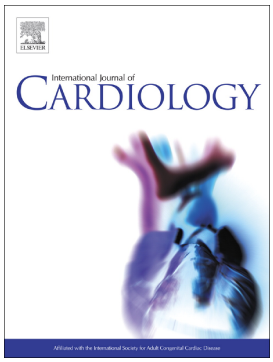


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# Long term prognostic importance of late gadolinium enhancement in first-presentation non-ischaemic dilated cardiomyopathy

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**Key Words:** Heart Failure; Cardiomyopathy; Magnetic Resonance Imaging (MRI); Prognosis

## ABSTRACT

### Background

Presence of myocardial fibrosis in well-established non-ischaemic dilated cardiomyopathy (NIDCM) is associated with adverse clinical outcomes. However, the impact of myocardial fibrosis at first presentation in NIDCM, and its long-term association with left ventricular (LV) dysfunction, heart failure (HF) and ventricular arrhythmia (VA) remains unclear. We investigated whether the presence of myocardial fibrosis quantified by late gadolinium enhancement cardiovascular magnetic resonance (LGE-CMR) at presentation, is independently associated with long term major adverse cardiovascular events (MACE) in patients with first presentation NIDCM.

### Methods

Consecutive patients with a first diagnosis of NIDCM were recruited. Patients underwent LGE-CMR at baseline. Replacement myocardial fibrosis by LGE-CMR was quantified by experienced observers blinded to patient outcome. MACE was defined as a composite end-point including cardiac death, HF rehospitalisation and the occurrence of sustained VA.

### Results

Fifty-one patients with first presentation NIDCM were included, of which 49 (96%) had follow up and outcome data. Median follow up was 8.2 years. Both the LGE positive and LGE negative groups had similar clinical characteristics at follow up. In univariate Cox regression analysis, positive LGE was associated with MACE (HR:3.44; 95% CI:1.89 to 6.24, p-value<0.001) and HF rehospitalisation (HR:2.89; 95% CI:1.42 to 5.85, p-value=0.003). In multivariate Cox regression, positive LGE-CMR was independently associated with MACE (HR:3.53; 95% CI:1.51 to 8.27, p-value=0.004) and HF rehospitalisation (HR:3.07; 95% CI:1.24 to 7.59, p-value=0.015).

**Conclusions**

The presence of myocardial fibrosis in first presentation NIDCM is independently associated with an increased risk of HF rehospitalisation, at long term follow-up.

## INTRODUCTION

Non-ischaemic dilated cardiomyopathy (NIDCM) is characterised by impairment in systolic left ventricular (LV) function following a non-ischaemic, mechanistically variable but often poorly defined, myocardial insult. Clinical management of this condition is generally determined by the patient's symptoms, the electrocardiogram and the LV ejection fraction (LVEF) on echocardiogram. This approach has limitations in specifically identifying patients who are unlikely to respond to medical therapy or who are at higher risk of sudden cardiac death (1). This is graphically displayed in a study of 8000 patients with ischaemic and non-ischaemic cardiomyopathy and LVEF <40%, which demonstrated that despite the use of modern therapies, there is a 20% mortality rate at 2 years (2).

Over the last two decades cardiovascular magnetic resonance (CMR) has been utilised in the diagnostic assessment of patients with NIDCM. Late gadolinium enhancement cardiovascular magnetic resonance (LGE-CMR) has shown that ≈30% of patients with established NIDCM have mid-wall LGE, which represents replacement fibrosis, and that this provides incremental prognostic information to LVEF (3). In particular, multiple studies have shown that the presence of LGE-CMR in the NIDCM population portends to increase risk of heart failure events, ventricular arrhythmias (VA) and sudden cardiac death (SCD) (4, 5).

All previous studies have focused on patients with established NIDCM for a duration of at least 6 months. Whether mid-wall LGE identifies high risk patients at their first presentation NIDCM, is unknown. Using a unique cohort of patients with first presentation NIDCM, we have previously demonstrated that the presence of mid-wall LGE at presentation leads to adverse LV remodeling at 5 months (6). Whether this is associated with adverse clinical outcome over the long term is unknown. Accordingly, we investigated whether first

presentation NIDCM with LGE-CMR is associated with major adverse clinical events (MACE) over a long term follow up. We hypothesized that the presence of myocardial fibrosis as detected by LGE-CMR in patients at their first presentation of NIDCM would be independently associated with MACE.

## METHODS

### Study population and protocol

The details of the subject characteristics, inclusion and exclusion criteria have been previously reported (6). In summary, consecutive patients were recruited from 3 university hospitals where they had presented with new onset heart failure (HF) with NIDCM diagnosed after routine clinical, echocardiography and coronary angiography work-up. The inclusion criterion was the presence of LV ejection fraction ≤45% at baseline echocardiography or CMR. Exclusion criteria included the diagnosis of significant coronary artery disease (defined as >70% luminal stenosis in an epicardial coronary artery at angiography, non-invasive stress imaging suggestive of ischemia, or prior myocardial infarction), severe valvular heart disease, thyroid dysfunction, infiltrative cardiomyopathy or extra-cardiac systemic features to suggest sarcoidosis or amyloidosis, chemotherapy-induced cardiomyopathy, hypertrophic cardiomyopathy, peripartum cardiomyopathy, alcohol-induced cardiomyopathy and myocarditis. Myocarditis was excluded by the absence of classic clinical features, the presence of normal serum troponin I concentration at presentation, and by the lack of evidence of myocardial oedema on T2-weighted CMR (7). Patients were excluded from CMR when renal impairment (eGFR <60mL/min), or other conventional CMR contra-indications were present. HF therapies were administered in accordance with the 2008 European Society of Cardiology (ESC) guidelines of diagnosis and treatment of acute and chronic heart failure (8).

Research LGE-CMR and transthoracic echocardiography was performed within two weeks of presentation with first diagnosis NIDCM when clinically stable. To minimise variability due to loading conditions, CMR and echocardiography were performed in immediate succession for each individual. All patients provided written and informed consent to the study which was approved by the relevant Human Research Ethic Committee.

**Cardiac Magnetic Resonance Protocol and Analysis**

The full protocol has been described elsewhere (6); in brief, CMR was performed using commercially available 1.5T machines (Siemens Avanto, Erlangen, Germany or Philips Intera, Best, The Netherlands). Electrocardiographically-gated steady-state free precession imaging of the LV in the short-axis plane was undertaken. LGE-CMR imaging was undertaken 10 minutes following intravenous administration of gadolinium-DTPA 0.1mmol/kg using an inversion-recovery segmented gradient echo sequence. CMR data analysis was performed by 2 experienced (SCMR Level 3) observers, using commercially available software (CAAS MRV Version 3.3, PIE, Netherlands) (6, 9). Any disagreements were adjudicated by a third observer.

**Clinical Outcomes Data**

The primary study endpoint was the total number of MACE. MACE was defined as the composite of cardiac death, acute unplanned HF hospitalisation and the occurrence of ventricular arrhythmia (VA). VA events are defined as nonfatal ventricular fibrillation (VF), sustained ventricular tachycardia (VT) requiring external cardioversion or appropriate therapy by implantable cardioverter defibrillator (ICD) device triggered by VF or VT. VA that occurred during acute HF hospitalisations or leading to sudden cardiac death was not included and was separated from total VA event. Relevant clinical information (including new significant

valvular disease or myocardial infarction) in the interim period was obtained annually from the outpatient follow up clinical notes. Outcome, clinical events and mortality data were obtained from a state-wide hospital database with clinical information coded according to the international classification of diseases. Adjudication was made by two physicians blinded to CMR results with an overall third senior cardiologist involved when first two cardiologists disagreed.

**Statistical Analysis**

All analysis was performed in Stata version 14.2 (StataCorp, College Station, Texas, USA). The association of LGE was separately assessed on overall mortality, overall MACE (cardiac death, HF hospitalisation or VT/VF) and each type of MACE using log-rank analysis, univariate and multivariate Cox regression. Subjects were followed from their date of enrolment until the end date of the study (31$^{st}$ October 2017) or until the date of death if this was earlier. Subjects with more than one MACE continued in the study so that multiple events per subject were possible. Standard errors were adjusted for within-subject correlation using the cluster(id) vce(robust) option in Stata. For each of the outcomes, univariate Cox regression was used to test for unadjusted associations. Then, variables that were significant at $p<0.20$ were entered into a multivariate Cox regression model. For consistency across outcomes, age and RV ejection fraction (RVEF) were included as adjustment variables in all models as these were each significant ($p<0.05$) at the univariate level for MACE (all events). The assumption of proportional hazards for the overall model and LGE variable alone were tested using the proportional hazards test based on the Schoenfeld residuals. The effect of LGE was considered significant when $p<0.05$. The estimated survival rates by LGE status was shown using unadjusted Kaplan-Meier curves with log-rank p-values. In a sensitivity analysis, the

association with LGE and each non-mortality outcome (VT/VF, rehospitalisation and all MACE) was assessed using only the first event for each patient.

## RESULTS

### Clinical Characteristics

Follow up data were available in 49 (96%) patients. Table 1 shows the clinical characteristics of these patients. Seventeen (35%) patients had myocardial fibrosis (LGE positive) at baseline CMR. LGE was found in the mid-wall or at the insertion point of the right ventricular free wall and the interventricular septum. No ischaemic pattern of LGE was observed in this cohort. In total there was cumulative follow up of 321 years. Both the LGE positive and LGE negative groups were well matched for age, sex, rhythm and QRS duration, as well as baseline echocardiography and CMR variables prior to study enrolment (Table 1a). At follow up (median time 72 months for LGE positive group and 75 months for LGE negative group) there was no difference in echocardiographic LVEF (p=0.756) and no new development of significant valvular heart disease or myocardial infarction. Seven patients (five LGE positive) had ICD implanted for primary prevention while two patients (one LGE positive) for secondary prevention. In addition, no significant difference in HF medication (loop diuretics, beta-blockers, angiotensin-converting enzymes or angiotensin receptor blockers (ACEi/ARB) and mineralocorticoid receptor antagonist (MRA)) was noted between the LGE positive and LGE negative groups (Table 1b).

### Myocardial Fibrosis (positive LGE CMR) and Outcomes.

Patients were followed-up for a median duration of 8.2 years (interquartile range 7.1 – 9.1 years) with a maximum follow up of 9.4 years. The presence of myocardial fibrosis was associated with increased risk of sustaining an index primary end point. Overall, 30 MACE

events occurred amongst 10 of 17 patients (59%) with LGE and 17 MACE events in 10 of 32 patients (31%) without LGE. On Kaplan-Meier analysis, LGE was associated with a higher occurrence of MACE (log-rank p = <0.001) (Figure 1a). Within this composite end point, a total of 19 recorded HF hospitalisations occurred in 9 of 17 patients (53%) with LGE and 13 HF hospitalisation events in 7 of 32 patients (22%) without LGE. In patients with multiple HF rehospitalisation events, the median duration between each acute rehospitalisations was 337 days. On Kaplan-Meier analysis, LGE was associated with HF hospitalisation (log-rank p = 0.002) (Figure 1b). Moreover, there were 9 documented VA events in 3 of 17 patients (18%) with LGE in contrast to 2 VA events in 2 of 32 patients (6%) without LGE. On Kaplan-Meier analysis, LGE was associated with increased VA events (log-rank p = 0.001) (Figure 1c). Both positive and negative LGE group had 2 patients with cardiac mortality. In the group with LGE the 2 cardiac deaths were due to sudden cardiac death. In the group without LGE, one patient died of sudden cardiac death and the other died of myocardial infarction. The presence of LGE was not associated with increased cardiac mortality (log-rank p = 0.47) (Figure 1d).

In Cox regression analysis (Table 2a), the independent variables considered for inclusion into the model in addition to LGE were age, QRS duration, atrial fibrillation (AF), N-terminal pro-brain natriuretic peptide (NT-pro-BNP), echocardiography and CMR parameters. In univariate analysis Cox regression analysis, LGE was predictive of MACE (HR: 3.44; 95% CI: 1.89 to 6.24, p-value < 0.001), HF hospitalisation (HR: 2.89; 95% CI: 1.42 to 5.85, p-value = 0.003) and VA events (HR: 8.4; 95% CI: 1.81 to 39.7, p-value = 0.007) (Table 2b). Variables with p<0.20 were included in the multivariate cox regression model (Table 2a). LGE was significantly and independently associated with total MACE (HR: 3.53; 95% CI: 1.51 to 8.27, p-value = 0.004) and HF hospitalisation (HR: 3.07; 95% CI: 1.24 to 7.59, p-value = 0.015) but not with VA events and cardiac death (Table 2b).

In the sensitivity analysis using the first event for each patient only, the multivariate hazard ratio was reduced for MACE (HR=2.22, p=0.0168 versus HR=3.53, p=0.004) but almost identical for HF rehospitalisation (HR=3.22, p=0.069 versus HR=3.07, p=0.015). The analysis for first VA event was identical since all of the subjects included in the previous analysis had only 1 event (41 subjects of whom 3 had 1 VT/VF). The smaller number of events in the sensitivity analysis of MACE (14 versus 30) resulted in much wider confidence intervals for the estimated hazard ratio and the non-significant p-value.

## DISCUSSION

This study shows that LGE in patients at first presentation with NIDCM is independently associated with increased heart failure rehospitalisation for almost a decade after diagnosis. Heart failure events are associated with the presence of essentially pre-diagnosis replacement myocardial fibrosis, thereby representing a group who may warrant more aggressive therapy and intensified follow up. This is evident with a recent study demonstrating that the presence of myocardial fibrosis predicts unfavourable long term survival in heterogeneous population of new-onset of HF (10). Additionally, our findings increase the clinical impetus for aggressive management of patients at risk of heart failure or those with asymptomatic left ventricular dysfunction where the syndrome of chronic heart failure has not yet evolved. Our study further highlights the long-term implications of myocardial fibrosis in a well described population with first presentation NIDCM.

We found that the presence of mid-wall LGE on the presentation CMR scan (performed within the first 2 weeks after clinical presentation) was independently associated with MACE, being driven mainly by a higher rate of HF hospitalisations. It is likely that this observation is explained by reduced reverse remodelling to HF treatment in patients having LGE, as demonstrated in our previous study of the same cohort (6). Our unique, prospective, longitudinally followed cohort study links presentation mid-wall LGE and the lack of echocardiographic LVEF improvement at 5 months to long term MACE, comprising mainly of HF hospitalisation's. Importantly, while NIDCM presentation can occur at any age, most patients are first seen between ages 20 and 50 years (11), thereby magnifying the potential benefit of risk stratification allowing targeted and optimised medical therapy.

Initial studies focusing on patients with established NIDCM of at least 12 months duration have demonstrated that LGE was the sole independent predictor of cardiovascular hospitalisation and death (12, 13). In the largest study to date, Halliday et al reported a remarkably similar prevalence of LGE of 34.3% (14). This study of 874 patients with NIDCM demonstrated that patients with myocardial fibrosis on LGE are more likely to have significant VA events and death (14). The same group prospectively studied patients with NIDCM with an LVEF ≥40% and demonstrated an increased risk of SCD in patient with presence of LGE (15). A recent meta-analysis has validated the presence of myocardial fibrosis detected via LGE-CMR in NIDCM as an independent predictor of MACE (HR 2.88; $p<0.001$) and VA/SCD (HR 4.32; $p<0.001$) (16).

The association of HF hospitalisation with LGE in first presentation NIDCM may largely reflect the relative frequency of this endpoint, however the independent association with a marker of symptomatic heart failure needs to be acknowledged and is potentially mechanistically instructive. NIDCM is generally a global pathogenic process. Autopsy data has shown the substrate for diffuse fibrosis is perivascular and interfibre fibrosis (17). Furthermore, the pressure-volume overload and wall stress would lead to compensatory process that mainly affects the middle circumferential myocardial layer (18, 19). Hence mid-wall LGE could potentially represent the final pathway of these aforementioned patho-physiological mechanisms (20). Recent advancements in CMR parametric T1 mapping techniques which were not available at study enrolment, enables the quantitative assessment of diffuse myocardial fibrosis (21, 22). This technique has demonstrated that besides the presence of LGE, the abnormalities in native T1 times are independent markers of all-cause mortality, HF death and HF hospitalisations (23).

Whilst the prior studies looked at patients with established NIDCM, our study focused on the long-term outcome of consecutive patients with first presentation NIDCM. We found a remarkably similar incidence of LGE at NIDCM presentation (35%) to the vast literature on established NIDCM (12-14). This essentially represents "pre-diagnosis" fibrosis highlighting the significant duration of pre-clinical disease in NIDCM and providing impetus for study of preventative therapy in high risk subgroups (e.g. genotypic positive familial cardiomyopathy carriers). These findings have potential important clinical implications. A reliable early marker of poor outcome as well as both heart failure and ventricular arrhythmic events could be used to rationalise early and intensified treatment to patients most in need. Previous animal models have shown that angiotensin II receptor blocker neprilysin inhibitor (ARNI) have attenuating effects on cardiac fibrosis and cardiac remodelling (24, 25). Hence, this could potentially reverse or blunt the progression of first presentation or even at risk NIDCM – an important direction for future research, in which hard clinical endpoints might be examined.

It is increasingly recognised that myocardial scar induced re-entry arrhythmias make up the majority of VA in the cardiomyopathic heart (26, 27). Intuitively, scar represented by LGE would be expected to be mechanistically associated with VA events. The lack of independent association between LGE and life-threatening VA seen in our study, goes against prior findings in established NIDCM. This could be explained by the low number of patients or the low number of VA event observed in this observational study. Present day guidelines recommend primary prevention ICD implantation in NIDCM for those with LVEF <35% (28, 29). However, the majority of patients who succumb to SCD have LVEF > 35%, hence, our tools of risk stratifying these patients for likelihood of SCD are poor (30). Furthermore, Kober et al have recently demonstrated that ICD implantation guided solely by LVEF may not confer a survival benefit in non-ischaemic cardiomyopathy (31). Whilst randomised clinical trials are

currently underway to answer the question of whether a CMR guided approach is superior to standard care in NIDCM patients with mild-moderate systolic dysfunction (32) and myocardial fibrosis, LGE-CMR has already shown utility in guiding implantation of cardiac resynchronisation therapy (CRT) devices (33, 34). In addition CRT with defibrillation (CRT-D) has been shown to be superior to CRT in non-ischaemic cardiomyopathy patients with myocardial fibrosis on LGE-CMR (35).

Study Limitations

Our study has some limitations. Firstly, it is observational in nature and hence there may have been residual confounding due to differences in length of patient symptoms, patient characteristics and disease course prior to diagnosis that were not measured. In addition, the study was relatively small and there were only a small number of specific events, although the total number was similar to those observed in larger studies. Still a larger study could provide better understanding into patient symptoms and characteristics which may be clinically relevant. The low uptake of ACEi/ARB could confound this further. However, it could reflect the current clinical uncertainty on how the long term management of these patients should be. While the significant associations that were observed cannot have been underpowered, the low number of events for VA and mortality will have reduced the power for determining predictive capacity of LGE-CMR for these events. In addition there is a notable lack of a univariable association between outcomes and NTproBNP, LAVi and CMR LVEF which is likely due to the study being under powered. Similarly, although hazard ratios were similar for MACE and acute HF rehospitalisation, when we used first events only in the sensitivity analysis, the smaller number of events reduced our power still further. However, assuming that the point estimate for our observed effect were retained in future larger studies, a dataset with at least 30 first events would provide sufficient power to demonstrate a statistically significant

association. In contrast, strengths of the study include its long follow up (to the best of our knowledge the longest study of this type), the well described population, and immediate follow-up after presentation allowing a unique, prospective, longitudinal link between LGE-CMR and HF rehospitalisation.

## CONCLUSION

The presence of myocardial replacement fibrosis as detected by CMR-LGE is independently associated with an increased risk of HF rehospitalisation in first presentation NIDCM. This finding has potential therapeutic implications in the heart failure management of patients with first presentation NIDCM.

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**Figures**

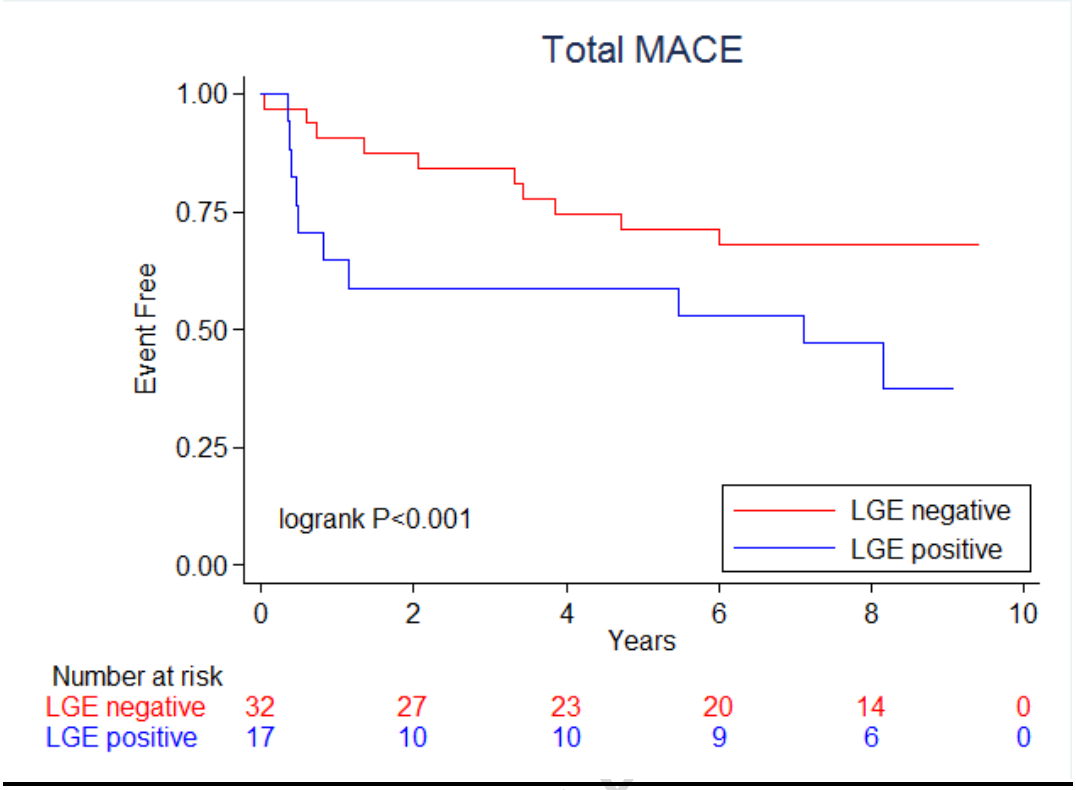


Figure 1a: Positive LGE was associated with higher MACE

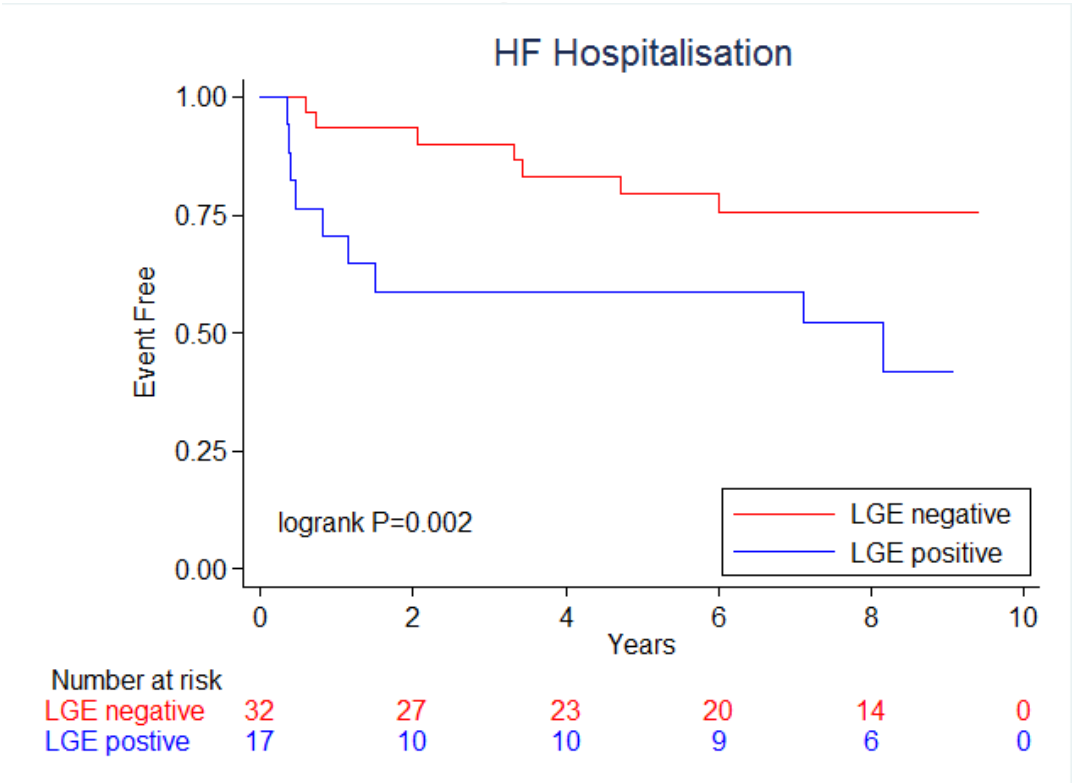


Figure 1b: Positive LGE was associated with higher HF Hospitalisations

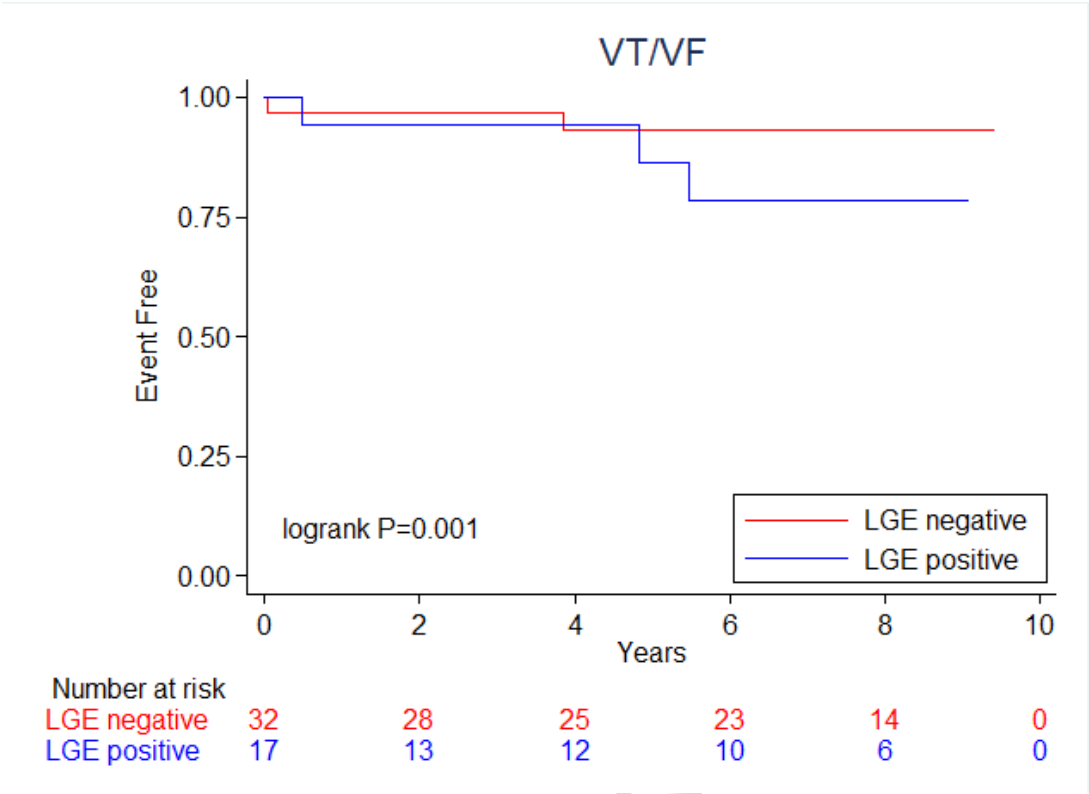


Figure 1c: Positive LGE was associated with higher VA

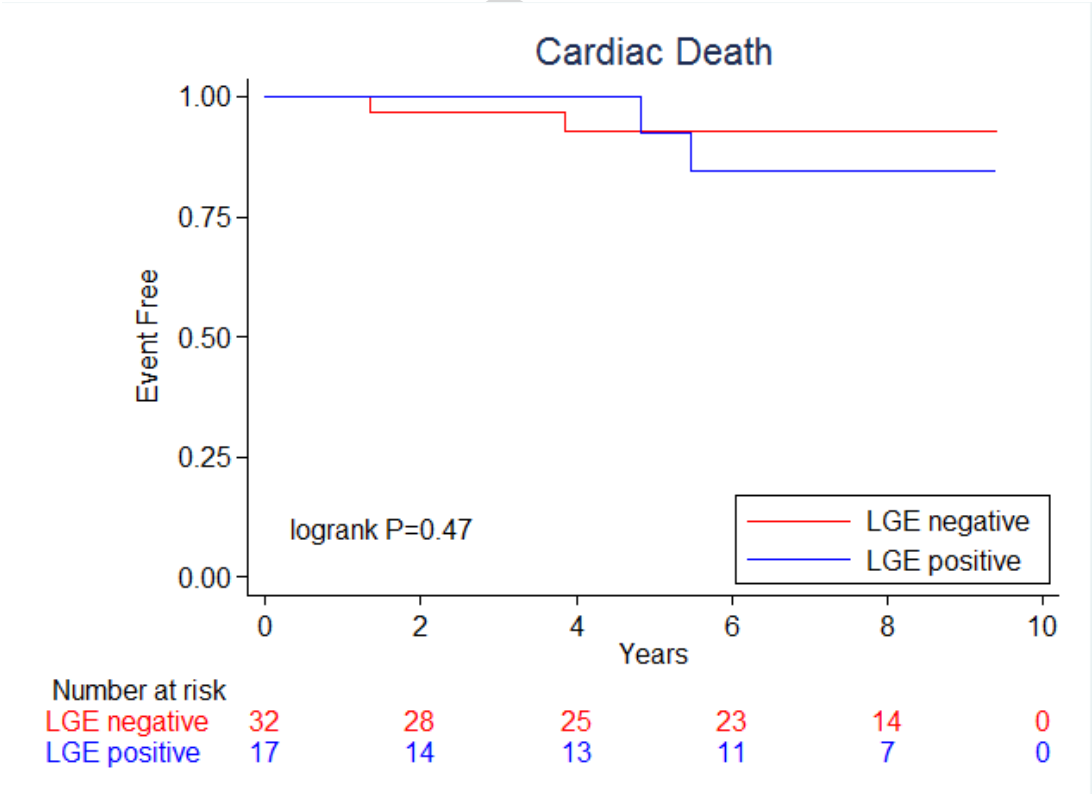


Figure 1d: Positive LGE was not associated with cardiac deaths

Table 1a: Characteristics of NIDCM patients at baseline.

| **Characteristics** | **LGE Positive (N=17)** | **LGE Negative (N=32)** | **P-value** |
|---|---|---|---|
| Age (years) | 61 (54-67) | 57 (49-66) | 0.475 |
| Male gender, n (%) | 13 (76%) | 22 (69%) | 0.724 |
| AF, n (%) | 5 (29%) | 7 (22%) | 0.589 |
| QRS duration (ms) | 118 (94-142) | 97 (82-111) | 0.115 |
| Median NT-pro BNP (ng/l) | 720 (609-2870) | 683 (446-3718) | 0.771 |
| Baseline ECHO LVEF (%) | 29 (24-33) | 29 (24-34) | 0.98 |
| ECHO LAVi | 40 (29-50) | 38 (29-47) | 0.769 |
| CMR LVEF (%) | 20 (15-26) | 26 (23-30) | 0.057 |
| CMR LV EDVi ($ml/m^2$) | 121 (94-147) | 107 (90-124) | 0.3796 |
| CMR LV ESVi ($ml/m^2$) | 94 (72-115) | 78 (64-92) | 0.205 |
| CMR LV Mass Index ($g/m^2$) | 69 (53-86) | 78 (64-92) | 0.409 |
| CMR RVEF (%) | 38 (27-49) | 45 (39-51) | 0.283 |
| CMR RV EDVi ($ml/m^2$) | 64 (48-79) | 63 (52-73) | 0.925 |
| CMR RV ESVi ($ml/m^2$) | 38 (25-50) | 33 (19-32) | 0.518 |

Legend: AF = atrial fibrillation, NT-pro BNP = N-terminal pro-brain natriuretic peptide, LGE = late gadolinium enhancement, ECHO = echocardiogram, LAVi = left atrial volume index, LVEF = left ventricular ejection fraction, RVEF = right ventricular ejection fraction, EDVi = end-diastolic volume index, ESVi = end-systolic volume index, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker

Table 1b: Characteristics of NIDCM patients at follow-up.

| **Characteristics** | **LGE Positive (N=17)** | **LGE Negative (N=32)** | **P-value** |
|---|---|---|---|
| Follow up ECHO LVEF (%) (Median time to ECHO follow up) | 45 (38-52) (72 months) | 46 (37-55) (75 months) | 0.756 |
| Frusemide (%) | 43 % | 47 % | 0.867 |
| Beta-blocker (%) | 86 % | 87 % | 0.952 |
| ACEi/ARB (%) | 57 % | 73 % | 0.448 |
| Spironolactone (%) | 57 % | 67 % | 0.665 |
| Sacubitril/Valsartan (%) | 14 % | 0 % | 0.98 |

Legend: ECHO = echocardiogram, LVEF = left ventricular ejection fraction, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker

Table 2a: Cox Regression Analyses for MACE

| Variable | Univariate | | Multivariate * | |
|---|---|---|---|---|
| | HR (95% CI) | p-value | HR (95% CI) | p-value |
| LGE | 3.44 (1.89 – 6.24) | p<0.001 | 3.53 (1.51 – 8.27) | 0.004 |
| Age (years) | 0.97 (0.95 – 1.00) | 0.016 | 0.99 (0.96 – 1.02) | 0.615 |
| QRS duration (ms) | 1.00 (0.99 – 1.01) | 0.497 | | |
| AF | 2.09 (1.13 – 3.86) | 0.019 | 1.47 (0.63 – 3.42) | 0.375 |
| NT-pro BNP | 1.00 (0.99 – 1.00) | 0.990 | | |
| ECHO LAVi | 1.00 (0.97 – 1.04) | 0.814 | | |
| CMR LVEF (%), per 1 SD | 0.86 (0.60 – 1.24) | 0.417 | | |
| CMR LV EDVi (ml/m$^2$) , per 1 SD | 1.11 (0.80 – 1.54) | 0.538 | | |
| CMR LV ESVi (ml/m$^2$) , per 1 SD | 1.19 (0.84 – 1.67) | 0.323 | | |
| CMR LV Mass Index (g/m$^2$) , per 1 SD | | 0.378 | | |
| CMR RVEF (%), per 1 SD | 0.87 (0.63 – 1.19) | 0.015 | 0.35 (0.02 – 7.57) | 0.504 |
| CMR RV EDVi (ml/m$^2$) , per 1 SD | 0.62 (0.42 – 0.91) | 0.983 | | |
| CMR RV ESVi (ml/m$^2$) , per 1 SD | 1.00 (0.68 – 1.49) | 0.129 | 0.61 (0.30 – 1.24) | 0.171 |
| | 1.33 (0.92 – 1.92) | | | |

Legend: AF = atrial fibrillation, NT-pro BNP = N-terminal pro-brain natriuretic peptide, LGE = late gadolinium enhancement, CMR = cardiovascular magnetic resonance, ECHO = echocardiogram, LAVi = left atrial volume index, LVEF = left ventricular ejection fraction, RVEF = right ventricular ejection fraction, EDVi = end-diastolic volume index, ESVi = end-systolic volume index, SD=standard deviation.

*Model included all variables significant at p<0.20 in univariate analysis.

Table 2b: Hazard ratios for LGE from univariate and multivariate Cox regression for each end point

| Outcome | LGE Status | Events | Univariate | | Multivariate * | |
|---|---|---|---|---|---|---|
| | | | HR (95% CI) | p-value | HR (95% CI) | p-value |
| MACE | LGE + | 30 | 3.44 (1.89 – 6.24) | p<0.001 | 3.53 (1.51 – 8.27) | 0.004 |
| | LGE - | 17 | | | | |
| Heart Failure Rehospitalisations | LGE + | 19 | 2.89 (1.42 – 5.85) | 0.003 | 3.07 (1.24 – 7.59) | 0.015 |
| | LGE - | 13 | | | | |
| Ventricular Arrhythmia Events | LGE + | 9 | 8.48 (1.81 – 39.72) | 0.007 | 4.88 (0.39 – 60.54) | 0.217 |
| | LGE - | 2 | | | | |
| Cardiac Death | LGE + | 2 | 2.01 (0.28 – 14.31) | 0.484 | 2.69 (0.17 – 42.55) | 0.482 |
| | LGE - | 2 | | | | |

Legend: LGE = late gadolinium enhancement, LGE + = LGE positive, LGE - = LGE negative

* Adjusted for age, atrial fibrillation, cardiovascular magnetic resonance right ventricular ejection fraction (CMR RVEF), CMR RV end-systolic volume index (CMR RV ESVi)

**Highlights:**

Most CMR trials have demonstrated the poor prognostic outcomes of myocardial fibrosis in established NIDCM. This is the first study to have demonstrated the presence of myocardial replacement in patients at first presentation NIDCM is independently associated with increased HF events. This may warrant a more proactive approach to medical therapy in patients who are at risk of HF or with asymptomatic left ventricular dysfunction where the syndrome of chronic HF has yet to evolve.

Graphical abstract

Figure 1a

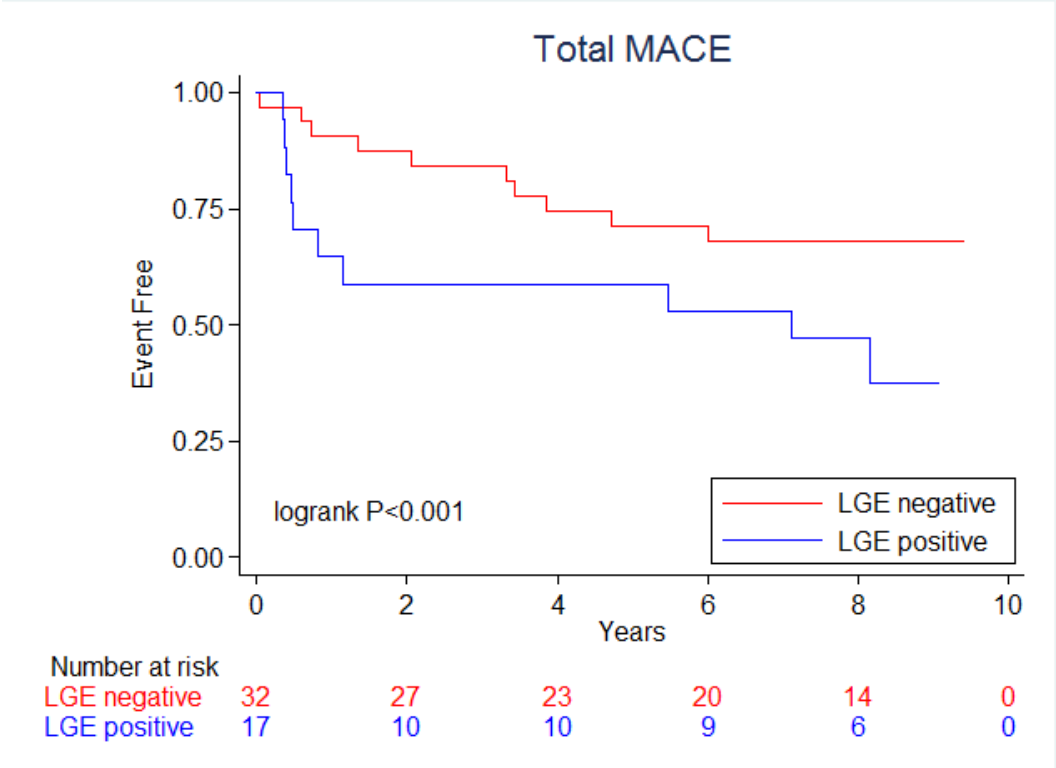


Figure 1b