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iREVIEWS

STATE-OF-THE-ART PAPERS

Prognostic Value of Microvascular Obstruction and Infarct Size, as Measured by CMR in STEMI Patients

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ABSTRACT

The aim of this study was to evaluate the value of microvascular obstruction (MO) and infarct size as a percentage of left ventricular mass (IS%LV), as measured by contrast-enhanced cardiac magnetic resonance, in predicting major cardiovascular adverse events (MACE) at 2 years in patients with ST-segment elevation myocardial infarction reperfused by primary percutaneous coronary intervention. Individual data from 1,025 patients were entered into the pooled analysis. MO was associated with the occurrence of MACE, defined as a composite of cardiac death, congestive heart failure, and myocardial re-infarction (adjusted hazard ratio: 3.74; 95% confidence interval: 2.21 to 6.34). IS% LV ≥25% was not associated with MACE (adjusted hazard ratio: 0.90; 95% confidence interval: 0.59 to 1.37). The authors conclude that MO is an independent predictor of MACE and cardiac death, whereas IS%LV is not independently associated with MACE. (J Am Coll Cardiol Img 2014;7:930–9) © 2014 by the American College of Cardiology Foundation.

In the setting of ST-segment elevation myocardial infarction (STEMI), primary percutaneous coronary intervention (pPCI) is the preferred reperfusion strategy and a cornerstone in the treatment of patients with STEMI (1). A substantial proportion of STEMI patients display a "no-reflow" phenomenon despite successful epicardial reperfusion (2). This phenomenon is characterized by either absent

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or inadequate myocardial tissue reperfusion despite successful reopening of the infarct-related artery (3).

No-reflow is thought to be a consequence of microvascular obstruction (MO), caused by numerous components, including distal atherothrombotic embolization, ischemic injury, reperfusion injury, and susceptibility of the coronary microcirculation to injury (2). No-reflow can be assessed with cine coronary angiography, ST-segment resolution measured on electrocardiography, and noninvasive imaging techniques such as myocardial contrast echocardiography and contrast-enhanced cardiac magnetic resonance (CE-CMR).

SEE PAGE 953

In patients with STEMI, the presence and magnitude of MO are visualized by CE-CMR, with accurate and reproducible measurements of left ventricular ejection fraction (LVEF) and infarct size (IS) (4). Compared with myocardial segments without MO, segments with MO are more likely to demonstrate wall thinning and are less likely to demonstrate improvement of segmental wall thickening during follow-up study (5). Moreover, MO is an important predictor of global functional recovery after STEMI (6). Several studies suggest that MO is associated with worse prognosis (7–13). However, previous studies in this regard have been hampered by a limited number of patients, evaluated a combined clinical endpoint, and were single-center studies (7–13). Furthermore, although intuitively IS measured within 2 weeks after STEMI is an important independent determinant of outcome, there is conflicting evidence to support its independent predictive value for major adverse cardiac events (MACE) (9,12,14).

We performed a meta-analysis of individual patient data to evaluate the hypotheses that MO and IS expressed as a percentage of left ventricular (LV) mass (IS%LV) are independent predictors of MACE and cardiac death in patients with STEMI undergoing pPCI.

METHODS

STUDY SELECTION. The MEDLINE database was searched for citations of in-human studies published in English from January 2004 to April 2012, using the following terms: microcirculation(MESH), magnetic resonance imaging, myocardial infarction, and microvascular obstruction. A total of 134 publications were identified. Related studies from the reference lists of retrieved papers, and the bibliographies of the coauthors, were included. Observational studies in STEMI patients who underwent pPCI within 12 h of symptom onset, followed by CE-CMR within 14 days, were eligible for inclusion. Studies in >60 patients were invited to participate. In the case of experimental studies, data from only the placebo groups were included in the analysis.

DATA COLLECTION. Requested variables consisting of baseline characteristics, variables used in the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) risk score (15), the Zwolle primary PCI index (16), and the Thrombolysis in Myocardial Infarction (TIMI) risk score (17); baseline CE-CMR variables; and clinical outcomes (MACE) were mentioned beforehand in a protocol, along with study rationale and study design. The protocol was sent to participating centers. Previous approval of the individual study design by a local ethics committee was necessary for participation. Datasets from participating centers were merged by the coordinating center (Erasmus Medical Center, Rotterdam, the Netherlands). Queries were sent to the primary investigators in cases in which further data and clarification were needed.

DEFINITIONS/CE-CMR. *STEMI* was defined on the basis of the definitions used by the authors of the primary publications (8–13,18,19). All clinical and angiographic variables were study based. Angiographic left main coronary artery lesions were categorized as left anterior descending artery lesions. Imaging was performed in different centers on 1.5-T scanners from different vendors (Online Table 1). The scanning protocols, CE-CMR parameters, and data analysis have been described in the included studies (8–13,18,19). All investigators but one used a steady-state, free-precession sequence for cine CMR (Online Table 1). LV end-diastolic volume, LV end-systolic volume, and LVEF were short-axis based, as provided by the investigators. If LV end-diastolic and end-systolic volume were not indexed, the Mosteller equation was used to adjust these for body surface area. Late gadolinium enhancement was performed by the different centers by use of a (phase-sensitive) inversion recovery gradient echo sequence. *MO,* as visualized with late gadolinium enhancement, was defined as any region of hypoenhancement within the hyperenhanced area. IS was determined on short-axis images. IS was expressed

ABBREVIATIONS AND ACRONYMS

CE-CMR = contrast-enhanced cardiac magnetic resonance

IS = infarct size

LV = left ventricular

MACE = major adverse cardiac events

MO = microvascular obstruction

pPCI = primary percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

both in grams and as a percentage of the LV mass (IS% LV). IS%LV was determined by manual or automated tracing of the infarct border. In patients with MO, regions of hypoenhancement were included in the IS. In 2 studies, patients with prior infarction were included (8,12). In patients with prior myocardial infarction, only the region indicative of acute infarction (8), corresponding with edema in T_2-weighted imaging (12), was measured in delayed-enhancement images.

ENDPOINTS. The primary endpoint was the prevalence of *major adverse cardiovascular events* (MACE), defined as a composite of cardiac death, myocardial re-infarction, and new congestive heart failure, at 2 years. The secondary endpoint was cardiac mortality. *Congestive heart failure* was defined as any symptom of cardiac decompensation requiring hospitalization. The individual study investigators provided previously defined and used events (Online Table 1). If a patient experienced more than one event, the first event was chosen for the combined clinical endpoint. Patients were considered at risk from the time of admission for the treatment of STEMI.

STATISTICAL ANALYSIS. Continuous data with normal distribution are presented as mean ± SD. Non-normally distributed variables are reported as median with corresponding interquartile range (IQR). Categorical variables are represented by frequencies and percentages. Patients were categorized according to the presence of MACE. Differences in continuous variables between categories of patients were studied by the unpaired Student *t* test or the Mann-Whitney *U* test (in cases of non-normal distribution). Proportions were compared using the chi-square test or the Fisher exact test, where applicable. The incidences of the primary and secondary endpoints are reported as Kaplan-Meier estimates at a follow-up of 2 years. As small infarcts and minor decreases in LVEF might not have an impact on outcome, the relationship between these variables on outcome was investigated by plotting IS%LV and LVEF against event-free survival. A log-rank test was used to evaluate differences in freedom from study endpoints between categories of patients. Univariate and multivariate Cox regression analyses, stratified by study, were used to determine the prognostic value of MO, IS%LV, and LVEF with respect to the primary and secondary endpoints. Predictors of cardiac death and MACE in published reports—namely, age (>65 years); sex (female); the presence of diabetes, hypertension, anterior myocardial infarction (culprit lesion in the left anterior descending artery), or multivessel disease; TIMI flow grade after PCI (reference: TIMI flow grade after PCI of 0 or 1); and CMR-based LVEF (12,16,17)—were entered into the univariate regression model, along with MO, IS%LV, LV end-diastolic volume index, and LV end-systolic volume index (9). Variables that resulted in a p value of <0.10 in the univariate Cox model were entered into the multivariate Cox proportional hazards model, with respect to multicollinearity. LV end-systolic volume index was not entered into the multivariate model due to a collinear relation with LVEF (Pearson correlation: -0.774). We applied the method of backward selection; all variables with a p value of <0.05 remained. The proportional hazards assumption was validated graphically. In cases of missing data (the requested variable data were unavailable in >5.0% of the cohort), these variables were not taken into account in the regression analysis (e.g., time to reperfusion and Killip class). We report unadjusted hazard ratios (HRs) and adjusted hazard ratios (aHRs), 95% confidence intervals (CIs), and p values. We determined the *c*-index (20) to report on the performance of the models to discriminate between patients with and without the study endpoints. The incremental value of IS%LV, LVEF, and MO was compared with that from a model with established clinical variables. *c*-Index models were developed on the basis of multivariate Cox models. We applied, for these models, a backward variable-selection method; all

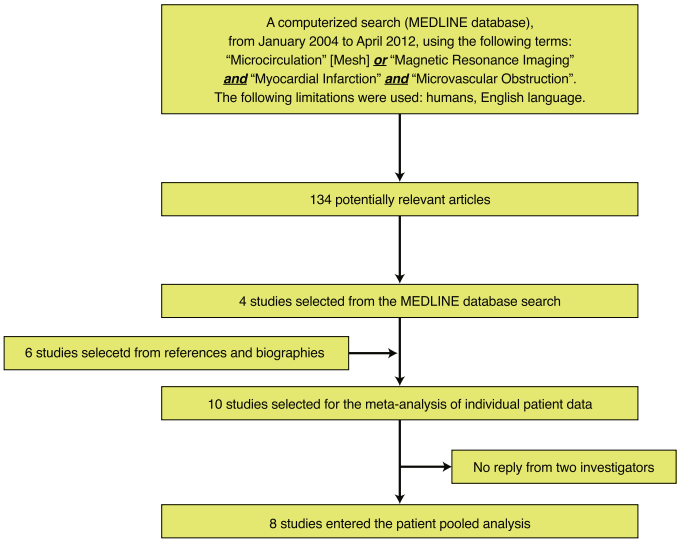

FIGURE 1 Computerized Search

A computerized literature search of citations was performed.

variables with a p value of <0.05 remained. Two-sided probability values with an α level of ≤0.05 were considered to be statistically significant. Statistical analysis was performed using the statistical packages IBM SPSS Statistics version 20.0.01 (IBM SPSS Statistics, IBM Corporation, Armonk, New York) and SAS version 9.2 (SAS Institute Inc., Cary, North Carolina). Kaplan-Meier curves were drawn with GraphPad Prism version 4.00 (GraphPad Software Inc., San Diego, California).

RESULTS

PATIENT CHARACTERISTICS. We identified 10 eligible observational and experimental studies. The principal investigators of these studies were invited to participate in this collaborative analysis. Eight of 10 investigators provided individual patient data (**Figure 1**). In this pooled analysis, 2 studies with 193 potentially eligible patients were not included due to investigator unresponsiveness (14,21).

The individual study characteristics are summarized in Online Table 1. The inclusion procedure is shown in **Figure 2**. Of 1,488 AMI patients, 150 patients (10.1%) were unable to have a CMR examination, and 313 patients were excluded due to other reasons (**Figure 2**). Consequently, data from 1,025 STEMI patients who underwent reperfusion by pPCI between April 9, 1999 and September 28, 2008 were included in the patient pooled analysis. The mean age at inclusion was 59.7 ± 12.7 years, and 77.7% of the cohort were men (n = 796). The median time to reperfusion was 3.3 h (IQR: 2.1 to 4.9 h). CE-CMR was performed within a median of 4 days (IQR: 2 to 6 days) after the occurrence of STEMI. MO was present in 56.3% of patients in the overall cohort. Of patients with TIMI flow grade after PCI of 3 (927 of 1,019 [91.0%]), MO was present in 54.9%. The mean LVEF was 48.0 ± 12.3%. Of the entire cohort, 14.7% had a severely depressed (<35%) LVEF. The baseline characteristics of patients with MACE and patients without MACE are compared in **Table 1**. The median duration of available follow-up was 12 months (IQR: 4 to 21 months).

PREDICTORS OF MACE. The composite endpoint occurred in 130 patients within 2 years of follow-up. In 9 patients, an event occurred between the index event and the CE-CMR study. Cardiac death occurred in 25 patients; myocardial re-infarction, in 47 patients; and congestive heart failure, in 58 patients. The Kaplan-Meier estimate of freedom from MACE at 2 years was 76.5% in patients with MO versus 93.0% in patients without MO (p < 0.001).

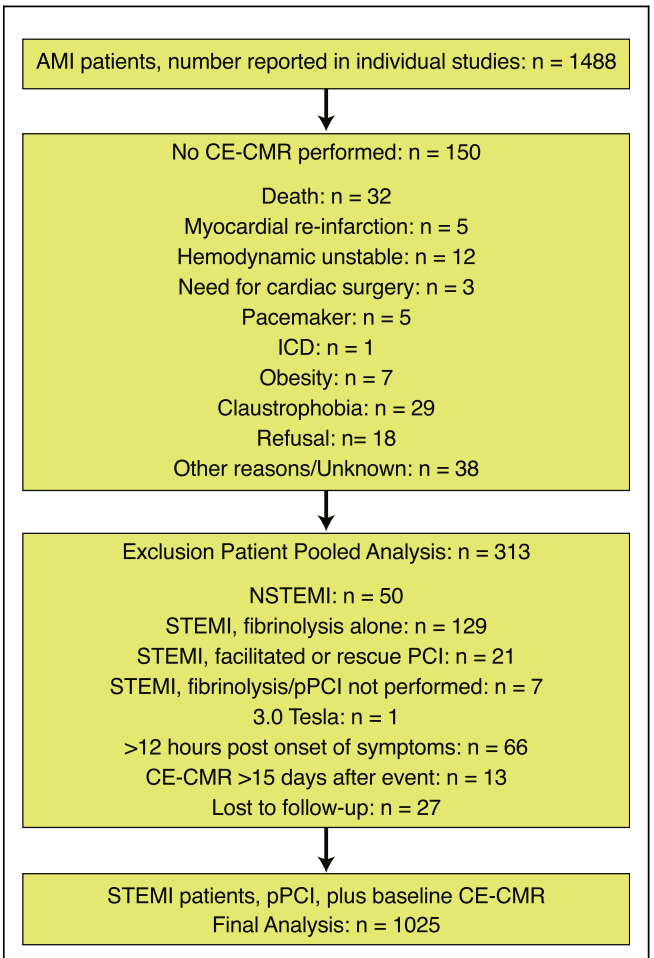

FIGURE 2 Study Flow Chart

AMI = acute myocardial infarction; CE-CMR = contrast-enhanced cardiac magnetic resonance; ICD = implantable cardioverter-defibrillator; NSTEMI = non–ST-segment elevation myocardial infarction; pPCI = primary percutaneous coronary intervention.

For both LVEF and IS%LV, nonlinear relationships were observed (**Figures 3 and 4**). Therefore, these 2 variables were categorized using tertiles, which provides a large number of events per category while respecting nonlinearity. For LVEF, the first tertile (cutoff: 42.7%, simplified to ≤40%, used in the CADILLAC risk score [15]) was compared to the reference group (LVEF >40%). For IS%LV, the last tertile (cutoff: 24.7%, simplified to ≥25%) was compared to the reference group (IS%LV <25%). The Kaplan-Meier estimate of freedom from MACE at 2 years was 74.3% in patients with IS%LV ≥25% versus 87.4% in patients with IS%LV <25% (p < 0.001). Kaplan-Meier curves for MACE by MO and IS%LV in the entire cohort, and grouped by MO and

TABLE 1 Patient Characteristics

	Entire Cohort (n = 1,025)	MACE (n = 130)	No MACE (n = 895)	p Value
Demographics				
Age, yrs	59.7 ± 12.7	61.8 ± 13.3	59.4 ± 12.6	0.04
Male	796 (77.7)	94 (72.3)	702 (78.4)	0.12
BMI, kg/m^2*	27.0 ± 3.8	27.2 ± 4.1	27.0 ± 3.7	0.60
CV risk factors				
Hypertension	530/1,012 (52.4)	70/128 (54.7)	460/884 (52.0)	0.58
Hypercholesterolemia	380/1,010 (37.6)	57/128 (44.5)	323/882 (36.6)	0.08
Current or prior smoking	507/1,023 (49.6)	54/130 (41.5)	455/893 (51.0)	0.02
Family history of MI†	278/937 (29.7)	37/121 (30.6)	241/816 (29.5)	0.81
Diabetes	176/1,012 (17.4)	35/128 (27.3)	141/884 (16.0)	<0.001
Prior MI‡	47/948 (5.0)	12/123 (9.8)	35/825 (4.2)	0.009
Prior CABG§	10/947 (1.1)	2/123 (1.6)	8/824 (1.0)	0.51
Angiographic variables				
Time to reperfusion	3.3 (2.1–4.9)	3.5 (2.1–4.9)	3.2 (2.1–4.9)	0.57
Infarct-related artery				
LAD	514/1,023 (50.2)	73/128 (57.0)	441/895 (49.3)	0.10
RCA	413/1,023 (40.4)	43/128 (33.6)	370/895 (41.3)	0.10
LCA	96/1,023 (9.4)	12/128 (9.4)	84/895 (9.4)	0.99
N-vessel disease				
1	563/1,004 (56.1)	53/126 (42.1)	510/878 (58.1)	<0.001
2	280/1,004 (27.9)	39/126 (31.0)	241/878 (27.4)	0.41
3	161/1,004 (16.0)	34/126 (27.0)	127/878 (14.5)	<0.001
Multivessel disease	441/1,013 (43.5)	73/127 (57.5)	368/886 (41.5)	<0.001
TIMI flow grade after PCI				
0	14/1,019 (1.4)	6/129 (4.7)	8/890 (0.9)	<0.001
1	14/1,019 (1.4)	5/129 (3.9)	9/890 (1.0)	0.009
2	64/1,019 (6.3)	9/129 (7.0)	55/890 (6.2)	0.73
3	927/1,019 (91.0)	109/129 (84.5)	818/890 (91.9)	0.006
Enzymatic IS				
Maximal CK‖	2,161 (1,040–4,160)	2,729 (1,169–6,024)	2,109 (1,031–3,913)	0.04
CE-CMR variables				
Time from MI to CE-CMR, days¶	4 (2–6)	4 (2–6)	4 (2–6)	0.57
Presence of MO	577 (56.3)	109 (83.8)	468 (52.3)	<0.001
IS, %LV#	18.5 (9.2–28.3)	24.9 (14.4–37.4)	18.0 (8.9–26.7)	<0.001
IS, g	22.3 (10.8–37.4)	33.7 (15.3–54.1)	21.0 (10.2–34.7)	<0.001
LVEF, %	48.0 ± 12.3	41.4 ± 13.3	48.9 ± 11.9	<0.001
LVESV, ml	80.5 ± 35.7	94.7 ± 42.0	78.4 ± 34.2	<0.001
LVESV index, ml/m^2	41.3 ± 17.2	48.4 ± 19.6	40.3 ± 16.6	<0.001
LVEDV, ml	150.5 ± 42.4	156.3 ± 45.3	149.6 ± 41.9	0.09
LVEDV index, ml/m^2	77.4 ± 19.6	80.5 ± 20.9	77.0 ± 19.4	0.05

Values are mean ± SD, n (%), n/N (%), or median (IQR). Data missing in the following number of cases: *124 (12.1%), †88 (8.6%), ‡77 (7.5%), §78 (7.6%), ‖278 (27.1%), and ¶446 (43.5%) (reperfusion within 12 h). #Data missing in >7.5% of the cohort.

BMI = body mass index; CABG = coronary artery bypass grafting; CE-CMR = contrast-enhanced cardiac magnetic resonance; CK = creatine kinase; CV = cardiovascular; IQR = interquartile range; IS = infarct size; LAD = left anterior descending; LCA = left circumflex artery; %LV = percentage of LV mass; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MI = myocardial infarction; MO = microvascular obstruction; PCI = percutaneous intervention; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

IS%LV, are depicted in Figures 5 to 7. The Kaplan-Meier estimate of freedom from MACE was 71.3% in patients with IS%LV ≥25% with MO versus 94.9% in patients with IS%LV <25% without MO ($p < 0.001$).

Univariate Cox regression is summarized in Table 2. MO (HR: 4.68; 95% CI: 2.86 to 7.66), IS% LV ≥25% (HR: 2.04; 95% CI: 1.42 to 2.92), and LVEF ≤40% (HR: 3.45; 95% CI: 2.40 to 4.97) were associated with MACE on univariate Cox regression analysis. Sex (HR: 1.34; 95% CI: 0.89 to 2.00) and anterior myocardial infarction (HR: 1.30; 95% CI: 0.90 to 1.87) were not associated with MACE on univariate Cox regression analysis.

Multivariate Cox regression is summarized in Table 3. MO (aHR: 3.74; 95% CI: 2.21 to 6.34) and

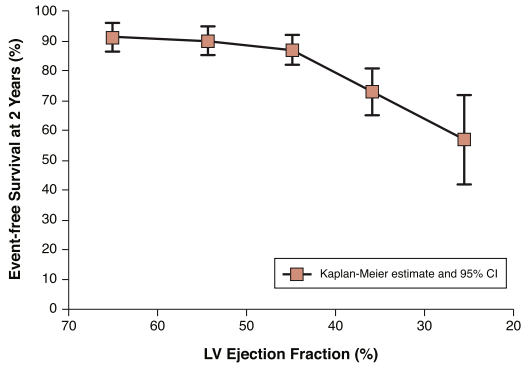

FIGURE 3 Relationship Between LV Ejection Fraction and Event-Free Survival

Values are Kaplan-Meier estimates (95% confidence interval), by LV ejection fraction category (>60%, 50% to ≤60%, 40 to ≤50%, 30% to ≤40%, or <30%). LV = left ventricular.

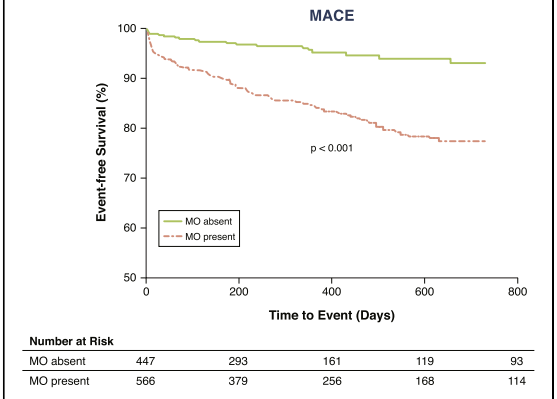

FIGURE 5 Relationship Between MO and Event-Free Survival

Values are Kaplan-Meier estimates in patients with microvascular obstruction (MO) versus patients without MO, indicating the time to major adverse cardiovascular events (MACE), follow-up 2 years.

LVEF ≤40% (aHR: 2.30; 95% CI: 1.48 to 3.58) were associated with MACE, whereas IS%LV ≥25% and diabetes were not independently associated with MACE (model I). After the application of the backward variable-selection method, five variables (age, multivessel disease, TIMI flow grade after PCI, MO, and LVEF ≤40%) remained significant (model II). In a separate analysis, IS%LV, unadjusted for MO and LVEF, but adjusted for age, multivessel disease, and TIMI flow grade after PCI, was associated with the occurrence of MACE (aHR: 1.82; 95% CI: 1.26 to 2.63) (data not shown).

The addition of IS%LV ≥25% to a model with age, multivessel disease, and TIMI flow grade after PCI (model a) resulted in an increase of the *c*-index from 0.59 to 0.61 (model b) in the prediction of MACE. The addition of LVEF ≤40% resulted in an increase from 0.59 to 0.66 (model c), with a further increase to 0.70 (model e) when MO was added (Table 4).

PREDICTORS OF CARDIAC DEATH. The Kaplan-Meier estimate of freedom from cardiac death at 2 years was 96.7% (MO vs. no MO: 99.8% vs. 94.6%;

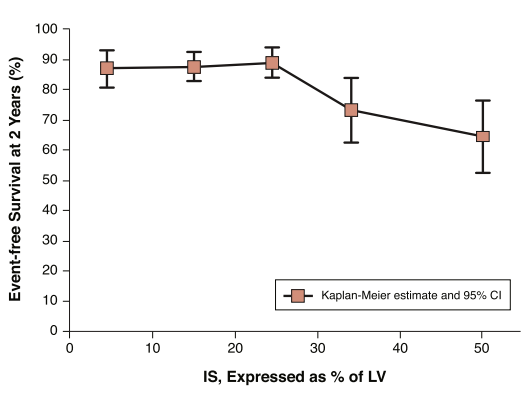

FIGURE 4 Relationship Between IS%LV and Event-Free Survival

Values are Kaplan-Meier estimates (95% confidence interval), by IS%LV category (0 to ≤10%, 10% to ≤20%, 20% to ≤30%, 30 to ≤40%, or >40%). IS%LV = infarct size expressed as a percentage of left ventricular mass.

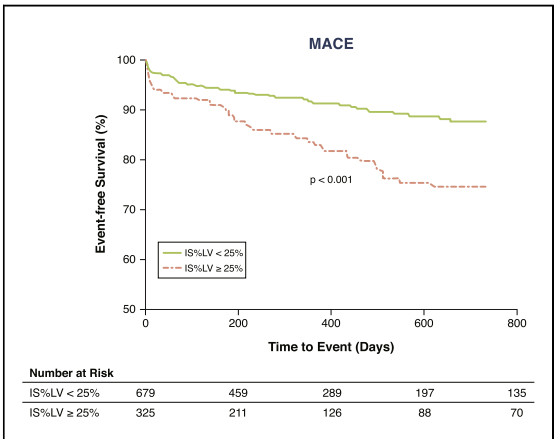

FIGURE 6 Relationship Between IS%LV and Event-Free Survival

Values are Kaplan-Meier estimates in patients with IS%LV ≥25% versus <25%, indicating the time to MACE, follow-up 2 years. Abbreviations as in Figures 4 and 5.

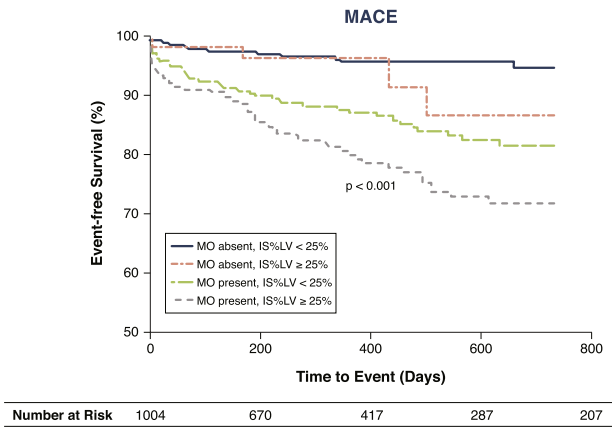

FIGURE 7 Relationship Between MO and IS%LV and Event-Free Survival

Values are Kaplan-Meier estimates in patients with IS%LV ≥25% versus <25%, grouped by the presence or absence of MO, indicating the time to MACE, follow-up 2 years. Abbreviations as in Figures 4 and 5.

TABLE 3 Association of Patient Characteristics With MACE at 2 Years: Multivariate Cox Regression Analysis

	aHR	95% CI	p Value
Model I*			
Age	1.54	1.04–2.27	0.03
Diabetes	1.25	0.80–1.94	0.33
Multivessel disease	1.56	1.07–2.28	0.02
TIMI flow grade after PCI	2.11	1.04–4.27	0.04
Presence of MO	3.74	2.21–6.34	<0.001
IS%LV ≥25%	0.90	0.59–1.37	0.63
LVEF ≤40%	2.30	1.48–3.58	<0.001
LVEDV index	1.00	0.99–1.01	0.58
Model II†			
Age	1.58	1.08–2.30	0.02
Multivessel disease	1.56	1.08–2.27	0.02
TIMI flow grade after PCI	2.25	1.14–4.45	0.02
Presence of MO	3.72	2.22–6.25	<0.001
LVEF ≤40%	2.40	1.63–3.53	<0.001

*Before backward variable selection in 970 patients, 118 events. †Backward variable selection in 984 patients, 118 events.

aHR = adjusted hazard ratios; other abbreviations as in Tables 1 and 2.

p < 0.001). The Kaplan-Meier estimate of freedom from cardiac death at 2 years was 95.2% in patients with IS%LV ≥25% versus 97.3% in patients with IS% LV <25% (p < 0.21) (data not shown).

Univariate Cox regression is summarized in Table 5. MO (HR: 15.02; 95% CI: 2.01 to 112.24) and LVEF ≤40% (HR: 2.26; 95% CI: 1.01 to 5.05) were associated with cardiac death on univariate Cox regression analysis. IS%LV ≥25% was not associated with cardiac death in a univariate Cox model (HR: 1.77; 95% CI: 0.80 to 3.89).

TABLE 2 Association of Patient Characteristics With MACE at 2 Years: Univariate Cox Regression Analysis

	HR	95% CI	p Value
Demographics			
Age	1.60	1.11–2.31	0.01
Sex	1.34	0.89–2.00	0.16
CV risk factors			
Diabetes	1.66	1.09–2.53	0.02
Hypertension	0.97	0.67–1.42	0.89
Anterior MI	1.30	0.90–1.87	0.16
Angiographic variables			
Multivessel disease	1.65	1.13–2.40	0.009
TIMI flow grade after PCI	3.31	1.70–6.43	<0.001
CE-CMR variables			
Presence of MO	4.68	2.86–7.66	<0.001
IS%LV ≥25%	2.04	1.42–2.92	<0.001
LVEF ≤40%	3.45	2.40–4.97	<0.001
LVESV index	1.03	1.02–1.04	<0.001
LVEDV index	1.02	1.01–1.02	<0.001

CI = confidence interval; HR = hazard ratio; MACE = major cardiovascular events; other abbreviations as in Table 1.

Independent predictors on multivariate Cox regression and their respective aHRs for cardiac death at 2 years are summarized in Table 6. MO was associated with the occurrence of cardiac death (aHR: 13.22; 95% CI: 1.75 to 99.82) when adjusted for age (aHR: 2.21; 95% CI: 0.96 to 5.06) and LVEF ≤40% (aHR: 1.66; 95% CI: 0.74 to 3.75).

DISCUSSION

The main findings of this study were that: 1) MO was present in >50% of patients with STEMI reperfused by pPCI (even in patients with TIMI flow grade post pPCI of 3, MO was present in >50% of patients); 2) MO, IS%LV, and LVEF were predictors for MACE, with value added to clinical risk factors; 3) MO was

TABLE 4 Incremental Value (*c*-Statistic) of MO, IS%LV, and LVEF ≤40% in the Prediction of MACE at 2 Years

	c-Statistic
Model a: age + multivessel disease + TIMI flow grade after PCI	0.59
Model b: age + multivessel disease + TIMI flow grade after PCI + IS%LV ≥25%	0.61
Model c: age + multivessel disease + TIMI flow grade after PCI + LVEF ≤40%	0.66
Model d: age + multivessel disease + TIMI flow grade after PCI + LVEF ≤40% + IS%LV <25%	0.66
Model e: age + multivessel disease + TIMI flow grade after PCI + LVEF ≤40% + MO	0.70

Abbreviations as in Tables 1 and 2.

TABLE 5 Association of Patient Characteristics With Cardiac Death at 2 Years: Univariate Cox Regression Analysis

	HR	95% CI	p Value
Demographics			
Age	2.18	0.95–5.01	0.07
Sex	1.33	0.50–3.54	0.57
CV risk factors			
Diabetes	2.25	0.96–5.25	0.06
Hypertension	1.05	0.44–2.49	0.91
Anterior MI	1.41	0.64–3.10	0.40
Angiographic variables			
Multivessel disease	0.78	0.35–1.76	0.55
TIMI flow grade after PCI	2.51	0.58–10.87	0.22
CE-CMR variables			
Presence of MO	15.02	2.01–112.24	0.01
IS%LV ≥25%	1.77	0.80–3.89	0.16
LVEF ≤40%	2.26	1.01–5.05	0.05
LVESV index	1.01	0.99–1.04	0.22
LVEDV index	1.00	0.98–1.02	0.91

Abbreviations as in Tables 1 and 2.

associated with cardiac death when adjusted for age and LVEF; and 4) IS%LV, adjusted for MO and LVEF, was not an independent predictor of MACE or cardiac death.

Previous studies that evaluated the prognostic value of MO, IS%LV, and LVEF in STEMI patients were limited by the inclusion of relatively small study sample sizes; evaluated composite clinical endpoints with "soft" components, including revascularization or angina; and were single-center studies (7–13). In the present internationally representative patient pooled analysis, we were able to assess the impact of CE-CMR variables on more clinically relevant events. With a sample size of 1,025 patients, the statistical power of the present pooled analysis was increased compared with that of previous single-center studies, which led to more robust predictions.

Our finding that the value of IS%LV, measured within 14 days after STEMI, is secondary to those of MO and LVEF is remarkable. It is important to realize that IS%LV is correlated with LVEF; however, LVEF is affected by additional factors, such as previous cardiovascular conditions, which might explain the importance of LVEF as a predictor of MACE in the present study. However, the univariate association of IS with MACE, its correlation with LVEF, and its contribution to the model as shown by an improvement in the *c*-index suggest that IS%LV is an attractive option as an endpoint in studies investigating new treatments. The measurement of LVEF is influenced by the presence of stunned myocardium, the relevance of which remains a topic of research, because most CMR studies are performed 4 to 7 days after STEMI, when stunning may be only partially resolved.

TABLE 6 Association of Age, MO, and LVEF ≤40% With Cardiac Death at 2 Years: Multivariate Cox Regression Analysis

	aHR	95% CI	p Value
Age	2.21	0.96–5.06	0.06
Presence of MO	13.22	1.75–99.82	0.01
LVEF ≤40%	1.66	0.74–3.75	0.22

N = 760 patients, 25 events.
Abbreviations as in Tables 1, 2, and 3.

The finding that MO was, in addition to IS%LV and LVEF, an independent predictor of MACE is in concordance with findings from previous single-center studies. In the largest study to date, by de Waha et al. (12), IS adjusted for TIMI risk score, MO, and LVEF was not an independent predictor of adverse outcomes. We draw the same conclusion in the present study, in which IS%LV and LVEF were analyzed as continuous variables.

The cause of the detrimental effect of MO remains speculative. Baks et al. (5) demonstrated that the presence of MO in dysfunctional myocardial segments was associated with significantly greater thinning of the myocardium compared with that in segments without MO at follow-up. In contrast to segments without MO, segments with MO demonstrated no improvement in segmental wall thickening in a follow-up study at 5 months. Nijveldt et al. (6) found that a significant proportion of patients with MO developed a significant increase in LV end-diastolic volume, with no improvement in LVEF, whereas patients without MO showed a significant improvement in LVEF, at 4 months of follow-up. Both of those studies suggest an important relation between MO and LV remodeling that potentially might result in heart failure used as a MACE, as in the present study.

In addition to having predictive value for congestive heart failure, MO seems to be an important predictor of cardiac death. Reasons for cardiac death in patients with MO have been demonstrated by Ito et al. (22). Patients with no-reflow more often had malignant arrhythmias, cardiac tamponade, and early congestive heart failure compared with patients without no-reflow. An explanation of those findings might have been the reduced end-diastolic wall thickness in MO-positive segments, which might result in an increase in wall stress in the affected and adjacent segments (5).

The findings from the present study demonstrate, in a large cohort, the prognostic value of MO in patients who sustained a STEMI. MO was present in >50% of the study population, even, importantly, in a large subgroup of patients with angiographic TIMI flow grade after PCI of 3. These findings suggest that pPCI is not optimal yet and that there is a need for future novel treatment strategies. Of the current variables, MO is still the best predictor and probably indicates which patients should be investigated further. Screening for arrhythmias and progressive dilation, with follow-up echocardiography or CE-CMR, could potentially identify a high risk for cardiac death. The findings of this study are relevant in CMR trial design for the evaluation of the effects of, for example, thrombectomy devices, vasodilators, coronary post-conditioning, cell therapy, and glycoprotein IIb/IIIa inhibitors (23) in patients with STEMI. It is advisable to use, in addition to the measurement of LVEF and IS%LV, MO as surrogate endpoint in CMR trials in STEMI patients as MO and IS%LV might be variables that represent separate pathophysiological processes.

STUDY LIMITATIONS. The results of our study should be viewed in light of limitations inherent to the design of meta-analyses of individual patient data. These limitations include publication bias, data-availability bias, unmeasured heterogeneity in the patients included, and the use of event adjudication by different clinical events committees (24).

CE-CMR was performed at a wide range of days (up to 14) after STEMI, at different time points after contrast injection, and with different concentrations of gadolinium-based contrast agents (25). These variations may have influenced the detection of MO and may have influenced the measurement of IS (26). CE-CMR analysis was conducted in different ways, which also might have influenced the measurements of IS and MO.

In this analysis, we evaluated the prognostic value of MO only, without investigation of the extent of MO. A previous study (12) showed that the extent of MO provided incremental prognostic information. Unfortunately, this variable was available in only one study and therefore could not be included in the pooled analysis.

In cases of missing data, variables that may have influenced the primary endpoint (e.g., extent of MO, myocardial salvage [27], and the presence of a hypointense infarct core [28]) were not taken into account. Due to a low cardiac death rate, we were not able to add more variables in the multivariate Cox regression analysis.

CONCLUSIONS

MO is an independent predictor of the occurrence of MACE and cardiac death at 2 years in patients with STEMI. IS%LV is not independently associated with the occurrence of MACE, but might be used, in addition to MO and LVEF, as a surrogate endpoint in clinical trials investigating new treatment options.

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APPENDIX For a supplemental table, please see the online version of this article.