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ORIGINAL RESEARCH

Prognostic Value of Stress CMR Perfusion Imaging in Patients With Reduced Left Ventricular Function

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ABSTRACT

OBJECTIVES The aim of this study was to investigate the prognostic value of stress cardiac magnetic resonance imaging (CMR) in patients with reduced left ventricular (LV) systolic function.

BACKGROUND Patients with ischemic cardiomyopathy are at risk from both myocardial ischemia and heart failure. Invasive testing is often used as the first-line investigation, and there is limited evidence as to whether stress testing can effectively provide risk stratification.

METHODS In this substudy of a multicenter registry from 13 U.S. centers, patients with reduced LV ejection fraction (<50%), referred for stress CMR for suspected myocardial ischemia, were included. The primary outcome was cardiovascular death or nonfatal myocardial infarction. The secondary outcome was a composite of cardiovascular death, nonfatal myocardial infarction, hospitalization for unstable angina or congestive heart failure, and unplanned late coronary artery bypass graft surgery.

RESULTS Among 582 patients (mean age 62 ± 12 years, 34% women), 40% had a history of congestive heart failure, and the median LV ejection fraction was 39% (interquartile range: 28% to 45%). At median follow-up of 5.0 years, 97 patients had experienced the primary outcome, and 182 patients had experienced the secondary outcome. Patients with no CMR evidence of ischemia or late gadolinium enhancement (LGE) experienced an annual primary outcome event rate of 1.1%. The presence of ischemia, LGE, or both was associated with higher event rates. In a multivariate model adjusted for clinical covariates, ischemia and LGE were independent predictors of the primary (hazard ratio [HR]: 2.63; 95% confidence interval [CI]: 1.68 to 4.14; $p < 0.001$; and HR: 1.86; 95% CI: 1.05 to 3.29; $p = 0.03$) and secondary (HR: 2.14; 95% CI: 1.55 to 2.95; $p < 0.001$; and HR 1.70; 95% CI: 1.16 to 2.49; $p = 0.007$) outcomes. The addition of ischemia and LGE led to improved model discrimination for the primary outcome (change in C statistic from 0.715 to 0.765; $p = 0.02$). The presence and extent of ischemia were associated with higher rates of use of downstream coronary angiography, revascularization, and cost of care spent on ischemia testing.

CONCLUSIONS Stress CMR was effective in risk-stratifying patients with reduced LV ejection fractions. (Stress CMR Perfusion Imaging in the United States [SPINS] Study; NCT03192891) (J Am Coll Cardiol Img 2020;13:2132-45)

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In patients with acute coronary syndromes, left ventricular (LV) systolic function is a potent predictor of all-cause mortality (1,2). In patients suspected of having stable coronary artery disease (CAD), those with ischemic cardiomyopathy represent a distinct, high-risk subgroup (3,4) and remain challenging to risk-stratify. Noninvasive imaging of patients with reduced LV function may be limited by thinned LV myocardial wall and multivessel disease with a propensity for balanced ischemia. In patients with heart failure and chest pain, the latest American Heart Association (AHA)/American College of Cardiology guidelines continue to recommend a low threshold for the use of invasive angiography as a first-line test (5). Stress cardiac magnetic resonance (CMR) has been shown to be an effective prognostic tool in many clinical subgroups of patients with suspected CAD (6–9). It also has demonstrated high diagnostic utility in patients with left main stem or equivalent CAD (10). However, whether stress CMR can adequately risk-stratify patients with impaired LV systolic function remains unclear. We therefore conducted an analysis of patients with impaired LV ejection fraction (LVEF) referred for stress CMR for suspected myocardial ischemia, using a combined dataset from the multicenter SPINS (Stress CMR Perfusion Imaging in the United States) registry and a tertiary referral center.

METHODS

SPINS REGISTRY. The details behind the design, rationale, and infrastructure of the SPINS registry have been previously described in detail (11,12). In brief, SPINS included 13 participating experienced CMR centers across the United States (7 university hospitals, 2 cardiovascular group practices, 2 multispecialty practices, and 2 U.S. government or military hospitals). Sites were required to have an active stress CMR program of at least 10 years' duration and to contribute between 100 and 500 consecutive patients. Study-related protected health information-free data were entered into an encrypted web-based database.

STUDY POPULATION. The study cohort included patients referred for stress CMR from either the SPINS registry or a single-center registry. Between 2008 and 2013, SPINS enrolled consecutive, intermediate-risk patients who: 1) were 35 to 85 years of age at the time of the study; 2) underwent vasodilator stress CMR for the evaluation of chest pain, dyspnea, abnormal electrocardiographic results, or other clinical presentation that raised suspicion of myocardial ischemia as determined by the treating clinician; and 3) had at least 2 of the following cardiac risk factors: age >50 years for men or >60 years for women, diabetes mellitus, hypertension, hypercholesterolemia, family history of premature CAD as defined by diagnosis in a first-degree male relative ≤55 years of age or a female relative ≤65 years of age, body mass index ≥30 kg/m^2, peripheral vascular disease, and history of percutaneous coronary intervention (PCI)

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting surgery

CAD = coronary artery disease

CHF = congestive heart failure

CI = confidence interval

CMR = cardiac magnetic resonance

HR = hazard ratio

IQR = interquartile range

LGE = late gadolinium enhancement

LV = left ventricular

LVEF = left ventricular ejection fraction

MI = myocardial infarction

PCI = percutaneous coronary intervention

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or myocardial infarction (MI). In this study, we included patients with evidence of reduced LV systolic function as defined by LVEF <50% measured on CMR. Exclusion criteria included history of coronary artery bypass graft surgery (CABG), recent MI within 30 days preceding the index CMR study, severe-grade valvular heart disease, previously known and documented nonischemic cardiomyopathy with LVEF <40%, infiltrative or hypertrophic cardiomyopathy, constrictive pericarditis, active pregnancy, competing medical illnesses with expected survival <2 years, and known inability to undergo follow-up. In addition to SPINS, we included patients meeting the same inclusion and exclusion criteria from the Brigham and Women's Hospital who underwent stress CMR during the same years of 2008 to 2013. LVEF <50% was chosen as the criterion for reduced LV systolic function because it represents a value that was >3 SDs below a normal population reference for both sexes (13,14). At each participating site, local Institutional Review Board approval was obtained to conduct this clinical follow-up study, with a waiver of the requirement to obtain written informed consent.

STRESS CMR PROTOCOL AND DEFINITION. The CMR protocol consisted of, in order, stress perfusion (fast low angle single-shot [FLASH], echo-planar imaging [EPI], or steady-state free precession [SSFP]), ventricular function (SSFP), late gadolinium enhancement (LGE) (inversion recovery prepared gradient-echo [IR-GRE]), and rest myocardial perfusion and included the use of scanners at both 1.5 and 3.0 T, as well as equipment from all 3 major vendors. Vasodilator agents used included adenosine, regadenoson, and dipyridamole. The following CMR variables were collected: LV volumes and dimensions, with papillary muscles and trabeculae included as LV cavity volume, segmental (presence or absence) stress perfusion according to the AHA 16-segment model, and LGE according to the AHA 17-segment model. A perfusion defect was present if there was a region of hypoenhancement densest in the endocardium with a transmural gradient across the wall thickness, which persisted beyond peak myocardial enhancement and conformed to a coronary distribution. An MI was present if there was a finding of LGE in a coronary disease pattern in at least 1 myocardial segment. Inducible ischemia was defined as the presence of a perfusion defect during stress, in the absence of matching LGE in a segment (15). Peri-infarct ischemia was defined by any ischemic segment that immediately neighbored an LGE infarct segment either circumferentially or longitudinally. Mild, moderate, and severe defects were defined as the involvement of 1 or 2, 3 to 5, and ≥6 segments, respectively. Mildly reduced LVEF was defined as 40% to 50%, whereas moderately to severely reduced LVEF was defined as <40%. Study image quality was rated on a scale ranging from 1 to 5 for cine, perfusion, and LGE sequences using the following criteria: 5 = excellent quality, no artefacts; 4 = good quality, mild artefacts; 3 = fair quality, moderate artefacts; 2 = poor quality, severe artefacts; 1 = nondiagnostic.

CLINICAL FOLLOW-UP. Detailed follow-up of all patients was mandated for at least 4 years following index stress CMR. Clinical outcomes were ascertained from electronic medical records and by direct patient contact using a standardized checklist questionnaire or scripted telephone conversation. End of follow-up data collection and locking of the database occurred on May 25, 2018. Major clinical cardiovascular outcomes were in accordance with previously published recommendations (16). The primary outcome was defined as cardiovascular death or nonfatal MI. Only type 1 or type 2 events, according to the third universal definition, were counted (17). Post-procedural MI after coronary revascularization was not included in the primary endpoint, given its limited association with downstream hard cardiac outcomes (18) and the possibility of creating bias for worsened outcomes in patients referred for revascularization. The secondary outcome was defined by a composite of cardiovascular death, nonfatal MI, hospitalization for unstable angina (worsening chest pain or anginal equivalent with evidence of myocardial ischemia by cardiac imaging or obstructive lesion on coronary angiography), hospitalization for congestive heart failure (CHF), and unplanned late CABG (performed more than 6 months after index stress CMR). For either the primary or secondary outcome, only the first event was counted when multiple events occurred in a patient.

In addition, subsequent performance of all noninvasive tests for CAD (exercise stress testing, stress echocardiography, nuclear perfusion imaging, coronary computed tomographic angiography, repeat stress CMR), as well as invasive coronary angiography and revascularization procedures, was also collected. The cost of downstream testing for myocardial ischemia was determined as previously described (12), on the basis of published average national payment rates from the Medicare Hospital Outpatient Prospective Payment System, specific to the technical component of the most common Healthcare Common Procedure Coding System code and the year of the procedure. Costs due to complications of test procedures, subsequent hospitalization, and revascularization were not collected.

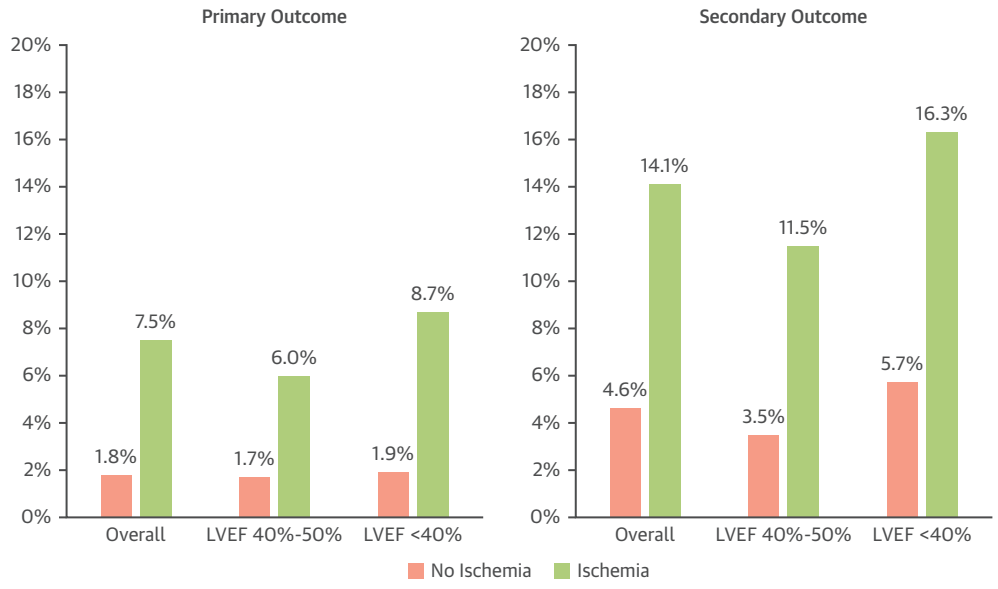
TABLE 1 Demographics and Baseline Characteristics

	Overall (N = 582)	No Ischemia or LGE (n = 261)	Ischemia or LGE (n = 321)	p Value
Clinical data				
Follow-up (yrs)	5.0 (4.0-6.3)	5.1 (4.2-6.3)	4.9 (3.8-6.2)	0.13
Age (yrs)	62 ± 12	61 ± 12	62 ± 12	0.22
Female	197 (34)	105 (45)	92 (29)	0.003
BMI (kg/m^2)	30 ± 7	30 ± 7	30 ± 7	0.80
Number of cardiac risk factors	3 (2-4)	3 (2-3)	4 (3-4)	<0.001
Risk factors				
Hypertension	452 (78)	184 (71)	268 (83)	<0.001
Hypercholesterolemia	352 (60)	140 (54)	212 (66)	0.002
Diabetes mellitus	176 (30)	59 (23)	117 (36)	<0.001
Significant smoking (>10 pack-yrs)	218 (38)	89 (34)	129 (40)	0.13
History of premature CAD in first-degree relative	165 (29)	66 (26)	99 (32)	0.12
CAD Consortium score (basic)	34 (24-54)	34 (17-44)	44 (32-54)	<0.001
History of PCI	114 (20)	16 (6)	98 (31)	<0.001
History of MI	136 (24)	9 (3)	127 (40)	<0.001
History of heart failure	234 (40)	102 (39)	132 (40)	0.60
Presenting reason				
Chest pain	206 (35)	76 (29)	130 (41)	0.004
Dyspnea	236 (41)	120 (46)	116 (36)	0.02
Arrhythmias	37 (6)	21 (8)	16 (5)	0.13
Abnormal ECG results	40 (7)	17 (7)	23 (7)	0.76
Other symptoms/reasons	63 (11)	27 (10)	36 (11)	0.74
Medications				
Aspirin	348 (60)	115 (44)	233 (74)	<0.001
Beta-blocker	397 (69)	153 (59)	244 (76)	<0.001
Calcium-channel blocker	83 (14)	43 (17)	40 (13)	0.19
ACE inhibitor or ARB	371 (64)	149 (57)	222 (70)	0.002
Aldosterone receptor antagonist	42 (7)	20 (8)	22 (7)	0.74
Statin	343 (59)	124 (48)	219 (69)	<0.001
Stress CMR				
Scanner field strength				
1.5-T	320 (55)	149 (57)	171 (53)	0.34
3.0-T	262 (45)	112 (43)	150 (47)	
CMR manufacturer				
Siemens	439 (76)	194 (74)	245 (77)	0.13
GE	98 (17)	41 (16)	57 (18)	
Phillips	44 (8)	26 (10)	18 (6)	
Quality of cine sequence				
Score	5 (4-5)	5 (4-5)	5 (4-5)	0.62
Quality of perfusion sequence				
Score	5 (4-5)	5 (4-5)	5 (4-5)	0.31
Quality of LGE sequence				
Score	5 (4-5)	5 (4-5)	5 (4-5)	0.56
LVEF (%)	39 (28-45)	39 (29-45)	39 (27-44)	0.17
LVEDVi (ml/m^2)	100 (79-125)	99 (76-120)	101 (81-129)	0.06
LVESVi (ml/m^2)	60 (44-84)	58 (42-81)	62 (46-87)	0.07
LVEF <40%	308 (53)	135 (52)	173 (54)	0.60
Ischemia	175 (30)	0	175 (55)	<0.001
Ischemic segments (number)	0 (0-1)	0	1 (0-3)	<0.001
LGE	277 (48)	0	277 (86)	<0.001
LGE segments (number)	0 (0-5)	0	4 (2-7)	<0.001

Values are median (interquartile range), mean ± SD, or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CAD = coronary artery disease; CMR = cardiac magnetic resonance; ECG = electrocardiographic; LGE = late gadolinium enhancement; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVi = left ventricular end-systolic volume index; MI = myocardial infarction; PCI = percutaneous coronary intervention.

FIGURE 1 Primary and Secondary Outcome Event Rates



Annualized rates of primary **(left)** and secondary **(right)** outcomes, stratified by presence versus absence of ischemia and left ventricular ejection fraction (LVEF) 40% to 50% versus <40%.

STATISTICAL ANALYSIS. For descriptive statistics, continuous variables are expressed as mean ± SD and median with interquartile range (IQR) for normal and skewed distributions, respectively. Categorical variables are expressed as counts with percentages. Comparison between groups was performed using Student's *t*-test or the Wilcoxon rank sum test for continuous data and the chi-square or Fisher exact test for categorical data. Event-free survival was estimated using the Kaplan-Meier method and compared using a log-rank test. Univariate Cox regression models were used to estimate the unadjusted hazard ratios (HRs) of selected clinical and CMR covariates for primary and secondary outcomes. To determine the independent prognostic value of CMR parameters, we first constructed a multivariate Cox model for the primary outcome by the inclusion of significant clinical covariates on univariate screening using a stepwise forward selection algorithm ($p < 0.05$ for model retention). We a priori forced LVEF into the model because of its recognized prognostic importance. We then added the presence or absence of ischemia and LGE to determine whether they each provided incremental prognostic value. The goodness of fit of each model (−2 log likelihood) was calculated and compared using the likelihood ratio test, and discriminative capacity was determined according to Harrell's C statistic at baseline and after the addition of CMR-assessed ischemia and LGE.

In addition, to evaluate the ability of stress CMR to reclassify patients, we calculated net reclassification improvement and integrated discrimination improvement (19) using pre-determined AHA/American College of Cardiology guideline-based risk categories of <1%, 1% to 3%, and >3% per year event rates of cardiac death or acute MI (20), to define low, moderate, and high risk for the primary outcome. We tested for a significant interaction between LVEF, as a continuous variable, and CMR-detected ischemia or LGE. The proportional hazards assumption was evaluated using visual inspection of the log-log survival curves and the Schoenfeld residual test. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina), and a p value <0.05 was used to establish statistical significance.

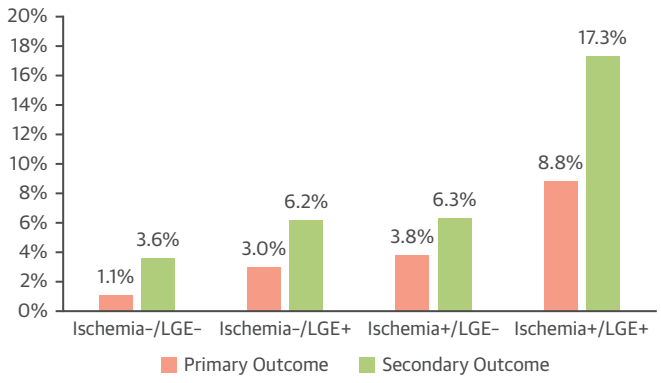
RESULTS

BASELINE PATIENT DEMOGRAPHICS AND CMR CHARACTERISTICS. Of the 2,349 patients enrolled in the SPINS registry, 403 met the LVEF <50% cutoff to be included in this study. An additional 179 patients were identified from the clinical registry at Brigham and Women's Hospital; thus, the overall study cohort

included a total of 582 patients. Vasodilator stress CMR was well tolerated, with no occurrence of serious adverse events. Baseline demographic and clinical characteristics are summarized in Table 1, stratified by absence versus presence of inducible ischemia or LGE. The mean age in the overall cohort was 62 ± 12 years, and 34% of subjects were women. The median number of cardiac risk factors was 3 (IQR: 2 to 4), and slightly fewer than one-quarter of patients had prior MI and PCI. Forty percent of the cohort had a history of CHF. Compared with patients without ischemia or LGE, those with ischemia or LGE were less likely to be female (29% vs. 45%; p = 0.003) and had more cardiac risk factors (median 4 [IQR: 3 to 4] vs. 3 [IQR: 2 to 3]; p < 0.001). They were also more likely to have prior PCI (31% vs. 6%; p < 0.001), MI (40% vs. 3%; p < 0.001), but not CHF (40% vs. 39%; p = 0.60). Patients with ischemia or LGE were more likely to have chest pain as the initial symptom for test referral (41% vs. 29%; p = 0.004) and were also more likely to have been on aspirin (74% vs. 44%; p < 0.001), beta-blockers (76% vs. 59%; p < 0.001), angiotensin-conversion enzyme inhibitors or angiotensin II receptor blockers (70% vs. 57%; p = 0.002), and statins (69% vs. 48%; p < 0.001).

Baseline CMR characteristics are displayed in Table 1. Median study quality for all 3 key sequences was 5 (excellent) and did not differ between the 2 groups. The overall cohort had a median LV end-diastolic volume index of 100 ml/m² (IQR: 79 to 125 ml/m²), a median LV end-systolic volume index of 60 ml/m² (IQR: 44 to 84 ml/m²), and a median LVEF of 39% (IQR: 28% to 45%). Moderate or severe LV dysfunction was present in 53%. Thirty percent had ischemia on stress CMR, and 48% had evidence of

FIGURE 2 Primary and Secondary Outcome Event Rates



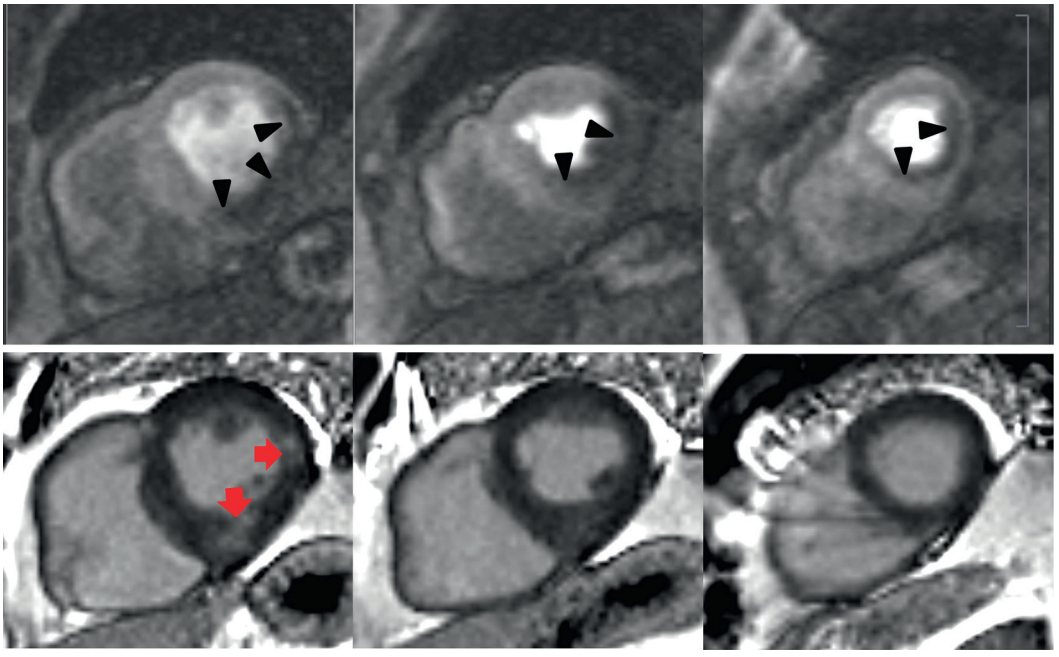
Annualized rates of primary and secondary outcomes, stratified by presence versus absence of ischemia and late gadolinium enhancement (LGE).

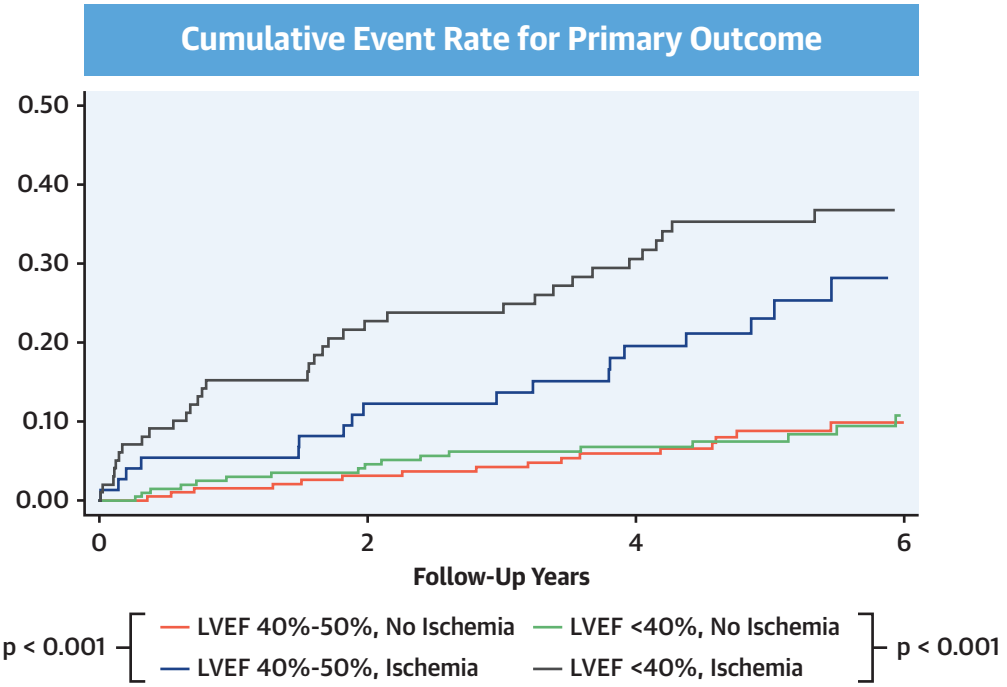
TABLE 2 Univariable Cox Associations of Clinical and Stress Cardiac Magnetic Resonance Indexes With Outcomes

	Primary Outcome			Secondary Outcome		
	HR	95% CI	p Value	HR	95% CI	p Value
Demographics						
Age (per yr)	1.02	1.01–1.04	0.006	1.02	1.01–1.03	0.001
Female	0.58	0.36–0.94	0.03	0.76	0.55–1.05	0.10
BMI (per 1 kg/m²)	0.98	0.95–1.01	0.17	0.99	0.97–1.01	0.33
Cardiac risk factors						
Hypertension	1.41	0.84–2.39	0.20	1.71	1.13–2.58	0.01
Hypercholesterolemia	1.10	0.73–1.67	0.64	0.91	0.68–1.24	0.56
Diabetes mellitus	2.22	1.48–3.32	<0.001	1.87	1.39–2.53	<0.001
Smoking	1.56	1.04–2.35	0.03	1.34	0.99–1.81	0.06
Family history of CAD	0.69	0.42–1.13	0.14	0.92	0.66–1.29	0.64
History of PCI	1.62	1.04–2.53	0.03	1.56	1.12–2.18	0.009
History of MI	2.62	1.74–3.93	<0.001	1.94	1.42–2.65	<0.001
History of CHF	1.90	1.27–2.84	0.002	1.59	1.18–2.14	0.002
Stress CMR						
LVEF (per +5% Δ)	0.88	0.80–0.97	0.009	0.85	0.80–0.91	<0.001
LVEF <40% (vs. ≥40%)	1.38	0.92–2.08	0.12	1.61	1.19–2.20	0.002
LVEDVi (per +5 ml/m² Δ)	1.03	1.01–1.06	0.009	1.03	1.01–1.05	0.001
LVESVi (per +5 ml/m² Δ)	1.03	1.01–1.06	0.01	1.04	1.02–1.06	<0.001
Ischemia	4.02	2.66–6.07	<0.001	3.00	2.23–4.04	<0.001
Extent of ischemia (per segment)	1.14	1.09–1.19	<0.001	1.12	1.08–1.16	<0.001
LGE	3.64	2.28–5.83	<0.001	2.63	1.91–3.62	<0.001
Extent of LGE (per segment)	1.06	1.02–1.10	0.004	1.05	1.01–1.08	0.003

CHF = congestive heart failure; CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

CENTRAL ILLUSTRATION **Cardiac Magnetic Resonance Findings and Clinical Outcomes**





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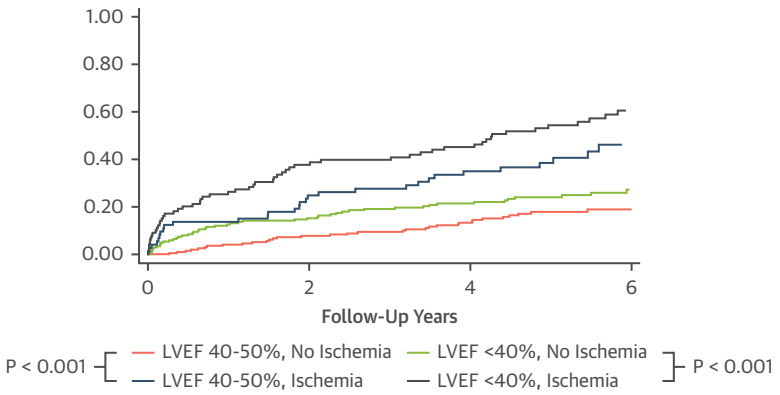
The **top panel** shows an example of a cardiac magnetic resonance study showing a stress perfusion defect **(solid arrowheads)** with its myocardial extent exceeding the 2 foci of subsegmental late gadolinium enhancement **(red arrows)**. This suggested ischemia from flow-limiting coronary stenosis in the right coronary artery. The **bottom panel** shows time-to-event curves of the study cohort for primary outcome, stratified by presence versus absence of ischemia and according to left ventricular ejection fraction 40% to 50% versus <40%.

FIGURE 3 Cumulative Event Rate for Secondary Outcome



Time-to-event curves of the study cohort for secondary outcomes, stratified by presence versus absence of ischemia and according to left ventricular ejection fraction (LVEF) 40% to 50% versus <40%.

prior MI by LGE. Compared with patients without ischemia or LGE, those with ischemia or LGE had similar LV chamber size and LVEF.

ASSOCIATION OF STRESS CMR WITH THE PRIMARY AND SECONDARY OUTCOMES. Successful follow-up of ≥4 years was achieved in 95% of the study cohort, with median duration of 5.0 years (IQR: 4.0 to 6.3 years). During study follow-up, the primary outcome occurred in 97 patients, whereas the secondary outcome occurred in 182 patients. Annualized event rates, stratified by the presence of ischemia and LVEF, are presented in **Figure 1**. For the primary outcome, patients without ischemia and with LVEF 40% to 50% experienced an event rate of 1.7% per year, whereas those with ischemia and LVEF <40% experienced an event rate of 8.7% per year. **Figure 2** provides annualized event rates, stratified by the presence of ischemia and LGE. Patients without the presence of either experienced the lowest rate of primary (1.1% per year) and secondary (3.6% per year) outcomes. Event rate, according to CMR findings for individual components of the primary endpoint, are shown in Supplemental Figures 1 and 2. Patients without the presence of either ischemia or LGE experienced an annualized cardiovascular mortality rate of 0.9% and nonfatal MI rate of 0.2%. In contrast, those with both ischemia and LGE had event rates of 5.8% and 3.8% for cardiovascular mortality and nonfatal MI, respectively.

Univariate analysis of patient and CMR characteristics for association with primary and secondary outcomes is presented in **Table 2**. Age, male sex, history of diabetes, history of smoking, history of PCI, history of MI, history of CHF, LVEF, LV end-diastolic volume index, LV end-systolic volume index, presence and extent of ischemia, and presence and extent of LGE were all significantly associated with the primary outcome in univariate Cox models. Ischemia and LGE were also strongly associated with individual components of the primary outcome, namely, cardiovascular death (HR: 3.60; 95% confidence interval [CI]: 2.23 to 5.80; $p < 0.001$; and HR: 3.20; 95% CI: 1.87 to 5.47; $p < 0.001$, respectively) or nonfatal MI (HR: 5.08; 95% CI: 2.54 to 10.2; $p < 0.001$; and HR: 7.11; 95% CI: 2.77 to 18.3; $p < 0.001$, respectively). Of the 175 patients with presence of ischemia, 125 (71%) had peri-infarct ischemia. Presence of peri-infarct ischemia and number of peri-infarct ischemia segments both demonstrated significant association with the primary outcome (HR: 4.37; 95% CI: 2.92 to 6.53; and HR: 1.28; 95% CI: 1.18 to 1.38; $p < 0.001$ for both). However, when entered into a multivariate model, presence of peri-infarct ischemia was no longer associated with the primary outcome once adjusted for the presence of ischemia and presence of LGE (adjusted HR: 1.15; 95% CI: 0.49 to 2.69; $p = 0.74$). Kaplan-Meier cumulative event rates for the primary and secondary outcomes stratified by the presence versus absence of inducible ischemia and LVEF 40% to 50% versus <40% are shown in the **Central Illustration and Figure 3**. Patients with LVEF 40% to 50% and ischemia had higher cumulative events compared with those with LVEF <40% and no ischemia ($p < 0.001$). There was no significant

TABLE 3 Multivariate Analysis for Prediction of Primary and Secondary Outcomes

	Primary Outcome				Secondary Outcome			
	Clinical Model		Clinical Model + CMR		Clinical Model		Clinical Model + CMR	
	Statistic	p Value	Statistic	p Value	Statistic	p Value	Statistic	p Value
Harrell's C statistic	0.715	–	0.765	0.02*	0.678	–	0.716	0.03*
Covariates	**HR (95% CI)**		**HR (95% CI)**		**HR (95% CI)**		**HR (95% CI)**	
Age	1.03 (1.01–1.05)	0.004	1.02 (1.01–1.04)	0.01	1.02 (1.01–1.03)	0.002	1.02 (1.00–1.03)	0.008
Female	0.62 (0.38–1.00)	<0.05	0.72 (0.44–1.19)	0.20	0.81 (0.58–1.12)	0.21	0.93 (0.66–1.31)	0.67
Diabetes mellitus	1.90 (1.25–2.88)	0.003	1.56 (1.02–2.39)	0.04	1.69 (1.24–2.29)	0.001	1.40 (1.02–1.91)	0.04
History of MI	2.27 (1.50–3.43)	<0.001	1.39 (0.88–2.19)	0.16	1.68 (1.22–2.31)	0.001	1.14 (0.81–1.61)	0.45
History of CHF	1.76 (1.12–2.75)	0.01	1.83 (1.17–2.86)	0.008	1.30 (0.94–1.81)	0.12	1.31 (0.95–1.82)	0.10
LVEF (per +5% Δ)	0.96 (0.86–1.06)	0.39	1.00 (0.98–1.02)	0.99	0.89 (0.83–0.97)	0.005	0.92 (0.85–0.99)	0.03
Ischemia	–		2.63 (1.68–4.14)	<0.001	–		2.14 (1.55–2.95)	<0.001
LGE	–		1.86 (1.05–3.29)	0.03	–		1.70 (1.16–2.49)	0.007

*Compared with clinical model.
Abbreviations as in Tables 1 and 2.

interaction between LVEF and CMR-detected ischemia or LGE. Visual inspection of the log-log survival curves and calculation of the Schoenfeld residuals showed that the proportionality assumption was not violated.

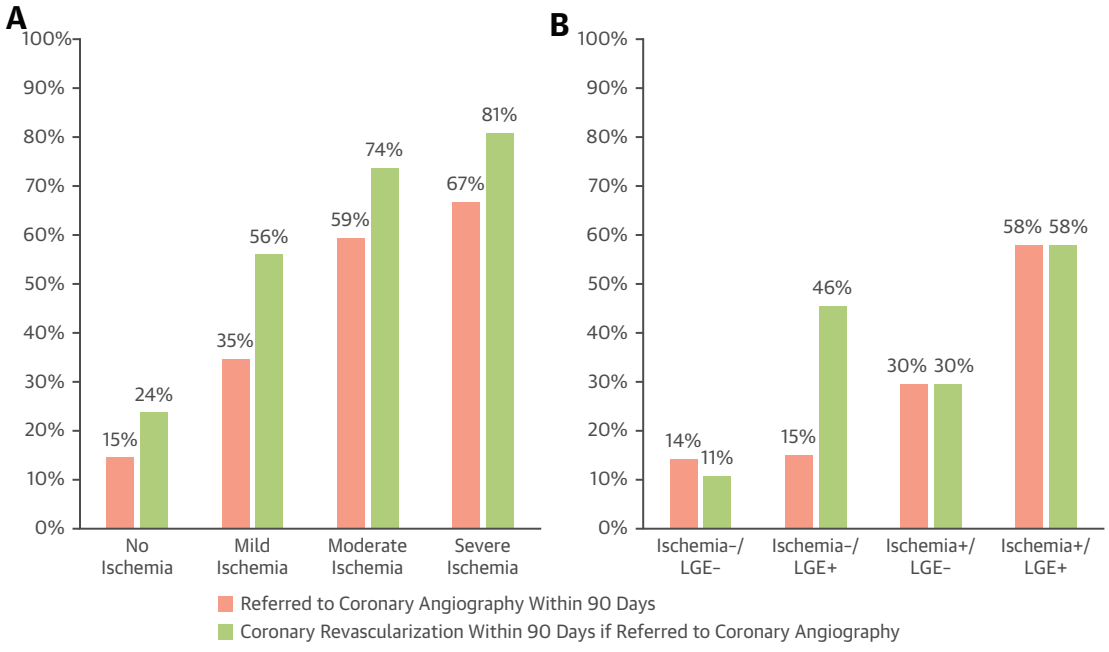
MULTIVARIATE ASSOCIATIONS, MODEL DISCRIMINATION, AND RISK RECLASSIFICATION IMPROVEMENT. For the primary outcome, age, sex, history of diabetes, history of MI, history of CHF, and LVEF were chosen by the forward selection algorithm to form the baseline clinical multivariate model (−2 log likelihood = 1,081) (Table 3, clinical model). Adjusted for the effects of the covariates in the clinical model and for each other, presence of ischemia (HR: 2.63; 95% CI: 1.68 to 4.14; $p < 0.001$) and LGE (HR: 1.86; 95% CI: 1.05 to 3.29; $p = 0.03$) maintained significant associations with the primary outcome. Presence of ischemia and presence of LGE independently improved this clinical model for the primary outcome when they were separately added (−2 log likelihood = 1,055 and 1,069 for ischemia and LGE, respectively; $p < 0.001$ for both) or when both were added (−2 log likelihood = 1,051; $p<0.001$) to the model. The addition of ischemia and LGE to the clinical model for the primary outcome also improved the model discrimination (Harrell's C statistic = 0.715 to 0.765; $p = 0.02$). Finally, the addition of ischemia and LGE resulted in a net reclassification improvement of 0.21 (95% CI: 0.10 to 0.32) and integrated discrimination improvement of 0.069 (95% CI: 0.041 to 0.096) ($p < 0.001$ for both), across pre-determined AHA/American College of Cardiology guideline-based risk categories.

Table 3 further displays the multivariate model for the secondary outcome. Adjusted to the effects of the clinical covariates and to each other, presence of ischemia (HR: 2.14; 95% CI: 1.55 to 2.95; $p < 0.001$) and LGE (HR: 1.70; 95% CI: 1.16 to 2.49; $p = 0.007$) maintained significant associations with the secondary outcome. Their addition improved baseline model goodness of fit (−2 log likelihood = 2,048 to 2,010; $p < 0.001$) and discrimination (Harrell's C statistic = 0.678 to 0.716; $p = 0.03$).

DOWNSTREAM TESTING, REVASCULARIZATION, AND COST. Referral rates to invasive coronary angiography and subsequent performance of revascularization procedures within the first 90 days of CMR, stratified by the presence and extent of ischemia, are shown in Figure 4A and by the presence or absence of ischemia and LGE in Figure 4B. Both the presence and extent of myocardial ischemia were associated with incrementally higher probability of undergoing coronary angiography and revascularization procedures (p for trend <0.001 for all). Among patients without evidence of ischemia on stress CMR, 59 (15%) underwent coronary angiography at 90 days per discretion of the caring physician, with 14 of 59 (24%) undergoing any type of coronary revascularization, including CABG (6 of 59 [10%]). Of these 14 patients, 10 were shown to have had prior infarct by LGE. All 6 patients who underwent CABG had prior infarct by LGE.

Figure 5 illustrates the average cost spent in cardiac tests according to follow-up periods. The difference was most marked during the first 90 days after CMR, when patients with ischemia incurred an approximately 3-fold higher cost compared to those without ($510 vs. $165; $p < 0.001$), driven mostly by higher referral rates to coronary angiography. After the first

FIGURE 4 **Invasive Coronary Angiography and Revascularization at 90 Days**



Referral to invasive angiography at 90 days, with corresponding percentage of patients undergoing revascularization, stratified by presence and extent of ischemia **(A)** and presence or absence of ischemia and late gadolinium enhancement (LGE) **(B)**.

90 days, cost spent in cardiac tests was low (average $74 per year) across all years of follow-up for patients without ischemia. Whereas coronary angiography contributed the most to overall costs during the first year, single-photon emission computed tomography contributed the most in later years.

DISCUSSION

In this retrospective cohort of patients with reduced LVEF referred to stress CMR for suspicion of CAD, we observed that stress CMR-detected myocardial ischemia and LGE provided incremental value to a clinical model for hard cardiovascular outcomes. Furthermore, in this cohort with evidence of cardiomyopathy, those with neither CMR ischemia nor infarct by LGE constituted a low-risk group with an annualized hard event rate of 1.1%.

Previous and contemporary observational studies (7,9), as well as randomized controlled trials (21–23) of stress CMR, have mostly included LVEF with median or mean in the normal range. In a meta-analysis of 19 studies and 11,636 patients with known or suspected CAD undergoing stress CMR, Lipinski et al. (8) reported an annualized hard outcome (cardiovascular death or nonfatal MI) rate of 4.9% and 0.8% for positive versus negative ischemia and 4.6% and 1.4% for positive versus negative LGE at median follow-up of 25 months. Mean LVEF for the included studies, however, ranged between 55% and 67%. Few studies have examined the prognostic impact of stress CMR in a population with impaired LVEF. Husser et al. (24) reported on 391 patients with reduced LVEF (mean 39%) undergoing stress CMR. At median follow-up of 1.8 years, presence of perfusion defect, but not LGE, was associated with major cardiovascular events. However, that study was limited by its relatively short follow-up duration and lack of adjustment for history of heart failure and LVEF. Our study significantly expands upon prior results and demonstrated that at median follow-up of 5.0 years, independent of LVEF, CMR-detected myocardial ischemia and LGE provided incremental prognostic value to a clinical model for cardiovascular outcomes.

In patients with heart failure, particularly in those with depressed LVEF, assessment of etiology is of paramount importance in determining prognosis and treatment. Studies have previously demonstrated that both the presence and extent of coronary disease are predictive of long-term mortality in patients with cardiomyopathy (25,26). Although pharmacological

FIGURE 5 Costs of Downstream Ischemia Testing at 4 Years

Costs of cardiac tests to detect myocardial ischemia incurred during follow-up, stratified by stress cardiac magnetic resonance (CMR) findings with breakdown by modality. Costs are displayed in U.S. dollars spent per patient. CCTA = coronary computed tomographic angiography; SPECT = single-photon emission computed tomography.

therapy remains the mainstay treatment for LV dysfunction in either ischemic or nonischemic cardiomyopathies (5,27), there are significant differences in interventional therapies, including options for revascularization. There is also emerging evidence to support differential effectiveness of implantable defibrillator therapy for protection against sudden cardiac death (28).

Accurate detection of CAD in LV dysfunction, however, remains a challenge using traditional stress imaging modalities. Single-photon emission computed tomography relies on the presence of regional wall motion abnormalities and reversible perfusion defects to detect CAD. In the presence of LV dysfunction, however, a significant portion of nonischemic cardiomyopathies may already display baseline regional wall motion abnormalities (29,30). Regional perfusion abnormalities can also occur in nonischemic dilated cardiomyopathies (31,32), and to further complicate matters, relative perfusion can remain normal in the presence of multivessel disease and "balanced ischemia" (33). For stress echocardiography, relatively few studies have examined its performance in patients with reduced LVEF. The largest series, including 70 patients, reported sensitivity and specificity of 83% and 71%, respectively (34). Because of its excellent spatial resolution, LGE imaging by CMR has the ability to accurate characterize the location and extent of myocardial scar. Previous studies examining patients with known obstructive CAD and reduced LVEF have detected ischemic pattern LGE in 80% to 100% of cases (35-37). Diagnostic accuracy of CMR to discern ischemic etiology in patients with new-onset heart failure was >95%, similar to coronary angiography (38). This is of particular significance, given the proportion of patients with prior infarct, but no clinical history of MI, and the prognostic importance of unrecognized MI (39). In our study, ischemic-pattern LGE was present in 48% of the cohort but a history of MI in only 24%.

A few studies using different imaging modalities have examined the prognostic value of noninvasive stress testing in patients with low LVEF. Majmudar et al. (40) studied 510 consecutive patients referred for stress positron emission tomography with resting LVEF ≤45%. The presence of scar, but not ischemia, was a univariate predictor of major adverse

cardiovascular events. In a multivariate model including etiology of LV dysfunction, neither ischemia nor scar was a significant predictor of cardiovascular events. In a substudy of the STITCH trial, which enrolled patients with ischemic heart failure with LVEF ≤35% and randomized them to CABG in addition to medical therapy, Panza et al. (41) evaluated 399 patients who underwent stress testing. Approximately one-half underwent single-photon emission computed tomography and the other one-half dobutamine stress echocardiography. Sixty-four percent had evidence of ischemia, and at median follow-up of 56 months, the presence of ischemia did not predict all-cause mortality, cardiovascular mortality, or all-cause mortality plus cardiovascular hospitalization. Our results suggest that stress CMR provides incremental value above a clinical model in predicting long-term hard cardiovascular outcomes and that this finding was independent of LVEF. A few key differences, however, exist between the present study and that reported by Panza et al., including differences in noninvasive modalities, population (suspected or known CAD vs. known CAD), LVEF (median 39% vs. mean 26%), and LV volumes.

We reported on the downstream use of invasive angiography, revascularization, and cost of ischemic testing. Consistent with current guidelines (5) and clinical practice, the presence and extent of ischemia were strong drivers behind invasive investigation and revascularization therapy. Referral to angiography remained at the discretion of the treating physician. We observed that 35% of patients with mild, 59% with moderate, and 67% with severe ischemia on stress CMR were referred to angiography. Many studies that have shown benefit of revascularization in ischemic cardiomyopathy (42) were published toward the end of the eligibility period of SPINS (2008 to 2013), which may explain the relatively lower rate of invasive therapy in those with higher burden of ischemia. Fifteen percent of patients with no evidence of ischemia still underwent diagnostic coronary angiography at 90 days, which likely reflects clinical practice at the time of study performance and the clinical recognition of high-risk features. In patients without CMR-detected ischemia who underwent revascularization, the majority had prior infarct. Because this study was conducted before the widespread adoption of fractional flow reserve to guide revascularization, we do not know whether all these interventions would have been performed under current indications. In terms of the cost of care of downstream ischemic testing, presence of ischemia was significant driver of resource use, particularly in the first 90 days, when it was associated with a 3-fold higher cost. The difference in cost was no longer significant after the second year of follow-up.

STUDY LIMITATIONS. First, our participating sites consisted of experienced, high-volume CMR centers, and therefore it is unclear whether the results can generalize to less experienced centers.

Second, given the retrospective design and limited number of patients who underwent revascularization, we were unable to assess for CMR guidance of medical therapy or coronary revascularization toward improvement of cardiovascular outcomes.

Third, there was a limited number of patients with severe LV dysfunction (LVEF <30%), and hence our results may not be generalizable to this population or to those with end-stage ventricular remodeling.

Fourth, LVEF determination was by CMR only, so the prognostic value of ischemia and LGE, adjusted to LVEF, may be different than if non-CMR-based LVEF was used.

Finally, we excluded patients with a history of CABG from our study; this will have to be addressed in a future study.

CONCLUSIONS

In this study of patients with impaired LVEF referred for clinical assessment for CAD, presence of ischemia and LGE on stress CMR was associated with worsened long-term cardiovascular prognosis. Presence of ischemia increased downstream referral to coronary angiography and revascularization and increased the cost of care from subsequent ischemic testing.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with reduced LVEF, stress CMR perfusion imaging can identify those at lower risk for ischemic events and guide referral for subsequent coronary angiography.

TRANSLATIONAL OUTLOOK: Future studies should compare the cost-effectiveness of a stress CMR–first strategy with other noninvasive and invasive modalities in the evaluation of patients with LV dysfunction suspected of having underlying ischemic heart disease.

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APPENDIX For supplemental figures, please see the online version of this paper.