JACC: CARDIOVASCULAR IMAGING VOL. 15, NO. 1, 2022

PUBLISHED BY ELSEVIER

ORIGINAL RESEARCH

Prognostic Value of Stress Cardiac Magnetic Resonance in Patients With Known Coronary Artery Disease

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ABSTRACT

OBJECTIVES This study sought to determine whether stress cardiac magnetic resonance (CMR) provides clinically relevant risk reclassification in patients with known coronary artery disease (CAD) in a multicenter setting in the United States.

BACKGROUND Despite improvements in medical therapy and coronary revascularization, patients with previous CAD account for a disproportionately large portion of CV events and pose a challenge for noninvasive stress testing.

METHODS From the Stress Perfusion Imaging in the United States (SPINS) registry, we identified consecutive patients with documented CAD who were referred to stress CMR for evaluation of myocardial ischemia. The primary outcome was nonfatal myocardial infarction (MI) or cardiovascular (CV) death. Major adverse CV events (MACE) included MI/CV death, hospitalization for heart failure or unstable angina, and late unplanned coronary artery bypass graft. The prognostic association and net reclassification improvement by ischemia for MI/CV death were determined.

RESULTS Out of 755 patients (age 64 ± 11 years, 64% male), we observed 97 MI/CV deaths and 210 MACE over a median follow-up of 5.3 years. Presence of ischemia demonstrated a significant association with MI/CV death (HR: 2.30; 95% CI: 1.54-3.44; $P < 0.001$) and MACE (HR: 2.24 ([95% CI: 1.69-2.95; $P < 0.001$). In a multivariate model adjusted for CV risk factors, ischemia maintained strong association with MI/CV death (HR: 1.84; 95% CI: 1.17-2.88; $P = 0.008$) and MACE (HR: 1.77; 95% CI: 1.31-2.40; $P < 0.001$) and reclassified 95% of patients at intermediate pretest risk (62% to low risk, 33% to high risk) with corresponding changes in the observed event rates of 1.4% and 5.3% per year for low and high post-test risk, respectively.

CONCLUSIONS In a multicenter cohort of patients with known CAD, CMR-assessed ischemia was strongly associated with MI/CV death and reclassified patient risk beyond CV risk factors, especially in those considered to be at intermediate risk. Absence of ischemia was associated with a <2% annual rate of MI/CV death. (Stress CMR Perfusion Imaging in the United States [SPINS] Study; NCT03192891) (J Am Coll Cardiol Img 2022;15:60–71) © 2022 by the American College of Cardiology Foundation.

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ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2021.06.025

More than 18 million American adults suffer from coronary artery disease (CAD), and the number is estimated to surpass 50 million by 2030 (1). Despite advances in medical therapy and coronary revascularization, patients with known CAD account for more than one-third of more than a million cardiovascular (CV) deaths and nonfatal myocardial infarctions (MIs) registered each year in the United States. Given the significantly higher event rates and burden of CV risk factors compared with patients without CAD, effective risk stratification in patients with known CAD represents a major clinical challenge (2).

Appropriate patient selection for coronary angiography is an important consideration, given that more than one-half of those referred for invasive assessment are eventually found to not have obstructive disease (3). In the higher-risk population of patients with established CAD, a high burden of CV risk factors may accelerate the rate of CAD progression and affect the decision to proceed with first-line invasive investigation. In this population, stress cardiac magnetic resonance (CMR) possesses unique strengths, being the gold standard technique for assessment of LV volumes and function, providing high-resolution imaging of prior myocardial scar and excellent specificity and sensitivity for detection of myocardial ischemia (4-7). However, the ability of stress CMR to effectively reclassify risk in patients with previous CAD has not yet been studied in a multicenter setting.

Therefore, in a multicenter cohort of consecutive patients with established CAD, the aims of the present study were to: 1) investigate the independent association of CMR-assessed ischemia and unrecognized MI (UMI) with nonfatal MI/CV death and major adverse cardiovascular events (MACE); 2) assess the ability of stress CMR to effectively reclassify patient risk above standard clinical models and LV function; and 3) evaluate downstream procedures and costs subsequent to stress CMR findings.

METHODS

STUDY POPULATION AND DESIGN. The patient population and design of the retrospective multicenter SPINS (Stress CMR Perfusion Imaging in the United States) study of the Society for Cardiovascular Magnetic Resonance registry have been described previously (8). Inclusion criteria for this analysis were: 1) aged 35 years-85 years; 2) referral for evaluation of chest pain, dyspnea, abnormal ECG, or other clinical presentation that raised a suspicion of myocardial ischemia as determined by the treating clinician; 3) the presence of previously documented CAD (including history of MI, percutaneous coronary intervention [PCI], or CAD according to coronary angiography); and 4) the presence of at least 2 of the following coronary risk factors: age >50 years for men or >60 years for women, diabetes mellitus, hypertension, hyperlipidemia, family history of premature CAD, body mass index ≥30 kg/m^2, and documented peripheral vascular disease. Exclusion criteria included history of coronary artery bypass graft surgery (CABG), recent MI within 30 days preceding the index CMR, severe-grade valvular heart disease, nonischemic cardiomyopathy with a left ventricular ejection fraction (LVEF) <40%, infiltrative or hypertrophic cardiomyopathy, constrictive pericarditis, active pregnancy, competing medical illnesses with expected survival <2 years, and known inability to participate in follow-up. Vasodilator stress included intravenous infusion of adenosine, bolus of regadenoson, or dipyridamole.

An enrolling center was required to have an active stress CMR imaging program for at least 10 years; to be able to contribute between 100-500 consecutive patients undergoing stress CMR from January 1, 2008, and December 31, 2013, so that at least 4 years of clinical follow-up could be achieved at study

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease
CV = cardiovascular
CMR = cardiac magnetic resonance
UMI = unrecognized myocardial infarction
MACE = major adverse cardiovascular event(s)
PCI = percutaneous coronary intervention
CABG = coronary artery bypass graft
IDI = integrated discrimination improvement
LVEF = left ventricular ejection fraction
LGE = late gadolinium enhancement
LVESVi = left ventricular end-systolic volume index
NRI = net reclassification improvement

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Eike Nagel, MD, served as Guest Editor for this paper.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received January 19, 2021; revised manuscript received June 2, 2021, accepted June 24, 2021.

conclusion; and to have access to electronic medical records. Each center was required to have all CMR scans interpreted by a level II/III reader, with at least 1 level III supervising reader. Enrolling centers must have performed CMR studies with the use of either a 1.5-T or a 3-T scanner and pulse sequences for stress perfusion, cine, and late gadolinium enhancement (LGE) imaging. At each site, the study received proper ethical oversight, and local institutional review board approval was obtained with a waiver of written informed consent.

DATA COLLECTION AND OUTCOMES. Clinical variables included patient demographics and characteristics at the time of the stress CMR. CMR variables included LV volumes, stress perfusion and LGE. Enrolling centers were required to report the myocardial extent of abnormal stress perfusion and LGE according to the 16- or 17-segment American Heart Association nomenclature. A stress perfusion defect was considered to be present if it was densest in the subendocardium with a transmural gradient across the wall thickness, persisted beyond peak myocardial enhancement for several R-R intervals, and conformed to a coronary artery distribution. Inducible ischemia was defined as the presence of a stress perfusion defect, in the absence of matching LGE, in at least 1 myocardial segment. Mild, moderate, and severe defects were defined as the involvement of 1 or 2, 3 to 5, and >5 segments, respectively. UMI was defined as absence of history of MI on medical documentation, but presence of LGE involving the subendocardium in 1 or more segments in a coronary artery distribution, thus conforming to an infarction pattern (9). Ischemia and LGE extent were assessed by the number of myocardial segments involved. Transmural scar was defined as LGE involving >50% of the myocardial wall in at least 1 LV segment with the use of the 17-segment model.

Study investigators were trained during the initiation period by group webinars, and study documents on definitions of all study variables were posted on a web-based database. All centers were instructed to systematically obtain follow-up data using the same methodology, on all enrolled patients, for as long as possible but at least for 4 years after the index stress CMR. Clinical follow-up used both electronic medical records and direct patient contact with either a standardized checklist questionnaire or scripted telephone interview. The mortality status of all study participants was further verified by each site's principal investigator via local death registries and the Social Security Death Index at the end of the study period.

The primary outcome was CV death or nonfatal MI. The secondary outcome was MACE defined by CV death, nonfatal MI, hospitalization for HF or unstable angina, and late (>6 months after the index CMR) unplanned CABG. CV deaths were deaths preceded by acute MI, malignant ventricular arrhythmia, or decompensated heart failure, per current recommendations (10). For either study outcome, only the first event was counted when multiple events occurred in a subject. Successful follow-up was defined as achieving an assessment of all events for at least 4 years after the index CMR. Patients who discontinued follow-up or were lost to follow-up were censored at the time of last clinical contact. End of follow-up data collection and locking of the database occurred on May 25, 2018.

STATISTICAL ANALYSIS. Clinical and CMR variables were compared using the chi-square test for categorical variables and Student's *t*-test or Mann-Whitney *U* test for continuous variables, depending on the distribution. Annualized event rates were calculated by dividing the number of patients who experienced the event by patient-years of follow-up and compared using the Mantel-Haenszel method for rate ratios. Cox proportional hazards were used to assess the association between CMR-assessed ischemia and/or UMI with outcomes. Kaplan-Meier curves were generated by plotting cumulative incidence of study outcomes by years of follow-up and compared by means of log-rank test.

To assess patients' baseline (pretest) risk, we constructed a multivariable clinical risk model with a stepwise forward Cox regression strategy, considering all clinical covariates with a P value of <0.10 on univariable screening. For nonfatal MI/CV death, the baseline multivariable model included age, sex (forced into the model), and history of smoking, as well as LV end-systolic volume index (LVESVi) as a continuous variable. To further define abnormal LVESVi, we selected a threshold of LVESVi >45 mL/m^2 (11). For MACE, the baseline multivariable model included age, sex (forced into the model), history of hypertension, and history of diabetes and LVEF as a continuous variable. Adding CMR-assessed ischemia and UMI to those models allowed assessment of post-test risk. The goodness-of-fit of each model was assessed by means of the −2log likelihood test and compared using the likelihood ratio test. The discriminative capacity of each model was determined according to the Harrell C-statistic at baseline and after addition of CMR-assessed ischemia and UMI. After assessing pretest and post-test risk categories for all patients, we further calculated the

magnitude of risk reclassification by stress CMR. For calculation of net reclassification improvement (NRI), we derived cutoffs of patient risk for nonfatal MI/CV death based on prognostic thresholds from previous stress imaging studies in patients with known CAD (12-14). Thus, patients with a predicted annual nonfatal MI/CV death rate of <2%, 2%-3%, and >3% per year were considered to be at low, intermediate, and high risk, respectively (12-14). Statistical analyses were performed with the use of SAS version 9.2, (SAS Institute). A 2-tailed *P* value of <0.05 was considered to be significant.

RESULTS

CLINICAL AND CMR CHARACTERISTICS OF THE STUDY POPULATION. Clinical and CMR characteristics of the cohort are summarized in Table 1. Mean age was 64 ± 11 years, and 64% were male. Forty-eight percent of the cohort had a history of MI and 71% a history of PCI. The main clinical presentation was chest pain (61%). Rates of CV medications were >80% for aspirin and statin and >70% for beta-blockers. Median LVEF was in the normal range (62%; IQR: 52%-69%), 46% (n = 346) of patients had presence of LGE, which in 35% (n = 121) of them corresponded to UMI. Ischemia by stress CMR was present in 28% (n = 212) of the cohort.

Compared with those without ischemia, patients with ischemia were younger, with a higher prevalence of diabetes mellitus, history of MI, and use of aspirin, beta-blocker, and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers. Regarding CMR parameters, patients with ischemia presented with lower LVEF, higher LVESVi, and a higher prevalence of LGE and UMI ($P < 0.001$ for all). The prevalence of transmural scar was not significantly different in patients with ischemia compared to those without (51% vs 50%; $P = 0.788$).

UNIVARIATE ASSOCIATIONS OF CMR-ASSESSED ISCHEMIA AND UMI WITH OUTCOMES. We observed 97 (13%) nonfatal MI/CV deaths and 210 (28%) MACE during a median follow-up of 5.3 years (IQR: 4.5-6.6 years). The univariate associations of clinical and CMR characteristics with outcomes are presented in Table 2 and Supplemental Table 1.

Annualized event rates for nonfatal MI/CV death according to the extent of ischemia, extent of LGE, and normal vs abnormal LVESVi are described in Figure 1. Presence of ischemia, myocardial scar, or LVESVi >45 mL/m^2 were associated with a significant increase in annualized rates for nonfatal MI/CV death ($P < 0.001$ for all). Subjects with absence of ischemia, absence of myocardial scar, and LVESVi ≤45 mL/m^2 represented 43% of the cohort and presented a low annualized risk for CV death/MI at 1.3%.

In univariate analysis, presence of ischemia was strongly associated with nonfatal MI/CV death (HR: 2.30; 95% CI: 1.54-3.44; $P < 0.001$) and MACE (HR: 2.24; 95% CI: 1.69-2.95; $P < 0.001$). In Kaplan-Meier analysis, patients with presence of ischemia experienced a substantial increase in cumulative incidence

TABLE 1 Baseline Clinical and Stress CMR Characteristics of the Study Population

	Overall (N = 755)	No Ischemia (n = 543)	Ischemia (n = 212)	*P* Value
Clinical parameters				
Age, y	64 ± 11	65 ± 11	63 ± 11	0.015
Male	483 (64)	340 (63)	143 (67)	0.213
Hypertension	618 (82)	443 (82)	175 (83)	0.664
Hyperlipidemia	642 (85)	459 (85)	183 (86)	0.535
Diabetes mellitus	245 (32)	158 (29)	87 (41)	0.002
Smoking	285 (38)	196 (36)	89 (43)	0.105
Number of CV risk factors	4 (4-5)	4 (3-5)	4 (4-5)	0.009
History of PCI	538 (71)	395 (73)	143 (68)	0.152
History of MI	358 (48)	242 (45)	116 (55)	0.016
Clinical presentation				
Abnormal ECG	69 (9)	58 (11)	11 (5)	0.019
Chest pain	463 (61)	327 (60)	136 (64)	0.319
Dyspnea	247 (33)	189 (35)	58 (27)	0.050
Syncope	44 (6)	36 (7)	8 (4)	0.132
Medications				
Aspirin	613 (81)	425 (78)	188 (90)	<0.001
Statin	612 (81)	433 (80)	179 (85)	0.108
Beta-blockers	525 (70)	357 (66)	168 (79)	<0.001
ACEi/ARB	461 (61)	317 (58)	144 (68)	0.016
Diuretics	235 (31)	160 (30)	75 (36)	0.113
Stress CMR				
LVEF, %	62 (52-69)	63 (54-70)	58 (43-68)	<0.001
LVEDVi, mL/m^2	65 (51-81)	61 (48-75)	76 (62-97)	<0.001
LVESVi, mL/m^2	24 (16-35)	22 (15-31)	31 (22-53)	<0.001
LVMi, g/m^2	61 (51-75)	59 (50-73)	65 (51-82)	0.057
Presence of LGE	346 (46)	204 (38)	142 (67)	<0.001
Nontransmural LGE	170 (49)	99 (49)	71 (50)	0.788
Transmural LGE[a]	176 (51)	105 (51)	71 (50)	
1-2 segments	119 (34)	80 (39)	39 (27)	0.071
3-5 segments	129 (37)	72 (35)	57 (40)	
>5 segments	98 (28)	52 (25)	46 (32)	
Presence of UMI	121 (16)	72 (13)	49 (23)	<0.001
1-2 segments	57 (47)	37 (51)	20 (41)	0.426
3-5 segments	38 (31)	22 (31)	16 (33)	
>5 segments	26 (21)	13 (18)	13 (27)	

Values are mean ± SD, n (%), or median (IQR). [a]Defined as presence of at least 1 myocardial segment with transmural LGE.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CAD = coronary artery disease; CMR = cardiac magnetic resonance; CV = cardiovascular; ECG = electrocardiography; LGE = late gadolinium enhancement; LVEDVi = left ventricular end-diastolic volume indexed; LVEF = left ventricular ejection fraction; LVESVi = left ventricular end-systolic volume indexed; MI = myocardial infarction; PCI = percutaneous coronary intervention; UMI = unrecognized myocardial infarction.

TABLE 2 Univariate and Multivariate Associations of Clinical and CMR Characteristics With CV Death and Nonfatal MI

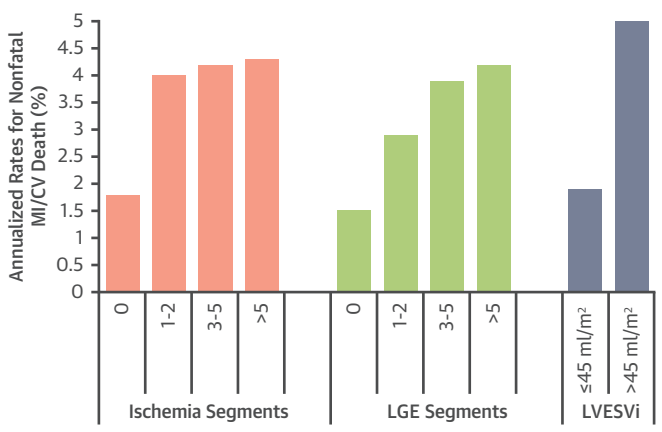
	Univariate Association With CV Death/MI	*P* Value	Multivariate Association With CV Death/MI	*P* Value
Clinical parameters				
Age (per 10 y)	0.99 (0.82-1.19)	0.921	1.09 (0.90-1.34)	0.373
Male	1.10 (0.72-1.68)	0.658	1.15 (0.74-1.80)	0.531
Hypertension	0.91 (0.55-1.51)	0.721		
Hyperlipidemia	0.63 (0.39-1.02)	0.059		
Diabetes mellitus	1.50 (1.00-2.26)	0.052		
Smoking	1.58 (1.06-2.37)	0.026	1.60 (1.04-2.45)	0.032
History of PCI	0.83 (0.53-1.28)	0.390		
History of MI	2.09 (1.37-3.18)	0.001		
Stress CMR				
LVEF (per 5%)	0.87 (0.82-0.92)	<0.001		
LVEDVi (per 10 mL/m^2)	1.13 (1.07-1.19)	<0.001		
LVESVi (per 10 mL/m^2)	1.14 (1.08-1.20)	<0.001	1.08 (1.02-1.15)	0.009
LVMi (per 10 g/m^2)	1.16 (1.07-1.26)	<0.001		
Presence of ischemia	2.30 (1.54-3.44)	<0.001	1.84 (1.17-2.88)	0.008
Extent of ischemia (per segment)[a]	1.08 (1.02-1.14)	0.009		
Presence of LGE	2.47 (1.61-3.77)	<0.001		
Nontransmural LGE	1.81 (1.07-3.07)	0.028		
Transmural LGE[b]	3.15 (1.98-5.02)	<0.001		
Extent of LGE (per segment)[c]	1.09 (1.04-1.14)	<0.001		
Presence of UMI	3.23 (1.62-6.45)	<0.001	2.27 (1.10-4.70)	0.027

Values are HR (95% CI). Stepwise forward selection of all variables with a *P* value of <0.10 in univariate association (age, sex forced into the model). [a]Refers to the average prognostic association per segment of myocardial ischemia with CV death/MI. [b]Defined as presence of at least 1 myocardial segment with transmural LGE. [c]Refers to the average prognostic association per segment of myocardial infarction with CV death/MI.

LVMi = left ventricular mass indexed; other abbreviations as in Table 1.

of outcomes compared with patients with absence of ischemia, for both nonfatal MI/CV death and MACE (Figure 2). Patients with absence of ischemia experienced low annual rates of nonfatal MI/CV death compared with patients with ischemia (1.8% vs 4.2% per year; $P < 0.001$). For CV death alone, we observed annual rates of 0.8% vs 1.3% ($P = 0.114$) in the absence versus presence of ischemia. MACE rates in the absence vs presence of ischemia were 4.4% versus 10.1% per year ($P < 0.001$). Presence of UMI was also significantly associated with nonfatal MI/CV death (HR: 3.23; 95% CI: 1.62-6.45; $P < 0.001$) and MACE (HR: 2.51; 95% CI: 1.67-3.77; $P < 0.001$). Compared with patients with no MI, patients with UMI experienced significantly higher annual rates of nonfatal MI/CV death (0.9% vs 3.1% per year; $P < 0.001$) and MACE (3.4% vs 8.7% per year; $P < 0.001$).

FIGURE 1 Annualized Rates for Nonfatal MI/CV Death, by Extent of Ischemia, Late Gadolinium Enhancement, and Left Ventricular End-Systolic Volume Index

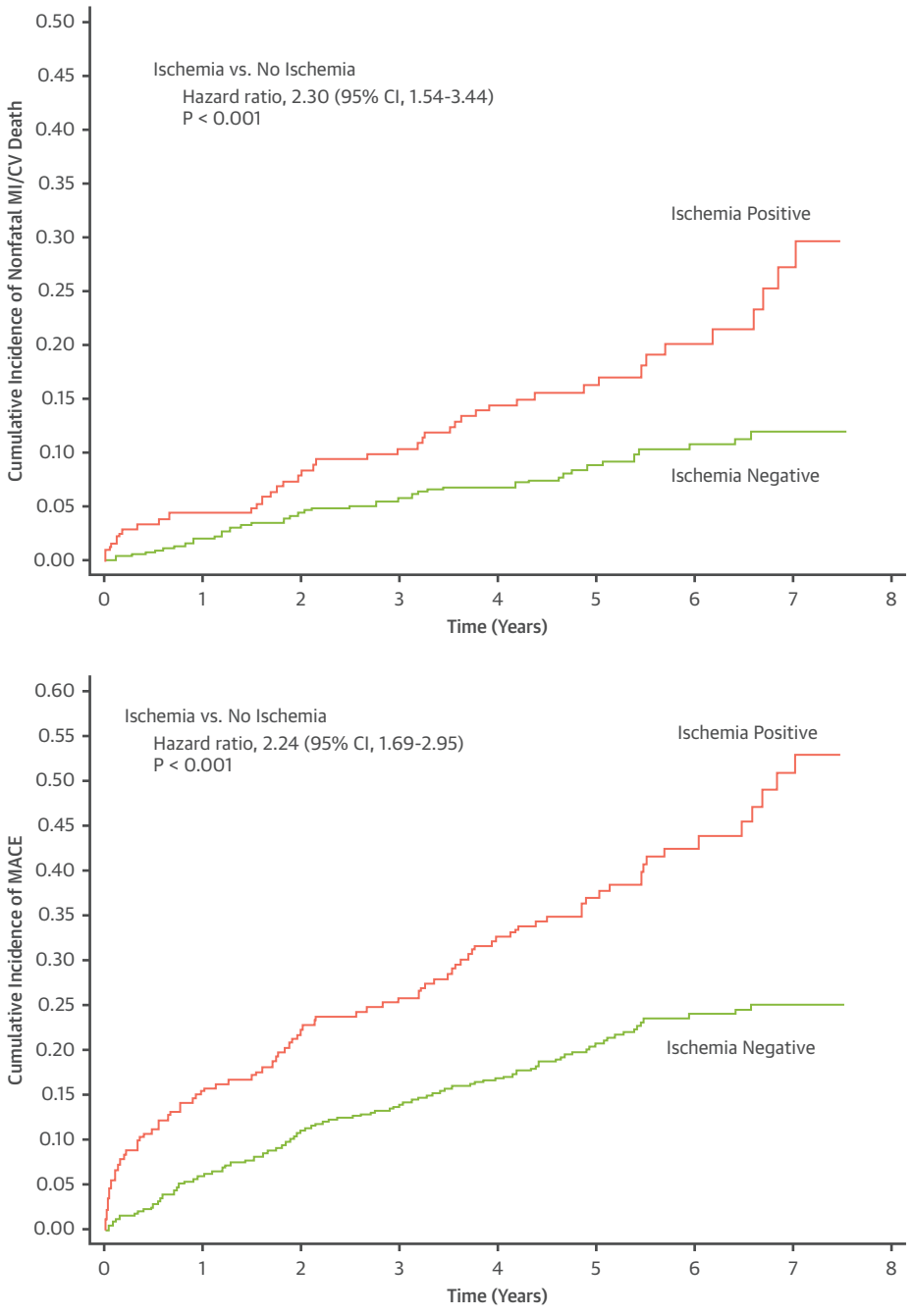


Rates by ischemic segments: 1.8% vs 4% vs 4.2% vs 4.3% for 0, 1-2, 3-5, >5, respectively ($P < 0.001$ for the comparison of 0 vs the rest). Rates by LGE segments: 1.5% vs 2.9% vs 3.9% vs 4.2% for 0, 1-2, 3-5, >5, respectively ($P < 0.001$ for the comparison of 0 vs the rest). Rates by LVESVi: 1.9% vs 5% for LVESVi ≤45 mL/m^2 vs LVESVi >45 mL/m^2 ($P < 0.001$). CV = cardiovascular; MI = myocardial infarction.

MULTIVARIATE ASSOCIATIONS OF CMR-ASSESSED ISCHEMIA AND UMI WITH OUTCOMES. We constructed baseline multivariate models using a stepwise forward Cox regression strategy by considering all covariates with a *P* value of <0.10 on univariable screening. For nonfatal MI/CV death, the selected model included age, sex (forced into the model), smoking, LVESVi, ischemia, and UMI; for MACE, the baseline model included age, sex (forced into the model), diabetes mellitus, hypertension, LVEF, ischemia, and UMI.

In multivariable analysis, both presence of ischemia and UMI were significantly associated with nonfatal MI/CV death (ischemia: HR: 1.84; 95% CI:

FIGURE 2 **Time-to-Event Curves for Nonfatal MI/CV Death and MACE**



Time-to-event curves for nonfatal MI/CV death **(top)** and MACE **(bottom)**. Event-free survival for patients with presence vs absence of stress CMR-assessed ischemia are shown in **red**, and **green** respectively. Statistical analysis using log-rank test. CV = cardiovascular; MACE = major adverse cardiovascular event(s); MI = myocardial infarction.

1.17-2.88; $P = 0.008$; UMI: HR: 2.27; 95% CI: 1.10-4.70; $P = 0.027$) and MACE (ischemia: HR: 1.77; 95% CI: 1.31-2.40; $P < 0.001$; UMI: HR: 1.73; 95% CI: 1.11-2.69; $P = 0.015$) (**Table 2,** Supplemental Table 1).

NET RECLASSIFICATION IMPROVEMENT AFTER ADDITION OF CMR-ASSESSED ISCHEMIA AND UMI. We further determined the discriminative capacity, goodness-of-fit, and reclassification improvement of

TABLE 3 Discrimination, Reclassification and Goodness-of-Fit Statistics for Nonfatal MI/CV Death and MACE, After Addition of CMR-Assessed Ischemia and UMI to the Baseline Model

	Model Discrimination	Model Reclassification		Goodness of Fit
Outcome	C-statistic (95% CI); *P* Value	IDI (95% CI); *P* Value	cNRI (95% CI); *P* Value	−2 Log Likelihood; *P* Value
CV death/MI				
Baseline model[a]	0.626 (0.561-0.691)	-	-	1,110
+ Ischemia	0.637 (0.570-0.703); $P = 0.547$[b]	0.016 (0.007-0.025); $P < 0.001$	0.433 (0.217-0.649); $P < 0.001$	1,101; $P = 0.002$[b]
+ Ischemia, UMI	0.681 (0.626-0.737); $P = 0.024$[b]	0.029 (0.015-0.042); $P < 0.001$	0.411 (0.276-0.679); $P < 0.001$	1,089; $P < 0.001$[b]
MACE				
Baseline model[c]	0.621 (0.579-0.662)	-	-	2,415
+ Ischemia	0.646 (0.606-0.686); $P = 0.035$[b]	0.025 (0.013-0.038); $P < 0.001$	0.423 (0.270-0.574); $P < 0.001$	2,399; $P < 0.001$[b]
+ Ischemia, UMI	0.656 (0.617-0.694); $P = 0.019$[b]	0.032 (0.018-0.046); $P < 0.001$	0.384 (0.196-0.545); $P < 0.001$	2,394; $P < 0.001$[b]

[a]Baseline model adjusted for age, sex, smoking, and LVESVi. [b]Compared with the baseline model. [c]Baseline model adjusted for age, sex, hypertension, diabetes, and LVEF.
cNRI = continuous net reclassification improvement; IDI = integrated discrimination improvement; other abbreviations as in Table 1.

prediction models before and after addition of stress CMR parameters on top of the multivariate baseline models. For nonfatal MI/CVdeath, the baseline model demonstrated a C-statistic of 0.626 (95% CI: 0.561-0.691) which improved to 0.637 (95% CI: 0.570-0.703) after addition of CMR-assessed ischemia alone and to 0.681 (95% CI: 0.626-0.737) after addition of both ischemia and UMI (Table 3). For MACE, the baseline model showed a C-statistic of 0.621 (95% CI: 0.579-0.662) which improved to 0.646 (95% CI: 0.606-0.686) after addition of CMR-assessed ischemia alone and to 0.656 (95% CI: 0.617-0.694) after addition of both ischemia and UMI (Table 3). Addition of ischemia and UMI to the baseline model also improved goodness-of-fit of the multivariable model (Table 3).

Furthermore, the addition of stress CMR imaging parameters to each baseline model significantly improved reclassification metrics (Table 3). Adding presence of ischemia yielded a significant integrated discrimination improvement (IDI) of 0.016 (95% CI: 0.007-0.025) and a continuous NRI of 0.433 (95% CI: 0.217-0.649) for nonfatal MI/CV death as well as an IDI of 0.025 (95% CI: 0.013-0.038) and a continuous NRI of 0.423 (95% CI: 0.270-0.574) for MACE. Similar results were obtained after addition of ischemia and UMI (Table 3).

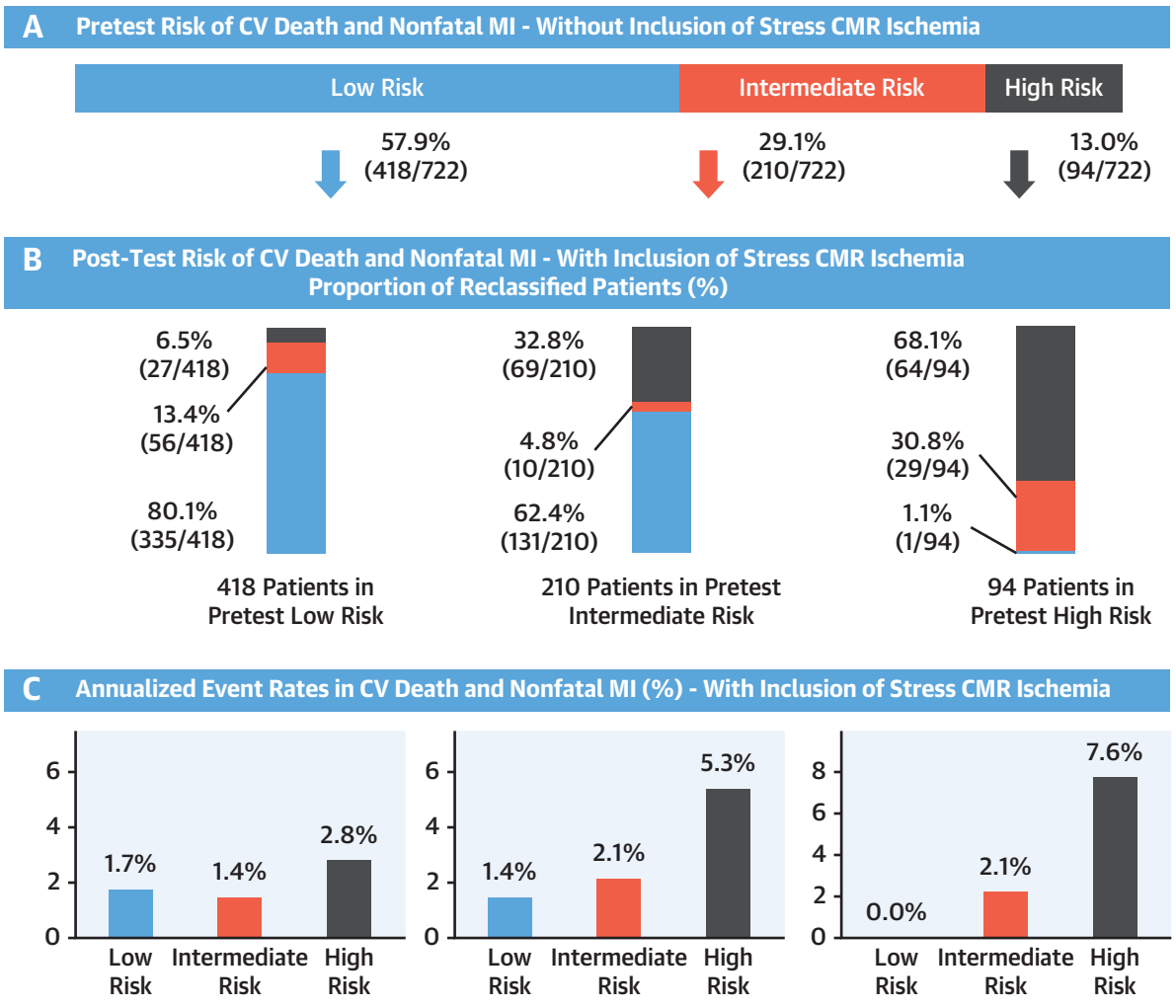
We further assessed NRI across validated risk cut-offs of annual event rates of <2% (low risk), 2%-3% (intermediate risk), and >3% (high risk) for nonfatal MI/CV death. Addition of ischemia alone to the baseline model yielded an NRI of 0.189 (95% CI: 0.048-0.330) (Supplemental Table 2), which improved further after addition of both ischemia and UMI (NRI: 0.263; 95% CI: 0.128-0.398) (Supplemental Table 3).

Addition of CMR-assessed ischemia reclassified 43% (313 of 722) of the overall cohort to a more appropriate post-test risk group for nonfatal MI/CV death. Risk reclassification showed the most substantial changes in patients at intermediate pretest risk for nonfatal MI/CV death, where addition of stress CMR-assessed ischemia reclassified 95% of patients (200 of 210; 62% reclassified to low risk, 33% to high risk) with corresponding changes in the observed event rates of 1.4% per year for low post-test risk vs 5.3% per year for high post-test risk (Central Illustration). Similar results were obtained after the addition of both ischemia and UMI (Supplemental Table 3, Supplemental Figure 1).

DOWNSTREAM TESTING, CORONARY REVASCULARIZATION, AND COST. Referral rates to invasive coronary angiography and subsequent revascularization procedures within the first 90 days of CMR, stratified by the presence and extent of ischemia, are shown in Figure 3, both overall and in patients that were found to have UMI on CMR. Both the presence and the 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 with evidence of moderate or severe ischemia that were referred to coronary angiography, 79% and 71%, were revascularized respectively (Figure 3, left). In case of concomitant presence of UMI on stress CMR, revascularization rates were higher at 80% and 75% for moderate and severe ischemia, respectively (Figure 3, right).

Figure 4 illustrates the average costs incurred for 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 6-fold higher cost compared with those without ($82 vs $471; $P < 0.001$), driven

CENTRAL ILLUSTRATION **Risk Reclassification Improvement for CV Death and Nonfatal MI, After Addition of Stress CMR-Assessed Ischemia**



Antiochos, P. et al. J Am Coll Cardiol Img. 2022;15(1):60–71.

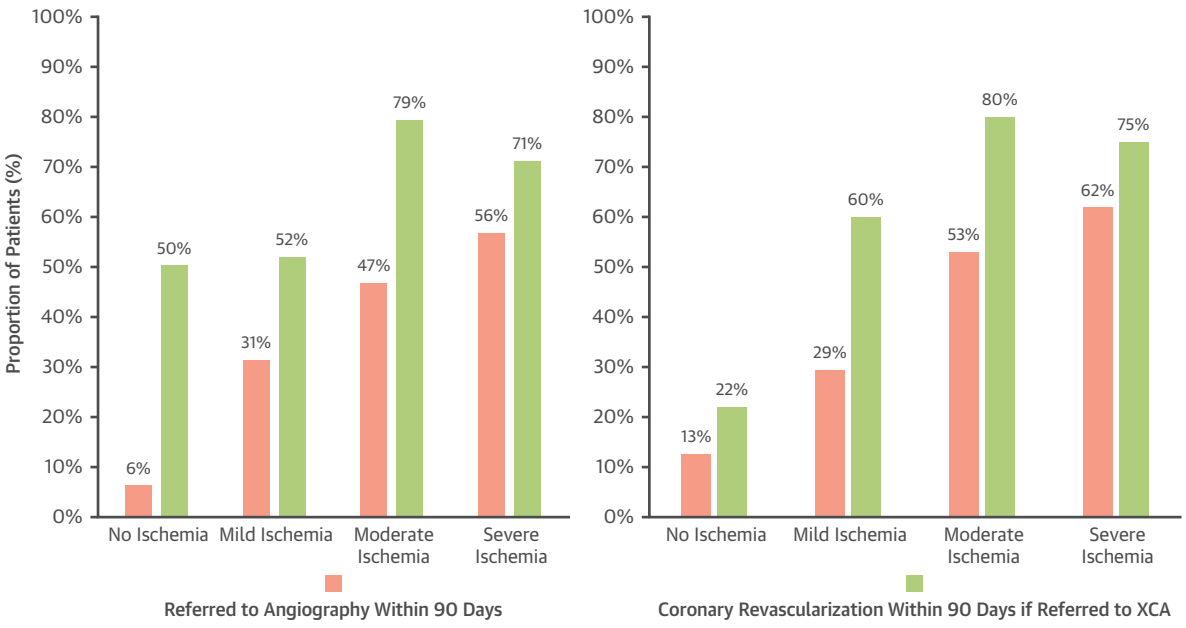
Stress cardiac magnetic resonance (CMR)-assessed ischemia was added to the multivariate baseline clinical risk model, and risk reclassification was assessed across recommended categories of <2% (low pretest risk), 2%-3% (intermediate pretest risk), and >3% (high pretest risk) annual rates for cardiovascular (CV) death and nonfatal myocardial infarction (MI) **(A)**. **(B)** Proportions of patients reclassified by the addition of stress CMR-assessed ischemia across pretest risk categories. **(Left)** Low pretest risk; **(center)** intermediate pretest risk; **(right)** high pretest risk. Low post-test risk: **blue**; intermediate posttest risk: **red**; high posttest risk: **black**. **(C)** Observed annualized rates of CV death and nonfatal MI for reclassified patients. **(Left)** Low pretest risk; **(center)** intermediate pretest risk; **(right)** high pretest risk.

mostly by higher referral rates to coronary angiography. After the first 90 days, costs incurred for cardiac tests were similar between the 2 groups, across all years of follow-up. Whereas coronary angiography contributed the most to overall costs during the first year, single-photon emission computed tomography (SPECT) contributed the most in later years.

DISCUSSION

In a multicenter cohort of patients with known CAD presenting with suspected myocardial ischemia, our findings indicate that: 1) presence of ischemia and UMI are independently associated with nonfatal MI/CV death and MACE; 2) absence of ischemia on stress CMR is associated with an annual rate of

FIGURE 3 Invasive Coronary Angiography and Revascularization Rates at 90 Days



Referral to invasive coronary angiography **(red)** with corresponding proportion of patients undergoing revascularization within 90 days **(green)**, stratified by extent of ischemia, overall **(left)** and in patients with unrecognized myocardial infarction (UMI) **(right)**. Numbers of patients: overall: 543 no ischemia, 86 mild, 71 moderate, 55 severe; with UMI (n = 121): 72 no ischemia, 17 mild, 19 moderate, 13 severe. XCA = invasive x-ray coronary angiography.

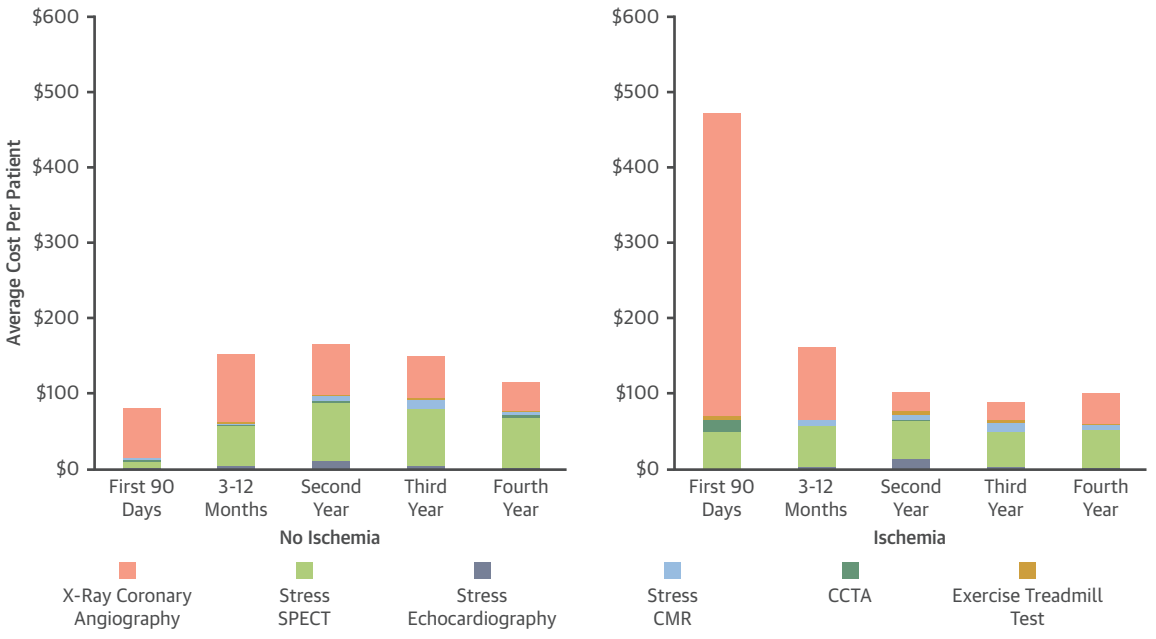
nonfatal MI/CV death of <2%; and 3) stress CMR imaging provides effective risk reclassification for nonfatal MI/CV death, incremental to CV risk factors and LV function, across recommended risk categories, especially for patients considered to be at intermediate risk (2%-3% per year). Addition of ischemia reclassified 95% of patients at intermediate risk for nonfatal MI/CV death, either to a low (62%) or high (33%) post-test risk category, with observed event rates at 1.4% vs 5.3% per year, respectively. These findings expand on previous work in populations of suspected CAD (7,15) and support the value of stress CMR imaging for risk stratification and clinical decision-making in patients with known CAD.

Despite improvements in medical therapy and coronary revascularization procedures, patients with established CAD account for a disproportionately large portion of CV events, with annual event rates consistently >2% for nonfatal MI/CV death and >5% for MACE in contemporary cohorts (2,12). This is in line with the observed event rates in our study, despite a high percentage of secondary prevention medical therapy (>80% on aspirin and statin, 70% on beta-blockers) and previous revascularization (>70%). Given the morbidity associated with previous CAD, stress CMR has the potential to play an increasing key role in the noninvasive risk stratification of this patient population.

In contrast to functional stress imaging, use of coronary computed tomographic angiography (CCTA) may be challenging in patients with heavy coronary calcifications or previous PCI and stents because of blooming artifacts that may lead to disease overestimation compared with functional imaging (16,17). Given these limitations, the latest appropriate use criteria (18) and CAD guidelines (19) indicate that functional imaging may be preferred in patients with known obstructive CAD with heavy calcifications, or after PCI. In the observational STRATEGY (Stress Cardiac Magnetic Resonance Versus Computed Tomography Coronary Angiography for the Management of Symptomatic Revascularized Patients) study, patients with prior CAD and revascularization underwent CCTA or stress CMR and were followed for 2 years (17). Compared with CCTA, stress CMR led to lower use of both invasive and noninvasive downstream cardiac testing, which translated into lower downstream costs. Despite this, patients who had undergone stress CMR experienced significantly lower rates of MACE at 2 years.

Knowledge on localization and extent of ischemia, presence of prior (unrecognized) myocardial scar, and

FIGURE 4 **Costs of Downstream Ischemia Testing at 4 Years Following the Index Stress CMR**



Costs incurred for cardiac tests to detect myocardial ischemia during follow-up, stratified by stress cardiac magnetic resonance (CMR) ischemia 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.

assessment of LV function and volumes are often useful to determine the need and type of downstream invasive interventions or appropriately adjust medical therapy in patients with known CAD (7,9). Stress CMR allows for a comprehensive evaluation of myocardial structure, function, perfusion, and scar without exposure to ionizing radiation. Obtained in a multicenter setting in the US, the present findings extend previous data on the risk stratification ability of stress CMR and could be integrated into a decision-making algorithm in clinical practice. In our cohort, patients with absence of ischemia, absence of myocardial scar, and LVESVi ≤45 mL/m^2 on stress CMR represented 43% of the cohort and carried a low (1.3%) annual risk of nonfatal MI/CV death. In clinical practice, this subgroup of patients could benefit from conservative treatment with optimal medical therapy (OMT), thus avoiding invasive coronary angiography in more than 40% of patients with known CAD.

Furthermore, CMR is uniquely able to assess for the presence of coexisting nonischemic etiologies in patients with a history of CAD. The relationship between the extent, localization, and pattern of LGE and the impact on regional wall motion and LVESVi can differentiate between nonischemic versus ischemic etiologies of cardiomyopathy. For instance, significant LV dysfunction that is out of proportion with ischemia and LGE extent or LGE patterns atypical of infarction should raise the suspicion of a coexisting nonischemic etiology. On the other hand, prospective studies are needed to assess whether ischemia extent may determine a subgroup with incremental benefit of invasive strategy over OMT alone. (20) Finally, for those with severe multivessel patterns of ischemia on stress CMR (5), or any patient with uncontrolled symptoms despite OMT, referral to coronary angiography should be considered.

We further report on downstream invasive procedures and costs of ischemic testing. Not surprisingly, the presence (and extent) of myocardial ischemia was a significant driver toward invasive angiography and subsequent revascularization procedures within the initial 90 days following stress CMR. After this period, the differences in cost were no longer perceptible between those with versus without ischemia. Patients with known CAD and previous PCI have been shown to undergo excess testing, with typically more than one-half of them undergoing stress imaging within 2 years of the procedure,

regardless of symptoms (21,22). An effective gatekeeping strategy for these patients, deemed to be at higher risk, is therefore of particular relevance. In those without evidence of ischemia, the present study demonstrates a low (<2%/year) rate of nonfatal MI/CV death, which was matched by a consistently low rate of spending on downstream cardiac testing. Although our study did not explicitly compare stress CMR with other modalities in this population, a previous analysis demonstrated stress CMR to be a cost-effective alternative when obstructive CAD prevalence was 10%-60% with the use of a decision analytic model (23).

STUDY LIMITATIONS. First, because of its retrospective design, the study could not capture all of the confounding factors regarding management decisions after the index stress CMR. Therefore, we could not quantify the outcomes of coronary revascularization incremental to medical therapy in patients with significant CMR-assessed ischemia. Second, we did not collect data on the time interval between diagnosis of prior CAD and the index stress CMR. According to the current appropriate use criteria (18), noninvasive stress tests in asymptomatic patients with known CAD are considered to be "rarely appropriate" at <5 years after CABG or <2 years after PCI. Nevertheless, within our cohort, all patients had suspicion of recurrent ischemia on the basis of clinical presentation, medical history, or ECG changes. Sites have reported segmental extent of ischemia over segmental LGE in guiding downstream management, so the independent prognostic value of ischemia transmurality was not assessed in this cohort. We observed a relatively high use of SPECT in the follow-up period, which likely reflects current practice patterns in the US. Potential reasons for the high use of stress SPECT compared with other modalities are likely multiple, including higher availability of SPECT scans, inertia to adapt to newer imaging methods, lower reimbursement rates for stress CMR than for stress SPECT, and a relative lack of trained physicians for stress CMR. Finally, by study design, centers needed to have at least 10 years of experience in stress CMR to participate. However, diverse practice environments were represented, including university hospitals (n = 7), cardiovascular group practices (n = 2), multispecialty practices (n = 2), and US government or military hospitals (n = 2) (8).

CONCLUSIONS

In a multicenter cohort of patients with known CAD presenting with suspected myocardial ischemia, the presence of stress CMR–assessed ischemia was independently associated with adverse CV outcomes and reclassified patient risk beyond clinical risk factors and LV function, especially in those considered to be at intermediate risk (2%-3% per year) for nonfatal MI and CV death. Overall, absence of ischemia on stress CMR was associated with a relatively low risk (<2%) for CV death and nonfatal MI in patients with known CAD.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The SPINS study of the Society for Cardiovascular Magnetic Resonance (SCMR) registry was funded by the SCMR with a research grant jointly sponsored by Siemens Healthineers (Erlangen, Germany) and Bayer (Leverkusen, Germany). These sponsors provided financial support for the study but did not play a role in study design, data collection, analysis, interpretation, or manuscript drafting. Dr Antiochos has received research funding from the Swiss National Science Foundation (grant P2LAP3_184037), the Novartis Foundation for Medical-Biological Research, the Bangerter-Rhyner Foundation, and the SICPA Foundation. Dr Bandettini is the principal investigator of one of the Bayer-sponsored GadaCAD2 (Gadavist-Enhanced Cardiac Magnetic Resonance Imaging to Detect Coronary Artery Disease) sites. Dr Patel has received a research grant from and served on the Speakers Bureau of Astellas. Dr Raman has received institutional research support from Siemens. Dr Schulz-Menger has research agreements with Siemens and serves on the Advisory Board of Bayer. Dr Shenoy has received support from a National Institutes of Health grant (K23HL132011). Dr Stuber has received nonmonetary research support form Siemens Healthineers. Dr Simonetti receives institutional research support from Siemens. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with known CAD, stress CMR perfusion imaging can effectively reclassify patient risk beyond CV risk factors and LV function. Absence of ischemia on stress CMR indicates a low (<2%) annual risk for nonfatal MI/CV death.

TRANSLATIONAL OUTLOOK: Future studies should compare the potential benefit and cost-effectiveness of a "stress CMR–first" strategy with other noninvasive and invasive modalities in the evaluation of patients with documented CAD, suspected of having recurrence of myocardial ischemia.

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KEY WORDS coronary artery disease, ischemia, risk reclassification, stress cardiac magnetic resonance

APPENDIX For supplemental tables and a figure, please see the online version of this paper.

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