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Association Between Mid-Wall Late Gadolinium Enhancement and Sudden Cardiac Death in Patients with Dilated Cardiomyopathy and Mild and Moderate Left Ventricular Systolic Dysfunction

Running Title: *Halliday et al.; Sudden Cardiac Death in Dilated Cardiomyopathy*

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Abstract

***Background*—**Current guidelines only recommend the use of an implantable cardioverter defibrillator (ICD) in patients with dilated cardiomyopathy (DCM) for the primary prevention of sudden cardiac death (SCD) in those with a left ventricular ejection fraction (LVEF)<35%. However, registries of out-of-hospital cardiac arrests demonstrate that 70-80% of such patients have a LVEF>35%. Patients with a LVEF>35% also have low competing risks of death from non-sudden causes. Therefore, those at high-risk of SCD may gain longevity from successful ICD therapy. We investigated whether late gadolinium enhancement cardiovascular magnetic resonance (LGE-CMR) identified patients with DCM without severe LV systolic dysfunction at high-risk of SCD.

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

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

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

***Clinical Trial Registration*—** https://clinicaltrials.gov/ Identifier: NCT00930735

Key-Words: dilated cardiomyopathy; sudden cardiac death; late gadolinium enhancement; cardiovascular magnetic resonance imaging; implantable cardioverter-defibrillator; mid-wall fibrosis

Clinical Perspective

What is new?

- This study demonstrates that mid-wall late gadolinium enhancement (LGE) identifies patients with dilated cardiomyopathy (DCM) and mild and moderate reductions in left ventricular ejection fraction (LVEF) at high-risk of sudden cardiac death (SCD).

What are the clinical implications?

- Patients with DCM and mid-wall LGE and mild or moderate reductions in LVEF should be recognised as having a high-risk of SCD.
- This is important because these patients are not currently offered ICDs for the primary prevention of SCD, on the basis of guideline recommendations.
- Due to low competing risks of death from non-sudden causes, it is possible that these patients will benefit from ICD implantation.
- Randomized trials investigating the benefit of pharmacological therapies and ICD implantation in patients with LGE and less severe reduction in LVEF are now required.

Introduction

Guidelines only recommend the use of implantable cardioverter defibrillators (ICDs) in patients with dilated cardiomyopathy (DCM) for the primary prevention of sudden cardiac death (SCD) in those with a left ventricular ejection fraction (LVEF) <35%.[1, 2] However, registries of out-of-hospital cardiac arrests demonstrate that 70-80% of such patients have a LVEF >35% indicating that, in fact, the major burden of SCD occurs in patients with less severe degrees of left ventricular (LV) impairment.[3, 4] The need to identify the sub-group of patients with mild and moderate reductions in LVEF at high risk of SCD has been highlighted by guidelines and statements from the American Heart Association, American College of Cardiology, European Society of Cardiology and Heart Rhythm Societies.[2, 5-7] Importantly, such patients are likely to have a lower risk of death from competing causes and fewer symptoms compared to patients with lower LVEF and may potentially have more to gain in terms of quality-adjusted life years from successful ICD therapy. This is particularly pertinent following the DANISH trial, which highlighted the importance of selecting patients with a low risk of death from other causes.[8] Late gadolinium enhancement cardiovascular magnetic resonance (LGE-CMR) has shown that approximately 30% of patients with DCM have mid-wall LGE which represents replacement fibrosis and that this provides incremental prognostic information to LVEF.[9-17] Whether mid-wall LGE also identifies a high-risk of SCD in patients with DCM and less severe reductions in LVEF, who might consequently benefit from an ICD, is unknown.[18] Accordingly, we investigated whether mid-wall LGE is associated with SCD and aborted SCD in a large cohort of consecutive patients with DCM and LVEF≥40%. A LVEF cut-off of ≥40% on CMR was chosen as this approximates to an LVEF of 35% on echocardiography, the current arbiter of primary prevention ICD implantation.[1, 2, 19-21]

Methods

Patients seen in our cardiomyopathy service or referred for CMR assessment between November 2000 and December 2011 with DCM and a LVEF≥40% were prospectively identified at the time of the scan and entered in a registry. Of 399 patients, 193 were included in a previous study of 'all-comers' with DCM investigating LGE and all-cause mortality regardless of LVEF.[9] These patients underwent extended follow-up for the current stand-alone, focused investigation in this select population. All participants provided informed consent and the study was approved by the National Research Ethics Service. The inclusion criterion was a diagnosis of DCM confirmed using the World Health Organization/International Society and Federation of Cardiology criteria, on the basis of an elevated left ventricular end-diastolic volume indexed to body surface area (LVEDVi) and reduced LVEF, compared to published age- and gender-specific reference values.[22] Exclusion criteria are listed in *Figure 1* and included the presence of significant coronary artery disease (CAD), defined as a stenosis of greater than 50% in a major coronary artery, infiltrative disease or valvular cardiomyopathy. To ensure patients with ischemic aetiologies were not included those with infarct patterns of LGE were also excluded.[23] Patients with a history of sustained ventricular tachycardia (VT), ventricular fibrillation (VF) or syncope were excluded given a potential pre-existing secondary prevention indication for ICD implantation. These patients have been included in an additional analysis in the *Supplemental Material (Supplemental Figure 1)*. No patients had a pre-existing indication for ICD implantation on the basis of primary prevention of SCD.

CMR was carried out on 1.5 Tesla scanners (Sonata/Avanto, Siemens, Erlangen, Germany), using a standardized protocol (*Supplemental Material*). The presence and location of mid-wall LGE were assessed by two independent Society of Cardiovascular Magnetic

Resonance level 3 accredited operators blinded to clinical outcomes, with a third providing adjudication if necessary (*MA, CI, FA*). LGE was considered present if mid-myocardial or sub-epicardial and visible in two phase-encoding directions and two orthogonal planes. The mass of LGE (grams) was quantified by a blinded operator using the full-width at half-maximum technique (CMR42, Circle Cardiovascular Imaging Inc, Calgary, Canada) and indexed as a percentage of left ventricular (LV) mass (*MA, CI).*

The pre-specified primary end-point was a composite of SCD or aborted SCD. SCD was defined as unexpected death either within 1 hour of the onset of cardiac symptoms in the absence of progressive cardiac deterioration; during sleep; or within 24 hours of last being seen alive.[24] Aborted SCD was defined as an appropriate ICD shock for ventricular arrhythmia, successful resuscitation following VF or sustained VT causing hemodynamic compromise and requiring cardioversion.[25] The principal secondary end-point was all-cause mortality. Additional secondary end-points were: (i) a composite of cardiovascular (CV) mortality (SCD, HF, stroke or thromboembolism), CV hospitalization or cardiac transplantation; and (ii) a HF composite of HF death, unplanned HF hospitalization or cardiac transplantation. Death was attributed to HF if preceded by progressive deterioration in symptoms and signs. HF hospitalization was defined as an admission with new or worsening signs and symptoms of HF requiring intensification of HF-specific treatment.[24]

Patients were followed-up throughout the study either by postal questionnaire and/or telephone interview, through family physicians, clinics and hospital notes. The duration of follow-up was calculated from the baseline scan until an end-point occurred or last patient contact. Specifically, for the primary end-point, any patients meeting the pre-specified criteria for an event were censored from that date. A committee of cardiologists blinded to CMR data

adjudicated outcomes (*VV, AL, UT, ZK, DA, NP, AV*). Deaths were also identified using the UK Health and Social Care Information Service to ensure none were missed. The adjudication committee established cause of death from death certification, post-mortem results and medical records using the ACC/AHA guidance.[24] Aborted SCD was confirmed from records including ICD electrograms when necessary.

Statistical Analysis

Baseline characteristics amongst those with and without LGE were compared using the Mann-Whitney U test for continuous data or Fisher's exact test for categorical data. Kaplan-Meier survival curves were generated and compared using the log-rank test. Event times were measured from the baseline CMR date for up to 8 years. The associations between end-points and the presence of LGE were analyzed using univariable and multivariable proportional hazard models. Results are presented as hazard ratios (HRs) with 95% confidence intervals. The multivariable model adjusted for the following covariates: LVEF, NYHA class and age. As part of a sensitivity analysis, the univariable model was also adjusted using inverse-probability weighting by a propensity score, taking into account a total of 13 baseline co-variates including the presence or absence of an ICD, allowing time varying weights for this during follow-up. Details and full results of the propensity score analysis can be found in *Supplemental Table 1&2 and Supplemental Figure 2*. In order to examine the dose-response relationship between LGE extent and the primary end-point, estimated HRs were calculated for four groups depending on the extent of LGE: 1) no LGE; 2) 0-2.5%, 3) 2.5-5% and 4) >5% of total LV mass using univariable proportional hazard models. We did not report estimates per 1% increase in LGE because of a clear non-linear relationship between LGE extent and the primary end-point. The percentage extent of LGE giving the largest c-statistic for the prediction of the primary end-point was

calculated from 1000 bootstrap samples. The C-statistic measured the degree to which a model can distinguish between cases and controls, taking values between 0.5 and 1.0 with larger values indicating better discrimination. In order to estimate the incremental predictive power of LGE above and beyond LVEF, a predicted 5-year risk of the primary end-point was calculated from a Cox proportional model which included LGE and categories of LVEF (40-43%, 44-47%, 48-51%, 52-55% and 56-59%).

For comparison of participants with and without LGE, the sample size was estimated to provide greater than 90% power to detect a significant difference in the primary end-point if the true hazard ratio was at least 3. Statistical analyses were performed using Stata version 14 (StatCorp, College Station, TX, USA; *SN* and *JG* performed analyses). A p value of <0.05 was taken as significant.

Results

At baseline, 424 patients met the inclusion criteria, of which 25 either withheld consent for follow-up or had moved abroad (*Figure 1)*. The report therefore focuses on 399 patients, of whom 145 were women, the median LVEF was 50% (IQR:46-54%) and mid-wall LGE was present in 25.3%. There was disagreement on the presence of LGE in 8 cases, requiring adjudication by a third reviewer. Median follow-up until an event or last contact was 4.6 years (IQR: 3.5 – 7.0) years.

Baseline characteristics are presented in *Table 1*. Patients with mid-wall LGE were older (p=0.03), more likely to be men (p<0.001), to have diabetes (p=0.015), and to receive loop diuretics (p=0.009). They also had lower heart rates (p=0.02) and diastolic blood pressure (p=0.02). The most common clinical presentation was with signs or symptoms of HF (n= 176;

44.1%). An additional 69 (17.2%) patients presented with symptoms of palpitation secondary to atrial arrhythmia or ventricular ectopy, 7 (1.8%) with symptoms of light-headedness or pre-syncope and 3 (0.8%) with 1st degree AV block or a blunted chronotropic response. A further 39 (9.8%) patients were diagnosed following referral for family screening. Common indications classified as 'Other' included diagnostic uncertainty or an abnormal electrocardiogram such as the finding of left-bundle branch block.

In line with guidelines, an ischemic aetiology was considered in all patients and excluded as follows.[23] All patients underwent LGE-CMR and those with infarct-patterns of enhancement were excluded.[23] In addition, 268 (67.1%) patients underwent invasive or computed tomography coronary angiography and a further 41 (10.3%) had perfusion imaging (nuclear or CMR) or stress echocardiography with no provocation of ischemia. Of the remaining, 60 (15.0%) were ≤40 years of age without a history of angina or a family history of premature CAD and further investigation was deemed unnecessary. All of the remaining 30 (7.5%) patients were free of angina and considered to have a low risk of CAD and in the absence of a class 1 indication, this was not performed[23]. Importantly, none of the patients underwent coronary revascularisation or suffered an acute coronary syndrome during the follow-up period.

Primary End-point - Sudden cardiac death and aborted sudden cardiac death

During follow-up, 18 of 101 patients (17.8%) with LGE reached the primary end-point compared to 7 of 299 patients (2.3%) without (HR 9.2; 95% CI 3.9-21.8; P<0.0001) (*Figure 2)*. After adjusting for LVEF, NYHA class and age, the presence of LGE predicted SCD and aborted SCD (HR 9.3; 95%CI 3.9-22.2; p<0.0001) (*Table 2)*. The results were qualitatively the same following adjustment based on the propensity score (*Supplemental Table 2*). There was little evidence of a dose-response relationship between LGE extent and the primary end-point.

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

Overall, 9 of 101 patients (8.9%) with LGE and 6 of 299 (2.0%) without died suddenly (HR 4.9; 95% CI 1.8-13.5; p=0.002). Correspondingly, 10 of 101 patients (9.9%) with LGE compared to 1 out of 299 patients (0.3%) without (HR 34.8; 95% CI 4.6-266.6; p<0.0001) suffered aborted SCD. After adjusting for LVEF, NYHA class and age, the presence of LGE predicted SCD (HR 4.8; 95% CI 1.7-13.8; p=0.003) and aborted SCD (HR 35.9; 95% CI 4.8-271.4; p<0.001) when analyzed individually (*Table 2)*. The results were qualitatively the same following adjustment based on the propensity score (*Supplemental Table 2*).

The predicted 5-year risk of aborted and actual SCD using a model including both LGE and LVEF was markedly different to a model using LVEF alone (*Figure 3)*. For example a patient with an ejection fraction of 45% had a 5-year predicted risk of 7.8% on the basis of LVEF alone, which fell to 3.2% in the absence of LGE but increased to 20.2% if LGE was present.

During follow-up, 32 patients (9.0%) had an ICD implanted before the occurrence of the primary end-point, 17 of whom also received cardiac resynchronization therapy. Eighteen patients received ICDs in line with primary prevention guideline recommendations following deterioration in LVEF from baseline, 2 following new episodes of sustained VT without haemodynamic compromise and 12 outside of conventional guideline recommendations following review at multidisciplinary meetings.[1, 2] Out of the latter 12 patients, 1 had a pathogenic Lamin A/C mutation, 2 had a pacing indication with non-sustained VT (NSVT), 3

had NSVT and a family history of SCD, 4 had a history of NSVT alone and 2 presented with worsening HF and left bundle branch block and had cardiac resynchronization therapy with a defibrillator. Of 32 patients who received an ICD system, 4 patients (23.5%) with and 0 patients (0.0%) without LGE had aborted sudden deaths. Of 367 patients without an ICD system, 9 patients (10.7%) with and 6 patients (2.1%) without LGE died suddenly.

Secondary End-points

All-cause mortality

During follow-up, there were 32 deaths, of which 19 were CV and 13 were not (cancer, end-stage lung-disease, sepsis and acute small bowel obstruction). The overall mortality rate was higher in patients with LGE (12.9% vs 6.4%; HR 2.3; 95% CI 1.1-4.6; p=0.02) (*Supplemental Figure 3)*. Following adjustment for LVEF, NYHA class and age, a trend towards higher mortality in those patients with LGE was noted, however this did not reach statistical significance (HR 2.0; 95%CI 1.0-4.1; p=0.056).

Cardiovascular death, hospitalization and transplantation

There were 19 CV deaths (including 15 SCDs and 3 HF deaths) and 42 unplanned CV hospitalizations. Two patients underwent cardiac transplantation, one of whom had full histopathological examination of the explanted heart. The gross and microscopic examinations correlated with LGE-CMR images (*Supplemental Figure 4*). Overall, this composite end-point was more common in patients with LGE compared to those without (30.7% vs 10.7%; HR 3.6; 95% CI 2.2-5.8; p<0.0001) (*Supplemental Figure 3).* After adjusting for LVEF, NYHA class and age, the presence of LGE remained an independent predictor of the CV composite end-point (HR 3.2; 95%CI 1.9-5.4; p<0.0001).

Heart failure death, heart failure hospitalization and transplantation

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

Discussion

This large study in a population of well-treated and well-characterised DCM patients with mild or moderate LV impairment is the first investigation to demonstrate mid-wall LGE on CMR is associated with a nine-fold increased risk of SCD and aborted SCD in this select sub-group. Importantly, none of the patients within the cohort had a pre-existing indication for ICD implantation at baseline, demonstrating the incremental value of LGE-CMR in risk stratification in this population. This focused investigation emphasises the importance of extending risk stratification beyond LVEF assessment and extends prior observations in HF populations including both ischemic and non-ischemic aetiologies.[12, 26] Prediction of SCD and aborted SCD was independent of established prognostic variables, including LVEF, NYHA class and age and qualitatively the same following adjustment for a large number of covariates based on a propensity score.

International guidelines and statements have highlighted the need to identify those patients with an LVEF>35% at highest risk of SCD because the major burden of SCD lies within this sub-group and this is currently not accounted for by primary prevention ICD guidelines.[3-7] Furthermore, as we move to an era of precision medicine, there is an expanding cohort of

patients identified with milder reductions in LVEF in whom optimal therapy remains unclear.[27] The DANISH trial has re-emphasised the need to refine our current approaches to risk stratification.[8] Although, the trial demonstrated a reduction in SCD in patients with severely reduced LVEF randomized to ICD implantation, this was not associated with a significant reduction in all-cause mortality because of high rates of non-sudden cardiac death and non-cardiac death.[8] In other words, in this population of sick patients, ICD therapy simply changed the mode of death but not the overall mortality rate. This illustrates the importance of selecting patients with a high-risk of SCD and low-risk of non-sudden death who will be exposed to longer periods at risk of arrhythmias and may therefore have the most to gain from ICD therapy. Indeed in sub-group analysis of the DANISH trial, those patients most likely to benefit from ICD therapy were those at low risk of non-sudden death, specifically patients <59 years of age and those with a NT-pro-BNP<1177pg/ml.[8] Patients with mild or moderate reductions in LVEF, not only have a low risk of non-sudden death, but are also less likely to have limiting HF symptoms compared to those with more severe LV impairment and may therefore have the potential to gain a greater number of quality-adjusted life years following an aborted SCD. Our new data suggest a role for LGE-CMR in the identification of patients with less severe left ventricular impairment who are at high risk of SCD, low risk of non-sudden death and who may therefore benefit from ICD implantation.

In patients with an LVEF≥40%, over a median follow-up of 4.6 years, the risk of the primary end-point in those with mid-wall LGE was 17.8%. In a similarly-designed study with marginally longer follow-up (median 5.3 years), the risk of SCD and aborted SCD in all-comer DCM patients with an LVEF≤35% was 17.9%, increasing to 27.9% in the subgroup with LGE, but dropping to only 11.1% in those without LGE.[9] We have therefore observed an

approximately equivalent rate of SCD events in patients with an LVEF≥40% and LGE compared to all those with an LVEF≤35%. This observation provides support for the CMR-Guide (NCT01918215) randomized trial which aims to evaluate the benefit of ICD therapy in patients with LVEF 36-50% and LGE.

The greatest increment in SCD risk occurred between patients with no LGE and those with the smallest extent (0-2.5%). This was confirmed by analysis of Harrell's C Statistic which demonstrated a LGE extent cut-off of >0% as the best discriminator of event-free survival time. The lack of a linear dose-response relationship between the extent of LGE and the primary end-point is novel and suggests that binary risk models based on the presence or absence of LGE are appropriate rather than models that examine risk based on the extent of LGE which assume linearity.[9, 16]

Myocardial fibrosis is a widely accepted substrate for ventricular arrhythmia, supporting the biological plausibility of the findings. An electro-mapping study in patients with DCM demonstrated LGE in all patients with inducible VT or a history of sustained VT and mapped the arrhythmia to the corresponding location.[28] Additionally, areas of fibrosis interacting with channels of healthy myocardium in the peripheral 'heterogeneous zone' of the scar have been associated with re-entry wavefronts and targeting of these at catheter ablation reduces VT.[29-32] It is therefore conceivable that the surface area of the 'gray-zone' between scar and healthy tissue determines the risk of VT, rather than the mass of the scar, explaining the lack of a dose-dependent association between LGE extent and SCD events in our study.[17, 18]

Limitations

This study was performed in a single, large-volume, experienced center. While this enables the use of a standardized protocol and scan interpretation from the same independent operators, it

introduces the possibility of referral bias. We do, however, report similar baseline characteristics to other registries.[13, 33] Moreover, the referral base is broad, from specialist and non-specialist centers and we report a range of common indications for the scan. Data from 193 of 399 patients were included in an earlier investigation on 'all-comers' with DCM.[9] These patients had extended follow-up in this study which is unique in examining a focused clinical question in a targeted population using an alternative pre-specified primary end-point in order to address an unmet clinical need.

We also recognise the modest number of events in the study. We specified strict criteria for the primary end-point, excluding appropriate ATP, in order to generate the most clinically meaningful data. Within this large study, we have identified a strong predictor of clinically important events responsible for a major burden of SCD in the DCM population. Based on the event rates in this study, a randomized trial of defibrillator therapy versus medical therapy in patients with a LVEF>40% and mid-wall LGE followed-up for 5 years would require 971 patients to have 80% power to detect a difference in all-cause mortality, at a significance level of 5%, assuming a 60% reduction in SCD with the intervention. This is comparable to the sample size of other large device trials.[8]

In this study, CAD was not excluded in all cases by coronary angiography. However, LGE-CMR has been shown to be as accurate in the diagnosis of the aetiology of HF. [23] In addition, the majority of patients who did not undergo coronary angiography were ≤40 years of age without a history of angina or a family history of premature CAD. Only 30 patients, all without a history of angina, were aged over 40 and had no additional investigations to exclude CAD. None of the patients suffered an acute coronary syndrome or had coronary revascularisation during the study. Whilst we accept that CAD cannot be definitively excluded in

this small group, significant CAD is nevertheless unlikely. The small size of this group means that this is unlikely to have biased the data to a significant extent.

ICD implantation was more frequent in patients with LGE; however our results were consistent after adjusting for this as part of the propensity score analysis (*Supplemental Table 2*). Whilst it is possible that the higher rate of ICD implantation reflects selection bias, the presence of LGE was not cited as an indication for implantation in any case. Amongst patients who had an ICD implanted, the rate of aborted SCD was higher in those with LGE compared to those without. Furthermore, despite the higher rate of ICD implantation in those with LGE, these patients had a higher rate of SCD. We acknowledge the limitations of aborted SCD as an end-point and recognise that a proportion of arrhythmias resulting in appropriate shocks may have terminated spontaneously. However, our data on the association with SCD adds robustness. We also recognise that a proportion of SCDs may relate to aneurysmal rupture and cerebral haemorrhage, however, in the absence of a biologically plausible link between LGE and these events, the effect of this would be to dilute the association between LGE and SCD rather than to enhance it. ICD programming was at the discretion of the individual units. We did not routinely measure B-type natriuretic peptide but we have included alternative variables which strongly predict prognosis in HF, such as LAVi and NYHA class. Contemporary CMR techniques such as T1-mapping were not available at the outset but we note a lack of consistency in the findings of other studies investigating its role in outcome prediction, with little evidence of incremental value in addition to LGE.[34, 35]

Conclusions

For the first time, we demonstrate that in patients with DCM and mild or moderate left ventricular systolic impairment, who do not meet conventional criteria for an ICD, the presence

of mid-wall LGE identifies a sub-group at high-risk of SCD. The risk of SCD in this sub-group was comparable to that seen in all-comer patients with a LVEF<35%, and importantly their risk of non-sudden cardiac death was low, suggesting that ICD therapy may have the potential to reduce all-cause mortality and extend 'quality life'.

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Table 1. Baseline demographics for patients based on the presence or absence of mid-wall LGE

		Midwall LGE		
	All Patients (n=399)	**No (n=298)**	**Yes (n=101)**	**p**
Age (years)	49.9 (15.3)	48.9 (15.5)	53.0 (14.2)	0.030
Male	254 (63.7)	175 (58.7)	79 (78.2)	<0.001
BSA (m^2)	1.96 (0.24)	1.95 (0.24)	1.98 (0.22)	0.11
Heart Rate (bpm)	69.8 (13.0)	70.7 (13.3)	67.3 (11.8)	0.020
Systolic blood pressure (mmHg)	122.7 (16.3)	123.4 (16.5)	120.8 (15.5)	0.22
Diastolic blood pressure (mmHg)	72.9 (9.9)	73.5 (9.8)	71.0 (10.2)	0.018
Atrial Fibrillation / Flutter	64 (16.0)	49 (16.4)	15 (14.9)	0.76
Hypertension	81 (20.3)	56 (18.8)	25 (24.8)	0.20
Diabetes	25 (6.3)	13 (4.4)	12 (11.9)	0.015
Hypercholesterolemia	74 (18.5)	55 (18.5)	19 (18.8)	1.00
Current Smoker	62 (15.5)	47 (15.8)	15 (14.9)	0.88
Excess Alcohol	33 (8.3)	25 (8.4)	8 (7.9)	1.00
Family History of DCM	51 (12.8)	35 (11.7)	16 (15.8)	0.30
Family History of SCD	36 (9.0)	26 (8.7)	10 (9.9)	0.69
Left bundle branch block	103 (25.8)	81 (27.2)	22 (21.8)	0.36
Medications				
Beta-blocker	259 (64.9)	187 (62.8)	72 (71.3)	0.15
ACE Inhibitor	268 (67.2)	193 (64.8)	75 (74.3)	0.087
ARB	80 (20.1)	61 (20.5)	19 (18.8)	0.78
Loop Diuretic	91 (22.8)	58 (19.5)	33 (32.7)	0.009
Aldosterone Inhibitor	78 (19.6)	58 (19.5)	20 (19.8)	1.00
Scan indication				
HF	176 (44.1)	132 (44.3)	44 (43.6)	0.50
Palpitations & presyncope	79 (19.8)	54 (18.1)	25 (24.8)	
Family Screening	39 (9.8)	30 (10.1)	9 (8.9)	
Other	105 (26.3)	82 (27.5)	23 (22.8)	
NYHA				
I	228 (57.3)	170 (57.2)	58 (57.4)	0.36
II	144 (36.2)	110 (37.0)	34 (33.7)	
III	25 (6.3)	17 (5.7)	8 (7.9)	
IV	1 (0.3)	0 (0.0)	1 (1.0)	
CMR parameters				
LVEDVi	111.1 (19.4)	110.0 (18.2)	114.2 (22.4)	0.16

LVESVi	56.1 (13.0)	55.3 (12.0)	58.6 (15.2)	0.072
LVEF (%)	49.6 (4.9)	49.9 (4.9)	49.0 (4.9)	0.11
LV Mass Index (g/m^2)	86.0 (22.5)	85.0 (24.0)	89.0 (17.2)	0.007
RVEDVi	88.6 (20.3)	87.7 (20.1)	91.0 (20.8)	0.15
RVESVi	38.9 (14.7)	38.3 (14.3)	40.8 (15.6)	0.13
RVEF (%)	57.4 (9.4)	57.8 (9.2)	56.1 (9.7)	0.15
LAVi	58.3 (22.6)	57.3 (22.3)	61.1 (23.4)	0.079

(ACE – angiotensin converting enzyme, ARB – angiotensin II receptor blocker, CMR – cardiovascular magnetic resonance, DCM – dilated cardiomyopathy, LAVi – indexed left atrial volume, LVEDVi – indexed left ventricular end-diastolic volume, LVEF – left ventricular ejection fraction, LVESVi – indexed left ventricular end-systolic volume, MRA – mineralocorticoid antagonist, RVEDVi – indexed right ventricular end-diastolic volume, RVEF – right ventricular ejection fraction, RVESVi – indexed right ventricular end-systolic volume, SCD – sudden cardiac death, SD – standard deviation, VT – ventricular tachycardia, VF - ventricular fibrillation)

Table 2. Univariable and multivariable analyses for the primary end-point

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

Analysis is included for end-point components individually. (*adjusted for left ventricular ejection fraction, New York Heart Association Class and age; CI – confidence intervals, IPW: inverse probability weighting, LGE+ – late gadolinium enhancement present, LGE- - late gadolinium enhancement absent; SCD – sudden cardiac death)

Figure Legends

Figure 1. Identification of the study population.

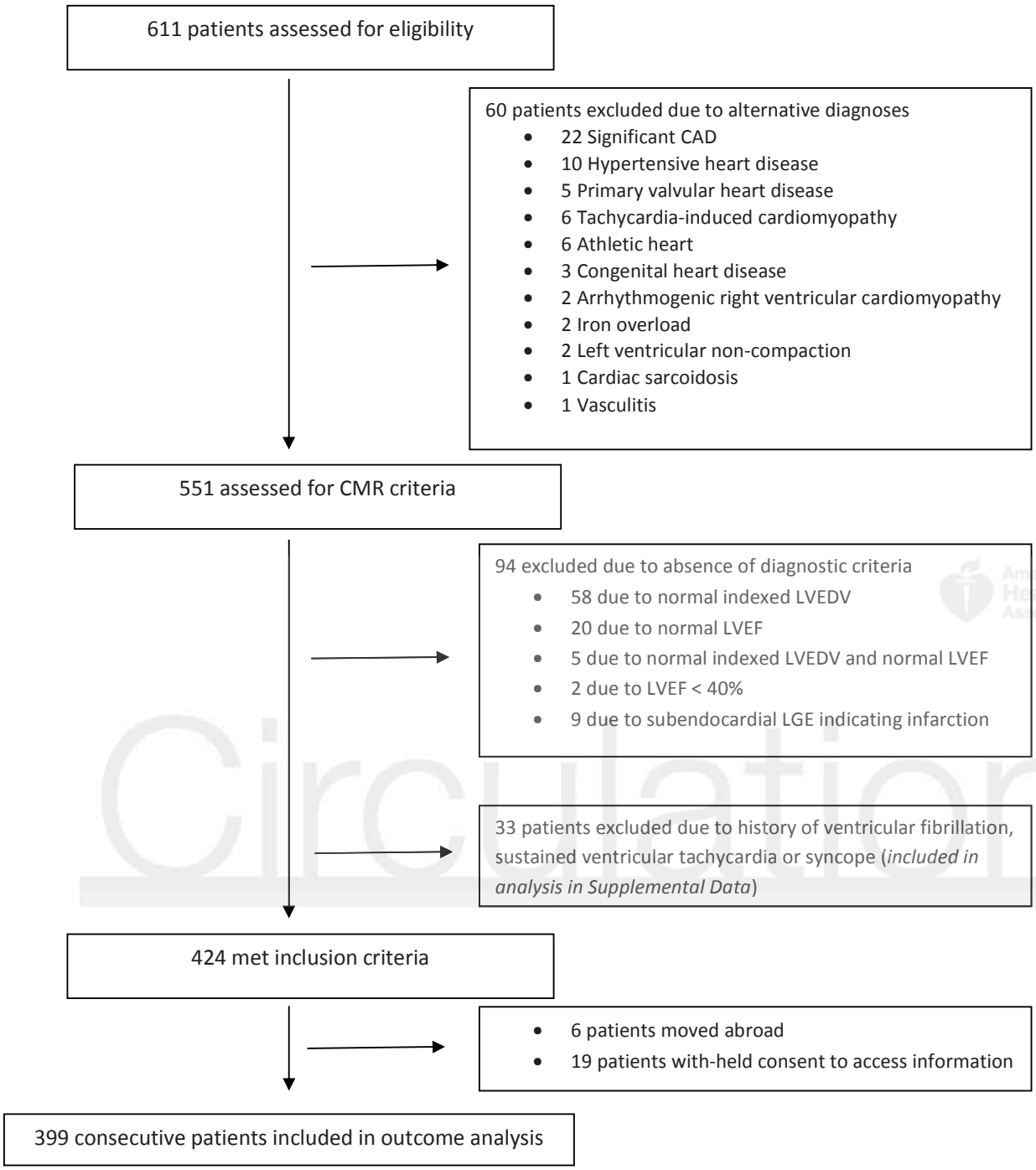
Flow chart detailing the identification, inclusion and exclusion of patients. (CAD – coronary artery disease; LVEDV – left ventricular end-diastolic volume, LVEF – left ventricular ejection fraction, LGE – late gadolinium enhancement)

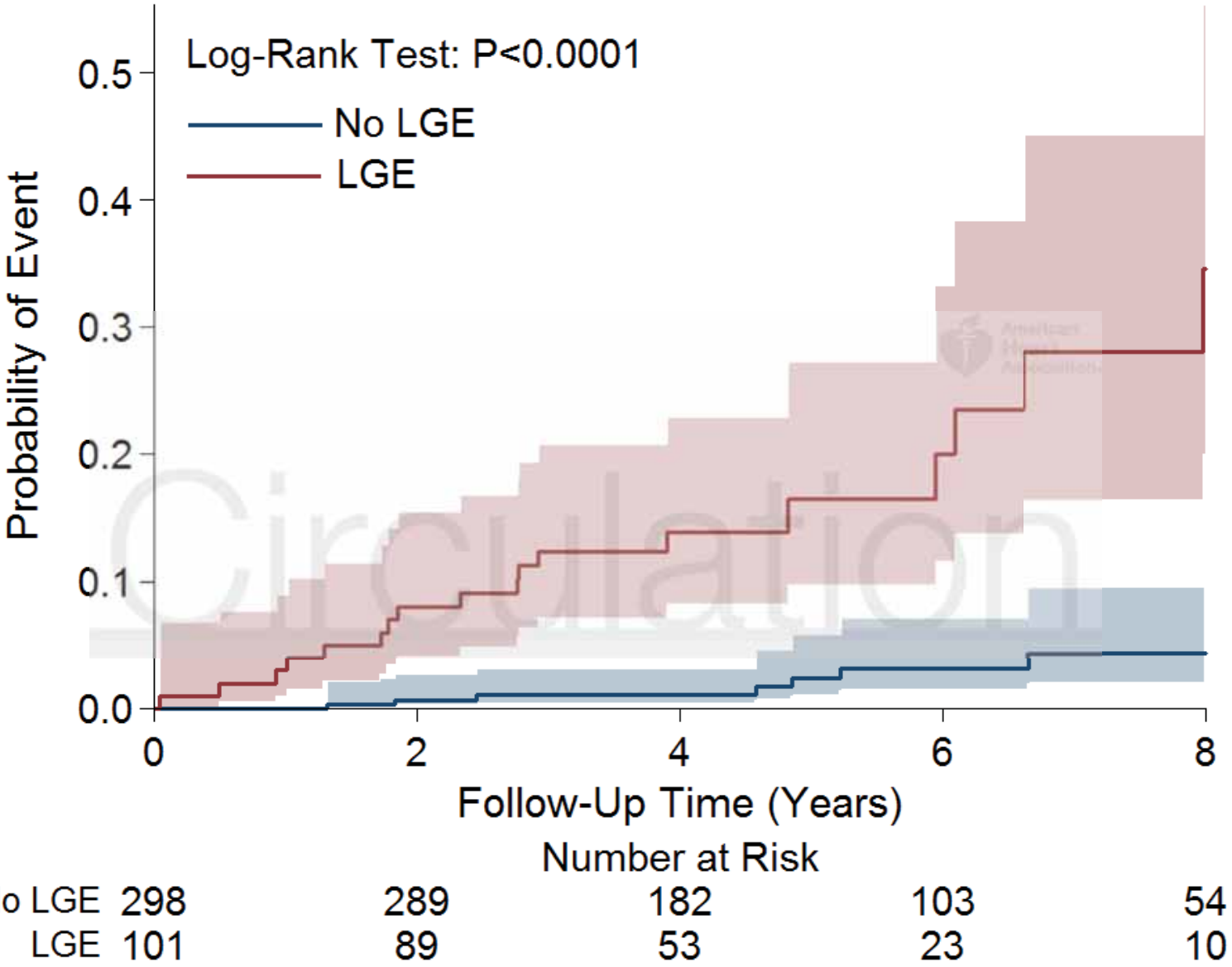
Figure 2. Primary end-point survival analysis

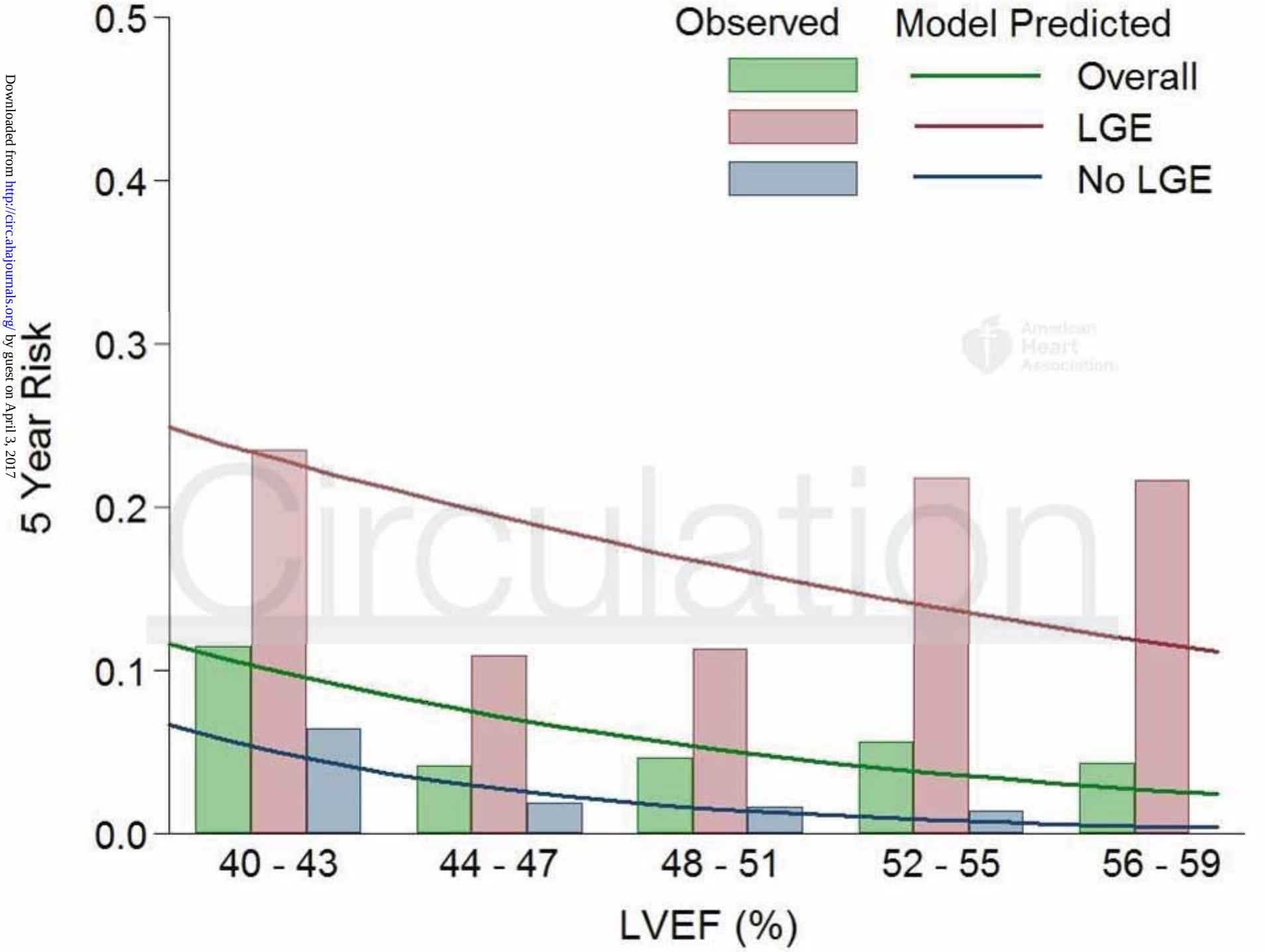
Kaplan-Meier curve of the time to first event for the primary end-point by presence (red-line) or absence (blue line) of mid-wall LGE.

Figure 3. 5-year risk estimates of the primary end-point

5-year risk estimates for primary end-point based on left ventricular ejection fraction (LVEF) alone (green line) and mid-wall LGE status in addition to LVEF (red line – presence of LGE, blue line – absence of LGE). (LGE – late gadolinium enhancement; LVEF – left ventricular ejection fraction)







Association Between Mid-Wall Late Gadolinium Enhancement and Sudden Cardiac Death in Patients with Dilated Cardiomyopathy and Mild and Moderate Left Ventricular Systolic Dysfunction

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SUPPLEMENTAL MATERIAL

Supplemental Methods

CMR protocol

Steady-state free-precession sequences were used to acquire cine images in standard long axis planes and in contiguous short axis slices from the atrioventricular ring to the apex. Intravenous gadopentetate dimeglumine or gadobutrol (Schering, Berlin, Germany) were used at a dose of 0.1mmol/kg. An inversion recovery gradient echo sequence was used to obtain LGE images, ten minutes after gadolinium administration, in identical planes to the cine images, in two phase-encoding directions. Inversion times were optimized to null the myocardium. Ventricular volumes and mass were calculated using dedicated software (CMRtools, Cardiovascular Imaging Solutions, London, UK). Left atrial volumes indexed to body surface area (LAVi) were measured using the biplane area-length method[1].

Supplemental Primary End-point Analysis

We report the primary end-point analyses for those patients meeting the inclusion criteria set out in the main manuscript and in addition, those patients with a prior history of ventricular fibrillation, ventricular tachycardia and syncope, excluded from the analysis in the main manuscript. Overall, 432 pateints were followed-up for a median of 4.5 (IQR: 3.4 – 6.6) years, of whom 159 were women, the median LVEF was 50% (IQR:46-54%) and mid-wall LGE was present in 25.7%.

During follow-up, 21 of 111 patients (18.9%) with LGE reached the primary end-point compared to 11 of 321 patients (3.4%) without (HR 6.5; 95% CI 3.2-13.5; P<0.0001) (*Figure A)*. After adjusting for LVEF, NYHA class, age and gender the presence of LGE predicted SCD and aborted SCD (HR 7.6; 95%CI 3.3-17.4; p<0.0001).

Overall, 9 of 111 patients (8.1%) with and 7 of 321 patients (2.2%) without fibrosis died suddenly (HR 4.1; 95% CI 1.6-10.9; p=0.004). Correspondingly, 13 of 111 patients (11.7%) with fibrosis compared to 4 out of 321 patients (1.2%) without (HR 10.7; 95% CI 3.5-32.9; p<0.0001) suffered aborted SCD. Following adjustment, the presence of fibrosis predicted SCD (HR 3.5; 95% CI 1.1-10.8; p=0.03) and aborted SCD (HR 14.6; 95% CI 4.7-46.2; p<0.001) when analyzed individually.

Supplemental Tables

Supplemental Table 1. Propensity score model

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

Baseline covariates used to construct the propensity score model were as follows: LVEF, NYHA class, age, gender, LAVi, LVEDVi, RVEF, ACE inhibitor and beta-blocker prescription, heart rate, scan indication and history of diabetes mellitus. ICD implantation was also included, allowing time-varying weights during follow-up.

(ACE – angiotensin converting enzyme, ARB – angiotensin II receptor blocker, HR – heart rate, LAVi – indexed left atrial volume, LVEDVi – indexed left ventricular end-diastolic volume, LVEF – left ventricular ejection fraction, RVEF –right ventricular ejection fraction, VT – ventricular tachycardia, VF - ventricular fibrillation)

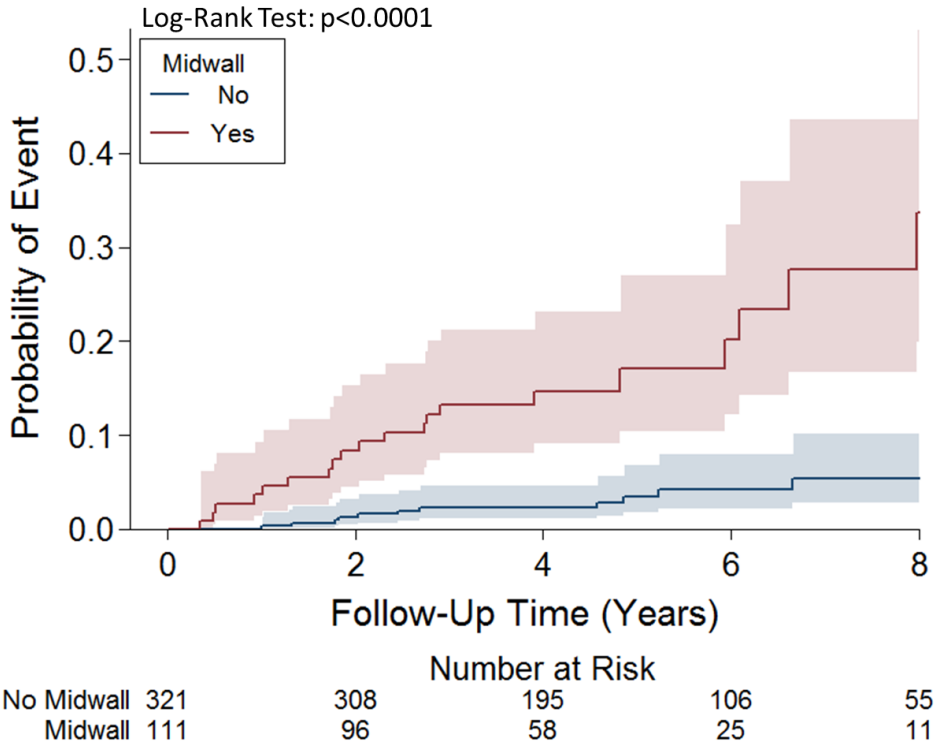
Supplemental Table 2. Results of the Propensity score analysis

Outcome	LGE Status	Events n (%)	IPW Estimate	
			HR (95% CI)	P Value
SCD or Aborted SCD	LGE -	7 (2.3)	8.0 (3.3, 19.5)	<0.0001
	LGE +	18 (17.8)		
SCD	LGE-	6 (2.0)	4.6 (1.6, 13.1)	0.005
	LGE+	9 (8.9)		
Aborted SCD	LGE-	1 (0.3)	32.9 (4.3, 249.9)	<0.001
	LGE+	10 (9.9)		
All-Cause Mortality	LGE-	19 (6.4)	2.0 (0.9, 4.2)	0.086
	LGE+	13 (12.9)		
HF Death, Hospitalisation or Transplant	LGE-	13 (4.4)	1.6 (0.6, 4.4)	0.32
	LGE+	8 (7.9)		
CV Death, Hospitalisation or Transplant	LGE-	32 (10.7)	3.1 (1.8, 5.4)	<0.0001
	LGE+	31 (30.7)		

Inverse probability weighting analyses for the primary and secondary end-points. (weights based on left and right ventricular ejection fraction, indexed left ventricular end-diastolic volume, New York Heart Association Class, age, gender, indexed left atrial volume, ACE inhibitor and beta-blocker prescription, heart rate, scan indication, history of diabetes mellitus and the presence or absence of an ICD allowing time carrying weights for the latter; CI – confidence intervals, CV – cardiovascular, HF – heart failure, IPW: inverse probability weighting, LGE+ – late gadolinium enhancement present, LGE- - late gadolinium enhancement absent; OR – odds ratio; SCD – sudden cardiac death)

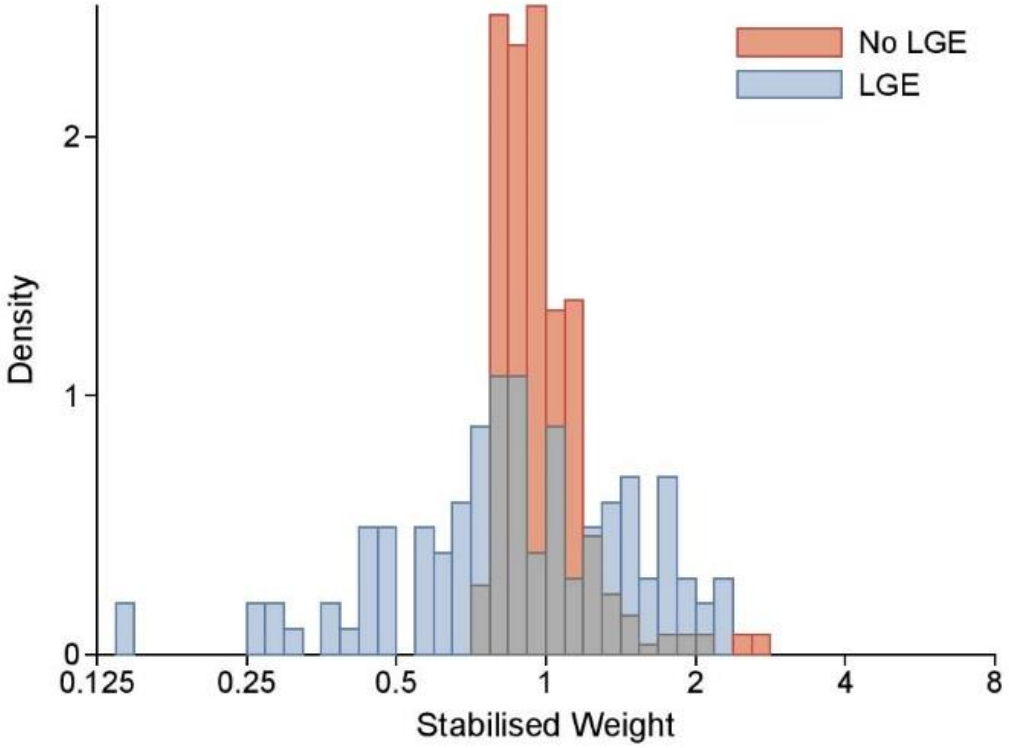
Supplemental Figures & Figure Legends

Supplemental Figure 1. Supplemental primary end-point analysis



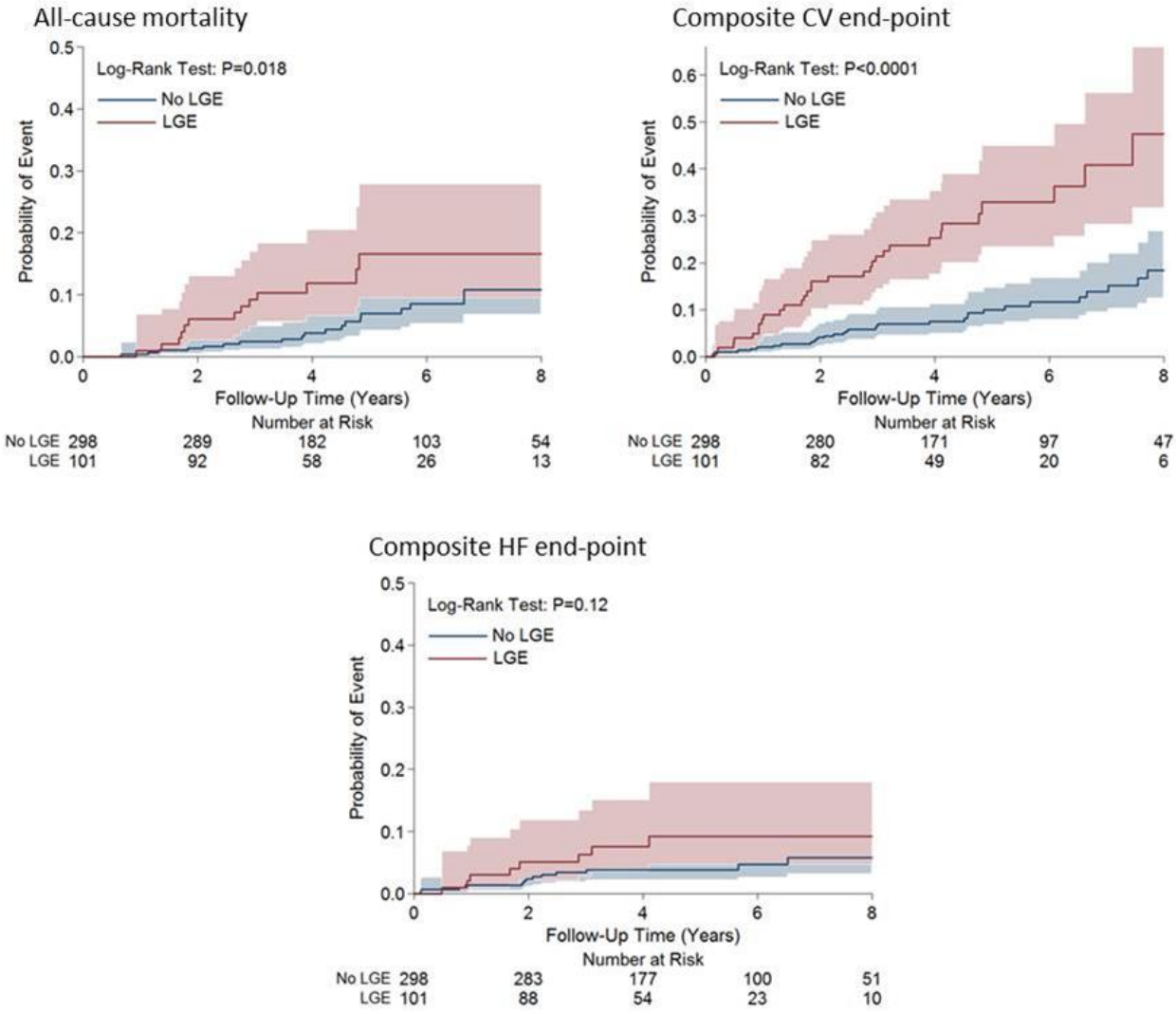
Kaplan-Meier curves of the time to first event for the primary end-points by presence (red-line) or absence (blue line) of mid-wall LGE, including patients with a prior history of sustained ventricular tachycardia, ventricular fibrillation or syncope.

Supplemental Figure 2. Histogram of the propensity score distribution in the groups with and without LGE



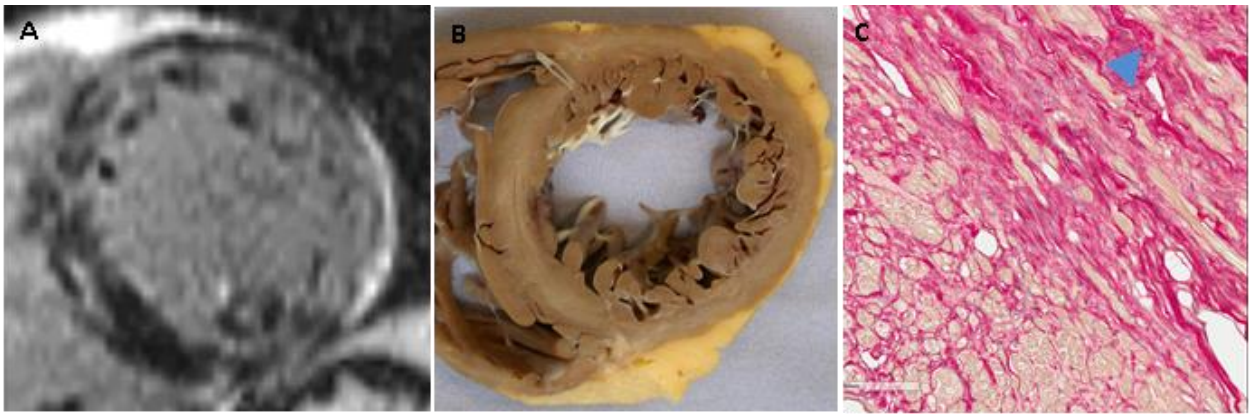
(LGE – late gadolinium enhancement)

Supplemental Figure 3. Secondary end-points



Kaplan-Meier curves of the time to first event for the secondary end-points by presence (red-line) or absence (blue line) of mid-wall LGE.

Supplemental Figure 4. Histological correlation



A: Pre-transplant late gadolinium enhancement (LGE) cardiovascular magnetic resonance demonstrating extensive mid-wall and sub-epicardial LGE, including the septum at mid-ventricular level. *B:* Post-transplant gross examination of a short-axis slice at mid-ventricular level confirming extensive mid-wall replacement fibrosis. *C:* Post-transplant micrscopic examination of a specimen from the septum of the explanted left ventricle, at x300 magnification, confirming replacement (arrow) and pericellular fibrosis.

References

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