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Long-term prognostic value of late gadolinium enhancement and periprocedural myocardial infarction after uncomplicated revascularization: MASS-V follow-up

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Aims Cardiac biomarkers elevation is common after revascularization, even in absence of periprocedural myocardial infarction (PMI) detection by imaging methods. Thus, late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) may be useful on PMI diagnosis and prognosis. We sought to evaluate long-term prognostic value of PMI and new LGE after revascularization.

Methods and results Two hundred and two patients with multivessel coronary disease and preserved ventricular function who underwent elective revascularization were included, of whom 136 (67.3%) underwent coronary artery bypass grafting and 66 (32.7%) percutaneous coronary intervention. The median follow-up was 5 years (4.8–5.8 years). Cardiac biomarkers measurement and LGE-CMR were performed before and after procedures. The Society for Cardiovascular Angiography and Interventions definition was used to assess PMI. Primary endpoint was composed of death, infarction, additional revascularization, or cardiac hospitalization. Primary endpoint was observed in 29 (14.3%) patients, of whom 13 (14.9%) had PMI and 16 (13.9%) did not ($P = 0.93$). Thirty-six (17.8%) patients had new LGE. Twenty (12.0%) events occurred in patients without new LGE and 9 (25.2%) in patients with it ($P = 0.045$). LGE was also associated to increased mortality, with 4 (2.4%) and 4 (11.1%) deaths in subjects without and with it ($P = 0.02$). LGE was the only independent predictor of primary endpoint and mortality ($P = 0.03$ and $P = 0.02$). Median LGE mass was estimated at 4.6 g. Patients with new LGE had a greater biomarkers release (median troponin: 8.9 ng/mL vs. 1.8 ng/mL and median creatine kinase-MB: 38.0 ng/mL vs. 12.3 ng/mL; $P < 0.001$ in both comparisons).

Conclusions New LGE was shown to be better prognostic predictor than biomarker-only PMI definition after uncomplicated revascularization. Furthermore, new LGE was the only independent predictor of cardiovascular events and mortality.

Clinical trial registration http://www.controlled-trials.com/ISRCTN09454308.

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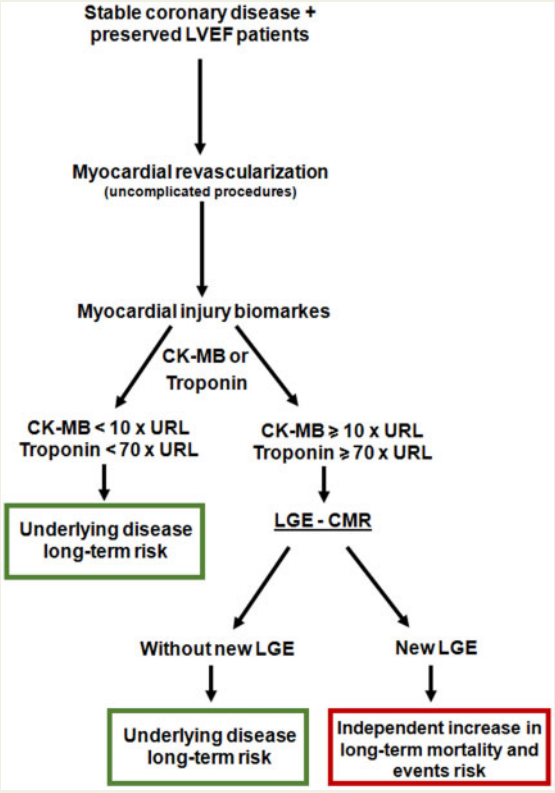
Graphical Abstract



Keywords Coronary artery disease • Myocardial infarction • Cardiac imaging techniques • Biomarkers • Magnetic resonance imaging • prognosis

Introduction

Cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE) identifies areas of myocardial infarction in acute and chronic coronary artery disease (CAD).[1] In patients with acute coronary syndromes, LGE presence seems to be an independent prognostic predictor for cardiovascular events.[2,3] Other studies, however, have not shown an association of the extent of infarction evaluated by LGE-CMR with increased risk of clinical outcomes.[4]

After myocardial revascularization procedures, there is no clear role for LGE-CMR after angioplasty or surgery. However, it could be useful as a diagnostic tool to identify patients presenting periprocedural myocardial infarction (PMI), including the small ones not detected by traditional imaging methods.[5–7] In fact, there is still controversy over which is the optimal definition for the diagnosis of PMI. These definitions differ regarding the cut-off values of myocardial injury biomarkers and the use or not of imaging methods.[8,9]

Thus, among patients with stable CAD undergoing elective revascularization procedures and presenting post-procedural elevation of cardiac biomarkers, there is a lack of evidence on which is the best method of risk stratification and prognostic prediction in long-term follow-up.

The aim of this study is to evaluate the prognostic value of occurrence of new LGE-CMR compared to PMI based only on myocardial biomarkers elevation after uncomplicated elective revascularization procedures in a long-term follow-up.

Methods

The present study is a prospective and pre-specified analysis of Medicine, Angioplasty, or Surgery Study V (MASS-V) trial. Details of MASS-V trial design, protocol, patient selection, and inclusion criteria have been previously reported.[10] Briefly, patients with angiographically documented proximal multivessel coronary stenosis of more than 70% by visual assessment were included. Ischaemia was documented by stress testing and angina was assessed by Canadian Cardiovascular Society (Class II or III) classification. All patients were candidates for elective percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) and referred to procedures according to physician's discretion. Left ventricular ejection fraction (LVEF) greater than 55% was documented by echocardiography and/or CMR. Patients were excluded if they experienced

any or all of previous mechanical interventions, recent thromboembolic phenomena, systemic inflammatory disease, or renal failure.

Myocardial revascularization

PCI was performed according to a standard protocol that included administration of aspirin and clopidogrel before the procedure. The interventional cardiologist was encouraged to treat all arteries that were likely to contribute to ischaemia and/or had lesions with >70% diameter stenosis. Device used were bare metal stents. Dilatation of a stenotic vessel was considered successful if residual stenosis of lumen diameter was <50%. Patients treated with coronary stents were maintained on dual antiplatelet regimen for at least 1 month in addition to lifelong aspirin.

For patients assigned to CABG, cardiac surgeon was encouraged to intervene in all feasible stenosed arteries in attempt to accomplish anatomic complete revascularization. Use of internal mammary conduits was strongly advised for all cases. The surgical team performed the appropriate coronary revascularization technique in accordance with current best practices. Surgeons with proven experience in both with and without cardiopulmonary bypass (CPB) surgery performed the procedures. Cold crystalloid cardioplegia for myocardial protection was used. The Octopus stabilizer (Medtronic, Inc, Minneapolis, MN, USA) was used for CABG without CPB.

Biomarkers measurement

Blood samples were collected for measurement of troponin (cTnI) and creatine kinase-MB (CK-MB) mass immediately before PCI and 6, 12, 24, 36, and 48 h after. For patients undergoing CABG, these markers were measured immediately before and 6, 12, 24, 36, 48, and 72 h after procedure. The treating surgeon and clinical team were blinded to CK-MB or cTnI data. All samples were centrifuged at 3000 rpm for 20 min and analysed within 2 h after collection. Analyses of cTnI and CK-MB were performed using an ADVIA Centaur immunoassay analyzer (Siemens Health Care Diagnostics, Tarrytown, NY, USA). According to manufacturer, lower limit of detection of cTnI is 0.006 ng/mL, and 99th percentile upper reference limit (URL) is 0.04 ng/mL. The assay precision represented by percentage coefficient of variation is 10% at 0.03 ng/mL. The detection limit of CK-MB mass kit is 0.18 ng/mL. Cut-off values at 99th percentile are 3.8 ng/mL for women and 4.4 ng/mL for men. Coefficient of variations for CK-MB mass, as specified by manufacturer, are 3.91% at 3.55 ng/mL and 3.67% at 80.16 ng/mL.

PMI was defined for CABG and PCI as the occurrence of CK-MB $\geq 10 \times$ URL or Troponin $\geq 70 \times$ URL, based on Society for Cardiovascular Angiography and Interventions (SCAI) definition. We have used only myocardial injury biomarkers cut-offs for PMI definition, regardless electrocardiogram abnormalities.[8]

Cardiac magnetic resonance

All patients were studied in CMR before procedure and after CABG or PCI during hospital stay. A 1.5 Tesla (Philips Achieva®) magnetic resonance scanner was used with images acquired on two long axes (two and four chambers) and between 8 and 10 short axes of left ventricle. The gadolinium-based contrast agent (GadoteratemeglumineGd-DOTA®, Guerbet SA®, France) was then injected intravenously (0.1 mmol per kg body weight), and contrast images acquired after an interval of 5–10 min same previous plans. The typical voxel size was $1.6 \times 2.1 \times 8$ mm, with a reconstruction matrix of 528 and a reconstructed voxel size of 0.6 mm. Delayed enhancement of CMR was performed with a phase-sensitive inversion recovery sequence (repetition time 6.1, echo time 3.0 ms, voxel size $1.6 \times 2.1 \times 8$ mm, flip angle 25°) following the administration of contrast agent. Images were acquired in two long-axis planes and in a short-axis stack covering the entire left ventricle. The inversion time was meticulously adjusted throughout the acquisition to obtain optimal nulling of remote normal myocardium. The slice thickness at the apex was reduced to 5 mm to avoid a partial volume effect. The method of obtaining and analysing CMR is standardized in our service and reproduced according to conventional techniques. Images were analysed by two experienced observers, with addition of a third one when consensus was not obtained initially, all without knowledge of biochemical and surgical data. New LGE areas were defined as an image intensity greater than 2 SDs above mean intensity in a remote region of the myocardium in same image and quantified with Computer-aided Planimetry program CMR42 (Circle Cardiovascular Image—Calgary—Canada). In order to avoid possible mistakes, after semi-automatic assessment, visual assessment was also performed. Moreover, preintervention and post-intervention scans were read side by side in all patients.

Patient follow-up

Patients were followed up on a periodic outpatient visits, initially 1 month after procedure, every 6 months in first year and thereafter every year. Optimal medical treatment was used to maintain patients without symptoms. All patients were placed on an optimal medical regiment consisting of a stepped-care approach using nitrates, aspirin, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, or a combination of these drugs, unless contraindicated. Statins were also prescribed, along with a low-fat diet on an individual basis. In addition, blood pressure, lipid and glucose levels were treated as recommended by current guidelines. The medications were provided for free by the Heart Institute. The protocol investigators were blinded to biochemical results regarding elevation of myocardial injury biomarkers and CMR reports. All patients received quite similar treatment, regardless biomarkers elevation or new LGE.

Trial outcomes

The primary outcome was the time to the first occurrence of a composite endpoint including death, myocardial infarction, additional revascularization, or hospitalization due to cardiovascular causes (unstable angina or heart failure). Secondary endpoints consisted of isolated evaluation of each component of primary endpoint.

Myocardial infarction during follow-up was defined as elevation of troponin above 99th percentile, associated to ischaemia evidence (clinical or electrocardiographic).[9] Hospitalizations considered were those related to unstable angina (worsening of angina pattern due to increased frequency, intensity, or duration) or to heart failure (dyspnoea on exertion associated with orthopnoea, nocturnal paroxysmal dyspnoea, or lower limb oedema).

Statistical analysis

Kolmogorov–Smirnov test was used to evaluate distribution of continuous variables. Quantitative variables were expressed as means and standard deviations, when normal, or median and interquartile ranges when normality test was rejected. Qualitative variables were expressed as absolute and relative frequencies. Continuous variables with normal distribution were compared using Student's *t*-test and those with non-normal distribution were compared using the Wilcoxon rank-sum test. Assessment of homogeneity between proportions was performed using χ^2 test.

Event rates were estimated using Kaplan–Meier method, and differences between groups using log-rank test. Univariate analysis of Cox proportional hazards regression was used to establish risk of new LGE and PMI at occurrence of primary endpoint. Besides, adjusted models were

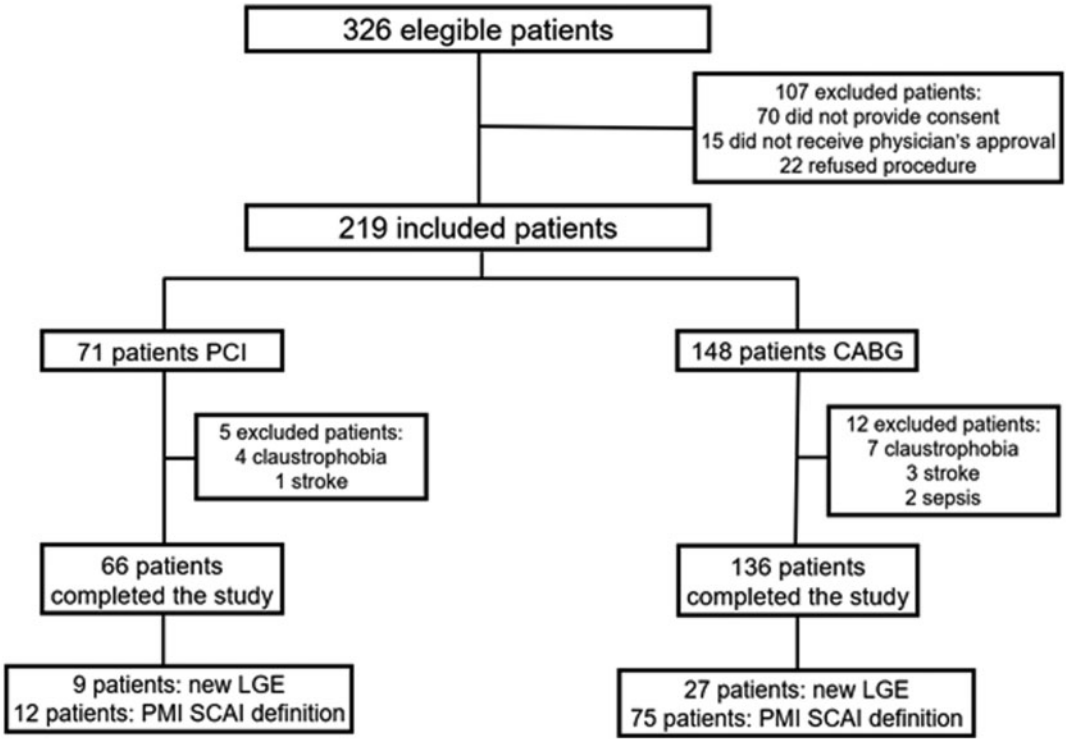


Figure 1 Derivation of patients included in this study. CABG, coronary artery bypass grafting; LGE, late gadolinium enhancement; PCI, percutaneous coronary intervention; PMI, periprocedural myocardial infarction; SCAI, Society for Cardiovascular Angiography and Interventions.

constructed including as covariates variables with association to clinical events with significant difference between compared groups. Demographic, clinical, laboratorial, and angiographic variables were considered in this analysis. The assumption of proportional hazards was verified for every model using time-dependent Cox models using time as a continuous variable. In addition, a multivariate analysis was performed to identify independent predictors of primary outcome and mortality. In this analysis, variables associated to primary outcome with marginal statistical significance ($P < 0.20$) in univariate analysis were included in the model. Stepwise backward method was used with criterion of $P < 0.05$ for permanence in final model.

The effects of treatment strategies according to the presence of LGE or PMI occurrence were estimated using a contrast of main effects and interaction effects for treatment without further covariate adjustment. The statistical significance of differences in the effect of LGE or PMI occurrence on each endpoint was evaluated using the full population and a multiplicative interaction term.

Statistical analysis was performed using SPSS software version 21 for Macintosh and tests were performed considering a significance level of 5%. The data underlying this article will be shared on reasonable request on the corresponding author.

Results

Between May 2012 and March 2014, 326 patients were allocated to elective myocardial revascularization procedures at Heart Institute (InCor) of Hospital das Clínicas-São Paulo, Brazil. From this sample, 202 individuals were included, of which 136 (67.3%) underwent CABG and 66 (32.7%) PCI (*Figure 1*). After procedures, patients were followed-up for a median follow-up of 5.0 years (interquartile range 4.8–5.8).

Demographic, laboratory, and angiographic characteristics

The sample had a total of 135 (66.8%) male patients and a mean age of 62.1 years. At admission, 171 (84.6%) individuals had hypertension, 90 (44.5%) were on diabetes mellitus treatment, 58 (28.7%) were actual or former smokers, and 65 (32.2%) had previous myocardial infarction (*Table 1*).

There was no baseline elevation of CK-MB (mean value: 1.34 ng/mL) or troponin (mean value: 0.037 ng/mL). Patients had preserved LVEF, and myocardial ischaemia was documented by non-invasive methods in 173 (79%) patients. Of these, 41 patients underwent scintigraphy and 132 patients underwent exercise testing. Most of patients (66.8%) had three-vessel CAD and lesion in left anterior descending artery was present in 181 (89.6%) cases. The mean value of SYNTAX Score was 21.

CABG was performed with CPB in 69 patients and without CPB in 67 patients. Five hundred and forty-four anastomoses were performed (mean of 3.4 per patient). In PCI group, 211 stents (mean of 3.1 per patient) were used. There was no death, myocardial infarction, and need for revascularization or major complications related to procedures in any of intervention groups.

PMI according to SCAI definition and outcomes

PMI occurred in 87 (43.1%) patients, of whom 12 (33.3%) and 75 (45.1%) individuals in percutaneous and surgical groups, respectively. Baseline characteristics of patients with and without PMI were quite similar, except for a higher proportion of surgical treatment and higher SYNTAX Score values in patients that met PMI SCAI criteria (*Table 2*).

During follow-up, primary outcome was observed in 29 (14.3%) patients, of whom 13 (14.9%) and 16 (13.9%) occurred in patients with and without PMI, respectively ($P = 0.93$) (*Figure 2* and *Table 3*).

There were no significant differences in the rates of death, myocardial infarction, additional revascularization, and hospitalization due to cardiovascular causes ($P = 0.77$, $P = 0.32$, $P = 0.38$, and $P = 0.11$, respectively) (*Table 3*).

New LGE and outcomes

After interventional procedures, 36 (17.8%) patients presented new LGE, which 27 (19.8%) and 9 (13.6%) in CABG and PCI groups, respectively. Patients who did not present new LGE had higher values of SYNTAX Score (*Table 2*). Patients underwent CMR in a median follow-up of 6 days from first CMR to procedure and 7 days from procedure to second CMR. The median LGE mass in grams was 4.6 g. Patients with post-procedure new LGE had a greater biomarkers release (median troponin 8.9 ng/mL vs. 1.8 ng/mL and median CK-MB 38.0 ng/mL vs. 12.3 ng/mL; $P < 0.001$ in both comparisons).

During follow-up, primary outcome was observed in 29 (14.3%) patients. Twenty (12.0%) of them occurred in group without new LGE and 9 (25.2%) in patients with new LGE ($P = 0.045$) (*Figure 2* and *Table 3*). Cox proportional risk analysis showed a higher risk for cardiovascular events in new LGE patients [hazard ratio (HR) 2.24: 95% confidence interval (CI) 1.02–4.93, $P = 0.04$]. This association persisted even after adjustment for SYNTAX Score (adjusted HR 2.45: 95% CI 1.10–5.50, $P = 0.03$) (*Table 4*).

New LGE was also associated to increased rate of mortality (*P* log-rank = 0.02, adjusted HR = 4.87, 95% CI 1.18–20.11; $P = 0.03$) (*Figure 3* and *Table 4*). Moreover, after multivariate analysis in a model including clinical, laboratorial, angiographic and imaging-derived variables, new LGE was shown to be the only independent predictor of primary endpoint and mortality (*Tables 5* and Supplemental data online, *Table S1*). *Figure 4* shows an example of post-procedure new LGE.

There was no significant difference in incidence of myocardial infarction, additional revascularization and hospitalization due to cardiovascular causes ($P = 0.25$, $P = 0.25$, and $P = 0.21$, respectively) (*Table 3*).

Therapeutic strategy choice (surgical or percutaneous) did not modify the effect of new LGE or PMI on the primary endpoint ($P_{interaction}$ were 0.70 and 0.93, respectively).

Of 202 patients, eight patients had a new Q wave on electrocardiogram. All of these patients had a post-procedure new LGE. New Q wave, however, was not a predictor of increased primary endpoint incidence (HR 0.98: 95% CI 0.13–7.23: $P = 0.98$).

Table 1 Baseline patient characteristics

Baseline characteristics ($n = 202$)	
Age (years)	62.1 ± 9.2
Male (%)	135 (66.8)
Hypertension (%)	171 (84.6)
Diabetes (%)	90 (44.5)
Smoking (%)	58 (28.7)
Previous infarction (%)	65 (32.2)
Creatinin (mean, mg/dL)	1.05 ± 0.27
LDL cholesterol (mean, mg/dL)	100.6 ± 36.2
LVEF (mean, %)	66 ± 11
ECG Q-wave (%)	15 (7.4%)
Heart rate (median, bpm)	64 (60–66)
SBP (median, mmHg)	130 (120–150)
DBP (median, mmHg)	80 (70–80)
GFR (median, mL/min/1.73 m^2)	71.6 (61.6–84.7)
Medication	
Acetylsalicylic acid (%)	202 (100)
Clopidogrel (%)	25 (12.4)
Statin (%)	194 (96)
Other hypolipidaemic drug (%)	21 (10.4)
ACE inhibitor (%)	99 (49)
Angiotensin receptor blocker (%)	58 (28.7)
Beta blocker (%)	182 (90.1)
Calcium channel blocker (%)	68 (33.7)
Nitrate (%)	49 (24.3)
Baseline troponin (mean, ng/mL)	0.037 ± 0.204
Baseline CK-MB (mean, ng/mL)	1.34 ± 1.22
3-vessel CAD (%)	135 (66.8)
LAD lesion (%)	181 (89.6)
SYNTAX Score (mean)	21 ± 9
Surgical treatment (%)	136 (67.3)
CMR variables	
LVEDVI (median, mL/m^2)	57 (49–65)
LVESVI (median, mL/m^2)	19 (14–25)
LV mass (median, g)	108 (95–135)
RVEDVI (mean, mL/m^2)	51 ± 13
RVESVI (mean, mL/m^2)	21 ± 7
RVEF (mean, %), mean ± SD	59 ± 8
Wall motion abnormality[a] (%)	77 (38.1)
Previous LGE (%)	47 (23.3)

ACE, angiotensin converting enzyme; CAD, coronary artery disease; CKD, chronic kidney disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; LAD, left artery descending; LDL, low-density lipoprotein; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; RVEDVI, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVI, right ventricular end-systolic volume index; SBP, systolic blood pressure.
[a]Wall motion abnormality was considered when present in at least two segments.

Discussion

Main results of our study highlight a strong association between new LGE with cardiovascular events and mortality after elective and

Table 2 Characteristics of subjects according PMI SCAI definition and new LGE

	No PMI SCAI ($n = 115$)	PMI SCAI ($n = 87$)	*P*-value	No LGE ($n = 166$)	New LGE ($n = 36$)	*P*-value
Age (years)	62.0 ± 8.77	62.3 ± 9.9	0.82	61.8 ± 8.8	63.7 ± 10.8	0.31
Male (%)	78 (67.8)	57 (65.5)	0.73	112 (67.4)	23 (63.8)	0.50
Hypertension (%)	95 (82.6)	76 (87.4)	0.35	140 (84.3)	31 (86.1)	0.87
Diabetes (%)	51 (44.3)	39 (44.8)	0.95	73 (43.9)	17 (47.2)	0.85
Smoking (%)	31 (26.9)	27 (31.0)	0.46	47 (28.3)	11 (30.5)	0.90
Previous infarction (%)	39 (33.9)	26 (29.9)	0.54	53 (31.9)	12 (33.3)	0.97
Creatinin (mean, mg/dL)	1.05 ± 0.26	1.04 ± 0.27	0.77	1.05 ± 0.26	1.05 ± 0.30	0.92
LDL cholesterol (mean, mg/dL)	100.3 ± 34.6	100.9 ± 38.4	0.91	99.6 ± 35.9	104.9 ± 37.8	0.44
LVEF (mean, %)	65 ± 9	64 ± 9	0.07	67 ± 9	62 ± 15	0.09
ECG Q-wave (%)	6 (5.2)	9 (10.3)	0.17	11 (6.6)	4 (11.1)	0.38
Heart rate (median, bpm)	64 (60–66)	65 (60–68)	0.38	64 (60–66)	65 (60–70)	0.63
SBP (median, mmHg)	130 (120–150)	130 (120–150)	0.41	130 (120–150)	140 (120–151)	0.22
DBP (median, mmHg)	80 (70–84)	80 (70–80)	0.36	80 (70–80)	80 (70–81)	0.71
GFR (median, mL/min/1.73 m^2)	72.9 (62.2–83.6)	71.2 (60.4–85.3)	0.74	72.4 (61.6–84.8)	70.0 (59.8–83.9)	0.58
IVDFVE (median, mL/m^2)	58 (49–65)	56 (50–67)	0.74	56 (49–65)	60 (52–69)	0.24
IVSFVE (median, mL/m^2)	18 (14–23)	21 (14–28)	0.22	19 (14–25)	20 (13–28)	0.71
LV mass (median, g)	108 (95–138)	110 (95–133)	0.92	108 (95–134)	118 (102–153)	0.29
IVDFRV (mean, mL/m^2)	51 ± 14	51 ± 13	0.86	51 ± 14	51 ± 13	0.90
IVSFRV (mean, mL/m^2)	21 ± 7	21 ± 8	0.53	21 ± 7	22 ± 8	0.39
RVEF (mean, %)	59 ± 8	59 ± 8	0.94	59 ± 8	57 ± 8	0.37
Wall motion abnormality[a] (%)	41 (35.6)	36 (40.2)	0.41	60 (36.1)	17 (47.2)	0.28
Previous LGE (%)	28 (24.3)	19 (21.8)	0.68	39 (23.5)	8 (22.2)	0.79
Baseline troponin (mean, ng/mL)	0.030 ± 0.073	0.047 ± 0.047	0.56	0.024 ± 0.062	0.100 ± 0.470	0.35
Baseline CK-MB (mean, ng/mL)	1.40 ± 1.34	1.26 ± 1.26	0.44	1.37 ± 1.30	1.19 ± 0.70	0.25
3-vessel CAD (%)	74 (64.3)	61 (70.1)	0.39	107 (64.4)	28 (77.7)	0.20
LAD lesion (%)	105 (91.3)	76 (87.4)	0.36	146 (87.9)	35 (97.2)	0.27
SYNTAX Score (mean)	20 ± 8	23 ± 10	0.03	22 ± 10	19 ± 6	0.02
Surgical treatment (%)	61 (53.0)	75 (86.2)	<0.001	109 (65.6)	27 (75)	0.42

ACE, angiotensin converting enzyme; CAD, coronary artery disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; LAD, left artery descending; LDL, low-density lipoprotein; LGE, late gadolinium enhancement; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; PMI, periprocedural myocardial infarction; RVEDVI, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVI, right ventricular end-systolic volume index; SBP, systolic blood pressure; SCAI, Society for Cardiovascular Angiography and Interventions.
[a]Wall motion abnormality was considered when present in at least two segments.

uncomplicated revascularization procedures. Furthermore, new LGE was found to be an independent predictor of these endpoints.

Thus, considering our results, the new LGE was able to evaluate residual risk in a population of moderate to low risk of cardiovascular events, since all patients had stable CAD, preserved ventricular function and, in the majority, underwent surgical revascularization. Therefore, complementary evaluation by CMR, by means of LGE technique, added significant prognostic impact prediction.

In the other hand, PMI according to SCAI definition was not associated to increased risk of primary endpoint. Biomarkers elevation could represent myocardial damage and, in some cases, cellular necrosis. However, in our study, biomarkers elevation based on SCAI definition of clinically relevant PMI was not associated to increased risk of cardiovascular events. In fact, the increasing higher sensitivity of biomarkers kits, especially troponin, may lead to detection of small regions of myocardial injury without clinical relevance and, consequently, without prognostic impact.[11]

In this scenario, several mechanisms were proposed to justify cardiac biomarkers release.[12] In surgical revascularization, for example, it occurs in almost all CABG patients.[13] In general, this increase is not related to myocardial necrosis due to coronary or graft occlusion, but to other factors such as reperfusion injury, poor myocardial protection, surgical trauma, manipulation of intramyocardial vessels, and vasospasm.[14] In addition, aortic cannulation, ischaemia induced during anaesthesia and cardioplegia, activation of inflammatory mediators, and embolization of air of oxygenators are also involved in CPB procedures.[15] In PCI, transient occlusion of manipulated vessel, involvement of adjacent small vessels, thrombus formation, no reflow phenomena, coronary dissection, and distal embolization are the main mechanisms described.[16–18]

The association between cardiac biomarkers elevation and increased incidence of cardiovascular events has been reported. Ben-Yehuda *et al.*[19] described that peak post-procedure CK-MB ≥ 10 × URL predicted 3-year mortality after CABG and PCI in patients with

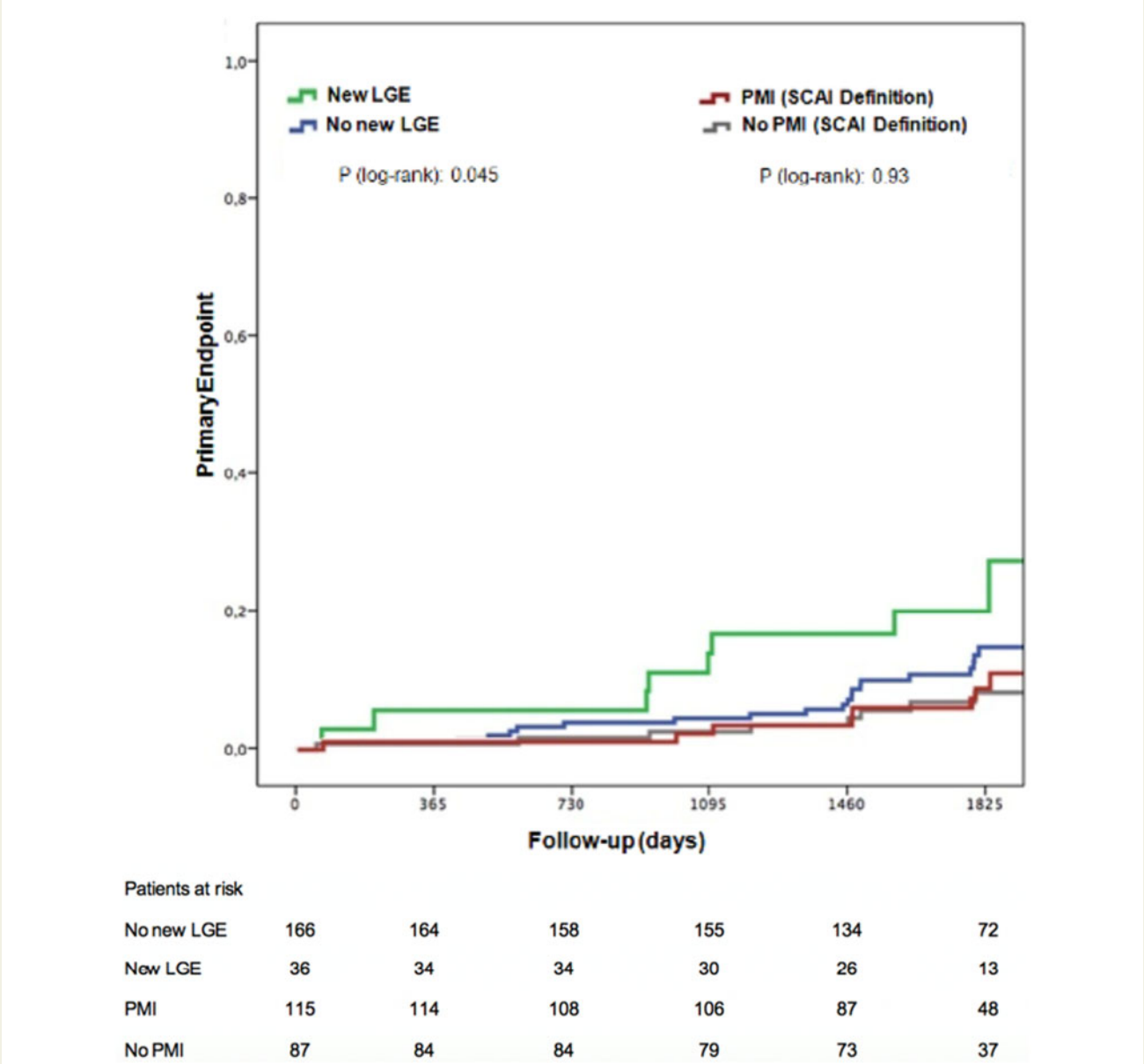


Figure 2 Cumulative incidence of primary endpoint in relation to PMI according to SCAI definition and new LGE. LGE, late gadolinium enhancement; PMI, periprocedural myocardial infarction; SCAI, Society for Cardiovascular Angiography and Interventions.

left main disease (adjusted HR 2.28, 95% CI 1.22–4.29; $P = 0.01$). This *post hoc* analysis of EXCEL trial, however, did not evaluate post-procedure troponin elevation or periprocedural non-invasive assessment of myocardial infarction by imaging methods. Conversely, Ndrepepa *et al.*[20] showed that troponin elevation after elective PCI was not associated with an increased risk of mortality (HR 1.04, 95% CI 0.85–1.28; $P = 0.68$).

Myocardial injury biomarkers elevation and onset of myocardial necrosis presents a linear pathophysiological rationale. Indeed, comparing troponin elevation peak and myocardial necrosis mass (in grams) estimated by CMR after angioplasty, Selvanayagam *et al.*[21] suggested a strong correlation between troponin values and amount of new LGE ($r = 0.84$, $P < 0.001$). We observed, like other studies,[7,22] a higher peak of myocardial injury biomarkers in patients with new LGE (median troponin 8.9 ng/mL vs. 1.8 ng/mL and median CK-MB 38.0 ng/mL vs. 12.3 ng/mL; $P < 0{,}00.1$ in both comparisons).

In our sample, even consisting only of patients undergoing elective revascularization procedures, we observed a high incidence of new LGE (17.8% of patients) and a median LGE mass of 4.6 g. Our findings are similar to those of Selvanayagam *et al.*,[21,23] who reported a higher incidence of post-procedure LGE, both in surgical and percutaneous interventions, and a greater amount of new LGE (6.0 g in PCI and 6.6 g in CABG patients). This difference may be due to the fact that our sample consists of patients undergoing uncomplicated procedures and the differences regarding study designs and temporal evolution of medical treatment and technical aspects of CABG and PCI.

Table 3 Event rates according to PMI SCAI definition and new LGE

	No PMI SCAI (*n* = 115)	PMI SCAI (*n* = 87)	*P*-value	No LGE (*n* = 166)	New LGE (*n* = 36)	*P*-value
Primary endpoint (death, myocardial infarction, additional revascularization, cardiac hospitalization)	16 (13.9%)	13 (14.9%)	0.93	20 (12.0%)	9 (25.2%)	0.045
Secondary endpoint						
Death	4 (3.4%)	4 (4.6%)	0.77	4 (2.4%)	4 (11.1%)	0.02
Myocardial infarction	2 (1.7%)	4 (4.6%)	0.32	6 (3.6%)	0	0.25
Additional revascularization	2 (1.7%)	3 (3.4%)	0.38	4 (2.4%)	1 (2.7%)	0.25
Cardiac hospitalization	10 (8.6%)	8 (9.2%)	0.11	13 (7.8%)	5 (13.8%)	0.21

LGE, late gadolinium enhancement; PMI, periprocedural myocardial infarction; SCAI, Society for Cardiovascular Angiography and Interventions.

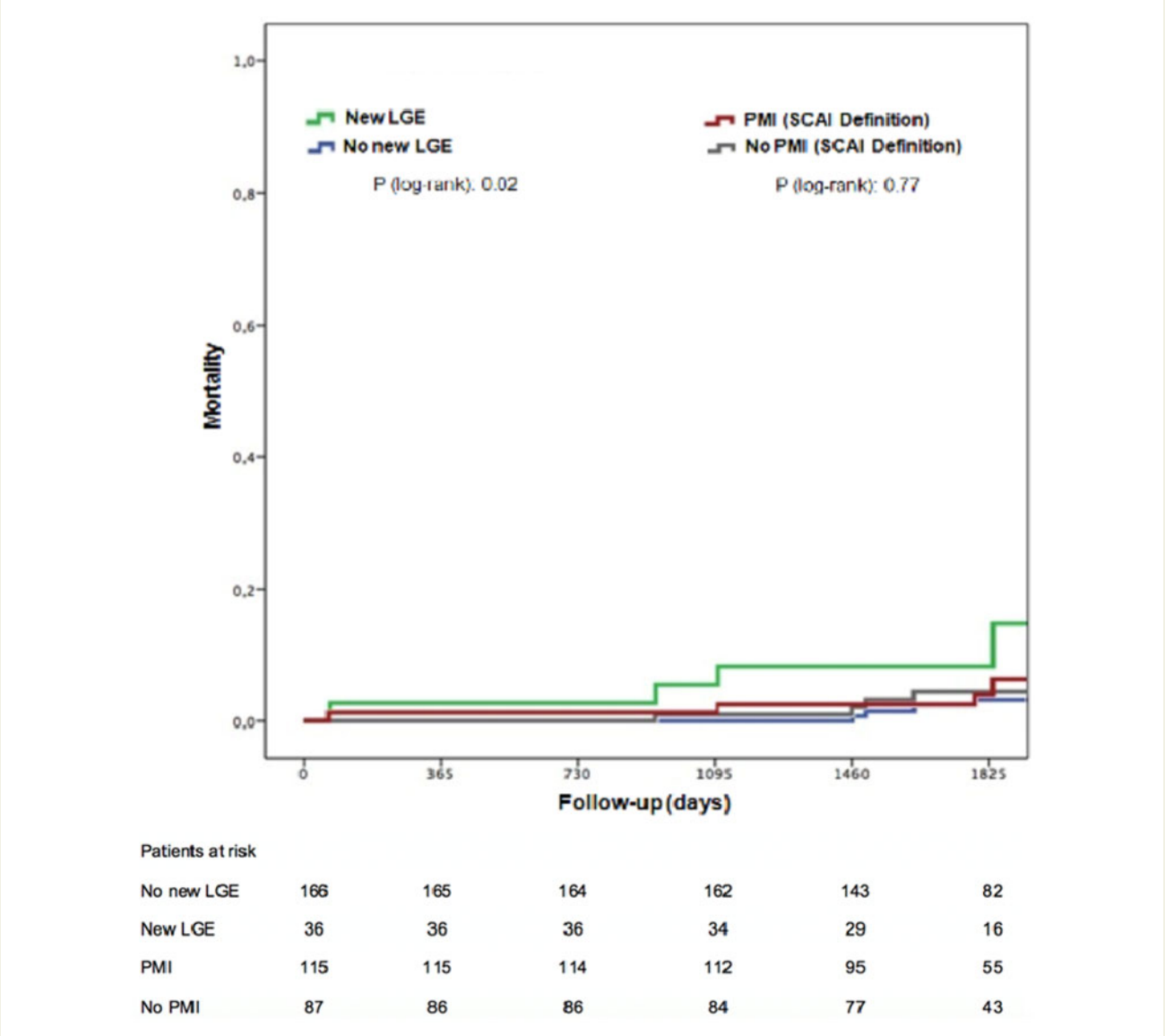


Figure 3 Cumulative incidence of mortality in relation to PMI according to SCAI definition and new LGE. LGE, late gadolinium enhancement; PMI, periprocedural myocardial infarction; SCAI, Society for Cardiovascular Angiography and Interventions.

Table 4 Risk of clinical events related to PMI SCAI definition and new LGE

	PMI SCAI			New LGE		
	HR[a]	95% CI	*P*-value	HR[b]	95% CI	*P*-value
Primary endpoint	0.94	0.44–1.99	0.86	2.45	1.10–5.50	0.03
Secondary endpoint						
Death	1.23	0.30–5.02	0.77	4.87	1.18–20.11	0.03
Myocardial infarction	2.15	0.37–12.46	0.39	2.43	0.46–13.03	0.30
Additional revascularization	2.50	0.36–17.43	0.36	3.01	0.41–21.91	0.28
Cardiac hospitalization	0.88	0.33–2.32	0.79	2.51	0.89–7.05	0.08

LGE, late gadolinium enhancement; PMI, periprocedural myocardial infarction; SCAI, Society for Cardiovascular Angiography and Interventions.
[a]Adjusted for SYNTAX Score and therapeutic strategy.
[b]Adjusted for SYNTAX Score.

Table 5 Univariate and multivariate analysis to identify independent predictors of primary endpoint

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age (each year)	1.008	0.96–1.04	0.68			
Male	0.40	0.15–1.07	0.07	0.62	0.38–1.01	0.05
Hypertension	0.88	0.30–2.56	0.82			
Diabetes	1.14	0.54–2.39	0.72			
Smoking	1.26	0.73–2.17	0.40			
Previous infarction	2.30	0.88–6.03	0.09	2.33	0.89–6.11	0.08
Creatinin (each mg/dL)	1.003	0.99–1.01	0.57			
LDL cholesterol (each mg/dL)	1.95	0.54–7.01	0.31			
LVEF (each %)	0.96	0.93–1.004	0.32			
CPR (each mg/dL)	0.99	0.96–1.03	0.85			
3-vessel CAD	1.48	0.63–3.46	0.36			
SYNTAX score (each unit)	1.02	0.98–1.06	0.22			
Surgical treatment	0.72	0.34–1.53	0.40			
Baseline troponin (each ng/mL)	1.008	1.002–1.01	0.01	1.01	0.99–1.01	0.11
Baseline CK-MB (each ng/mL)	1.03	1.005–1.05	0.02			
PMI SCAI	1.03	0.49–2.15	0.93			
New LGE	2.24	1.02–4.93	0.04	2.37	1.07–5.23	0.03

ACE, angiotensin converting enzyme; CAD, coronary artery disease; CRP, C-reactive protein; LAD, left artery descending; LDL, low-density lipoprotein; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; SCAI, Society for Cardiovascular Angiography and Interventions.

It is worth noting that, in a sample of patients with preserved LVEF and after revascularization, even a small amount of new LGE is able to predict an increased long-term risk of cardiovascular events.

In our study, new LGE was shown to be a better prognostic predictor than clinically relevant PMI according to SCAI definition and was the only independent predictor of cardiovascular events and mortality. This superiority may be justified by the fact that this finding is associated with a myocardial injury in a larger number of myocytes, representing a more significant and specific myocardial damage, consequently presenting greater accuracy in clinical outcomes prediction. Besides, it is an imaging representation of myocardial necrosis, thus it may cause long-term ventricular function reduction, and represent a ventricular arrhythmias substrate.

In this direction, Rahimi *et al.*[24] presented similar results. After a 2.9-year follow-up of patients submitted to interventional procedures (surgical and percutaneous), authors suggested that occurrence of new LGE was independently associated to increased incidence of cardiovascular events (HR: 3.11; 95% CI 1.43–6.77, $P = 0.004$). This study, however, presented some differences than ours like shorter follow-up time, absence of CK-MB biomarker measurement, and presence of acute coronary syndrome as initial presentation.

In clinical practice, myocardial injury biomarkers elevation is often documented after elective myocardial revascularization, even in patients with good clinical evolution and in absence of procedure complications. In addition, there is a common discrepancy between

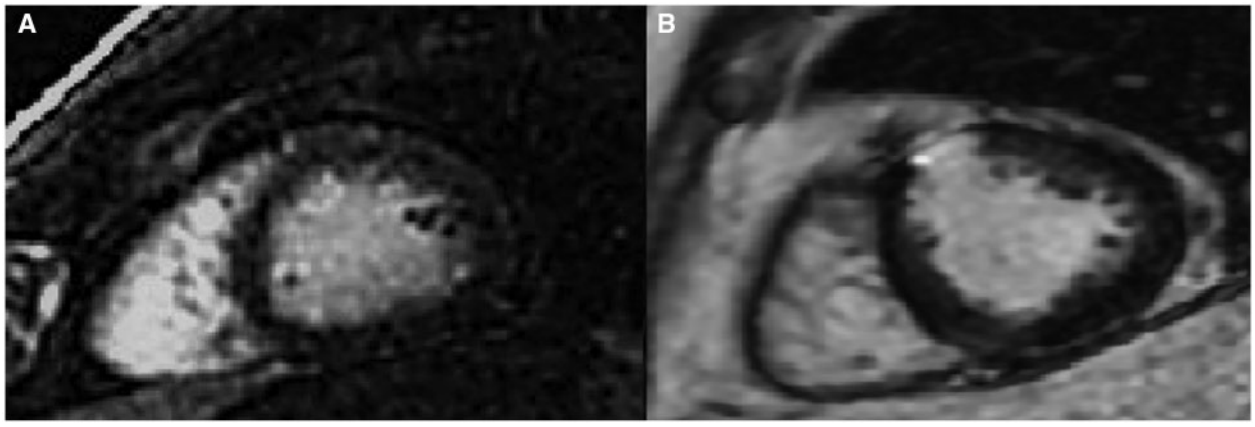


Figure 4 Short-axis CMR images in a patient (*A*) submitted to PCI without post-procedure LGE and a patient (*B*) with new LGE after PCI. CMR, cardiovascular magnetic resonance; LGE, late gadolinium enhancement; PCI, percutaneous coronary intervention.

release of these biomarkers and confirmation of structural myocardial damage by other diagnostic methods (electrocardiogram and echocardiogram, for example). Thus, isolated evaluation of biochemical markers may lead to misdiagnosis and inadequate medical practice. Still, since myocardial injury biomarkers are more accessible and available, as already described in stable CAD scenario, blood assay may be used as a routine gatekeeper,[25] and, in larger degrees of myonecrosis, more accurate imaging methods, such as CMR, could be useful.

In this context, CMR could contribute to a better understanding of myocardial injury, diagnostic support of periprocedural infarction, and a higher prognostic prediction after elective myocardial revascularization.

To our knowledge, this is the first study addressed to evaluate the 5-year prognostic role of periprocedural biomarkers, including cTn, CK-MB, and LGE-CMR in the same population. However, some limitations should be mentioned. First, this is a small non-randomized study with patients with CAD after revascularization procedures intended to determine the best myocardial injury biomarkers cut-off point for new LGE, hence it could explain the low rate of clinical events in the follow-up. Secondly, the results of this study should be applied to a specified subset of individuals with similar characteristics, such as patients with preserved ejection fraction in chronic coronary syndrome setting after uncomplicated revascularization procedures and cannot be extrapolated to other scenarios. Thirdly, in our PCI patients, devices used were bare metal stents. The results should be interpreted with caution in centres that use high sensitivity troponin, since our protocol have used contemporary troponin assays. Further studies are necessary to answer unsolved issues.

Conclusion

In this sample, new LGE was shown to be better prognostic predictor than a biomarker-only PMI definition after uncomplicated revascularization procedures. Furthermore, new LGE was the only independent predictor of cardiovascular events and mortality.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Conflict of interest: The authors declare that they have no conflict of interest.

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