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ORIGINAL RESEARCH

Prognostic Value of Initial Left Ventricular Remodeling in Patients With Reperfused STEMI

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ABSTRACT

OBJECTIVES This study sought to establish the best definition of left ventricular adverse remodeling (LVAR) to predict outcomes and determine whether its assessment adds prognostic information to that obtained by early cardiac magnetic resonance (CMR).

BACKGROUND LVAR, usually defined as an increase in left ventricular end-diastolic volume (LVEDV) is the main cause of heart failure after an ST-segment elevated myocardial infarction; however, the role of assessment of LVAR in predicting cardiovascular events remains controversial.

METHODS Patients with ST-segment elevated myocardial infarction who received percutaneous coronary intervention within 6 h of symptom onset were included (n = 498). CMR was performed during hospitalization (6.2 ± 2.6 days) and after 6 months (6.1 ± 1.8 months). The optimal threshold values of the LVEDV increase and the LV ejection fraction decrease associated with the primary endpoint were ascertained. Primary outcome was a composite of cardiovascular mortality, hospitalization for heart failure, or ventricular arrhythmia.

RESULTS The study was completed by 374 patients. Forty-nine patients presented the primary endpoint during follow-up (72.9 ± 42.8 months). Values that maximized the ability to identify patients with and without outcomes were a relative rise in LVEDV of 15% (hazard ratio [HR]: 2.1; p = 0.007) and a relative fall in LV ejection fraction of 3% (HR: 2.5; p = 0.001). However, the predictive model (using C-statistic analysis) failed to demonstrate that direct observation of LVAR at 6 months adds information to data from early CMR in predicting outcomes (C-statistic: 0.723 vs. 0.795).

CONCLUSIONS The definition of LVAR that best predicts adverse cardiovascular events should consider both the increase in LVEDV and the reduction in LV ejection fraction. However, assessment of LVAR does not improve information provided by the early CMR. (J Am Coll Cardiol Img 2019;12:2445-56) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

CI = confidence interval

CMR = cardiac magnetic resonance

HR = hazard ratio

IS = infarct size

LV = left ventricle

LVAR = left ventricular adverse remodeling

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

LVESV = left ventricular end-systolic volume

MI = myocardial infarction

MVO = microvascular obstruction

NRI = net reclassification improvement

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

Mortality during the acute phase of ST-segment elevation myocardial infarction (STEMI) has steadily decreased over the past 3 decades and appears now to have reached a plateau at lower values than those in the pre-reperfusion era (1). However, the main impact of STEMI is shifting from acute mortality to progressive left ventricular (LV) dysfunction and chronic heart failure (2).

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The main cause of heart failure after an acute myocardial infarction (AMI) is left ventricular adverse remodeling (LVAR) (3) in response to the increase in wall stress caused by cardiomyocyte loss and distension in the infarct area (4). Post-infarct LVAR is generally defined as a 20% increase in LV end-diastolic volume (LVEDV) (5,6) and has been associated with poorer outcomes (5,7).

The definition of LVAR is controversial. First, the increase in LV volume post-infarction may be associated with a rise or fall in left ventricular ejection fraction (LVEF), which has also been considered a major predictor of outcomes after AMI (8). Changes in LVEDV may reflect changes in LV volume, EF, or both, and its analysis provides less information than the combined analysis of LV volumes and LVEF. Furthermore, LVAR is determined 3 to 6 months after a STEMI (5,9), and, it has been shown that LVEF improves in most patients after 1-month post-STEMI, thereby implying that further delay in clinical decisions may not be warranted (10).

To overcome these limitations, early cardiac magnetic resonance (CMR)-derived parameters such as infarct size (IS), microvascular obstruction (MVO), and LVEF have been considered excellent predictors of adverse cardiovascular events during follow-up (11,12). A recent meta-analysis showed IS measured by CMR or technetium-99m sestamibi single-photon emission computed tomography within 1 month after the primary percutaneous coronary intervention (PCI) to be strongly associated with all-cause mortality and hospitalization for heart failure within 1 year (13). However, although several studies support the prognostic value of baseline CMR data, no studies to date have shown that they are superior to the direct assessment of early LVAR for predicting outcomes.

The present study first tested the hypothesis that changes in both LV volumes and LVEF better define the presence of LVAR because they provide additional prognostic information in patients with STEMI who are undergoing PCI. These changes were correlated with the primary outcome of ventricular arrhythmia, hospitalization for heart failure, or cardiovascular death during follow-up. We also sought to determine whether baseline CMR-derived parameters or LVAR constitutes the best predictor of cardiovascular events during follow-up.

METHODS

STUDY POPULATION. The present study compiled the databases of 2 previous studies (14,15). The first was a large prospective STEMI registry (14) that included consecutive patients admitted for a first STEMI as defined by current definitions (16), treated with PCI, and undergoing CMR pre-discharge. A subsample of 234 patients underwent a second CMR 6 months post-discharge, and they constituted the target population.

The second database stemmed from a double-blind randomized clinical trial in which 201 patients with a STEMI were randomized to receive 4.5 mg of adenosine or saline intracoronary injection immediately before PCI (15). The primary endpoint of this study was the infarct size (%LV) by CMR post-reperfusion.

Per protocol, in both clinical studies, all patients who met the inclusion criteria were scheduled for an early CMR during hospitalization and at 6-month follow-up.

Our target population were patients who survived at least 6 months after a STEMI and in whom LVAR could be assessed with a subsequent CMR after the acute phase and underwent a minimum of 1-year follow-up (**Figure 1**).

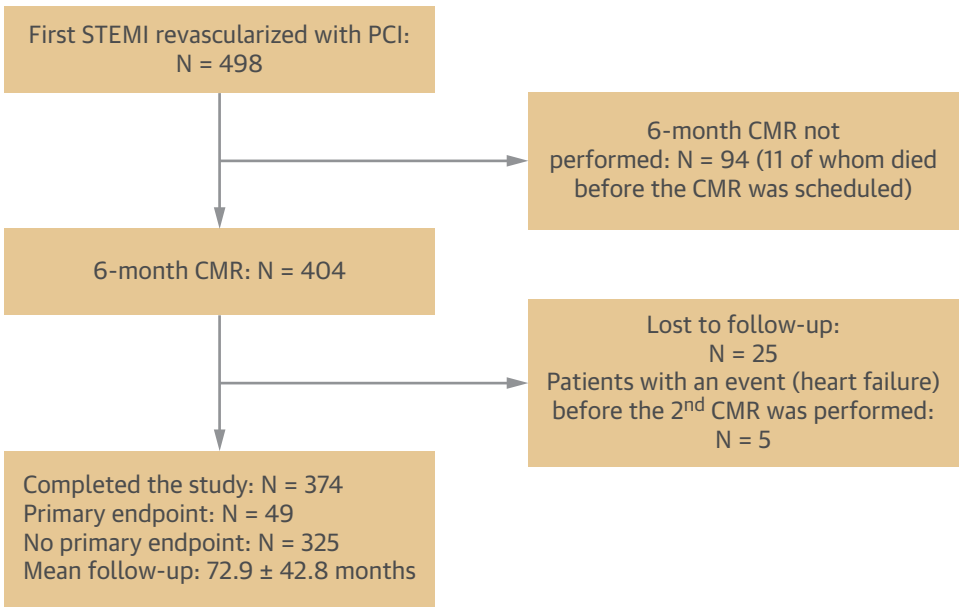
Exclusion criteria were death, previously documented MI, severe clinical instability during admission, and any contraindications to CMR, including claustrophobia, existing pacemaker, decision of the patient, and a history of adverse reactions to contrast.

Baseline characteristics were collected prospectively in all cases. The PCI technique was left to the discretion of the interventional cardiologists. Patients were managed both in-hospital and after discharge following specific STEMI guidelines (16).

Both study protocols were approved by the hospital Ethics Committee on Human Research and complied with the 1975 Declaration of Helsinki guidelines.

CMR. All CMR studies were performed with a 1.5-T clinical scanner (Sonata or Avanto scanner, Siemens, Erlangen, Germany). Further details on the technical aspects of CMR acquisition, sequences, and quantification can be found in the Supplemental Appendix. LVEF (%), LVEDV index (ml/m^2), left ventricular end-systolic volume (LVESV) index (ml/m^2), LV mass

FIGURE 1 Study Flow Chart



Flow chart of participants through the study. Graph showing selection and attrition of participants through the study. Primary endpoint is cardiovascular mortality, hospitalization for heart failure, or ventricular arrhythmia. CMR = cardiac magnetic resonance; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

index (g/m^2), IS (% of LV mass), microvascular obstruction (% of LV mass), myocardial edema (% of LV mass), and myocardial salvage index (% of LV mass) were calculated.

CMR studies were analyzed offline by an experienced observer blinded to all patient data using customized software (QMASS MR 6.15, Medis, Leiden, the Netherlands; or Cvi42, Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada).

STATISTICAL ANALYSIS. Continuous demographic variables were expressed as mean ± SD. Normality distribution was assessed by the Kolmogorov-Smirnov test. Differences between groups for continuous parameters were assessed by Student's *t*-test if they presented a normal distribution or analysis of variance with Bonferroni correction for multiple comparisons, and Mann-Whitney *U* test if they did not present a normal distribution. For categorical variables, general characteristics of the sample were assessed by percentages (chi-square test or Fisher exact test, accordingly).

Our main hypothesis was that both LVEDV and LVEF provide complementary prognostic information for STEMI after primary PCI and thus both should be considered in the definition of LVAR. The primary endpoint was cardiovascular mortality, hospitalization for heart failure, or ventricular arrhythmia.

The optimal threshold values of the LVEDV increase and the LVEF decrease associated with the primary endpoint were ascertained using a graphic method for biomarker cutoff optimization (17). The hazard ratios (HRs) including 95% confidence intervals (CIs) were plotted regardless of the cutoffs, and vertical lines designated the dichotomization showing the most significant correlation with survival. To avoid absurd estimations, 10% of extreme outliers of LVEDV and LVEF values were excluded as potential candidates to obtain the cutoff points. Finally, the values obtained were rounded up to a superior whole for pragmatic purposes. A scale of 1 percentage unit was used for the decrease in LVEF and a scale of 5 percentage units for LVEDV.

Survival free from the primary endpoint was compared using Kaplan-Meier curves, and log-rank test across the 4 subgroups of patients considered the cutoff points selected: 1) those whose LVEDV and LVEF did not change; 2) those whose LVEDV increased but LVEF did not decrease; 3) those whose LVEDV did not increase but the LVEF decreased; and 4) those whose LVEDV increased and LVEF

TABLE 1 Baseline Characteristics of the Entire Study Group and of Patients With or Without Cardiovascular Events

	All Patients (N = 374)		Patients With No Events (n = 325)		Patients With Events (n = 49)		
	N	Mean ± SD or n (%)	n	Mean ± SD or n (%)	n	Mean ± SD or n (%)	p Value
Demographics							
Age, yrs	374	59.2 ± 12	325	58.2 ± 11.8	49	65.5 ± 11.2	<0.001
Female	374	62 (16.6)	325	56 (17.2)	49	6 (12.2)	0.536
Hypertension	374	168 (44.9)	325	144 (44.3)	49	24 (49)	0.542
Hypercholesterolemia	374	144 (38.5)	325	128 (39.4)	49	16 (32.7)	0.432
Diabetes	374	63 (16.8)	325	56 (17.2)	49	7 (14.3)	0.687
Smoking	374	235 (62.8)	325	205 (63.1)	49	30 (61.2)	0.874
Prior coronary heart disease	374	34 (9.1)	325	31 (9.5)	49	3 (6.1)	0.597
Index episode							
AMI location	374		325		49		0.340
Anterior		211 (56.4)		179 (55.1)		32 (65.3)	
Inferior		146 (39)		130 (40)		16 (32.7)	
Lateral		17 (4.5)		16 (4.9)		1 (2)	
Heart rate	374	77.6 ± 18.8	325	76.3 ± 17.8	49	86.3 ± 22.4	0.003
Systolic blood pressure	374	129.1 ± 28.8	325	128.7 ± 28.8	49	131.8 ± 29	0.541
Killip class >I	374	51 (13.6)	325	43 (13.2)	49	8 (16.3)	0.510
PCI <12 h	368	247 (67.1)	319	215 (67.4)	49	32 (65.3)	0.747
Coronary artery	371		323		48		0.149
LAD		210 (56.6)		178 (55.1)		32 (66.7)	
LCX		130 (35)		115 (35.6)		15 (31.3)	
RCA		31 (8.4)		30 (9.3)		1 (2.1)	
Multivessel disease	366	116 (31.7)	317	103 (32.5)	49	13 (26.5)	0.510
Initial TIMI	369		321		48		0.052
Occlusion		236 (64)		210 (65.4)		26 (54.2)	
Low		24 (6.5)		22 (6.9)		2 (4.2)	
Intermediate		27 (7.3)		23 (7.2)		4 (8.3)	
Normal		82 (22.2)		66 (20.6)		16 (33.3)	
Final TIMI	374		325		49		0.850
Occlusion		6 (1.6)		6 (1.8)		0 (0)	
Low		2 (0.5)		2 (0.6)		0 (0)	
Intermediate		27 (7.2)		20 (6.2)		7 (14.3)	
Normal		339 (90.6)		297 (91.4)		42 (85.7)	
Drug-eluting stent	241	0.4 ± 0.5	219	0.4 ± 0.5	22	0.1 ± 0.4	0.009
Stents, total number	229	1.2 ± 0.6	208	1.2 ± 0.6	21	1.3 ± 0.9	0.544
CK-MB mass	319	267.4 ± 382.2	270	258.8 ± 404.1	49	314.9 ± 223.6	0.022

Continued on the next page

decreased. The association between LVEDV and LVEF changes were estimated in multivariable crude and adjusted Cox models. All baseline variables were analyzed for their association with the primary outcome (Supplemental Table 1). Specifically, the baseline variables of age, sex, heart rate, LVEF, IS, and MVO were selected for statistical adjustment.

The estimated best model to identify patients with the primary outcome during follow-up was based on the C-statistic. The objective of this analysis was to compare the predictive ability of 4 different models: 1) models including information exclusively from the early CMR; 2) models including information exclusively from the 6-month CMR; 3) models that included information related to the change between the early and 6-month CMR; and 4) models that included information from the early CMR and the change in LVEDV and LVEF. All models were adjusted for age and sex.

Finally, the discrimination ability of each model to classify patients at a higher risk for the primary outcome was additionally assessed by the net reclassification improvement (NRI). Considering a baseline model including only the variables age and sex, the NRI was estimated for each new model. NRI was estimated at the median follow-up (297 weeks) and considered a threshold of 20% to define a high-risk patient.

TABLE 1 Continued

	All Patients (N = 374)		Patients With No Events (n = 325)		Patients With Events (n = 49)		
	N	Mean ± SD or n (%)	n	Mean ± SD or n (%)	n	Mean ± SD or n (%)	p Value
CMR baseline data							
LVEF, %	374	51.6 ± 12	325	52.5 ± 11.5	49	45.8 ± 13.3	0.001
LVEDV, ml	374	79.7 ± 21.9	325	79.1 ± 20.8	49	83.9 ± 28.2	0.422
LVESV, ml	374	39.6 ± 18.8	325	38.4 ± 17.6	49	47.6 ± 23.9	0.018
Edema, % of LV mass	360	31.3 ± 16	312	30.6 ± 15.8	48	36 ± 16.5	0.038
Myocardial salvage index, %	359	22 ± 22.9	311	23.2 ± 23.8	48	14.5 ± 14.4	0.039
IS, % of LV mass	373	21.9 ± 14.3	324	20.8 ± 13.8	49	28.7 ± 15.6	0.001
MVO, % of LV mass	373	1.8 ± 3.8	324	1.6 ± 3.6	49	2.9 ± 4.3	0.004
Global CS, %	229	−16.5 ± 4	198	−16.8 ± 3.8	31	−14.3 ± 4.2	0.001
Global LS, %	229	−10.4 ± 3.1	198	−10.7 ± 3.1	31	−8.5 ± 2.5	<0.001
Global RS, %	229	38.5 ± 11.7	198	39 ± 11.6	31	34.8 ± 11.9	0.066
Medication at follow-up							
Antiplatelet agent	374	374 (100)	325	325 (100)	49	49 (100)	NA
Anticoagulation	374	43 (11.5)	325	41 (12.6)	49	2 (4.1)	0.094
Beta-blockers	373	306 (82)	324	271 (83.6)	49	35 (71.4)	0.046
ACE Inhibitors	374	251 (67.1)	325	220 (67.7)	49	31 (63.3)	0.625
Angiotensin II receptor antagonist	374	42 (11.2)	325	38 (11.7)	49	4 (8.2)	0.629
Statin	374	354 (94.7)	325	307 (94.5)	49	47 (95.9)	1.000

Values are n, mean ± SD, or n (%).

ACE = angiotensin-converting enzyme inhibitor; AMI = acute myocardial infarction; CK-MB = creatine kinase-myocardial band; CMR = cardiac magnetic resonance; CS = circumferential strain; IS = infarct size; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LS = longitudinal strain; LV = left ventricle; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV= left ventricular end-systolic volume; MVO = microvascular obstruction; NA = not applicable; PCI = percutaneous coronary intervention; RCA = right coronary artery; RS = radial strain; TIMI = Thrombolysis In Myocardial Infarction flow grade.

All analyses were made with SPSS statistical package (SPSS Statistics 23.0, IBM, Armonk, New York) and R (version 3.4.3, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

BASELINE CHARACTERISTICS. Ninety-four of the 498 patients with a first STEMI revascularized with PCI were excluded because a second CMR was not performed at 6 months. Twenty-five patients (6.2%) were lost to follow-up, and 5 (1.2%) had an event (heart failure) before the second CMR was scheduled; thus, 374 patients were finally included in the study. The mean time between the PCI and early CMR was 6.2 ± 2.6 days. Baseline data of the study population are shown in Table 1. Most patients had an anterior STEMI (n = 211; 56.4%). The culprit artery was the left anterior descending coronary artery (n = 210; 56.6%), which in most cases was completely occluded (n = 236; 64%). Multivessel coronary artery disease was present in 116 patients (31.7%). PCI was performed in the first 12 h after initial chest pain in the majority of patients (n = 247; 67.1%), in most of whom (n = 339; 90.6%) it achieved normal coronary flow. Early CMR showed a baseline EF of 51.6 ± 12% and mean IS (%LV) was 21.9 ±14.3%. No differences

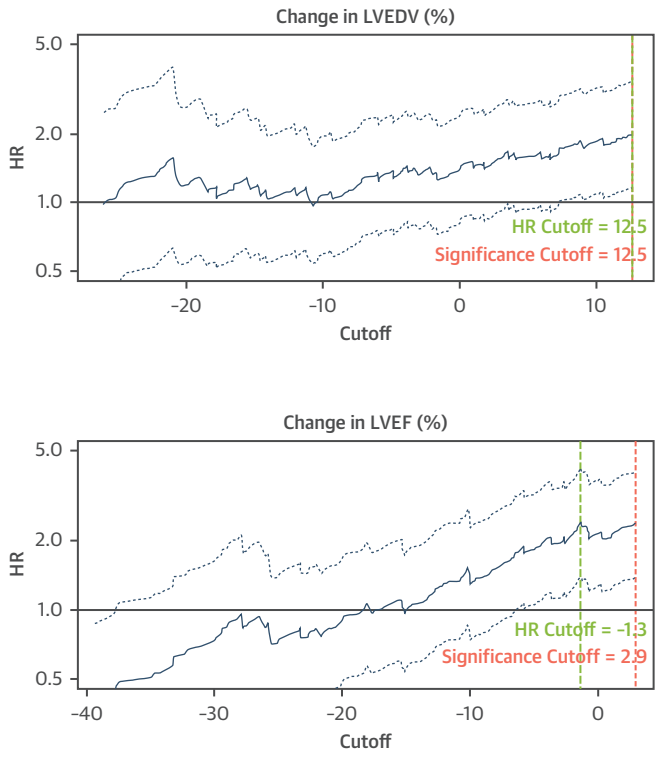
TABLE 2 Differences Between Baseline and 6-Month LVEDV, LVESV, LVEF, and IS (%LV Mass) in Patients With and Without the Cardiovascular Event

	Global (n = 374)	Event (n = 49)	No Event (n = 325)	p Value
LVEDV				
Baseline	80 ± 22	84 ± 28	79 ± 21	0.422
6-month	82 ± 26	90 ± 37	80 ± 24	0.278
Difference	2 ± 17.8	6 ± 23.1	1.4 ± 16.8	0.255
Relative difference, %	4 ± 23.2	8.3 ± 26.6	3.4 ± 22.7	0.224
p Value	0.031	0.076	0.136	
LVESV				
Baseline	40 ± 19	48 ± 24	38 ± 18	0.018
6-month	39 ± 23	52 ± 32	37 ± 20	0.005
Difference	−0.3 ± 12.8	4.4 ± 18.4	−1 ± 11.6	0.052
Relative difference, %	1.6 ± 34.5	12.1 ± 41.8	0.1 ± 33	0.032
p Value	0.662	0.099	0.122	
LVEF				
Baseline	52 ± 12	46 ± 13	53 ± 12	0.001
6-month	55 ± 12	46 ± 14	56 ± 11	<0.001
Difference	3 ± 8.4	0.6 ± 10	3.4 ± 8.1	0.018
Relative difference, %	7.6 ± 20	3.4 ± 27.2	8.3 ± 18.6	0.017
p Value	<0.001	0.689	<0.001	
IS (% of LV mass)				
Baseline	25.4 ± 13	31.7 ± 14.4	24.2 ± 12.4	<0.001
6-month	22.9 ± 13.7	28.7 ± 15.8	21.7 ± 13.1	0.001
Difference	−2.5 ± 6	−3.1 ± 7.9	−2.4 ± 5.6	0.499
Relative difference, %	−10.9 ± 19.9	−10.9 ± 21	−10.9 ± 18.7	0.985
p Value	<0.001	0.009	<0.001	

Values are mean ± SD unless otherwise indicated. Event is considered a cardiovascular mortality, hospitalization for heart failure, or ventricular arrhythmia.

Abbreviations as in Table 1.

FIGURE 2 HR Curves



Hazard ratio (HR) curves to ascertain the best cutoff point in left ventricular end-diastolic volume (LVEDV) and left ventricular ejection fraction (LVEF) to predict the event. Values that maximized the ability to distinguish between patients with and without a subsequent event were a relative increase of 12.5% in LVEDV and a relative decrease in LVEF of 2.9%.

existed in medical treatment at discharge between groups.

FOLLOW-UP AND CMR CHANGES. After discharge, a second CMR was performed at a mean time of 6.1 ± 1.8 months, and patients were followed up for a mean of 72.9 ± 42.8 months. Forty-nine patients (13.1%) presented with the primary outcome: 3 ventricular arrhythmias (0.8%); 28 hospitalization for heart failure (7.5%); and 26 cardiovascular death (7%). In 325 patients (86.9%), none of the primary outcomes occurred. All-cause mortality also occurred in 26 patients (7%). Differences between patients with and without the primary outcome are presented in Table 1. Patients with cardiovascular events were older; had a higher heart rate at admission; lower LVEF and myocardial salvage index at the baseline CMR; and higher LVESV, area at risk, IS, and MVO ($p < 0.005$ in all cases).

After 6 months, LVEDV presented a relative increase of 4 ± 23.2% (Table 2). This increase tended to be greater in patients who had the primary outcome during follow-up (6 ± 23.1 ml; 8.3 ± 26.6%; $p = 0.076$) than in those without an event (1.4 ± 16.8 ml; 3.4 ± 22.7%; $p = 0.136$), although these differences were not statistically significant ($p = 0.224$). Also, LVEF presented a relative increase of 7.6 ± 20% ($p < 0.001$). This increase was greater ($p = 0.017$) in patients without the primary outcome during follow-up (relative increase 8.3 ± 18.6%; $p < 0.001$) than in those with events (relative 3.4 ± 27.2%; $p = 0.689$). A decrease in infarct size of 10.9 ± 19.9% was observed in the overall population with no differences between patients with or without major cardiovascular events ($p = 0.985$).

These results show that patients with and without events during follow-up can present similar changes in LVEDV and IS during the first 6 months after STEMI; however, they do present differences in the change in LVEF during this period.

CLINICAL EVENTS AND LV REMODELING. In the univariate analysis, age, heart rate, Killip class >I, infarction in the left anterior descending artery, basal LVEF (%), LVESV (ml), myocardial edema (% of LV mass), myocardial salvage index (%), MVO, and infarct size (% of LV mass) constituted the main predictors of cardiovascular events during follow-up (Supplemental Table 1). After analysis of the association with the primary outcome, the following baseline variables were selected for adjustment: age, sex, heart rate, IS, MVO, and LVEF.

HR for the primary outcome across the whole range of values of relative change in LVEDV and relative change in LVEF at 6 months after the index episode are shown in Figure 2. Values that maximized the ability to distinguish between patients with and without a subsequent event were a relative increase of 12.5% in LVEDV (HR: 1.98; 95% CI: 1.16 to 3.4; $p = 0.013$) and a relative decrease in LVEF of 2.9% (HR: 2.38; 95% CI: 1.39 to 4.06; $p = 0.001$). Rounding up to the superior whole corresponded to a relative increase in LVEDV of 15% (HR: 2.10; 95% CI: 1.22 to 3.61; $p = 0.007$) and a relative decrease in LVEF of 3% (HR: 2.50; 95% CI: 1.47 to 4.27; $p = 0.001$).

Classification of the population according to the relative changes in LVEDV and LVEF resulted in 4 groups with different prognoses (Figure 3). Thus, the survival rate of patients with neither an increase in LVEDV (<15%) nor a decrease in LVEF (<3%) was the highest, whereas the presence of both an increase in LVEDV >15% and a decrease in LVEF >3% identified a subgroup of patients with the poorest prognosis.

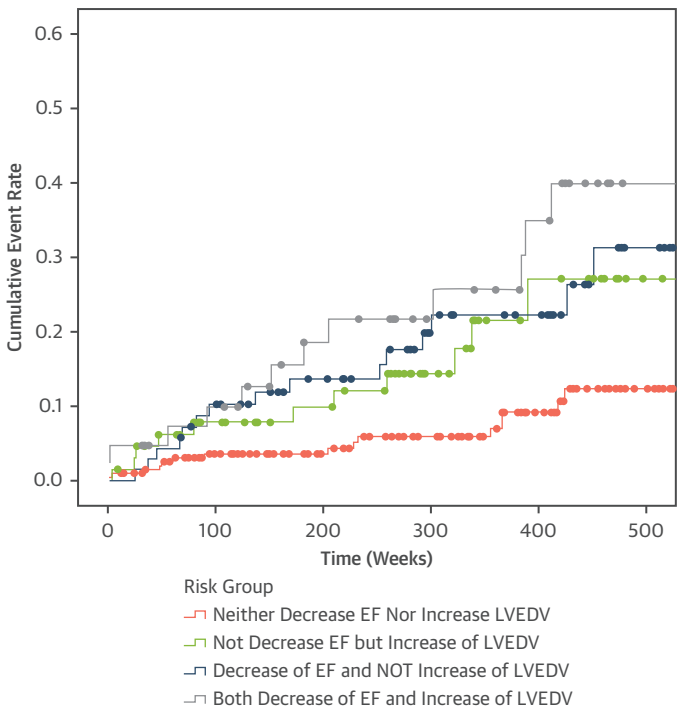
The association between the changes in LVEDV and LVEF at 6 months and the primary outcome

was also present on crude Cox regression analyses (Table 3), which showed HR for the primary outcome of 2.8 (95% CI: 1.2 to 6.4; p = 0.015) in patients with no decrease in LVEF (<3%) but an increase in LVEDV >15%, an HR of 3.5 (95% CI: 1.7 to 7.2; p = 0.001) in those with a decrease in LVEF >3% without an increase in LVEF (<15%), and an HR of 3.9 (95% CI: 1.7 to 8.8; p = 0.001) in those with both conditions, an increase in LVEDV, and a decrease in LVEF.

In the Cox-adjusted regression analysis, the poorest prognosis was observed in patients with both conditions (HR: 6.4; 95% CI: 2.6 to 15.4; p < 0.001). Patients in this group were predominantly men (p = 0.022), who at admission presented lower initial TIMI (Thrombolysis In Myocardial Infarction) flow grade (p = 0.026), a higher area at risk (p = 0.023), larger IS (p = 0.039), and a higher MVO (p = 0.044) (Table 4).

CMR PREDICTORS OF CLINICAL EVENTS. The ability of different models, assessed by the C-statistic, to detect patients with a higher risk for the primary outcome is shown in Table 5. We observed that the combination of a decrease in LVEF associated with an increase in LVEDV exceeded the predictive ability of the individual change for these parameters. However, this predictive ability was lower than that of the model including exclusively the baseline CMR-derived parameters LVEDV, LVEF, and IS: C-statistic: 0.714 (95% CI: 0.661 to 0.766) versus 0.770 (95% CI: 0.707 to 0.823). In addition, complementing the information from the baseline CMR-derived parameters with the occurrence of LVAR did not significantly increase the prediction capacity for cardiovascular events: C-statistic: 0.775 (95% CI: 0.707 to 0.823) versus 0.798 (95% CI: 0.741 to 0.848). These results suggest that the information provided by a second CMR at 6 months does not increase the prognostic implications of the baseline CMR. The same data were obtained using the NRI that showed a higher improvement in the reclassification based on the

FIGURE 3 Kaplan-Meier Cumulative Event Curves



Kaplan-Meier cumulative event curves for the presence of the primary endpoint (cardiovascular death, hospitalization for heart failure, and ventricular arrhythmias) in the 4 different groups based on the variations in LVEF and LVEDV during follow-up (n = 379). Abbreviations as in Figure 2.

TABLE 3 Association Between LV Remodeling and the Primary Outcome

	Crude Model			Adjusted Model		
	HR	(95% CI)	p Value	HR	(95% CI)	p Value
Risk group (reference no decrease LVEF nor increase LVEDV)	1.00		0.002	1.00		0.000
No decrease LVEF and Increase LVEDV >15%	2.80	(1.22-6.4)	0.015	1.89	(0.80-4.50)	0.149
Decrease LVEF >3% and not increase LVEDV	3.48	(1.67-7.24)	0.001	4.02	(1.88-8.62)	0.000
Decrease LVEF >3% and increase of LVEDV >15%	3.86	(1.69-8.8)	0.001	6.38	(2.64-15.42)	0.000
Age				1.07	(1.05-1.10)	0.000
Female				0.65	(0.26-1.60)	0.348
Heart rate, beats/min				1.01	(1.00-1.03)	0.079
Baseline IS, % of LV mass				1.00	(0.99-1.02)	0.605
Baseline LVEF, %				0.95	(0.92-0.97)	<0.000
MVO, % of LV mass				0.99	(0.93-1.06)	0.832

Association between LV remodeling defined by LVEDV and LVEF changes and the primary outcome when adjusted for sex (female), heart rate (beats/min), baseline IS (% of LV mass), baseline LVEF (%), and MVO (% of LV mass).

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

TABLE 4 Baseline Characteristics of the 4 Different Groups of Patients

	No Changes LVEF (n = 265)					Decrease LVEF >3% (n = 109)					
	No Changes LVEDV		Increase LVEDV >15%			No Changes LVEDV		Increase LVEDV >15%			
	n	Mean ± SD or n (%)	N	Mean ± SD or n (%)	p Value	n	Mean ± SD or n (%)	n	Mean ± SD or n (%)	p Value	p Value
Age, yrs	200	59.2 ± 11.7	65	59.4 ± 12	0.992	69	60.3 ±12.7	40	56.5 ± 12	0.121	0.436
Female	200	43 (21.5)	65	6 (9.2)	0.028	69	9 (13)	40	4 (10)	0.765	0.022
Hypertension	200	82 (41)	65	31 (47.7)	0.387	69	34 (49.3)	40	21 (52.5)	0.843	0.098
Hypercholesterolemia	200	82 (41)	65	24 (36.9)	0.662	69	21 (30.4)	40	17 (42.5)	0.218	0.462
Diabetes	200	32 (16)	65	11 (16.9)	0.848	69	12 (17.4)	40	8 (20)	0.800	0.551
Smoking	200	125 (62.5)	65	41 (63.1)	1.000	69	43 (62.3)	40	26 (65)	0.839	0.837
Prior coronary heart disease	200	22 (11)	65	3 (4.6)	0.149	69	6 (8.7)	40	3 (7.5)	1.000	0.364
Index episode											
AMI location	200		65		0.830	69		40		0.649	0.964
Anterior		112 (56)		35 (53.8)			39 (56.5)		25 (62.5)		
Inferior		81 (40.5)		28 (43.1)			25 (36.2)		12 (30)		
Lateral		7 (3.5)		2 (3.1)			5 (7.2)		3 (7.5)		
Heart rate	200	76.8 ± 17.1	65	78.6 ± 23	0.942	69	79.3 ± 17	40	77 ± 22.3	0.558	0.759
Systolic blood pressure	200	130.5 ± 29.1	65	121.1 ± 19.5	0.019	69	134.1 ± 34.7	40	127 ± 27.2	0.444	0.086
Killip class >I	200	25 (12.5)	65	9 (13.8)	0.831	69	11 (15.9)	40	6 (15)	1.000	0.483
PCI <12 h	197	126 (64)	63	48 (76.2)	0.090	68	42 (61.8)	40	31 (77.5)	0.136	0.258
Coronary artery	198		65		0.930	68		40		0.940	0.947
LAD		111 (56.1)		35 (53.8)			40 (58.8)		24 (60)		
RCA		72 (36.4)		26 (40)			21 (30.9)		11 (27.5)		
LCX		15 (7.6)		4 (6.2)			7 (10.3)		5 (12.5)		
Multivessel disease	194	63 (32.5)	65	15 (23.1)	0.164	68	24 (35.3)	39	14 (35.9)	1.000	0.656
Initial TIMI	196	0.9 (1.3)	65	0.6 (1.1)	0.045	68	1.1 (1.4)	40	0.6 (1.1)	0.026	0.026
Final TIMI	200	2.9 (0.5)	65	2.9 (0.2)	0.443	69	2.9 (0.3)	40	2.8 (0.6)	0.154	0.252
Drug-eluting stent	128	0.4 ± 0.5	47	0.4 ± 0.5	0.519	42	0.3 ± 0.5	24	0.3 ± 0.5	1.000	0.568
Stents, total number	121	1.2 ± 0.6	45	1.2 ± 0.5	0.948	40	1.3 ± 0.7	23	1.2 ± 0.5	0.949	0.995
CMR data											
LVEF, %	200	51.8 ± 10.9	65	46.1 ± 12.4	0.001	69	55.3 ± 12.1	40	53.7 ± 13.2	0.571	<0.001
LVEDV	200	82 ± 19.8	65	67.7 ± 19.8	<0.001	69	84.5 ± 22.5	40	79.7 ± 27.6	0.162	<0.001
LVESV	200	40.6 ± 17.5	65	37.2 ± 17	0.204	69	39.2 ± 20.1	40	39.7 ± 24.6	0.602	0.302
Edema, % of LV mass	190	29.8 ± 15.6	63	36.6 ± 16	0.003	68	29.9 ± 15.8	39	33 ± 16.6	0.485	0.023
Myocardial salvage index, %	190	23.4 ± 22.9	63	19.3 ± 17.4	0.521	68	19.2 ± 24.1	38	24.9 ± 28.4	0.323	0.339
IS, % of LV mass	200	19.9 ± 12.3	65	25.7 ± 13.3	0.003	69	22.7 ± 17.3	39	23.7 ± 17.8	0.778	0.039
MVO, % of LV mass	200	1.1 ± 2.1	65	2.4 ± 3.5	0.005	69	1.7 ± 3	39	4.1 ± 8.5	0.335	0.044

Values are n, mean ± SD, or n (%). Baseline characteristics in the 4 different groups based on the variations in LVEF and LVEDV during follow-up.
Abbreviations as in Table 1.

baseline CMR variables (12.9%) compared with the presence of LVAR (4.7%) (Table 5).

DISCUSSION

During the weeks following a STEMI, the LV may undergo changes in volume, geometry, and function associated with the development of heart failure and worse prognosis, a process known as adverse post-infarction remodeling (5,18,19). Although there is no universally accepted definition of adverse post-infarction remodeling, a 15% to 20% increase in LVEDV is the most widely used criterion (5,20). The incidence and extent of LVAR after an AMI have declined in the era of PCI and the almost systematic use of "antiremodeling" medications (such as angiotensin-converting enzyme inhibitors and beta-blockers). However, these improvements in AMI management have not abolished LVAR, which remains a relatively frequent event after an anterior MI (21,22).

The present study shows that the incidence of major cardiovascular events during a mean follow-up of 72.9 months in patients treated with PCI after a STEMI is not trivial (13.1%). Our data also show that the definition of LVAR should necessarily consider not only changes in LVEDV but also changes in LVEF to increase its prognostic significance. Moreover, after adjustment for baseline LVEF and other variables, the isolated increase in LVEDV was not statistically associated with an adverse outcome. However, the

increase in LVEDV in the presence of a decrease in LVEF implied worse prognosis. The cutoff analysis identified an increase in LVEDV of 15% or more and an absolute reduction of 3% or more in LVEF during the 6 months following a STEMI as the criteria that best identify patients according to their risk of cardiovascular death, readmission for heart failure, or ventricular arrhythmias in subsequent years. Patients not fulfilling either of the 2 criteria had the best prognosis, and those fulfilling both criteria had the worst. However, analysis of changes in LVEDV and LVEF over the first 6 months after STEMI did not increase the prognostic value of the principal CMR-derived variables obtained during hospitalization. These results underline the importance of considering both LVEDV and LVEF to define LVAR but do not favor the routine analysis of early LVAR with CMR to identify patients at high risk of cardiovascular events, because this strategy provides delayed prognostic information and does not improve that provided by CMR-derived variables determined in the early setting.

TABLE 5 C-Statistic and NRI for Evaluation of Added Benefit of Different CMR Variables Alone and in Combined Models in Predicting the Primary Endpoint

	C-Statistic* (95% CI)	NRI† (95% CI) (%)
Decrease LVEF >3% and increase of LVEDV >15% at 6 months	0.714 (0.661 to 0.766)	4.7 (−19.8 to 14.5)
Change in LVEF at 6 months, %	0.694 (0.625 to 0.757)	3.3 (−12.5 to 23.4)
Change in LVEDV at 6 months, ml	0.708 (0.658 to 0.762)	−9.6 (−22.4 to 12.0)
Baseline IS, % of LV mass	0.701 (0.637 to 0.759)	−2.0 (−13.6 to 13.9)
Baseline LVEF, %	0.768 (0.707 to 0.820)	10.2 (−10.9 to 33.1)
Baseline LVEDV, ml	0.705 (0.645 to 0.762)	2.1 (−11.7 to 22.3)
6-month IS, % of LV mass	0.700 (0.636 to 0.762)	−0.3 (−14.7 to 19.1)
6-month LVEF, %	0.792 (0.732 to 0.846)	10.8 (−9.9 to 32.9)
6-month LVEDV, ml	0.746 (0.694 to 0.796)	1.3 (−21.2 to 28.7)
Model 1: Baseline LVEF (%) + IS (%) + LVEDV (ml)	0.770 (0.707 to 0.823)	12.9 (−8.4 to 33.7)
Model 2: Model 1 + decrease LVEF >3% and increase of LVEDV >15% at 6 months	0.798 (0.741 to 0.848)	8.0 (4.1 to 12.1)
Model 3: 6-month LVEF (%) + IS (%) + LVEDV (ml)	0.795 (0.737 to 0.848)	8.7 (−7.7 to 39.9)

The primary endpoint is cardiovascular death, heart failure, or ventricular arrhythmias. *Adjusted for sex and age. †NRI assessed at median follow-up. Every value represents the NRI of patients with a higher risk (>20%) for the primary outcome, of each model over a baseline model including the variables sex and age.

NRI = net reclassification improvement; other abbreviations as in Tables 1 and 3.

LVEF AND LVEDV IN POST-INFARCTION REMODELING. LVEF is a key prognostic factor in coronary heart disease and should be assessed in all patients after a STEMI (23). Patients with reduced LVEF have a greater likelihood of developing progressive LVEDV and LVESV dilation during follow-up. However, a subgroup of patients with normal baseline LVEF can also increase the ventricular volumes over time (24). Wu et al. (24) showed that 15% of patients with a smaller infarct size (<18.5% of LV mass) developed LVAR (defined as an increase in LVEDV >10 ml/m^2) and 60% of patients with larger IS (≥18.5% of LV mass) did not present LVAR. Thus, IS and LV function in the acute phase do not permit accurate prediction of LVAR occurrence. This could be explained in part by subtle abnormalities of segmental LV function that are not amenable to quantification with a global endpoint such as LVEF. Thus, LVAR has been proposed as a surrogate marker in clinical trials (21,25) and as a parameter to predict outcomes (26,27). Variables measuring LVAR are expected to be more closely correlated with clinical outcomes because they integrate different aspects of post-infarction pathophysiology. Some are global (e.g., LV volumes) and some regional (e.g., LVEF or strain).

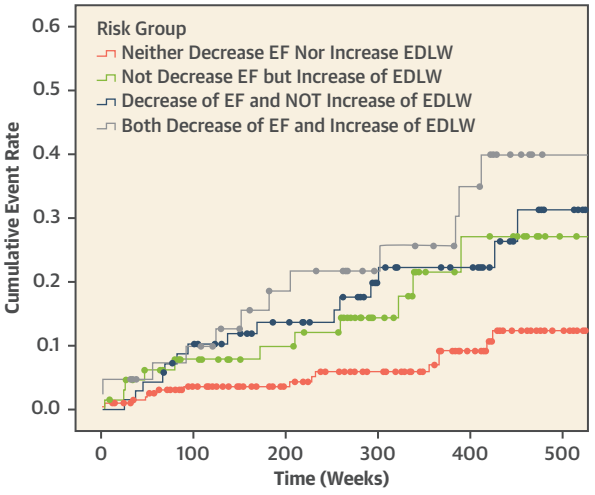
After a STEMI, the loss of contractile activity in the infarct segments and its expansion may increase wall tension in distant LV wall segments. In the infarcted segments, early neutrophil infiltration and proinflammatory cytokine liberation recruit other inflammatory cells that are involved in removing necrotic cardiomyocytes and in the differentiation of fibroblasts into myofibroblasts that play an essential role in the healing process (28). The reparative phase is associated with reductions in proinflammatory cells and an increase in anti-inflammatory Ly6C^{low}, mononuclear cell, and M2 macrophages. Increased wall stress in the healthy distant myocardium may lead to progressive eccentric hypertrophy, LV dilation, heart failure, and LVAR (29). It is important to note that salvaged and distant myocardia are also infiltrated by inflammatory cells that modulate hypertrophy and fibrosis (30,31).

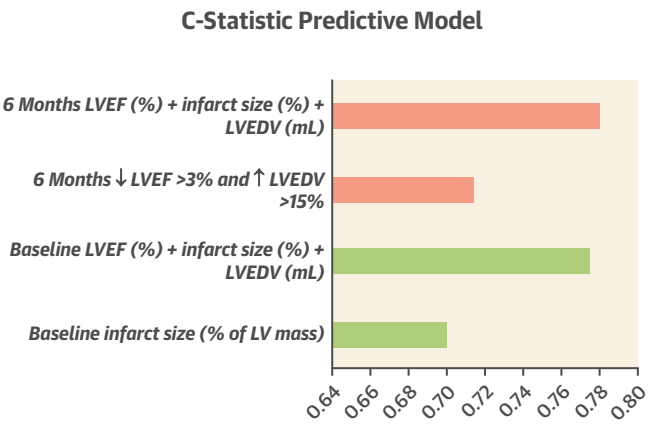
Our results showed that patients with major cardiovascular events presented a trend toward a higher increase in LVEDV at 6 months when compared with those without events; however, these differences did not reach statistical significance ($p = 0.224$). Furthermore, the predictive model (using C-statistic analysis and the NRI) of the combination of increase in LVEDV and reduction in LVEF was superior (C-statistic: 0.714; 95% CI: 0.661 to 0.766) to that estimated by the LVEDV individually. Although a 3% reduction in LVEF may be subtle, these variations can be identified (32) because of the accuracy and reproducibility of CMR. A recent study showed that treatment with intravenous beta-blockers in STEMI patients can induce changes in LVEF of the same magnitude (an improvement in LVEF of 3.49%) (33). Our results, however, failed to demonstrate that direct observation of LVAR at 6 months is superior to data from CMR in the acute phase for predicting outcomes.

CENTRAL ILLUSTRATION **Best Definition of LV Adverse Remodeling and its Prognostic Implications**

379 patients with STEMI receiving PCI
CMR at baseline and at 6 months follow-up
Mean follow-up: 72.9 ± 42.8 months

Primary endpoint:
- Cardiovascular death
- Hospitalization for heart failure
- Ventricular arrhythmias





LV remodeling definition with best prognostic implications : ↓ LVEF >3% and ↑ LVEDV >15% at 6 months

LV adverse remodeling does not add prognostic information over basal CMR

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LV adverse remodeling definition with best prognostic implications includes an increase in LVEDV >15% and a concomitant reduction of LVEF >3%. However, the occurrence of LV adverse remodeling during the first 6 months of evolution post-STEMI does not add prognostic information over that provided by basal CMR. CMR = cardiac magnetic resonance; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

IS AND LV CHANGES IN THE ACUTE PHASE OF STEMI. CMR has been considered the gold standard technique in the assessment of both acute and chronic MI (34). Several studies in STEMI patients have shown IS and LV dysfunction severity to be closely related (5,24). Hence, the main objective of myocardial reperfusion is to reduce of IS (35), and PCI, when performed early, may limit adverse post-infarction remodeling (9). However, different studies have shown that PCI results in little myocardial salvage in most patients when performed beyond 4 h after symptom onset and, in a substantial number of patients, myocardial salvage is slight after shorter ischemic times (13,23,35,36). However, there is solid evidence that reperfusion within 12 h of symptom onset improves the prognosis of patients with STEMI, and that this effect is mediated somehow in part through the beneficial effect on infarct healing and scar formation (35,37). Our results show that a model based on the information provided by early CMR (LVEDV, IS, and LVEF) is superior to a model based on the presence of LVAR (C-statistic: 0.770 [95% CI: 0.707 to 0.823] vs. 0.714 [95% CI: 0.661 to 0.766]) and as good as a model based on the information provided by CMR at 6 months (**Central Illustration**). These results are consistent with previous studies showing the prognostic significance of acute IS to predict outcomes after a STEMI (11,13). In a recent multicenter study, Eitel et al. (11) demonstrated that after an AMI, an LVEF ≤47%, IS ≥19% LV, and the presence of MVO

predicted the occurrence of major adverse cardiac events.

A recent meta-analysis showed IS measured by CMR or single-photon emission computed tomography 1 month after PCI to be strongly associated with 1-year hospitalization for heart failure and all-cause mortality (13). Furthermore, both microvascular obstruction and intramyocardial hemorrhage are associated with larger IS, adverse LV remodeling, and worse clinical outcomes. Given the prognostic significance of the information obtained from the early CMR, it is not surprising that the information obtained from the follow-up CMR does not increase its prognostic value. Also, the reduction in the IS at follow-up usually occurs in the first 4 months after a STEMI with few subsequent changes, and thus it is not justified to delay the evaluation of the patient 6 or more months (38). Finally, in our study, the early CMR was performed at a mean of 6.2 days after the STEMI when most of the dynamic changes in the infarcted area (e.g., edema, microvascular obstruction) had occurred and the necrosis was more stable (39). This could also potentially influence the absence of an increase in the prognostic value of the follow-up CMR.

Overall, these results are consistent with the notion that early changes in the LV in the acute phase of STEMI, as evaluated by CMR, summarize both effects of reperfusion and are important in determining LVAR and outcomes.

STUDY LIMITATIONS. CMR at 6 months could not be performed in 94 of 498 patients, which could imply a risk of selection bias. However, baseline data of these patients were like those who had the second CMR performed (Supplemental Table 2). Additionally, 25 patients were lost to follow-up; however, their baseline characteristics did not differ from those of patients followed up and with 2 CMR studies (Supplemental Table 3).

CONCLUSIONS

The definition of LV remodeling that best predicts adverse cardiovascular events should consider both the increase in LVEDV and the reduction in LVEF. In this regard, an increase in LVEDV (>15%) in the presence of a decrease in LVEF (>3%) implies worse prognosis. However, assessment of LVAR does not increase the prognostic value of the principal CMR-derived variables provided by the early CMR.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Our results show that the criteria for defining LVAR should include not only changes in LVEDV but also in LVEF to provide better prognostic information and yield optimal cutoff values for LVEDV and LVEF in the case of CMR. The present study also helps to establish which patients may benefit most from this technique and at what time after PCI it should be performed to give the most useful clinical information. Our data show that CMR during the acute phase of STEMI may identify patients at higher risk of developing adverse outcomes during the following months and years, whereas a routine second examination at 6 months does not add significant prognostic information and has the major limitation of not permitting prediction of events during the first 6 months of follow-up.

TRANSLATIONAL OUTLOOK: LV remodeling after STEMI is a long-term process; however, most studies evaluate LVAR between the third and sixth months post-AMI. Further studies should determine the best time to evaluate its presence for prognostic purposes. Furthermore, LVAR defined considering changes in LVEF in addition to LVEDV better predicts adverse events and has more potential value as a surrogate endpoint in clinical studies in patients with STEMI receiving PCI.

REFERENCES

1. Mehta RH, Harjai KJ, Cox D, et al., for the PAMI Investigators. Clinical and angiographic correlates and outcomes of suboptimal coronary flow in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention. J Am Coll Cardiol 2003;42:1739–46.

2. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. Circulation 2011;123:e18–209.

3. Carrick D, Haig C, Rauhalammi S, et al. Pathophysiology of LV remodeling in survivors of STEMI inflammation, remote myocardium, and prognosis. J Am Coll Cardiol Img 2015;8:779–89.

4. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction: experimental observations and clinical implications. Circulation 1990;81:1161–72.

5. Bolognese L, Neskovic AN, Parodi G, et al. Left ventricular remodeling after primary coronary angioplasty: patterns of left ventricular dilation and long-term prognostic implications. Circulation 2002;106:2351–7.

6. Bulluck H, Go YY, Crimi G, et al. Defining left ventricular remodeling following acute ST-segment elevation myocardial infarction using cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2017;19:26.

7. St. John Sutton M, Pfeffer MA, Moye L, et al. Cardiovascular death and left ventricular remodeling two years after myocardial infarction: baseline predictors and impact of long-term use of captopril: information from the Survival and Ventricular Enlargement (SAVE) trial. Circulation 1997;96:3294–9.

8. Brooks GC, Lee BK, Rao R, et al. Predicting persistent left ventricular dysfunction following myocardial infarction. J Am Coll Cardiol 2016;67:1186–96.

9. Sheiban I, Fragasso G, Rosano GMC, et al. Time course and determinants of left ventricular function recovery after primary angioplasty in patients with acute myocardial infarction. J Am Coll Cardiol 2001;38:464–71.

10. Sjöblom J, Muhrbeck J, Witt N, Alam M, Frykman-Kull V. Evolution of left ventricular ejection fraction after acute myocardial infarction implications for implantable cardioverter-defibrillator eligibility. Circulation 2014;130:743–8.

11. Eitel I, de Waha S, Wöhrle J, et al. Comprehensive prognosis assessment by CMR imaging after ST-segment elevation myocardial infarction. J Am Coll Cardiol 2014;64:1217–26.

12. Izquierdo M, Ruiz-Granell R, Bonanad C, et al. Value of early cardiovascular magnetic resonance for the prediction of adverse arrhythmic cardiac events after a first noncomplicated ST-segment-elevation myocardial infarction. Circ Cardiovasc Imaging 2013;6:755–61.

13. Stone GW, Selker HP, Thiele H, et al. Relationship between infarct size and outcomes following primary PCI: patient-level analysis from 10 randomized trials. J Am Coll Cardiol 2016;67:1674–83.

14. Bodí V, Sanchis J, López-Lereu MP, et al. Usefulness of a comprehensive cardiovascular magnetic resonance imaging assessment for predicting recovery of left ventricular wall motion in the setting of myocardial stunning. J Am Coll Cardiol 2005;46:1747–52.

15. Garcia-Dorado D, García-del-Blanco B, Otaegui I, et al. Intracoronary injection of adenosine before reperfusion in patients with ST-segment elevation myocardial infarction: a randomized controlled clinical trial. Int J Cardiol 2014;177:935–41.

16. Ibanez B, James S, Agewall S, et al., for the ESC Scientific Document Group. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119–77.

17. Budczies J, Klauschen F, Sinn BV, et al. Cutoff finder: a comprehensive and straightforward Web application enabling rapid biomarker cutoff optimization. PLoS One 2012;7:e51862.

18. Gheorghiade M, Bonow RO. Chronic heart failure in the United States: a manifestation of coronary artery disease. Circulation 1998;97:282–9.

19. Goldberg RJ, Konstam MA. Assessing the population burden from heart failure: need for sentinel population-based surveillance systems. Arch Intern Med 1999;159:15–7.

20. Gaudron P, Eilles C, Kugler I, Ertl G. Progressive left ventricular dysfunction and remodeling after myocardial infarction: potential mechanisms and early predictors. Circulation 1993;87:755–63.

21. Cung TT, Morel O, Cayla G, et al. Cyclosporine before PCI in patients with acute myocardial infarction. N Engl J Med 2015;373:1021–31.

22. Savoye C, Equine O, Tricot O, et al. Left ventricular remodeling after anterior wall acute myocardial infarction in modern clinical practice (from the REmodelage VEntriculaire [REVE] study group). Am J Cardiol 2006;98:1144–9.

23. Ndrepepa G, Mehilli J, Martinoff S, Schwaiger M, Schömig A, Kastrati A. Evolution of left ventricular ejection fraction and its relationship to infarct size after acute myocardial infarction. J Am Coll Cardiol 2007;50:149–56.

24. Wu E, Ortiz JT, Tejedor P, et al. Infarct size by contrast enhanced cardiac magnetic resonance is a stronger predictor of outcomes than left ventricular ejection fraction or end-systolic volume index: prospective cohort study. Heart 2008;94:730–6.

25. Perin EC, Willerson JT, Pepine CJ, et al., for the CCTRN Investigators. Effect of transendocardial delivery of autologous bone marrow mononuclear cells on functional capacity, left ventricular function, and perfusion in chronic heart failure: the FOCUS-CCTRN trial. JAMA 2012;307:1717–26.

26. Torabi A, Cleland JGF, Khan NK, et al. The timing of development and subsequent clinical course of heart failure after a myocardial infarction. Eur Heart J 2008;29:859–70.

27. Kramer DG, Trikalinos TA, Kent DM, Antonopoulos GV, Konstam MA, Udelson JE. Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction. J Am Coll Cardiol 2010;56:392–406.

28. Frangogiannis NG. The inflammatory response in myocardial injury, repair, and remodelling. Nat Rev Cardiol 2014;11:255–65.

29. Shah AM, Solomon SD. A unified view of ventricular remodelling. Eur J Heart Fail 2010;12:779–81.

30. Inserte J, Hernando V, Garcia-Dorado D. Contribution of calpains to myocardial ischaemia/reperfusion injury. Cardiovasc Res 2012;96:23–31.

31. Frangogiannis NG. Regulation of the inflammatory response in cardiac repair. Circ Res 2012;110:159–73.

32. Grothues F, Smith GC, Moon JC, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. Am J Cardiol 2002;90:29–34.

33. Pizarro G, Fernández-Friera L, Fuster V, et al. Long-term benefit of early pre-reperfusion metoprolol administration in patients with acute myocardial infarction: results from the METOCARD-CNIC trial (Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction). J Am Coll Cardiol 2014;63:2356–62.

34. Kim RJ, Fieno DS, Parrish TB, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation 1999;100:1992–2002.

35. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13–20.

36. Fieno DS, Hillenbrand HB, Rehwald WG, et al. Infarct resorption, compensatory hypertrophy, and differing patterns of ventricular remodeling following myocardial infarctions of varying size. J Am Coll Cardiol 2004;43:2124–31.

37. Chan W, Duffy SJ, White DA, et al. Acute left ventricular remodeling following myocardial infarction: coupling of regional healing with remote extracellular matrix expansion. J Am Coll Cardiol Img 2012;5:884–93.

38. Pokorney SD, Rodriguez JF, Ortiz JT, Lee DC, Bonow RO, Wu E. Infarct healing is a dynamic process following acute myocardial infarction. J Cardiovasc Magn Reson 2012;14:62.

39. Bulluck H, Hammond-Haley M, Weinmann S, Martinez-Macias R, Hausenloy DJ. Myocardial infarct size by CMR in clinical cardioprotection studies: insights from randomized controlled trials. J Am Coll Cardiol Img 2017;10:230–40.

KEY WORDS cardiac magnetic resonance, infarct size, left ventricular ejection fraction, left ventricular end-diastolic volume, left ventricular end-systolic volume, left ventricular remodeling, microvascular obstruction, prognosis, ST-segment elevation myocardial infarction

APPENDIX For a supplemental appendix including tables, please see the online version of this paper.