Assessment of Myocardial Scarring Improves Risk Stratification in Patients Evaluated for Cardiac Defibrillator Implantation

Igor Klem, MD[1,2], **Jonathan W. Weinsaft, MD**[1,2,*], **Tristram D. Bahnson, MD**[2], **Don Hegland, MD**[1,2], **Han W Kim, MD**[1,2], **Brenda Hayes, BS**[1], **Michele A Parker, MS**[1,2], **Robert M Judd, PhD**[1,2,3], and **Raymond J Kim, MD**[1,2,3]

[1]Duke Cardiovascular Magnetic Resonance Center, Duke University Medical Center, NC

[2]Division of Cardiology, Duke University Medical Center, NC

[3]Department of Radiology, Duke University Medical Center, NC

Abstract

Objectives—We tested whether an assessment of myocardial scarring by cardiac magnetic resonance (CMR) would improve risk stratification in patients evaluated for implantable cardioverter-defibrillator implantation.

Background—Current SCD risk stratification emphasizes left-ventricular ejection fraction (LVEF), however the majority of patients suffering SCD have a preserved LVEF and many with poor LVEF do not benefit from ICD prophylaxis.

Methods—One hundred thirty-seven patients undergoing evaluation for possible ICD placement were prospectively enrolled and underwent CMR assessment of LVEF and scar. The prespecified primary endpoint was death or appropriate ICD discharge for sustained ventricular tachyarrhythmia.

Results—During a median follow-up of 24 months the primary endpoint occurred in 39 patients. Whereas the rate of adverse events steadily increased with decreasing LVEF, a sharp step-up was observed for scar size >5% of LV mass (HR=5.2 [95% CI, 2.0-13.3]). On multivariable Cox proportional hazards analysis, including LVEF and electrophysiological-study results, scar size (as a continuous variable or dichotomized at 5%) was an independent predictor of adverse outcome. Among patients with LVEF >30%, those with significant scarring (>5%) had higher risk than those with minimal-or-no (5%) scarring (HR=6.3 [1.4-28.0]). Those with LVEF >30% and significant scarring had similar risk to patients with LVEF 30% (p=0.56). Among patients with LVEF 30%, those with significant scarring again had higher risk than those with minimal-or-no scarring (HR=3.9 [1.2-13.1]). Those with LVEF 30% and minimal scarring had similar risk to patients with LVEF >30% (p=0.71).

Corresponding author: Raymond J. Kim, MD, Duke Cardiovascular MRI Center, DUMC-3934, Durham, NC 27710. (919)668-3539, (919)668-3554(FAX) Raymond.Kim@duke.edu.
*JWW is currently at: Division of Cardiology, Weill Cornell Medical College, NY

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Raymond Kim and Robert Judd are inventors of a US patent on Delayed Enhancement MRI, which is owned by Northwestern University. There are no other conflicts of interest or financial relationships to disclose.

Conclusions—Myocardial scarring detected by CMR is an independent predictor of adverse outcome in patients being considered for ICD placement. In patients with LVEF >30%, significant scarring (>5% LV) identifies a high-risk cohort similar in risk to those with LVEF 30%. Conversely, in patients with LVEF 30%, minimal-or-no scarring identifies a low-risk cohort similar to those with LVEF >30%.

Keywords

cardiovascular magnetic resonance; implantable cardioverter-defibrillator; myocardial scarring

INTRODUCTION

Sudden cardiac death (SCD) is a leading cause of mortality responsible for approximately 325,000 deaths annually in the United States alone.(1) Currently, risk stratification for SCD emphasizes left-ventricular ejection fraction (LVEF), and significant LV dysfunction has become the primary basis for determining a patient's eligibility for an implantable cardioverter-defibrillator (ICD).(2-5) However, LVEF has limitations in predicting clinical events. SCD typically results from ventricular tachyarrythmias,(6) and LVEF provides an indirect measure of the arrhythmic potential. Not surprisingly, in population studies, up to 70% of patients suffering SCD have a preserved LVEF and are not identified for prophylactic ICD implantation.(7) On the other hand, in patients with poor LVEF—who are eligible for ICD prophylaxis—many do not benefit. Recent trials suggest that approximately 14 to18 patients with ventricular dysfunction need to have an ICD implanted to prevent one death.(3,5) Moreover, considering the substantial cost(8) and the potential for complications, (9) improved risk stratification to identify patients who would benefit most from ICD implantation remains an important public health challenge.

Myocardial scar tissue is known to serve as a substrate for malignant ventricular tachyarrhythmias in both ischemic(10,11) and nonischemic cardiac disorders.(12,13) Importantly, the presence and extent of scarring may not be concordant with LVEF. For instance, some patients with extensive scarring may have preserved LVEF either because the scar is not full-thickness and/or because there is hyperkinesia of remote segments.(14,15) Conversely, some patients without myocardial scarring may have severely reduced LVEF. (16,17)

We postulated that an assessment of myocardial scarring would improve risk stratification for SCD beyond that provided by LVEF. Delayed-enhancement cardiovascular magnetic resonance (DE-CMR) provides high spatial resolution images of scar tissue that directly correlate with pathology.(18,19) Additionally, DE-CMR has shown prognostic utility above and beyond common clinical and functional indices in a variety of cohorts with ischemic(20-23) or nonischemic(19,20,24) cardiac disorders. However, in most studies evaluating prognosis there were few hard events and the primary endpoint was a composite including hospitalization for heart failure. Thus, additional studies evaluating the prognostic value of DE-CMR are essential.

The present investigation was designed to directly compare the predictive value of scar to LVEF—both simultaneously assessed during the same CMR session—for adverse outcome in patients being considered for ICD implantation.

METHODS

Population and Design

We prospectively screened patients referred to the electrophysiology service and scheduled for an electrophysiology study (EPS) and/or ICD placement between July 1, 2002 and July 1, 2004. Since we wished to evaluate both patients with preserved and impaired LVEF, a broad population was chosen and only those with contraindications for CMR (prior pacemaker or defibrillator) or were under 18 years of age were excluded. The reasons for referral to the electrophysiology service were low ejection fraction meeting criteria for an ICD in 69 (50%) patients, mild LV dysfunction not meeting criteria but with palpitations, frequent premature ventricular contractions, and/or non-sustained ventricular tachycardia in 22 (16%), evaluation of wide-complex tachycardia in 25 (18%), syncope in 17 (13%), and presumed cardiac arrest in 4 (3%). Of the 137 patients that were enrolled, CMR was performed for research purposes (only this specific protocol) in 109 patients and scan results were not used to guide clinical decision-making. The remaining 28 patients were screened concurrently and in the same prospective manner but had a clinically ordered scan for the assessment of LVEF. This group was similar to the 109 scanned only for the purpose of research with respect to age, gender, prevalence of coronary artery disease (CAD), LVEF, prevalence and extent of scar, as well as clinical outcome during follow-up (all p>0.10). All patients gave written informed consent. The study was approved by the Duke Institutional Review Board.

A comprehensive medical history including CAD risk factors, heart failure functional class (NYHA), and medications at the time of CMR was obtained in all patients. Additionally, 12-lead electrocardiography (ECG) was performed a median of 2 days (interquartile range [IQR]: 1, 5 days) from CMR and interpreted blinded to clinical and CMR data. Established criteria(3) were used to categorize patients as having ischemic or nonischemic heart disease: ischemic disease was considered present if there was 70% stenosis of a major epicardial coronary artery on x-ray angiography,(25) history of enzymatically proven myocardial infarction, or evidence of ischemia or infarction on clinical stress-testing. The majority of patients (n=122, 89%) had previously undergone x-ray coronary angiography.

Follow-up

Information concerning arrhythmic events and mortality status were obtained at regular intervals of 6 months via: 1) telephone interview with the patient, or if deceased, with family members, 2) contact with the patient's physician(s), and 3) hospital records. Additionally, in patients with ICDs, stored electrograms were downloaded at 3-month intervals and reviewed by an electrophysiologist blinded to clinical data and CMR findings. The prespecified primary endpoint was all-cause mortality or appropriate ICD discharge for ventricular tachycardia or fibrillation.(26) There were two secondary endpoints: 1) all-cause mortality alone, 2) sudden cardiac death or appropriate ICD discharge. For the primary endpoint, all-cause rather than cardiac mortality was included (as recommended by a policy statement on endpoints for trials that include ICDs written by the North American Society for Pacing and Electrophysiology(27) since the former is objective, clinically relevant, and unbiased, which is often not the case for cardiac mortality.(28) The secondary endpoint of SCD or appropriate ICD discharge was included to explore the mechanism of adverse outcome, and SCD was defined as death within 1 hour of symptom onset, or an unobserved death in which the patient was seen and known to be doing well within 24 hours of death.(29) All event information was obtained and classified without knowledge of clinical or CMR findings.

Patients were enrolled before the recent Federal Drug Administration alerts regarding the rare occurrence of nephrogenic systemic fibrosis associated with gadolinium contrast

administration.(30) Two patients had end-stage renal disease and were receiving dialysis (one hemodialysis, one peritoneal dialysis) at the time of enrollment. None of the study participants developed nephrogenic systemic fibrosis during the follow-up period.

Cardiovascular Magnetic Resonance

Acquisition—Clinical 1.5-T scanners (Siemens Sonata or Avanto) with phased-array receiver coils and standard protocols were used.(31) Briefly, cine images were acquired in multiple short-axis (every 10 mm throughout the entire LV) and 3 long-axis views using a steady-state free precession sequence (slice thickness, 6 mm; inter-slice gap, 4 mm; TR, 3.0 ms; TE, 1.5 ms; temporal resolution, 35-40 ms; flip angle, 60°; in-plane resolution 1.7×1.4 mm). DE-CMR was performed using a segmented inversion-recovery gradient-echo sequence (slice thickness, 6 mm; inter-slice gap, 4 mm; TR, 9.5 ms; TE, 3.8 ms; flip angle, 25°; in-plane resolution 1.8x1.4 mm) 10 minutes after contrast administration (gadoversetamide, 0.15 mmol/kg) in the identical locations as cine-CMR. Inversion delay time was set to null signal from normal myocardium, and was typically 280-360 ms.

Analysis—Cine-CMR and DE-CMR images were evaluated separately masked to all patient information. Left ventricular volumes, mass, and ejection fraction were quantitatively measured from the stack of short-axis cine images using standard techniques. (32) Presence or absence of left ventricular aneurysm was noted. The presence and location of hyperenhanced tissue on DE-CMR, which was interpreted as representing scarred myocardium,(31) was determined by visual inspection using the AHA 17-segment model. (33) Regional enhancement was scored according to the spatial extent of hyperenhanced tissue within each segment (0=no hyperenhancement, 1=1-25% hyperenhanced, 2=26-50%, 3=51-75%, 4=76-100%).(14) Scar size was measured by planimetry from the stack of short-axis DE-CMR images in our CMR core laboratory by a single, blinded reader. Inter- and intraoberver agreement for scar size is routinely tested in the core laboratory for quality assurance; Bland-Altman analysis demonstrated a bias of 1.0% and -0.1%, respectively with a standard deviation of differences of 2.6% and 0.8%, respectively;(22) the intra class correlation coefficients were 0.942 and 0.982, respectively. We also assessed other morphological characteristics of scar. These included the number of separate scars, scar surface area (determined from the scar circumference on the stack of short-axis DE-CMR images(34)), and scar pattern (classified as CAD-type when subendocardial or transmural in a typical vascular distribution, or non CAD-type when mid-myocardial or epicardial(35)). The extent of the "grey-zone" (i.e. regions with partial hyperenhancement) was also determined.(36) As described previously,(36) grey zones were defined as those regions with image intensity between 2 and 3 SD above that of reference, remote myocardium, and was expressed as a percentage of LV mass.

Electrophysiologic Testing

A total of 105 (77%) patients underwent EPS within a median of 0 days (IQR 0, 3.5) of CMR. No patient experienced a change in clinical status in the time between CMR and EPS. EPS was performed using standard techniques. Briefly, programmed stimulation was performed using two drive trains followed by one to three ventricular extrastimuli that were 2 ms in duration at twice the diastolic threshold at two right ventricular sites.(37) All EPS data were reinterpreted at a later timepoint by an experienced electrophysiologist blinded to patient information and CMR findings by reviewing the intracardiac electrograms and the surface ECG stored on the commercial recording system (Prucka Cardiolab, GE Healthcare). The EPS endpoint included the induction of a sustained monomorphic ventricular tachycardia (VT), polymorphic VT, or ventricular fibrillation (VF), or completion of the protocol.(37) Similar to previous studies, a sustained ventricular arrhythmia was defined as one lasting 30 seconds or requiring termination sooner because of hemodynamic

compromise, monomorphic VT was defined as a VT with a uniform beat-to-beat QRS morphology, polymorphic VT had a variable QRS morphology, and VF was defined as a rapid, disorganized rhythm without consistently identifiable complexes.(37)

Statistical Analysis

Normally distributed data are presented as the mean ± SD or, in cases where the distribution is not normal, as median and interquartile range. Two sample *t* tests were used to compare mean values of continuous data between two groups. Chi square tests were used to compare discrete data between groups; in those cases where the expected cell count was <5, Fisher's exact test was used. Cumulative event rates were calculated according to the Kaplan-Meier method. Differences in event rates between groups were assessed with the log-rank test without adjustment for multiple comparisons. In order to identify the baseline characteristics associated with adverse outcome, univariable Cox proportional hazards regression analysis was performed. For patients with two or more events during follow-up (several arrhythmic events or an arrhythmic event followed by death), only the time to the first event was considered per patient. Because coronary revascularization may result in procedure-related myocardial injury,(38,39) patients who underwent coronary bypass graft surgery or percutaneous coronary intervention after study enrollment were censored at the date of the procedure. Patients were to be censored on the date of heart transplantation, but none underwent heart transplantation during follow-up.

Two Cox regression multivariable models were subsequently developed. In the first, candidate variables showing a possible association with prognosis by univariable analysis (p<0.10) were considered one at a time starting with the most significant variable. Significant variables were determined by stepwise selection (and backwards elimination) at the 0.05-level of significance. In the subgroup with EPS a separate analysis was performed with monomorphic VT added as a covariate. Relative risks were expressed as hazard ratios with associated 95% confidence intervals (HR [95% CI]). In the second multivariable model, only 3 variables were included to avoid the potential for overfitting. These were NYHA functional class (the most significant clinical predictor), LVEF, and scar size>5%. Formal risk reclassification analyses were conducted with both integrated discrimination improvement (IDI) and net reclassification improvement (NRI) methods.(40) All statistical tests were two tailed and p<0.05 was regarded as significant. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

RESULTS

Baseline Characteristics

Of the 137 enrolled patients, all successfully underwent CMR and their baseline characteristics are shown in **Table 1**. Briefly, the mean age was 59 years, 63% were male, about half (53%) had ischemic heart disease, and the mean LVEF was 35%. Just over 60% had NYHA functional class II or higher, and two-thirds were treated with a beta-blocker and an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. The majority (n=105) underwent EPS, and monomorphic VT was induced in 21 (20%) patients. Myocardial scar was found in 107 patients (78%) with a median scar size of 7.8% of the left ventricular mass (IQR 1.1, 15.8). Patients with ischemic heart disease were older, more often male, more likely to have diabetes, hypertension, and hypercholesterolemia, and had lower LVEF and higher prevalence of myocardial scar, compared to those without ischemic disease.

Follow-up

The median follow-up time was 24 months (IQR 19.9, 29.0). No patient was lost to follow-up. 104 patients (75%) had an ICD placed, generally during the initial evaluation, 2 days (IQR 1, 7) after enrollment. The decision for ICD implantation was guided by standard consensus criteria(2,41) including LVEF and EPS results, but was at the discretion of the treating physician after discussion with the patient. The indication for ICD implantation was primary prophylaxis in 92 patients and secondary prophylaxis (sustained VT or presumed cardiac arrest) in 12. The primary endpoint of death or appropriate ICD discharge occurred in 39 (28%) patients: 19 died (5 of whom also had an ICD discharge) and 20 had ICD discharge only. Sudden cardiac death occurred in 5 patients. Four patients underwent revascularization (all percutaneous coronary interventions) at 9, 12, 12, and 21 months after enrollment, and were censored at that time.

Predictors of Adverse Events

Patient characteristics related to the primary endpoint are listed in **Table 1**. Patients who died or had an appropriate ICD discharge were more likely to have ischemic heart disease, worse NYHA functional class, and monomorphic VT elicited on EPS. Among the CMR parameters, patients with events had worse LVEF, larger end-diastolic and end-systolic volumes, and more frequently had a LV aneurysm. Additionally, they were more likely to have myocardial scar, and scar size as a percentage of left ventricular mass was larger compared to patients without events.

Figure 1a details the relationship between LVEF and events. For each decrement in LVEF, there was a monotonically increasing event rate. **Figure 1b** demonstrates a different relationship between scar size and events. There was a marked step-up in event rate in patients with a scar size exceeding 5% of LV mass (HR=5.2 [2.0-13.3], p=0.0006), without further rise with each increment in scar size. Among the 84 patients with scar >5%, 34 had events—17 died (4 of whom also had an ICD discharge) and 17 had ICD discharge only—representing an event rate of 19.6%/year and a mortality rate of 9.8%/year. Conversely, among the 53 patients with scar 5%, 5 had events—2 died (1 of whom also had an ICD discharge) and 3 had ICD discharge only—representing an event rate of 4.25%/year and a mortality rate of 1.7%/year. Among the 30 patients without any myocardial scar, there were 2 events (both ICD discharges, no deaths) representing a total event rate of 2.8%/year.

In **Table 2** the hazard ratios for the significant clinical and CMR predictors of adverse events are shown. For the primary endpoint of death or ICD discharge, multivariable analysis demonstrated that NYHA functional class (HR=1.7 [1.2-2.4], p=0.003) and scar size >5% (HR=4.6 [1.8-11.8], p=0.002) were the only independent predictors. Scar size >5% remained an independent predictor for the secondary endpoints of SCD or ICD discharge, and all-cause mortality. Notably, although LVEF was a significant univariable predictor of adverse events (primary and both secondary endpoints), it was not an independent predictor on multivariable analysis, either as a continuous variable or using a cutoff of 30% or 35%. Multivariable analysis excluding the 28 patients with a clinically ordered scan demonstrated the same independent predictors as in the entire population. For the primary endpoint, NYHA functional class (HR=1.9 [1.3-2.9], p=0.002) and scar size >5% (HR=4.9 [1.7-14.0], p=0.003), again were the only independent predictors.

When scar size was included as a continuous (% LV mass) rather than dichotomous variable, it remained an independent predictor of the primary endpoint, death or ICD discharge (HR=1.03 [1.01-1.07], p=0.03) and the secondary endpoint, SCD or ICD discharge (HR=1.04 [1.01-1.07], p=0.03).

An analysis of the subgroup of patients undergoing EPS (n=105) was performed after including inducible monomorphic VT as a covariate (**Table 2**). Scar size >5% was an independent predictor for all endpoints. Inducible monomorphic VT was a significant univariable predictor of death or ICD discharge, and SCD or ICD discharge but not all-cause death. On multivariable analysis, inducible monomorphic VT was not an independent predictor of the primary or secondary endpoints.

In a separate multivariable modeling approach, only three variables (NYHA class, LVEF, and scar size >5%) were included to avoid the potential for overfitting. In this model, scar size >5% was the strongest predictor of the primary endpoint (HR=4.5 [1.7-11.6], p=0.002). While NYHA class was an independent predictor (HR=1.6 [1.0-2.4], p=0.04), LVEF was not (HR=0.1 [0.97-1.20], p=0.58).

To assess the incremental prognostic value of the scar data over NYHA class and over LVEF, we performed a risk reclassification analysis for the primary endpoint. The IDI showed significant reclassification when adding scar data to the model with NYHA class (IDI=0.134, p=0.0004) and when adding scar data to the model with LVEF (IDI=0.111, p=0.003). The NRI was calculated using 4 risk categories (0-20%, 20-40%, 40-60%, and >60%), and also showed significant reclassification when adding scar data to the model with NYHA class (NRI=41%, p=0.03) and to the model with LVEF (NRI=32%, p=0.049).

Improved Risk Stratification in LVEF subgroups

Survival analysis in subgroups with >30% and LVEF 30%(5,42) are shown in **Figures 2** and **3**, respectively. Among patients with LVEF >30%, those with significant scarring (>5%) had higher incidence of death or ICD discharge compared to those with minimal-or-no (5%) scarring (HR=6.3 [1.4-28.0], p=0.02; **Figure 2a**). Despite an LVEF >30%, the high-risk subcohort with scar >5% had a similar event rate to the entire group with LVEF 30% (HR=0.8 [0.4-1.6], p=0.56). Similar relationships were observed for the secondary endpoints (**Figure 2b and c**).

Among patients with LVEF 30%, again those with scar >5% had higher incidence of death or ICD discharge compared to those with scar 5% (HR=3.9 [1.2-13.1, p=0.03]; **Figure 3a**). Similar trends were found for the secondary endpoints, but these did not reach statistical significance (**Figure 3b and c**). Despite an LVEF 30%, the low-risk subcohort with scar 5% had a similar event rate (for all 3 endpoints) to the entire group with LVEF >30%.

Survival analysis using an LVEF cutoff of 35% (rather than 30%) demonstrated similar findings. Despite an LVEF >35%, those patients with scar >5% had a similar event rate to the entire group with LVEF 35% (HR=0.6 [0.3-1.5], p=0.29). Conversely, among patients with an LVEF 35%, the subgroup of patients with scar 5% had a similar event rate to the entire group with LVEF >35% (HR=0.8 [0.2-2.8], p=0.69). **Figure 4** illustrates typical CMR images in patients with various levels of myocardial scarring and left ventricular function.

Scar Morphology and Events

A number of characteristics of scar morphology were evaluated, and their relationships to outcome are shown in **Table 3**. Many parameters were associated with adverse outcome (primary and both secondary endpoints) on an unadjusted basis. However, a multivariable analysis including only scar morphology covariates, demonstrated that scar size >5% (p=0.03, HR=3.1 [1.1, 8.6]) and the number of separate scars (p=0.02, HR=1.7 [1.1, 2.5]) were independent predictors of the primary endpoint.

DISCUSSION

The main finding of this study is that myocardial scarring detected by DE-CMR strongly predicts death or appropriate ICD discharge for sustained ventricular arrhythmia in patients undergoing evaluation for possible ICD placement. On multivariable analysis, which included LVEF and electrophysiological study results, scar size was an independent predictor of adverse outcome when considered as a continuous variable or dichotomized at 5% of LV mass. For the latter, the hazard ratio was 4.6 [1.8-11.8] in all patients and 4.4 [1.7-11.6] in patients undergoing EPS (n=105). Furthermore, scar size >5% was an independent predictor of both secondary endpoints, SCD or ICD discharge and all-cause mortality alone.

Scar tissue is believed to be a fundamental component of the anatomical substrate for lethal ventricular arrhythmias.(10-13,43) In the setting of coronary disease, electrical mapping studies have revealed that reentrant VT usually originates from the subendocardial surface of infarcted myocardium, adjacent to dense scar.(11,43,44) In the setting of nonischemic cardiomyopathy, scar is less common and some characteristics are different (less confluence, less endocardial involvement)(17,45,46) but again VT appears primarily the result of myocardial reentry associated with scar.(13,47) In both settings, histological analysis of myocardial specimens have shown that regions that are crucially involved in the reentry circuit consist of isolated bundles of surviving myocytes interwoven with strands of fibrous scar tissue—the consequence of which is nonuniform anisotropic conduction and other electrophysiological abnormalities that can result in VT.(11,12,43)

The potential relevance of scar as detected by DE-CMR was initially investigated by comparisons with electrophysiological testing. Bello et al.(34) observed that infarct scar size (or surface area) was a better predictor of inducible monomorphic VT on EPS than LVEF in patients with coronary disease. Similarly, Nazarian et al.(48) demonstrated that DE-CMR assessment of scar distribution was the strongest predictor of inducible VT in patients with nonischemic cardiomyopathy. More recently, in patients referred for radiofrequency ablation of VT or symptomatic premature ventricular complexes, Bogun et al.(46) reported that DE-CMR diagnosed scar in all patients with history of sustained VT; and when a critical site of VT was identified, it occurred within areas of scar in all cases. Moreover, the location of scar was a reliable guide to catheter ablation—for predominantly endocardial scar, an endocardial approach was necessary, for epicardial scar, an epicardial approach was needed, and for mid-wall intramural scar, ablation was uniformly ineffective. Thus, these data present compelling evidence that DE-CMR identified scar is associated with ventricular arrhythmias, and offer mechanistic insight into why scar assessment may be better at predicting prognosis than LVEF or indices of LV morphology.

The results of the present study corroborate and extend those of earlier reports investigating the prognostic significance of scarring identified by DE-CMR.(19,21,22,24,49,50) These studies have consistently demonstrated the additive value of scar (or infarct) assessment for predicting adverse outcome. However, most studies had few hard endpoints(19,23,24) and/ or were retrospective evaluations of patients who had undergone clinically ordered CMR in which scan results were used to determine patient management.(21,49,50) In the current study, all patients were prospectively enrolled prior to CMR and in most (80%) CMR was performed only for research purposes and scan results were not used to guide clinical decision-making. The overall crude mortality rate of 6.8%/year was similar to that in comparable populations at risk for arrhythmia,(3,5) and 39 patients reached the prespecified primary endpoint of death or appropriate ICD discharge. Although still relatively small, the number of events compares favorably with recently published prospective CMR studies by

Wu,(23) Assomull,(19) and Wu et al.(24) that involved 18, 23, and 15 events, respectively overall, and 2, 10, and 7 events after excluding hospitalization events.

The present study is the first to directly compare CMR scar assessment with invasive EPS for predicting prognosis. EPS has distinct advantages over LVEF in that the actual induction of VT directly establishes the presence of an arrhythmic substrate, is more specific for predicting an arrhythmic death,(51) and a risk stratification strategy involving EPS has higher efficiency (fewer ICDs needed /life saved) than one focused primarily on LVEF.(52) Nonetheless, a negative EP study is not reassuring and does not indicate low likelihood for arrhythmic death especially in patients with low LVEF or with nonischemic cardiomyopathy.(37,52,53) In our relatively broad patient population we observed that inducibilty of VT on EPS was a significant univariable predictor of adverse events, but on multivariable analysis DE-CMR scar assessment was superior to EPS in predicting both primary and secondary endpoints.

Clinical Implications

Although significant left ventricular dysfunction identifies a cohort at particularly high risk for SCD, it is a well-recognized paradox that most patients that die suddenly have less severe dysfunction. For instance, the Maastricht prospective registry found that 81% of patients experiencing SCD had an LVEF >30% before the event.(54) Likewise, the Oregon sudden death study reported that 70% of patients suffering SCD had an LVEF >35% before the event. The present investigation was not a community-wide population study, but it is notable that of the 72 patients that would have been considered low-risk solely from an LVEF perspective (LVEF >30%), 14 died or had an appropriate ICD discharge during followup. Importantly, scar >5% on DE-CMR classified 12 of these 14 as high- rather than low-risk individuals. DE-CMR images of two of these patients are shown in Figure 4 (*Patient C* and *D*).

On the other hand, it is also recognized that among patients that meet the current definition of high-risk LVEF (30%-35%), the majority will not derive any benefit from ICD implantation, since 14-18 patients with high-risk LVEF need to have an ICD implanted to prevent one death.(3,5) In the present study 65 patients had LVEF 30%, among whom 25 died or had an appropriate ICD discharge during followup. However, those with scar 5% had a 3-year event rate that was below or similar to that of the entire group with low-risk LVEF (Figure 3a).

Eligibility for ICD implantation is based primarily on the presence of LV dysfunction, since LVEF is considered the strongest independent predictor of SCD among traditional clinical markers.(55) However, our data corroborate prior investigations reporting LVEF lacks both sensitivity and specificity in predicting clinical events.(55) Although preliminary, our findings highlight the potential of scar assessment by DE-CMR to improve the sensitivity of risk stratification by identifying patients with relatively preserved LVEF who nevertheless are at considerable risk for poor outcome. Because most SCD occurs in patients with preserved LVEF substantial effort is justified in evaluating new noninvasive risk stratification strategies in this group.(55) Our results also suggest that DE-CMR scar assessment may be useful in identifying patients with low LVEF who may not benefit from ICD therapy. This hypothesis requires extensive further testing but seems warranted given the substantial cost of ICD therapy and the potential for harm, from unnecessary shocks, procedural complications, manufacturer recalls, and possible proarrhythmia.(56)

Study Limitations

There are limitations in using ICD discharges—even after classification as appropriate or not based on stored electrograms—as a surrogate for SCD.(57) However, our findings were similar when using all-cause mortality as the endpoint (Table 2) and we believe the main associations between scar and adverse outcome in the study are unlikely to be spurious.

We compared scar with LVEF, EPS, QRS duration, and many other clinical indices, but several others with high potential for improving risk stratification, such as T-wave alternans and heart rate variability, were not tested. A systematic comparison between scar and these other risk metrics was beyond the scope of the present study but would be an important area of future research.

An exploratory analysis of scar morphology (Table 3) suggests other characteristics besides size may be important for risk stratification, such as the number of separate scars, but this will require prospective testing to fully explore their significance. There are several ways to quantitatively assess the grey zone, and it is possible that a different analysis method than the one used in the present study may have provided different results. Likewise, there may be different thresholds in scar size to optimally stratify risk when considering CAD and non-CAD patients separately. Interestingly, similar to the results of the present study, we note that Assomull et al.(19) found that scar >4.8% was the optimal threshold to predict outcome in patients with nonischemic cardiomyopathy, and Kwong et al.(21) observed a sharp step-up in risk with even a small amount of scarring in patients with coronary disease. It is speculative, but these results are consistent with experimental investigations that have suggested that a "critical mass" of scar is necessary for reentrant VT to occur.(58,59)

Finally, an important limitation is that the conclusions are based on a limited number of events (the primary endpoint occurred in 39 patients), and this raises the possibility of overfitted multivariable models; larger studies are vital to confirm these findings.

Conclusions

In patients undergoing evaluation for possible ICD implantation, myocardial scarring detected by DE-CMR predicts worse outcome. Even in patients with LVEF >30% considered low-risk from an LVEF perspective, significant scarring (>5%) identifies a cohort with a high rate of adverse events and one similar in risk to those with LVEF ≤30%. Additionally, in patients with LVEF ≤30%, minimal-or-no scarring identifies a cohort with lower risk similar those with LVEF >30%. The findings suggest that DE-CMR scar assessment is superior to LVEF for risk stratification, and justify future studies prospectively testing whether patient management guided by CMR findings can improve patient outcome.

Acknowledgments

ABBREVIATIONS

CAD	coronary artery disease
CMR	cardiac magnetic resonance
DE-CMR	delayed-enhancement cardiovascular magnetic resonance
EPS	electrophysiology study

ICD	implantable cardioverter-defibrillator
LVEF	left-ventricular ejection fraction
SCD	sudden cardiac death

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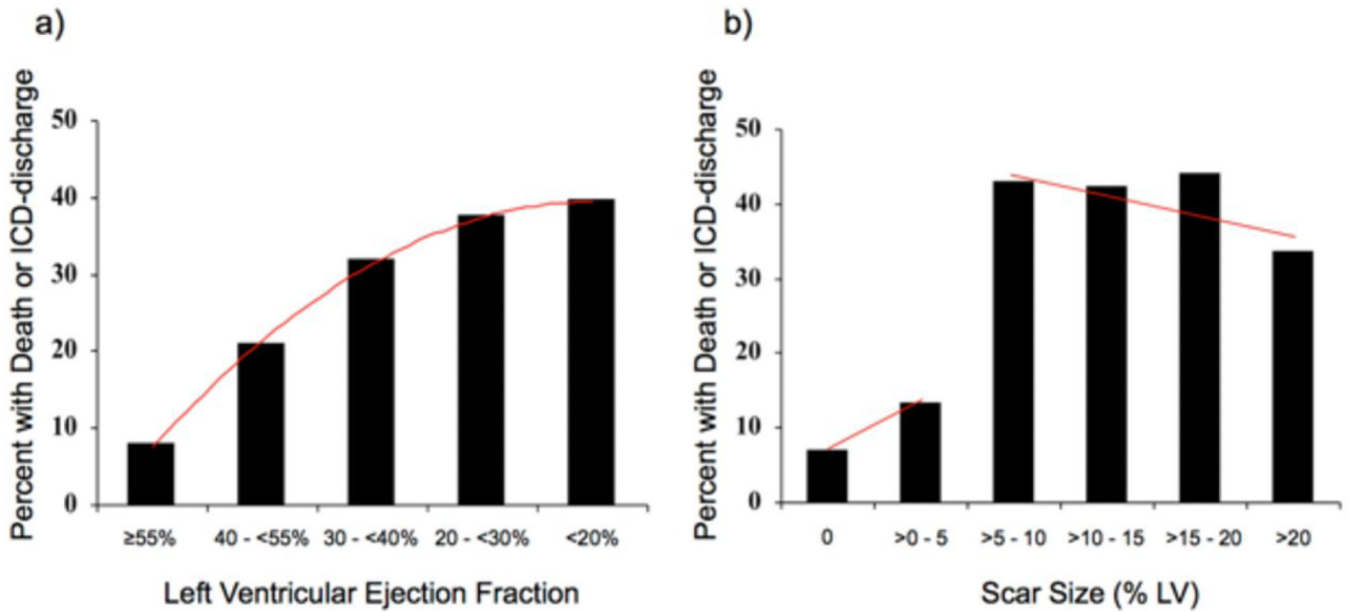
Figure 1. Event Rate Depending on LVEF and Scar Size
The percentage of patients with the primary endpoint of death or appropriate ICD discharge is shown according to different levels of left ventricular ejection fraction (**Panel a)** and scar size (**Panel b**). For ejection fraction, the trendline (red line) shows a positive slope over the entire range, indicating that event rate monotonically increases with decreasing LVEF. In contrast, a marked step-up in event rate is noted for scar size greater than 5% of left ventricular mass, which however does not rise further with increasing scar size.
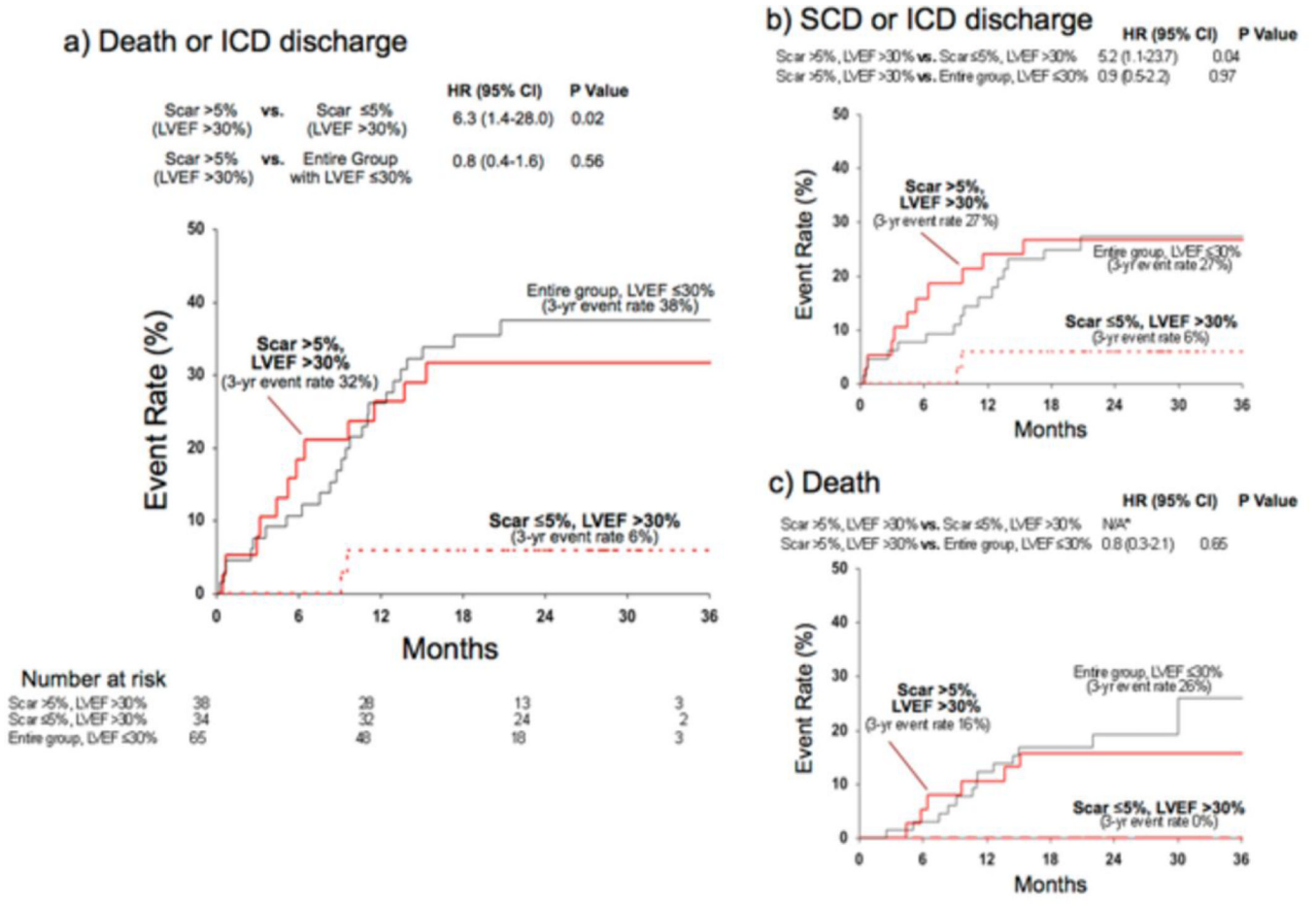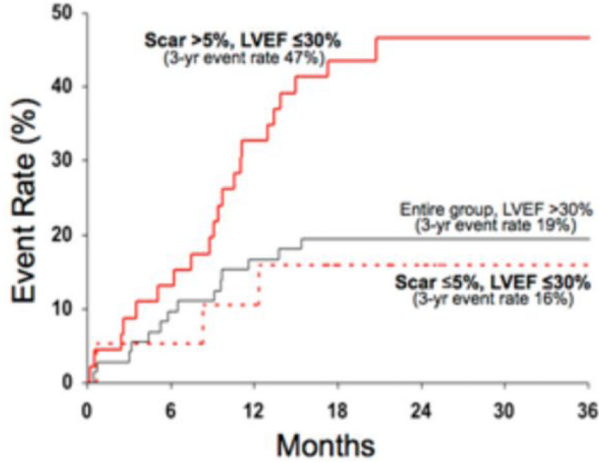
a) Death or ICD discharge

			HR (95% CI)	P Value
Scar >5% (LVEF >30%)	vs.	Scar ≤5% (LVEF >30%)	6.3 (1.4-28.0)	0.02
Scar >5% (LVEF >30%)	vs.	Entire Group with LVEF ≤30%	0.8 (0.4-1.6)	0.56

b) SCD or ICD discharge

	HR (95% CI)	P Value
Scar >5%, LVEF >30% vs. Scar ≤5%, LVEF >30%	5.2 (1.1-23.7)	0.04
Scar >5%, LVEF >30% vs. Entire group, LVEF ≤30%	0.9 (0.5-2.2)	0.97

c) Death

	HR (95% CI)	P Value
Scar >5%, LVEF >30% vs. Scar ≤5%, LVEF >30%	N/A*	
Scar >5%, LVEF >30% vs. Entire group, LVEF ≤30%	0.8 (0.3-2.1)	0.65

Number at risk

Scar >5%, LVEF >30%	38	28	13	3
Scar ≤5%, LVEF >30%	34	32	24	2
Entire group, LVEF ≤30%	65	48	18	3

Figure 2. Kaplan-Meier Estimates of Adverse Events in Patients With LVEF >30%
In patients with LVEF >30%, those with significant scarring (>5% of LV mass) had a higher event rate than those with minimal-or-no scarring (5%) for both the primary (**panel a**) and the two secondary endpoints (**panels b, c**). Those with LVEF >30% and significant scarring had similar event rate to the entire group of patients with LVEF 30%. * For the secondary endpoint of death alone, the hazard ratio between scar >5%, LVEF >30% and scar 5%, LVEF >30% cannot be calculated because there were no deaths in the latter group.

a) Death or ICD discharge

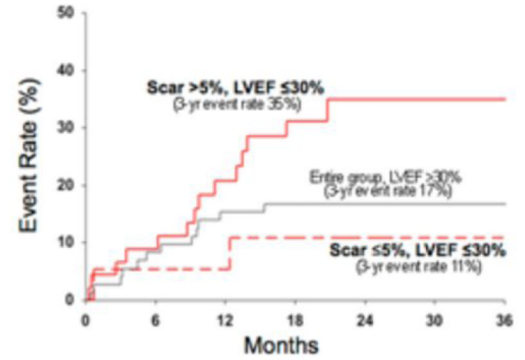|			HR (95% CI)	P Value
Scar >5% (LVEF ≤30%)	vs.	Scar ≤5% (LVEF ≤30%)	3.9 (1.2-13.1)	0.03
Scar ≤5% (LVEF ≤30%)	vs.	Entire Group with LVEF >30%	0.8 (0.2-2.8)	0.71

Number at risk

Scar >5%, LVEF ≤30%	46	31	11	1
Scar ≤5%, LVEF ≤30%	19	17	7	2
Entire group LVEF >30%	72	60	37	5

b) SCD or ICD discharge

	HR (95% CI)	P Value
Scar >5%, LVEF ≤30% vs. Scar ≤5%, LVEF ≤30%	4.2 (0.9-18.7)	0.06
Scar ≤5%, LVEF ≤30% vs. Entire group, LVEF >30%	0.6 (0.1-2.8)	0.53

c) Death

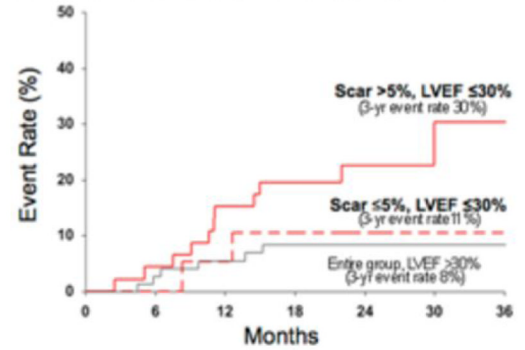|	HR (95% CI)	P Value
Scar >5%, LVEF ≤30% vs. Scar ≤5%, LVEF ≤30%	2.2 (0.5-10.2)	0.29
Scar ≤5%, LVEF ≤30% vs. Entire group, LVEF >30%	1.3 (0.3-6.3)	0.77

Figure 3. Kaplan-Meier Estimates of Adverse Events in Patients With LVEF 30%
In patients with LVEF 30%, those with significant scarring (>5% of LV mass) had a higher event rate than those with minimal-or-no scarring (5%) for both the primary (**panel a**) and the two secondary endpoints (**panels b, c**). Those with LVEF 30% and minimal-or-no scarring had similar event rate to the entire group of patients with LVEF >30%.
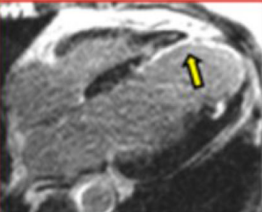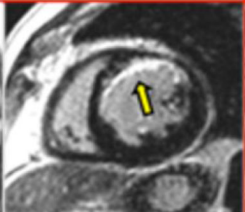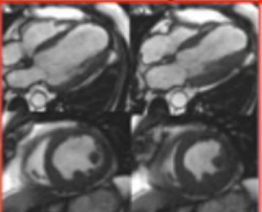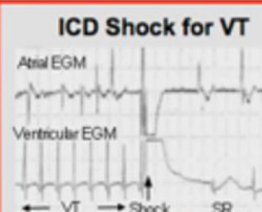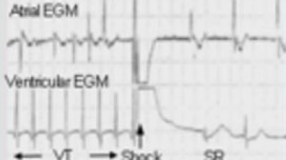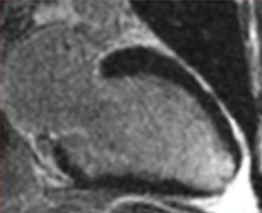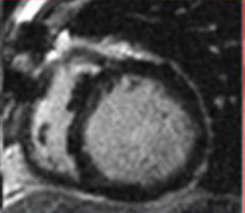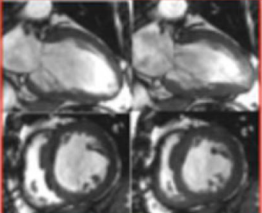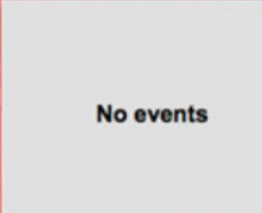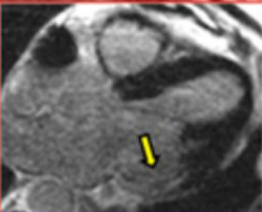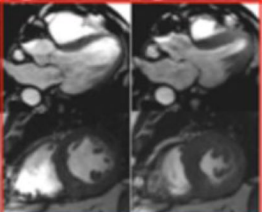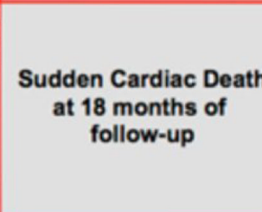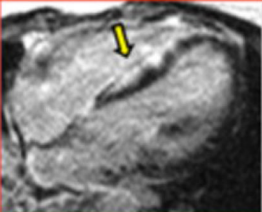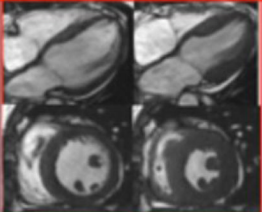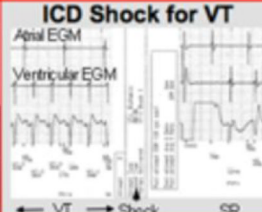
Figure 4. Typical CMR Images In Patients With Various Levels Of Myocardial Scarring And Left Ventricular Function
Example CMR images are shown in patients with concordance (Patient A) and discordance (Patient B, C, and D) in the assessment of risk as determined by LVEF and myocardial scarring (yellow arrows). The last column reports findings during follow-up including the ICD electrograms when available. Patient A had poor LVEF and substantial scarring. This patient, who had both parameters concordant for high risk, had an ICD discharge for ventricular tachycardia during the first month of follow-up. Conversely, Patient B had poor LVEF but no myocardial scar, representing discordance in risk between these two parameters. This patient received an ICD based on LVEF criteria, however had no adverse events during follow-up (29 months). Patients C and D represent examples of those with significantly higher LVEF (46% and 49%, respectively) in whom there was discordance in risk in that substantial scarring was found. Patient C had CAD-type scarring (involves LV subendocardium), whereas patient D had non-CAD-type scarring (spares the LV subendocardium). Both patients had events during follow-up (patient C: sudden cardiac death 18 months after study enrollment; patient D: appropriate ICD discharge to terminate VT at one month and again at 10 months of follow-up).

Table 1

Baseline Patient Characteristics

Characteristic	All patients (n=137)	Death or ICD discharge (n=39)	No Death or ICD discharge (n=98)	P	CAD (n=73)	No CAD (n=64)	P
Age (yr)	59.2±15.1	61.6±15.9	58.2±14.9	0.23	65.3±10.9	52.3±16.2	**<0.0001**
Male gender	86 (63%)	26 (67%)	60 (61%)	0.55	54 (74%)	32 (50%)	**0.004**
Clinical History							
Diabetes mellitus	32 (23%)	13 (33%)	19 (19%)	0.08	27 (37%)	5 (8%)	**<0.0001**
Hypertension	73 (53%)	23 (59%)	50 (51%)	0.40	49 (67%)	24 (38%)	**0.0005**
Cigarette Smoker	25 (18%)	9 (23%)	16 (16%)	0.36	16 (22%)	9 (14%)	0.24
Hypercholesterolemia	67 (49%)	21 (54%)	46 (47%)	0.47	55 (75%)	12 (19%)	**<0.0001**
Ischemic Heart Disease	73 (53%)	26 (67%)	47 (47%)	**0.04**	...	...	
Prior Revascularization	54 (39%)	16 (41%)	38 (39%)	0.81	...	...	
CABG	38 (70%)	11 (69%)	27 (71%)	0.94	...	...	
PCI	16 (30%)	5 (31%)	11 (29%)	0.79	...	...	
Prior Myocardial Infarction [*]	48 (35%)	15 (38%)	33 (34%)	0.60	...	...	
NYHA functional class [†]				**0.003**			0.15
I	51 (37%)	7 (18%)	44 (45%)		21 (29%)	30 (47%)	
II	34 (25%)	10 (26%)	24 (24%)		21 (29%)	13 (20%)	
III	45 (33%)	17 (44%)	28 (29%)		26 (36%)	19 (27%)	
IV	7 (5%)	5 (13%)	2 (2%)		5 (7%)	2 (3%)	
Medications							
ACE-Inhibitor	75 (55%)	22 (56%)	53 (54%)	0.80	44 (66%)	31 (48%)	0.16
ARB	15 (11%)	6 (15%)	9 (9%)	0.24	9 (12%)	6 (9%)	0.58
Antiarhythmic Class I	2 (1%)	1 (3%)	1 (1%)	0.49[#]	0 (0%)	2 (3%)	0.12[#]
Antiarhythmic Class III	16 (12%)	4 (10%)	12 (12%)	0.78[#]	8 (11%)	8 (13%)	0.78[#]
Antiplatelet	96 (70%)	30 (77%)	66 (67%)	0.27	63 (86%)	33 (52%)	**<0.0001**
Beta-blocker	92 (67%)	31 (79%)	61 (62%)	0.053	57 (78%)	35 (55%)	**0.004**
Calcium-channel Blocker	18 (13%)	4 (10%)	14 (14%)	0.59[#]	7 (10%)	11 (17%)	0.19[#]
Digitalis	36 (26%)	11 (28%)	25 (26%)	0.75	21 (29%)	15 (23%)	0.48
Diuretics	71 (52%)	24 (62%)	47 (48%)	0.15	42 (58%)	29 (45%)	0.15

Characteristic	All patients (n=137)	Death or ICD discharge (n=39)	No Death or ICD discharge (n=98)	P	CAD (n=73)	No CAD (n=64)	P
Spironolactone	31 (23%)	10 (26%)	21 (21%)	0.60	18 (25%)	13 (20%)	0.54
Statin	66 (48%)	19 (49%)	47 (48%)	0.94	51 (70%)	15 (23%)	**<0.0001**
Electrocardiogram							
Heart rate (bpm)	74.0±14.8	77.6±15.3	72.6±14.3	0.07	72.4±13.4	75.8±16.0	0.18
QRS (ms)	111.9±31.8	116.2±29.9	110.3±32.4	0.33	115.2±30.3	108.3±33.2	0.21
Left bundle branch block	21 (16%)	7 (18%)	14 (14%)	0.57	11 (15%)	10 (16%)	0.92
Right bundle branch block	18 (13%)	5 (13%)	13 (13%)	0.97	10 (14%)	8 (13%)	0.84
Electrophysiologic Study [§]							
Monomorphic VT	21 (20%)	10 (34%)	11 (14%)	**0.02**	15 (28%)	6 (11%)	**0.02**
Polymorphic VT or VF	22 (21%)	5 (17%)	17 (22%)	0.56	14 (27%)	8 (15%)	0.14
Non inducible[‡]	57 (54%)	14 (48%)	43 (57%)	0.45	33 (44%)	24 (45%)	0.89
CMR							
LVEF(%)	35.3±18.1	27.9±14.3	38.3±18.8	**0.002**	30.5±14.0	40.9±20.6	**0.0008**
LV EDV (ml)	207.7±111.0	246.0±155.5	192.4±83.5	**0.048**	224.0±98.9	183.0±90.6	0.13
LV ESV (ml)	147.7±110.6	190.0±152.2	130.9±84.1	**0.03**	165.1±96.8	122.1±94.2	**0.01**
LV mass (g)	196.8±71.0	201.2±73.1	194.9±70.4	0.64	204.4±63.1	186.8±76.4	0.14
LV aneurysm	12 (9%)	6 (21%)	6 (6%)	**0.01**	10 (14%)	2 (3%)	**0.03**
Any scar on DE-CMR	107 (78%)	37 (95%)	70 (71%)	**0.003**	70 (96%)	37 (58%)	**<0.0001**
Scar size (% of LV mass)	7.8 (1.1, 15.8)	12.9 (6.3, 19.2)	5.2 (0.0, 14.7)	**0.002**	13.9 (6.2-19.3)	1.9 (0-8.5)	**<0.0001**

ARB = angiotensin receptor blocker, ACE-Inhibitor = angiotensin-converting-enzyme inhibitor, CAD = coronary artery disease, CABG = coronary artery bypass graft surgery, CMR = cardiovascular magnetic resonance imaging, DE-CMR = delayed enhancement CMR, EDV = enddiastolic volume, ESV = endsystolic volume, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, PCI = percutaneous coronary intervention, VF = ventricular fibrillation, VT = ventricular tachycardia.

[*]
10 patients with subacute infarction (<30 days of CMR study).

[†]
NYHA functional class was documented at time of hospital admission; P value pertains to the comparison between the groups with and without events, and with and without CAD in the distribution of patients according to NYHA class.

[#]
Fisher exact test (two-tailed).

[§]
Performed in 105 patients.

[‡]
Includes 5 patients without structural heart disease in whom bundle branch re-entry tachycardia was induced.

Table 2

Clinical and CMR Predictors of Time to Event

Parameter	Death or ICD discharge				SCD or ICD discharge				Death			
* Only parameters with p < 0.10 for one or more endpoints are shown	Univariable HR (95% CI)	P	Multivariable HR (95% CI)	P	Univariable HR (95% CI)	P	Multivariable HR (95% CI)	P	Univariable HR (95% CI)	P	Multivariable HR (95% CI)	P
All (n=137)												
Clinical												
Male gender	…	…	…	…	…	…	…	…	3.43 (1.00-11.80)	0.05	…	…
Ischemic Heart Disease	1.98 (1.01-3.86)	0.05	…	…	…	…	…	…	3.76 (1.25-11.33)	0.02	…	…
Diabetes mellitus	1.81 (0.93-3.53)	0.08	…	…	…	…	…	…	3.51 (1.43-8.66)	0.006	…	…
NYHA functional class	1.81 (1.29-2.56)	0.0007	1.70 (1.19-2.41)	0.003	1.50 (1.01-2.21)	0.042	…	…	2.86 (1.65-4.96)	0.0002	2.19 (1.29-3.70)	0.004
Beta-blocker	2.12 (0.97-4.62)	0.06	…	…	…	…	…	…	…	…	…	…
Heart rate (bpm)	1.017 (0.997-1.038)	0.10	…	…	…	…	…	…	1.05 (1.02-1.08)	0.0004	1.05 (1.02-1.08)	0.002
QRS (ms)	…	…	…	…	…	…	…	…	1.01 (1.00-1.02)	0.09	…	…
CMR												
LVEF (%)	0.971 (0.952-0.991)	0.005	…	…	0.977 (0.955-0.999)	0.04	…	…	0.957 (0.927-0.989)	0.009	…	…
LVEF ≤ 30%	2.17 (1.13-4.17)	0.02	…	…	1.73 (0.83-3.63)	0.15	…	…	2.56 (0.97-6.73)	0.06	…	…
LVEF ≤ 35%	2.65 (1.26-5.60)	0.01	…	…	2.11 (0.93-4.78)	0.07	…	…	4.16 (1.21-14.28)	0.02	…	…
LV EDV (ml)	1.003 (1.001-1.006)	0.03	…	…	1.003 (1.000-1.006)	0.06	…	…	1.006 (1.003-1.009)	0.0004	…	…
LV ESV (ml)	1.003 (1.001-1.006)	0.01	…	…	1.003 (1.001-1.006)	0.04	…	…	1.006 (1.003-1.009)	0.0002	…	…
LV mass (g)	…	…	…	…	…	…	…	…	1.005 (0.999-1.010)	0.09	…	…
LV aneurysm	…	…	…	…	2.65 (1.08-6.51)	0.03	…	…	…	…	…	…
Any scar on DE-CMR	6.15 (1.48-25.5)	0.01	…	…	4.50 (1.07-18.9)	0.04	…	…	NA#	NA#	…	…
Scar size (% LV mass)	1.038 (1.008-1.069)	0.01	…	…	1.038 (1.003-1.074)	0.03	…	…	…	…	…	…
Scar size > 5%	5.18 (2.02-13.3)	0.0006	4.59 (1.79-11.8)	0.002	4.76 (1.65-13.7)	0.004	4.76 (1.65-13.7)	0.004	5.89 (1.36-25.5)	0.02	8.75 (1.89-41.0)	0.006
Electrophysiology Study (EPS) Subgroup (n=105)												
Clinical												
Ischemic Heart Disease	2.20 (1.02-4.73)	0.04	…	…	…	…	…	…	3.85 (1.06-13.99)	0.04	…	…
Cigarette Smoker	…	…	…	…	2.23 (0.91-5.46)	0.08	…	…	…	…	…	…
Diabetes mellitus	…	…	…	…	…	…	…	…	2.94 (0.99-8.76)	0.05	…	…

Parameter	Death or ICD discharge				SCD or ICD discharge				Death			
	Univariable		Multivariable		Univariable		Multivariable		Univariable		Multivariable	
*Only parameters with p <0.10 for one or more endpoints are shown	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
NYHA functional class	1.66 (1.11-2.50)	0.01	1.53 (1.00-2.33)	0.05	...	...	...	...	2.32 (1.23-4.43)	0.009	...	...
Heart rate (bpm)	1.02 (1.00-1.04)	0.05	...	...	...	...	...	...	1.05 (1.02-1.09)	0.0006	1.06 (1.03-1.10)	0.0006
QRS (ms)	1.011 (1.000-1.021)	0.05	...	...	...	...	...	...	1.018 (1.003-1.033)	0.02	...	...
LBBB	...	...	...	...	...	...	...	...	3.14 (0.96-10.24)	0.06	...	...
EPS												
Monomorphic VT	2.47 (1.15-5.30)	0.02	...	...	3.26 (1.39-7.63)	0.007	...	...	...	...	...	...
CMR												
LVEF(%)	0.972 (0.950-0.994)	0.01	...	...	0.977 (0.950-1.002)	0.07	...	...	0.965 (0.930-1.000)	0.05	...	...
LVEF ≤30%	2.25 (1.06-4.78)	0.03	...	...	2.00 (0.86-4.69)	0.11	...	...	2.06 (0.67-6.26)	0.21	...	...
LVEF ≤35%	2.31 (1.02-5.22)	0.04	...	...	1.90 (0.77-4.66)	0.16	...	...	2.86 (0.79-10.41)	0.11	...	...
LV EDV (ml)	...	...	...	...	...	...	...	...	1.004 (1.001-1.008)	0.01	...	...
LV ESV (ml)	1.003 (1.000-1.006)	0.08	...	...	...	...	...	...	1.005 (1.001-1.008)	0.01	...	...
LV aneurysm	...	...	...	...	...	...	...	...	NA[†]	NA[†]	...	...
Any scar on DE-CMR	6.37 (1.51-26.8)	0.01	...	...	4.72 (1.10-20.18)	0.04	...	...	NA[#]	NA[#]	...	...
Scar size (% LV mass)	1.034 (1.001-1.067)	0.04	...	...	1.033 (0.996-1.071)	0.08	...	...	...	...	...	...
Scar size > 5%	5.16(1.97-13.6)	0.0009	4.36 (1.65-11.6)	0.003	4.83 (1.63-14.3)	0.004	4.83 (1.63-14.3)	0.004	5.28 (1.17-23.8)	0.03	5.81 (1.26-26.8)	0.02

*Only variables with p<0.10 by univariable analysis were considered for inclusion in the multivariable model.

[†]Not available because no patient in the EPS subgroup who died had an LV aneurysm.

[#]Not available because all patients who died had scar tissue.

Table 3

Relationship of Scar Morphology Variables With Time to Event

Parameter	Death or ICD discharge Univariable		SCD or ICD discharge Univariable		Death Univariable	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Any scar	6.15 (1.48-25.53)	0.01	4.50 (1.07-18.89)	0.04	NA[#]	NA[#]
CAD type[*]	5.69 (1.33-24.39)	0.02	4.02 (0.91-17.76)	0.07	NA[#]	NA[#]
Non-CAD type[†]	4.71 (1.02-21.82)	0.05	3.23 (0.65-16.02)	0.15	NA[#]	NA[#]
Scar size (% of LV mass)	1.04 (1.01-1.07)	0.01	1.04 (1.00-1.07)	0.03	1.03 (0.99-1.08)	0.2
Scar size >5%	5.18 (2.02-13.25)	0.0006	4.76 (1.66-13.69)	0.004	5.89 (1.36-25.48)	0.02
Scar surface area (cm²)	1.005 (1.001-1.008)	0.008	1.005 (1.001-1.009)	0.03	1.006 (1.001-1.011)	0.03
Number of separate scars	2.07 (1.46-2.94)	<0.0001	1.91 (1.28-2.87)	0.002	3.11 (1.83-5.28)	<0.0001
Largest separate scar size (% of LV mass)	1.03 (1.00-1.06)	0.09	1.03 (1.00-1.07)	0.08	1.01 (0.96-1.06)	0.7
Largest separate surface area (cm²)	1.004 (1.000-1.008)	0.06	1.005 (1.000-1.009)	0.06	1.003 (0.997-1.009)	0.4
Segments with transmural scar (>75%)	1.06 (0.85-1.32)	0.6	1.11 (0.87-1.41)	0.4	0.80 (0.51-1.26)	0.3
Segments with transmural scar (>50%)	1.07 (0.93-1.25)	0.4	1.10 (0.93-1.29)	0.3	0.90 (0.69-1.17)	0.4
Segments with non-transmural scar (1-50%)	1.13 (1.04-1.22)	0.005	1.10 (1.00-1.22)	0.05	1.18 (1.05-1.32)	0.007
Segments with non-transmural scar (26-75%)	1.17 (1.04-1.31)	0.01	1.17 (1.02-1.34)	0.02	1.07 (0.89-1.29)	0.5
Grey zone (% of LV mass)	1.011 (0.994-1.027)	0.20	1.003 (0.980-1.026)	0.81	1.019 (1.000-1.039)	0.052

[*] CAD-type scar required involvement of the subendocardium. Hazard ratios were calculated excluding patients with non-CAD type scar.

[†] Isolated midwall or epicardial scar was considered Non-CAD type. Hazard ratios were calculated excluding patients with CAD type scar.

[#] Not available because all patients who died had scar tissue.