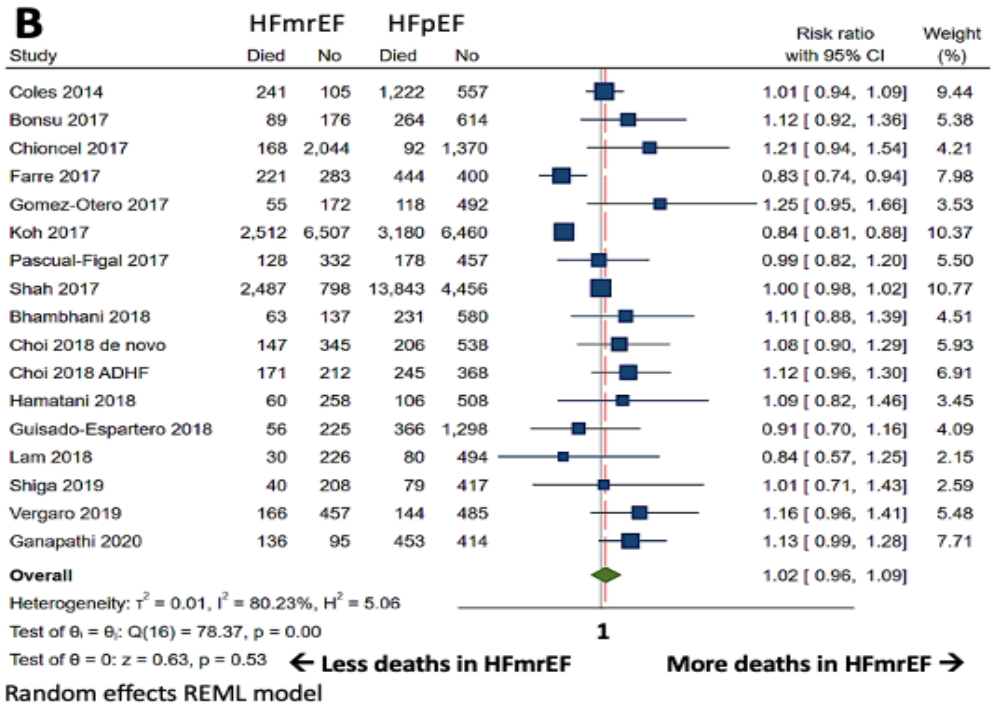


Figure 2-3: Forest plots of sub-group analysis of long-term all-cause mortality in (A) HFmrEF and HFrEF, and (B) HFmrEF and HFpEF; HFmrEF- heart failure with mid-range (borderline) ejection fraction, HFrEF- heart failure with reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction

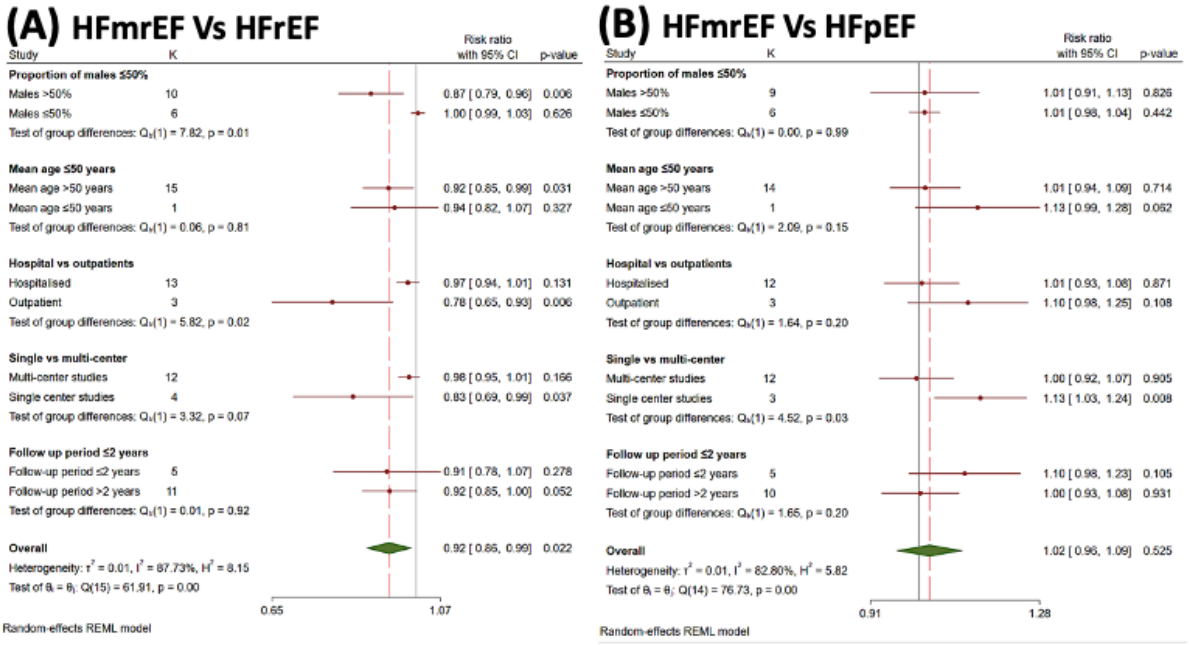


Figure 2-4: Forest plots demonstrating annual all-cause deaths in (A) HFmrEF and HFrEF, and (B) HFmrEF and HFpEF; HFmrEF- heart failure with mid-range (borderline) ejection fraction, HFrEF- heart failure with reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction

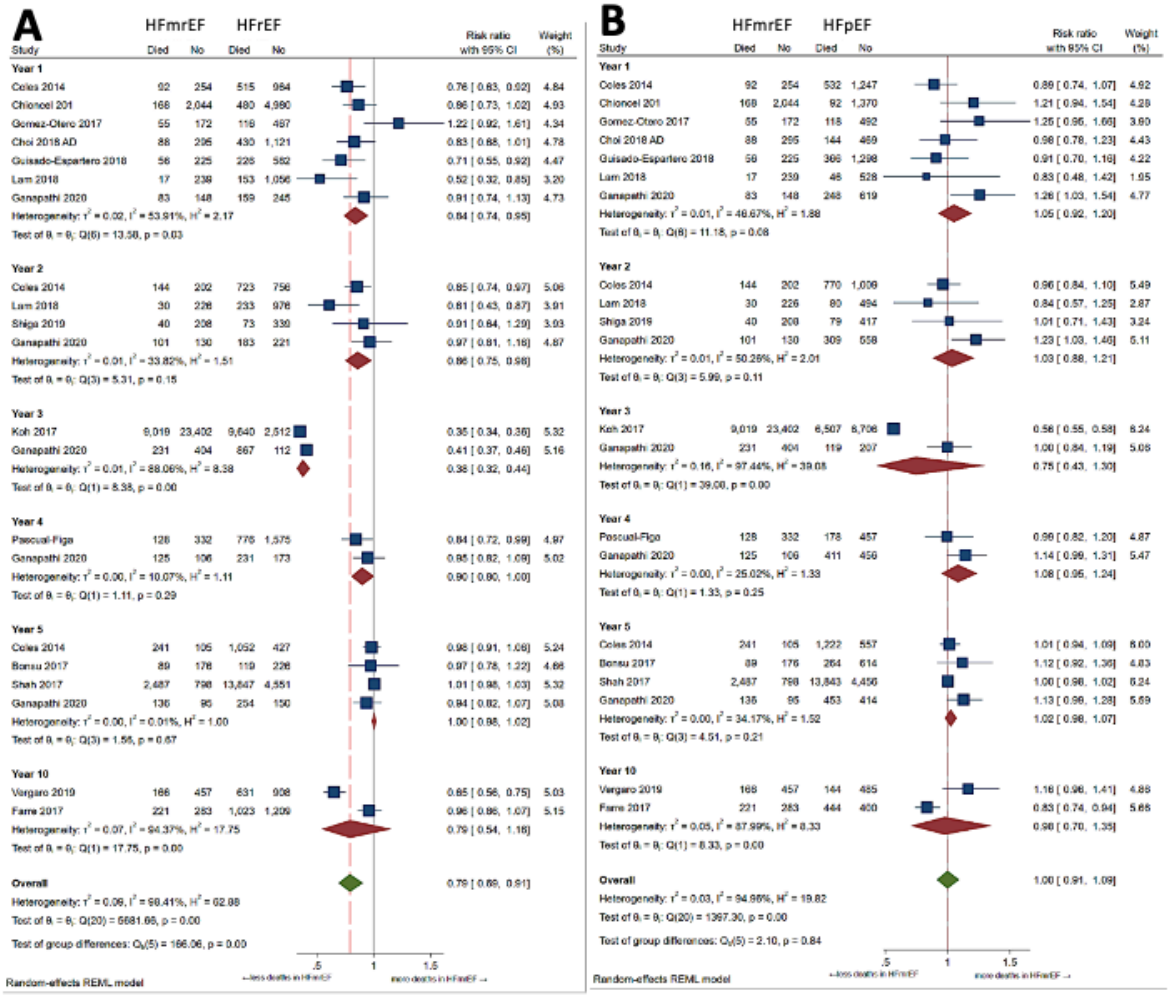
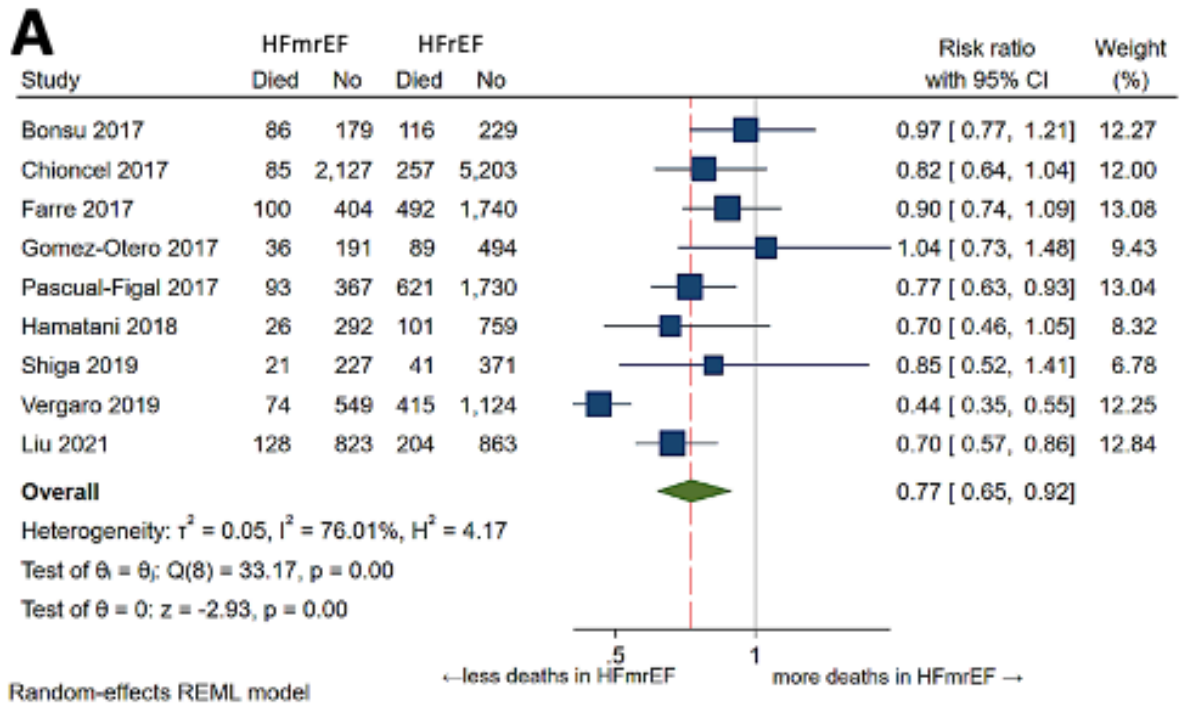
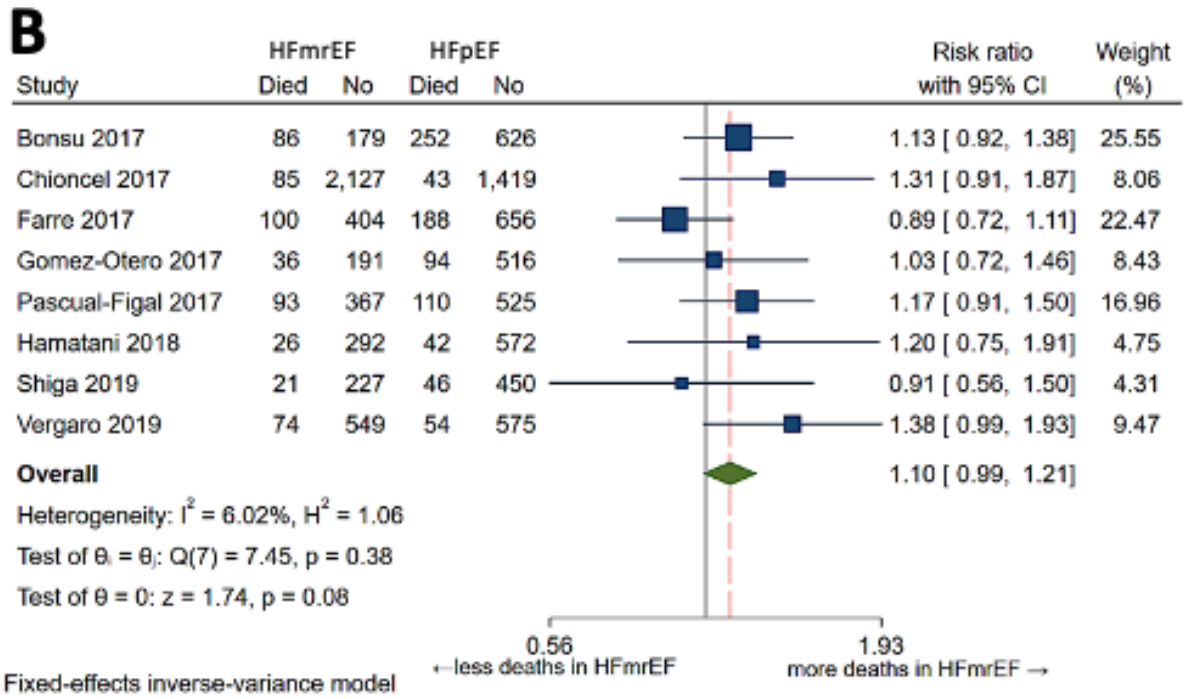


Figure 2-5: Forest plots demonstrating cardiovascular deaths in (A) HFmrEF and HFrEF, and (B) HFmrEF and HFpEF; HFmrEF- heart failure with mid-range (borderline) ejection fraction, HFrEF- heart failure with reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction





Supplementary Material

- **Figure 2-6, Supplementary Figure 1:** Forest plots demonstrating non-cardiovascular deaths in (A) HFmrEF and HFrEF, and (B) HFmrEF and HFpEF; HFmrEF- heart failure with mid-range (borderline) ejection fraction, HFrEF- heart failure with reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction
- **Figure 2-7, Supplementary Figure 2:** Forest plots demonstrating heart failure deaths in (A) HFmrEF and HFrEF, and (B) HFmrEF and HFpEF; HFmrEF- heart failure with mid-range (borderline) ejection fraction, HFrEF- heart failure with reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction
- **Figure 2-8, Supplementary Figure 3:** Forest plots demonstrating sudden cardiac deaths in (A) HFmrEF and HFrEF, and (B) HFmrEF and HFpEF; HFmrEF- heart failure with mid-range (borderline) ejection fraction, HFrEF- heart failure with reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction

Supplementary Figures

Figure 2-6: Supplementary Figure- Forest plots demonstrating non-cardiovascular deaths in (A) HFmrEF and HFrEF, and (B) HFmrEF and HFpEF; HFmrEF- heart failure with mid-range (borderline) ejection fraction, HFrEF- heart failure with reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction

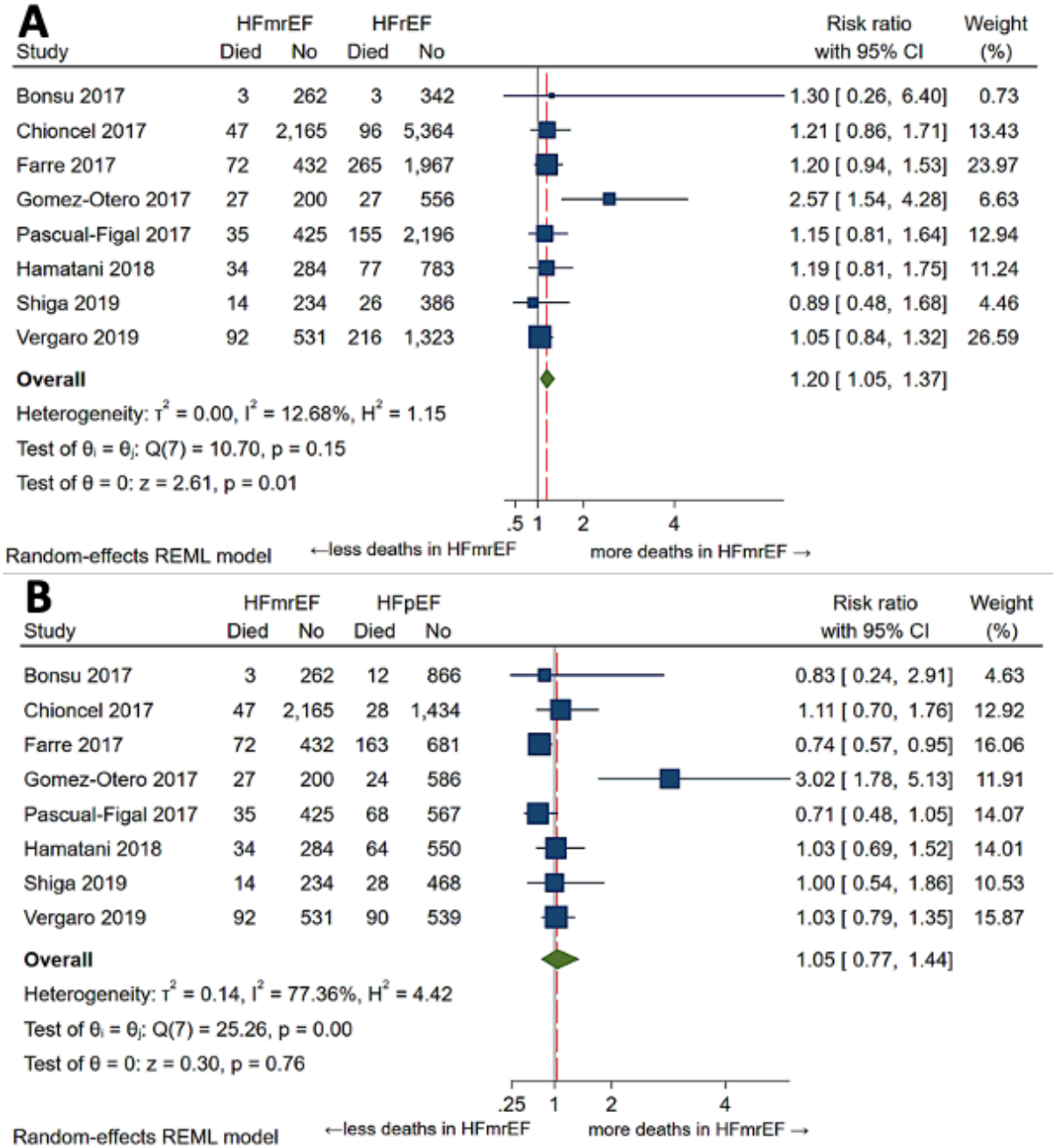


Figure 2-7: Supplementary Figure- Forest plots demonstrating heart failure deaths in (A) HFmrEF and HFrEF, and (B) HFmrEF and HFpEF; HFmrEF- heart failure with mid-range (borderline) ejection fraction, HFrEF- heart failure with reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction

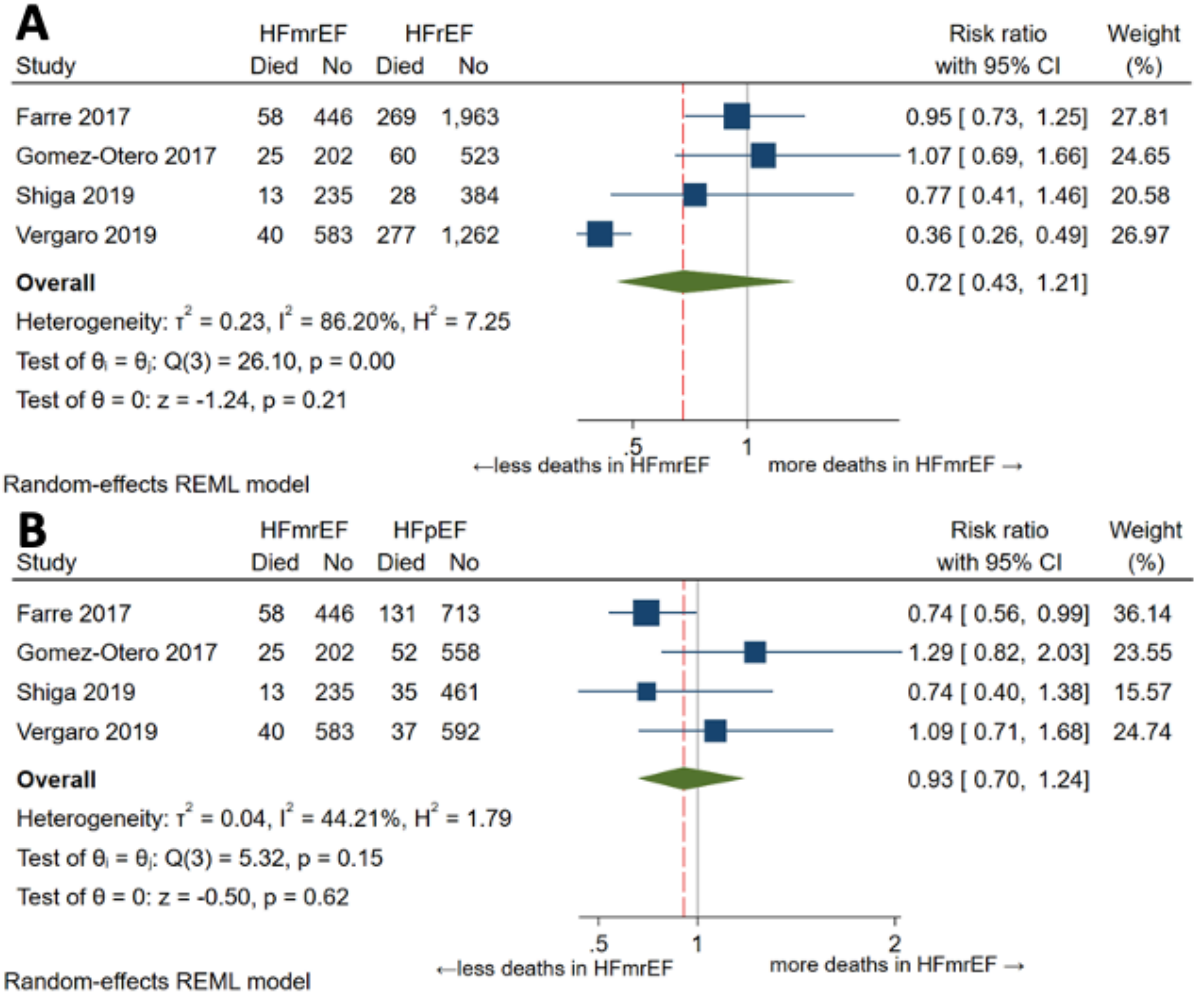
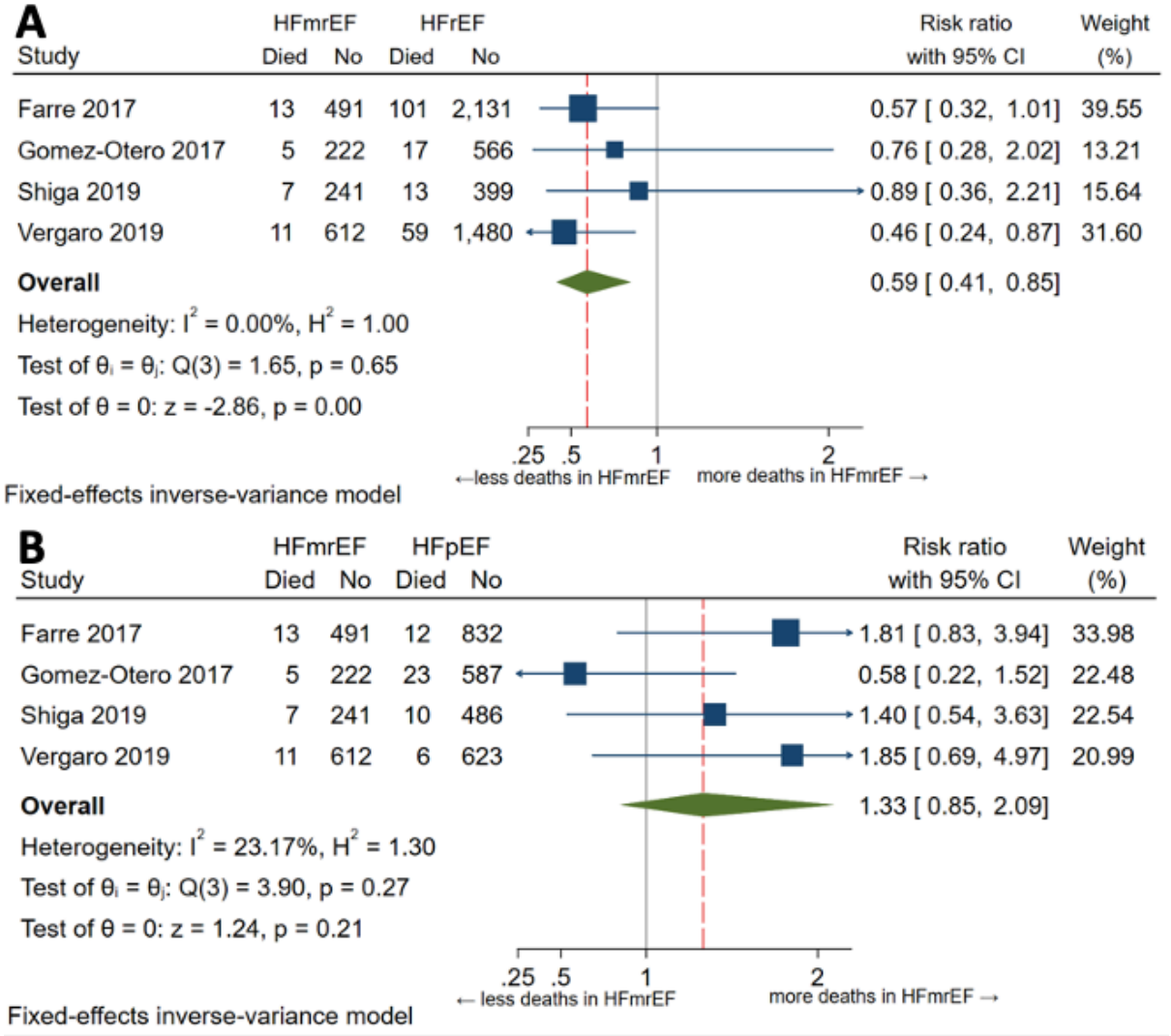


Figure 2-8: Supplementary Figure- Forest plots demonstrating sudden cardiac deaths in (A) HFmrEF and HFrEF, and (B) HFmrEF and HFpEF; HFmrEF- heart failure with mid-range (borderline) ejection fraction, HFrEF- heart failure with reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction



Supplementary table 1 – Enumeration of the detailed search strategy

The search strategy was developed with the collaboration of Murray Turner, Liaison Librarian for Faculty of Health, Library, University of Canberra.

Table 2-2: Supplementary Table 1– Enumeration of the detailed search strategy

Sources	MEDLINE, PubMed, Web of Science, EMBASE, Cochrane Central Register of Controlled Trials database
Search dates	all the studies up to 30 September 2021
Language	English only
Database and search terms	MEDLINE (TI ((((HF*EF OR ejection-fraction OR heart-failure OR heart-diseases OR cardio-renal-syndrome OR dyspn* OR paroxysmal OR *edema) AND (death* OR mortalit* OR *hospitali* OR readmission*) AND (cohort AND hazard-ratio*)) NOT (review OR meta-analysis OR systematic-review)))) OR (AB ((((HF*EF OR ejection-fraction OR heart-failure OR heart-diseases OR cardio-renal-syndrome OR dyspn* OR paroxysmal OR *edema) AND (death* OR mortalit* OR *hospitali* OR readmission*) AND (cohort AND hazard-ratio*)) NOT (review OR meta-analysis OR systematic-review)))) Web of Science (TI ((((HF*EF OR ejection-fraction OR heart-failure OR heart-diseases OR cardio-renal-syndrome OR dyspn* OR paroxysmal OR *edema) AND (death* OR mortalit* OR *hospitali* OR readmission*) AND (cohort AND hazard-ratio*)) NOT (review OR meta-analysis OR systematic-review)))) OR (AB ((((HF*EF OR ejection-fraction OR heart-failure OR heart-diseases OR cardio-renal-syndrome OR dyspn* OR paroxysmal OR *edema) AND (death* OR mortalit* OR *hospitali* OR readmission*) AND (cohort AND hazard-ratio*)) NOT (review OR meta-analysis OR systematic-review)))) EMBASE (((HF?EF OR ejection-fraction OR heart-failure OR heart-diseases OR cardio-renal-syndrome OR dyspn* OR paroxysmal OR *edema) AND (death* OR mortalit* OR *hospitali* OR readmission*) AND (cohort AND hazard-ratio*)) AND NOT (review OR meta-analysis OR systematic-review)) Cochrane Central Register of Controlled Trials database (TI ((((HF*EF OR ejection-fraction OR heart-failure OR heart-diseases OR cardio-renal-syndrome OR dyspn* OR paroxysmal OR *edema) AND (death* OR mortalit* OR *hospitali* OR readmission*) AND (cohort AND hazard-ratio*)) NOT (review OR meta-analysis OR systematic-review)))) OR (AB ((((HF*EF OR ejection-fraction OR heart-failure OR heart-diseases OR cardio-renal-syndrome OR dyspn* OR paroxysmal OR *edema) AND (death* OR mortalit* OR *hospitali* OR readmission*) AND (cohort AND hazard-ratio*)) NOT (review OR meta-analysis OR systematic-review))))

Table 2-3: Supplementary Table 2- Newcastle-Ottawa quality assessment scale (NOS) for cohort studies

Study ID	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts
Cheng 2014	*	*	*	*	*	*	*	*	*
Coles 2014	*	*	*	*	*	*	*	*	*
Bonsu 2017	*	*	*	*	*	*	*	*	*
Chioncel 2017	*	*	*	*	*	*	*	*	*
Farre 2017	*	*	*	*	*	*	*	*	
Gomez-Otero 2017	*	*	*	*	*	*	*	*	
Koh 2017	*	*	*	*	*	*	*	*	*
Pascual-Figal 2017	*	*	*	*	*	*	*	*	*
Shah 2017	*	*	*	*	*	*	*	*	*
Bhambhani 2018	*	*	*	*	*	*	*	*	*
Choi 2018	*	*	*	*	*	*	*	*	
Hamatani 2018		*	*	*	*	*	*	*	*
Guisado-Espartero 2018		*	*	*	*	*	*	*	*
Lam 2018	*	*	*	*	*	*	*	*	*
Miro 2018	*	*	*	*	*	*	*	*	*
Shiga 2019	*	*	*	*	*	*	*	*	*
Vergaro 2019	*	*	*	*	*	*	*	*	*
Ganapathi 2020	*	*	*	*	*	*	*	*	*
Liu 2021	*	*	*	*	*		*	*	

The distribution of patient characteristics between the three groups

Table 2-4: Supplementary Table 3: Distribution of patient characteristics

Comorbidities	HFrEF	HFmrEF	HFpEF	P value HFmrEF vs HFrEF	P value HFmrEF vs HFpEF
Hypertension	36345 (28.8%)	12242 (9.7%)	29416 (23.3%)	< 0.001	< 0.001
Diabetes mellitus	21697 (17.2%)	6529 (5.2%)	14270 (11.3%)	< 0.001	< 0.001
Kidney disease	6989 (10.8%)	2062 (3.2%)	5505 (8.5%)	0.04	< 0.001
Atrial fibrillation	23767 (18.8%)	8849 (7.0%)	18391 (14.6%)	< 0.001	0.01
CAD	31739 (27.0%)	9513 (8.1%)	14353 (12.2%)	0.002	< 0.001
NYHA class III	7748 (17.0%)	2071 (4.5%)	2511 (5.5%)	< 0.001	0.11
NYHA class IV	944 (2.1%)	196 (0.4%)	294 (0.6%)	< 0.001	0.005

HFrEF- heart failure with reduced ejection fraction; HFmrEF- heart failure with mid-range ejection fraction; HFpEF- heart failure with preserved ejection fraction; CAD- Coronary artery disease; NYHA- New York Heart Association classification

Chapter 3: Exploring the prognosis of a new phenotype– 'Mixed Cardiomyopathy'– a group of non-ischemic cardiomyopathy with concomitant moderate CAD

3.1 Preface to This Chapter

Coronary artery disease, though moderate in burden, could have a debilitating influence especially when the patients have a coexisting nonischemic cardiomyopathy. This phenotype can be termed as 'mixed cardiomyopathy', as the underlying heart disease is a mixed representation of ischemic and nonischemic etiologies. While we have clinical trials addressing the prognosis and treatment in ischemic and nonischemic forms of cardiomyopathy, the clinical phenotype of 'mixed cardiomyopathy' has not been studied. A large-scale study would be needed to understand the prognosis in this phenotype. More insights would be gained if prognosis in mixed cardiomyopathy can be compared to ischemic and nonischemic forms of cardiomyopathy. ***Hypothesis:*** The phenotype of mixed cardiomyopathy is similar to ischemic cardiomyopathy. All-cause and cardiac mortaliy in mixed cardiomyopathy patients is similar to ischemic cardiomyopathy and worse than patients with nonischemic cardiomypathy.

CHAPTER 3 HAS BEEN PUBLISHED IN PEER-REVIEWED JOURNAL

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Journal name- Journal of Interventional Cardiovascular Electrophysiology

Raja DC, Samarawickrema I, Menon SK, Singh R, Mehta A, Tuan LQ, Pandurangi U, Jain S, Callans DJ, Marchlinski FE, Abhayaratna WP, Sanders P, Pathak RK. Characteristics of the phenotype of mixed cardiomyopathy in patients with implantable cardioverter-defibrillators. J Interv Card Electrophysiol. 2023 Jun 5.

doi: 10.1007/s10840-023-01577-x. **https://link.springer.com/article/10.1007/s10840-023-01577-x**

Abstracts from this study presented to international societies: 2

Cardiology Society of ANZ 2021, Adelaide

- Survival characteristics in 566 patients receiving ICD: Real-world data from The Canberra Hospital device (TCH-ICD) registry
- Characteristics of patients and the device therapies: Real world-data from The Canberra Hospital device (TCH-ICD) registry

Citations received as on 31/10/2023- 1

Journal of Interventional Cardiac Electrophysiology
https://doi.org/10.1007/s10840-023-01577-x

Characteristics of the phenotype of mixed cardiomyopathy in patients with implantable cardioverter-defibrillators

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Received: 15 April 2023 / Accepted: 22 May 2023

Abstract

Background or Purpose The prognosis of mixed cardiomyopathy (CMP) in patients with implanted cardioverter-defibrillators (ICDs) has not been investigated. We aim to study the demographic, clinical, device therapies and survival characteristics of mixed CMP in a cohort of patients implanted with a defibrillator.

Methods The term mixed CMP was used to categorise patients with impaired left ventricular ejection fraction attributed to documented non-ischemic triggers with concomitant moderate coronary artery disease. This is a single center observational cohort of 526 patients with a mean follow-up of 8.7 ± 3.5 years.

Results There were 42.5% patients with ischemic cardiomyopathy (ICM), 26.9% with non-ischemic cardiomyopathy (NICM) and 30.6% with mixed CMP. Mixed CMP, compared to NICM, was associated with higher mean age (69.1 ± 9.6 years), atrial fibrillation (55.3%) and greater incidence of comorbidities. The proportion of patients with mixed CMP receiving device shocks was 23.6%, compared to 18.4% in NICM and 27% in ICM. The VT cycle length recorded in mixed CMP (281.6 ± 43.1 ms) was comparable with ICM (282.5 ± 44 ms; $p = 0.9$) and lesser than NICM (297.7 ± 48.7 ms; $p = 0.1$). All-cause mortality in mixed CMP (21.1%) was similar to ICM (20.1%; $p = 0.8$) and higher than NICM (15.6%; $p = 0.2$). The Kaplan–Meier curves revealed hazards of 1.57 (95% CI: 0.91, 2.68) for mixed CMP compared to NICM.

Conclusion In a cohort of patients with ICD, the group with mixed CMP represents a phenotype predominantly comprised of the elderly with a higher incidence of comorbidities. Mixed CMP resembles ICM in terms of number of device shocks and VT cycle length. Trends of long-term prognosis of patients with mixed CMP are worse than NICM and similar to ICM.

Keywords Ischemic cardiomyopathy · Nonischemic cardiomyopathy · Mixed cardiomyopathy · Implantable-cardioverter defibrillator · Device shocks · Mortality

Abbreviations

CAD	Coronary artery disease
CAG	Coronary angiogram
CKD	Chronic kidney disease
CMP	Cardiomyopathy
CMRi	Cardiac magnetic resonance imaging
DCM	Dilated cardiomyopathy
EGM	Electrogram

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3.2 Introduction

Significant progress has been made with the tools in diagnosis and management of heart failure. One of these advances is the prevention of sudden cardiac death (SCD) with implantable cardioverter-defibrillators (ICD).[86] Regardless, the long-term mortality rates in heart failure patients, even with ICD, continue to remain as high as 50% at 10 years.[87,88] These trends are worse in ischemic (ICM) than in nonischemic (NICM) forms of cardiomyopathy (CMP).[89] It may not be right to simplify the burden of coronary artery disease (CAD) in patients with cardiomyopathies as a binary component of epicardial stenosis of more than or less than 75%, and thus attribute the heart failure to ischemic or nonischemic aetiologies.[90] There is ongoing research on ways to detect ischemia in cardiomyopathies.[91] The studies on prognosis of concomitant CAD in dilated cardiomyopathies (DCM) are few and these studies have reported the prognosis of the association of CAD in only idiopathic DCM.[14,15,92] Thus, the effect of moderate CAD coexisting with DCM with definite non-ischemic triggers is largely unexplored. The resultant phenotype of 'mixed cardiomyopathy' might identify clinical and outcome characteristics that are distinct from ICM or NICM and may impact on clinical management. This phenotype is gaining attention of late and the prognosis in terms of increased ventricular arrhythmia burden seems to parallel ICM.[16,93] We aim to study the demographic, clinical, device therapies and survival characteristics of mixed CMP in a cohort of patients implanted with a defibrillator.

3.3 Methods

The Canberra Hospital (TCH) device registry is a prospectively maintained database of implanted cardiac devices. The demographic and clinical data is being recorded at scheduled clinic visits and the device data is being interrogated through scheduled or unscheduled clinic visits and remote monitoring of the devices. In this study, consecutive patients receiving an ICD between January 2005 to June 2019 who had regular interrogation (clinical or remote transmission) of the implanted ICD in the follow-up and with an invasive coronary angiogram to rule out coronary artery disease were included. The identity of these patients was linked with the National Death Index (NDI) obtained from the Australian Institute of Health and Welfare (AIHW) to confirm the survival status and cause of death. The following patients were

excluded from the study: incomplete clinical or device data; no survival data; in-hospital or immediate post-procedure (<30 days) deaths; channelopathies.

The study complies with the Declaration of Helsinki and was approved by the Human Research Ethics Committee (2019/LRE/0127) and the AIHW Ethics Committee (EO2020/1/1102). The primary objective of the study was to analyse the characteristics of the demographic variables, clinical variables, device therapies and survival data of patients receiving an ICD in patients with mixed CMP in comparison with ICM and NICM. The secondary objectives were to analyse the characteristics of clinical, device therapies and mortality in non-survivors in the total cohort and to identify the significant predictors of mortality in the total cohort.

3.3.1 Data collection

Demographic and clinical variables including history of diabetes mellitus, hypertension, chronic kidney disease (CKD), lung disease, malignancy, alcohol/ drug abuse, renal functions and echocardiographic findings including type and severity of valve pathologies were recorded. The left ventricular ejection fraction (LVEF) at implant and at the last follow-up was recorded. History of CAD, myocardial infarction (MI), percutaneous coronary intervention (PCI); history of bypass surgery, valve replacement; documented atrial and ventricular arrhythmias; list of anti-arrhythmic and heart failure medications; symptoms of syncope or sudden cardiac arrest (SCA); history of radiofrequency ablation (RFA) for VT in relation to the time of ICD implant was collected. The following device characteristics were collected: information on clinical interrogation during a scheduled clinic visit or remote transmission, type of ICD, the programming zones of the ICD, date of first and second therapy from the device, verification of the type of tachyarrhythmia and the type of therapies delivered verified with the stored intracardiac electrograms (EGMs), change in the programming parameters, ventricular tachyarrhythmia (VT) storms, minimum cycle length of the recorded VT (1st and 2nd episode was taken into account), date and number of generator changes, therapies after generator change. The survival characteristics were collected from the NDI.

3.3.2 Study definitions

1. Coronary artery disease (CAD) was defined by the presence of stenosis ≥50%

in atleast one of three major epicardial vessels or ≥30% in the left main vessel. Lesions on coronary angiography (CAG) were graded visually by two cardiologists on the following ordinal scale: 0% to <50%, ≥ 50% to <75%, ≥ 75% and 100%. The interobserver agreement for both grading of stenosis and location of CAD was calculated. The final consensus was reached upon by mutual agreement.

2. **ICM** was defined as those patients with impaired LVEF in whom there was a history of MI, evidence of prior MI in form of q-waves in ECG or regional wall motion abnormalities in echocardiogram or ≥ 75% coronary artery stenosis in one of the major epicardial vessels or ≥ 50% coronary artery stenosis in the left main coronary artery as evidenced in a diagnostic coronary angiogram (CAG).[94]

3. **NICM** was defined as those patients with depressed LV systolic function (<50%) in whom moderate to severe CAD (≥ 50% stenosis in one of the epicardial coronary vessels) was ruled out by a CAG and with no history suggestive of MI. After corroborative evidence from electrocardiography, echocardiography, cardiac MRI, PET scan and genomic assessment, the aetiopathogenesis of NICM was assigned and included the following; post-myocarditis sequelae, arrhythmogenic right ventricular cardiomyopathy, sarcoidosis, hypertrophic cardiomyopathy, infiltrative cardiomyopathy (amyloidosis, hemochromatosis), non-compaction (dilated and low LVEF associated with features of non-compaction documented by echocardiogram or cardiac MRI), valvular heart disease (severe valvular stenosis/ regurgitation leading to dilatation of heart and low LVEF), alcohol-related (documented alcohol abuse or dependence leading to deterioration in LVEF), congenital heart disease (including post-operative patients with persisting heart defects or new onset valvular diseases), tachy-cardiomyopathy, and chemotherapy-related cardiomyopathy. Patients with no known aetiology other than those stated above, but with LVEF ≤35% were classified as idiopathic dilated cardiomyopathy (DCM).

4. The term **mixed CMP** was used in this study to categorise patients with depressed LV systolic function (<50%), a documented non-ischemic aetiology and with moderate CAD (≥ 50% and < 75% stenosis) in one or more of left anterior descending artery (LAD), left circumflex artery (LCX), right coronary artery (RCA), or 30-50% stenosis involving the left main coronary artery.

5. Minimum cycle length of VT was calculated based on the least measured near-field EGM intervals in the available intracardiac traces. The average of first 10 intervals was

considered in case of unstable intervals. Additional study definitions are incorporated in the supplement.

3.3.3 Statistical analysis

Categorical variables are summarized as percentages. Normally distributed continuous data is expressed as mean ± SD and non-normally distributed data is expressed as median with interquartile range of 25^{th} and 70^{th} percentiles. For comparing variables, we used a $\chi 2$-test (categorical variables), a t-test (normally distributed continuous variables) and a Mann-Whitney U test (non-normal continuous variables). Kappa statistics were used to calculate the inter-observer variability in the extent and location of CAD detected in the coronary angiograms. Cumulative hazard and the survival curves following ICD intervention were analysed with the Kaplan-Meier survival analysis method and the statistical comparison using the log-rank test. Cox proportional hazards regression models were used to determine the predictors of survival. The co-efficients were expressed as hazard ratios with 95% confidence intervals. P value <0.05 was considered statistically significant.

3.4 Results

In this study, 526 patients were followed up for a mean period of 8.7±3.5 years. The total cohort comprised of 224 patients of ICM (42.5%), 141 patients of NICM (26.9%) and 161 patients of mixed CMP (30.6%). (**Figure 3-1**)

3.4.1 Demographic and clinical characteristics (Table 3-1)

The mean age of patients with mixed CMP (69.1±9.6 years) was higher compared to both ICM (66.3±10.9 years; p=0.008) and NICM (54.4±14.5 years; p<0.001). The mean LVEF in patients with mixed CMP (32.9±8.6%) was comparable to patients with ICM (32.7±8.3%; p=0.8) and lower compared to patients with NICM (40.9±14.2%; p<0.001). The proportion of male gender was 82% in mixed CMP, 92% in ICM and 66.7% in NICM. Patients with mixed CMP, in comparison with ICM, had lesser proportions of diabetes mellitus (33.5% vs 44.8%; p=0.03), higher proportions of alcohol abuse (22.4% vs 8%; p<0.001) and malignancy (30.4% vs 2.7%; p<0.001), and comparable proportions of hypertension, chronic lung diseases and chronic kidney diseases. (**Table 3-1; Supplemental Table 3-4**). Patients with mixed CMP, in comparison with NICM, had higher proportions of diabetes mellitus (33.5% vs 13.5%; p<0.001), systemic

hypertension (62.1% vs 36.2%; p<0.001), chronic lung disease (13% vs 2.1%; p<0.001), chronic kidney disease (22.4% vs 7.1%; p<0.001), malignancy (30.4% vs 11.3%; p<0.001) and comparable proportions of alcohol abuse (22.4% vs 17%; p=0.2).

The distribution of moderate CAD in patients with mixed CMP was LM/LAD (22.4%), LCX/RCA (1.8%), double vessel disease (56.6%) and triple vessel disease (18.6%). The level of agreement was strong (kappa=0.81 for grading of stenosis and 0.83 for location of CAD) between the two cardiologists. Coexisting nonischemic aetiologies in the patients of mixed CMP were post myocarditis sequelae (32.9%), chemotherapy-related (24.2%), tachycardiomyopathy (19.3%), alcohol-related (16.1%) and hypertrophic cardiomyopathy (7.5%). The nonischemic aetiologies in the patients of NICM were idiopathic (23%), ARVC (11%), restrictive CMP (22.7%), valvular heart diseases (12.8%), inflammatory (10.6%), chemotherapy-related (5%), tachycardiomyopathy (6.4%), alcohol-related (7.1%) and congenital heart diseases (1.4%).

The proportion of patients receiving ICD for secondary prevention in mixed CMP was 44.1% compared to 56.3% in ICM (p=0.02) and 38.3% in NICM (p=0.3). While history of sudden cardiac arrest was comparable amongst all the 3 groups (23.6% in mixed CMP, 20.5% in ICM and 16.3% in NICM), incidence of atrial fibrillation was higher in mixed CMP (55.3%) compared to ICM (28.6%; p<0.001) and NICM (30.5%; p<0.001). While usage of beta blockers was comparable amongst all 3 groups (>95%), amiodarone usage was highest in ICM (38%). With respect to the distribution of type of ICD implant, patients with mixed CMP had higher proportions of CRT-d (29.2%) compared to patients with ICM (18.4%; p=0.04) and NICM (18.4%; p=0.03).

3.4.2 *Analysis of device therapies* (Table 3-1; Supplemental Table 3-5)

The proportion of patients with mixed CMP receiving device therapies (34.2%) and device shocks (23.6%) was intermediate between ICM (device therapies 41.1%; device shocks 27.2%) and NICM (device therapies 29.1%; device shocks 18.4%). These differences were not significant between mixed CMP and the other groups. Among the patients receiving device shocks, the distribution of appropriate and inappropriate shocks was comparable between all the 3 groups. The minimum VT cycle length recorded in patients with mixed CMP (281.6 ± 43.1ms) was comparable to that in ICM (282.5 ± 44ms; p=0.9) in ICM and lesser than in NICM (297.7 ± 48.7ms; p=0.1).

3.4.3 Survival characteristics

The all-cause mortality in patients in mixed CMP (21.1%) was similar to that observed in ICM (20.1%; p=0.8) and higher than in NICM (15.6%; p=0.2). Time-adjusted survival estimated using Kaplan-Meir curves revealed hazards of 1.57 (95% CI: 0.91, 2.68; p=0.1) for mixed CMP compared to NICM. (**Figure 3-2**) The mean age at death in patients with mixed CMP (79±8years) was significantly higher than in ICM (73±12years; p=0.01) and NICM (66±14years; p<0.001). Analysis of the cause of death revealed higher proportion of non-cardiac deaths in patients with mixed CMP (52.9%), compared to ICM (26.7%; p=0.04) and NICM (18.2%; p=0.02). The distribution of heart failure related deaths and sudden cardiac deaths were similar between all the 3 groups. (**Table 3-2**)

Cox-regression analysis **(Table 3-3)** revealed the following significant predictors of mortality- age (HR: 1.04; 95% C.I: 1.02-1.06), LVEF (HR: 0.96; 95% C.I: 0.93-0.99), CKD (HR: 2.9; 95% C.I: 1.9-4.5), NYHA class (HR: 1.7; 95% C.I:1.1-2.4) and CAD (HR: 1.9; 95% C.I: 1.1-3.2). This model accounted for various confounding variables including age, gender, clinical variables, presence or absence of moderate-severe CAD and documented nonischemic triggers. Compared to the survivors in the whole cohort, the non-survivors had significantly (p<0.05) higher mean age (69.1±11.8y vs 62.7±13y), lower LVEF (29.7±6.6% vs 36.2±11.3%), higher NYHA class III (51.5% vs 19.8%), lower GFR (65.8±27.8 vs 85.5±25.2), and significantly higher incidences of comorbidities- hypertension (64.4% vs 52.9%), chronic kidney disease (46.5% vs 10%), malignancy (23.8% vs 11%). The distribution of ICM, NICM and mixed CMP was similar. (**Supplemental Table 3-6**) The proportion of patients receiving therapies was significantly higher in the non-survivors compared to the survivors (50% vs 32.3%, p= 0.001). Among the patients receiving device therapies, significantly higher proportion of patients received shocks in non-survivors compared to survivors (79.6% vs 63.7%, p=0.04).

3.5 Discussion

The salient features of our study are: 1) The phenotype of mixed CMP, when compared to NICM, is associated with higher mean age and higher incidence of comorbidities; 2) Ventricular arrhythmias in mixed CMP resembles ICM in terms of number of device shocks and VT cycle length; and 3) Trends of long-term prognosis of patients with mixed CMP is worse than NICM and similar to ICM.

3.5.1 Extent of CAD in dilated cardiomyopathy

When accounted for moderate CAD, our study reveals that at least 53% of the NICM cohort, with known nonischemic triggers, would be reclassified as mixed CMP. This cohort accounts to 30.6% of the total cohort of cardiomyopathies in our study. Cardiomyopathies with overlapping ischemic and nonischemic aetiologies is not uncommon in clinical practice.[16] In a histopathological study on hearts excised at transplantation in patients diagnosed with idiopathic DCM, coronary atherosclerosis was diagnosed in 65.5% of the hearts with 43.6% showing moderate to severe lesions.[95]

In our study, nearly 77% of the mixed CMP patients had moderate CAD in more than one epicardial vessel and the majority had double vessel involvement. Concomitant CAD in DCM has been studied previously; however, they have been largely on idiopathic DCM. In addition, the results of prognosis reported in these studies are contradictory. In a study on idiopathic DCM patients, CAD burden had significant correlation with major adverse cardiovascular events.[14] Yet another large-scale study in over 12,000 heart failure patients had also shown that the prognosis in nonobstructive CAD (<70% stenosis) is worse than in heart failure with no CAD.[92] However, a few other studies did not show differences in survival between idiopathic DCM with moderate CAD and no CAD.[15,89] Our study is different from the above studies in that it reveals poor prognosis in patients with implanted defibrillators and CMP secondary to definite nonischemic triggers and with concomitant CAD ($\geq$ 50% to < 75% stenosis). This subset has been largely excluded from the previous studies of DCM with coexisting CAD.

3.5.2 The phenotype of mixed CMP

We found mixed CMP more common in the elderly and male patients when compared to both ICM and NICM. Also, the clinical phenotype in mixed CMP seem to represent a subset of patients with higher incidences of comorbidities especially hypertension, chronic kidney diseases, atrial fibrillation and malignancies when compared to NICM. It is perceivable that these risk factors would also explain a relatively higher burden of CAD found in the group with mixed CMP compared to NICM.[96,97] This finding is also consistent with the studies on idiopathic DCM with coexisting CAD.[14,15,92] While the proportion of device therapies and device shocks in mixed CMP falls in an intermediate category between ICM and NICM, the

recorded minimum VT cycle length is comparable to patients with ICM. In a very recent study, albeit in a small cohort of 24 patients with mixed CMP undergoing catheter ablation for ventricular arrhythmias, it was shown that this subset had a higher incidence of ventricular arrhythmias and all-cause mortality than both ICM and NICM.[93] Our study reveals all-cause mortality rates of nearly 20% in both the ICM and mixed CMP cohorts. As the mean age and incidences of coexisting illnesses especially chronic kidney diseases and malignancies are higher in the cohort of mixed CMP, it is not surprising that most of the deaths in this cohort are non-cardiac, unlike the predominantly cardiac deaths in ICM and NICM. The mixed CMP group revealed higher hazards of all-cause mortality when compared to NICM (HR: 1.57; 95% CI: 0.91 to 2.68; p=0.1). In a larger study of 2254 heart failure patients with nonobstructive CAD, when compared to 2656 heart failure patients with no CAD, there was an increased hazard of cardiovascular death (HR: 1.82; 95% CI: 1.27 to 2.62; p<0.001) and all-cause mortality (HR: 1.18; 95% CI: 1.05 to 1.33; p<0.005).[92]

3.5.3 Possible pathogenesis in mixed CMP (Central Illustration- Figure 3-3)

While epicardial CAD is only one determinant of myocardial ischemia, there are multiple contributing factors: 1) Supply-demand mismatch due to the low coronary perfusion pressures in the setting of severe myocardial dysfunction, 2) Coronary microvascular dysfunction secondary to atherosclerosis, 3) Impaired myocardial metabolic control due to the underlying CMP.[98] Coronary perfusion indices like flow reserves and microvascular resistance have been shown to be associated with poor prognosis in heart failure independent of ischemic or nonischemic classification.[91,99,100] Electro anatomical mapping studies have highlighted the mixed pathophysiological substrate in this subset of mixed CMP.[40,93,101] Such mixed pathological substrates have also been documented in small-scale studies with LGE-CMRi as well as with perfusion-CMRi.[14,102,103] While these can be plausible explanations for the bad prognosis in mixed CMP, there could be several other contributing factors as well like age and coexisting illnesses.

3.6 Limitations

This is a retrospective study focussing on characterising the phenotype of mixed CMP and hence the causal relationship between moderate CAD and depressed systolic function could not be sought. Whether or not myocardial revascularisation would benefit these

patients in the presence of a demonstrable myocardial ischemia has to be explored prospectively. Also, scoring of the extent of CAD and its burden with indices or variables like focal or diffuse involvement and location is likely to throw more light into the incremental effect of each variable on the perfusion abnormality.[14,89] A larger sample size could have established statistical significance to the observed higher trends of mortality in mixed CMP compared to NICM. Finally, though this is the first study to address the phenotype of mixed CMP in patients implanted with defibrillators and hence arbitrary definitions were employed for the categorisation of mixed CMP.

3.7 Future Directives

The influence of concomitant coronary artery disease in patients with NICM cannot be underestimated. This phenotype of mixed cardiomyopathy seems to have a poor prognosis, as explored in our study. Large-scale studies focusing on this phenotype need to assess the mediators of poorer prognosis due to underlying pathophysiological substrate and the associated coexisting illnesses.

3.8 Conclusion

Our study characterizes the mixed phenotype of dilated cardiomyopathies who have established nonischemic triggers and concomitant moderate CAD, in a cohort who had received an ICD. The prognosis in patients with mixed CMP, with regards to device therapies and all-cause mortality, resembles ICM. The prognosis in patients with mixed CMP is poorer than NICM in terms of significantly higher burden of comorbidities, poorer LV functions and trend towards higher proportions of device shocks and higher mortality. The higher mortality seems to be driven by higher incidences of non-cardiac deaths thus representing a sicker subset than NICM.

3.9 Figure Legends

- **Figure 3-1** is the flow diagram illustrating the selection of the patients from the ICD registry and grouping of the cohort into the three forms of cardiomyopathy.
- **Figure 3-2 Panel A** shows the Kaplan-Meier curves of survival in the three groups of cardiomyopathies with event rates at different time intervals; **Panel B** shows the distribution of cause of deaths in the three groups of cardiomyopathies

- **Figure 3-3 Central Illustration** summarises the key findings and elaborates the possible pathogenesis in Mixed Cardiomyopathy

Table 3-1: Clinical and device therapy characteristics in the three groups of cardiomyopathies in patients with ICD implant

Variables	Total (n=526)	ICM (n=224)	NICM (n=141)	Mixed CMP (n=161)
Age at implant (years)	64±13	66.3±10.9 *	54.4±14.5	69.1±9.6 +, $
Men	432 (82.1)	206 (92) *	94 (66.7)	132 (82) +, $
Diabetes mellitus	173 (33)	100 (44.8) *	19 (13.5)	54 (33.5) +, $
Hypertension	290 (55.1)	139 (62.1) *	51 (36.2)	100 (62.1) $
Chronic lung diseases	45 (8.6)	21 (9.4) *	3 (2.1)	21 (13) $
Chronic kidney disease	91 (17.3)	45 (20.1) *	10 (7.1)	36 (22.4) $
Alcohol abuse	60 (11.4)	0 (0) *	24 (17)	36 (22.4) +
Malignancy	71 (13.5)	6 (2.7) *	16 (11.3)	49 (30.4) +, $
Atrial fibrillation	196 (37.3)	64 (28.6)	43 (30.5)	89 (55.3) +, $
Left ventricle ejection fraction (in %)	35±10.9	32.7±8.3 *	40.9±14.2	32.9±8.6 $
Estimated glomerular filtration rate	81.7±26.8	79±29 *	89±25.7	79.2±23.4 $
Coronary artery disease (≥50% stenosis)	385 (73.2)	224 (100) *	0 (0)	161 (100) $
Percutaneous coronary intervention	117 (30.7)	117 (53.2) *	0 (0)	0 (0) +
Coronary artery bypass surgery	100 (26)	100 (44.8) *	0 (0)	0 (0) +
Syncope	119 (22.6)	39 (17.4) *	45 (31.9)	35 (21.7)
Cardiac arrest	107 (20.3)	46 (20.5)	23 (16.3)	38 (23.6)
NYHA class 2	282 (53.6)	150 (67) *	56 (39.7)	76 (47.2) +, $
NYHA class 3	136 (25.9)	50 (22.3) *	33 (23.4)	53 (32.9)
Secondary prevention	251 (47.7)	126 (56.3) *	54 (38.3)	71 (44.1) +
Betablocker usage	504 (96.4)	215 (96)	133 (95.7)	156 (97.5)
Amiodarone usage	169 (32.3)	85 (37.9)	39 (28.1)	45 (28.1)
ACEi-ARB usage	383 (73.2)	174 (77.7) *	78 (56.1)	131 (81.9) $
Cardiac resynchronisation therapy	121 (23)	48 (21.4)	26 (18.4)	47 (29.2) $
Minimum VT cycle length (milliseconds)	286.8±45.6	282.5±44	297.7±48.7	281.6±43.1
Therapies received	184 (35.7)	88 (41.1) *	41 (29.1)	55 (34.2)
Shocks received	125 (23.7)	61 (27.2)	26 (18.4)	38 (23.6)
Appropriate shocks	86 (16.3)	42 (18.8)	17 (12.1)	27 (16.7)
Inappropriate shocks	39 (7.4)	19 (8.4)	9 (6.4)	11 (6.8)
Median number of therapies	5 (2, 15.8)	4.5 (1, 12)	4 (2, 16)	8 (2, 27)
VT storms	44 (8.3)	18 (8)	14 (9.9)	12 (7.4)
Generator change	96 (18.3)	40 (17.9)	31 (22)	25 (15.5)
Therapies post generator change	34 (34.7)	16 (39)	9 (29)	9 (34.6)
Time-to-first therapy (years)	2.4±2.8	2.4±2.7	2.8±3.4	2±2.3
Time-to first appropriate shock (years)	2.3±2.8	2.4±2.9	2.6±3.5	1.8±1.9

- P values <0.05 have been denoted as * for the significant differences between ICM and NICM groups, + for the significant differences between mixed CMP and ICM groups, $ for the significant differences between Mixed CMP and NICM groups
- Categorical variables have been presented as frequencies (proportions in %), Continuous variables have been presented as mean ± standard deviation with 95% confidence intervals, Medians have been presented as average (25^{th}, 70^{th} percentiles)
- ICD-Implantable Cardioverter-Defibrillator, ICM- ischemic cardiomyopathy, NICM- nonischemic cardiomyopathy, Mixed CMP- mixed cardiomyopathy, NYHA- New York Heart Association classification, VT-Ventricular tachycardia

Table 3-2: Mortality characteristics in the three groups of cardiomyopathies in patients with ICD implant

Variables	Total (n= 101)	ICM (n= 224)	NICM (n= 141)	Mixed CMP (n= 161)
Age at death (years)	70±13	73±12	66±14	79±8 [+, $]
Time-to-death (years)	5.2±3.9	5.4±4	5.4±4.1	4.7±3.5
All-cause mortality	101 (19.2)	45 (20.1)	22 (15.6)	34 (21.1)
Cardiac deaths	53 (52.5)	28 (62.2)	14 (63.6)	11 (32.4) [+, $]
Noncardiac deaths	34 (33.7)	12 (26.7)	4 (18.2)	18 (52.9) [+, $]
Multiple causes	11 (10.9)	4 (8.9)	2 (9.1)	5 (14.7)
Unknown deaths	3 (3)	1 (2.2)	2 (9.1)	0 (0)
Heart failure related	40 (39.6)	19 (42.2)	11 (50)	10 (29.4)
Arrhythmia related	23 (22.8)	12 (26.7)	5 (22.7)	6 (17.6)
Unknown cardiac deaths	1 (0.1)	1 (2.2)	0 (0)	0 (0)

- P values <0.05 have been denoted as + for the significant differences between mixed CMP and ICM groups, $ for the significant differences between Mixed CMP and NICM groups
- Categorical variables have been presented as frequencies (proportions in %), Continuous variables have been presented as mean ± standard deviation with 95% confidence intervals
- ICD-Implantable Cardioverter-Defibrillator, ICM- ischemic cardiomyopathy, NICM- nonischemic cardiomyopathy, Mixed CMP- mixed cardiomyopathy

Table 3-3: Cox-regression stepwise model for significant predictors of mortality

Variables*	Hazards ratio	95% C.I (lower)	95% C.I (upper)	P value
Age at time of ICD implant	1.04	1.02	1.06	<0.001
Chronic kidney disease	2.93	1.89	4.51	<0.001
NYHA class	1.65	1.13	2.41	0.01
Coronary artery disease $	1.88	1.11	3.17	0.02
Left ventricular ejection fraction	0.96	0.93	0.99	0.03

* Other nonsignificant variables in the model: male gender, diabetes mellitus, hypertension, chronic lung diseases, malignancy, alcohol abuse, history of ventricular tachycardia or sudden cardiac arrest and documented nonischemic triggers

$ Coronary artery disease represents angiography-detected epicardial stenosis ≥50%

ICD- Implantable Cardioverter-Defibrillator, NYHA- New York Heart Association classification

FIGURES

Figure 3-1 is the flow diagram illustrating the selection of the patients from the ICD registry and grouping of the cohort into the three forms of cardiomyopathy.

Figure 3-1: The selection of the patients from the ICD registry

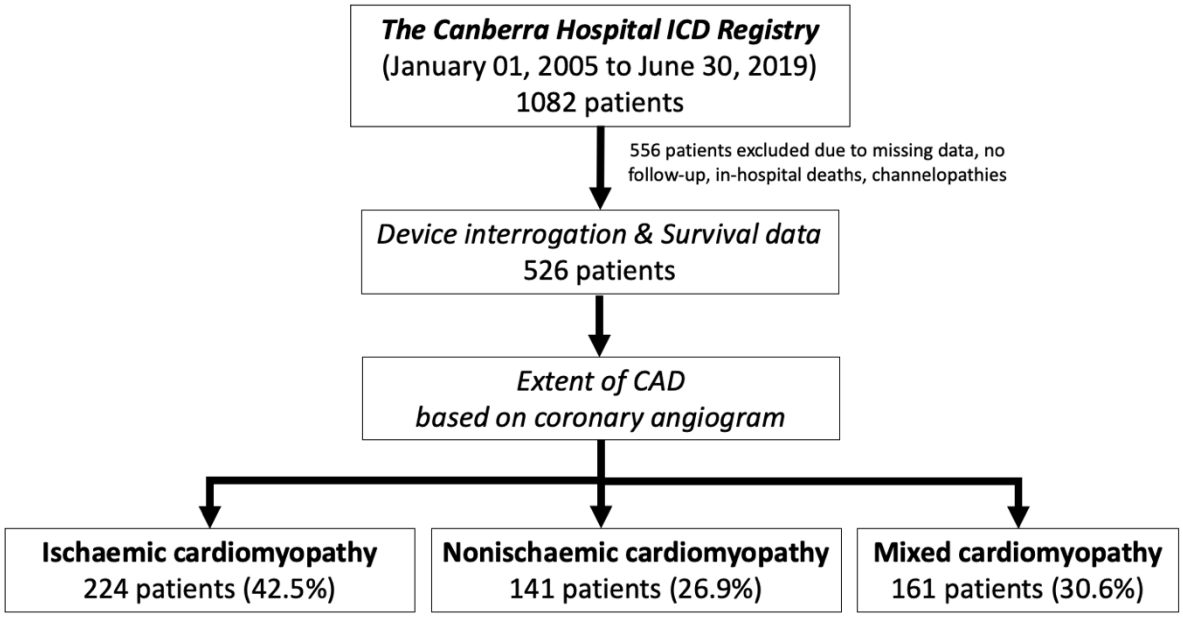
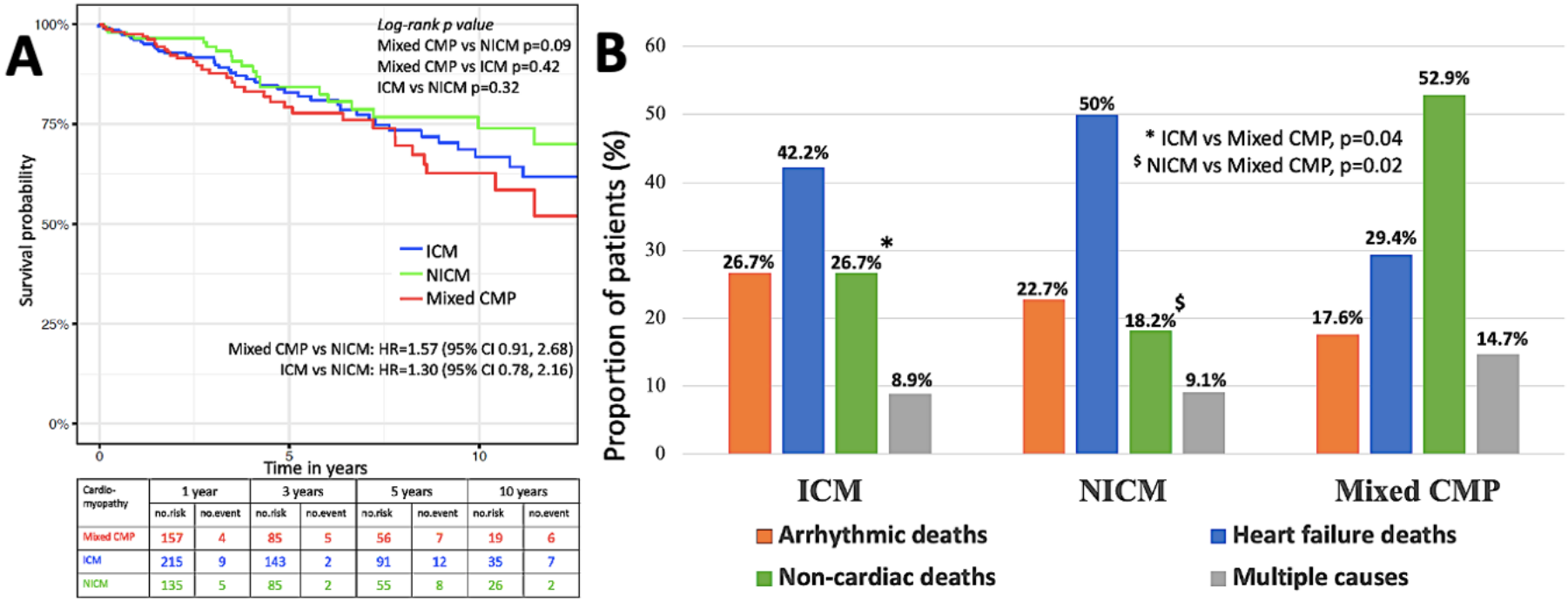


Figure 3-2 Panel A shows the Kaplan-Meier curves of survival in the three groups of cardiomyopathies with event rates at different time intervals; **Panel B** shows the distribution of cause of deaths in the three groups of cardiomyopathies

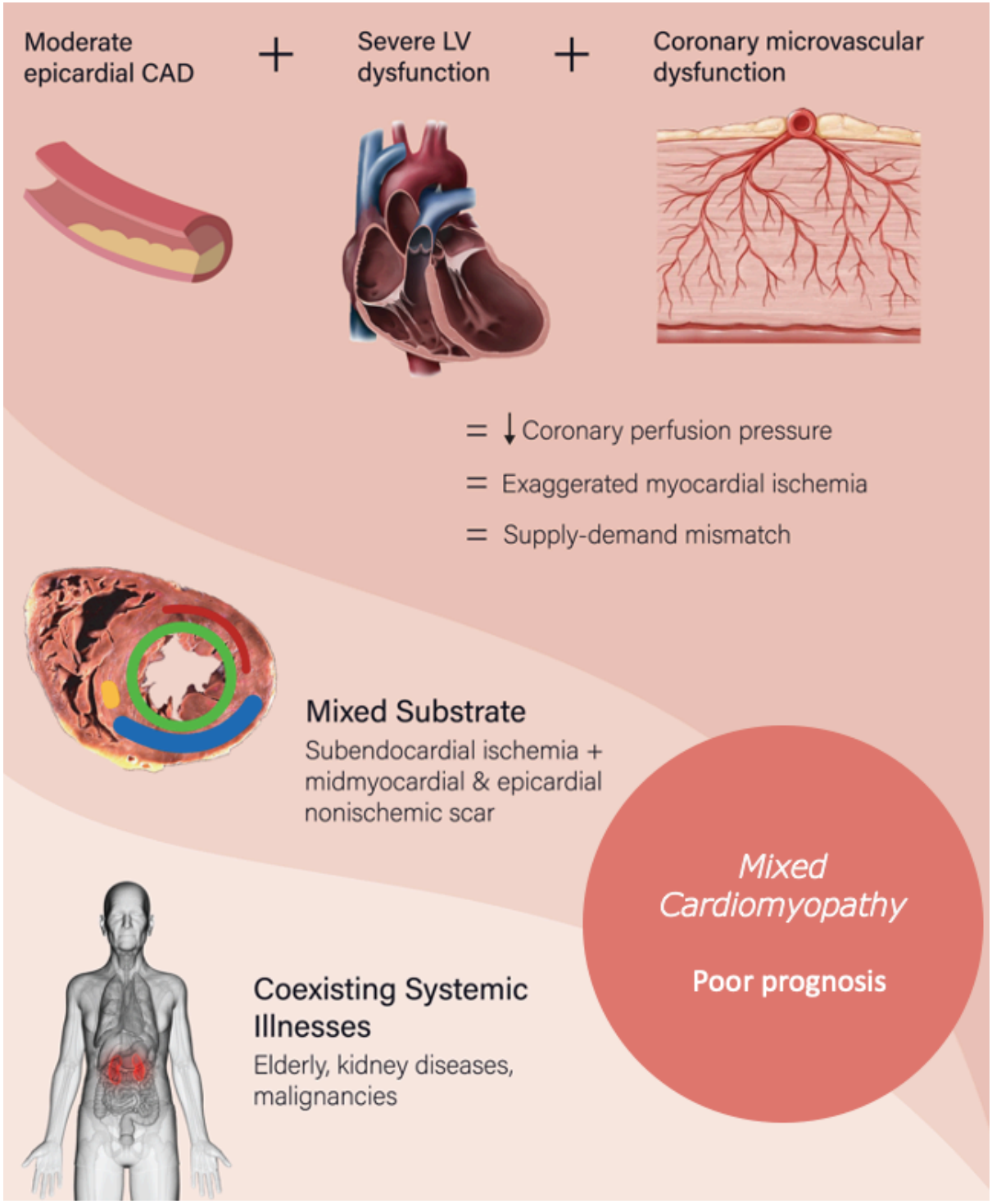
Figure 3-2: a) The Kaplan-Meier curves of survival; b) The distribution of cause of deaths



Cardio-myopathy	1 year		3 years		5 years		10 years	
	no.risk	no.event	no.risk	no.event	no.risk	no.event	no.risk	no.event
Mixed CMP	157	4	85	5	56	7	19	6
ICM	215	9	143	2	91	12	35	7
NICM	135	5	85	2	55	8	26	2

Figure 3-3 Central Illustration summarises the key findings and elaborates the possible pathogenesis in Mixed Cardiomyopathy

Figure 3-3: Mixed Cardiomyopathy



SUPPLEMENTARY MATERIAL

Inclusion criteria:

1. All patients who received an ICD anytime from January 01, 2005 until June 30, 2019 at the Canberra hospital.
2. Patients who had atleast one interrogation (clinical or remote transmission) of the implanted ICD in the follow-up.
3. Patients who had an invasive coronary angiogram to rule out coronary artery disease.

Exclusion criteria:

1. Those patients with not even one interrogation of the implanted ICD in the follow-up were excluded for analysis of device therapies.
2. Those patients with an in-hospital or 30-day mortality after the procedure were excluded for analysis of survival characteristics.
3. Those patients with incomplete hospital records limiting collection of any meaningful clinical data.

Data collection:

1. Name, age, gender, treating physician, history of diabetes, hypertension, chronic kidney disease (CKD), lung disease, malignancy, alcohol/ drug abuse.
2. Kidney functions namely serum creatinine and estimated glomerular filtration rate (eGFR) and echocardiographic findings including type and severity of valve pathologies, left ventricular ejection fraction (LVEF) at implant were recorded. LVEF at the last follow-up was recorded.
3. History of coronary artery disease (CAD)/ myocardial infarction (MI)/ type of MI- ST elevation (STEMI) and non-ST elevation (NSTEMI)/ percutaneous coronary intervention (PCI)/ history of bypass surgery/ valve replacement/ major non-vascular surgeries.
4. Documented arrhythmias- supraventricular (inclusive of atrial flutter and fibrillation) and ventricular (shockable rhythms like ventricular fibrillation, monomorphic and polymorphic ventricular tachycardias).
5. List of anti-arrhythmic and heart failure medications.
6. Symptoms of syncope or sudden cardiac arrest (SCA) or documented VT.
7. Categorization of patients into inherited channelopathies or cardiomyopathies were

done as per study definitions.

8. History of radiofrequency ablation (RFA) for SVT and VT in relation to the time of ICD implant.
9. Device characteristics: information on clinical interrogation during a scheduled clinic visit or remote transmission, type and manufacturer of ICD, complications during implant, the programming zones of the ICD, date of first and second therapy from the device, verification of the type of tachyarrhythmia and the type of therapies delivered verified with the stored intracardiac electrograms (EGMs), change in the programming parameters, minimum cycle length of the recorded ventricular tachyarrhythmia (both 1^{st} and 2^{nd} episode), VT storms, date and number of generator changes, therapies after generator change.
10. Survival characteristics: Survival data as of end of June 2020, cause and date of death.

Study definitions:

1. Syncope was defined as a witnessed episode of loss of consciousness associated with loss of postural tone with spontaneous recovery.
2. Sudden cardiac arrest (SCA) was defined as out-of-hospital events of successful cardio-pulmonary resuscitation with or without direct current shocks delivered by an external cardioverter-defibrillator.
3. Non-sustained ventricular tachycardia (NSVT) was defined as ≥ 3 consecutive ventricular premature beats with a rate >100 beats/min, lasting < 30s and without hemodynamic instability. NSVT should have been documented during exercise testing, loop monitoring or 24-h Holter monitoring.
4. Diabetes mellitus and hypertension were considered if the patient was on long standing medications for treatment of these conditions.
5. Chronic kidney disease was diagnosed if the patients were already categorised so by the treating physician based on evidence of kidney damage like elevated serum creatinine or reduced estimated glomerular filtration rate (<60ml/mt/1.73sq.mt) with or without ongoing haemodialysis.
6. Chronic lung disease was diagnosed if the patients were already categorised so by the treating physician based on evidence of suggestive clinical symptoms requiring treatment for the same.
7. Malignancy was diagnosed if the patients were already categorised so by the treating

physician based on evidence of clinical symptoms, biochemical markers or imaging evidence requiring one or more of chemotherapy or radiation therapy or surgical removal. The organ involved was also noted.

8. Coronary artery disease (CAD) was defined by the presence of stenosis ≥50% in atleast one of three major epicardial vessels or ≥30% in the left main vessel. Lesions on coronary angiography (CAG) were graded visually by two cardiologists on the following ordinal scale: 0% to <50%, ≥ 50% to <75%, ≥ 75% and 100%. The interobserver agreement for both grading of stenosis and location of CAD was calculated. The final consensus was reached upon by mutual agreement.
9. Primary prevention of SCD referred to use of ICDs in individuals who are at risk for but have not yet had an episode of sustained VT, VF or cardiac arrest. Patients with inducible VT on electrophysiology studies, but with no documented evidence of prior VT were also categorised under primary prevention.
10. Secondary prevention referred to an indication for an ICD exclusively for patients who have survived one or more cardiac arrests or sustained ventricular tachycardia.
11. Device therapies were recorded as events of either shock or anti-tachycardia pacing (ATP) delivered by the device. Number of patients receiving therapies, shocks, appropriate and inappropriate shocks, and number of each therapy per patient were noted.
12. Appropriate ICD therapy was defined as an intervention (either shock or antitachycardia pacing) triggered by a ventricular arrhythmia classified as a true event by two separate cardiac electrophysiologists.
13. Appropriate ICD shock was defined as an ICD shock triggered by a sustained ventricular arrhythmia.
14. Inappropriate ICD shock was defined as ICD shock triggered by non-sustained ventricular arrhythmias, supraventricular arrhythmias, sinus tachycardia, oversensing, or device malfunction (such as lead fracture leading to inappropriate shocks).
15. VT storm was used to denote 3 or more separate therapies either in form of ATP or shock delivered by the device in a 24-hour interval.
16. Device-related complications were grouped under pocket revisions due to local infection or hematoma, lead revisions including lead extractions and reimplantation due to pacemaker-related infection or lead malfunctions (dislodgement, fracture,

insulation break, cardiac perforation) or lead repositioning, and generator replacements due to malfunctions.

17. Follow-up duration was calculated from time of implant to the latest date of data interrogation.
18. Time to therapy was calculated from time of implant to first device therapy.
19. Time to death was calculated from time of implant to death.
20. Time to generator change was calculated from time of implant to time of first generator change.
21. Comorbidity index was used as a composite scale ranging from 1 to 5 inclusive of diabetes mellitus, hypertension, chronic kidney disease, chronic lung disease and malignancy
22. All-cause mortality was recorded as death due to any cause retrieved from the National Death Index (NDI). Cardiac and noncardiac deaths were defined respectively based on the recorded causes of death in the NDI. Heart failure and arrhythmia-related deaths were the only causes of the recorded cardiac deaths.

SUPPLEMENTARY TABLES

Table 3-1: Supplementary table- Clinical characteristics in the three groups of cardiomyopathies in patients with ICD implant

Variables	Total (n=526)	ICM (n=224) Group A	NICM (n=141) Group B	Mixed CMP (n=161) Group C	P value A vs B	P value A vs C	P value B vs C
Age (years)	64±13	66.3±10.9	54.4±14.5	69.1±9.6	<0.001	0.008	<0.001
Male	432 (82.1)	206 (92)	94 (66.7)	132 (82)	<0.001	0.004	0.003
Diabetes mellitus	173 (33)	100 (44.8)	19 (13.5)	54 (33.5)	<0.001	0.03	<0.001
Hypertension	290 (55.1)	139 (62.1)	51 (36.2)	100 (62.1)	<0.001	1	<0.001
Chronic lung diseases	45 (8.6)	21 (9.4)	3 (2.1)	21 (13)	0.01	0.3	<0.001
CKD	91 (17.3)	45 (20.1)	10 (7.1)	36 (22.4)	0.001	0.6	<0.001
Alcohol abuse	60 (11.4)	0 (0)	24 (17)	36 (22.4)	<0.001	<0.001	0.2
Malignancy	71 (13.5)	6 (2.7)	16 (11.3)	49 (30.4)	0.001	<0.001	<0.001
Atrial fibrillation	196 (37.3)	64 (28.6)	43 (30.5)	89 (55.3)	0.7	<0.001	<0.001
LVEF at baseline	35±10.9	32.7±8.3	40.9±14.2	32.9±8.6	<0.001	0.8	<0.001
Creatinine	94.5±45.9	101.5±54	84.6±37.5	93.1±38	0.002	0.09	0.06
GFR	81.7±26.8	79±29	89±25.7	79.2±23.4	0.001	0.9	0.001
CAD	385 (73.2)	224 (100)	141 (100)	161 (100)	<0.001	-	<0.001
MI	216 (41)	216 (96)	0 (0)	0 (0)	-	-	-
PCI	117 (30.7)	117 (53.2)	0 (0)	0 (0)	<0.001	<0.001	-
CABG	100 (26)	100 (44.8)	0 (0)	0 (0)	<0.001	<0.001	-
Primary prevention	270 (52.3)	98 (43.8)	87 (61.7)	90 (55.1)	0.001	0.02	0.3
Secondary prevention	251 (47.7)	126 (56.3)	54 (38.3)	71 (44.1)			
NYHA class 2	282 (53.6)	150 (67)	56 (39.7)	76 (47.2)	<0.001	0.001	0.001
NYHA class 3	136 (25.9)	50 (22.3)	33 (23.4)	53 (32.9)			
NYHA class 4	4 (0.8)	1 (0.4)	0 (0)	3 (1.9)			
History of syncope	119 (22.6)	39 (17.4)	45 (31.9)	35 (21.7)	0.02	0.5	0.2
Cardiac arrest	107 (20.3)	46 (20.5)	23 (16.3)	38 (23.6)	0.3	0.5	0.2
Documented VT	165 (31.4)	88 (39.3)	34 (24.1)	43 (26.7)	0.002	0.002	0.4
Betablocker usage	504 (96.4)	215 (96)	133 (95.7)	156 (97.5)	0.9	0.5	0.5
Amiodarone usage	169 (32.3)	85 (37.9)	39 (28.1)	45 (28.1)	0.07	0.05	1
ACEi-ARB usage	383 (73.2)	174 (77.7)	78 (56.1)	131 (81.9)	<0.001	0.3	<0.001
VT ablation	56 (10.6)	27 (12.1)	16 (11.3)	13 (8.1)	0.9	0.2	0.4

Categorical variables are expressed in number (proportion in %); Continuous variables are expressed as mean ±SD with 95% confidence intervals; ICD- Implantable Cardioverter-Defibrillator; ICM- ischaemic cardiomyopathy; NICM- nonischaemic cardiomyopathy; Mixed CMP- mixed cardiomyopathy; CKD- chronic kidney disease; LVEF- left ventricular ejection fraction; CAD- coronary artery disease; MI- myocardial infarction; PCI- percutaneous coronary intervention; CABG- coronary artery bypass surgery; NYHA- New York heart association; VT- ventricular tachycardia; ACEi- angiotensin converting enzyme inhibitor; ARB- angiotensin receptor blocker

Table 3-2: Supplementary table- Device therapy characteristics in the three groups of cardiomyopathies in patients with ICD implant

Variables	Total (n=526)	ICM (n=224) Group A	NICM (n=141) Group B	Mixed CMP (n=161) Group C	P value A vs B	P value A vs C	P value B vs C
Single chamber	196 (37.3)	81 (36.2)	59(41.8)	56 (34.8)	0.04	0.3	0.06
Dual chamber	190 (36.1)	90 (40.2)	46 (32.6)	54 (33.5)			
CRT	121 (23)	48 (21.4)	26 (18.4)	47 (29.2)	0.5	0.09	0.03
Remote monitoring	194 (36.9)	70 (31.3)	59 (41.8)	65 (40.4)	0.04	0.06	0.8
Pacemaker type 1 complications	9 (1.7)	5 (2.2)	1 (0.7)	3 (1.8)	0.2	0.2	0.3
Pacemaker type 2 complications	23 (4.3)	9 (4.1)	8 (5.6)	6 (3.7)			
Pacemaker type 3 complications	6 (1.1)	5 (2.2)	1 (0.7)	0 (0)			
Min VT Cycle length (millisec)	286.8±45.6	282.5±44	297.7±48.7	281.6±43.1	0.1	0.9	0.09
Therapies	184 (35.7)	88 (41.1)	41 (29.1)	55 (34.2)	0.04	0.3	0.3
Shocks received	125 (23.7)	61 (27.2)	26 (18.4)	38 (23.6)	0.05	0.3	0.4
Appropriate shocks received	86 (16.3)	42 (18.8)	17 (12.1)	27 (16.7)	0.09	0.6	0.2
Inappropriate shocks received	39 (7.4)	19 (8.4)	9 (6.4)	11 (6.8)	0.5	0.6	0.9
No. of therapies	5 (2, 15.8)	4.5 (1, 12)	4 (2, 16)	8 (2, 27)	0.3	0.5	0.2
No. of shocks	3 (1, 8.5)	3 (1, 9)	4 (2, 7)	3 (2, 8.5)	0.3	0.4	0.6
No. of approp. shocks	4 (2, 9)	4 (1, 9)	5 (3, 16)	3 (2, 8)	0.8	0.8	0.1
No. of inapprop. shocks	2 (1, 3)	1 (1, 3)	2 (1, 2)	3.5 (1, 6.5)	0.8	0.2	0.1
VT storms	44 (8.3)	18 (8)	14 (9.9)	12 (7.4)	0.9	0.9	0.7
No. of VT storms	1 (1, 2)	1 (1, 2.3)	1 (1, 2.3)	1.5 (1, 2)	0.9	0.7	0.6
No. of AADs	1 (1, 2)	1 (1, 2)	1 (1, 1)	1 (1, 1)	0.01	0.01	0.8
Box change	96 (18.3)	40 (17.9)	31 (22)	25 (15.5)	0.3	0.6	0.2
No. of box changes	1 (1, 1)	1 (1, 1)	1 (1, 1)	1 (1, 1)	0.9	0.8	0.8
Therapies post box change	34 (34.7)	16 (39)	9 (29)	9 (34.6)	0.5	0.8	0.7
Time to device therapy (years)	2.4±2.8	2.4±2.7	2.8±3.4	2±2.3	0.5	0.5	0.3
Time to approp. shock (years)	2.3±2.8	2.4±2.9	2.6±3.5	1.8±1.9	0.7	0.2	0.2

Categorical variables are expressed in number (proportion in %); Continuous variables are expressed as mean ±SD with 95% confidence intervals; No. are presented in medians (25^{th}, 70^{th} percentiles)
ICD- Implantable Cardioverter-Defibrillator; CRT- Cardiac resynchronisation therapy; AAD- antiarrhythmic drugs; Type 1 complications- pocket infection/ erosion/ hematoma/ device extraction; Type 2 complications- lead revision/ fracture/ perforation; Type 3 complications- generator malfunction; VT- ventricular tachycardia; No- number; Approp.- appropriate; Inapprop.- inappropriate

Table 3-3: Supplementary table- Clinical and device therapy characteristics in survivors and nonsurvivors in patients with ICD implant

Variables	Survivors	Nonsurvivors	P value	Variables	Survivors	Nonsurvivors	P value
Age (years)	62.7±13	69.1±11.8	<0.001	Single chamber	153 (36)	43 (42.6)	0.2
Male	345 (81.2)	87 (86.1)	0.3	Dual chamber	154 (36.2)	36 (35.6)	
Diabetes	136 (32.1)	37 (36.6)	0.4	CRT	99 (23.3)	22 (21.8)	0.8
Hypertension	225 (52.9)	65 (64.4)	0.04	Pacemaker type I complications	8 (22.2)	1 (50)	0.6
COPD	29 (6.8)	16 (15.8)	0.005	Pacemaker type 2 complications	22 (61.1)	1 (50)	
CKD	44 (10)	47 (46.5)	<0.001	Pacemaker type 3 complications	6 (16.7)	0 (0)	
Alcohol abuse	57 (13.4)	3 (3)	0.01	Therapies received	135 (32.3)	49 (50)	0.001
Malignancy	47 (11.1)	24 (23.8)	0.003	Shocks received	86 (63.7)	39 (79.6)	0.04
AF	152 (35.8)	44 (43.6)	0.2	Appropriate shocks received	55 (66.3)	30 (83.3)	0.08
LVEF	36.2±11.3	29.7±6.6	<0.001	Inappropriate shocks received	28 (33.7)	6 (16.7)	0.07
GFR	85.5±25.2	65.8±27.8	<0.001	VT storms	26 (6)	18 (17.8)	<0.001
Cardiac arrest	84 (19.8)	23 (22.8)	0.5	Min VT CL-ms	292.5±46	269.4±38	0.007
Syncope	94 (22.1)	25 (24.8)	0.7	Box change	70 (17.6)	21 (20.8)	0.5
Documented VT	124 (29.2)	41 (40.6)	0.1	Therapies post box change	22 (28.9)	12 (54.5)	0.04
ICM	179 (42.1)	45 (44.6)	0.6	No. of therapies	4 (2, 13)	6 (2, 25.5)	0.2
NICM	119 (28)	22 (21.8)	0.2	No. of shocks	3 (1, 9)	3 (2, 8)	0.9
Mixed CMP	127 (29.9)	34 (33.7)	0.4	No. of approp. shocks	3 (1, 10)	4.5 (2, 9)	0.5
CAD	306 (72)	79 (78.2)	0.2	No. of inapprop. shocks	2 (1, 4.5)	1 (1, 3)	0.8
PCI	97 (31.9)	20 (26)	0.3	No of VT storms	1 (1, 3)	1 (1, 2)	0.8
CABG	80 (26.1)	20 (25.6)	0.9	No of box changes	1 (1, 1)	1 (1, 1)	0.5
Noncardiac surgeries	10 (2.4)	6 (5.9)	0.09	Time to first approp. shock	2.3±3	2.3±2.5	0.9
Secondary prevention	193 (45.4)	58 (57.4)	0.03	No of AADs	1 (1, 2)	1 (1, 2)	0.1
NYHA II	242 (56.9)	40 (39.6)	<0.001	Betablocker usage	405 (95.7)	99 (99)	0.2
NYHA III/IV	86 (20.3)	54 (53.5)		ACEi-ARB usage	308 (72.8)	70 (70)	0.7

Categorical variables are expressed in number (proportion in %); Continuous variables are expressed as mean ±SD with 95% confidence intervals; No. are presented in medians (25^{th}, 70^{th} percentiles)
ICD- Implantable Cardioverter-Defibrillator; COPD- Chronic obstructive pulmonary disease; CKD- chronic kidney disease; AF- atrial fibrillation; LVEF- left ventricular ejection fraction; GFR- estimated glomerular filtration rate; VT- ventricular tachycardia; ICM- ischaemic cardiomyopathy; NICM- nonischaemic cardiomyopathy; Mixed CMP- mixed cardiomyopathy; CAD- coronary artery disease; PCI- percutaneous coronary intervention; CABG- coronary artery bypass surgery; NYHA- New York heart association; CRT- cardiac resychronisation therapy; Type 1 complications- pocket infection/ erosion/ hematoma/ device extraction; Type 2 complications- lead revision/ fracture/ perforation; Type 3 complications- generator malfunction; CL- cycle length in milliseconds (ms); No.- number; Approp.- appropriate; Inapprop.- inappropriate; ACEi- angiotensin converting enzyme inhibitor; ARB- angiotensin receptor blocker; AAD- antiarrhythmic drugs

Chapter 5: Search for a Cardiac MRI Tool to Correlate with Invasive Electroanatomical Mapping Variables

5.1 Preface to This Chapter

A screening tool for risk-stratification should be easily available at an affordable cost so that it can be used to risk-stratify patients. While Late Gadolinium Enhancement (LGE) by Cardiac MRI (CMR) has been extensively studied as a prognostic tool in patients with non-ischemic cardiomyopathy (NICM), the limitations of LGE being a subjective assessment and false negativity with patchy, diffuse deep intramural scars are also well known. Alternative CMR tools like T1 mapping, ECV estimation, CMR-strain are being explored in this respect. In our study, we explored the possibility of using CMR-derived myocardial strain. We have studied CMR-strain compared to LGE for correlation with LV ejection fraction and invasively derived endocardial unipolar voltages in patients with ventricular tachycardia.

Hypothesis: Cardiac MRI-derived circumferential, longitudinal and radial strain has good correlation with LV ejection fraction and LV endocardial unipolar and bipolar voltage. The classification rate of Cardiac MRI-derived strain parameters is better than LGE-detected scar for detection of LV endocardial unipolar and bipolar low voltage zones.

CHAPTER 5 HAS BEEN PUBLISHED IN PEER-REVIEWED JOURNAL

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Correlation of myocardial strain by CMR-feature tracking with substrate abnormalities detected by electro-anatomical mapping in patients with nonischemic cardiomyopathy

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Abstract

Background Late gadolinium enhancement (LGE) detected by cardiac MRI (CMR) has low correlation with low voltage zones (LVZs) detected by electroanatomical mapping (EAM). We aim to study correlation of myocardial strain by CMR- Feature Tracking (FT) alongside LGE with LVZs detected by EAM.

Methods Nineteen consecutive CMRs of patients with EAM were analyzed offline by CMR-FT. Peak value of circumferential strain (CS), longitudinal strain (LS), and LGE was measured in each segment of the left ventricle (17-segment model). The percentage of myocardial segments with CS and LS > −17% was determined. Percentage area of LGE-scar was calculated. Global and segment–wise bipolar and unipolar voltage was collected. Percentage area of bipolar LVZ (<1.5 mV) and unipolar LVZ (<8.3 mV) was calculated.

Results Mean age was 62±11 years. Mean LVEF was 37±13%. Mean global CS was −11.8±5%. Mean global LS was −11.2±4%. LGE-scar was noted in 74% of the patients. Mean percentage area of LGE-scar was 5%. There was significant correlation between percentage abnormality detected by LS with percentage bipolar LVZ ($r = +0.5$, $p = 0.03$) and combined percentage CS+LS abnormality with percentage unipolar LVZ ($r = +0.5$, $p = 0.02$). Per-unit increase in CS increased the percentage area of unipolar LVZ by 2.09 ($p = 0.07$) and per-unit increase in LS increased the percentage area of unipolar LVZ by 2.49 ($p = 0.06$). The concordance rates between CS and LS to localize segments with bipolar/unipolar LVZ were 79% and 95% compared to 63% with LGE.

Conclusions Myocardial strain detected by CMR-FT has a better correlation with electrical low voltage zones than the conventional LGE.

Keywords Electroanatomical mapping · Cardiac magnetic resonance imaging · Myocardial strain · Circumferential strain · Longitudinal strain · Low voltage zone

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5.2 Introduction

Cardiac magnetic resonance (CMR) imaging is one of the most important diagnostic tools for characterization of myocardial diseases.[115] Late gadolinium enhancement (LGE) detected by CMR has shown to predict ventricular arrhythmic events in dilated non-ischemic cardiomyopathy (NICM).[85] However, the correlation of LGE with substrate abnormalities detected by invasive electroanatomical mapping (EAM) is modest in NICM.[44] Studies have noted that 52% of EAM-scars in the RV and 36% of EAM-scars in the LV can be missed by LGE.[44,116] This is mainly because of the inability of LGE to detect the complex scar patterns in NICM.

Novel CMR parameters such as T1 mapping have recently been shown to be better predictors of the intramural concealed fibrosis seen in NICM.[48] Myocardial deformation parameters studied by CMR-strain imaging have the ability to detect deep intramural mechanical abnormalities within the myocardium of the left ventricle (LV).[117] Moreover, CMR-strain is a reproducible measure which has been shown to have strong association with clinical outcomes such as death and SCD in dilated CMP.[33] However, CMR-strain has never been correlated with electrical abnormalities detected by EAM. In this study, we sought to investigate the correlation of global and segment-wise CMR-strain parameters along with the LGE-scar analysis with global and segment-wise low voltage zones picked up by EAM.

5.3 Methods

Our study population consisted of consecutive patients with NICM enrolled prospectively for CMR studies presenting to the Canberra Heart Rhythm Centre, in the period between November 2019 and November 2021. The patients underwent invasive electrophysiological studies with voltage mapping and radiofrequency ablation when deemed necessary. The diagnosis of NICM was made with corroborative evidence of LV dysfunction (LV ejection fraction <50%), in the absence of significant coronary artery disease (>50% stenosis as assessed by coronary angiography). The following categories of NICM were excluded: congenital heart diseases; hypertrophic cardiomyopathy; arrhythmogenic right ventricular cardiomyopathy (ARVC); and LV noncompaction. In addition, pacing-dependent patients, persistent/long standing atrial fibrillation patients were excluded for the study. The study was

conducted as per the ethical guidelines of the Declaration of Helsinki and was approved by the Human Research and Ethics Committee of The Canberra Hospitals. (2019/ETH13256)

5.3.1 CMR acquisition protocol

CMR was performed on a 1.5 T scanner (Ingenia; Philips Healthcare, the Netherlands) with a cardiac phased-array receiver surface coil and electrocardiogram (ECG) gating. For the assessment of LV functions, cine imaging was performed by using a steady-state free precession (SSFP) sequence in the vertical long axis, horizontal long axis and short axis. In patients with devices, Turbo Spin echo for cine imaging was used when significant susceptibility artifact was present on SSFP imaging. Patients with significant artifacts due to devices were excluded from the study. Pacing-dependent patients were excluded from the study. In patients with cardiac resynchronization devices, biventricular pacing was on. Standard parameters were repetition time/echo time 3.6/1.8 ms; sense factor 2, flip angle-60°; section thickness- 8 mm; field of view- 300 mm. For scar assessment, LGE images covering the entire LV were acquired approximately 15 minutes after an intravenous injection of 0.2 mmol/kg gadobenate dimeglumine contrast agent. The LGE-images were acquired using a magnitude inversion-recovery (IR) or phase sensitive inversion recovery (PSIR) gradient-recalled echo sequence with 8.0mm slice thickness. A wideband LGE sequence was used to minimize artifacts from the battery pack in subjects with device implants.

5.3.2 Myocardial strain and LGE-scar assessment by CMR

All the CMR studies were analysed offline by using a dedicated software called the Segment Medviso version 3.3 RX[118] (**www.medviso.com/segment**). The base and the apex of the LV were defined from the short-axis slices. The endocardial and epicardial borders were traced manually in the short axis, apical 3-chamber long-axis, apical 2-chamber long-axis and apical 4-chamber long-axis images in end-diastole and end-systole. Adequate precaution was exercised to avoid blood pool contamination and to exclude the papillary muscles. CMR studies with poor image quality or missing slices were excluded from the analysis. Segmentation of the LV into the standard 17-segments was carried out by the software.[119] LV dimensions, volume, mass and LVEF were estimated automatically. Myocardial strain was measured throughout the cardiac cycle by myocardial Feature-Tracking (FT).[120] The peak measurements of three strain parameters – circumferential strain, radial strain, and

longitudinal strain – were considered for analysis. Global and segment-wise strain values were extracted from the software. Circumferential strain and radial strain were measured from 16 segments (excluding apical segment). Longitudinal strain was measured from all 17 segments. The strain measurements were performed in a blinded fashion by two experienced analysts.

Inter-observer reproducibility of all the three strain parameters was studied. Due to high inter-observer variability with radial strain, only circumferential strain and longitudinal strain were considered for localization of abnormalities in each segment. Peak circumferential strain and longitudinal strain values of >-17% were considered abnormal. This cut-off was chosen arbitrarily based on multiple studies reporting outcomes with the same cut-offs.[30,33,121,122] However, there are no existing large-scale studies which have validated abnormal segmental strain values. The number of abnormal segments were counted for circumferential strain, longitudinal strain and composite of circumferential strain and longitudinal strain (circumferential + longitudinal strain). Percentage abnormal myocardium was derived as a proportion of abnormal segments. LGE-scar was determined in each segment by the EWA-algorithm.[123] Automatic delineation of scar borders was performed and was verified by an experienced CMR-analyst. The percentage area of LGE-scar for the total LV and in each segment was extracted from the software. Segmental circumferential strain, longitudinal strain and percentage area of LGE-scar was displayed on a 17-segment color polar plots.

5.3.3 Electro-anatomical mapping and catheter ablation

A systematic protocol for EAM was followed uniformly in all patients. All antiarrhythmic drugs were discontinued routinely at least 5 half-lives before the procedure. Three-dimensional (3D) left ventricular geometry was reconstructed by intracardiac echocardiography (ICE; 64-element, 5.5 to 10Hz; SOUNDSTAR™, CARTOSOUND™ module Biosense Webster, La Jolla, California, USA). EAM of the endocardial LV was performed using the CARTO 3 Version 7 mapping system (Biosense Webster) using a multi-electrode mapping catheter (PENTARAY™, Biosense Webster). The geometry created using ICE was registered to an endocardial 3D shell of LV acquired by the mapping catheter. High density mapping of the LV was performed at all the segments of the LV. The low voltage zones were addressed further by point-by-point mapping using a deflectable 3.5-mm irrigated-tip mapping catheter with contact force (THERMOCOOL SMARTTOUCH-SF™, Biosense Webster) during sinus rhythm. In

patients with cardiac resynchronization devices, biventricular pacing was on. Geometry, bipolar and unipolar electrograms (EGMs) were simultaneously recorded and all segments of the ventricle were sampled. The mitral and aortic annuli were defined by ICE. In addition, the mitral annulus was verified as that with a 1:1 ratio between atrial and ventricular electrograms. Low voltage points acquired with <3g contact force, <10mm from the endocardial shell, points with unstable cycle length, points within 1 cm of the aortic and mitral valve annulus were all excluded from analysis. Bipolar signals were filtered at 30 to 400 Hz. Unipolar signals were measured between the tip electrode and Wilson-central terminal and were filtered at 1 to 240 Hz. The fill threshold was set to 10 mm.

Ventricular Tachycardia (VT) induction was attempted in all patients with programmed ventricular stimulation with triple extrastimuli from at least two right ventricular or LV sites with at least two drive cycle lengths. Induced VTs were identified as clinical if they matched the cycle length and morphology of the stored electrograms from the ICD or the 12-lead ECG when available. VT entrainment was performed if the VTs were hemodynamically stable. Pace mapping at threshold was performed to match the inducible VT, in case the VT was hemodynamically unstable or non-sustained and repetitive. Substrate modification was performed at the regions of good pace map, aiming at elimination of local abnormal ventricular activity potentials, late potentials, and low amplitude fractionated electrograms. The contact force catheter was also used for ablation. The primary endpoint for ablation was elimination of the clinical VT and monomorphic nonclinical VT.

5.3.4 Segmental analysis of EAM data

The raw EAM datasets were exported from the CARTO system and imported into an EP Lab Research Works application (www.eplabworks.com). Automatic annotation of all EGMs and automatic segmentation of the LV into 17-segments was performed. The landmarks for LV segmentation were set in cooperation with 2 experienced electrophysiologists. The EGM analysis was performed in each segment. Annotation of all electrograms were individually reviewed. Low voltage and scar regions were defined based on standard abnormal values for bipolar low voltage zones (Bi-LVZ; <1.5 mV), bipolar scar (Bi-Scar; <0.5mV) and unipolar low voltage zone (Uni-LVZ; <8.3 mV).[37,111] The bipolar and unipolar low voltage maps were displayed on 17-segment color polar plots. The extent of the low voltage zones in the entire endocardial surface as well as in each segment were quantified as endocardial surface area

(cm^2) and proportion (%) of abnormal to the total LV endocardial surface area and proportion (%) of the abnormal area within each segment.

5.3.5 Clinical follow-up

The duration of follow-up was calculated from the time of the EAM study. The patients were followed up every 6 months at the heart failure out-patient clinic, or earlier if symptomatic. All patients with device implants were followed up with remote monitoring-based device interrogations every month. Device therapies were reviewed for appropriateness by experienced cardiac electrophysiologists.

5.3.6 Statistical analysis

Continuous variables which were normally distributed were expressed as mean±SD. Categorical variables were presented as proportions in percentages. The inter-observer variability was assessed with Bland-Altman analysis, coefficient of variation (CV) and the 95% limits of agreement (LOA) were studied for the dispersion around the mean. The correlation was tested by Spearman's rank coefficients for parameters detected by CMR and % bipolar LVZs and by Pearson's correlation for parameters detected by CMR and % unipolar LVZs. Correlation values were ranked as mild (0-0.3), moderate (0.4-0.6) and high (0.7-1.0). Linear regression models were studied for each variable, to determine the increase of LVZ per-unit increase in the independent variable. Student-t test was carried out to identify the differences in the mean LVZ in the patients with and without VT. The 17-segment bull's eye maps of the CMR circumferential strain, CMR longitudinal strain, CMR LGE, bipolar voltage EAM and unipolar voltage EAM were used for side-by-side comparisons. The segmental abnormalities detected by LGE, abnormal circumferential strain and abnormal longitudinal strain in each patient was classified as concordant with EAM, if the segments also had bipolar/ unipolar voltage abnormalities. The concordance rates were thus presented as proportion of correct classifications. Differences, correlation-coefficients, and the odds ratio were considered statistically significant at the two-sided $p < 0.05$ level. All the analyses were performed using STATA 17.0 (STATA Corporation, Texas, USA).

5.4 Results

5.4.1 Study recruitment and patient characteristics

In the period from November 2019 to November 2021, 44 patients of NICM who underwent CMRs, were screened for enrolment. Of these, based on the exclusion criteria for the study, the following category of NICM patients (n=25) were excluded: pacing-dependent (n=6); persistent atrial fibrillation (n=4); hypertrophic cardiomyopathy (n=4); ARVC (n=3); non-compaction (n=2); congenital heart disease (n=2). Due to artifacts from existing leads in patients with device implants resulting in poor quality of the CMR images, 4 patients were excluded for the offline analysis.

The characteristics of the 19 patients included in the study are summarized in Table 1. The mean age was 61.8±11 years. Fifty eight percent were male. The categories of NICM patients included in the analysis were: idiopathic dilated cardiomyopathy (n=10); presumed sarcoidosis based on clinical in addition to findings on CMR and PET-CT scan imaging (n=4); PVC cardiomyopathy with 24-hour PVC burden>20% (n=4); alcoholic cardiomyopathy (n=1). Diabetes was prevalent in 21% and hypertension in 26% of patients. Among the heart failure medications, 84% were on betablockers, 68% on neprilysin/ angiotensin converting enzyme inhibitor/ angiotensin receptor blockers; 32% on aldosterone blockers. In addition to betablockers, amiodarone was used in 4 patients and mexiletine was used in 2 patients with history of VT. The mean LVEF was 37.4±13%. LVEF <35% was noted in 42% patients. Ablation was performed in 58% patients, defibrillator was implanted in 53% and cardiac resynchronization devices were implanted in 26% patients.

5.4.2 CMR-strain, LGE-scar and EAM characteristics (Table 2)

Mean peak global circumferential strain was -11.8±4.5%, mean peak global radial strain was +22.4±8.7% and mean peak longitudinal strain was -11.2±3.8%. Among the three measures of strain, the inter-observer variability was highest with peak radial strain (LOA -37.9–8.1; CV 17.3%) followed by peak longitudinal strain (LOA 2.2-19; CV 9.3%) then peak circumferential strain (LOA 2.4–19.9; CV 5.4%). Hence, peak longitudinal and peak circumferential strain was considered for further analysis. Percentage segmental abnormalities detected was 75±20% with circumferential strain, 70±16% with longitudinal

strain and 54±20% with the composite of circumferential + longitudinal strain. LGE-scar was detected in 63% patients (n=12), of whom 75% had patchy scar in a single focus and 25% had multifocal scar. Among the 7 patients with no LGE-scar, 5 patients had idiopathic dilated cardiomyopathy and 2 patients had presumed PVC-cardiomyopathy. The mean % total LGE-scar area was 5%, ranging between 1.3% – 11%. The distribution of LGE was predominantly mid-myocardial in 50% cases, epicardial in 25% cases, transmural in 17% cases and subendocardial in 8% cases. Septal LGE was detected in 67% patients, free wall in 25% patients and combined (septal and free wall) in 8% patients.

Bipolar LVZ was detected in 12 (63%) patients and unipolar LVZ was detected in all the 19 patients (100%). Mean percentage area of bipolar LVZ was 29±22%. Mean percentage area of unipolar LVZ was 37.5±22.5%. The most common locations of electrical LVZ were basal anteroseptal (63%) followed by basal inferolateral (53%), basal anterolateral (42%), and mid anterior (32%) segments. The segmental values of circumferential strain, longitudinal strain, radial strain, LGE-scar, mean bipolar voltage, mean unipolar voltage and percentage area of bipolar and unipolar LVZ are presented in ***Supplementary Table 5-4***.

5.4.3 Correlation between myocardial strain, LGE-scar by CMR and low voltage zones by EAM

(Supplementary Table 5-5; Figure 5-1)

Moderate correlation (p=0.07) was noted between % unipolar LVZ and global circumferential strain (r=+0.4), and between % unipolar LVZ and global longitudinal strain (r=+0.4). Percentage segmental abnormalities detected with longitudinal strain had significant correlation with % area of bipolar LVZ (r=+0.5; p=0.03). Percentage segmental abnormalities detected with a combined circumferential and longitudinal strain had significant correlation with % area of unipolar LVZ (r=+0.5; p=0.02). Percentage area of LGE-scar showed insignificant correlation with both % area of bipolar LVZ (r=+0.2; p=0.2) and % area of unipolar LVZ (r=+0.3; p=0.2).

The linear regression analysis revealed a positive relationship between global circumferential strain and global longitudinal strain with % area of unipolar LVZ– one unit increase in global circumferential strain increased the % area of unipolar LVZ by 2.09 (p=0.07) and one unit increase in global longitudinal strain increased % area of unipolar LVZ by 2.49

(p=0.06). However, there was no strong relationship between global circumferential strain and global longitudinal strain with % area of bipolar LVZ.

5.4.4 Localization of segmental abnormalities with myocardial strain (Table 5-3, Figure 5-2, Figure 5-3)

The concordance rate between LGE-scar and bipolar LVZ was 50%. The concordance rate between LGE-scar and electrical abnormalities detected by either bipolar or unipolar LVZ was 63%. Segmental abnormalities of peak circumferential strain had higher concordance rates than LGE-scar, with bipolar LVZ (75%). Similarly, segmental abnormalities of peak circumferential strain had concordance rate of 79% with electrical abnormalities detected by either bipolar or unipolar LVZ. Segmental abnormalities of peak longitudinal strain had better concordance rates than LGE-scar and peak circumferential strain, with bipolar LVZ (92%) and with electrical abnormalities detected by either bipolar or unipolar LVZ (95%). While accounting for combined abnormalities in segmental circumferential and longitudinal strain, the concordance rate was 83% with segmental bipolar LVZ and 89% with segmental bipolar or unipolar LVZ.

5.4.5 Clinical outcomes

Induction of VT by invasive electrophysiological study was performed in all the patients. Overall, 3 patients had hemodynamically stable monomorphic VTs, and 13 patients had repetitive non-sustained monomorphic VTs or hemodynamically unstable VTs. The mean number of monomorphic VTs induced per patients was 1.1$\pm$0.73. Bipolar and unipolar low voltage zones were detected in all the patients with inducible VT. VT ablation in form of substrate modification of the low voltage zones was performed in 16 patients. Acute success, as defined by non-inducibility of VT, was achieved in all the patients who had induction of VT. There were no major complications. In patients with no history of VT (n=8), 5 patients had inducible VT. In these 5 patients with inducible VT, but with no history of VT, only 2 had detectable LGE-scar, while all these patients had abnormal CMR circumferential and longitudinal strain.

The mean follow-up period was 14$\pm$3 months. There were no deaths reported in the cohort. Device therapies were noted in 32% patients. Patients with VT had higher % area of

unipolar LVZ (47±7%) than those without VT (27±5%; p=0.05). There was no significant difference in the means of other variables in patients with and without VT.

5.5 Discussion

The salient findings of our study are: 1) Global circumferential and longitudinal strain has moderate correlation with percentage area of bipolar and unipolar LVZs; 2) Percentage segmental abnormality detected with combined circumferential and longitudinal strain has good correlation with percentage area of unipolar LVZs; 3) Localization of abnormalities with CMR-FT strain resulted in better concordance rates of 89% with a composite of circumferential and longitudinal strain compared to only 63% with LGE, for detection of bipolar or unipolar LVZs.

5.5.1 Basis for investigating beyond LGE in NICM

The distribution of fibrosis in NICM is complex. A histological validation of fibrosis patterns in NICM showed patchy and/or diffuse distribution.[53] The interstitial fibrosis predominantly involves the basal septal, and basal inferolateral segments of the LV.[39,49] The endocardial bipolar voltages are more sensitive to changes in the subendocardium.[111] However, the substrate in NICM is more likely to be in the deeper myocardial layers like mid-myocardium and epicardium which are more likely to be represented by reduction in the unipolar voltages.[40] LGE has been the conventional modality to detect myocardial scarring. Whilst LGE has an excellent diagnostic value in detection of macroscopic scars as in ischemic cardiomyopathy, it is insensitive to pick up microscopic and diffuse distribution of scars as in NICM.[124] Moreover, detection of LGE relies on the visual assessment of regional differences in uptake of gadolinium.[44] At cut-offs of unipolar voltage <8.3 mV, LGE had a low diagnostic value with sensitivity and specificity of 78% and 43% respectively to detect these low voltage zones.[52]

The architecture of the LV myocardium is such that the subendocardial and epicardial fibers are longitudinally oriented and the midmyocardial fibers are circumferentially oriented. Considering the more common mid-wall patchy distribution of scar in NICM, circumferential strain is likely to pick up these abnormalities.[117] Longitudinal strain is sensitive to abnormalities in the subendocardium and epicardium.[30,117] A composite of these strain measures is likely to be more representative of the underlying myocardial abnormalities. In

our study, the percentage abnormal myocardium of only longitudinal strain had good correlation with percentage bipolar-LVZ. The composite of circumferential and longitudinal strain had good correlation with percentage unipolar-LVZ.

5.5.2 Correlation of CMR-strain with LVZs in NICM (Figure 5-2)

The highlight of our study is the higher concordance rate of myocardial strain compared to LGE to detect electrical abnormalities. In patients with right ventricle cardiomyopathies, the correlation between LGE and EAM-LVZs was only 48%. In the same study, 91% of patients with percentage area of EAM-LVZ <20% had no LGE, and endomyocardial biopsy was considered a better tool to correlate with EAM-LVZs.[116] LGE may fail to detect any level of fibrosis variably between 31-70% patients with NICM.[44] In a study on 90 patients with non-ischemic LV ventricular tachycardia/ventricular premature depolarizations, LGE-to-EAM voltage discordance was noted in 36% patients.[44] In our study, the concordance rates between LGE-scar and the EAM-LVZs was only 63%. In 80% of patients, with percentage area bipolar or unipolar LVZ <20%, there was no LGE. In addition, the percentage area of LGE-scar had poor correlation with the percentage bipolar and percentage unipolar LVZs.

5.5.3 Methods to measure myocardial deformation

Myocardial strain analysis can be performed by speckle-tracking echocardiography (STE) as well. In a recent study, endocardial longitudinal strain by STE correlated strongly with percentage bipolar low voltage zone and mid-myocardial longitudinal strain correlated strongly with percentage unipolar low voltage zone. In the same study, the concordance rate for regional abnormalities of strain with the LVZs was 75%.[30] As myocardial contraction occurs circumferentially and radially as well, it is likely that circumferential strain, which was not measured in the study, would have improved the concordance rates. While myocardial strain measured by both STE and CMR-FT have good agreement, the reproducibility of CMR-strain is better owing to the high intrinsic contrast and better delineation of blood-endocardial tissue borders.[117] Myocardial strain can also be measured by tissue tagging methods like fast strain-encoded MR (fast-SENC). Fast-SENC has recently been investigated in a large cohort of patients with heart failure and has shown to be predictive of poorer clinical outcomes like death and heart failure hospitalisations.[33] In our study, strain analysis was performed by CMR-FT. The

advantage of this technique is that this can be applied to standard cine exams retrospectively and does not require additional time-consuming sequences (as for CMR tagging).[120] Also, myocardial strain by CMR-FT has reasonable agreement with tissue tagging methods.[122]

Alternative CMR diagnostic tools, such as T1 mapping and ECV estimation, are being explored to see whether they better correlate with electrical abnormalities in NICM. In a study on 36 patients with dilated cardiomyopathy, native T1 mapping values and ECV estimation had strong correlation with the collagen fraction noted in the biopsy and was better than LGE in detection of diffuse microscopic fibrosis.[125] In another study with 50 NICM patients with negative LGE, there was a significant inverse correlation between T1 values and the extent of both bipolar and unipolar low voltage areas.[125]

In a large cohort of patients with NICM, the presence of LGE and epicardial or transmural distribution of LGE were significant predictors of ventricular arrhythmic events across different strata of LVEF.[85] Though our study was not adequately powered to detect ventricular arrhythmia events and all-cause mortality, large scale studies looking at CMR parameters beyond LGE like CMR strain and T1 mapping values are necessary to ascertain the prognostic significance of these variables.[124]

5.6 Limitations

The results of the study should be interpreted in the context of the relatively small sample size of the study and small number of events over follow-up. The cut-off of -17% applied for segmental strain abnormalities was the same as for global strain values, however this needs large scale validation. CMR analysis might not be accurate in patients with bundle branch blocks (5 patients) and high PVC burden (4 patients), though this number was small in this study. This study did not test strain measurements by tissue tagging methods, such as Fast-SENC strain. CMR-FT, despite its distinct advantages, is subject to through-plane motion artefacts. This study did not test other CMR measures like T1 mapping values, assessment of ECV and perfusion scores. Further studies are needed to determine whether these investigations can complement LGE in the risk stratification for sudden cardiac death. Since the introduction of 8.3mV as the cut-off for defining unipolar low voltage zones, a lot of studies have retained this value. We have also used the same cut-off for defining the unipolar low voltage zones. However, these cut-off values are likely to change, while using high-density mapping with multi-electrode catheters.

5.7 Future Directives

CMR-strain, T1 mapping, ECV estimation can all be tools to complement LGE-assessment and thus a composite CMR-tool can give higher diagnostic accuracies for detection of the substrate in NICM. Such CMR-risk scores can then be prospectively studied in patients for association with VT and SCD in NICM.

5.8 Conclusion

Our study concludes that abnormal myocardial strain detected by CMR-FT method is more closely related to electrical abnormalities, than the conventional LGE detected by CMR. Localization of low voltage zones with CMR-strain has better concordance than LGE. Thus, CMR-strain can inform the operator about specific regions of substrate abnormalities during a VT ablation procedure, especially in the absence of LGE scar. Our study emphasizes the need to look beyond LGE detected by CMR with novel parameters such as CMR-strain while correlating with the LV electrical abnormalities.

5.9 Figure Legends

- **Figure 5-1** Panel A shows the correlation between percentage abnormalities detected with longitudinal strain and percentage area of bipolar low voltage zone (LVZ); Panel B shows the correlation between percentage abnormalities detected with combined circumferential + longitudinal strain and percentage area of unipolar low voltage zone (LVZ).
- **Figure 5-2 Case demonstration:** Panel A shows the bipolar voltage map by electroanatomical mapping in a patient of non-ischemic cardiomyopathy with low voltage zones in the superior and inferior basal and mid-interventricular septum; Panels B and C show the localization of the bipolar and unipolar low voltage zones respectively in the same patient on the segmental polar plots; Panel D shows the late gadolinium enhancement (yellow box) in the basal anteroseptum. Also seen in the inset is the segmental representation of LGE in the polar plot; Panels E and F show the segmental distribution of peak longitudinal and circumferential strain respectively in this patient with abnormalities detected in the entire basal and mid septum

- **Figure 5-3 Case demonstration:** Panel A shows the bipolar voltage map by electroanatomical mapping in a patient of non-ischemic cardiomyopathy with low voltage zones in the inferolateral basal left ventricle; Panel B shows the unipolar voltage map by electroanatomical mapping in the same patient with low voltage zones in the anterolateral and inferolateral basal left ventricle; Panels C and D show the polar plot of segmental distribution of peak longitudinal and circumferential strain respectively in this patient which correlates with both the bipolar and unipolar low voltage zones. Cardiac Magnetic Resonance imaging with late gadolinium enhancement had failed to detect any abnormality in this region

Figure 5-1 Panel A shows the correlation between percentage abnormalities detected with longitudinal strain and percentage area of bipolar low voltage zone (LVZ); Panel B shows the correlation between percentage abnormalities detected with combined circumferential + longitudinal strain and percentage area of unipolar low voltage zone (LVZ).

Figure 5-1: a) Correlation between percentage abnormalities detected with longitudinal strain and percentage area of bipolar low voltage zone (LVZ); b) Correlation between percentage abnormalities detected with combined circumferential + longitudinal strain and percentage area of unipolar low voltage zone (LVZ)

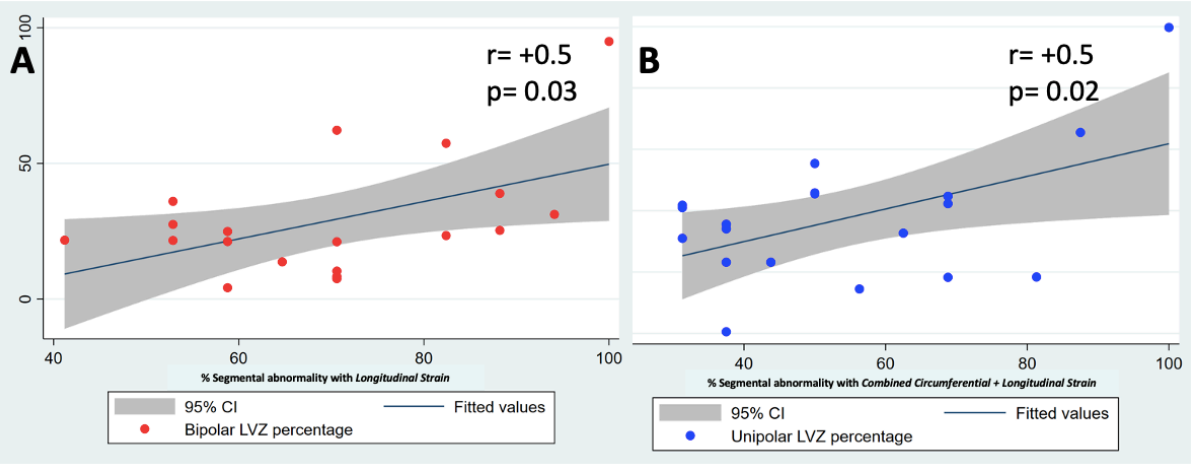


Figure 5-2 Case demonstration: Panel A shows the bipolar voltage map by electroanatomical mapping in a patient with septal low voltage zones; Panels B and C show the localization of the bipolar and unipolar low voltage zones respectively on the segmental polar plots; Panel D shows the late gadolinium enhancement (yellow box) in the basal anteroseptum. Also seen in the inset is the segmental representation of LGE in the polar plot; Panels E and F show the segmental distribution of peak longitudinal and circumferential strain respectively

Figure 5-2: a) The bipolar voltage map by electroanatomical mapping; b) The late gadolinium enhancement (yellow box) in the basal anteroseptum

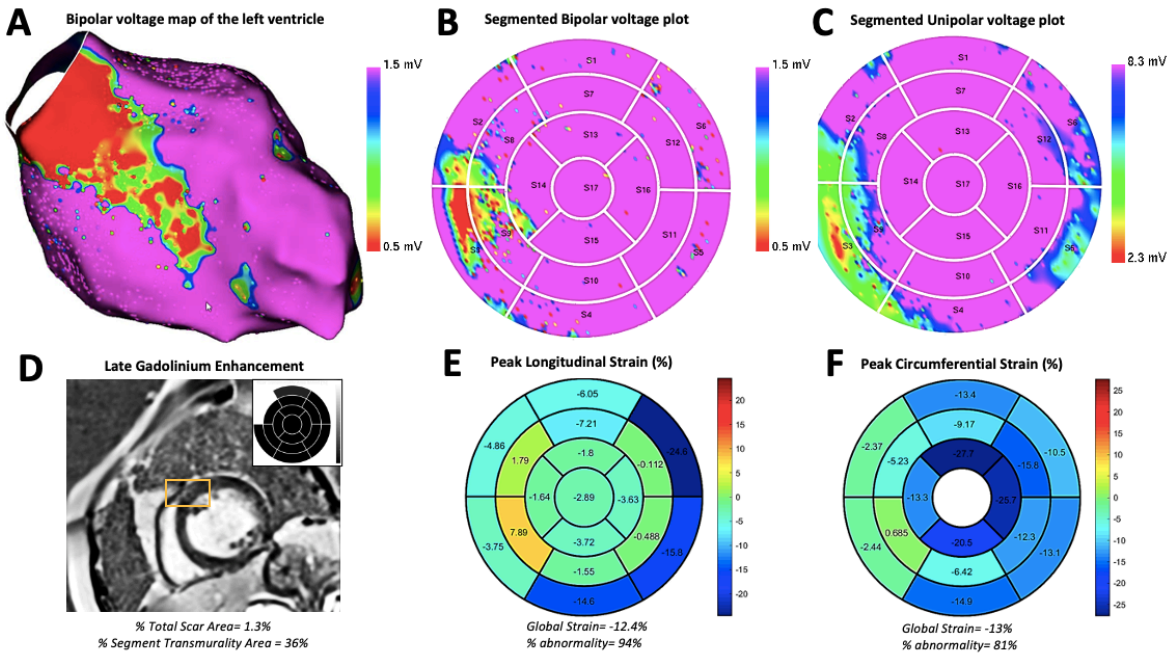


Figure 5-3 Case demonstration: Panel A shows the bipolar voltage map by electroanatomical mapping in a patient of non-ischemic cardiomyopathy with low voltage zones in the inferolateral basal left ventricle; Panel B shows the unipolar voltage map by electroanatomical mapping in the same patient with low voltage zones in the anterolateral and inferolateral basal left ventricle; Panels C and D show the polar plot of segmental distribution of peak longitudinal and circumferential strain respectively in this patient which correlates with both the bipolar and unipolar low voltage zones. Cardiac Magnetic Resonance imaging with late gadolinium enhancement had failed to detect any abnormality in this region

Figure 5-3: Case demonstration

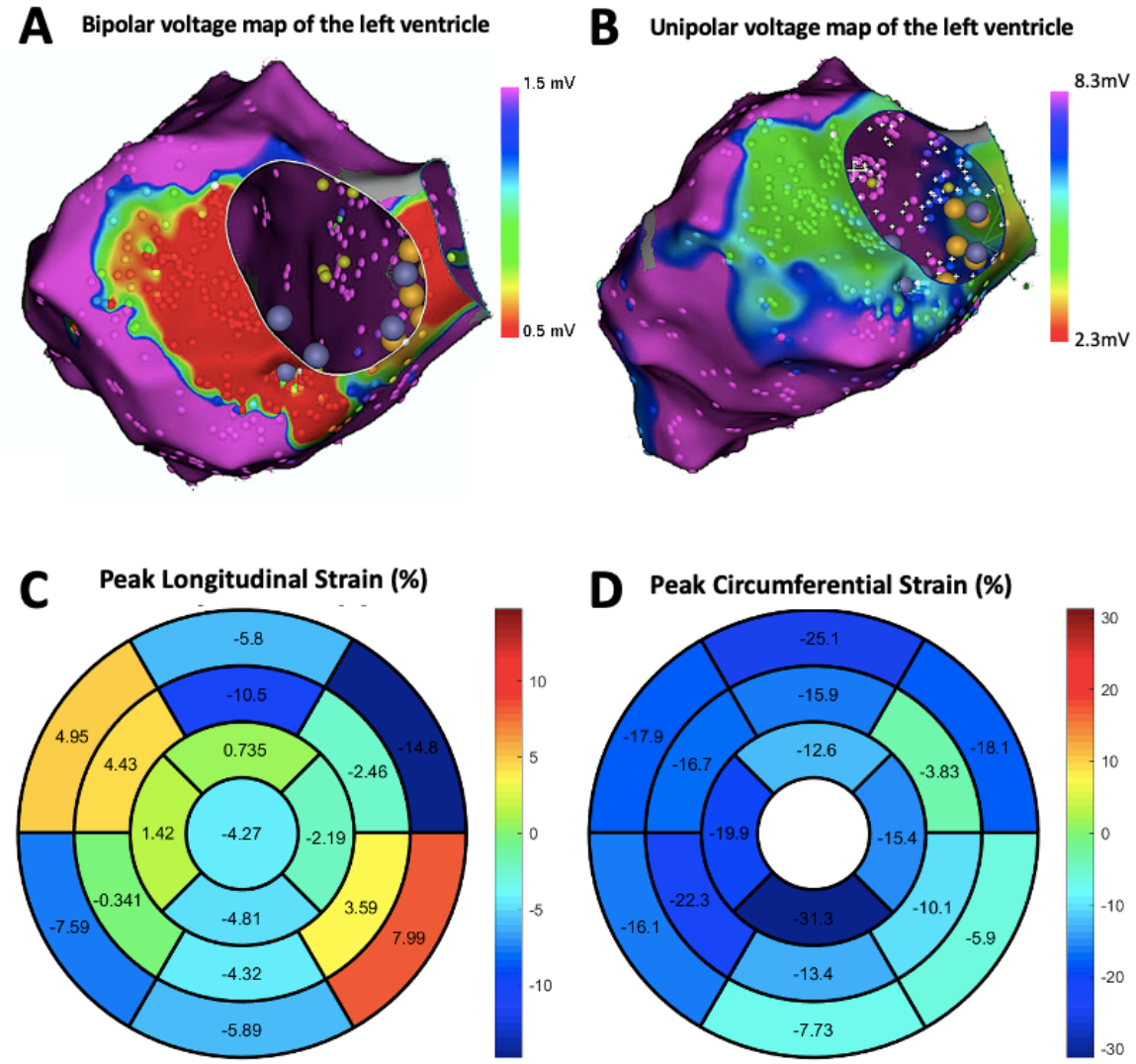


Table 5-1: Demographic and clinical variables in patients with nonischemic cardiomyopathy

Variable (n=19)	Frequency (Proportion)	Variable (n=19)	Frequency (Proportion)
Age, years	61.8±11.2	Diabetes	4 (21.1%)
Men	11 (57.9%)	Hypertension	5 (26.3%)
Chest pain	2 (10.5%)	Mean EDD (mm)	48±14
Dyspnoea	13 (68.4%)	Mean ESD (mm)	32±9
Syncope	4 (21.1%)	Mean LVEF, %	37.4±12.7
Duration of symptoms, months	13.1±12.4	LVEF <35%	8 (42.1%)
NYHA I	4 (21.1%)	Hb, g/L	143.9±13.4
NYHA II	12 (63.2%)	Creatinine, μmol/L	85.5±20.9
NYHA III	3 (15.8%)	eGFR, ml/min/m^2	74.8±13.6
History of AF	3 (15.8%)	ICD	10 (52.6%)
History of VT	11 (57.9%)	CRTd	5 (26.3%)
Inducible VT	16 (84%)	Beta blockers	16 (84.2%)
VT ablation	16 (84%)	ARNi/ ACEi/ARB	13 (68.4%)
Serum BNP (pg/ml)	158±126	Spironolactone	6 (31.6%)
QRS>120ms (LBBB)	5 (26.3%)	Amiodarone/ Mexiletene	4 (21%)/ 2 (11%)
QRS≤120ms	14 (74%)	Failed antiarrhythmic drugs	6 (32%)

Values are mean ± SD or n (%)

Abbreviations: SD- standard deviation, Hb- haemoglobin, eGFR – estimated glomerular filtration rate, AF- atrial fibrillation, VT – Ventricular tachycardia, BNP- Brain Natriuretic Peptide, LBBB- left bundle branch block, EDD- End-diastolic diameter, ESD- End-systolic diameter, LVEF- LV Ejection fraction, Hb- Hemoglobin, eGFR_ estimated glomerular filtration rate, ICD – implantable cardiac defibrillators, CRTd – cardiac resynchronization therapy device, ARNi- angiotensin receptor and neprilysin inhibitor, ACE – angiotensin-converting enzyme, ARB- angiotensin II receptor blocker,

Table 5-2: Description of variables analysed from cardiac MRI and Electroanatomical mapping

CMR variables	Frequency (Proportion)	EAM variables	Frequency (Proportion)
Mean LV EDVi	93.3±26.3	Mean number of data points	1046.7±897.1
Mean LV ESVi	60±28.4	Mean LV surface area, sq.cm	143.9±41.8
Mean LV mass, grams	151.7±69.3	Map density, per sq.cm	8.7±8.9
Peak global circumferential strain, %	-11.8±4.5	Mean bipolar voltage, mV	2.9±0.2
Peak global radial strain, %	+22.4±8.7	Mean unipolar voltage, mV	10.3±0.6
Peak global longitudinal strain, %	-11.2±3.8	Mean % area of bipolar LVZ	29.0±22.1
Mean, % segmental abnormality (CS)	75.3±20.0	Mean % area of unipolar LVZ	37.5±21.5
Mean % segmental abnormality (LS)	70.0±15.9	**Location of bipolar/ unipolar LVZ (in order of frequency)**	
Mean % segmental abnormality (CS + LS)	54.3±20.4	Basal anteroseptal	12 (63%)
LGE-scar	12 (63%)	Basal inferolateral	10 (53%)
Focal LGE-scar	9 (75%)	Basal inferoseptal	9 (47%)
Multifocal LGE-scar	3 (25%)	Basal anterolateral	8 (42%)
Endocardial/ Mid-myocardial/ Epicardial/ Transmural LGE-scar	1 (8%)/ 6 (50%)/ 3 (25%)/ 2 (17%)	Mid anterior	6 (32%)
Septal/ Free wall/ Combined	8 (67%)/3 (25%)/1 (8%)	Basal anterior	5 (26%)
Mean scar mass, grams	9.3±8.3	Basal inferior	4 (21%)
Mean scar volume, ml	8.9±7.9	Mid anteroseptal	4 (21%)
Mean % LGE-scar area	4.0±3.9		

Values are mean ± SD or n (%)
Abbreviations: SD- standard deviation, CMR- Cardiac Magnetic Resonance imaging, EAM- electroanatomical mapping, LV- left ventricle, CS- circumferential strain, LS- longitudinal strain, LGE- late gadolinium enhancement, bipolar LVZ- low voltage zone <1.5mV, unipolar LVZ- low voltage zone <8.3mV

Table 5-3: Concordance rate of CMR variables for localization of segmental EAM-LVZs

CMR variables	Bipolar LVZ (n=12)	Bipolar or Unipolar LVZ (n=19)
LGE-scar	6 (50%)	12 (63%)
Peak circumferential strain	9 (75%)	15 (79%)
Peak longitudinal strain	11 (92%)	18 (95%)
Peak circumferential + longitudinal strain	10 (83%)	17 (89%)
Abbreviations: CMR-cardiac magnetic resonance imaging, LGE- late gadolinium enhancement, bipolar LVZ- low voltage zone <1.5mV, unipolar LVZ- low voltage zone <8.3mV		

SUPPLEMENTARY MATERIAL

Table 5-4: Supplemental Table- Segmental values of measured parameters from cardiac MRI and Electroanatomical mapping

Measures	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14	S15	S16	S17
Mean circumferential strain (%)	-13.6± 6.1	-10.4± 7.5	-8.8± 7.2	-11.9± 5.0	-13.9± 8.2	-14.6± 6.8	-11.8± 6.0	-9.6± 10.5	-9.2± 7.8	-8.6± 5.6	-10.7± 4.3	-8.6± 5.3	-11.3± 6.8	-14.2± 12.0	-17.3± 10.0	-10.8± 7.0	NA
Mean radial strain (%)	17.1± 20.8	4.0± 11.3	4.9± 8.6	24.5± 13.8	25.5± 13.2	31.2± 18.7	30.9± 14.7	18.4± 19.3	23.2± 17.4	27.1± 14.7	27.2± 13.1	31.4± 12.8	25.3± 15.5	15.5± 17.3	23.8± 17.5	25.2± 15.7	NA
Median longitudinal strain (%)	-13.6± 7.5	-15.5± 9.6	-19.8± 9.1	-21.1± 7.1	-25.6± 12.1	-23.5± 10.3	-12.7± 5.5	-6.0±8.8	-1.1±6.1	-5.3±7.1	-9.8±8.2	-10.9± 7.8	-8.9±5.2	-8.3±6.7	-4.9±4.8	-4.2±4.4	-10.4± 7.4
% LGE-scar area	10.3± 19.5	16.8± 22.5	6.2± 13.5	7.6± 14.0	12.2± 21.3	6.3± 14.2	4.0±9.6	3.0±6.9	3.4±6.1	7.9±11.3	7.1±12.1	5.0±11.0	0.4±1.8	0.9±3.3	2.8±6.1	1.1±3.4	0.0±0.1
Mean bipolar voltage	2.9 ±1.2	2.5±1.0	2.5±1.0	2.7±0.9	2.6±1.0	2.8±1.1	3.0±1.2	3.1±1.3	3.2±1.0	3.6±1.6	3.1±1.1	3.2±1.4	2.9±1.3	3.2±1.3	3.4±1.7	3.0±1.5	3.2±1.7
Mean unipolar voltage	9.1±3.1	7.5±3.1	8.6±3.2	8.9±3.2	8.9±2.4	9.8±2.7	12.1± 3.8	12.0± 4.0	12.6± 3.6	12.3± 3.4	11.4± 2.5	12.1± 3.0	12.1± 3.9	12.2± 3.5	12.6± 3.3	12.5± 3.7	11.6± 3.6
% area Bipolar LVZ	28.2± 29.6	38.6± 32.5	35.8± 29.9	29.0± 27.8	32.5± 30.1	30.7± 30.1	24.9± 29.2	27.2± 27.4	19.9± 26.4	17.9± 25.5	17.7± 26.3	19.9± 21.6	25.5± 28.1	18.6± 29.7	19.4± 27.5	28.9± 31.0	22.0± 27.1
% area Unipolar LVZ	49.1± 27.5	66.8± 32.7	56.6± 33.1	57.0± 34.9	48.6± 32.2	40.3± 31.0	18.2± 30.5	21.8± 32.1	19.7± 33.0	21.4± 29.5	16.5± 28.0	15.1± 26.6	18.6± 34.2	18.0± 34.6	13.4± 26.7	14.0± 28.7	21.2± 34.6

Values are mean ± SD or n (%); S1- S17 based on American Heart Association standardised myocardial segmentation
Abbreviations: SD- standard deviation, CMR- Cardiac Magnetic Resonance imaging, EAM- electroanatomical mapping, LV- left ventricle, CS- circumferential strain, LS- longitudinal strain, LGE- late gadolinium enhancement, bipolar LVZ- low voltage zone <1.5mV, unipolar LVZ- low voltage zone <8.3mV

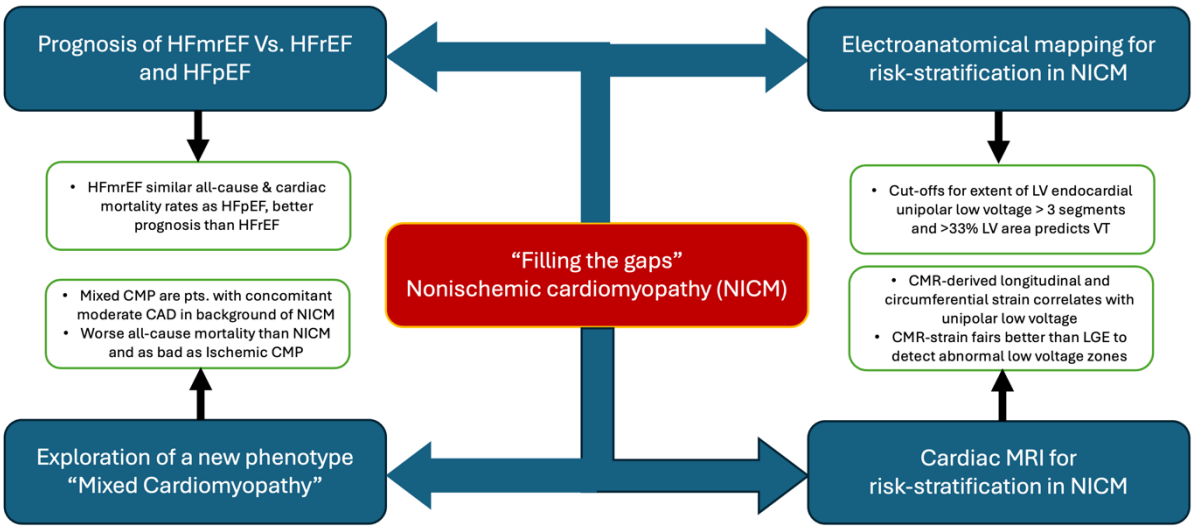
Table 5-5: Supplementary Table- Bivariate correlation between the measured parameters

	LVEF	Global CS	Global LS	% segmental abnormality with CS	% segmental abnormality with LS	% segmental abnormality with CS+LS	% area of LGE-scar	% area of Bipolar LVZ	% area of Unipolar LVZ
LVEF		-0.8 *	-0.6 *	-0.7*	-0.3	-0.7 *	-0.1	-0.05	-0.2
Global CS	-0.8 *		+0.6 *	+0.9 *	+0.2	+0.8 *	+0.08	+0.2	+0.4 $
Global LS	-0.5 *	+0.6 *		+0.3	+0.7 *	+0.7 *	+0.3	+0.2	+0.4 $
% segmental abnormality with CS	-0.7 *	+0.9 *	+0.3		+0.1	+0.7 *	+0.06	+0.05	+0.3
% segmental abnormality with LS	-0.3	+0.2	+0.7 *	+0.1		+0.7 *	+0.06	+0.5 *	+0.3
% segmental abnormality with CS+LS	-0.7 *	+0.8 *	+0.7 *	+0.7 *	+0.7 *		+0.01	+0.2	+0.5 *
% area of LGE-scar	-0.1	+0.08	+0.3	+0.06	+0.06	+0.06		+0.2	+0.3
% area of Bipolar LVZ	-0.04	+0.2	+0.2	+0.05	+0.5 *	+0.2	+0.2		+0.5
% area of Unipolar LVZ	-0.2	+0.4 $	+0.4 $	+0.3	+0.3	+0.5 *	+0.3	+0.5	

Values are correlation coefficients expressed in the range from -1 to +1; Values marked with * have significance at p value <0.05; Values marked with $ have significance at p value <0.10

Abbreviations: CS- circumferential strain, LS- longitudinal strain, LGE- late gadolinium enhancement, bipolar LVZ- low voltage zone <1.5mV, unipolar LVZ- low voltage zone <8.3Mv

Chapter 7: Conclusions and Ongoing research



7.1 Conclusions

1. Our meta-analysis of 18 studies and 126,239 heart failure patients concludes that risk of long-term all-cause mortality is less in patients with HFmrEF compared to HFrEF till 3-years, beyond which the differences in mortality risk were insignificant, for which transition in LVEF could play an important role. The insignificant differences in the risk-ratio between HFmrEF and HFrEF while considering studies representing greater proportion of women, suggests that gender disparity may play a divisive role in determining outcomes. The differences in risk of long-term all-cause mortality were comparable between patients with HFmrEF compared to HFpEF, thus suggesting the need to explore the mortality risks with tools other than LVEF.
2. Our retrospective analysis on 526 ICD recipients characterizes the 'mixed' phenotype of dilated cardiomyopathies who have established nonischemic triggers and concomitant moderate CAD. The prognosis in patients with mixed CMP, with regards to device therapies and all-cause mortality, resembles ischemic cardiomyopathy. The prognosis in patients with mixed CMP is poorer than NICM in terms of significantly higher burden of comorbidities, poorer LV functions and trend towards higher proportions of device shocks and higher mortality.
3. Our prospective study on 43 patients with NICM concludes that unipolar voltage of LV endocardium and the extent of distribution of unipolar low voltage zones has good correlation with LVEF and importantly can predict VT. Extent of distribution of unipolar

LVZ is a significant predictor of VT. At cut-offs of >3 segments of unipolar LVZ and >33% area of unipolar LVZ, patients with VT can be predicted with good diagnostic accuracy.

4. Our prospective study on 19 patients who underwent electroanatomic mapping and cardiac MRI concludes that abnormal myocardial strain detected by CMR-FT method is more closely related to electrical abnormalities, than the conventional LGE detected by CMR. Localization of low voltage zones with CMR-strain has better concordance than LGE. Thus, CMR-strain can inform the operator about specific regions of substrate abnormalities during a VT ablation procedure, especially in the absence of LGE scar.

7.1.1 Ongoing projects

1. We aim to compare outcomes of left bundle branch CRT to BiV-CRT in heart failure patients with LVEF ≤35%. We aim to conduct an observational study and an RCT to evaluate LBBP against BiV-CRT. Right ventricular (RV) pacing is known to be associated with pacing induced cardiomyopathy (PICM) as it causes non-physiologic activation of ventricles. PICM leads to heart failure, atrial fibrillation and high mortality. Patients with underlying left ventricular (LV) dysfunction are prone to develop PICM. However, LBBP recruits conduction system and leads to physiologic LV activation. We aim to compare performance of LBBP against RV pacing in patients with mid-range ejection fraction (LVEF 35-50%) in an observational clinical trial and then in an RCT.

7.1.2 Abstract presentations

L. Tuan L, J. Shroff, A. Tokich, P.A. Sreevilasam, D. Raja, W. Abhayaratna, R. Pathak, Initial Experience, Safety, and Feasibility of Left Bundle Branch Area Pacing: A Prospective Cohort Study, Heart, Lung and Circulation, Volume 32, Supplement 3,2023, Page S339, https://doi.org/10.1016/j.hlc.2023.06.773.

2. Data around activation of LV in LBBP is still emerging. It is also unclear why LBBP leads to different responses in different individuals. To understand physiology of LV activation propagation and its correlation with clinical outcomes, we aim to conduct an observational study which will enrol patients with variable response (super-response, average response and non-response) to LBBP. An epicardial activation map will be created using Medtronic's Cardioinsight technology and differences in activation of LV will be evaluated.

3. Builiding on our preliminary work on HFmrEF, a prospective study on outcomes in HFmrEF is being analysed. We aim to study the cardiovascular outcomes in HFmrEF and risk-stratification tools to predict sudden cardiac death in this category of patients.

   Abstract presentations: Natasha Jones-Lewis, Lukah Q Tuan, Adriana Tokich, Kaushik Thungathurthi, Sumithnath Tharaparambil Gangadharan, Taylah Abbott, Troy Rimando, Rajeev K Pathak. Patient Characteristics And Five-Year Clinical Outcomes Of Patients With Heart Failure With Mid-Range Ejection Fraction. Heart Rhythm, Volume 20, Issue 5, S541 - S542
   https://www.heartrhythmjournal.com/article/S1547-5271(23)01462-5/fulltext

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