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Prognostic Value of Myocardial Viability by Delayed-Enhanced Magnetic Resonance in Patients With Coronary Artery Disease and Low Ejection Fraction

Impact of Revascularization Therapy

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Objectives The purpose of this study was to evaluate the impact of myocardial viability assessment by delayed-enhanced cardiac magnetic resonance (DE-CMR) and of revascularization therapy on survival in patients with coronary artery disease (CAD) and low ejection fraction (EF).

Background Prior studies have shown that DE-CMR predicts recovery of left ventricular (LV) dysfunction after revascularization.

Methods The authors prospectively evaluated survival of 144 consecutive patients (130 males, age 65 ± 11 years) with CAD and LV dysfunction (EF: 24 ± 7%) undergoing DE-CMR. Eighty-six patients underwent complete revascularization of dysfunctional myocardium (79 coronary artery bypass grafting, 7 percutaneous coronary intervention), whereas 58 patients remained under medical treatment.

Results Over the 3-year median follow-up, 49 patients died. Three-year survival was significantly worse in medically treated patients with dysfunctional viable than with nonviable myocardium (48% vs. 77% survival, p = 0.02). By contrast, in revascularized patients, survival was similar whether myocardium was viable or not (88% and 71% survival, respectively, p = NS). Hazard of death of viable myocardium remaining under medical treatment versus complete revascularization was 4.56 (95% confidence interval [CI]: 1.93 to 10.8). Cox multivariate analysis indicated that interaction of revascularization and viability provided significant additional value (chi-square test = 13.1, p = 0.004) to baseline predictors of survival (New York Heart Association functional class, wall motion score, and peripheral artery disease). More importantly, in 43 pairs of propensity score–matched patients, hazard of death (hazard ratio: 2.5 [95% CI: 1.1 to 6.1], p = 0.02) remained significantly higher for medically treated patients rather than for those with fully revascularized viable myocardium.

Conclusions Without revascularization, presence of dysfunctional viable myocardium by DE-CMR is an independent predictor of mortality in patients with ischemic LV dysfunction. This observation may be useful for pre-operative selection of patients for revascularization. (J Am Coll Cardiol 2012;59:825–35) © 2012 by the American College of Cardiology Foundation

Delayed-enhancement (DE) cardiac magnetic resonance (CMR) detects replacement of normal viable myocytes by necrosis or fibrosis with high spatial resolution, and excellent correlation to histopathology (1). Accordingly, DE-CMR has become a preferred method for assessment of structural changes in ischemic and nonischemic cardiomyopathies (2). Several studies have demonstrated that DE-CMR can predict myocardial viability in coronary artery disease (CAD) (3–7).

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Indeed, they showed that dysfunctional segments with DE, corresponding to infarcted nonviable myocardium, do not improve in function after revascularization, whereas dysfunctional myocardium without DE, and thus without necrosis and suppos-

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Abbreviations and Acronyms

CABG = coronary artery bypass graft
CAD = coronary artery disease
CI = confidence interval
CMR = cardiac magnetic resonance
DE = delayed enhancement
EF = low ejection fraction
HR = hazard ratio
LV = left ventricular
MI = myocardial infarction
NYHA = New York Heart Association
PCI = percutaneous coronary intervention

edly viable, may recover after revascularization and contribute to increase left ventricular (LV) ejection fraction (EF).

Yet, the impact of DE-CMR viability assessment on prognosis remains incompletely understood. Several reports (8–12) indicated that the presence of DE by CMR, i.e., nonviable myocardium, predicts increased risk in patients with and without CAD, but did not evaluate the potential benefit of revascularization on survival. Moreover, these studies conflict with earlier work using nuclear or stress echocardiography imaging (13), which showed that viable rather than nonviable myocardium is associated with poor prognosis, whenever patients are treated medically.

We hypothesized that the presence or absence of myocardial viability detected by DE-CMR might affect survival differently in patients undergoing revascularization versus medical treatment. Accordingly, we evaluated survival of CAD patients with EF ≤35% stratified according to presence or absence of DE by CMR in dysfunctional segments and to revascularization therapy. We used Cox survival analysis to assess whether the interaction of myocardial viability by DE-CMR with revascularization therapy provides independent prognostic information over baseline clinical, hemodynamic, and angiographic data. We also used propensity score matching to assess survival corrected for potential differences of treatment strategies.

Materials and Methods

Patient population. We evaluated survival of consecutive patients undergoing DE-CMR for assessment of myocardial viability between January 1, 2002, and December 31, 2009. In the present study, we only considered patients with CAD whose LVEF was ≤35% by CMR, who satisfied Felker's criteria for ischemic cardiomyopathy (14), i.e., having either >70% luminal diameter stenosis of the proximal left anterior descending coronary artery or multivessel disease of proximal coronary arteries, and who had not been revascularized. Accordingly, we excluded patients with nonischemic cardiomyopathy or without cardiac catheterization within 3 months before CMR, patients with significant valve disease (grade >2 mitral or aortic insufficiency or significant mitral or aortic stenosis), and all patients who had already been revascularized at the time of the study. We also excluded patients who had a life expectancy <1 year because of other comorbidities and patients with infarct complications. One hundred forty-four patients satisfied the inclusion criteria (Fig. 1) and constituted the final study population. All participants gave informed consent to participate in this institutional review board–approved study.

Cardiac magnetic resonance. All patients underwent a standardized CMR protocol for myocardial viability on a 1.5-T scanner (Intera CV, Philips Medical Systems, Best, the Netherlands) as described previously (7). Briefly, 10 to 12 consecutive short-axis images covering the entire left ventricle and, respectively, one 2-, 3-, and 4-chamber long-axis cine SSFP images were acquired for assessment of myocardial function. Ten to 15 min after injection of 0.2 mmol/kg gadolinium-based contrast, identical prescriptions of short- and long-axis slices were acquired using a 2-dimensional- or 3-dimensional inversion recovery sequence allowing for the assessment of myocardial viability.

CMR images were analyzed on a commercial workstation (Viewforum 4.1, Philips Medical Systems, Best, the Netherlands). LV volumes and EF were obtained by manual tracing of contours on the short-axis images in end-diastole and end-systole. Regional wall motion was graded visually by consensus of 2 reviewers blinded to follow-up data on a 3-level Likert scale (1: normal contraction, 2: hypokinesia, 3: akinesia) using a standard 17-segment American Heart Association model. Transmurality of DE was determined visually by the same readers on a 5-point Likert scale (0: absent, 1: 1% to 25% transmurality, 2: 26% to 50% transmurality, 3: 51% to 75% transmurality, 4: 76% to 100% transmurality) in the same segments. A dysfunctional segment (wall motion score ≥2) was considered viable when transmurality was ≤50%. Overall wall motion and transmurality score, and number of dysfunctional viable segments were reported per patient. According to Bax et al. (15), a patient was considered to have viable myocardium when ≥4 dysfunctional segments were viable (transmurality of DE ≤50%).

Follow-up. Survival status was obtained by phone contact with the patients, their relatives, or their physicians. Patient's history and treatment was retrieved from medical files and from review of visit or hospital records. The cause of death was categorized as cardiac or noncardiac. Cardiac death was defined as death attributable to congestive heart failure (i.e., death preceded by acute worsening or exacerbation of heart failure), myocardial infarction (MI), sudden death (i.e., unexpected, unwitnessed, or witnessed death in absence of other apparent causes), or occurring after cardiac revascularization procedure. Heart transplantation was censored.

Statistical methods. Statistical analyses were performed using SPSS version 15 (SPSS Corp., Somers, New York) and STATA version 11 (Stata Corp. LP, College Station, Texas) software. All tests were 2-sided, and a p value <0.05 was considered statistically significant. Continuous variables were expressed as mean ± 1 SD, categorical variables as counts and percentages. Hazard ratios (HR) were expressed as mean and 95% confidence intervals (CIs). Baseline characteristics of patients undergoing revascularization versus medical treatment were compared using chi-square test or unpaired *t* test. Survival in revascularized patients with or

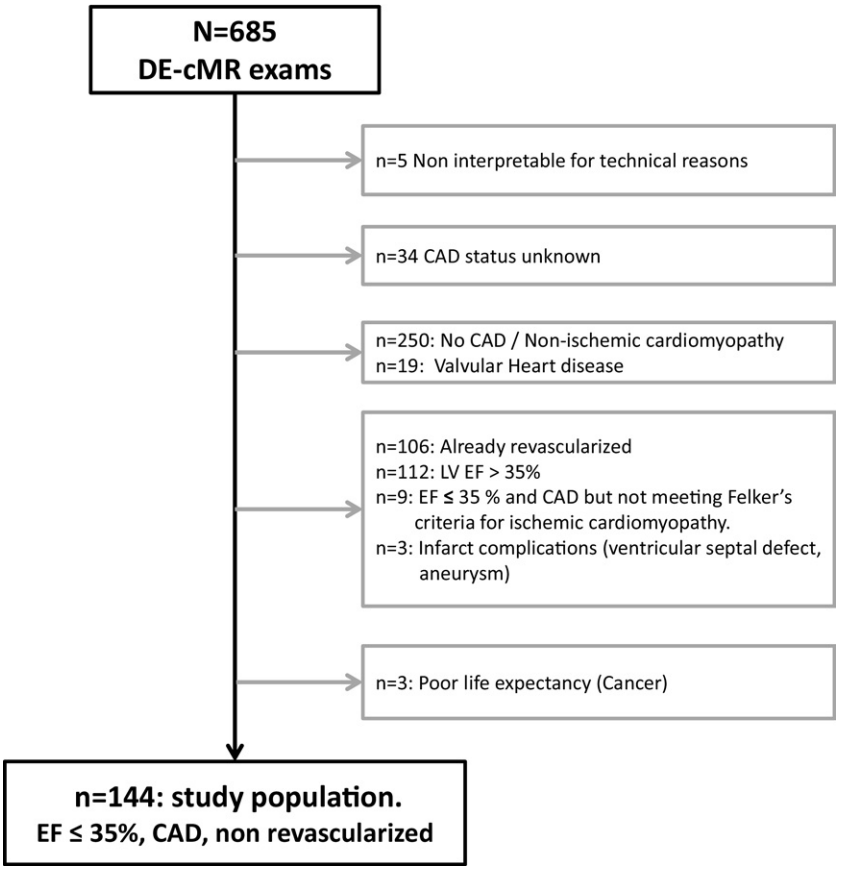

Figure 1 **Selection of the Study Population**

CAD = coronary artery disease; DE-CMR = delayed-enhancement cardiac magnetic resonance; EF = ejection fraction; LV = left ventricular.

without viable myocardium was evaluated using the Kaplan-Meier method and the Mantel-Cox test. The index date was the date of the CMR. The primary endpoint was all-cause death. The secondary endpoint was cardiovascular mortality. All clinical parameters were proposed for inclusion in a univariate Cox proportional hazard model. To assess the potential additive prognostic value of revascularization and myocardial viability over and beyond other predictors of mortality, we computed a backward stepwise multivariate Cox model from all significant ($p < 0.10$) univariate correlates of survival excluding revascularization and viability. We then evaluated the ability of myocardial viability and revascularization treatment to improve the prediction of death of this baseline model by comparing the additional increase of the chi-square value of the combined model over the baseline model using the log-likelihood test. Two different models were tested, evaluating the additional value of the number of dysfunctional viable segments as continuous variables (Model 1), or the binary presence or absence of viability (4 dysfunctional segments) (Model 2), and their respective interaction with revascularization therapy. Relative HRs for each specific covariate of the final models were computed as the exponent of the regression coefficient. The total HR in each patient was calculated as the product of all relative HRs.

To reduce the effect of treatment selection bias and to balance observed differences between revascularized and medically treated patients, we also performed a propensity score analysis. The propensity scores were obtained using a binary logistic regression model where treatment was the dependent variable, and significant correlates of the therapeutic decision acted as independent variables. The computed propensity score included 6 variables (New York Heart Association [NYHA] functional class, number of diseased coronary arteries, history of infarction, atrial fibrillation, wall motion score, and number of dysfunctional viable segments) and had an area under the curve of 0.80 ($p < 0.001$) to predict treatment. We then selected pairs of patients in the 2 treatment groups (1:1 match) using a nearest-neighbor matching algorithm within a caliper of 0.25 SD of the propensity score, using the psmatch2 routine within STATA. Overall survival in the matched treatment groups according to presence or absence of myocardial viability was then compared using the Kaplan-Meier method. The propensity score was also entered together with the therapeutic and the myocardial viability into a Cox proportional hazards

regression model to estimate the 3-year propensity score–adjusted HR associated with the therapeutic decision.

Results

Study population and treatment. Table 1 shows characteristics of the study population. After CMR, 79 patients underwent coronary artery bypass graft (CABG) within a median of 7 days, and 19 underwent percutaneous coronary intervention (PCI) within a median of 3 days. Eighty-six revascularization procedures (all CABG and 7 PCI) were considered complete, fully revascularizing all diseased vessels and dysfunctional segments. Twelve patients had incomplete PCI procedures, revascularizing only nondysfunctional myocardium. Although all patients had CAD suitable for revascularization therapy, 46 remained under medical treatment, the decision taking into account risks and clinical status, including 10 patients who refused CABG. Six medically treated patients (1 with viable, 5 with nonviable myocardium) received an implantable cardioverter-defibrillator. One medically treated patient and 1 patient after CABG underwent cardiac resynchronization therapy. Patients undergoing complete revascularization had a similar age, CAD risk factors, comorbidities, LV volumes, EF, and surgical risk by EuroSCORE than medically treated or incompletely revascularized patients. However, medically treated or incompletely revascularized patients had higher NYHA functional class, greater proportion of 2- rather than 3-vessel disease, more prevalence of myocardial infarcts, higher transmurality of DE, and less dysfunctional viable segments by CMR than fully revascularized patients. There was also a nonsignificant trend for higher prevalence of pulmonary hypertension and atrial fibrilla-

Table 1 Characteristics of the Patient Population

		All (N = 144)	Fully Revascularized (n = 86)	Incomplete PCI (n = 12)	Remaining Under Medical Treatment (n = 46)	p Value
Demographics	Age, yrs	65 ± 11	65 ± 10	66 ± 9	63 ± 1 2	0.45 (NS)
	Male/female	130/14	75/11	12/0	43/3	0.37 (NS)
Clinical history	Prior MI	93 (65%)	49 (58%)	8 (67%)	36 (78%)	0.05
Risk factors	Hypertension	93 (65%)	55 (65%)	10 (83%)	28 (61%)	0.37 (NS)
	Current smoker	16 (11%)	8 (9%)	1 (8%)	7 (15%)	0.73 (NS)
	Former smoker	70 (49%)	42 (49%)	4 (33%)	24 (52%)	0.50 (NS)
	Hyperlipidemia	80 (56%)	46 (54%)	7 (58%)	27 (59%)	0.28 (NS)
	Family history of CAD	47 (33%)	26 (31%)	4 (33%)	17 (37%)	0.76 (NS)
	Diabetes	49 (34%)	28 (33%)	6 (50%)	15 (33%)	0.52 (NS)
Symptoms	CCS class 0	93 (64%)	51 (59%)	4 (33%)	38 (82%)	
	CCS class 1–2	24 (17%)	16 (19%)	3 (25%)	5 (11%)	0.008
	CCS class 3–4	27 (19%)	19 (22%)	5 (42%)	3 (6%)	
	NYHA functional class 1–2	59 (41%)	43 (50%)	4 (33%)	12 (26%)	
	NYHA functional class 3–4	85 (59%)	43 (50%)	8 (66%)	34 (74%)	0.25
ECG	Q-wave	75 (52%)	41 (48%)	8 (67%)	26 (56%)	0.36 (NS)
	LBBB	13 (9%)	9 (11%)	2 (17%)	2 (4%)	0.26 (NS)
	AF	19 (14%)	8 (9%)	4 (33%)	7 (15%)	0.06 (NS)
Angiography	1 vessel	11 (8%)	8 (9%)	0 (0%)	3 (6%)	
	2 vessels	38 (26%)	13 (15%)	5 (42%)	20 (43%)	0.003
	3 vessels	95 (66%)	65 (76%)	7 (58%)	23 (50%)	
Comorbidity	PAD	26 (18%)	15 (17%)	4 (33%)	7 (15%)	0.35 (NS)
	Prior stroke	15 (10%)	7 (8%)	1 (8%)	7 (15%)	0.39 (NS)
	COPD gold >II	14 (10%)	10 (12%)	0 (0%)	4 (8%)	0.63 (NS)
	PHT >60 mm Hg	13 (9%)	5 (6%)	1 (8%)	7 (15%)	0.18 (NS)
	GFR, ml/min/m^2	78 ± 35	76 ± 30	88 ± 52	80 ± 34	0.43 (NS)
EuroSCORE	Additive	5 ± 2	5 ± 2	5 ± 3	5 ± 2	0.61 (NS)
	Logistic	8 ± 7	7 ± 7	10 ± 10	8 ± 8	0.58 (NS)
MR	EF	24 ± 7	24 ± 7	23 ± 9	23 ± 7	0.48 (NS)
	EDVi, ml/m^2	141 ± 42	138 ± 42	131 ± 21	149 ± 44	0.25 (NS)
	ESVi, ml/m^2	108 ± 39	106 ± 40	102 ± 27	115 ± 41	0.34 (NS)
	Dysfunctional	12 ± 4	12 ± 4	12 ± 3	11 ± 3	0.14 (NS)
	Average WMS	36 ± 5	36 ± 5	38 ± 5	37 ± 5	0.89 (NS)
	Dysfunctional viable segments	8 ± 5	9 ± 5	6 ± 5	6 ± 5	<0.001
	Average transmurality	20 ± 13	15 ± 11	27 ± 12	27 ± 12	<0.001

Values are mean ± SD, n, or n (%).

AF = atrial fibrillation; CAD = coronary artery disease; CCS = Canadian Cardiac Society angina score; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; EF = ejection fraction; EDVi = indexed end-diastolic volume; ESVi = indexed systolic volume; GFR = glomerular filtration rate; LBBB = left bundle branch block; MI = myocardial infarct; MR = magnetic resonance; NS = nonsignificant; NYHA = New York Heart Association functional class; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; PHT = pulmonary hypertension; WMS = wall motion score.

tion in medically treated patients than in fully revascularized patients.

Events at follow-up. Follow-up was 100% complete for a median duration of 3 years. During follow-up, 49 patients died, 40 of cardiovascular causes: 7 postoperatively, 17 of heart failure, 12 suddenly, 3 of stroke, and 1 of vascular cause. Six patients developed worsening heart failure (5 patients under medical treatment and 1 after CABG) requiring heart transplantation. One patient with an implantable cardioverter-defibrillator died after 405 days of worsening heart failure, another underwent heart transplantation. Both had nonviable myocardium. No shocks occurred during follow-up.

Survival according to treatment and myocardial viability. To assess the potential prognostic value of myocardial viability by DE-CMR and its interaction with revascularization on long-term survival, the study population was divided into several subgroups (Fig. 2): 1) patients with completely revascularized viable myocardium (n = 68); 2) patients with viable myocardium undergoing incomplete revascularization not including the dysfunctional region (n = 7); 3) patients with viable myocardium remaining under medical treatment (n = 26); 4) patients with completely revascularized nonviable myocardium (n = 18); 5) patients with nonviable myocardium remaining under medical treatment (n = 20); and 6) patients undergoing incomplete revascularization not including the dysfunctional nonviable myocardium (n = 5). Figure 2 shows that the 3-year overall survival was significantly worse in the subgroups of patients with dysfunctional viable myocardium remaining under medical treatment (46%) or undergoing incomplete revascularization (54%) than in incompletely revascularized (100%) or medically treated patients without viable myocardium (77%), and in completely revascularized patients with and without dysfunctional viable myocardium (83% and 71% for the completely revascularized viable and nonviable myocardium subgroups, respectively).

Because survival in patients undergoing incomplete revascularization not including the dysfunctional myocardium was similar to that of patients remaining under medical treatment alone, and because the objective of our study was to evaluate the impact of revascularization of dysfunctional myocardium, patients with incomplete revascularization not including dysfunctional myocardium were merged with the group of medically treated patients for further analysis (Figs. 3A and 3B). Figure 4 shows that 3-year HR of death in patients with viable myocardium (≥4 viable segments) was significantly higher (4.56) when they remained under medical treatment or when revascularization did not include

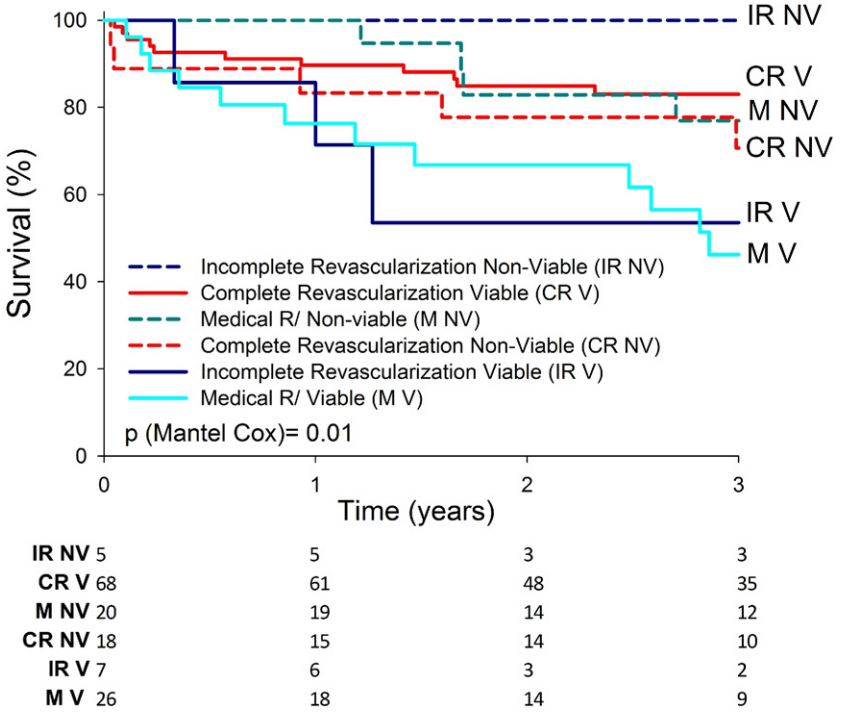

Figure 2 Kaplan-Meier Survival Curves Comparing Overall 3-Year Survival in Subgroups of Patients According to Treatment and Presence of Myocardial Viability in Dysfunctional Myocardium

Survival was significantly worse in patients with dysfunctional viable myocardium remaining under medical treatment or undergoing incomplete revascularization not including dysfunctional myocardium than in other subgroups. CR = complete revascularization; IR = incomplete revascularization not including dysfunctional region; M = medical treatment; NV = nonviable myocardium; R/ = remaining under medical treatment; V = viable myocardium.

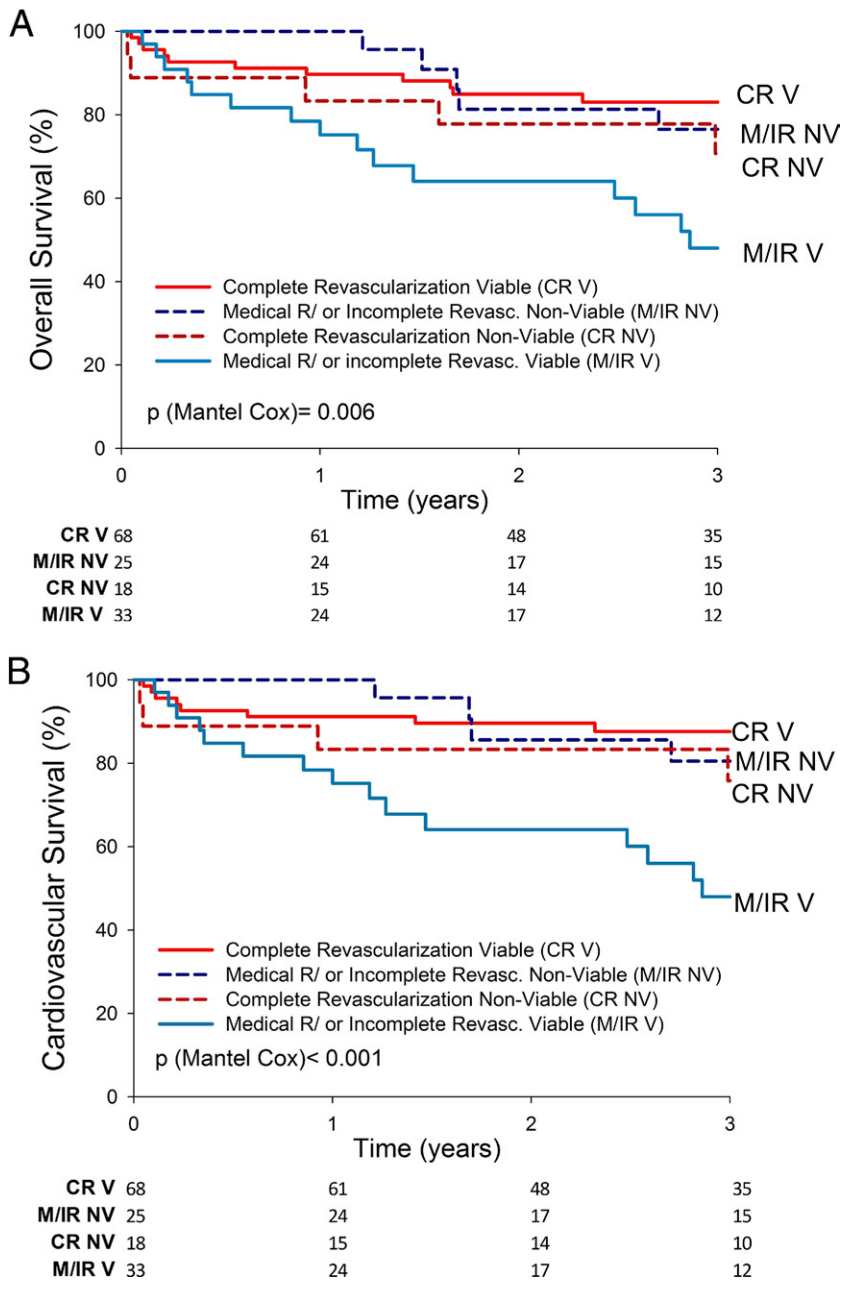

Figure 3 **Kaplan-Meier Survival Curves Comparing Overall and Cardiovascular 3-Year Survival According to Treatment and Presence of Myocardial Viability in Dysfunctional Myocardium**

Overall **(A)** and cardiovascular **(B)** 3-year survival were significantly worse in patients with viable myocardium who remained under medical treatment or undergoing incomplete revascularization not including dysfunctional regions. Abbreviations as in Figure 2.

the dysfunctional region, as opposed to when dysfunctional myocardium was completely revascularized. By contrast, in patients without viable myocardium, there was no benefit of revascularization therapy on survival.

Cox proportional hazard analysis of survival. Univariate predictors of overall survival in our patient population are shown in Table 2. Table 3 demonstrates that the interaction between viability, both as continuous variable (number of dysfunctional viable segments—Model 1) and on per patient basis (≥4 dysfunctional viable segments per patient—Model 2), and treatment had significant additional value to improve the prediction of death over all baseline clinical parameters.

Propensity score–matched analysis. Propensity score matching selected 43 matched pairs of patients with identical characteristics undergoing complete revascularization, or remaining under medical treatment or undergoing in-

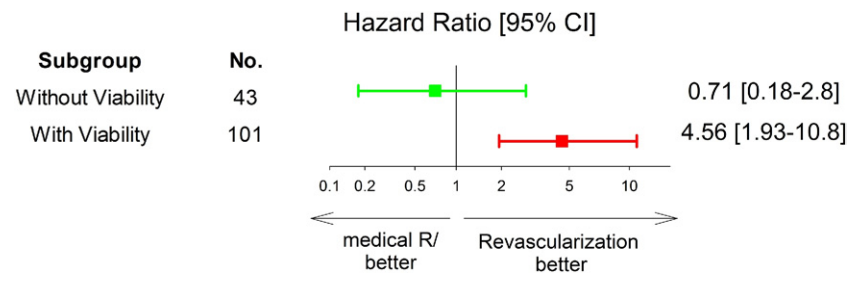

Figure 4 Hazard Ratio of Risk of 3-Year Death According to Presence or Absence of Viability and Treatment

Patients with dysfunctional viable myocardium had a 4.56 higher risk of death when remaining under medical treatment, or when revascularization was incomplete, not including the dysfunctional myocardium. CI = confidence interval; R/ = remaining under medical treatment.

complete revascularization. In post-matching analysis, there were no significant differences for any of the covariates between the 2 groups of patients. Kaplan-Meier survival curves constructed for these 43 pairs of propensity score–matched patients showed a persistent significant risk of overall and cardiovascular death in medically treated or incompletely revascularized patients with viable myocardium (Figs. 5A and 5B).

Also, when the propensity score was entered into a Cox model, medical treatment in the presence of myocardial viability (HR: 2.5; 95% CI: [1.1 to 6.1]; p = 0.02) and the interaction of revascularization treatment with the number of dysfunctional viable segments still provided additional prognostic value (additional chi-square test: 5.14, p = 0.02) over and above the propensity score alone.

Discussion

The salient findings of our study were that the interaction between presence of myocardial viability by DE-CMR and revascularization significantly predicted survival in CAD patients with low EF. Indeed, overall survival was significantly worse when dysfunctional viable myocardium was not revascularized than when it was completely revascularized. By contrast, we observed no significant difference in survival in patients with nonviable myocardium whether they underwent revascularization or not.

Several studies have evaluated the value of DE-CMR to predict outcomes (8–12) and reported that presence of DE identifies patients with higher risk of events. At first sight, this appears to conflict with the results of our data, where we observed that viable myocardium, i.e., dysfunctional regions showing absence or <50% transmurality of DE was associated with worse survival, when such viable myocardium was not revascularized. However, these apparent discrepancies likely reflect differences in study design and patient populations, in particular with respect to the presence of CAD and revascularization therapy. Indeed, some studies that demonstrated that DE-CMR predicts worse outcomes were performed in unselected patients with unknown CAD status (8–10). In this setting, the identification of DE by CMR likely detects patients with CAD from those with nonischemic cardiomyopathies, which are known to have better outcomes. Other works were performed in patients with acute reperfused ST-segment elevation MI (16–18), demonstrating that infarct size measured by DE-CMR is a stronger predictor of events than EF. This likely occurs because in revascularized acute MI, the extent of myocardial injury may be overestimated by EF at the time of

Table 2 Cox Univariate Analysis of Parameters Significantly Associated With Risk of Overall 3-Year Mortality

Parameters	HR (95% CI)	Chi-Square	p Value
PAD	2.29 (1.57–3.34)	4.81	0.03
Creatinine clearance	0.986 (0.979–0.993)	5.15	0.04
NYHA functional class III/IV	4.79 (2.61–8.82)	7.72	0.01
EF	0.955 (0.933–0.977)	4.00	0.04
EuroSCORE logistic	1.057 (1.037–1.077)	5.50	0.003
EuroSCORE additive	1.170 (1.083–1.265)	4.08	0.04
Wall motion score	1.085 (1.050–1.120)	6.05	0.01
Dysfunctional viable segments per patient (continuous variable)	0.996 (0.964–1.028)	0.02	0.88
Medical treatment or incomplete vs. complete revascularization	2.05 (1.45–2.89)	4.30	0.04
Revascularization × dysfunctional viable segments per patient (continuous variable)	1.09 (1.06–1.13)	7.69	0.005
Medical treatment or incomplete revascularization and presence of viable myocardium (≥4 dysfunctional viable segments per patient)	3.77 (2.51–5.69)	12.51	0.001

× = interaction between 2 factors; CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

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Table 3 Additional Prognostic Value of Myocardial Viability and Revascularization to Predictors of Survival

Parameters	Partial HR	Chi-Square Test to Remove	p Value
NYHA functional class	3.59 (1.04–12.4)	4.09	0.04
Wall motion score	1.06 (0.99–1.13)	3.18	0.07
PAD	2.07 (0.98–4.38)	3.68	0.05
Combined baseline model		17.10	0.004
		Chi-Square Test to Enter	
Model 1 (# of dysfunctional viable segments used as continuous variable)			
Revascularization of dysfunctional segments	0.54 (0.15–1.99)	0.85	0.35
Absolute # of dysfunctional viable segments	0.90 (0.80–1.00)	3.77	0.05
Revascularization × absolute # of dysfunctional viable segments	1.15 (1.00–1.33)	3.88	0.05
Additional value of Model 1 to baseline model		7.56	0.05
Model 2 (viability defined ≥4 dysfunctional viable segments/patient)			
Medical treatment and viable myocardium (presence of ≥4 dysfunctional viable segments)	3.47 (1.50–8.01)	8.47	0.004
Revascularization and nonviable myocardium (presence of <4 dysfunctional viable dysfunctional segments)	5.93 (1.61–21.9)	7.18	0.007
Additional value of Model 2 to baseline model		13.10	0.004

× = interaction in Cox Model; other abbreviations as in Table 1.

the acute event, since a substantial part of dysfunctional myocardium may be acutely stunned and spontaneously recover function over time. Yet, final EF, LV volumes, and post-MI remodeling, which are important predictors of outcomes in patients with acute MI, are well known to be predicted by the extent of irreversible injury as measured by initial infarct size (16,19).

So far, only a few studies have been performed to assess the potential value of myocardial viability by CMR in patients with chronic nonrevascularized CAD (11,12). Kwon et al. (11) demonstrated in 349 patients with similar severe reduction of EF as in our study (mean EF: 24%), of presumed ischemic etiology (history of MI, of coronary revascularization, or presence of at least 1 epicardial coronary vessel stenosis) that more events occurred when patients had higher extent and transmurality of scar by DE-CMR. However, coronary angiography was not systematically performed, and the patient population was heterogeneous with respect to whether CAD was still present or had been revascularized at the time of the study. An important aspect, which also may explain different results, is that in the prior studies, viability was not determined in relation to regional dysfunction. Indeed, these studies evaluated the magnitude of DE in the entire heart, rather than assessing presence or absence of DE in dysfunctional segments. Finally, none of the prior works evaluated the influence of revascularization of dysfunctional myocardium on outcomes. Our study is the first to our knowledge to specifically examine the question whether revascularization of dysfunctional but viable myocardium detected by DE-CMR is associated with different outcomes.

The findings of the present study are in agreement with earlier work performed using dobutamine echocardiography, positron emission tomography, and conventional nuclear imaging, which demonstrated that patients with dysfunctional but viable myocardium have better outcomes when revascularized than when medically treated. Indeed, in a meta-analysis of these studies (13), revascularization of dysfunctional but viable myocardium was associated with a 79% reduction of annual death rate. By contrast, and similar to our findings, this meta-analysis reported that revascularization of patients with nonviable myocardium did not influence survival.

The observation that nonrevascularized viable myocardium has worse clinical outcome is also supported by animal studies, which reported increased arrythmogenic vulnerability, leading to sudden cardiac death in dysfunctional, nonrevascularized viable myocardium (20,21). This is likely due to the fact that such dysfunctional hibernating or chronically stunned myocardium in nonrevascularized CAD is exposed to repeated episodes of ischemia and reperfusion (22,23) causing electrical instability due to depolarization of membrane potentials. The fact that viable rather than nonviable myocardium increases risk in CAD patients is also supported by other DE-CMR works, which indicated that the peri-infarct zone (24,25), that is, regions where infarct is not transmural, but where viable myocytes coexist with minute amounts of scar, predict arrhythmic events.

Clinical implications. The long-term survival of patients with severely depressed LV function and CAD is poor. A major goal in the management of these patients consists to identify those who may benefit from revascularization strategies. Indeed, revascularization of dysfunctional but viable myocardium was shown to improve LVEF and symptoms of heart failure. Yet, surgical revascularization in patients with poor EF is associated with significant perioperative risk. It is therefore important to balance this operative risk with a potential benefit in survival by reduction of further adverse cardiac events after revascularization (26,27).

Our study suggests that similar to positron emission tomography, dobutamine echocardiography, and nuclear imaging, DE-CMR may be useful to predict, not only functional improvement of patients with CAD and LV

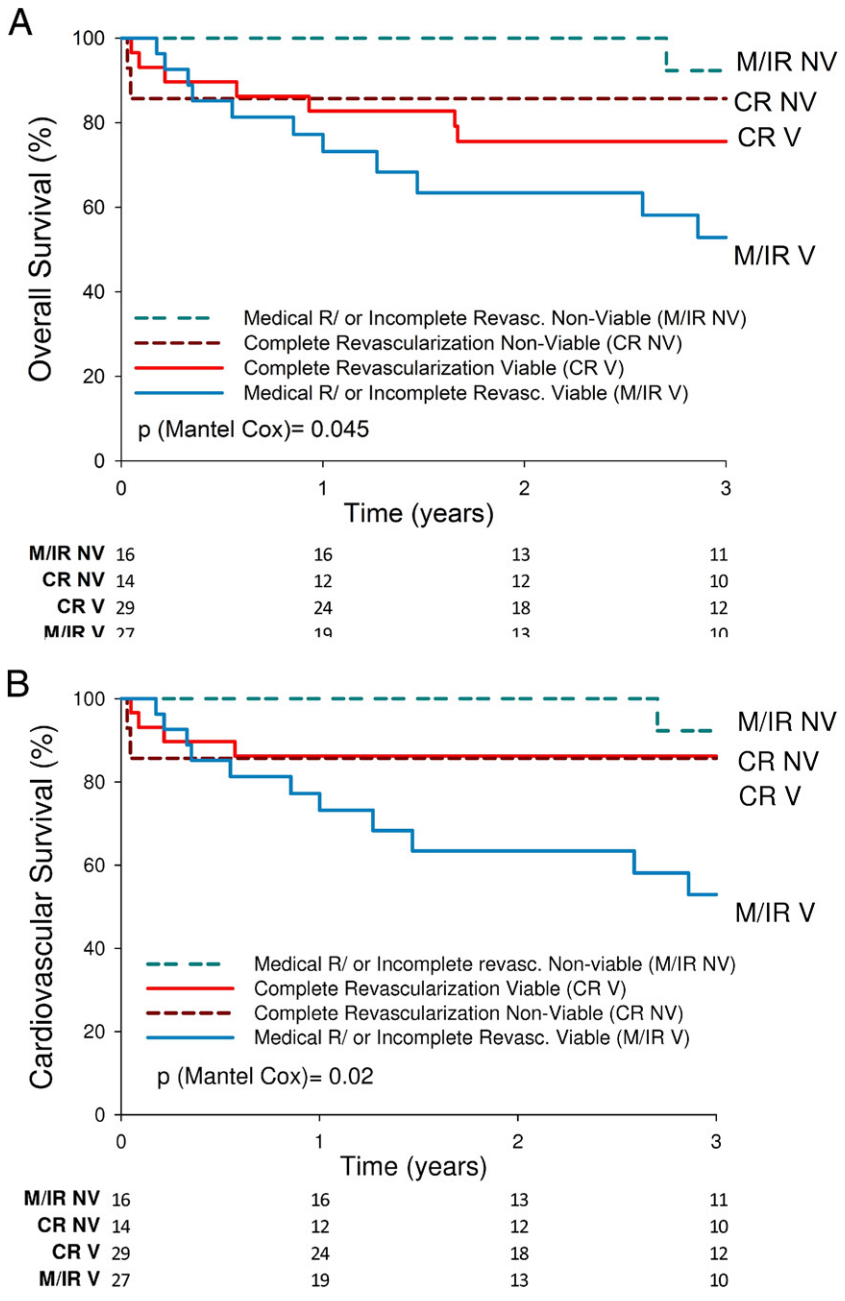

Figure 5 **Kaplan-Meier Survival Curves Comparing Overall and Cardiovascular 3-Year Survival in 43 Pairs of Propensity Score–Matched Patients**

In these propensity score–matched patients, overall **(A)** and cardiovascular **(B)** 3-year survival remained significantly worse in patients with viable myocardium who remained under medical treatment or undergoing incomplete revascularization not including dysfunctional regions. Abbreviations as in Figure 3.

dysfunction, but also survival. Indeed, our study showed that revascularization of dysfunctional viable myocardium provides a significant improvement in patient outcomes versus medical treatment. It thus suggests that patients with viable myocardium should be revascularized to improve survival. Also, it evokes that incomplete revascularization of nondysfunctional myocardium is not protective when dysfunctional viable myocardium is not revascularized. Interestingly, however, this could not be confirmed in the recently published randomized STICH (Surgical Treatment for Ischemic Heart Failure) trial (28). Several reasons may account for this. Even though the STICH trial enrolled patients with roughly similar EF (mean: 28%) as our study, it included a majority of patients with angina rather than heart failure symptoms. Also, severity of LV dilation and of degree of CAD was significantly less than in our study, resulting in

lower mortality in the STICH trial (3-year mortality 25%) than in our population. In addition, viability assessment was not mandated, but at the discretion of investigators, and a heterogeneous protocol for assessment of myocardial viability, either dobutamine echocardiography or single-photon emission computed tomography was used. Finally and most importantly, the definition of myocardial viability by single-photon emission computed tomography did not mandate myocardial viability to be found in dysfunctional segments, but rather required a threshold number of segments with normal perfusion to identify patients with viability. All this may explain the surprising negative outcome of the STICH viability substudy.

Study limitations. As with most other works evaluating the value of myocardial viability on survival, the present study was not randomized, and results from CMR were not blinded to physicians involved in treatment strategies, potentially resulting in treatment selection bias. Although most baseline characteristics were similar for patients undergoing revascularization and medically treated patients, the 2 groups differed in severity of heart failure symptoms and the amount of myocardial viability. This might have influenced outcomes in the groups. Therefore, we performed a propensity score analysis, where we matched revascularized and nonrevascularized patients with similar baseline characteristics, particularly myocardial viability, pairwise and compared survival in the different subgroups. Because both types of analysis demonstrated significant additional prognostic value of the interaction of myocardial viability and revascularization, we believe that these parameters may not have played a major confounding factor in the present study.

Conclusions

Our data clearly indicate that patients with severe LV dysfunction of ischemic etiology, who remain under medical treatment despite the presence of myocardial viability detected by DE-CMR, incur significant excess of mortality. These observations may be useful to determine which patients with impaired LV function are most likely to benefit from revascularization therapies.

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