Jeopardized Myocardium Defined by Late Gadolinium Enhancement Magnetic Resonance Imaging Predicts Survival in Patients With Ischemic Cardiomyopathy: Impact of Revascularization

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***Background*—**The prognostic impact of jeopardized myocardium (JM) in patients with advanced ischemic cardiomyopathy (ICM) is unclear. We hypothesized that JM is an independent predictor of mortality in patients with advanced ICM.

***Methods and Results*—**Patients with ICM who underwent cardiac magnetic resonance imaging between January 2002 and January 2013 were included in our study. JM was identified as a vascular territory with <50% myocardial scarring on cardiac magnetic resonance imaging and with >70% stenosis in a major coronary vessel that was not subsequently revascularized. A propensity score was developed for revascularization. A multivariable Cox proportional hazards model was used to evaluate the association of JM with all-cause mortality. We evaluated 631 patients over a mean follow-up of 5.1 years. Overall, 336 patients underwent subsequent revascularization during the follow-up period, among whom 23% had remaining JM, while 295 patients were medically treated (57% with JM). There were 204 deaths (32%). On multivariable analysis, JM (hazard ratio, 1.88; 95% confidence interval, 1.38–2.55 [*P*<0.001]) was independently associated with all-cause mortality after adjusting for multiple other factors. The risk associated with the presence of JM increased by 5% for every 10-unit increase in left ventricular end-systolic volume index.

Conclusions*—**JM is an independent and incremental predictor of mortality in patients with advanced ICM. Patients undergoing revascularization with residual JM had similar risk of mortality compared with medically treated patients with JM. The risk associated with JM significantly increased in the presence of worsening adverse left ventricular remodeling. Cardiac magnetic resonance viability assessment may provide important risk stratification in patients with ICM. (J Am Heart Assoc***. 2018;7: e009394. DOI: 10.1161/JAHA.118.009394.)**

Key Words: ischemic cardiomyopathy • magnetic resonance imaging • revascularization • survival • viability imaging

Previous studies have demonstrated that angiographically defined incomplete revascularization is associated with adverse outcomes.[1–3] However, patients with significant left ventricular (LV) systolic dysfunction were not included in these prior studies, and presence or absence of jeopardized myocardium (JM), defined by viability assessment, has also not been adequately assessed. The detrimental impact of JM in the setting of ischemic cardiomyopathy (ICM) is therefore unproven and whether the assessment of myocardium in jeopardy in this setting can further inform revascularization strategies, has not been adequately evaluated. Prior studies have suggested that viability assessment may help to identify which patients will derive the greatest benefit from revascularization.[4,5] Although the STICH (Surgical Treatment of Ischemic Heart Failure) viability study failed to demonstrate an impact of viability on predicting differential outcomes,[6] viability testing in STICH was not randomized, and more sensitive, higher-resolution imaging techniques, such as positron-emission tomography and magnetic resonance imaging (MRI), were not used. In addition, viability assessment was not analyzed in the context of epicardial coronary anatomy. Of even greater importance, the presence of myocardium in jeopardy as assessed by the correlation of functional anatomy and epicardial coronary anatomy was not determined.

Furthermore, there has been a growing body of evidence to suggest that viability assessment with positron-emission tomography and cardiac MRI can predict survival benefit with revascularization.[7–10] Utilizing myocardium in jeopardy enables one to aggregate the totality of heart muscle both hibernating and ischemic into one summated parameter. In this study, we evaluate the utility of identifying myocardium in jeopardy, as assessed by MRI, with angiographic correlation in ischemic cardiomyopathy.

Myocardial scar burden assessed by late gadolinium enhancement (LGE) MRI has been shown to be a powerful independent predictor of mortality in ICM.[11–13] Because of its superior spatial resolution, LGE-MRI is considered the reference standard for the quantification of myocardial infarct size, LV volumes, and ejection fraction (EF).[14–16] Therefore, we sought to integrate coronary angiographic anatomy with the presence of viable myocardium, assessed by LGE-MRI, to determine the overall myocardium in jeopardy and the impact of JM on survival. Furthermore, we sought to eliminate potential confounders by utilizing a robust propensity analysis to determine the ability for viability assessment with LGE-MRI to predict differential outcomes in patients undergoing medical therapy versus revascularization.

Methods

Study Design

We examined 1109 patients with LV systolic dysfunction who were referred for cardiac MRI assessment between January 2002 and January 2013. Among these, 631 patients met our criteria for advanced ICM (LVEF ≤40% with ≥70% stenosis in ≥1 epicardial coronary vessel on angiography and/or history of myocardial infarction or coronary revascularization) and were referred for myocardial viability assessment with cardiac magnetic resonance (CMR) imaging, as previously described.[11] Patients were included in our study if they had coronary angiography performed within 1 year of the CMR study obtainable via medical chart review as well as echocardiographic assessment within 1 month of the CMR study for assessment of severity of ischemic mitral regurgitation (Figure 1). Patients were retrospectively categorized into 1 of 2 comparison groups based on whether they underwent coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) at any time after the index CMR. Patients who did not undergo subsequent revascularization were considered to have been treated medically. The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Clinical and demographic variables were entered prospectively into electronic medical records. Medical therapy, including β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, spironolactone, and statin therapy, was recorded. Post-CMR coronary revascularization (either percutaneous or surgical) and implantable cardioverter-defibrillator (ICD)/cardiac resynchronization therapy implantation were also recorded.

All-cause mortality was ascertained by social security death index and was used as the primary end point. This study was approved by the institutional review board with a waiver of individual consent.

CMR Protocol

CMR examinations were performed on 1.5-T MR scanners (Sonata and Avanto, Siemens Medical Solutions, for imaging between 2002 and 2006, and Philips Achieva XR, for imaging between 2007 and 2013), using 40 to 45 mT/m maximum gradient strength, 200 T/m per second maximum slew rate with electrocardiographic gating. For assessment of global cardiac function, steady-state free precession images were acquired (slice thickness 8–10 mm in contiguous short-axis images). LV volumes and LVEF were calculated on short-axis steady-state free precession images. LGE-CMR images were obtained in long- and short-axis orientations ≈15 to 20 minutes after injection of 0.2 mmol/kg of Gadolinium chelate,
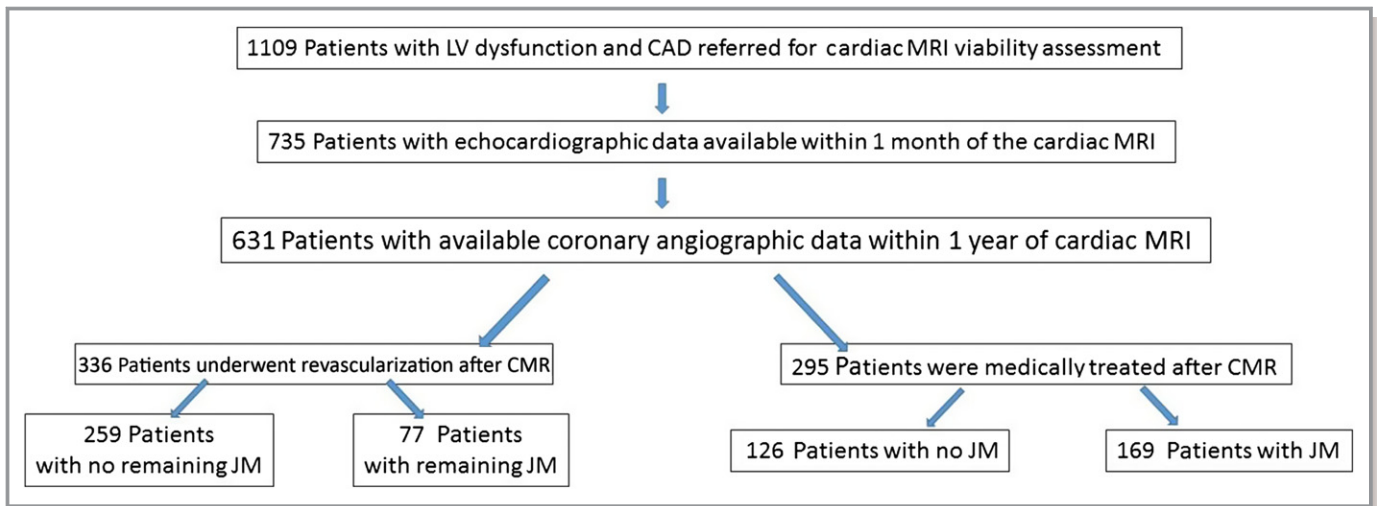
Figure 1. Flow chart for patients included in the study. CAD indicates coronary artery disease; CMR, cardiac magnetic resonance; JM, jeopardized myocardium; LV, left ventricular; MRI, magnetic resonance imaging.

with segmented inversion-recovery gradient echo sequences for studies performed in 2002–2003 and phase-sensitive inversion-recovery spoiled gradient echo sequences for studies performed after 2003 (spatial resolution of 1.5–2.1×1.1–1.4 mm).

LGE-CMR Analysis

LGE-CMR images were analyzed using a custom analysis multivendor package (cvi42; Circle Cardiovascular Imaging). Endocardial and epicardial myocardial edges were manually delineated on LGE-CMR images. Scar was defined by intensity ≥2 SDs above user-defined viable myocardium, as previously described.[11] Scar burden was automatically determined as percentage of total myocardium (infarct volume/mass divided by total LV volume/mass). CMR analysis was completely blinded from the clinical analysis.

JM was considered present when a patient had ≥1 major epicardial coronary arteries with >70% stenosis (and without patent bypass graft in patients with prior CABG) with viable/potentially ischemic myocardium in its corresponding vascular territory. Coronary angiographic images were not available in 12% of our patient population, and the anatomy was derived from clinical reports. Coronary stenosis >70% in the major epicardial vessels (left main, left anterior descending, left circumflex, and right coronary artery) and the location of the stenosis (proximal, mid, distal) was integrated with the CMR viability assessment. Viability was defined myocardium with <50% scarring in the corresponding myocardial segments according to the 17-segment AHA model. Vascular territories with >50% of their segments having >50% scarring were determined to be nonviable. Furthermore, viable myocardial segments within areas of scarred segments were not

considered to be in jeopardy if there was no corresponding severe epicardial coronary artery stenosis. JM was defined as viable myocardium with severe corresponding epicardial stenosis that was not subsequently revascularized after the index cardiac MRI. Patients who underwent post-CMR revascularization were deemed to have incomplete revascularization/JM if there were viable territories with severe corresponding epicardial disease that were not revascularized.

Statistical Analysis

The primary objective of our study was to assess the independent effect of JM on all-cause mortality. Based on clinical experience, 2 main risk factors for this patient population are baseline demographic and risk factors and the treatment they received (ie, revascularization). Thus, we first built a medical risk score. From the literature, we identified variables that correlated with all-cause mortality and constructed a multivariable Cox proportional hazards model predicting all-cause mortality. The variables in the medical risk score included age, body mass index, sex, diabetes mellitus, glomerular filtration rate, hypertension, dyslipidemia, medications (β-blocker, angiotensin-converting enzyme inhibitor/receptor blocker, left or right bundle branch block, QRS duration, and an interaction term for sex and diabetes mellitus). Second, we reasoned that presence/absence of revascularization was not sufficient to account for differences in treatment effects on patient outcome because patients were not randomized to treatment. Thus, a propensity score model was built to account for differences in patient mix between the post-CMR treatment groups. Logistic regression was used to build the propensity model. Post-CMR treatment group (ie, medically treated or revascularization) was the dependent variable and

the following were the independent variables: clinical risk score described above, number of vessels with CAD, pre-CMR CABG or PCI, medications, end-systolic volume index (ESVI), and age. The final model had a C-index of 0.70 and provided good balance in covariates. The patients' propensity scores from this model were then used as a covariate in a model to assess the effect of JM on patient outcome. Since the goal of our study was to assess the effect of JM on outcome, we did not match revascularized and medically treated patients on the propensity scores (as we would have if our goal had been to compare the outcomes of the 2 treatment groups), but rather we used the scores as a covariate to adjust for baseline differences between the treatment groups.

Once the medical risk and propensity scores were completed, we evaluated the effect of JM on patient outcome. The null hypothesis was that JM has no effect on patient outcome (ie, hazard ratio [HR] of 1), versus the alternative hypothesis that JM does have an effect on patient outcome (ie, HR not equal to 1). Several multiple-variable Cox proportional hazard models were built to test whether JM is a predictor of all-cause mortality. The following variables were adjusted for in these analyses: propensity score for treatment as described above, treatment group (medical versus revascularization), medical risk score as described above, ESVI, total scar percentage, ICD (modeled as a time-dependent predictor), severity of mitral regurgitation, and pre-MRI CABG or PCI. (Note that revascularization occurred within 90 days of CMR imaging for 96% of patients, and thus was not treated as a time-dependent covariate.) For the primary analysis, the predictive ability of JM as a main effect in the model was tested. The 2-way interactions of JM and ESVI, JM and treatment, and JM and VC1 were then tested to determine whether the effect of JM on patient outcome was mediated by these other variables. In all models, a significance level of 0.05 was used for testing the effect of JM. The proportional hazards model assumption was evaluated in the final models. For illustration of the model results, the predicted survival was plotted, holding the covariates constant at their mean values.

Statistical analyses were performed with SPSS version 20.0 (IBM) and SAS version 9.2 (SAS Institute).

Results

Patient Characteristics

Our study sample (N=631) was predominantly male (77%), with a mean age of 62±11 years. Patients were divided into groups undergoing medical management versus CABG (Table 1). There were 295 medically treated patients and 336 patients with revascularization. Among those who underwent revascularization, 29 (9%) underwent PCI and 307 (91%) underwent surgical CABG. Furthermore, among

patients with revascularization, 96% had revascularization within 90 days of the MRI. Table 1 summarizes the baseline characteristics of the patients. Medically treated patients tended to be younger, with a lower prevalence of dyslipidemia. Medically treated patients were less likely to be on β-blocker therapy than patients with revascularization.

Imaging Findings

Our study population had significant LV dysfunction and LV dilation, with a mean LVEF of 25±10% and mean LV end-diastolic volume index of 107±45 cc/m^2 (Table 1). Patients who were medically managed had more extensive myocardial scar burden and increased severity of ischemic mitral regurgitation. Of the patients who were medically treated, 44% had undergone complete revascularization in the past, with no residual JM. Among the patients who were medically treated without subsequent revascularization following their CMR viability assessment, 66% had at least 1 vascular territory with JM, with only 12% having all 3 vascular territories demonstrating JM. On the other hand, 77% of the patients who underwent subsequent revascularization experienced complete revascularization. The presence of subendocardial scarring in the vascular territories with JM is listed in Table 1.

Of patients who had residual JM after revascularization, 21% had JM in 1 vascular territory and 1.5% had JM in 2 vascular territories. It is important to note that only 5 patients had 2 vascular territories with JM after revascularization, and all 5 patients had undergone PCI as opposed to CABG subsequent to their CMR. There were no patients who had 3 vascular territories with JM. Table 2 lists the reasons of incomplete revascularization among patients who underwent post-MRI revascularization.

Effect of JM on Survival

Over a mean follow-up of 5.1 years, there were 204 deaths (94 in post-MRI patients with revascularization and 110 medically treated patients). Among the 336 patients who underwent subsequent revascularization after CMR, 76 patients underwent incomplete revascularization and 260 patients underwent complete revascularization. See Figure 2 for an illustration of medically managed patients versus those with revascularization, with and without JM.

A main effects multivariable model was constructed to assess the effect of residual JM on patient outcome. After adjusting for medical risk factors and treatment, JM emerged as a highly significant predictor of all-cause mortality ($P<0.001$). The estimated HR for patients with JM was 1.88 (95% confidence interval [CI], 1.38–2.55), representing an 88% increase in the risk of mortality (see the "Main Effects" column in Table 3).

Table 1. Clinical and Imaging Characteristics

	All Patients	Medically Treated	Revascularization	P Value*
Patients, No.	631	295	336	
Mean age (SD), y	62.4 (11.1)	60.7 (12.0)	63.8 (10.3)	0.001
Women, %	23.4	26.1	22.6	0.309
BMI	28.6 (5.3)	28.4 (5.6)	28.8 (5.1)	0.244
GFR	85.7 (37.4)	86.4 (38.6)	85.1 (36.3)	0.544
Pre-MRI CABG or PCI, %	43.1	48.1	38.7	0.017
Hypertension, %	52.9	53.2	52.7	0.892
Diabetes mellitus, %	36.9	33.2	40.2	0.071
Hyperlipidemia, %	52.3	57.0	48.2	0.028
Statin, %	80.2	83.1	77.7	0.091
ACEI, %	81.5	79.7	83.0	0.277
β-Blocker, %	84.6	81.4	87.5	0.033
Spironolactone, %	22.7	25.4	20.2	0.121
Imaging characteristics				
LVEF, %	25.4 (10.4)	27 (11.7)	24.0 (8.7)	<0.001
ESVI, cc/m^2	106.5 (44.5)	103.7 (48.5)	109.0 (40.5)	0.008
Total scar percentage	23.3 (15.7)	25.2 (15.5)	21.7 (15.7)	0.003
Ischemic mitral regurgitation severity measured by vena contracta width	0.31 (0.32)	0.32 (0.35)	0.29 (0.30)	0.904
Post-MRI therapy				
CABG or PCI, %	53.3	0	100	...
Surgical mitral valve intervention, %	19.5	5.1	32.1	<0.001
ICD, %	32.0	31.2	32.7	0.677
CRT, %	9.8	10.2	9.5	0.786
Presence of JM, %	38.8	57.3	22.6	<0.001
No. of vascular territories with JM, %				
0	61	44	77	
1	24	27	21	
2	9	17	1.5	
3	6	12	0	
No. of vascular territories with subendocardial infarct in the areas of JM, %				
0	61	41	79	
1	25	30	20	
2	9	18	1	
3	5	11	0	

ACEI indicates angiotensin-converting enzyme inhibitor; BMI, body mass index; CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; ESVI, end-systolic volume index; GFR, glomerular filtration rate; ICD, implantable cardioverter-defibrillator; JM, jeopardized myocardium; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MRI, magnetic resonance imaging; PCI, percutaneous coronary intervention.

JM and Therapy

To address the question of the impact of JM on outcomes based on therapeutic intervention, we compared medically treated patients with and without JM and patients with revascularization with and without JM. Although the presence of JM was a highly significant predictor of all-cause mortality (HR, 1.88; 95% CI, 1.38–2.55 [*P*<0.001]), the effect of JM was similar for medically treated patients and patients with revascularization. Figure 3 demonstrates the differences in survival based on the presence of JM. The blue curve represents predicted survival for patients with subsequent

Table 2. Reasons for Incomplete Revascularization

	Patients (N=77), No. (%)
Epicardial vessel not surgically revascularized because of severe, diffuse disease	44 (57)
Vascular territory deemed not viable despite MRI findings	18 (23)
Totally occluded epicardial vessel not amenable for PCI	8 (10)
Vessel felt to be too small for PCI	4 (4)
PCI not performed in second vessel with viability—reason not specified	3 (4)

MRI indicates magnetic resonance imaging; PCI, percutaneous coronary intervention.

revascularization with complete revascularization, the red curve depicts predicted survival for patients with subsequent revascularization with JM, and the green curves depict predicted survival for medically treated patients (those with JM are green dashed and those without JM are green solid). Regardless of treatment, patients with JM were at higher risk than those without JM. Specifically, patients with revascularization with JM were at similar risk to medically treated patients with JM. The increased risk associated with the presence of JM was similar for medically treated patients and patients with revascularization. Specifically, among the subgroup of patients who were medically treated, the estimated HR for those with JM was 2.01 and, similarly, the estimated HR was 1.83 among the subgroup of patients who had subsequent revascularization. Interestingly, there was no difference in survival between patients who were medically treated with JM compared with patients who had subsequent revascularization with JM (P=0.808).

To address the question of the impact of the number of vascular territories with JM on outcomes, we also included the number of vascular territories with JM in the multivariable main effects model (Table 3). This model demonstrates that risk significantly increased with increasing number of vascular territories with JM. However, the risk associated with 2 or 3 vascular territories with JM were similar. Figure 4 illustrates survival in our study population, based on the number of vascular territories with JM.

Interaction With Incomplete Revascularization

In a second model, we explored the significance of 2-way interaction with ESVI and JM. To determine this, the multivariate model was reanalyzed with the addition of the interaction term ESVI×JM (see Table 3, "Final Model With Interaction" column). ESVI×JM emerged as a novel

independent and significant predictor of mortality (P=0.026), with an estimated HR of 1.05 per 10-unit increase in ESVI among patients with JM (95% CI for HR, 1.0−1.10). This model suggests that among patients with JM, for every 10-unit increase in ESVI, the estimated HR increases by 5% compared with those with complete revascularization. This highly significant interaction demonstrates that the relationship between JM and the hazard of dying is mediated by ESVI and that the hazard associated with JM should not be determined in isolation. The final model demonstrates that the association of JM with mortality is more completely explained in the context of LV end-systolic volume index (LVESVI).

Figure 5 illustrates the HRs based on the interaction of ESVI×JM and stratified to the number of vascular territories with JM. HRs associated with the number of vascular territories with JM are depicted relative to patients who experienced complete revascularization. In this figure, complete revascularization is attributed to an HR of 1. The blue curve illustrates survival in patients with 1 vascular territory with JM, and the orange curve illustrates survival in patients with 2 and 3 vascular territories with JM. Of note, patients with 2 and 3 vascular territories were pooled together, based on the findings of the main effects multivariable model.

This figure demonstrates that risk associated with increasing ESVI increases more precipitously in patients with 2 and 3 vascular territories with JM compared with those with only 1 vascular territory with JM, relative to patients who underwent complete revascularization. Increasing ischemic mitral regurgitation severity (P<0.001), higher medical risk score (P<0.001), and larger myocardial scar burden (P<0.001) were also independent predictors of mortality in our study population.

Discussion

Utilizing a large CMR data set, our study demonstrates that JM is a powerful independent predictor of all-cause mortality in patients with advanced ICM. Although our study is based on observational data, we utilized a propensity analysis in an attempt to adjust for confounding variables so as to mimic a randomized controlled trial to determine the effectiveness of viability assessment and its association with outcomes in patients undergoing revascularization versus medical treatment. The mortality rate in our study population was relatively high (32% over a median follow-up of 5.1 years). The results of our study further inform our risk-modulating management strategies for patients with significant ICM with the following novel findings: (1) Patients with incomplete revascularization with remaining JM had a similar risk of mortality compared with medically treated patients with JM; (2) Patients with ≥2 vascular territories are at higher risk than patients with only 1 vascular territory; (3) Risk associated with JM significantly
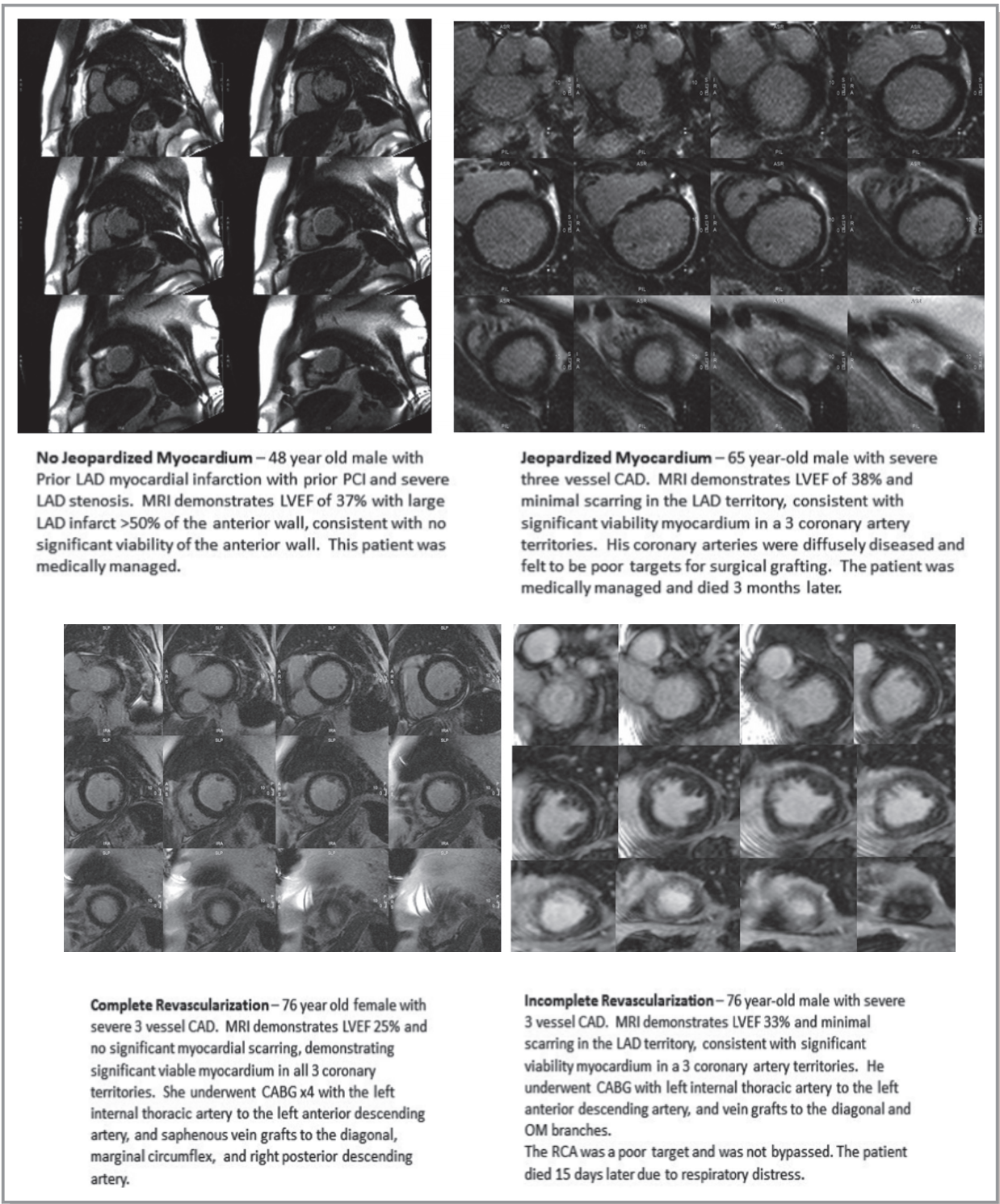
Figure 2. Illustrated examples of medically treated patients with and without jeopardized myocardium (JM; A), as well as patients who underwent subsequent revascularization, with and without remaining JM (B). CAD indicates coronary artery disease; CABG, coronary artery bypass grafting; LAD, left anterior descending; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; OM, obtuse marginal; RCA, right coronary artery.

increased in the presence of worsening adverse LV remodeling; (4) While myocardial scar burden, defined by LGE-CMR, is an independent and incremental predictor of adverse outcomes, its prognostic significance has increased relevance when taken in the functional context of corresponding epicardial coronary disease.

Table 3. Main Effect and Final Multivariable Model for Predicting All-Cause Mortality

	HR (95% CI)	P Value in Final Model		HR (95% CI)	P Value in Final Model
	Main Effect Model		Final Model With Interaction		
Medical risk score	2.88 (2.31–3.60)	<0.001	Medical risk score	2.99 (2.38–3.74)	<0.001
Pre-MRI CABG or PCI	1.01 (0.76–1.35)	0.928	Pre-MRI CABG or PCI	1.02 (0.77–1.36)	0.883
Total scar percentage	1.02 (1.01–1.03)	<0.001	Total scar percentage	1.022 (1.01–1.03)	<0.001
Ischemic mitral regurgitation severity	2.45 (1.57–3.82)	<0.001	Ischemic mitral regurgitation severity	2.33 (1.49–3.66)	<0.001
ICD (time covariate)	0.91 (0.65–1.27)	0.582	ICD	0.92 (0.66–1.28)	0.607
Propensity score (medical vs revascularized)	0.98 (0.79–1.21)	0.830	Propensity score (medical vs revascularized)	0.99 (0.80–1.22)	0.919
Revascularization	1.25 (0.91–1.71)	0.170	Revascularization	1.21 (0.89–1.66)	0.228
ESVI, cc/m^2 (per 10-unit increase)	1.01 (0.99–1.01)	0.504	ESVI, cc/m^2 (per 10-unit increase): When no JM: When JM present:	1.0 (0.99–1.00) 1.05 (1.0–1.10)	0.026
JM territories (relative to 0)		<0.001			
1	1.61 (1.15–2.27)				
2	2.48 (1.53–4.02)				
3	2.43 (1.33–4.44)				

CABG indicates coronary artery bypass grafting; CI, confidence interval; ESVI, end-systolic volume index; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; JM, jeopardized myocardium; MRI, magnetic resonance imaging; PCI, percutaneous coronary intervention.

JM and Outcome

Our findings further inform the ongoing debate regarding the utility of viability testing in patients with advanced ischemic cardiomyopathy. While the STICH viability substudy did not demonstrate the ability to predict differential outcomes for patients undergoing CABG, based on the presence of viability, this substudy did not utilize imaging modalities such as CMR or positron-emission tomography imaging, which are more sensitive in the detection of scar/viability.[6] Recently, several studies have demonstrated the utility of viability assessment with advanced imaging techniques, such as CMR and positron-emission tomography.[7–10] LGE-CMR is a highly accurate technique in the assessment of myocardial viability.[14–16] Transmural extent of scar, assessed by LGE-CMR, has been correlated with functional recovery after revascularization.[1,17] However, the prognostic implications of viability assessment and the benefit of revascularization in patients with severe ICM has not been well defined.[4,5,17,18–20]

While patients with ICM exhibit severe LV dysfunction, the extent of myocardium in jeopardy, the ability to provide complete revascularization, the presence of ischemic mitral regurgitation, the degree of LV remodeling, and right ventricular function varies from one patient to another. To the best of our knowledge, this study represents the largest study of patients with ICM and severe LV dysfunction undergoing viability assessment with CMR. The assessment of the extent of JM and the completeness of revascularization is unique to this study and provides mechanistic insights on the relative merits of revascularization in subsets of ischemic cardiomyopathy. Our study population had severe LV dysfunction, EF 25±10%, LV enlargement, and ESVI 106.5±44.5 mL (normal LV ESVI 15–38 cc/m^2)[21] in the setting of a significant extent of myocardial scarring and mild-moderate mitral regurgitation. In our study population, the mortality rate was 32% over a mean follow-up of 5.1 years. Furthermore, the rate of surgical revascularization was high (53%), despite the high-risk nature of our patient population.

Multiple previous studies have demonstrated the importance of complete revascularization (either surgically or percutaneously).[22–24] A recent meta-analysis of the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery), PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease), and BEST (Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients With Multivessel Coronary Artery Disease Trial) studies demonstrated the importance of survival benefit derived for complete revascularization.[1] This pooled analysis demonstrated that patients with incomplete revascularization
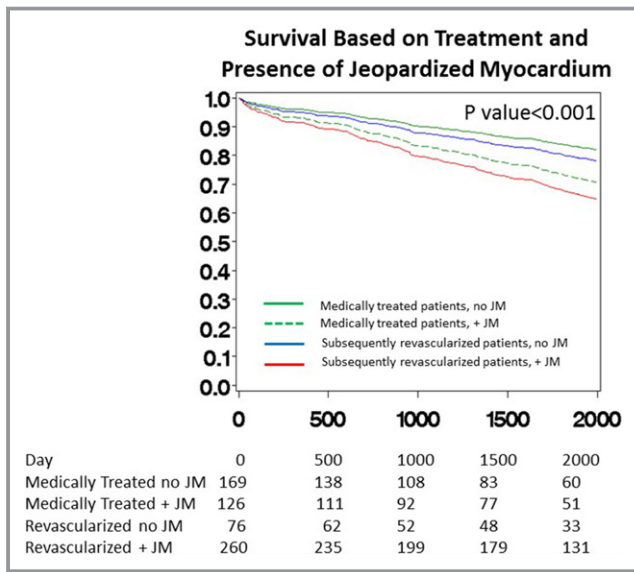
Figure 3. Association of treatment type and presence of jeopardized myocardium (JM) with survival. The blue curve represents the predicted survival for patients with average revascularization without JM, the red curve depicts predicted survival for patients with average revascularization with JM, and the green curves depict predicted survival for medically treated patients (those with JM are green dashed and those without JM are green solid). CABG indicates coronary artery bypass grafting; CAD, coronary artery disease; LAD, left anterior descending; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; OM, obtuse marginal; RCA, right coronary artery.
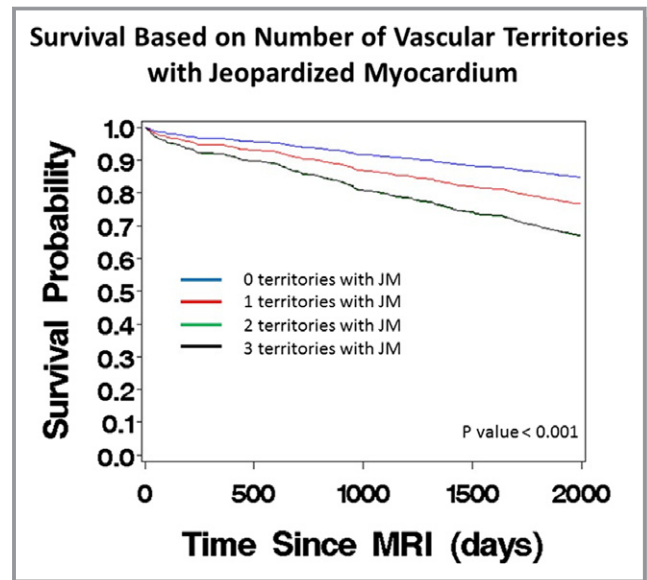

Figure 4. Survival based on the number of vascular territories with jeopardized myocardium (JM). The blue curve represents patients with no vascular territories with JM, the red curve depicts survival in patients with 1 territory with JM, the green curve illustrates survival in patients with 2 vascular territories with JM, and the black curve illustrates survival in patients with 3 vascular territories with JM. Of note, the green and black lines are directly overlapping, demonstrating no increase in risk with 2 vs 3 vascular territories with JM. MRI indicates magnetic resonance imaging.

experienced significantly increased mortality. Furthermore, the rate of incomplete revascularization was substantial in this pooled analysis: 43% of patients undergoing percutaneous intervention and 32% of patients who underwent CABG. However, these studies did not incorporate viability testing with their definition of incomplete revascularization, and the designation of completeness of revascularization was based purely on angiographic analysis. Furthermore, the majority of patients in these studies had normal LV size and function. Our study is the first to demonstrate the utility of incorporating viability assessment in the definition of completeness of revascularization, particularly in patients with advanced ICM with underlying significant myocardial scarring. Our study population was high risk, based on the degree of LV dysfunction and dilation with significant myocardial scarring; however, the rate of JM in our study population was 22.6%, which was significantly lower than previously reported rates of JM in randomized controlled trials.[1,22–24]

Our study confirms the importance of achieving complete revascularization, particularly in patients with advanced ischemic cardiomyopathy. The striking and novel finding in our study is that patients who were referred for subsequent revascularization that was incomplete had similar outcomes to medically treated patients with JM, based on the integration of

epicardial disease on angiography and location of viability/myocardial scarring on MRI. This suggests that partial revascularization does not result in incremental survival benefit over medical therapy. Furthermore, our findings suggest that the assessment of underlying viable myocardium is important to identify the presence of JM in patients in this clinical setting.

In our study population of patients with advanced ICM, we found that the risk of mortality/heart transplant significantly increased with increasing number of vascular territories with JM. However, the survival curves for patients with 2 and 3 vascular territories with JM were overlapping, demonstrating that increased risk is nearly identical in patients with 2 to 3 vascular territories in our patient population. This finding of similar risk in patients with ≥2 vascular territories with JM was also recently demonstrated in a large New York PCI registry, which evaluated 41 639 patients who underwent PCI.[25] However, in this study, incomplete revascularization was determined purely on angiographic imaging, as viability imaging was not included in this study analysis. While a large proportion of patients in the New York registry study were left with ≥2 vascular territories with JM after PCI, the majority of patients in our study underwent surgical revascularization, and only 5 patients had residual JM in 2 vascular territories. Among those who underwent subsequent revascularization,
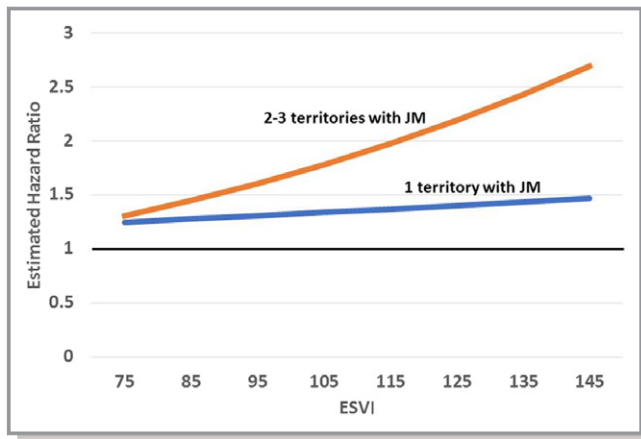
Figure 5. Relationship of jeopardized myocardium (JM) with end-systolic volume index (ESVI). Hazard ratios associated with the number of vascular territories with JM vs ESVI is depicted relative to patients who experienced complete revascularization. In this figure, complete revascularization is attributed to a hazard ratio of 1. The blue curve illustrates survival in patients with 1 vascular territory with JM, and the orange curve illustrates survival in patients with 2 or 3 vascular territories with JM. Of note, patients with 2 or 3 vascular territories were pooled together, based on the findings of Figure 4.

there were no patients in our study who had 3 vascular territories with JM. On the other hand, 29% of patients who were medically treated in our study were found to have ≥2 vascular territories with JM.

Recently, the extended 10-year follow-up of patients with ischemic cardiomyopathy, severe LV dysfunction (LVEF <35%), and CAD amenable to CABG demonstrated that the rate of death of any cause over 10 years was significantly reduced by an absolute difference of 8% in patients who underwent CABG in addition to optimal medical therapy compared with those receiving optimal contemporary medical therapy alone.[26] However, it is important to recognize that the mortality in the CABG group was extraordinarily high: 62.5% in 10 years. Furthermore, the CABG group demonstrated increased early mortality within 30 days, likely as a result of the increased operative risk in patients with advanced ICM. The completeness of revascularization was not reported in this study, and it is not clear how incomplete revascularization with remaining JM impacted outcomes in the extended survival study findings. Our study suggests that if complete revascularization cannot be achieved in patients with advanced ICM, their outcomes may be similar to patients who are medically treated.

Interaction of JM and End-Systolic Volume

Our study findings further elucidate the impact of increasing LV dilation on the risk associated with JM. A novel interaction between JM and ESVI demonstrated that the hazard associated with JM significantly increases in the presence of worsening adverse LV remodeling. Our main effect multivariable model suggests that risk associated with JM increased by 7% for every 10-unit increase in ESVI. We then tested the significance of the interaction ESVI×JM by adding this interaction to the main effect model. This highly significant interaction demonstrated that the relationship between JM and the hazard of dying is significantly mediated by ESVI. Therefore, our analysis illustrates that the risk associated with JM should not be determined in isolation, as its association with mortality is more completely explained in the context of LVESVI.

Our group has previously demonstrated that patients with advanced ICM with increasing scar burden and LV dilation derive the most benefit from revascularization,[8] and this interaction was also demonstrated in a subgroup analysis of the STICH trial.[27] This subgroup analysis of the STICH viability substudy also demonstrated increased mortality in patients with higher ESVI and nonviability. While mortality was the highest in patients with severely dilated left ventricles with nonviability in this study, the authors could not find significant difference in outcomes in patients who were medically treated compared with those who were revascularized. Our study demonstrated similar findings in that scar burden and JM demonstrated similar response to treatment effect. However, our study was able to further expand on these findings by evaluating not only the presence of viable myocardium but the presence of JM in the context of angiographic data and the completeness of subsequent revascularization. While scar burden continued to remain an independent predictor of all-cause mortality in our current study, myocardial scar burden taken in the context of coronary anatomy to define JM emerged as an incremental predictor of adverse events. In addition, JM demonstrated a novel and significant interaction with adverse LV remodeling. Patients with increasing LV dilation demonstrated the worst survival if any JM was left unrevascularized. We also found that the risk associated with increased vascular territories with JM is better described in the context of ESVI in patients with advanced ICM. Our study demonstrated that risk increased more precipitously in patients with vascular territories with 2 or 3 territories with JM and increasing LVESVI, compared with patients with only 1 vascular territory with JM and increasing LVESVI. This suggests that patients with severely increased ESVI likely have increased risk because of increased ischemic substrate, which may be the result of increased wall tension resulting from increased LV dilation. This clinically important finding suggests that the number of territories with JM should not be considered in isolation, but should be taken in the context of the size of the ventricle. Because risk significantly increased with increasing size of the ventricle, and more substantially so when there are ≥2 vascular territories with JM, our data suggest that every effort should be made to achieve as

complete revascularization as possible for patients with significantly increased LVESVI. In other words, the significant interaction between ESVI and JM suggests that patients with advanced LV remodeling may be those at highest risk for adverse outcomes even with revascularization, if the revascularization was incomplete. This heightened risk associated with JM in the presence of increasing LVESVI is likely the result of an increased ischemic burden due to increased ESVI, increased potential for progressive adverse remodeling, and increased arrhythmic substrate due to the presence of ischemia in the presence of significant LV dilation. On the other hand, patients with advanced LV remodeling are at highest risk and may derive the most survival benefit from revascularization if all territories of JM are completely revascularized. Furthermore, our data also suggest that patients with severely enlarged left ventricles have a high risk of mortality if complete revascularization cannot be achieved and may benefit from early referral for advanced therapies versus heart transplant. Conversely, patients with smaller or more normal-sized ventricles resulted in relatively mild increased risk when only 1 vascular territory was left unrevascularized.

Limitations

Although our patient cohort represents the patient population seen at a tertiary referral center, the impact of selection biases and missing/unmeasured variables may impact the findings in this study. Similarly, the limitations of multivariable modeling are also well known, and additional studies, preferably randomized trials, are necessary to confirm our findings. Formal evaluation for ischemia was not included in this analysis and was inferred from the integration of the coronary angiography and CMR viability assessment. Patients with prior cardiac resynchronization therapy±ICD were excluded from this study because of the contraindications for MRI, potentially further impacting selection bias. Additionally, it is possible that some patients may have undergone cardiac resynchronization therapy/ICD implantation outside of our institution. Assessment for optimal medical therapy in our patient population was complex, as medical therapy changed in a significant portion of our population during follow-up. While additional medications were added to optimize the medical regimen during follow-up in a proportion of our patients, some medications were discontinued because of relative hypotension or development of acute renal failure/hyperkalemia/elevated liver enzymes postoperatively. Lastly, quality of life and improvement of heart failure symptoms during follow-up was not included in our analysis. This limited follow-up data may impact the results of our study. Therefore, further studies are needed to determine how the risk of JM and increased scar burden could be mitigated by optimal medical therapy and cardiac resynchronization therapy/ICD when compared with revascularization alone.

Because CMR findings were used to guide therapy, we used propensity analysis to investigate the presence of significant associations with post-CMR treatment. Because propensity matching severely reduces power, we chose to risk adjust our models with propensity scoring. However, propensity methods can only account for variables that are measured. It is possible that patients who were not referred for revascularization were at higher risk in ways that were not measured. Importantly, these comparisons of post-CMR survival by treatment are based on retrospective categorization of patients, an approach with its own limitations. Because post-CMR treatment was defined retrospectively, misclassification bias of events may have occurred.

Finally, cause of death was not available in all of the patients who died during follow-up. Therefore, all-cause mortality was used as a primary end point, in addition to heart transplant. However, relying on death certificates for ascertainment of cardiac death has been shown to be inaccurate and fraught with bias.[28] Because of the high-risk nature of our patient population, we believe that it is safe to assume that the cause of death in our patient cohort is likely to be cardiac related in >90% of the patients who died.

Clinical Relevance

Because mortality in patients with advanced ICM remains high, the decision to proceed with revascularization must be informed with the balance of survival benefit of revascularization versus predicted periprocedural risks. Because of the absence of randomized controlled trials utilizing CMR for viability assessment, we used a propensity analysis to compare outcomes based on treatment strategies in the context of JM. Our study demonstrates the importance of viability assessment with CMR in patients with advanced ICM to further elucidate potential survival benefit with revascularization. CMR provides comprehensive and precise assessment of LV systolic function, extent of LV remodeling, and quantification of myocardial scar burden. Viability defined by the integration of coronary anatomy and CMR defined scar assessment, and ESVI×JM may identify the highest-risk patients. Patients who underwent subsequent revascularization appear to experience favorable survival if complete revascularization is achieved. However, patients who underwent revascularization with remaining unrevascularized JM experienced similar survival to patients with JM who were medically treated. Furthermore, our study demonstrated that the hazard associated with JM significantly increased in the presence of worsening adverse LV remodeling. Our findings suggest that risk associated with JM increased by 7% for every 10-unit increase in ESVI. This suggests that patients with advanced LV remodeling may not benefit from revascularization if any territory of JM is left unrevascularized. Therefore, our study findings infer that the decision to refer patients with

advanced ICM for revascularization should be based not only on the presence of JM but also on the extent of LV remodeling and the likelihood of achieving complete revascularization.

Conclusions

JM is a powerful predictor in patients with advanced ICM. Patients revascularized incompletely had similar risk of mortality compared with patients with JM who were medically treated. Furthermore, the risk associated with JM significantly increased in the presence of worsening adverse LV remodeling. CMR viability assessment may provide important risk stratification in patients with ICM.

Disclosures

None.

References

1. Ahn JM, Park DW, Lee CW, Chang M, Cavalcante R, Sotomi Y, Onuma Y, Tenekecioglu E, Han M, Lee PH, Kang SJ, Lee SW, Kim YH, Park SW, Serruys PW, Park SJ. Comparison of stenting versus bypass surgery according to the completeness of revascularization in severe coronary artery disease: patient-level pooled analysis of the SYNTAX, PRECOMBAT, and BEST Trials. *JACC Cardiovasc Interv*. 2017;10:1415–1424.

2. Hannan EL, Racz M, Holmes DR, King SB III, Walford G, Ambrose JA, Sharma S, Katz S, Clark LT, Jones RH. Impact of completeness of percutaneous coronary intervention revascularization on long-term outcomes in the stent era. *Circulation*. 2006;113:2406–2412.

3. Hannan EL, Wu C, Walford G, Holmes DR, Jones RH, Sharma S, King SB III. Incomplete revascularization in the era of drug-eluting stents: impact on adverse outcomes. *JACC Cardiovasc Interv*. 2009;2:17–25.

4. Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. *J Am Coll Cardiol*. 2002;39:1151–1158.

5. Schinkel AF, Bax JJ, Poldermans D, Elhendy A, Ferrari R, Rahimtoola SH. Hibernating myocardium: diagnosis and patient outcomes. *Curr Probl Cardiol*. 2007;32:375–410.

6. Bonow RO, Maurer G, Lee KL, Holly TA, Binkley PF, Desvigne-Nickens P, Drozdz J, Farsky PS, Feldman AM, Doenst T, Michler RE, Berman DS, Nicolau JC, Pellikka PA, Wrobel K, Alotti N, Asch FM, Favaloro LE, She L, Velazquez EJ, Jones RH, Panza JA; STICH Trial Investigators. Myocardial viability and survival in ischemic left ventricular dysfunction. *N Engl J Med*. 2011;364:1617–1625.

7. Gerber BL, Rousseau MF, Ahn SA, le Polain de Waroux JB, Pouleur AC, Phlips T, Vancraeynest D, Pasquet A, Vanoverschelde JL. Prognostic value of myocardial viability by delayed-enhanced magnetic resonance in patients with coronary artery disease and low ejection fraction: impact of revascularization therapy. *J Am Coll Cardiol*. 2012;59:825–835.

8. Kwon DH, Hachamovitch R, Popovic ZB, Starling RC, Desai MY, Flamm SD, Lytle BW, Marwick TH. Survival in patients with severe ischemic cardiomyopathy undergoing revascularization versus medical therapy: association with end-systolic volume and viability. *Circulation*. 2012;126:S3–S8.

9. Ling LF, Marwick TH, Flores DR, Jaber WA, Brunken RC, Cerqueira MD, Hachamovitch R. Identification of therapeutic benefit from revascularization in patients with left ventricular systolic dysfunction: inducible ischemia versus hibernating myocardium. *Circ Cardiovasc Imaging*. 2013;6:363–372.

10. Mc Ardle B, Shukla T, Nichol G, deKemp RA, Bernick J, Guo A, Lim SP, Davies RA, Haddad H, Duchesne L, Hendry P, Masters R, Ross H, Freeman M, Gulenchyn K, Racine N, Humen D, Benard F, Ruddy TD, Chow BJ, Mielniczuk L, DaSilva JN, Garrard L, Wells GA, Beanlands RS. Long-term follow-up of outcomes with F-18-fluorodeoxyglucose positron emission tomography imaging-assisted management of patients with severe left ventricular dysfunction secondary to coronary disease. *Circ Cardiovasc Imaging*. 2016;9:e004331.

11. Kwon DH, Halley CM, Carrigan TP, Zysek V, Popovic ZB, Setser R, Schoenhagen P, Starling RC, Flamm SD, Desai MY. Extent of left ventricular scar predicts outcomes in ischemic cardiomyopathy patients with significantly reduced systolic function: a delayed hyperenhancement cardiac magnetic resonance study. *JACC Cardiovasc Imaging*. 2009;2:34–44.

12. Solomon SD, Skali H, Anavekar NS, Bourgoun M, Barvik S, Ghali JK, Warnica JW, Khrakovskaya M, Arnold JM, Schwartz Y, Velazquez EJ, Califf RM, McMurray JV, Pfeffer MA. Changes in ventricular size and function in patients treated with valsartan, captopril, or both after myocardial infarction. *Circulation*. 2005;111:3411–3419.

13. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation*. 1987;76:44–51.

14. Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O, Bundy J, Finn JP, Klocke FJ, Judd RM. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. *Circulation*. 1999;100:1992–2002.

15. Mahrholdt H, Wagner A, Holly TA, Elliott MD, Bonow RO, Kim RJ, Judd RM. Reproducibility of chronic infarct size measurement by contrast-enhanced magnetic resonance imaging. *Circulation*. 2002;106:2322–2327.

16. Roes SD, Kelle S, Kaandorp TA, Kokocinski T, Poldermans D, Lamb HJ, Boersma E, van der Wall EE, Fleck E, de Roos A, Nagel E, Bax JJ. Comparison of myocardial infarct size assessed with contrast-enhanced magnetic resonance imaging and left ventricular function and volumes to predict mortality in patients with healed myocardial infarction. *Am J Cardiol*. 2007;100:930–936.

17. Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, Klocke FJ, Bonow RO, Judd RM. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med*. 2000;343:1445–1453.

18. Bonow RO, Maurer G, Lee KL, Holly TA, Binkley PF, Desvigne-Nickens P, Drozdz J, Farsky PS, Feldman AM, Doenst T, Michler RE, Berman DS, Nicolau JC, Pellikka PA, Wrobel K, Alotti N, Asch FM, Favaloro LE, She L, Velazquez EJ, Jones RH, Panza JA. Myocardial viability and survival in ischemic left ventricular dysfunction. *N Engl J Med*. 364:1617–1625.

19. Bourque JM, Hasselblad V, Velazquez EJ, Borges-Neto S, O'Connor CM. Revascularization in patients with coronary artery disease, left ventricular dysfunction, and viability: a meta-analysis. *Am Heart J*. 2003;146:621–627.

20. Camici PG, Prasad SK, Rimoldi OE. Stunning, hibernation, and assessment of myocardial viability. *Circulation*. 2008;117:103–114.

21. Alfakih K, Plein S, Thiele H, Jones T, Ridgway JP, Sivananthan MU. Normal human left and right ventricular dimensions for MRI as assessed by turbo gradient echo and steady-state free precession imaging sequences. *J Magn Reson Imaging*. 2003;17:323–329.

22. Bell MR, Gersh BJ, Schaff HV, Holmes DR Jr, Fisher LD, Alderman EL, Myers WO, Parsons LS, Reeder GS. Effect of completeness of revascularization on long-term outcome of patients with three-vessel disease undergoing coronary artery bypass surgery. A report from the coronary artery surgery study (CASS) registry. *Circulation*. 1992;86:446–457.

23. Garcia S, Sandoval Y, Roukoz H, Adabag S, Canoniero M, Yannopoulos D, Brilakis ES. Outcomes after complete versus incomplete revascularization of patients with multivessel coronary artery disease: a meta-analysis of 89,883 patients enrolled in randomized clinical trials and observational studies. *J Am Coll Cardiol*. 2013;62:1421–1431.

24. Jones EL, Craver JM, Guyton RA, Bone DK, Hatcher CR Jr, Riechwald N. Importance of complete revascularization in performance of the coronary bypass operation. *Am J Cardiol*. 1983;51:7–12.

25. Hannan EL, Zhong Y, Berger PB, Jacobs AK, Walford G, Ling FSK, Venditti FJ, King SB III. Association of coronary vessel characteristics with outcome in patients with percutaneous coronary interventions with incomplete revascularization. *JAMA Cardiol*. 2018;3:123–130.

26. Panza JA, Velazquez EJ, She L, Smith PK, Nicolau JC, Favaloro RR, Gradinac S, Chrzanowski L, Prabhakaran D, Howlett JG, Jasinski M, Hill JA, Szwed H, Larbalestier R, Desvigne-Nickens P, Jones RH, Lee KL, Rouleau JL. Extent of coronary and myocardial disease and benefit from surgical revascularization in LV dysfunction. *J Am Coll Cardiol*. 2014;64:553–561.

27. Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, Michler RE, Bonow RO, Doenst T, Petrie MC, Oh JK, She L, Moore VL, Desvigne-Nickens P, Sopko G, Rouleau JL. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. *N Engl J Med*. 2016;374:1511–1520.

28. Bonow RO, Castelvecchio S, Panza JA, Berman DS, Velazquez EJ, Michler RE, She L, Holly TA, Desvigne-Nickens P, Kosevic D, Rajda M, Chrzanowski L, Deja M, Lee KL, White H, Oh JK, Doenst T, Hill JA, Rouleau JL, Menicanti L. Severity of remodeling, myocardial viability, and survival in ischemic LV dysfunction after surgical revascularization. *JACC Cardiovasc Imaging*. 2015;8:1121–1129.

29. Lauer MS, Blackstone EH, Young JB, Topol EJ. Cause of death in clinical research: time for a reassessment? *J Am Coll Cardiol*. 1999;34:618–620.