Prognostic Stratification of Patients With ST-Segment–Elevation Myocardial Infarction (PROSPECT)

A Cardiac Magnetic Resonance Study

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Background—Cardiac magnetic resonance (CMR) is a robust tool to evaluate left ventricular ejection fraction (LVEF), myocardial salvage index, microvascular obstruction, and myocardial hemorrhage in patients with ST-segment–elevation myocardial infarction. We evaluated the additional prognostic benefit of a CMR score over standard prognostic stratification with global registry of acute coronary events (GRACE) score and transthoracic echocardiography LVEF measurement.

Methods and Results—Two hundred nine consecutive patients with ST-segment–elevation myocardial infarction (age, 61.4±11.4 years; 162 men) underwent transthoracic echocardiography and CMR after succesful primary percutaneous coronary intervention. Major adverse cardiac events (MACE) were assessed at a mean follow-up of 2.5±1.2 years. MACE occurred in 24 (12%) patients who at baseline showed higher GRACE risk score (P<0.01), lower LVEF with both transthoracic echocardiography and CMR, lower myocardial salvage index, and higher per-patient myocardial hemorrhage and microvascular obstruction prevalence and amount as compared with patients without MACE (P<0.01). The best cut-off values of transthoracic echocardiography-LVEF, CMR-LVEF, myocardial salvage index, and microvascular obstruction to predict MACE were 46.7%, 37.5%, 0.4, and 2.6% of left ventricular mass, respectively. Accordingly, a weighted CMR score, including the following 4 variables (CMR-LVEF, myocardial salvage index, microvascular obstruction, and myocardial hemorrhage), with a maximum of 17 points was calculated and included in the multivariable analysis showing that only CMR score (hazard ratio, 1.867 per SD increase [1.311–2.658]; P<0.001) was independently associated with MACE with the highest net reclassification improvement as compared to GRACE score and transthoracic echocardiography-LVEF measurement.

Conclusions—CMR score provides incremental prognostic stratification as compared with GRACE score and transthoracic echocardiography-LVEF and may impact the management of patients with ST-segment–elevation myocardial infarction. **(*Circ Cardiovasc Imaging*. 2017;10:e006428. DOI: 10.1161/CIRCIMAGING.117.006428.)**

Key Words: humans ■ magnetic resonance ■ prognosis ■ ST-segment–elevation myocardial infarction

Primary percutaneous coronary intervention (pPCI) has significantly reduced cardiovascular mortality of patients with ST-segment–elevation myocardial infarction (STEMI).[1,2]

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However, even rapid and complete restoration of culprit vessel flow may not guarantee adequate myocardial perfusion and may be associated with poor recovery of left ventricular (LV) function and unfavorable remodeling, which are major predictors of morbidity and mortality.[3] Prediction of future cardiovascular events after STEMI aroused much interest during the past few decades.[4] Typically, risk stratification is performed using electrocardiography, laboratory angiography and echocardiography parameters, and proven risk scores.[5,6] Cardiac magnetic resonance (CMR) has emerged as the gold standard technique for the measurement of the LV ejection fraction (LVEF), the amount of saved myocardium as expressed by myocardial salvage index (MSI), microvascular obstruction (MVO), and myocardial hemorrhage (MH).[7,8] These variables may predict LV functional recovery[9] and risk of major adverse cardiovascular events (MACE).[10,11] Thus, we hypothesized that a multiparametric CMR score has incremental prognostic value as compared with standard prognostic stratification.

Methods

Study Population

Two hundred fifty-five consecutive patients with STEMI, referred to our hospital between January 2012 and December 2014, were prospectively screened to identify those meeting the following inclusion criteria: (1) chest pain suggestive of myocardial ischemia lasting >30 minutes, (2) ST-segment elevation >0.1 mV in ≥2 limb leads or >0.2 mV in ≥2 contiguous precordial leads, or presumed new left bundle-branch block, and (3) successful treatment with pPCI within 12 hours from symptom onset. Exclusion criteria were prior myocardial infarction (MI) or revascularization, time to pPCI >12 hours, atrial fibrillation, Killip class >III, renal failure (glomerular filtration <30 mL/min), claustrophobia or other contraindications to CMR, and insufficient T2w-image quality. The study complied with the declaration of Helsinki; the ethics committee approved the research protocol, and each patient gave informed consent (protocol number, R49416).

Collection of Clinical Variables

Clinical history and the following variables were collected in each patient: demographic characteristics, cardiovascular risk factors, medical therapy, vital parameters including blood pressure and heart rate, MI location, peak CK-MB and troponin I, Killip class, and time to pPCI defined as the interval time between onset of continuous chest pain and recanalization of the infarct-related artery by pPCI. Finally, global registry of acute coronary events (GRACE) 2.0 risk score was calculated for each patient.[12]

Invasive Coronary Angiography

All coronary angiograms were analyzed by an experienced interventional cardiologist (A.L.B, with >10 years of clinical experience in invasive coronary angiography performance and analysis). The following parameters were collected: medications before pPCI, infarct-related artery, Rentrop grade,[13] collateral circulation defined as Rentrop grade ≥2, and thrombolysis in MI flow grade before and after pPCI.

Transthoracic Echocardiography

Transthoracic echocardiography (TTE) was performed the third day after pPCI using a commercially available system (IE33 system; Philips Medical System, Andover, MA) in the parasternal (long- and short-axis) and apical (2-, 3-, and 4-chamber) views. Echocardiographic measurements were performed twice to evaluate the intraobserver variability by an expert reader (M.G. with >5 years of clinical experience in TTE performance and analysis, certified by the Italian Society of Echocardiography) blinded to patient clinical history.[14] In each patient, LV end-diastolic (LVEDV) and end-systolic (LVESV) volumes were measured on apical 4-chamber and 2-chamber views by Simpson method. In detail, volume measurements were based on tracings of the blood tissue interface in the apical 4- and 2-chamber views. At the mitral valve level, the contour was closed by connecting the 2 opposite sections of the mitral ring with a straight line. LV length was defined as the distance between the middle of this line and the most distant point of the LV contour. Accordingly, we measured LVEF with the following equation: (LVEDV−LVESV)/LVEDV. For LV-wall motion analysis by using the American Heart Association 17-segment model.[15]

Tricuspid annular plane systolic excursion was derived by placing the M-mode cursor along the lateral tricuspid annulus measuring the distance of movement on an apical 4-chamber view. By means of a simplified Bernoulli equation, velocity of the tricuspid regurgitant jet was used to calculate pulmonary artery systolic pressure (PASP) according to the following equation: 4×(velocity of the tricuspid regurgitant jet)^2+right atrial pressure. Another expert reader (M.P. with >10 years of clinical experience in TTE performance and analysis, certified by the Italian Society of Echocardiography) repeated TTE measurements to assess interobserver variability.

CMR Protocol and Analysis

All patients were studied with a 1.5-T scanner (Discovery MR450; GE Healthcare, Milwaukee, WI) using dedicated cardiac software, phased-array surface receiver coils, and ECG triggering the third day after pPCI. Data were transferred to a dedicated postprocessing workstation (Report Card 4.0; GE Healthcare) and evaluated twice by a reader with 5 years of experience in CMR (G.P. with level III European Society of Cardiology certification). The operator was blinded to patients' clinical history and TTE results. Another reader with 5 years of experience in CMR (S.M. with level III ESC certification) repeated the CMR data analysis for intraobserver and interobserver variability assessment.

Briefly, after acquisition of localizer images breath-hold steady-state free-precession cine CMR was performed in cardiac vertical and horizontal long-axis and short-axis orientations (echo time, 1.57 ms; 15 segments; repetition time, 46 ms without view sharing; slice thickness, 8 mm; field-of-view, 350×263 mm; and pixel size, 1.4×2.2 mm).

The following parameters were measured: LVEDV and LVESV, LVEF, LV mass, right ventricular end-diastolic volume, right ventricular end-systolic volume, and right ventricular ejection fraction. Breath-hold black-blood T2-weighted short inversion time inversion-recovery fast spin-echo (T2w) was performed with the same prescription of cine CMR images. T2w-image quality was assessed using a 4-grade score: (1) poor, (2) moderate, (3) good, and (4) excellent. Exams with a score 1 were excluded. In the LV myocardial wall supplied by the infarct-related artery, myocardial tissue with a signal intensity (SI) 2 SD above the mean SI of the noninfarcted myocardium was considered area at risk (AAR). The contours of automatically detected AAR were manually adapted to exclude increased SI from the adjacent blood pool (slow flow) or artifacts because of cardiac motion or respiration. MH was defined as a ≥1 mL hypointense area of myocardium with a mean SI below 2 SD of that of the periphery of the AAR. MH was considered part of myocardial edema for calculating AAR. Ten minutes after a contrast bolus of 0.1 mmol/kg of gadolinium-BOPTA (Multihance; Bracco, Milan, Italy), breath-hold contrast-enhanced segmented T1-weighted inversion-recovery gradient-echo images were acquired with the same prescriptions for cine images to detect late gadolinium enhancement (LGE). The inversion time was individually adjusted to null normal myocardium. On postcontrast imaging, LGE was considered present if SI of the hyperenhanced myocardium was >5 SD above the mean SI of remote myocardium[16] and was measured as absolute mass or as percentage of entire LV mass. Postcontrast images were used to detect MVO defined as a hypoenhanced region within the infarcted myocardium. When present, MVO was included in the hyperintense myocardium for LGE quantification. Finally, the MSI was calculated according to the following equation (AAR-LGE)/AAR and expressed as absolute number ranging between 0 and 1.

Follow-Up and End Points

Trained physicians performed follow-up with office visits and phone contact. If a patient missed the follow-up visit, telephone contact, review of outpatient clinic or hospital records was performed and patient's primary care physician or cardiologist were contacted. The follow-up interviewer was blinded to baseline, TTE, and CMR data. An independent clinical events committee (G.P., A.I.G., and M.P.) adjudicated all MACE events in a blinded fashion using standard, prospectively determined definitions (Data Supplement). The following end points were evaluated in case of simultaneous or multiple events (for the definition of each end point, see the Data Supplement): (1) unplanned revascularization, (2) planned revascularization, (3) nonfatal MI, (4) periprocedural MI, (5) implantable cardioverter defibrillator implantation, (6) congestive heart failure, and (7) cardiovascular death or aborted cardiovascular death.

The primary end point was defined as any MACE including congestive heart failure or cardiac death or aborted cardiac death. In patients experiencing simultaneous or multiple events, the one that met the definition of MACE was counted.

Statistical Analysis

Statistical analysis was performed with SPSS, version 23, software (SPSS, Inc, Chicago, IL) and R version 2.15.2. Continuous variables were expressed as mean±SD or median (25th–75th percentile) as appropriate and discrete variables as absolute numbers and percentages. Intraobserver and interobserver variability for evaluation of TTE and CMR variables were performed by intraclass correlation coefficients for continuous variables and κ test for categorical variables. Student-independent *t* or Mann–Whitney *U* tests were used as appropriate to compare continuous variables between patients with and without MACE. Comparisons between groups of discrete variables were performed by χ^2 or Fisher exact test if the expected cell count was <5. Univariable Cox proportional hazard models were used to assess the association between baseline covariates expressed as continuous and dichotomous variables and the composite end point (results presented as hazard ratio and 95% confidence interval). To identify the optimal threshold for MACE diagnosis, the Youden index was computed for TTE and CMR parameters showing the lowest *P* value at univariate analysis. Then, a stepwise selection procedure was applied ($P<0.05$ for entry) for CMR parameters, and based on the result of the multivariate model, the additive value of each variable was evaluated on the basis of the increase of χ^2 of the model to create a CMR score. Finally, the incremental value in predicting the composite end point by inclusion of TTE-LVEF and CMR score in addition to GRACE score was assessed by the χ^2 using Omnibus test of model coefficients and by the comparison of area under the receiver operating characteristic curve (C statistic). Reclassification of patients was determined using net reclassification improvement analysis for MACE and obtained by adding TTE-LVEF and CMR score to the model based on GRACE score. All tests were 2 tailed, and a *P* value <0.05 was considered statistically significant.

Results

Figure 1 shows the workflow of our study population. Thirty-five patients who met exclusion criteria were excluded. Further, 6 patients with poor image quality of T2w images were excluded. Of note, these 6 patients were similar in terms of baseline characteristics as compared with the overall population (5 men; mean age, 61.6±11 years; body mass index, 26.7±3.5; TTE-LVEF, 52±9.8%; CMR-LVEF, 50±10.2%), and no MACE were observed during the follow-up. Therefore, the final study population included 209 patients.

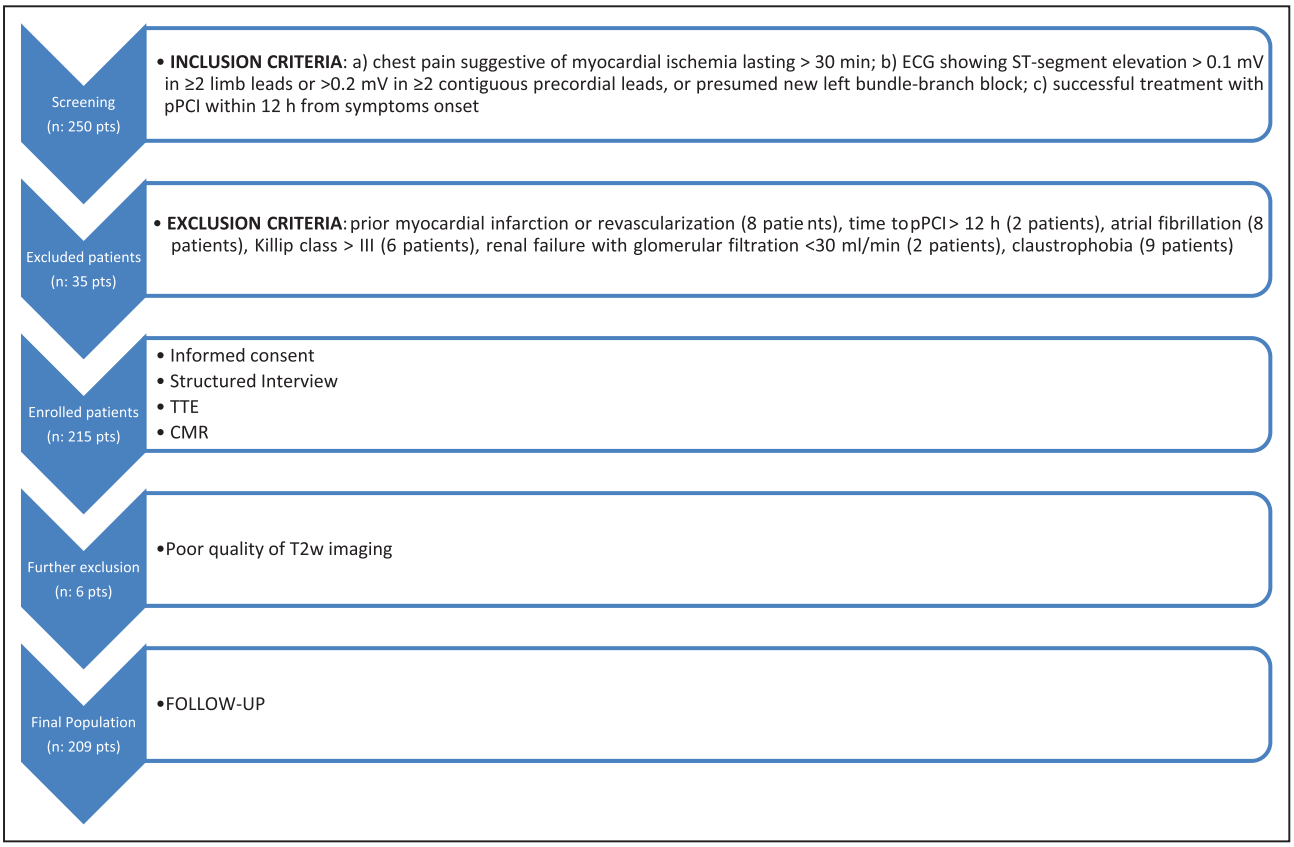

Figure 1. Study flow protocol. CMR indicates cardiac magnetic resonance; pPCI, primary percutaneous coronary intervention; and TTE, transthoracic echocardiography.

Baseline characteristics are listed in Table 1. Eighty-three (40%) patients had an anterior STEMI with a mean GRACE risk score of 10.6±6.5%.

TTE and CMR Findings

The mean LVEF at TTE and CMR was 51.5±10% and 49±10% (Table 2), respectively. CMR showed an AAR and LGE involving 26±20% and 17±15% of LV mass, respectively (Table 2). MVO and MH occurred in 70 (34%) and 34 (16%) patients (Table 2), respectively. Intraobserver and interobserver intraclass correlation for TTE-LVEF evaluation was 0.81 and 0.78, respectively. CMR intraobserver and interobserver intraclass correlation for LVEF, MSI, MVO, and MH detection were 0.88, 0.92, 0.89, 0.82 and 0.84, 0.86, 0.82, 0.75, respectively.

Major Adverse Cardiac Events

All patients were followed-up for an average of 2.5±1.2 years. No patient was lost to follow-up. Revascularization, nonfatal MI, implantable cardioverter defibrillator implantation, congestive heart failure, and cardiac death occurred in 44 (21%), 10 (5%), 10 (5%), 21 (10%), and 3 (1%) patients, respectively. In 34 patients with bystander disease, a further elective revascularization was performed within 45 days after the index angiogram according to local practice. No periprocedural MI occurred in this subset of patients. Further, 10 unplanned revascularizations were performed during the follow-up (4 patients for unstable angina and 6 patients for recurrent chest pain with a positive functional stress test). Among 10 patients with nonfatal MI, 2 were because of early stent thrombosis and 8 were secondary to progression or denovo coronary artery disease. Among 10 patients who experienced implantable cardioverter defibrillator implantation, no additional events were observed. Among 21 patients who experienced heart failure, 2 were implanted with implantable cardioverter defibrillator during follow-up. Finally, among the 3 patients who died, no events were observed before death. MACE occurred in 24 (11%) patients. Of note, no differences were found in terms of reinfarction distribution between the no-MACE and MACE groups (8 versus 2, P=0.38).

TTE and CMR Findings in Patients Without MACE Versus Patients With MACE

At follow-up, patients with MACE showed higher LVEDV, LVESV, and lower LVEF (P<0.01) with both imaging modalities as compared with those without MACE (Table 2). Additionally, patients with MACE showed similar AAR but higher LGE, MVO, and MH prevalence with lower MSI as compared with patients without MACE (P<0.001; Table 2). Of note, among patients with TTE-LVEF ≥55%, the prevalence of MACE was low compared with patients with TTE-LVEF <55% (3% versus 17%; P<0.01).

MACE and Survival Predictors

On univariable analysis, GRACE score, TTE-LVEF, CMR-LVEF, LGE, MVO, MH, and MVO were all predictors of MACE (Table 3). At Youden test analysis, among the TTE and CMR parameters, the best cut-off values of TTE-LVEF,

Table 1. Baseline Characteristics of Study Population

	All Patients	MACE	No MACE	
	n=209	n=24	n=185	*P* Value
Demographic characteristics				
Age, y	61.4±11.4	64.5±10.9	61.0±11.4	0.149
Sex, male	162 (78%)	16 (67%)	146(79%)	0.176
Body mass index, kg/m^2	26.5±3.7	26.9±4.7	26.5±3.6	0.551
Cardiovascular risk factors				
Hypertension	97 (46%)	16 (67%)	81 (44%)	0.034
Current or previous smoking	120 (57%)	9 (38%)	111 (60%)	0.036
Hyperlipidemia	68 (32%)	8 (33%)	60 (32%)	0.929
Diabetes mellitus	22 (10%)	4 (17%)	18 (10%)	0.297
Family history of CAD	74 (35%)	6 (25%)	68 (37%)	0.257
Chronic obstructive pulmonary disease	19 (9%)	3 (12%)	16 (9%)	0.530
Peripheral vascular disease	22 (11%)	4 (17%)	18 (10%)	0.297
Medication before hospital admission				
β-Blockers	18 (8%)	4 (17%)	14 (8%)	0.138
ACE/AR blockers	65 (31%)	9 (37%)	56 (30%)	0.482
Diuretic	23 (42%)	5 (21%)	18 (10%)	0.104
Calcium blockers	18 (9%)	2 (8%)	16 (9%)	0.953
Antithrombotic agents	20 (10%)	4 (17%)	16 (9%)	0.260
Dual antithrombotic agents	0 (0%)	0 (0%)	0 (0%)	…
Anticoagulant agents	1 (0.5%)	0 (0%)	1 (0.5%)	1.000
Nitrates	2 (1%)	1 (4%)	1 (0.5%)	0.218
Statin	19 (9%)	1 (4%)	18 (10%)	0.704
Amiodarone	1 (0.5%)	0 (0%)	1 (0.5%)	1.000
Propafenone	0 (0%)	0 (0%)	0 (0%)	…
Flecainide	1 (0.5%)	0 (0%)	1 (0.5%)	1.000
Sotalol	2 (1%)	0 (0%)	2 (1%)	0.61
Killip class >2	15 (7%)	3 (12%)	12 (6%)	0.389
Site of myocardial infarction (%)				0.274
Anterior myocardial infarction	83 (40)	12 (50)	70 (38)	
Nonanterior myocardial infarction	126 (60)	12 (50)	107 (62)	

(*Continued*)

Table 1. Continued

	All Patients	MACE	No MACE	
	n=209	n=24	n=185	*P* Value
Myocardial enzymes				
Peak CK-MB*, ng/mL	210.8±203.9	352.1±345.1	193.0±172.0	0.040
Peak troponin I†, ng/mL	67.9±87.8	108.1±109.9	62.7±83.4	0.017
Infarct-related artery				
LAD	90 (43%)	12 (50%)	78 (42%)	0.46
LCX	41 (20%)	6 (25%)	35 (19%)	0.48
RCA	78 (37%)	6 (25%)	72 (39%)	0.18
Pre-pPCI TIMI flow grade (%)				0.34
0/1	199 (95)	24 (100)	175 (94)	
2/3	10 (5)	0 (0)	10 (6)	
pPCI characteristics				
Bare metal stent	0 (0%)	0 (0%)	0 (0%)	1
Drug-eluting stent	209 (100%)	24 (100%)	185 (100%)	1
Stent number, per patient	1.66±0.71	1.72±0.70	1.61±0.64	0.382
Post-pPCI TIMI flow grade (%)				0.136
0/1	6 (3)	0 (0)	6 (3)	
2/3	203 (97)	24 (100)	179 (97)	
Rentrop grade	0.07±0.4	0.13±0.62	0.63±0.36	0.44
Glycoprotein IIb/IIIa inhibitors before pPCI	37 (18%)	2 (8%)	35 (19%)	0.209
Periprocedural complications				
Stroke	1 (0.5%)	0 (0%)	1 (0.5%)	0.78
Bleeding	10 (5%)	1 (4%)	9 (5%)	0.88
Renal insufficiency	12 (6%)	2 (8%)	10 (5%)	0.561
In-stent thrombosis	2 (1%)	0 (0%)	2 (1%)	0.718
GRACE risk score (% risk)	10.6±6.5	13.3±7.4	10.2±6.3	0.029
Medication at discharge				
β-Blockers	180 (86%)	21 (87%)	159 (85%)	0.836
ACE/AR blockers	159 (76%)	21 (87%)	138 (74%)	0.163
Diuretic	31 (15%)	12 (50%)	19 (10%)	<0.001
Ca-blockers	7 (3%)	0 (0%)	7 (4%)	1.000
Dual antiplatelet agents				
Clopidogrel+ aspirin	160 (76%)	16 (67%)	144 (78%)	0.22
Plasugrel+ aspirin	33 (16%)	5 (21%)	28 (15%)	0.47
Ticagrerol+ aspirin	16 (7%)	3 (12%)	13 (7%)	0.34
Anticoagulant agents	10 (5%)	2 (9%)	8 (4%)	0.292
Nitrates	15 (7%)	4 (17%)	11 (6%)	0.077
Statin	209 (100%)	24 (100%)	185 (100%)	…
Amiodarone	16 (50%)	7 (29%)	9 (5%)	0.001
Propafenone	1 (0.5%)	0 (0%)	1 (0.5%)	1.000
Flecainide	0 (0%)	0 (0%)	0 (0%)	…
Sotalol	0 (0%)	0 (0%)	0 (0%)	…

Continuous variables are expressed as mean±SD; discrete variables are expressed as absolute number and percentage. ACE indicates angiotensin-converting enzyme; AR, angiotensin receptor; CAD, coronary artery disease; GRACE, global registry of acute coronary events; LAD, left anterior descending artery; LCX, left circumflex coronary artery; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; RCA, right coronary artery; and TIMI, thrombolysis in myocardial infarction.

*CK-MB normal values, 0.6–6.3 ng/mL.

†TpI normal values, 0–0.05 ng/mL.

CMR-LVEF, MSI, and MVO to predict MACE were 46.7%, 37.5%, 0.4%, and 2.6% LV mass, respectively. Based on the global χ^2 (=169) of the multivariate analysis, including the CMR parameters, a risk score comprising 17 points was created assigning 12.5 points to MH, 2.5 points to MVO >2.6% LV mass, 1.7 points to CMR-LVEF <37.5%, and 0.3 points to MSI <0.4 (Table 4). The study population showed a mean CMR score of 2.17±4.83. At multivariable analysis, including GRACE score, TTE-LVEF ≤46.7% and CMR score weighted for 1 SD, only CMR score (hazard ratio, 1.867 [1.311–2.658]; *P*<0.001) was independently associated with MACE (Table 5). The 3 predictive models showed a C statistic of 0.63, 0.74, and 0.87, respectively. Figure 2 shows the comparison between the net reclassification improvement of each predictive model. Figure 3 shows the different CMR phenotypes and their relationship with outcome.

Discussion

In this single-center study, we found that an integrated model, including CMR findings, provided additional prognostic value as compared with clinical risk scores and TTE-derived LVEF.

Previous studies demonstrated that the estimation of LVEF is limited to stratify patients who experienced MACE. To this regard, in a series of 2130 patients with MI, Makikallio et al[17] found that 67% of cardiac deaths occurred in individuals with LVEF >35%. On the contrary, Huikuri et al,[18] showed that ventricular tachycardia occurred only in 8% of 312 patients with STEMI with reduced LVEF at 2-year follow-up. Therefore, further risk stratification of patients based on superior LVEF quantification and direct visualization of tissue damage is desirable. To this regard, several studies evaluated the prognostic value of CMR in post-STEMI patients. CMR imaging is a standardized technique

Table 2. TTE and CMR Baseline Characteristics

	All Patients	MACE	No MACE	
	n=209	n=24	n=185	*P* Value
TTE baseline characteristics				
LVEDV, mL/m²	50.1±13.4	57.5±15.6	49.1±12.8	0.003
LVESV, mL/m²	24.7±10.6	32.7±12.9	23.7±9.8	<0.001
LVEF, %	51.5±10.0	44.6±11.2	52.4±9.5	<0.001
TAPSE, mm	22.5±3.9	22.3±3.5	22.6±4.0	0.791
PASP, mm Hg	26.3±8.0	25.1±9.5	26.5±7.7	0.447
CMR baseline characteristics				
LVEDV, mL/m²	84.1±20.6	98.4±29.1	82.3±18.5	0.014
LVESV, mL/m²	43.9±19.3	62.3±27.6	41.5±16.6	0.001
LVEF, %	49.0±10.6	39.2±13.0	50.4±9.6	<0.001
LV mass, g	115.3±32.5	125.1±39.8	114.0±31.4	0.116
RVEDV, mL/m²	65.4±14.7	61.3±17.4	65.9±14.3	0.146
RVESV, mL/m²	26.2±9.8	25.9±12.3	26.2±9.5	0.919
RVEF, %	60.8±8.7	58.9±10.1	60.9±8.5	0.269
AAR, g	31.7±24.5	35.9±28.7	31.3±24.0	0.403
AAR, %	26±20	29±25	27±20	0.569
MH	34 (16%)	14 (58%)	20 (11%)	<0.001
LGE, g	19.9±18.3	28.7±15.7	19.0±18.4	0.024
LGE, % mass	17±15	26±15	16±14	0.002
MVO, prevalence	70 (34%)	15 (63%)	55 (30%)	0.001
MVO, % LV mass	0.89±1.5	3.0±2.5	0.6±1.0	<0.001
MSI	0.46±0.30	0.23±0.15	0.49±0.31	<0.001

Continuous variables are expressed as mean±SD; discrete variables are expressed as absolute numbers and percentages. AAR indicates area at risk; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MACE, major adverse cardiac events; MH, myocardial hemorrhage; MSI, myocardial salvage index; MVO, microvascular obstruction; PASP, pulmonary artery systolic pressure; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systolic volume; TAPSE, tricuspid annular plane systolic excursion; and TTE, transthoracic echocardiography.

with high spatial resolution that is independent of geometric assumptions and represents the standard modality for LV volume and LVEF measurements. Indeed, a significant discrepancy between CMR and TTE has been demonstrated, with the majority of studies indicating an overestimation of LVEF assessment by TTE.[10]

Wu et al[19] demonstrated that both infarct size and MVO predict long-term prognosis in 44 consecutive patients with acute infarction. However, beyond the small sample size of this preliminary experience, the technical limitation of the sequences used at that time allowed only 4 base-to-apex short-axis cross sections and required long and multiple breath holds. As a consequence, the role of MVO was evaluated as a dichotomous variable, and the rate of unevaluable cases was high. In a larger series, Hombach et al[20] showed that MVO predicts adverse remodeling, but also in this case, MVO was evaluated as a binary variable. Moreover, in both studies, the

Table 3. Univariable Predictors of Major Adverse Cardiac Events

	Univariate Analysis	
	HR (95% CI)	*P* Value
Demographic characteristics		
Age, y	1.028 (0.991–1.066)	0.136
Sex, male	1.693 (0.724–3.958)	0.224
Body mass index, kg/m²	1.018 (0.918–1.128)	0.740
Cardiovascular risk factors		
Hypertension	2.233 (0.954–5.228)	0.064
Current or previous smoking	0.435 (0.190–0.995)	0.059
Hyperlipidemia	0.959 (0.414–2.266)	0.942
Diabetes mellitus	1.542 (0.525–4.529)	0.431
Family history of CAD	0.582 (0.231–1.465)	0.250
STEMI characteristics		
Killip class ≥2	2.183 (0.649–7.340)	0.207
Anterior myocardial infarction	1.919 (0.855–4.305)	0.114
Peak CK-MB, mg/dL	1.002 (1.001–1.004)	0.001
Peak troponin I, ng/dL	1.003 (1.000–1.006)	0.040
Rentrop Grade ≥2	2.591 (0.346–19.399)	0.354
Glycoprotein IIb/IIIa inhibitors before PCI	0.438 (0.103–1.871)	0.265
GRACE score (% risk)	1.037 (0.999–1.076)	0.050
Medications		
β-Blockers	2.876 (0.977–8.469)	0.055
ACE/AR blockers	1.345 (0.589–3.075)	0.482
Diuretic	2.356 (0.880–6.312)	0.088
Calcium blockers	0.781 (0.181–3.368)	0.740
Dual antiplatelet agents	0.821 (0.256–2.132)	0.781
Antithrombotic agents	1.759 (0.599–5.168)	0.304
Statin	0.405 (0.055–2.998)	0.376
TTE		
LVEDV, mL/m²	1.035 (1.013–1.058)	0.002
LVESV, mL/m²	1.036 (1.018–1.054)	<0.001
LVEF, %	0.941 (0.913–0.970)	<0.001
LVEF<46.6%	5.501 (2.391–12.657)	<0.001
TAPSE, mm	0.980 (0.884–1.087)	0.707
PAP, mm Hg	0.978 (0.926–1.033)	0.432
CMR		
LVEDV, mL/m²	1.021 (1.010–1.032)	<0.001
LVESV, mL/m²	1.025 (1.015–1.035)	<0.001
LVEF, %	0.921 (0.891–0.952)	<0.001
LVEF<37.5%	9.219 (4.104–20.712)	<0.001
LV mass, g	1.009 (0.997–1.021)	0.142
RVEDV, mL/m²	0.977 (0.948–1.006)	0.121
RVESV, mL/m²	0.998 (0.956–1.041)	0.917

(*Continued*)

Table 3. Continued

	Univariate Analysis	
	HR (95% CI)	*P* Value
RVEF, %	0.974 (0.931–1.018)	0.247
AAR, g	1.000 (0.982–1.018)	0.995
AAR, %	1.129 (0.125–10.187)	0.914
MH	8.040 (3.599–17.960)	<0.001
LGE mass, g	1.019 (1.002–1.037)	0.028
LGE mass, %	21.707 (2.496–188.761)	0.005
LGE>30%	5.473 (2.402–12.473)	<0.001
MVO, presence	4.242 (1.813–9.923)	0.001
MVO, g	1.936 (1.622–2.311)	<0.001
MVO>2.6% LV mass	17.101 (7.212–40.552)	<0.001
MSI	0.037 (0.006–0.210)	<0.001
MSI<0.40	29.717 (4.011–220.158)	0.001

AAR indicates area at risk; ACE, angiotensin-converting enzyme; AR, angiotensin receptor; CAD, coronary artery disease; CI, confidence interval; CMR, cardiac magnetic resonance; GRACE, global registry of acute coronary events; HR, hazard ratio; LGE, late gadolinium enhancement; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; HR, hazard ratio; MH, myocardial hemorrhage; MSI, myocardial salvage index; MVO, microvascular obstruction; PAP, pulmonary artery pressure; PCI, percutaneous coronary intervention; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; STEMI, ST-elevation myocardial infarction; TAPSE, tricuspid annular plane systolic excursion; and TTE, transthoracic echocardiography.

combined end points included cardiac events not directly correlated with MI, such as reinfarction, elective revascularization, or unstable angina.

More recently, in a study of 278 patients with STEMI, De Waha et al[21] demonstrated that a CMR model including LVEF, infarct size, MVO, and MSI added incremental prognostic value above traditional outcome markers alone. Eitel et al[4] enrolled 738 patients with STEMI from 8 centers and showed that infarct size and MVO provided incremental prognostic value above clinical risk assessment plus LVEF evaluation with a c-index increase from 0.761 to 0.801 (P=0.036). However, despite the latter studies having used more recent CMR technology, they were limited by the lack of information on the additional value of CMR findings compared with standard clinical scores and TTE.

Similar to MVO, MH is an index of microvascular pathology that may have clinical value. Carrick et al,[8] using T2 mapping instead of T2-weighted images, detected MH in 41% of 286 consecutive patients with STEMI and demonstrated that this index was more closely associated with adverse outcomes than MVO.

Our study has several strengths compared with previous articles. First, few reports have tested the additional prognostic value of microvascular function indices detectable by CMR compared with the integrated use of GRACE score and TTE-assessed LVEF. Second, different from other studies, in our prognostic model we included CMR parameters, such as MVO, as a continuous rather than dichotomous variable. Third, to consider prespecified adverse health outcomes that are pathophysiologically linked with STEMI, MACE included congestive heart failure and cardiac death. This may explain the low number of MACE events but further reinforces the prognostic value of CMR indices in the prediction of hard clinical events. Fourth, a committee adjudicated all end points. Finally, the ratio between anterior and inferior STEMI was more balanced compared with previous studies in which anterior STEMI were the majority.

Table 4. Stepwise Inclusion Procedure for the Multivariate Analysis of Cardiac Magnetic Resonance Parameters

	HR (95% CI)	*P* Value	χ^2		
			Step	Global Model	*P* Value
Step 1					
MH	1.395 (1.219–1.597)	<0.001	125.936	125.936	<0.001
Step 2					
MH	1.228 (1.067–1.412)	0.004			
MVO>2.60% LV mass	13.912 (5.700–33.953)	<0.001	23.046	148.982	<0.001
Step 3					
MH	1.287 (1.109–1.493)	0.001			
MVO>2.6% LV mass	8.619 (3.341–22.238)	<0.001			
LVEF<37.5%	5.533 (2.298–13.325)	<0.001	17.756	166.738	<0.001
Step 4					
MH	1.259 (1.086–1.460)	0.002			
MVO>2.6% LV mass	5.513 (2.151–14.125)	<0.001			
LVEF<37.5%	3.796 (1.609–8.959)	0.002			
MSI<0.40	10.618 (1.332–84.660)	0.026	2.685	169.423	0.003

CI indicates confidence interval; HR, hazard ratio; LV, left ventricle; LVEF, left ventricular ejection fraction; MH, myocardial hemorrhage; MSI, myocardial salvage index; MVO, microvascular obstruction.

Table 5. Multivariable Predictors of Major Adverse Cardiac Events

	HR (95% CI)	*P* Value
GRACE score*	1.047 (0.988–1.09)	0.119
TTE-LVEF<46.6%	2.247 (0.807–6.258)	0.121
CMR Score*†	1.867 (1.311–2.658)	0.001

CI indicates confidence interval; CMR, cardiac magnetic resonance; GRACE, global registry of acute coronary events; HR, hazard ratio; LV, left ventricle; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; MH, myocardial hemorrhage; MSI, myocardial salvage index; MVO, microvascular obstruction; and TTE, transthoracic echocardiography.

*Hazard ratio is calculated per score increase.

†CMR score per 1-SD increase (4.83): 12.5 points to MH, 2.5 points to MVO >2.6% LV mass; 1.7 points to CMR-LVEF <37.5%, and 0.3 points to MSI <0.4.

Our findings may have several clinical implications. First, the low rate of MACE in patients with normal TTE-LVEF after STEMI suggests performing CMR mainly in patients with STEMI showing LV dysfunction as detected by TTE. In this setting, LV geometry reclassification by CMR after STEMI[22] with the addition of tissue characterization, including MSI, MVO, and MH, may be used to identify STEMI survivors who might benefit from more intensive drug therapies and novel strategies for prevention of LV remodeling. In a nationwide registry, Herttua et al[23] demonstrated that nonadherence to statins led to a 1.8-fold increase in MACE, whose short- and long-term rate of adverse events was associated with a stepwise decline in adherence. Prolonged treatment with glycoprotein IIb/IIIa inhibitors[24] and new approaches with stem cells[25] may counteract MVO providing clinical benefit in patients with STEMI.

Study Limitations

Several limitations of our study should be acknowledged. First, the small sample size and the single-center nature of the study limit the robustness of results. For this reason, to split the study population in a derivation and validation cohort is not feasible. Second, MACE rate was low and, therefore, our predictive model may have experienced overfitting. Third, AAR and MH were detected by dark blood T2-weighted images that may have been hampered by imaging artifacts. On the contrary, both T1 and T2 mapping may overcome this limitation.[26] Verhaert et al[27] showed that recent ischemic

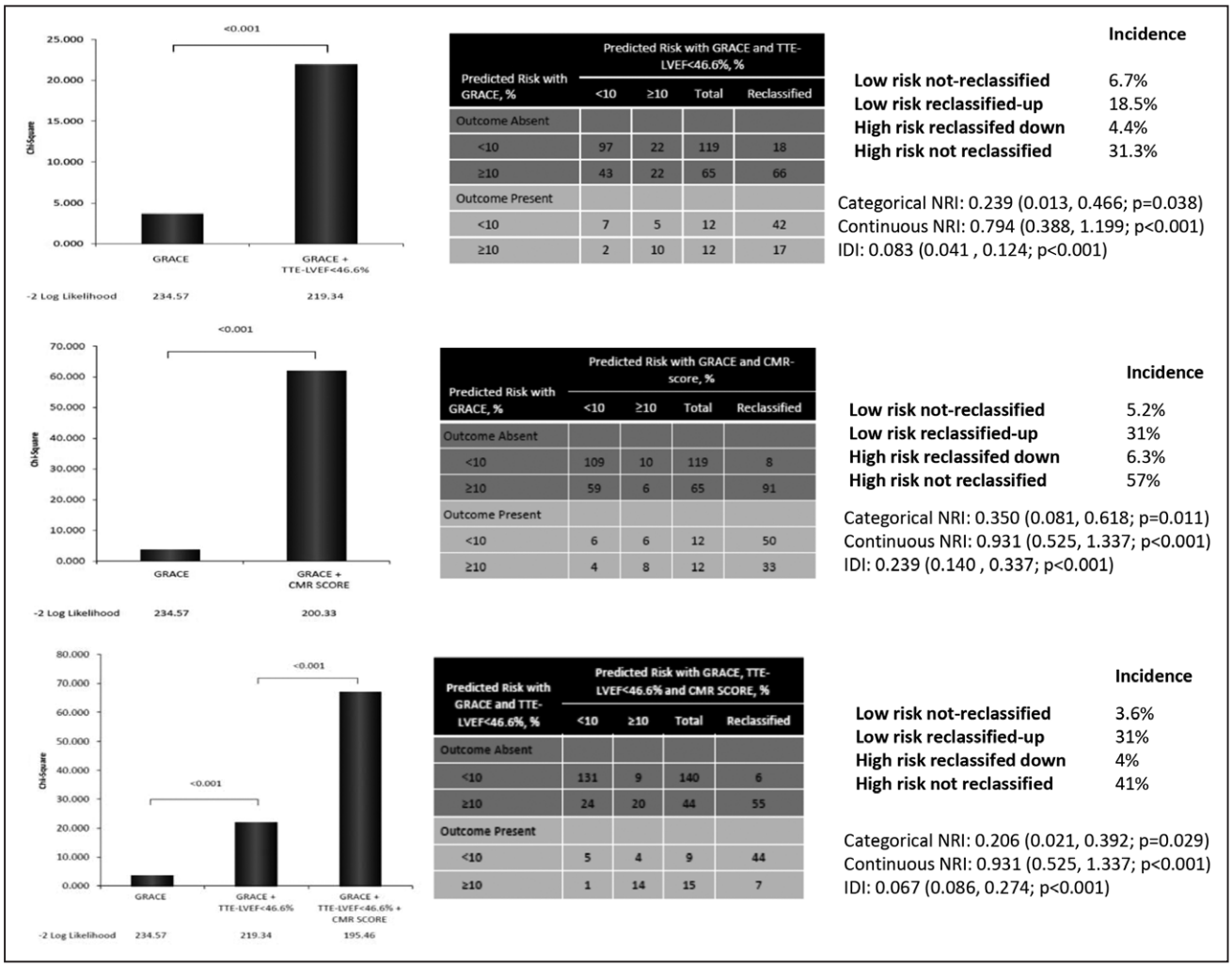

Figure 2. Incremental value of cardiac magnetic resonance (CMR) score in predicting major adverse cardiac events when compared with models including global registry of acute coronary events (GRACE) score in combination with transthoracic echocardiography (TTE)–left ventricular ejection fraction (LVEF). IDI indicates integrated discrimination improvement; and NRI, net reclassification improvement.

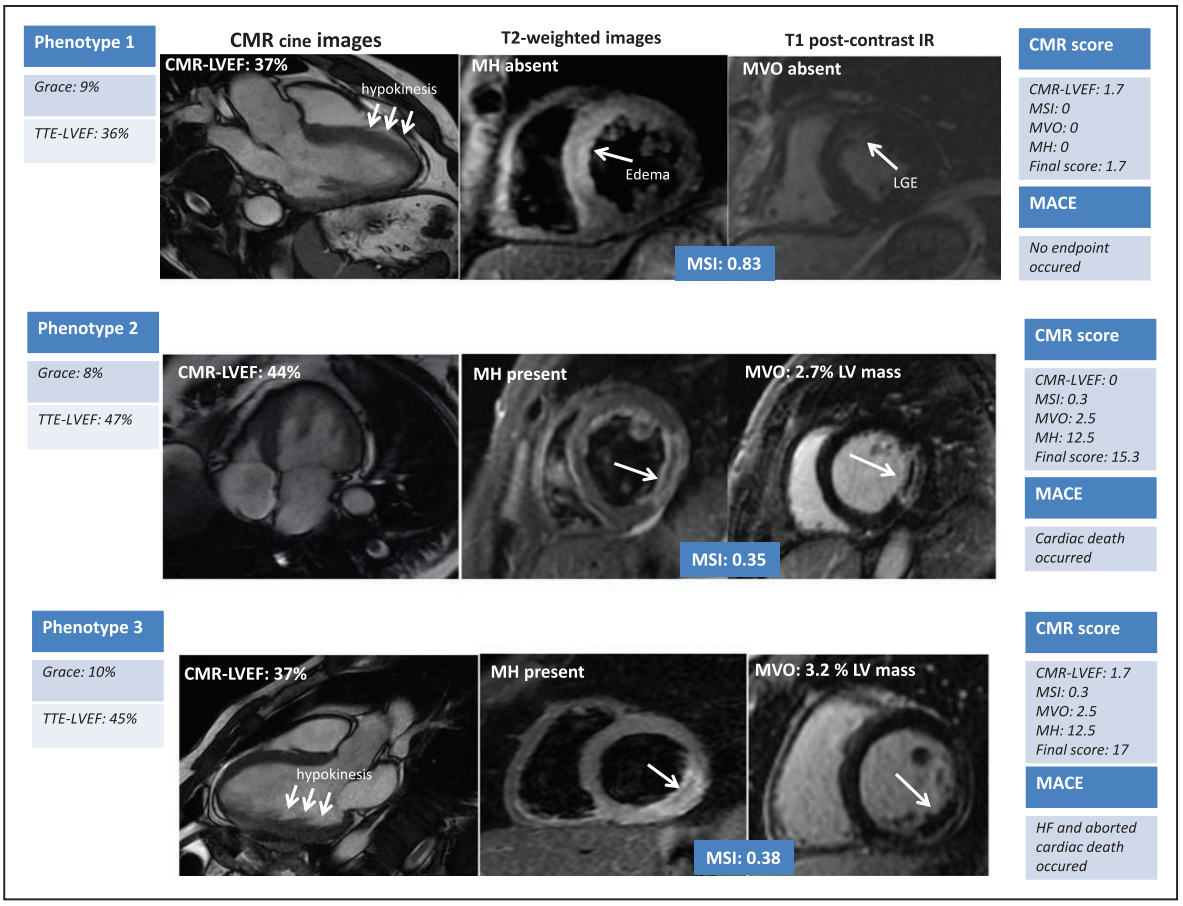

Figure 3. Three different cardiac magnetic resonance (CMR) phenotypes are shown. Phenotype 1: patient with severe left ventricular (LV) dysfunction with both imaging modalities, high myocardial salvage index (MSI), and no evidence of myocardial hemorrhage (MH) and microvascular obstruction (MVO) who did not experience major adverse cardiac events (MACE); phenotype 2: patient with moderate LV dysfunction with both imaging modalities, low MSI, and evidence of both MH and MVO who died; phenotype 3: patient with moderate LV dysfunction with transthoracic echocardiography (TTE) who was reclassified as having severe LV ejection fraction (LVEF) reduction by CMR. Moreover, low MSI and presence of both MH and MVO were detected by CMR. The patient experienced HF and aborted cardiac death. HF indicates heart failure; IR, inversion recovery; and LGE, late gadolinium enhancement.

injury was quantitatively differentiated from remote myocardium by its higher T2 value in 96% of patients enrolled in the study compared with 67% by black-blood T2-weighted imaging, highlighting the superiority of quantitative T2 mapping. Several reasons can explain the limited robustness of black-blood T2-weighted imaging, such as surface coil intensity inhomogeneity leading to variability in myocardial signal, subendocardial bright signal artifact caused by stagnant blood, cardiac motion leading to reduced myocardial signal, and the subjective nature of qualitative T2-weighted image analysis.[28] However, black-blood T2-weighted imaging is the most widely used technique in clinical practice and, therefore, more clinically applicable compared with a model including T2 mapping.

Of note, we only included patients with CMR exams showing adequate T2-weighted images. Fourth, breath-hold contrast-enhanced segmented T1-weighted inversion-recovery gradient-echo images were used to detect scar rather than phase-sensitive inversion-recovery sequences. Fifth, we excluded high-risk patients, including patients with advanced Killip class at presentation who may have low compliance to CMR. Indeed, it is difficult to avoid CMR dropout of STEMI patients, a limitation currently shared by all CMR studies in this clinical setting. However, Larsen et al[29] found that higher baseline risk in the dropout group did not affect clinical outcomes.

Sixth, we did not include promising prognostic markers, such as brain natriuretic peptide and soluble ST2, in our model. Indeed several studies[30,31] have shown that both markers were independently associated with adverse prognosis beyond other biomarkers, such as cardiac troponin. Whether CMR findings provide additional prognostic information compared with these novel biomarkers is still unknown, and further studies in this area are warranted.

Finally, whether all patients who experience STEMI or a subgroup of STEMI individuals should undergo CMR cannot be evaluated in this study because of the small sample size and low number of MACE.

Conclusions

We found that a CMR score based on LVEF estimation, MSI, and presence and amount of MVO and MH provides incremental prognostic value compared with standard prognostic stratification, including GRACE score and TTE-LVEF. Future

prospective multicenter studies with larger sample sizes are warranted because CMR parameters may impact the management of patients with STEMI.

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CLINICAL PERSPECTIVE

Although primary percutaneous coronary intervention has significantly reduced cardiovascular mortality of patients with ST-segment–elevation myocardial infarction, in some specific settings it may be associated with poor recovery of left ventricular (LV) function and unfavorable remodeling, which are major predictors of morbidity and mortality. Typically, risk stratification after ST-segment–elevation myocardial infarction is performed using electrocardiography, laboratory angiography and transthoracic echocardiography–LV ejection fraction measurement, and proven risk scores, such as global registry of acute coronary events score. More recently, cardiac magnetic resonance (CMR) has emerged as the gold standard technique for the measurement of the amount of saved myocardium as expressed by myocardial salvage index, microvascular obstruction, and myocardial hemorrhage. In this single-center study, we found that an integrated model, including CMR findings, provided additional prognostic value as compared with clinical risk scores and transthoracic echocardiography–derived LV ejection fraction. More specifically, a CMR score assigning 12.5 points to myocardial hemorrhage, 2.5 points to microvascular obstruction >2.6% LV mass, 1.7 points to CMR-LV ejection fraction <37.5%, and 0.3 points to myocardial salvage index <0.4 showed a significant improved C statistic to predict major adverse cardiac events (0.87) as compared with the global registry of acute coronary events score alone (0.63) or in combination with transthoracic echocardiography–LV ejection fraction (0.74). These data are a further demonstration of the additional value of CMR in the risk stratification of ST-segment-elevation myocardial infarction patients as compared with standard of care. Future prospective multicenter studies with larger sample sizes are warranted because CMR parameters may impact the management of patients with ST-segment–elevation myocardial infarction.

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Cardiovascular Imaging

Prognostic Stratification of Patients With ST-Segment–Elevation Myocardial Infarction (PROSPECT): A Cardiac Magnetic Resonance Study

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SUPPLEMENTAL MATERIAL

SUPPLEMENTAL METHODS

Outcome Definition

a) unplanned revascularization: any non-elective PCI or cardiac surgery required in order to minimize the chance of further clinical deterioration such as worsening sudden chest pain, congestive heart failure, acute myocardial infarction, unstable angina requiring intravenous nitroglycerin or rest angina;

b) planned revascularization: any revascularization that does not meet the definition for unplanned revascularization

c) non-fatal MI, defined as a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile upper reference limit (URL), and with at least one of the following: angina, ischemic ECG changes (e.g. new ST-T changes or left bundle branch block), pathologic Q waves, or imaging evidence of new loss of viable myocardium or regional wall motion abnormality.

d) peri-procedural MI was defined as serum CK-MB >3 times or >5 times the URL after PCI or bypass grafting, respectively;

e) implantable cardioverter defibrillator (ICD) implantation;

f) congestive heart failure defined as onset of typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that are accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality"

g) cardiovascular death or aborted cardiac death due to immediate cardiac causes (e.g. MI, heart failure, fatal arrhythmia) or vascular causes (e.g. cerebrovascular disease, pulmonary embolism, aortic rupture or dissection or other vascular causes). Unwitnessed death and death of unknown causes were classified as cardiovascular death.