Extent of Left Ventricular Scar Predicts Outcomes in Ischemic Cardiomyopathy Patients With Significantly Reduced Systolic Function

A Delayed Hyperenhancement Cardiac Magnetic Resonance Study

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OBJECTIVES The objective of the study was to determine whether the extent of left ventricular scar, measured with delayed hyperenhancement cardiac magnetic resonance (DHE-CMR), predicts survival in patients with ischemic cardiomyopathy (ICM) and severely reduced left ventricular ejection fraction (LVEF).

BACKGROUND Patients with ICM and reduced LVEF have poor survival. Such patients have a high myocardial scar burden. CMR is highly accurate in delineation of myocardial scar.

METHODS We studied 349 patients (76% men) with severe ICM ($\geq$70% disease in $\geq$1 epicardial coronary, and mean LVEF of 24%) that underwent DHE-CMR (Siemens 1.5-T scanner, Erlangen, Germany), between 2003 and 2006. Scar (quantified as percentage of myocardium) was defined on DHE-MR images as an intensity >2 standard deviations above the viable myocardium. Transmurality score was semiquantitatively recorded in a 17-segment model as: 0 = no scar, 1 = 1% to 25% scar, 2 = 26% to 50%, 3 = 51% to 75%, and 4 = >75%. The LVEF, demographic data, risk factors, need for cardiac transplantation (CTx), and all-cause mortality were recorded.

RESULTS The mean age and follow-up were 65 $\pm$ 11 years and 2.6 $\pm$ 1.2 years (median 2.4 years [1.1, 3.5]), respectively. There were 56 events (51 deaths and 5 CTx). Mean scar percentage and transmurality score were higher in patients with events versus those without (39 $\pm$ 22 vs. 30 $\pm$ 20, p = 0.003, and 9.7 $\pm$ 5 vs. 7.8 $\pm$ 5, p = 0.004). On Cox proportional hazard survival analysis, quantified scar was greater than the median (30% of total myocardium), and female gender predicted events (relative risk 1.75 [95% Confidence Interval: 1.02 to 3.03] and relative risk 1.83 [95% Confidence Interval: 1.06 to 3.16], respectively, both p = 0.03).

CONCLUSIONS In patients with ICM and severely reduced LVEF, a greater extent of myocardial scar, delineated by DHE-CMR is associated with increased mortality or the need for cardiac transplantation, potentially aiding further risk-stratification.   (J Am Coll Cardiol Img 2009;2:34–44) © 2009 by the American College of Cardiology Foundation

Heart failure is responsible for approximately 2.6 million annual hospital stays, and there is a rising incidence that is expected to double in the next 40 years (1). The most common cause of systolic heart failure, particularly in developed nations, is ischemic cardiomyopathy (ICM), resulting from significant coronary artery disease (CAD) (2). Patients with ICM and severe systolic left ventricular (LV) dysfunction have a significantly higher mortality, compared with the general population, as a result of

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multiple factors, including progressive heart failure and tachyarrhythmia (3–5). Despite significant advancements in therapies (revascularization, device therapy, transplantation medicine, or medical therapies), outcomes in severe heart failure are generally poor (2). Furthermore, in specific subsets of patients (e.g., those with severe LV dysfunction), the potential benefits of revascularization must be weighed against increased periprocedural risks. Therefore, knowledge of myocardial viability might be useful in the decision-making process with regard to such patients.

Delayed hyperenhancement cardiac magnetic resonance (DHE-CMR), after administration of a gadolinium-based contrast agent, has been shown to identify areas of myocardial infarction (MI) with a high degree of accuracy and reproducibility (6–9). Studies have clearly demonstrated the role of DHE-CMR in predicting functional recovery after revascularization in patients with ICM (10,11). Furthermore, recent data also indicate that infarct size, quantified by DHE-CMR, identifies patients at risk for inducible ventricular tachycardia and mortality, more reliably than left ventricular ejection fraction (LVEF) (3,12).

In patients with systolic LV dysfunction due to ICM, LVEF has been shown to be a strong predictor of sudden death (13,14) and might be a surrogate marker for infarct size. However, it is unclear whether the amount of MI-related scar tissue further impacts survival in such patients. We sought to determine whether precise quantification of infarct (scar) size by DHE-CMR is associated with survival in patients with ICM and severe LV systolic dysfunction.

METHODS

This was an observational study of 349 patients with documented ICM (on the basis of ≥70% stenosis in at least 1 epicardial coronary vessel on angiography and/or history of MI or coronary revascularization), who were referred for the assessment of myocardial viability with cardiac magnetic resonance (CMR) between January 2003 and December 2006. Patients with standard CMR contraindications—including severe claustrophobia, atrial fibrillation, and the presence of pacemakers, defibrillators, or aneurysm clips—were not imaged. Also, no patients were imaged in the immediate peri-infarct period. Electronic medical records were queried to determine clinical and demographic variables, at a time temporally closest to the CMR study (within 1 month). Medication use, including beta-blockers, angiotensin-converting enzyme inhibitors (ACE-I) (angiotensin receptor blockers included in this group), spironolactone, and statins, were recorded. The incidence of post-CMR study coronary revascularization (either percutaneous or surgical) and placement of implantable cardioverter defibrillators (ICD)/cardiac resynchronization therapy (CRT) was also recorded. The institution's angiographic database was queried to assess for presence and degree of CAD. All patients had ≥70% stenosis in ≥1 epicardial coronary vessel or had a documented history of MI and/or previous coronary revascularization (corroborating the diagnosis of ICM). The institution's echocardiography database was similarly queried (data from surface echocardiogram performed within 1 week of the CMR study were recorded). All patients had to have an LVEF <45% on initial surface echocardiography, to be considered in the study population. The institution's cardiac transplantation (CTx) database was queried to ascertain any history of such, after the CMR study. All-cause mortality was ascertained by social security death index. We measured a composite end point of all-cause mortality or CTx in the period after CMR study. This study was approved by the institutional review board with a waiver of individual consent.

CMR protocol and analysis. The CMR examinations were performed on 1.5-T MR scanners (Siemens Medical Solutions, Erlangen, Germany), either Sonata (for examinations between 2002 and 2005, 40 mT/m maximum gradient strength, 200 T/m/s maximum slew rate) or Avanto (for examinations in 2006, 45 mT/m maximum gradient strength, 200 T/m/s maximum slew rate), with electrocardiographic gating. Scout images were acquired initially to identify the cardiac axes. For assessment of global cardiac function,

Figure 1. Short-Axis Delayed Hyperenhancement Image, Loaded on Custom VPT Software (Siemens Research), for Scar Analysis

Each short-axis level was segmented (**white lines**) according to the standard American Heart Association 17-segment model. The **blue circle** represents identification of the normal nulled myocardium and adjacent tissues, for the purpose of thresholding (as recommended by the developer of the software). The **green and red circles** represent delineation of epicardium and endocardium. The **bright red areas** within the myocardium represent the automatically detected myocardial scar.

balanced steady-state free precession (bSSFP) images were then acquired: echo time = 1.6 ms, repetition time = 3.3 ms, flip angle = 70°, and slice thickness = 6 mm (long-axis images) or 8 to 10 mm (contiguous short-axis images encompassing the entire LV volume, from apex to base). For short-axis images, the field of view varied from 228 to 330 in the x-direction and 260 to 330 in the y-direction, and matrix size varied from 140 to 180 in the x-direction (phase encoding direction) and 256 in the y-direction. This gave a spatial resolution of 1.5 to 2.1 mm (x-direction) × 1.1 to 1.4 mm (y-direction). In long-axis images, the field of view varied from 250 to 320 (x-direction) and 280 to 340 (y-direction). Matrix size varied from 120 to 210 in the x-direction (phase encoding direction) and 256 in the y-direction. This gave a spatial resolution of 1.5 to 2.1 mm (x-dir) × 1.1 to 1.6 mm (y-direction). For patients able to suspend respiration, breath hold duration was 10 to 15 s, depending on the heart rate; otherwise, images were acquired with 3 signal averages. The LV volumes and LVEF were calculated on the basis of short-axis bSSFP images.

Subsequently, DHE-CMR images were obtained in the same long- and short-axis orientations as the previously described bSSFP images, approximately 20 min after injection of 0.2 mmol/kg of Gadolinium dimenglumine (Magnevist, Berlex Imaging, Wayne, New Jersey), with a phase-sensitive inversion recovery spoiled gradient echo sequence: echocardiography time 4 ms, repetition time 8 ms, flip angle 30°, bandwidth 140 Hz/pixel, 23 k-space lines acquired every other RR-interval, field of view (varied from 228 to 330 in the x-direction and 260 to 330 in the y-direction), and matrix size (varied from 140 to 180 in the x-direction and 256 in the y-direction). This gave a spatial resolution of 1.5 to 2.1 mm (x-direction) by 1.1 to 1.4 mm (y-direction).

For DHE-CMR analysis, the images were first loaded on a custom analysis package (VPT software, Siemens Medical Solutions), and endocardial and epicardial myocardial edges were manually delineated on the DHE-CMR images. Scar was defined as having an intensity >2 standard deviations above viable myocardium (identified by a user-specified region of interest) (Fig. 1) (15,16). Any areas that were identified as scar by the software but not deemed to be scar by the user (e.g., areas outside of the epicardium that were included due to irregular heart borders) were excluded manually by the user. Scar burden was assessed both quantitatively and qualitatively (by investigators D.H.K., C.M.H., and M.Y.D.): 1) quantity of scar was automatically determined (as percentage of total myocardium; such quantitative scar analysis has been shown to be highly reproducible in a previous study from our institution with a bias of only 1% both between and within readers on Bland-Altman analysis and intraclass correlation coefficients of 0.84 and 0.88 for interobserver and intraobserver agreement, respectively [15]; and 2) each study was also semiquantitatively graded, with a standard American Heart Association 17-segment model (17), on a 5-point scale (segmental scar score), with 0 = absence of DHE; 1 = DHE of 1% to 25% of LV segment; 2 = DHE extending to 26% to 50%; 3 = DHE extending to 51% to 75%; and 4 = DHE extending to 76% to 100% (7). To further semiquantitatively define the extent/transmurality of scar tissue, the following definitions were used (18): 1) transmurality score, defined as number of segments with a segmental scar score of 3 or 4; and 2) total scar score, defined as summed segmental scar scores/patient divided by 17 (which reflects the damage/patient, with the maximum possible score being 4). The CMR analysis was completely blinded from the clinical analysis.

Statistical analysis. Baseline demographic data, risk factors, and clinical variables are descriptively summarized for the group. Continuous variables are

Table 1. Demographic Data of the Study Population, on the Basis of Composite End Points of Survival or Cardiac Transplantation

	Total (n = 349)	Group 1 No Events (n = 293)	Group 2 Composite Events (n = 56)	p Value
Age, yrs		65 ± 11	67 ± 11	0.17
Male		229 (78%)	33 (64%)	0.03
Hypertension		110 (38%)	17 (30%)	0.30
Diabetes mellitus		84 (28%)	15 (27%)	0.77
Documented myocardial infarction		23 (8%)	6 (11%)	0.49
History of prior coronary artery bypass grafting		27 (9%)	2 (4%)	0.12
Statins		165 (56%)	24 (43%)	0.06
Beta-blockers		176 (60%)	25 (45%)	0.03
ACE inhibitors		141 (48%)	22 (39%)	0.22
Aldosterone		75 (26%)	13 (23%)	0.70
LVEF (%)		24 ± 8	23 ± 7	0.39
Left ventricular end-diastolic volume (ml)		227 ± 100	235 ± 127	0.67
Left ventricular end-systolic volume (ml)		130 ± 83	141 ± 109	0.48
Post-CMR coronary revascularization		75 (26%)	14 (25%)	0.93
Post-CMR ICD or CRT		82 (28%)	13 (23%)	0.47

Values are n (%).
ACE = angiotensin-converting enzyme; CMR = cardiac magnetic resonance; CRT = cardiac resynchronization therapy with biventricular pacemaker; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction.

expressed as mean ± SD. Categorical data are presented as percentage frequency. Differences between the groups were compared with the use of the Student *t* test and analysis of variance for continuous variables and the chi-square test for categorical variables. To verify that the groups were well-matched according to their baseline characteristics, we calculated propensity scores with logistic regression analysis (19,20) with age, gender, diabetes mellitus, hypertension, medication usage, LVEF, post-CMR revascularization, or ICD/CRT as input variables. Both groups had similar propensity scores (−0.04 ± 0.36 vs. −0.10 ± 0.32, p = 0.4), which enabled comparison of 2 entire groups in a statistically unbiased manner. Further details of propensity analysis are shown in the Online Appendix. We measured a composite end point of all-cause mortality or CTx in the period after CMR study. Exclusion of 5 CTx cases as an end point did not alter the results presented herein. Univariable and multivariable survival analysis was performed

with Cox-proportional hazards analysis, and risk ratios were generated. For univariable survival analysis, the following variables were tested: age, gender, medications, history of hypertension, diabetes mellitus, post-CMR revascularization, post-CMR ICD or CRT implantation, LVEF >mean, and both semiquantitative (total scar score median of >2.3) and quantitative (automatically detected scar median of ≥30%) scar burden. For backward stepwise multivariable Cox proportional hazards analysis, we included only those variables with a p value of <0.10. For Kaplan-Meier survival analysis, patients were divided into 4 groups stratified according to quartiles of semiquantitative and quantitative scar burden, and between-group differences in survival were tested by log-rank statistics. Receiver-operating characteristic curve analysis was performed to test the association between scar burden and survival. Data assembly and basic statistical comparisons were performed with JMP Software version 6.0.2 (SAS Institute, Cary, North Caro-

Table 2. DHE-CMR Analysis of the Study Population, on the Basis of Composite End Points of Survival or Cardiac Transplantation

	Group 1 No Events (n = 293)	Group 2 Composite Events (n = 56)	p Value
Mean scar % on DHE-CMR	30 ± 20	39 ± 22	0.003
Transmurality score on DHE-CMR	7.8 ± 5	9.7 ± 5	0.004
Total scar score on DHE-CMR	2.0 ± 1.1	2.5 ± 1.1	0.004

DHE-CMR = delayed hyperenhancement cardiac magnetic resonance.
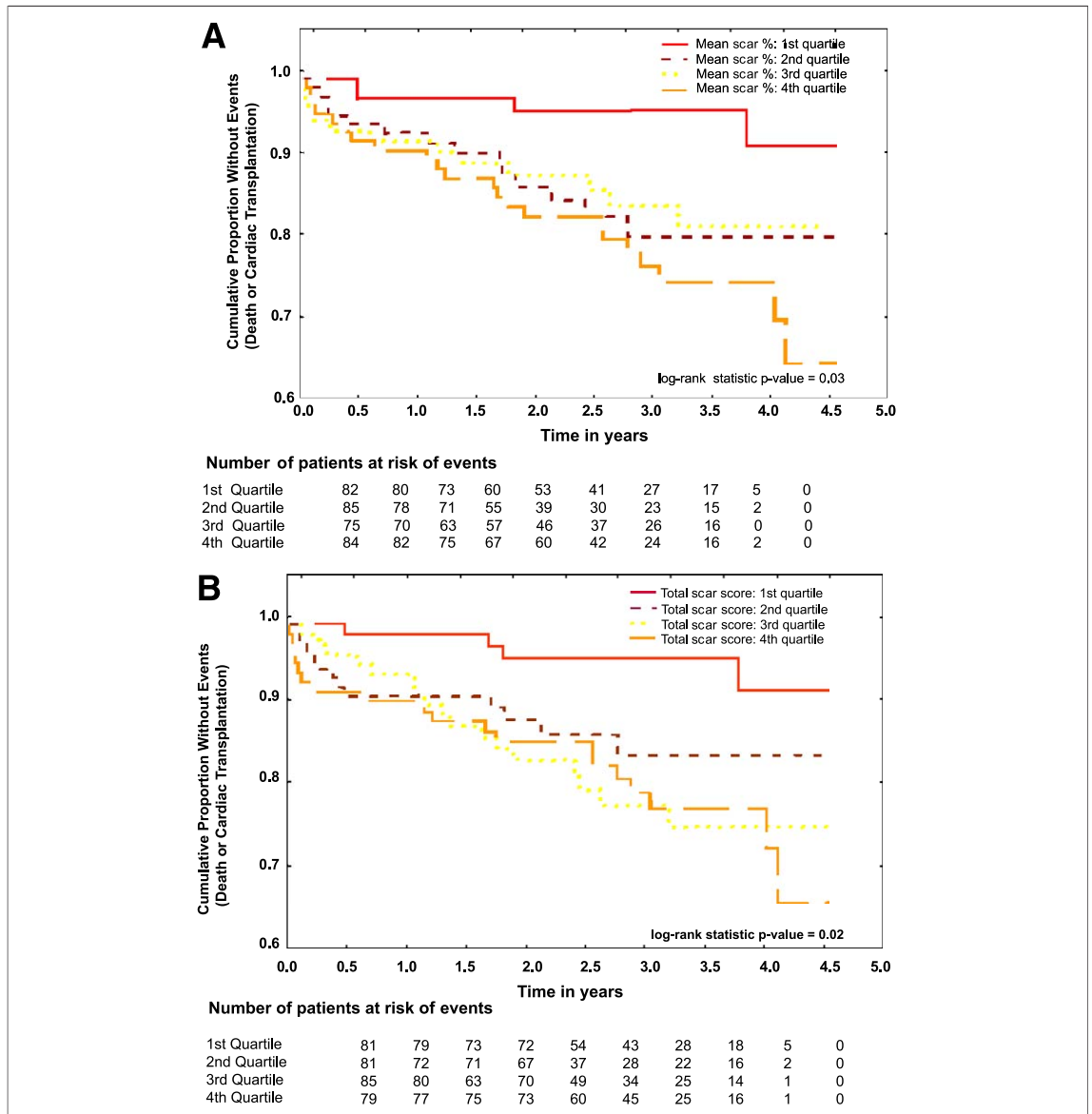
Figure 2. Kaplan-Meier Curves Demonstrating Difference in Outcomes Among 4 Quartiles

(A) Kaplan-Meier curves demonstrating difference in outcomes among 4 quartiles of automatically derived scar (as a percentage of total left ventricular myocardium); 0% to 14% = 1st quartile, 14.1% to 30% = 2nd quartile, 30.1% to 46% = 3rd quartile, and >46% = 4th quartile. **(B)** Difference in outcomes among 4 quartiles of semiquantitative total scar score; 0 to 1.3 = 1st quartile, 1.31 to 2.3 = 2nd quartile, 2.31 to 3.0 = 3rd quartile, and >3.1 = 4th quartile. *Continued on next page.*

lina). Advanced statistical analysis and graph generation was performed with SPSS version 10.0 (SPSS Inc., Chicago, Illinois) and Statistica version 6.1 (Statsoft, Tulsa, Oklahoma). A p value < 0.05 was considered significant.

RESULTS

Patient population. The mean age of the study population (n = 349) was 65 ± 11 years, with the majority being Caucasian (86%) and male (76%). In

the study, the mean age for men versus women was similar (66 ± 11 years vs. 64 ± 12 years, p = 0.20). Over a mean follow up of 2.6 ± 1.2 years (median 2.4 years [interquartile range 1.1, 3.5]), there were a total of 56 composite events (51 deaths and 5 CTxs). The patients were subsequently divided into 2 groups: group 1 (no events) and group 2 (composite events). Baseline characteristics of the 2 groups are provided in Table 1. The LVEF was depressed to a similar extent in both groups (75% of the study population had an LVEF <30%) along
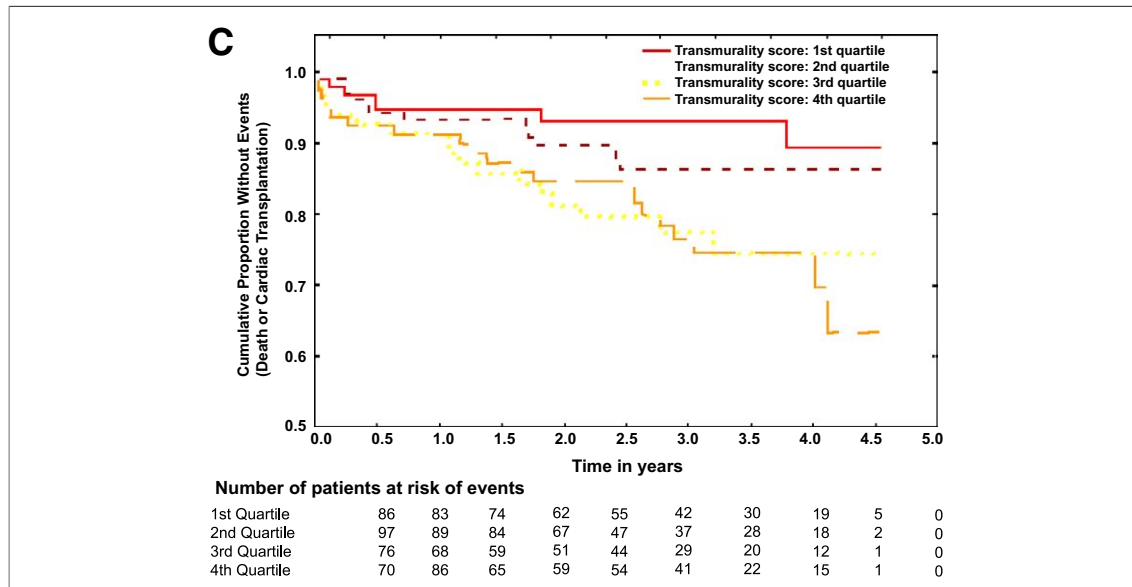
Figure 2. Continued

(C) Difference in outcomes among 4 quartiles of transmurality score; 0 to 4.0 = 1st quartile, 4.1 to 9.0 = 2nd quartile, 9.1 to 12.0 = 3rd quartile, and >12.0 = 4th quartile.

with a similar frequency of other cardiac risk factors (Table 1). The frequency of post-CMR-revascularization and ICD/CRT was also similar in both groups. In the follow-up period, 30% of patients that underwent revascularization had an improvement in LVEF >35%. In the follow-up period, there was no significant difference in the rate of ICD discharges between the 2 groups (4% vs. 7%, p = 0.26). To ascertain the similarity of baseline characteristics in 2 groups, we also calculated propensity scores.

DHE-CMR analysis and survival. In the entire study population, approximately one-third of the total myocardium was scarred on DHE-MR images (mean scar quantified as percentage of total LV myocardium was 31 ± 21%). Similarly, for the total population, close to 50% of all myocardial segments (assessed semiquantitatively) had transmural or near-transmural scar (mean transmurality score was 8 ± 5). Similarly, the total scar score (assessed semiquantitatively) was 2.1 ± 1.1, suggesting a high proportion of damaged myocardial segments/

Table 3. Cox Proportional Hazard Analysis Demonstrating the Association Among Various Factors and Combined Events

	Univariable Analysis		Multivariable Analysis	
	Relative Risk 95% CI	p Value	Relative Risk 95% CI	p Value
Age (yrs)	1.01 (0.99–1.04)	0.29		
Female gender	1.83 (1.06–3.16)	0.03	2.05 (1.18–3.57)	0.01
Diabetes mellitus	0.96 (0.53–1.74)	0.9		
Hypertension	0.73 (0.41–1.29)	0.28		
Statins	0.75 (0.44–1.26)	0.28		
Beta-blockers	0.65 (0.39–1.10)	0.09	0.60 (0.36–1.03)	0.06
ACE inhibitor	0.75 (0.44–1.26)	0.30		
LVEF	0.98 (0.95–1.02)	0.32		
Post-CMR revascularization	0.98 (0.53–1.79)	0.94		
Post-CMR ICD/CRT	0.81 (0.44–1.51)	0.54		
Quantitative scar (% of total LV myocardium)	1.02 (1.003–1.03)	0.01	1.02 (1.005–1.03)	0.005
Total scar score (semiquantitative)	1.38 (1.07–1.79)	0.01		

Chi-square for the multivariable model = 15.11, p = 0.002. Because of significant correlation between scar percentage (quantitative) and total scar score (semiquantitative), only scar percentage was entered into the multivariable model.
CI = confidence interval; other abbreviations as in Table 1.

patient (approximately 50%). In the transplant group (n = 5), the mean age was 61 ± 9 years, and all were men. The mean LVEF, scar percentage, and total scar score were 23 ± 8%, 54 ± 24%, and 3.3 ± 0.7, respectively. There was no perioperative mortality, and all patients in this group survived during follow-up.

Subsequently, we compared the scar burden in 2 groups. As shown in Table 2, the mean quantitative scar percentage and semiquantitative scores (transmurality score and total scar score) were significantly higher in those with events versus those without. Kaplan-Meier survival curves on the basis of quartiles of quantitative scar percentage, transmurality score, and total scar score are shown in Figures 2A to 2C. Finally, to account for multiple confounding factors impacting outcomes, we performed univariable and multivariable Cox proportional hazards analysis (Table 3). Receiver-operator characteristic curve analysis testing the association between quantitative scar percentage and events was significant (area under the curve 0.62, p = 0.003). Because of a significant association between quantitative and semiquantitative measures of scar burden, only 1 such measure (quantified scar percentage) was entered into the multivariable model. To account for the potential impact of revascularization (especially within 6 months of CMR) on outcomes, we also performed univariable Cox proportional hazards analysis in a subgroup of patients that did not have revascularization within 6 months of CMR (n = 292, mean age 65 ± 11 years, 219 men, mean LVEF 24 ± 8%). In this subgroup, the relative risk of quantitative scar percentage and total scar score was 1.01 (95% CI: 1.00 to 1.02, p = 0.04) and 1.30 (95% CI: 1.0 to 1.69, p = 0.04), respectively.

DISCUSSION

To the best of our knowledge, the current study is the largest to evaluate the ability of semiquantitative and quantitative infarct sizing by DHE-CMR to predict outcomes in high-risk patients with severe ICM. The study population had a high frequency of risk factors and a high degree of scarred myocardium on DHE-CMR, in the setting of significantly reduced LVEF. For outcomes, we included a composite end point of all-cause mortality and CTx. We included CTx as a hard end point, because those patients were deemed to be in end-stage heart failure and would have otherwise died without a CTx. The mortality rate of our population was significantly high (15% over a mean follow-up of 2.6 years). Our study demonstrates that the degree

of myocardial scar, assessed either semiquantitatively or quantitatively by DHE-CMR, is a strong predictor of the composite end point, independent of other risk factors, and LVEF, even in a high-risk group of patients with ICM and severe LV systolic dysfunction. Incidentally, we also demonstrate that, similar to previous suggestions, female gender was associated with worse survival in the study population (21,22). We confirmed the baseline similarity of the 2 groups by calculating propensity scores.

A recent study has also demonstrated the superiority of infarct size, with DHE-CMR, over LVEF and volumes in predicting outcomes in patients after a previous MI (12); however, the mean LVEF (43%) was substantially higher, and the mean LV volumes were substantially smaller, in contrast to the current study. Furthermore, the extent of myocardial scarring (transmurality score as well as total scar score) was substantially lower. The mortality rate was also substantially lower, likely reflecting a lesser-risk population. The current study addresses the incremental value of DHE-CMR in a population that is conceivably at a much higher risk (on the basis of much lower LVEF and higher scar burden), thus extending the spectrum of utility to such high-risk patients.

The characteristics of the current study population were also unique, likely representing the varied referral pattern of our large tertiary care center. The baseline medication data presented in Table 1, which appears suboptimal by modern standards, represents the therapy at the time of initial presentation to our institution. The vast majority of such severely compromised patients get referred to our tertiary care center for high-risk procedures, from outside our primary referral area, as demonstrated in a recent study from our institution (23). This baseline suboptimal therapy likely reflects the reality of medical therapy trends in such patients in non-academic centers. Indeed, multiple observational studies, from different countries, have demonstrated less-than-optimal medical therapy during follow-up after revascularization procedures (24,25).

In the current population, revascularization in the follow-up period did not provide any survival benefit. Although there could be many potential reasons, a likely reason for the lack of benefit could be that this is already a very high-risk population (because of significantly reduced LVEF and a very high scar burden), and the risks of revascularization potentially outweigh the benefits. However, this is speculative and needs further prospective confirmation. Also, in the current study, there was relatively

little difference in the effectiveness of ICD/CRT therapy between the 2 groups. There could be multiple reasons for that, including differences in patient populations between our study and some of the seminal trials of device therapy. Upon comparing our population with that of the MADIT-II (Multicenter Automatic Defibrillator Implantation Trial-II) (26), the mortality rate in the ICD group was similar: 16% over a 27-month follow-up in the MADIT-II versus 14% over 2.6 years' follow-up in our study. However, in the nondevice group for the MADIT-II, the mortality rate was substantially higher compared with our nondevice group (39% vs. 17%). A potential reason, although purely speculative, could be that the MADIT-II, unlike our study, excluded patients that underwent revascularization in close proximity to enrollment. Similar to our study, the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) study of CRT in patients with advanced heart failure (27) only demonstrated a difference in exercise capacity and quality of life, without a difference in overall mortality between patients with and without CRT. In a further analysis of the same study (28), even symptomatic improvements with CRT were less conspicuous in patients with ICM as opposed to nonischemic cardiomyopathy.

Previous studies have demonstrated that both the extent of MI and depressed LVEF are important predictors of survival (3,29,30). Although LVEF is a strong prognostic tool and has been shown to be inversely related to infarct size (31,32), LVEF and volumes are subject to preload, afterload, myopathic processes, and the extent of MI. Therefore, infarct size might be a more objective and superior prognostic indicator. Previous studies, with myocardial perfusion scintigraphy, have demonstrated the incremental prognostic value of infarct sizing over traditional LV volume-based variables (33,34).

DHE-CMR has emerged as an extremely accurate clinical tool in assessment of myocardial viability, with a demonstrated utility in an ischemic setting (9,35). Infarct sizing with DHE-CMR has been shown to correlate with LVEF and other clinical findings in acute infarcts (36) and is highly reproducible (8,37). Due to a higher spatial resolution, DHE-CMR has a greater ability for precise delineation of subendocardial infarctions (38). A recent study demonstrated that clinically unrecognized infarcts, identified by DHE-CMR, were the strongest predictors of major adverse cardiac events and mortality (39). In fact, infarct scar quantified by DHE-CMR was shown to be a better marker of inducible ventricular tachycardia than LVEF (3).

DHE-CMR has the ability to not only detect the presence of irreversible myocardial damage but also to delineate transmurality of myocardial scar and the remaining viable myocardium. The transmural extent seen on DHE-CMR has been negatively correlated to the functional outcome after revascularization (10,40).

Clinical implications. Several trials demonstrated that patients with ICM and systolic dysfunction benefit from various therapies (medications, revascularization, or device therapy) due to restoration of LV size, shape, and ejection fraction (41–43). However, despite such advances, the mortality in such patients remains relatively high, and in some instances (particularly in patients with severe LV dysfunction and severe CAD), the benefits of revascularization might be outweighed by the predicted periprocedural risks. Furthermore, with increasing use of CRT, it is being recognized that more than one-quarter have a progressive worsening of their heart failure despite therapy (44). In recent years, DHE-CMR has been used to help predict potential success for CRT (45–48). In a recent analysis of the MUSTIC (Multi-site Stimulation in Cardiomyopathy) trial, there were suggestions that patients with previous MI fail to respond to CRT, compared with patients with idiopathic dilated cardiomyopathy (49). Furthermore, Bello et al. (50) demonstrated an inverse relationship between absolute scar burden, quantified by DHE-CMR, and functional recovery at 6 months in response to beta-blocker therapy in 45 heart failure patients. In this study, scar burden also predicted recovery of systolic function after revascularization. Therefore, extent of myocardial scarring might be an important determinant of mortality and response to various therapies. It is intuitive to think that risk stratification in patients with congestive heart failure can effectively guide treatment strategies in a cost-effective manner. Our study demonstrates how scar burden is an important prognostic marker and might identify patients at higher risk for death. The STICH (Surgical Treatment for Ischemic Congestive Heart failure) trial is testing whether contemporary medical and device therapy is equivalent to surgical revascularization. A substudy will examine whether viability provides useful risk stratification. However, an important point that needs to be taken into consideration is that, although assessment of myocardial viability and scarring are important, the full picture of myocardium at risk is provided by additional evaluation of ischemia. Hence, future prognostic stud-

ies assessing the incremental value of stress-perfusion CMR in combination with DHE-CMR likely need to be conducted.

Study limitations. Because this is an observational study conducted at a large tertiary referral center, there is a distinct possibility of a selection bias. Only the patients with no contraindications to CMR underwent the examination. In the era of CRT and ICDs, a sizable proportion of patients would have not have qualified for a CMR study, thus leading to selection bias. A likely reason that these patients had not yet received ICD/CRT, despite such reduced LVEF, could be the anticipation that their LVEF would improve after revascularization. Not all patients had ICD/CRT implantation in the post-CMR period, especially because approximately 30% of patients revascularized in the post-CMR period had an improvement in EF >35%. However, there is a possibility that some patients could have had such devices implanted at their local institutions, thus potentially altering their survival. Also, reliance upon the Social Security Death Index for determination of death status might result in an underestimation of clinical outcomes due to the lag time in reporting. The difference in the amount of scar between the 2 groups in our study was modest. This is likely because we are attempting to further risk-stratify patients (on the basis of the amount of scar) that already have severely depressed LVEF, which is in itself is a very powerful prognostic marker. The baseline medication regimen was suboptimal, by today's standards, as discussed in the preceding text. Also, at baseline, there was a difference between groups in use of medical therapy, potentially affecting survival. In some cases, it was likely due to the inability to use some medications due to advanced heart failure. However, this difference should not have made a significant difference in our conclusions, because scar burden was a stronger predictor of death on multivariate survival analysis. Also, the overall propensity scores (generated out of baseline characteristics) were similar in 2 groups. Finally, we did not collect data on diuretic therapy (other than spironolactone) for this study. However, to the best of our knowledge, other than smaller substudies (51), there are no major randomized clinical trials demonstrating mortality association with diuretics.

CONCLUSIONS

In patients with ICM and reduced LV systolic dysfunction, higher LV myocardial scar burden detected on DHE-CMR is associated with significantly worse outcomes, including death or need for CTx, independent of other risk factors, including revascularization or device therapies. Delayed hyperenhancement cardiac magnetic resonance could aid further risk-stratification of this high-risk population.

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Key Words: delayed hyperenhancement CMR and outcomes ■ ischemic cardiomyopathy.

▶ **APPENDIX**

For a supplementary table, please see the online version of this article.