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ORIGINAL RESEARCH

Post–ST-Segment–Elevation Myocardial Infarction Platelet Reactivity Is Associated With the Extent of Microvascular Obstruction and Infarct Size as Determined by Cardiac Magnetic Resonance Imaging

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BACKGROUND: Despite optimized medical management and techniques of primary percutaneous coronary intervention, a substantial proportion of patients with ST-segment–elevation myocardial infarction (STEMI) display significant microvascular damage. Thrombotic microvascular obstruction (MVO) has been implicated in the pathogenesis of microvascular and subsequent myocardial damage attributed to distal embolization and microvascular platelet plugging. However, there are only scarce data regarding the effect of platelet reactivity on MVO.

METHODS AND RESULTS: We prospectively evaluated 105 patients in 2 distinct periods (2012–2013 and 2016–2018) who presented with first ST-segment–elevation myocardial infarction and underwent primary percutaneous coronary intervention. All patients were treated with dual antiplatelet therapy (DAPT). Blood samples were analyzed for platelet reactivity, and cardiac magnetic resonance imaging scans were evaluated for late gadolinium enhancement and MVO. DAPT suboptimal response was defined as hyporesponsiveness to either aspirin or P2Y12 receptor inhibitor agents and demonstrated in 31 patients (29.5%) of the current cohort. Suboptimal platelet response to DAPT was associated with a significantly greater extent of MVO when expressed as a percentage of the left ventricular mass, left ventricular scar, and the number of myocardial left ventricular segments showing MVO ($P<0.01$ for each). Adjusted multivariable logistic regression model revealed that suboptimal response to DAPT is significantly associated with both greater late gadolinium enhancement ($P<0.01$) and MVO extent (odds ratio, 3.7 [95% CI, 1.3–10.5]; $P=0.01$). Patients with a greater extent of MVO were more likely to sustain major adverse cardiovascular events at a 1-year follow-up (37% versus 11%; $P<0.01$).

CONCLUSIONS: In patients undergoing primary percutaneous coronary intervention for ST-segment–elevation myocardial infarction, platelet reactivity in response to DAPT is a key predictor of the extent of both myocardial and microvascular damage.

Key Words: adenosine diphosphate ■ arachidonic acid ■ dual antiplatelet therapy ■ late gadolinium enhancement ■ microvascular obstruction ■ platelet aggregation ■ ST-segment–elevation myocardial infarction

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CLINICAL PERSPECTIVE

What Is New?

- Adding to the previous literature describing the significance of microvascular obstruction as a powerful prognostic marker for patients who suffered an ST-segment–elevation myocardial infarction, we describe for the first time the association between response to platelet hindrance and the predication of microvascular obstruction and subsequent infarct size and myocardial damage.
- Our findings suggest that platelet reactivity plays an essential role in the pathophysiology of the no-reflow phenomenon and strengthens the notion that the thrombo-inflammatory processes underlay the no-reflow phenomenon.
- Suboptimal platelet response to dual antiplatelet therapy is associated with an almost 10 times higher extent of microvascular obstruction; multivariable logistic regression models adjusted for multiple clinical variables showed that response to dual antiplatelet therapy is a key predictor of a greater microvascular obstruction and late gadolinium enhancement extent.

What Are the Clinical Implications?

- Our message is that early and effective platelet inhibition via administration of dual antiplatelet therapy at the time or during the immediate course after recanalization could offer a protective effect for the cardiac microvasculature, and it is crucial in decreasing early cardiovascular complications following acute myocardial infarction.

Nonstandard Abbreviations and Acronyms

AA	arachidonic acid
AHA	American Heart Association
DAPT	dual antiplatelet therapy
LGE	late gadolinium enhancement
MACE	major adverse cardiovascular events
MVO	microvascular obstruction
PPCI	primary percutaneous coronary intervention

Timely primary percutaneous coronary intervention (PPCI) is the mainstay treatment of ST-segment–elevation myocardial infarction (STEMI).[1,2] However, despite significant advances in pharmacological treatment and recanalization techniques, a significant proportion of patients undergoing PPCI will not achieve adequate myocardial reperfusion.[2-4] This phenomenon where myocardial tissue remains underperfused despite the successful renewal of coronary flow in the epicardial culprit artery is known as "no-reflow," and it is thought to be the result of microvascular obstruction (MVO).[5]

MVO carries dire consequences for the geometry of the ventricular myocardium and is associated with larger infarct size and an independent predictor of morbidity and mortality after STEMI.[6-10] Several imaging modalities have been used to delineate MVO. Recently, contrast-enhanced cardiac magnetic resonance (CMR) was shown as a valuable tool to visualize the extent of MVO[6,7] in patients with acute myocardial infarction (MI) and to evaluate the extent of myocardial damage.[6,11,12]

No-reflow is a multifactorial phenomenon. Several mechanisms have been implicated in the pathogenesis of this phenomenon, among which are distal embolization of destabilized plaque and thrombi debris during percutaneous coronary intervention (PCI), the in situ formation of leukocyte–platelet aggregate leading to microvascular plugging, ischemic injury, and damage caused by postischemic reperfusion.[4,13] Thus, thrombus generation and mainly platelet activation might play essential roles in the pathogenesis of MVO. To the best of our knowledge, the impact of platelet reactivity on the extent of MVO has not been thoroughly described to date.

In this study, we prospectively correlated platelet reactivity as determined in the early course of patients with STEMI with the extent of microvascular injury using CMR.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

The cohort consisted of 105 patients who presented with a first STEMI and no prior documented ischemic heart disease. All study participants underwent PPCI using standard techniques within 12 hours of symptom onset. Patients were treated with DAPT, which included aspirin (300 mg loading dose and 100 mg/day thereafter), and a P2Y12 receptor inhibitor based on the physician's discretion and in compliance with the guidelines for STEMI management.[2] Loading doses of aspirin and P2Y12 receptor inhibitor were given before performing PPCI, in the mobile intensive coronary care unit, or immediately on admission. The use of glycoprotein IIb/IIIa and thrombus aspiration at the time of

PPCI were at the discretion of the treating angiographer and were documented as well.

Blood samples for platelet reactivity were drawn 72 hours after PPCI. All patients underwent a CMR study on day 5±1 after admission. Patients were stratified into DAPT optimal and suboptimal responders using commonly accepted cutoffs for arachidonic acid (AA) and adenosine diphosphate (ADP) platelet aggregation.[14-17]

Exclusion criteria included patients aged <18 years, prior documented ischemic heart disease, indication for anticoagulant therapy, and those unable or unwilling to undergo a detailed CMR scan.

Demographic characteristics, comorbidities, pain-to-balloon time, ECG findings including MI location, and ΣST-segment elevation at presentation were prospectively documented. Laboratory markers obtained from all patients during hospitalization included serial troponin levels, hemoglobin, platelet count, mean platelet volume, and C-reactive protein levels. Echocardiographic and angiographic parameters were documented as well.

The Hospital Helsinki Committee approved the study. Patients recruited between 2012 and 2013 provided informed consent for participation in the study and the use of their medical data. Due to clinical benefits emerged in favor of patients who underwent CMR, which positively influenced patient management, it became department protocoled for eligible patients. Between the years 2016 and 2018, after rigorous evaluation of the department's protocol, the hospital ethics committee provided the authors with permission to collect the data without individual consent.

Platelet Reactivity

Blood draws for platelet reactivity were obtained using a loose tourniquet through a short venous catheter. Blood was collected into cylindrical tubes containing 3.2% sodium citrate and evaluated for platelet function immediately after pumping. Platelet accumulation was assessed by an aggregometer platelet aggregation chromogenic kinetics system-4 (PACKS-4) turbidimetric (Helena Laboratories) using ADP (10 μmol/L) and AA (1.6 mmol/L) as agonists. Changes in light transmission were recorded for 5 minutes, and maximal amplitude was measured. All blood samples were evaluated at the same laboratory and by the same operators who were blinded to the patient's clinical and CMR findings.

Patients were considered as having an optimal response to DAPT if AA-induced platelet aggregation was <30% and ADP-induced platelet aggregation was <50%. Otherwise, patients were defined as suboptimal responders. These cutoffs were derived from the receiver operating characteristic analysis of our data as well as prior published studies.[14-17]

CMR Imaging Analysis

All patients underwent CMR on day 5±1 following admission. All scans were performed using a 1.5 T Tesla scanner (Optima MR450w geometry embracing method [GEM] version DV26; General Electric) and a 3-Tesla scanner (Philips Ingenia 3T version 5.4.1.2), according to scanner availability. Scans were performed using the following sequences: steady-state free precession (short axis, 4-chamber, 2-chamber, and 3-chamber planes) and late gadolinium enhancement (LGE; short axis, 4-chamber, 2-chamber, and 3-chamber planes). Typical steady-state free precession acquisition parameters were repetition time/time to echo=3/1, flip angle=45°, in-plane resolution 1.7×1.7, and slice thickness=8 mm for the 1.5 T scanner and repetition time/time to echo=4.3/2, flip angle=25°, and slice thickness=8 mm for the 3 T scanner. LGE was collected 10 to 15 minutes after the administration of 0.1 mmol/kg contrast agent (gadoterate meglumine; Guerbet). The inversion time was adjusted for optimal nulling of remote normal myocardium. Typical LGE T1-weighted gradient echo recall sequence phase-sensitive inversion recovery sequence acquisition parameters were repetition time/time to echo=5/1.4, flip angle=20°, in-plane resolution 1.7×1.7, and slice thickness=8 mm for the 1.5 T scanner and repetition time/time to echo=6/3, flip angle=25°, and slice thickness=8 mm for the 3 T scanner.

LGE and MVO were quantified as a percentage of the myocardial left ventricular (LV) mass (Medis Medical Imaging version 7.6). Left and right ventricular ejection fractions, LGE, and MVO percentages of LV mass were calculated in the short axis plane using a dedicated platform (Medis Medical Imaging version 7.6). The LGE signal intensity threshold for scar quantification was set at 5 SDs above the reference region of interest in the remote unaffected myocardium.[18] This threshold was used for the quantification of both LGE percentage and MVO percentage quantification.

LGE myocardial involvement was located in the affected myocardial segments according to the American Heart Association (AHA) 17-segment heart model.[18] The LGE extent was graded per segment according to the following scale: grade 1 (1%–25%), grade 2 (26%–50%), grade 3 (51%–75%), and grade 4 (76%–100%) of the myocardial wall thickness. It thus yielded a 68 point LGE severity score (LGE AHA). The presence or absence of microvascular obstruction was also documented per myocardial segment using the 17-segment AHA model (MVO AHA). Intraobserver variability was addressed by having all studies analyzed by 2 physicians with double-board certification in cardiology and radiology. The 2 readers independently assessed studies and were blinded to the clinical and laboratory

results. A weighted κ test was run to assess interobserver agreement.

We further divided the cohort into those with larger infarct size based on LGE (larger LGE defined as the upper third values of the cohort, whereas lower LGE is defined as the lower two-thirds). Additional comparison between higher versus lower percentages of MVO was performed (upper one-third versus lower two-thirds; Tables S1 and S2).

Clinical Follow-Up

Clinical follow-up for 1 year of major adverse cardiovascular events (MACE) was performed. MACE included recurrent MI, acute stroke, acute coronary syndrome necessitating urgent hospitalization and/or percutaneous coronary intervention, hospitalization for heart failure, and cardiovascular death.

Kaplan–Meier survival analysis (Kaplan & Meier, 1958)[19] was conducted to compare the incidence of MACE in patients with larger MVO extent versus others (upper one-third versus lower two-thirds). A similar analysis was conducted for patients with a greater LGE extent. A log-rank test was conducted to determine if there were differences in MACE incidence.

Statistical Analysis

All statistical tests were 2-sided, and a P value of <0.05 was considered significant. We described variables according to their properties. Categorical variables are reported in frequencies and percentages. The significance of categorical variables between groups was assessed using the χ^2 test or Fisher's exact test.

We tested all variables for normal distribution using the Kolmogorov–Smirnov test and by visualizing the QQ-plot, plotting the distribution and variance of the residuals. Normally distributed continuous variables were reported as mean and SD values, and differences between groups were assessed using the Student t test. Continuous variables not normally distributed were reported as median and interquartile range (IQR; 25th–75th percentiles) values, and significance was assessed using the Mann–Whitney U test.

We employed a binomial multivariable logistic regression model analysis to predict higher LGE and larger MVO extent in patients with STEMI. The variables included in both models were prioritized based on statistical significance in the univariate analysis and those assumed to be clinically relevant based on previous publications and clinical plausibility. A sensitivity subgroup analysis of the patients with anterior STEMI and of patients treated with ticagrelor or prasugrel was performed.

Statistical analysis was performed using the SPSS statistical software version 25.0.0 (IBM) and R version 4.0.0 software (The R Foundation).

RESULTS

Of the 105 patients with STEMI included in the present analysis, 95 (90%) were men. The mean age was 57±10 years. Of the patients, 74 (70%) had an optimal response to DAPT, and 31 (30%) had a suboptimal response. Patients with suboptimal platelet response as compared with those with optimal response had both higher AA-induced platelet aggregation (32% [IQR, 8%–25%] versus 15% [IQR, 10%–21%]; P<0.001) and ADP-induced platelet aggregation (47±18% versus 28±11%; P<0.001; Figure 1).

Baseline Characteristics

As shown in Table 1, epidemiologic and demographic baseline characteristics including age, sex, risk factors for coronary artery disease, comorbidities, and lipid profile were all similar in the 2 study groups. There were also no significant differences in hematologic parameters, including platelet count, mean platelet volume, and hemoglobin.

Clinical Characteristics

The 2 study groups were also comparable in their clinical characteristics (Table 2), including prior aspirin use, concomitant peripheral artery disease, and the time elapsed from symptom onset to catheterization (pain to balloon). The 2 study groups were also similar concerning the initial indexes of infarct size (jeopardized myocardium), including electrocardiographic ΣST-segment elevation and anterior location of the infarct (Table 2).

Angiographic Findings

Patients with optimal versus suboptimal platelet response were similar with respect to infarct-related artery distribution and incidence of a proximally located lesion within the infarct-related artery (Table S3). The study groups were also comparable regarding the extent of coronary artery disease, as reflected by the number of diseased coronary vessels (Table 2).

Importantly, patients in the 2 study groups were equally likely to undergo thrombus aspiration at the time of primary PCI (42% versus 51%; P=0.48) and to receive periprocedural glycoprotein IIb/IIIa inhibitor (52% versus 58%; P=0.45; Table 2).

MVO Extent

Suboptimal platelet response to DAPT was associated with a significantly higher extent of MVO both when expressed as a percentage of the LV mass (3.2 [IQR, 0.9–5] versus 0.32 [IQR, 0.2–2]; P=0.004) and when calculated according to the MVO segmental score (MVO AHA), which demonstrated a significantly higher number of myocardial LV segments showing MVO (3 [IQR, 2–5] versus 1 [IQR, 0–3]; P=0.001). Suboptimal platelet response was associated with an almost 10

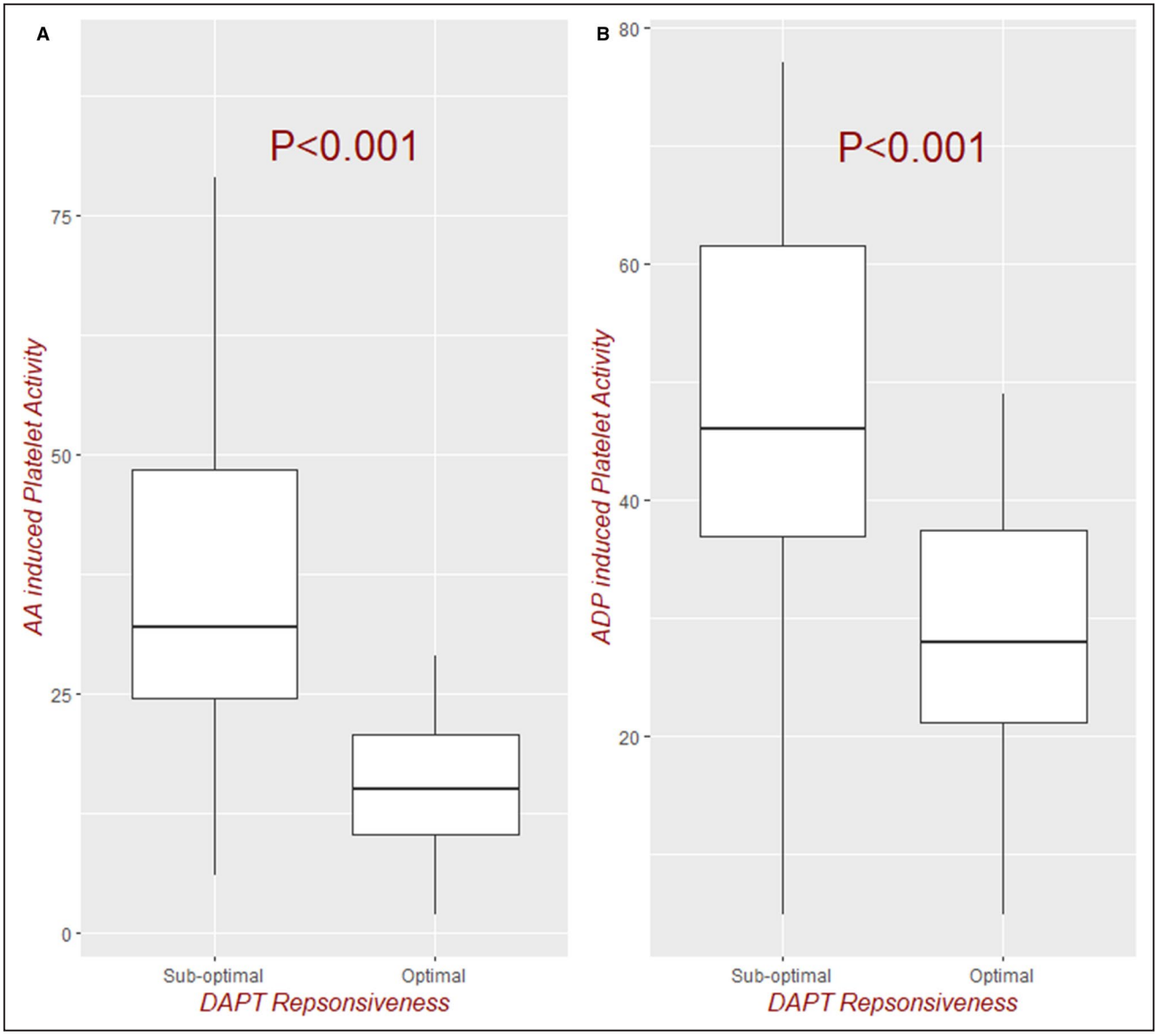

Figure 1. Platelet responsiveness under DAPT therapy.
From **left** to **right**: boxplot comparing platelets responsiveness to (**A**) AA and (**B**) ADP in optimal and suboptimal DAPT responders. AA indicates arachidonic acid; ADP, adenosine diphosphate; and DAPT, dual antiplatelet therapy.

times higher extent of MVO when expressed as a percentage of scar (8 [IQR, 2–14] versus 0.98 [IQR, 0–6]; *P*=0.001; Table 3, Figure 2).

A binomial multivariable logistic regression was performed to ascertain the effects of thrombolysis in MI flow pre-PCI, anterior location of the infarct, response to DAPT, and delayed pain-to-balloon time on the likelihood of patients having greater MVO extent. Patients with suboptimal response to DAPT had 3.7 times higher odds to exhibit larger MVO extent (odds ratio [OR], 3.7 [95% CI, 1.3–10.5]; *P*=0.013; Table 4). Anterior location of the infarct, thrombolysis in MI flow pre-PCI ≤1, and delayed pain-to-balloon time were also predictors for large MVO (Table 4).

Infarct Size

Suboptimal platelet response to DAPT was associated with more extensive myocardial damage as reflected by greater peak troponin (*P*=0.001), and lower LV ejection fraction as measured by 2-dimensional echocardiography and CMR (*P*=0.112 and *P*=0.036, respectively; Table 3). Importantly, patients with suboptimal response also had much higher LGE on CMR both when expressed as a percentage of LV mass (31±13% versus 24±12%; *P*=0.02) as well as when calculated according to the LGE segmental (LGE AHA) score (68 points based score system), which reflects both the number of involved segments as well as the transmurality of the LGE in each of the segments (18 [IQR, 12.5–22.5] versus 11 [IQR, 2.5–16.0]; *P*=0.009; Table 3).

Table 1. Baseline Characteristics

	All patients	DAPT optimal responders	DAPT suboptimal responder	*P* value
Total, n	105	74	31	
Age, y, mean (SD)	57.2 (10)	57.6 (9.8)	56.5 (10.7)	0.61
Male sex, n (%)	95 (90)	65 (88)	30 (97)	0.29
Active smoker, n (%)	45 (43)	33 (44)	12 (39)	0.73
Hypertension, n (%)	36 (34)	26 (35)	10 (32)	0.95
Diabetes, n (%)	17 (16)	10 (13)	7 (22)	0.39
Dyslipidemia, n (%)	44 (42)	31 (42)	13 (42)	>0.99
HDL, mg/dL, mean (SD)	39.6 (8.6)	39.9 (9.2)	39 (7.3)	0.67
LDL, mL/dL, mean (SD)	118 (29.5)	118 (29.6)	117 (29.6)	0.76
Triglycerides, mg/dL, median (IQR)	125 (94–165)	124 (93–162)	134 (93–169)	0.55
WBC on admission, k/μL, mean (SD)	11.8 (4)	11.6 (4)	12.3 (4)	0.43
Hb on admission, g/L, mean (SD)	14.5 (1.4)	14.4 (1.3)	14.8 (1.7)	0.23
Platelets on admission, k/μL, mean (SD)	233 (61)	234 (66)	232 (47)	0.87
MPV on admission, fL, mean (SD)	9 (1.2)	9 (1.2)	8.8 (1.1)	0.50

Overview of the relative frequency of comorbidities as well as laboratory values on admission. All laboratory values were taken within 30 minutes of admission. Continuous variables are presented as either mean (SD) or median (IQR), as detailed in the Methods section. DAPT indicates dual antiplatelet therapy; Hb, hemoglobin; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; MPV, mean platelet volume; and WBC, white blood cell.

A binomial multivariable logistic regression model was performed to ascertain the effects of thrombolysis in MI flow pre-PCI, anterior location of the infarct, response to DAPT, delayed pain-to-balloon time, resolution of ST-segment elevation post-PPCI, high-density lipoprotein (HDL), and left ventricular ejection fraction

Table 2. Clinical, Electrocardiographic, and Angiographic Characteristics

	All patients	DAPT optimal responders	DAPT suboptimal responder	*P* value
Total, n	105	74	31	
Prior ASA use, n (%)	14 (13)	10 (13)	4 (13)	>0.99
PAD, n (%)	2 (1.9)	1 (1.4)	1 (3.2)	>0.99
Pain-to-balloon time, h, median (IQR)	2.5 (2–5)	2.5 (2–5.8)	2 (2–3.5)	0.35
Delayed pain-to-balloon time (>3 h), n (%)	36 (34.2)	28 (37.8)	8 (25.8)	0.23
Sum of ST-elevation on first ECG, mm, mean (SD)	7.6 (4.6)	7.3 (4.8)	8.4 (4.1)	0.25
Anterior STEMI, n (%)	49 (46.7)	33 (44.6)	16 (51.6)	0.65
Diseased coronary arteries, n (%)				0.72
1	57 (54.3)	39 (52.8)	18 (58.1)	
2	33 (31.4)	25 (33.8)	8 (25.8)	
3	15 (14.3)	10 (13.5)	5 (16.1)	
Aspiration of thrombus, n (%)	47 (44)	31 (42)	16 (51.6)	0.48
Morphine use during hospitalization, n (%)	31 (29.5)	21 (28.4)	10 (32.3)	0.69
Administration of glycoprotein IIb/IIIa, n (%)	55 (52)	37 (50)	18 (58)	0.45
TIMI flow pre-PCI, n (%)				0.06
0 or 1	71 (67.7)	46 (61.2)	25 (80.7)	
2 or 3	34 (33.3)	28 (37.8)	6 (19.4)	
TIMI flow post-PCI, n (%)				0.65
0 or 1	2 (1.9)	2 (2.8)	1 (3.2)	
2 or 3	103 (98.1)	72 (97.3)	30 (96.8)	
ST-segment resolution after PPCI, no (%)	77 (73.3)	57 (77)	20 (64.5)	0.28

Electrocardiographic and angiographic characteristics in DAPT optimal vs suboptimal responders are compared. Variables are presented as either percentages or median (IQR). ASA indicates acetylsalicylic acid; DAPT, dual antiplatelet therapy; IIBIIIA, glycoprotein IIb/IIIa; IQR, interquartile range; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; and TIMI, thrombolysis in myocardial infarction.

Table 3. Indexes of Myocardial Injury

	All patients	DAPT optimal responders	DAPT suboptimal responder	*P* value
Total, n	105	74	31	
Peak troponin, μg/L, median (IQR)	60 (20–87)	42 (17–80)	80 (60–99)	0.001
LVEF echocardiography, mean (SD)	45.8 (9.4)	46.7 (9.6)	43.5 (8.6)	0.11
LVEDD, cm, mean (SD)	4.6 (0.4)	4.6 (0.4)	4.6 (0.4)	0.99
LVESD, cm, mean (SD)	3 (0.5)	3 (0.5)	3 (0.5)	0.69
LVEF MRI, mean (SD)	55 (11.2)	56.5 (10.5)	51.5 (12.1)	0.03
RVEF MRI, mean (SD)	51.8 (9.7)	52.72 (7.9)	49.8 (13)	0.16
LGE LV, mean (SD)	26.1 (14)	24 (11.4)	30.9 (13)	0.02
LGE AHA, median (IQR)	12 (4–20) (9.9)	10.5 (2.5–16)	18 (12.5–22.5)	0.007
MVO LV, median (IQR)	1 (0–3.4)	0.32 (0–2.2)	3.2 (0.9–5)	0.004
MVO AHA, median (IQR)	2 (0–4)	1 (0–3)	3 (2–5)	0.001
MVO of scar, median (IQR)	2.6 (0–9)	0.98 (0–6.2)	8 (2–14.2)	0.001
3-Tesla scanner, n (%)	35 (33.3)	25 (33.8)	10 (32.3)	>0.99
LV mass, mean (SD)	136 (34)	135 (34)	140 (33)	0.46

Assessments of myocardial involvement and LV function using echocardiographic and cardiac magnetic resonance imaging markers of injury. AHA indicates American Heart Association; DAPT, dual antiplatelet therapy; IQR, interquartile range; LGE, late gadolinium enhancement; LV, left ventricular; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; MRI, magnetic resonance imaging; MVO, microvascular obstruction; and RVEF, right ventricular ejection fraction.

on echocardiography on the likelihood that patients will have greater LGE extent. Patients with suboptimal response to DAPT had a 4.9 times higher odds to exhibit more extensive myocardial injury (OR, 4.9 [95% CI, 1.57–15.4]; *P*=0.006). Additional factors that were significantly associated with larger LGE were anterior MI (OR, 6.5 [95% CI, 1.7–24]; *P*=0.006) and HDL levels (Table 5).

Sensitivity subgroup analysis for patients with anterior MI (49 patients) revealed that suboptimal response to DAPT remained independently associated with a higher extent of LGE (OR, 5.08 [95% CI, 1.3–19.7]; *P*=0.019).

The κ score for CMR scan interpretations was calculated and showed good interobserver agreement. The κ score range for each myocardial segment is 0.64 to 0.82 (mean of 0.74).

Type of P2Y12 Receptor Inhibitor

A total of 59 patients (56%) were treated with prasugrel, 24 patients (23%) were treated with clopidogrel, and 22 patients (21%) were treated with ticagrelor. Patients treated with clopidogrel had significantly higher ADP-induced platelet aggregation compared with both third-generation antiplatelet agents prasugrel and ticagrelor (45±18% versus 33±15% versus 25±10% [*P*=0.02], respectively; Figure 3). Accordingly, patients who received clopidogrel compared with prasugrel and ticagrelor were more likely to have a suboptimal DAPT response (12/24 patients versus 16/59 and 3/22, respectively). Although suboptimal platelet response was a significant predictor of MVO extent, the type of P2Y12 receptor inhibitor was not associated with the extent of MVO (Table 5) after adjusting for differences in platelet reactivity. This holds even when the use of ticagrelor (compared with thienopyridines) was imposed on the regression model.

Sensitivity subgroup analysis for patients treated with prasugrel or ticagrelor (81/105) revealed that suboptimal response to DAPT remained strongly associated with greater MVO (OR, 3.75 [95% CI, 1.3–11.2]; *P*=0.018) and LGE extent (OR, 5.18 [95% CI, 1.3–15.5]; *P*=0.003). A binomial multivariable logistic regression models for greater LGE or MVO extent in this subgroup analysis was conducted (Tables S4 and S5).

One-Year Follow-Up

A 1-year clinical follow-up was available in 92 patients (88%). Patients were stratified based on their response to DAPT. The proportion of patients with an optimal response in the follow-up group (64 [70%]) was identical with that in the entire cohort. Similarly, the extent of MVO and LGE were similar in the follow-up group compared with those without available 1-year clinical follow-up (1% versus 0.34% [*P*=0.86], 27% versus 31% [*P*=0.21], respectively).

Overall, 17 patients (18.3%) sustained at least 1 major adverse cardiovascular event, defined as recurrent myocardial infarct (3.2%), stroke (1%), acute coronary syndrome necessitating urgent hospitalization and/or PCI (5.4%), and hospitalization for heart failure (8.7%). Stratifying based on the extent of MVO revealed that patients with larger MVO extent, defined as the upper third values of the cohort, as compared with the lower two-thirds, were more likely to sustain MACE during the 1-year

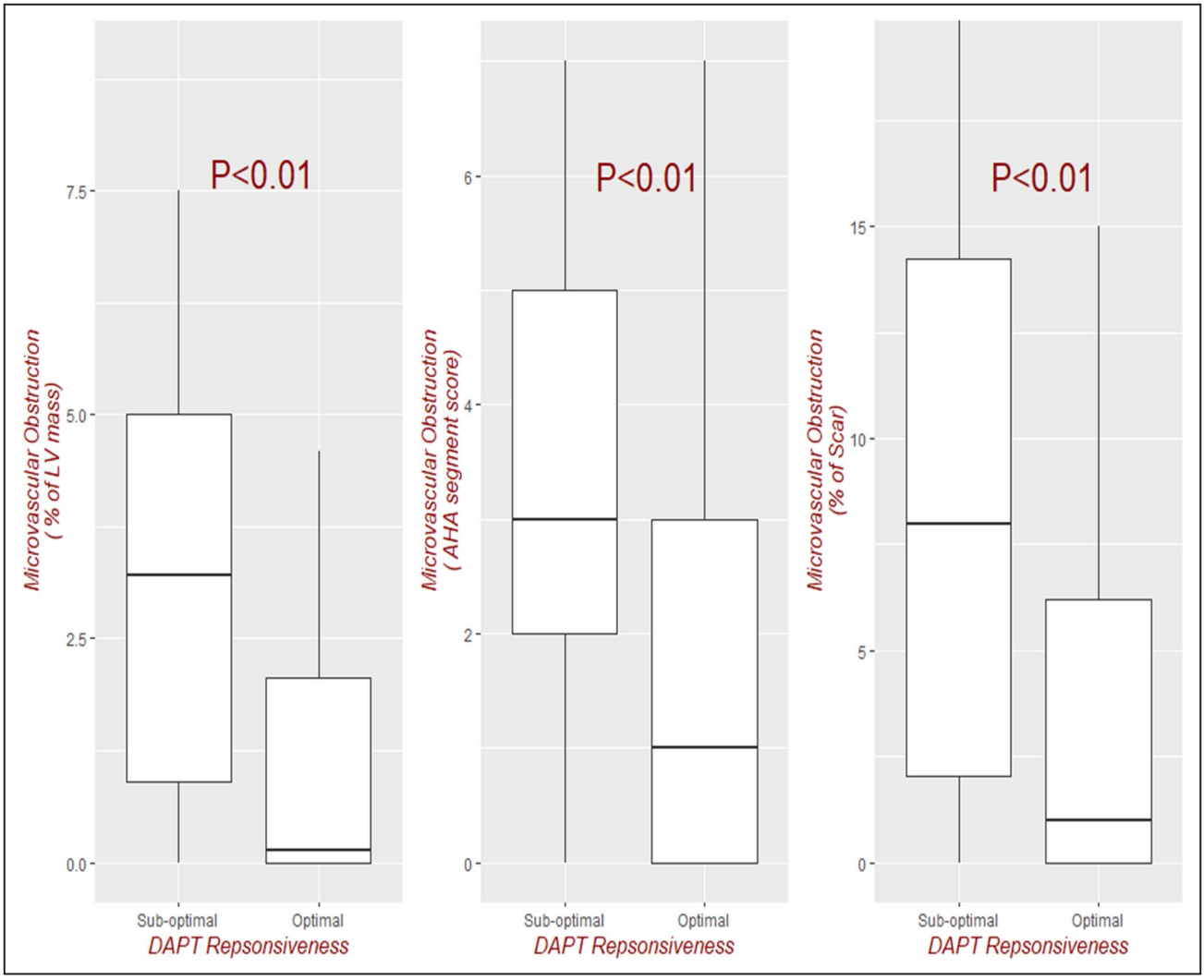

Figure 2. Microvascular obstruction and dual antiplatelet therapy.
From **left** to **right**: boxplot comparing microvascular obstruction as a percent of LV mass, AHA segment score, and percent of scar in DAPT optimal vs suboptimal responders. AHA indicates American Heart Association; DAPT, dual antiplatelet therapy; and LV, left ventricular.

follow-up (37% versus 11%; *P*=0.006). As shown by the Kaplan–Meier survival analysis curve (Figure 4), patients with extensive MVO showed significantly higher incidences of MACE (hazard ratio [HR], 3.9 [95% CI, 1.5–10.2]; *P*=0.005). The increase in MACE rate was derived mainly from an increase in acute coronary syndrome necessitating urgent hospitalization and/or PCI (11% versus 5%) and hospitalization for heart failure (21% versus 8%).

We also evaluated the relationship between MVO extent and MACE, with the accumulating event being only heart failure hospitalization and/or cardiovascular death. Our analysis again demonstrated that higher MVO is associated with increased adverse events (HR, 7.3 [95% CI, 1.9–26]; *P*<0.001; Figure S1). A further analysis using a Kaplan–Meier survival curve examining the relationship between DAPT response and MACE showed significantly fewer adverse events among DAPT optimal responders (HR, 3.2 [95% CI, 1.3–8.3]; *P*=0.01; Figure S2).

DISCUSSION

In the present study, we showed that the degree of platelet inhibition early in the course after PPCI in patients with STEMI is related to the extent of MVO and thus with the extent of myocardial damage. Suboptimal platelet inhibition in response to a standard DAPT regimen was shown to be a robust predictor of MVO as well as of the extent of myocardial damage as determined by CMR.

Krug et al[20] first described the no-reflow phenomenon in 1966 after coronary artery ligation and reopening of the occlusion in a rat model of MI. Our findings

Table 4. Predictors of Microvascular Obstruction

	Odds ratio	95% CI	*P* value
DAPT suboptimal response	3.7	1.3–10.5	0.013
TIMI flow pre-PCI (≤1)	4.2	1.25–14.2	0.021
Anterior STEMI	4.2	1.5–11.4	0.005
Delayed pain-to-balloon time (>3 h)	4	1.4–11.5	0.01

Multivariable binomial logistic regression model for predictors of microvascular obstruction. The logistic regression model was statistically significant, $\chi^2(4)=29.9$, $P<0.0001$. The model correctly classified 82% of cases. The area under the receiver operating characteristic curve was 0.77 (95% CI, 0.68–0.858), $P<0.001$. DAPT indicates dual antiplatelet therapy; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; and TIMI, thrombolysis in myocardial infarction.

that suggest a strong relationship between early platelet reactivity and the extent of MVO are in accord with the findings of early publications using animal models. In a canine model of ischemia/reperfusion, when the reflow of the coronary artery occurred after 90 minutes of ischemia, an electron microscopy study of the poorly perfused tissue demonstrated severe capillary damage and intraluminal fibrin thrombi.[20] Another study showed that an injection of homologous thrombotic material to create coronary microembolization in rats resulted in the expression of inflammatory cytokines and left ventricular dysfunction.[21,22] Moreover, microembolism during PCI is a predominant cause of no-reflow in humans. Micro-thrombo-emboli may dislocate from the atheromatous plaque during recanalization therapy and lodge in the microcirculation, causing a clinically significant reduction in flow.[1]

Prior studies examining the efforts to mitigate MVO using vasodilators[23] and antiaggregation agents such as P2Y12 receptor inhibitors[24] or glycoprotein IIb/IIIa[25] have not demonstrated clinical advantage. However, in the administration of ticagrelor in the cath lab or in the ambulance for new ST elevation myocardial infarction to open the coronary artery (ATLANTIC) trial,[26] ticagrelor therapy in the prehospital setting showed a small but significant benefit in preventing early stent thrombosis. It was associated with a higher incidence of post-PCI ST-segment resolution on ECG, especially in patients not receiving morphine, a well-known marker for myocardial reperfusion.[27] This finding agrees with the present study, suggesting that the early onset of DAPT therapy resulting in effective early inhibition of platelet activity at the time or during the immediate course after recanalization could offer a protective effect that extends to include the cardiac microvasculature.

Table 5. Predictors of Late Gadolinium Enhancement

	Odds ratio	95% CI	*P* value
DAPT suboptimal response	4.93	1.57–15.4	0.006
TIMI flow pre-PCI (≤1)	4	0.96–15.9	0.057
Anterior STEMI	6.52	1.7–24.7	0.006
Delayed pain-to-balloon time (>3 h)	1.85	0.6–5.8	0.29
HDL, mg/dL	0.92	0.85–0.99	0.029
ST-segment–elevation resolution (post-PCI)	0.64	0.19–2.1	0.46
LVEF first echocardiography	0.95	0.8–1.03	0.24

Multivariable binomial logistic regression model for predictors of late gadolinium enhancement. The logistic regression model was statistically significant, $\chi^2(7)=43$, $P<0.0001$. The model correctly classified 80% of cases. The area under the receiver operating characteristic curve was 0.86 (95% CI, 0.79–0.94), $P<0.001$. "First echocardiography" indicates the first echocardiography study performed after revascularization. DAPT indicates dual antiplatelet therapy; HDL, high-density lipoprotein; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; and TIMI, thrombolysis in myocardial infarction.

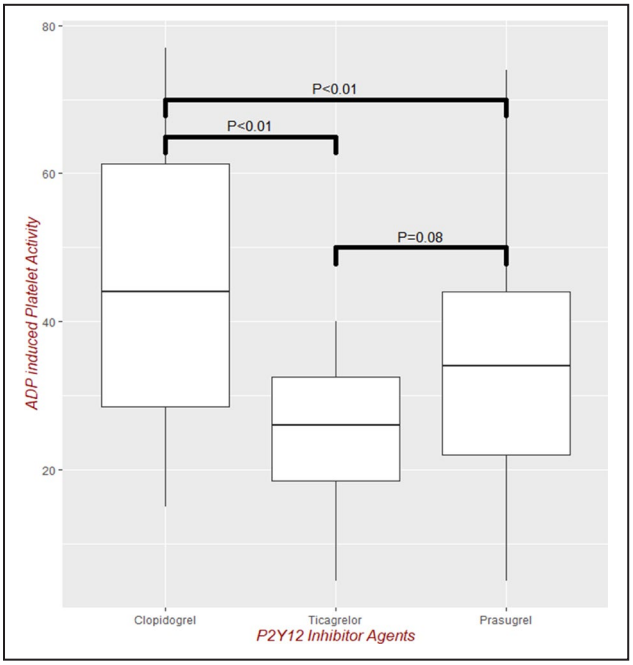

Figure 3. Comparison of P2Y12 receptor inhibitors.
Boxplot comparing platelet reactivity to ADP among P2Y12 receptor inhibitors. ADP indicates adenosine diphosphate.

Another significant predictor of larger infarct size in our study was low levels of HDL. This finding is supported by previous studies and is hypothesized to result from the protective effect offered by the protein particles of HDL.[28]

Our data suggest that platelet reactivity plays an essential role in the pathophysiology of the no-reflow phenomenon and strengthens the notion that the no-reflow phenomenon is underlaid by thrombo-inflammatory processes. Our findings highlight the potential importance of achieving an early antiplatelet effect and its crucial role in decreasing early cardiovascular complications following MI. Thus, early and effective platelet inhibition is achieved through prehospital antiplatelet agents administration via conventional or

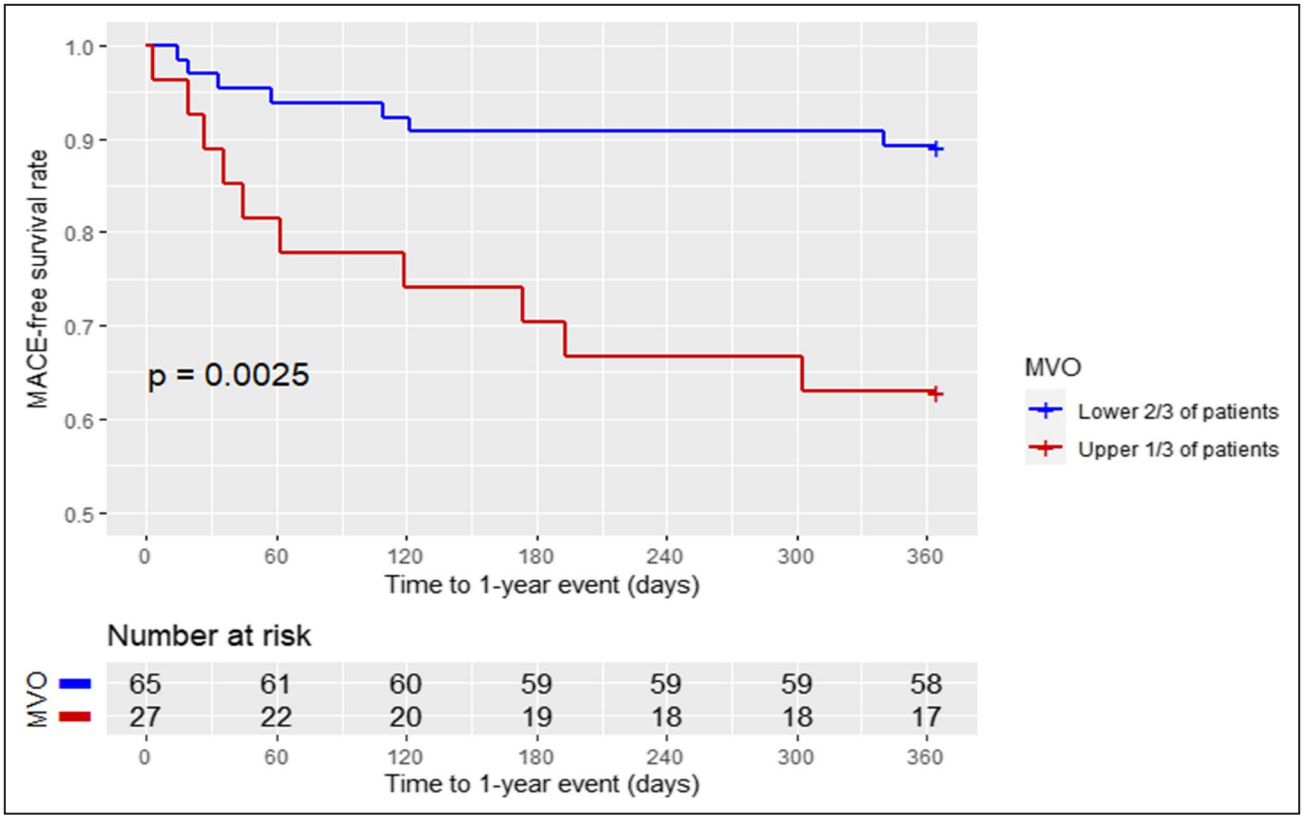

Figure 4. Kaplan-Meier curve for 1-year MACE.
Kaplan-Meier curve analysis with the accumulating events on the *y* axis (events) vs time on the *x* axis, stratified by MVO extent (upper one-third vs lower two-thirds). Log-rank *P*=0.0025. MACE indicates major adverse cardiovascular events; and MVO, microvascular obstruction.

the chewable route or the use of newer agents such as subcutaneous P2Y12 receptor inhibitor combined with platelet reactivity monitoring could offer a protective effect against MVO.[26,29,30] However, it should be noted that the design of the present study has not established a cause-and-effect relationship between platelet reactivity and the extent of MVO and infarct size, and therefore should be considered only as a hypothesis generating.

Limitations

This study had several limitations, the first of which is the relatively small sample size and single-center design. Consequently, the inability to meet statistical significance for some clinical variables may have been attributed to the insufficiently powered study. Second, 1 method for platelet function testing was used, and the definition of DAPT suboptimal responders is not well validated and established. Third, the true prevalence of MVO in patients with acute STEMI may have been underestimated because of the subselection of patients with hemodynamic and respiratory stability required to undergo a detailed CMR scan.

CONCLUSIONS

Platelet reactivity in patients with STEMI undergoing PPCI is a robust predictor for the CMR indexes of myocardial injury.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S5
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. A comparison of the Characteristics and indices of myocardial injury between Patients with Higher MVO versus lower MVO

	All Patients	*Patients with Large MVO*	*Patients with Low MVO*	*P-value*
Total no.	*105*	*29*	*76*	
Age – mean (SD), yr	57.29 (10.06)	54.79 (9.31)	58.24 (10.23)	0.117
Male – no. (%)	95 (90.5)	29 (100.0)	66 (86.8)	0.093
Active Smoker—no. (%)	45 (42.9)	14 (48.3)	31 (40.8)	0.637
HTN—no. (%)	36 (34.3)	9 (31.0)	27 (35.5)	0.839
DM—no. (%)	17 (16.2)	1 (3.4)	16 (21.1)	0.058
Dyslipidemia—no. (%)	44 (41.9)	9 (31.0)	35 (46.1)	0.241
HDL-- mean (SD), mg/dl	39.68 (8.65)	38.07 (7.03)	40.29 (9.16)	0.241
LDL-- mean (SD), ml/dl	118.17 (29.52)	123.66 (31.84)	116.08 (28.52)	0.241
Trigelicirides—Median [IQR], mg\dl	125.00 [95.00, 165.00]	154.00 [99.00, 202.00]	124.50 [94.25, 153.25]	0.136
Plt on admission-- mean (SD), k/microL	232.89 (60.88)	228.21 (39.41)	234.67 (67.44)	0.629
MPV on Admission-- mean (SD), fL	8.98 (1.23)	9.07 (1.06)	8.94 (1.29)	0.639
Prior ASA Use—no. (%)	14 (13.3)	2 (6.9)	12 (15.8)	0.38
PAD—no (%)	0.06 (0.25)	0.07 (0.27)	0.06 (0.24)	0.813
Pain to balloon-- median [IQR], hours	2.50 [2.00, 5.00]	2.50 [2.00, 5.00]	2.25 [2.00, 5.00]	0.343
Delayed Pain to balloon (>3 hours)- no. (%)	36 (34.2)	17 (50)	19 (26.8)	0.019
Sum of ST-elevation on First ECG--mean (SD), mm	7.64 (4.64)	9.86 (5.69)	6.80 (3.90)	0.002
Anterior STEMI—no. (%)	49 (46.7)	21 (72.4)	28 (36.8)	0.002

The number of diseased Coronary Arteries—no. (%)				0.36
1	56 (53.3)	17 (58.6)	39 (51.3)	
2	33 (31.4)	6 (20.7)	27 (35.5)	
3	15 (14.3)	6 (20.7)	9 (11.8)	
Aspiration of thrombus—no. (%)	47 (44.8)	16 (55.2)	31 (40.8)	0.269
Administration of IIBIIIA—no. (%)	0.52 (0.50)	0.52 (0.51)	0.53 (0.50)	0.934
TIMI Flow (Pre-PCI) -- no (%)				0.116
0	64 (61.0)	23 (79.3)	41 (53.9)	
1	7 (6.7)	1 (3.4)	6 (7.9)	
2	16 (15.2)	3 (10.3)	13 (17.1)	
3	18 (17.1)	2 (6.9)	16 (21.1)	
TIMI Flow (Post-PCI) -- no(%)				0.222
0	1 (1.0)	0 (0.0)	1 (1.3)	
2	1 (1.0)	1 (3.4)	0 (0.0)	
3	103 (98.1)	28 (96.6)	75 (98.7)	
PEAK TROPONIN -- median [IQR], micrg/l	60.00 [20.00, 87.92]	81.00 [74.62, 97.00]	32.00 [10.38, 74.78]	<0.001
Optimal DAPT responders-- no (%)	74 (70.5)	15 (51.7)	59 (77.6)	0.018
LVEF ECHO-- mean (SD)	45.82 (9.47)	42.24 (8.90)	47.18 (9.37)	0.016
LVEDD (cm)-- mean (SD)	4.68 (0.45)	4.77 (0.38)	4.65 (0.47)	0.237
LVESD (cm)-- mean (SD)	3.01 (0.52)	3.00 (0.50)	3.02 (0.53)	0.89
LVEF MRI --mean (SD)	55.05 (11.19)	49.90 (9.25)	57.01 (11.30)	0.003
RVEF MRI--mean (SD)	51.88 (9.69)	52.00 (9.87)	51.83 (9.69)	0.937

LGE LV--mean (SD)	27.00 [17.62, 35.00]	35.00 [28.00, 38.00]	23.00 [13.65, 32.50]	<0.001
LGE AHA--median [IQR]	12.00 [4.00, 20.00]	23.00 [20.00, 30.00]	8.00 [1.50, 14.00]	<0.001
MVO LV-- median [IQR]	0.90 [0.00, 3.40]	3.90 [3.15, 5.70]	0.00 [0.00, 1.37]	<0.001
MVO AHA--median [IQR]	2.00 [0.00, 4.00]	5.00 [5.00, 6.00]	0.00 [0.00, 2.00]	<0.001
MVO of scar--median [IQR]	2.65 [0.00, 9.00]	9.00 [5.00, 15.00]	0.30 [0.00, 4.15]	<0.001
3-Tesla –no. (%)	35 (33.3)	13 (44.8)	22 (28.9)	0.19
LV MASS—mean (SD)	136.51 (33.79)	147.34 (33.61)	132.33 (33.14)	0.042

Overview of the relative frequency of comorbidities as well as laboratory values, echocardiographic and electrocardiographic indices between the two groups(larger MVO defined as the upper third values of the cohort, while lower MVO defined as the lower two-thirds).
All at admission laboratory values were taken within 30 min of admission—MPV=mean platelet volume. Continuous variables are presented as either mean ±SD or median and IQR, as detailed in the Methods section

Table S2. A comparison of the Characteristics and indices of myocardial injury between Patients with Higher LGE versus lower LGE.

	All Patients	*Patients with High LGE*	*Patients with Low LGE*	*P-value*
n	*105*	*33*	*72*	
Age – mean (SD), yr	*57.29 (10.06)*	*56.73 (9.61)*	*57.54 (10.32)*	*0.702*
Male – no. (%)	*95 (90.5)*	*33 (100.0)*	*62 (86.1)*	*0.058*
Active Smoker—no. (%)	*45 (42.9)*	*13 (39.4)*	*32 (44.4)*	*0.785*
HTN—no. (%)	*36 (34.3)*	*8 (24.2)*	*28 (38.9)*	*0.213*
DM—no. (%)	*17 (16.2)*	*4 (12.1)*	*13 (18.1)*	*0.631*
Dyslipidemia—no. (%)	*44 (41.9)*	*13 (39.4)*	*31 (43.1)*	*0.889*
HDL-- mean (SD), mg/dl	*39.68 (8.65)*	*37.45 (6.81)*	*40.69 (9.24)*	*0.075*
LDL-- mean (SD), ml/dl	*118.17 (29.52)*	*117.55 (32.72)*	*118.46 (28.16)*	*0.884*
Trigelicirides—Median [IQR], mg\dl	*125.00 [95.00, 165.00]*	*153.00 [101.00, 188.00]*	*123.50 [91.25, 150.25]*	*0.086*
Hemoglobin on admission—(mean (SD)), g\dl	*14.54 (1.48)*	*14.76 (1.46)*	*14.44 (1.50)*	*0.315*
Plt on admission-- mean (SD), k/microL	*232.89 (60.88)*	*232.36 (42.15)*	*233.12 (68.03)*	*0.953*
MPV on Admission-- mean (SD), fL	*8.98 (1.23)*	*8.97 (1.19)*	*8.98 (1.25)*	*0.95*
Prior ASA Use—no. (%)	*14 (13.3)*	*2 (6.1)*	*12 (16.7)*	*0.24*
PAD—no (%)	*0.06 (0.25)*	*0.03 (0.19)*	*0.08 (0.27)*	*0.433*
Pain to balloon-- median [IQR], hours	*2.50 [2.00, 5.00]*	*3.00 [2.00, 6.00]*	*2.00 [1.88, 4.25]*	*0.068*

Delayed Pain to balloon (>3 hours)- no. (%)	*36 (34.2)*	*14 (42.4)*	*22 (30.6)*	*0.23*
Sum of ST-elevation on First ECG--mean (SD), mm	*7.64 (4.64)*	*9.73 (5.39)*	*6.69 (3.94)*	*0.002*
Anterior STEMI—no. (%)	*49 (46.7)*	*24 (72.7)*	*25 (34.7)*	*0.001*
The number of diseased Coronary Arteries—no. (%)				*0.915*
0	*1 (1.0)*	*0 (0.0)*	*1 (1.4)*	
1	*56 (53.3)*	*18 (54.5)*	*38 (52.8)*	
2	*33 (31.4)*	*10 (30.3)*	*23 (31.9)*	
3	*15 (14.3)*	*5 (15.2)*	*10 (13.9)*	
Aspirationofthrombusno0yes1 = 1 (%)	*47 (44.8)*	*20 (60.6)*	*27 (37.5)*	*0.046*
IIBIIIA_use (mean (SD))	*0.52 (0.50)*	*0.55 (0.51)*	*0.51 (0.50)*	*0.766*
TIMI Flow (Post-PCI) (%)				*0.266*
0	*1 (1.0)*	*0 (0.0)*	*1 (1.4)*	
2	*1 (1.0)*	*1 (3.0)*	*0 (0.0)*	
3	*103 (98.1)*	*32 (97.0)*	*71 (98.6)*	
PEAK TROPONIN -- median [IQR], micrg/l	*60.00 [20.00, 87.92]*	*87.92 [80.00, 101.00]*	*25.80 [8.89, 67.75]*	*<0.001*
Peak CRP-- median [IQR], mg/l	*16.78 [4.57, 35.43]*	*36.03 [26.94, 79.52]*	*9.90 [3.64, 23.10]*	*0.001*
Optimal DAPT response—no (%)	*74 (70.5)*	*16 (48.5)*	*58 (80.6)*	*0.002*
LVEF ECHO-- mean (SD)	*45.82 (9.47)*	*40.24 (7.79)*	*48.38 (9.10)*	*<0.001*
LVEDD (cm)-- mean (SD)	*4.68 (0.45)*	*4.80 (0.34)*	*4.62 (0.48)*	*0.06*
LVESD (cm)-- mean (SD)	*3.01 (0.52)*	*3.14 (0.45)*	*2.95 (0.54)*	*0.094*

LVEF MRI --mean (SD)	*55.05 (11.19)*	*47.36 (9.32)*	*58.57 (10.22)*	*<0.001*
RVEF MRI--mean (SD)	*51.88 (9.69)*	*49.39 (11.02)*	*53.02 (8.87)*	*0.075*
LGE LV--mean (SD)	*27.00 [17.62, 35.00]*	*35.00 [30.00, 38.00]*	*21.00 [11.55, 30.00]*	*<0.001*
LGE AHA--median [IQR]	*12.00 [4.00, 20.00]*	*23.00 [20.00, 28.00]*	*8.00 [0.00, 13.00]*	*<0.001*
MVO LV-- median [IQR]	*0.90 [0.00, 3.40]*	*3.80 [2.00, 5.00]*	*0.00 [0.00, 1.20]*	*<0.001*
MVO AHA--median [IQR]	*2.00 [0.00, 4.00]*	*5.00 [3.00, 6.00]*	*0.00 [0.00, 2.00]*	*<0.001*
MVO of scar--median [IQR]	*2.65 [0.00, 9.00]*	*8.00 [3.00, 12.00]*	*0.14 [0.00, 5.22]*	*<0.001*
3-Tesla –no. (%)	*35 (33.3)*	*12 (36.4)*	*23 (31.9)*	*0.824*
LV MASS—mean (SD)	*136.51 (33.79)*	*153.64 (32.71)*	*128.56 (31.44)*	*<0.001*

Overview of the relative frequency of comorbidities as well as laboratory values, echocardiographic and electrocardiographic indices between the two groups(larger LGE defined as the upper third values of the cohort, while lower LGE defined as the lower two-thirds).
All at admission laboratory values were taken within 30 min of admission—MPV=mean platelet volume. Continuous variables are presented as either mean ±SD or median and IQR, as detailed in the Methods section

Table S3. Description of the infarct-related artery and the infarct-related lesions.

	All Patients	*Optimal DAPT Responders*	*Suboptimal DAPT Responders*	*P-value*
n	*105*	*74*	*31*	
Stent to LAD-- no (%)				*0.317*
Proximal LAD	*41 (39.0)*	*26 (35.1)*	*15 (48.4)*	
Mid LAD	*8 (7.6)*	*7 (9.5)*	*1 (3.2)*	
Stent to LCX-- no (%)				*0.199*
Proximal	*12 (11.4)*	*6 (8.1)*	*6 (19.4)*	
Mid	*4 (3.8)*	*4 (5.4)*	*0 (0.0)*	
Distal	*2 (1.9)*	*1 (1.4)*	*1 (3.2)*	
Stent to RCA-- no (%)				*0.525*
Proximal	*29 (27.6)*	*23 (31.1)*	*6 (19.4)*	
Mid	*5 (4.8)*	*4 (5.4)*	*1 (3.2)*	
Distal	*7 (6.7)*	*4 (5.4)*	*3 (9.7)*	
Proximal lesion – no (%)	*81 (77.1)*	*55 (74.3)*	*26 (83.9)*	*0.419*

Comparing angiographic findings in DAPT optimal vs. suboptimal responders. Variables are presented as percentages.

Table S4. Sensitivity analysis: Predictors of MVO in patients treated with prasugrel or ticagrelor.

	Odds Ratio	Confidence Interval	P-value
DAPT Sub-Optimal Response	4.4	1.29-15.1	0.018
TIMI flow pre-PCI (≤1)	4.3	1.04-14.1	0.044
Anterior STEMI	4.13	1.2-13.5	0.017
Delayed pain to balloon time (>3 hours)	3.8	1.18-12.6	0.025

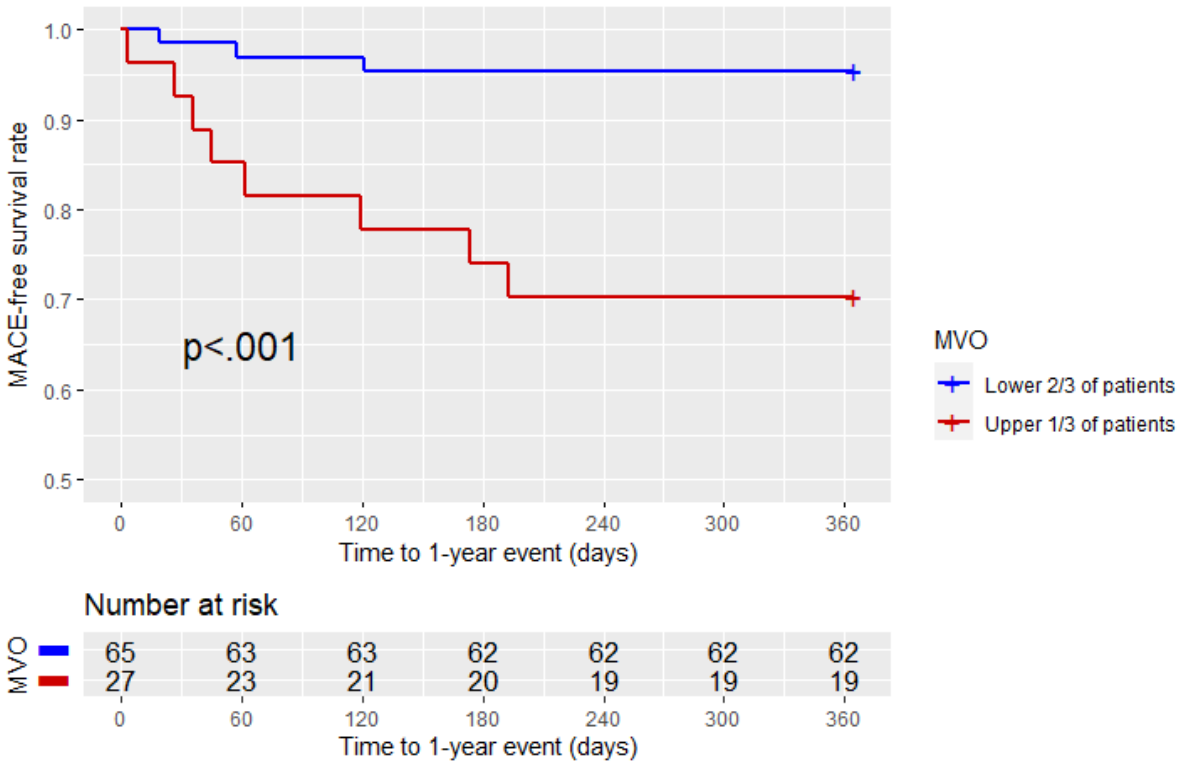
Multivariable binomial logistic regression model for predictors of MVO in patients treated with ticagrelor or prasugrel.

Table S5. Sensitivity analysis: Predictors of LGE in patients treated with prasugrel or ticagrelor.

	Odds Ratio	**Confidence Interval**	**P-value**
DAPT Sub-Optimal Response	4.04	1.07-15.2	0.03
TIMI flow pre-PCI (≤1)	2.5	0.5-11.8	0.22
Anterior STEMI	5.3	1.2-24.1	0.029
Delayed pain to balloon time (>3 hours)	1.39	0.39-4.9	0.6
HDL (mg/dl)	0.93	0.85-1.019	0.12
ST elevation resolution (post-PCI)	0.53	0.13-2.1	0.36
LVEF 1st ECHO	0.95	0.87-1.03	0.23

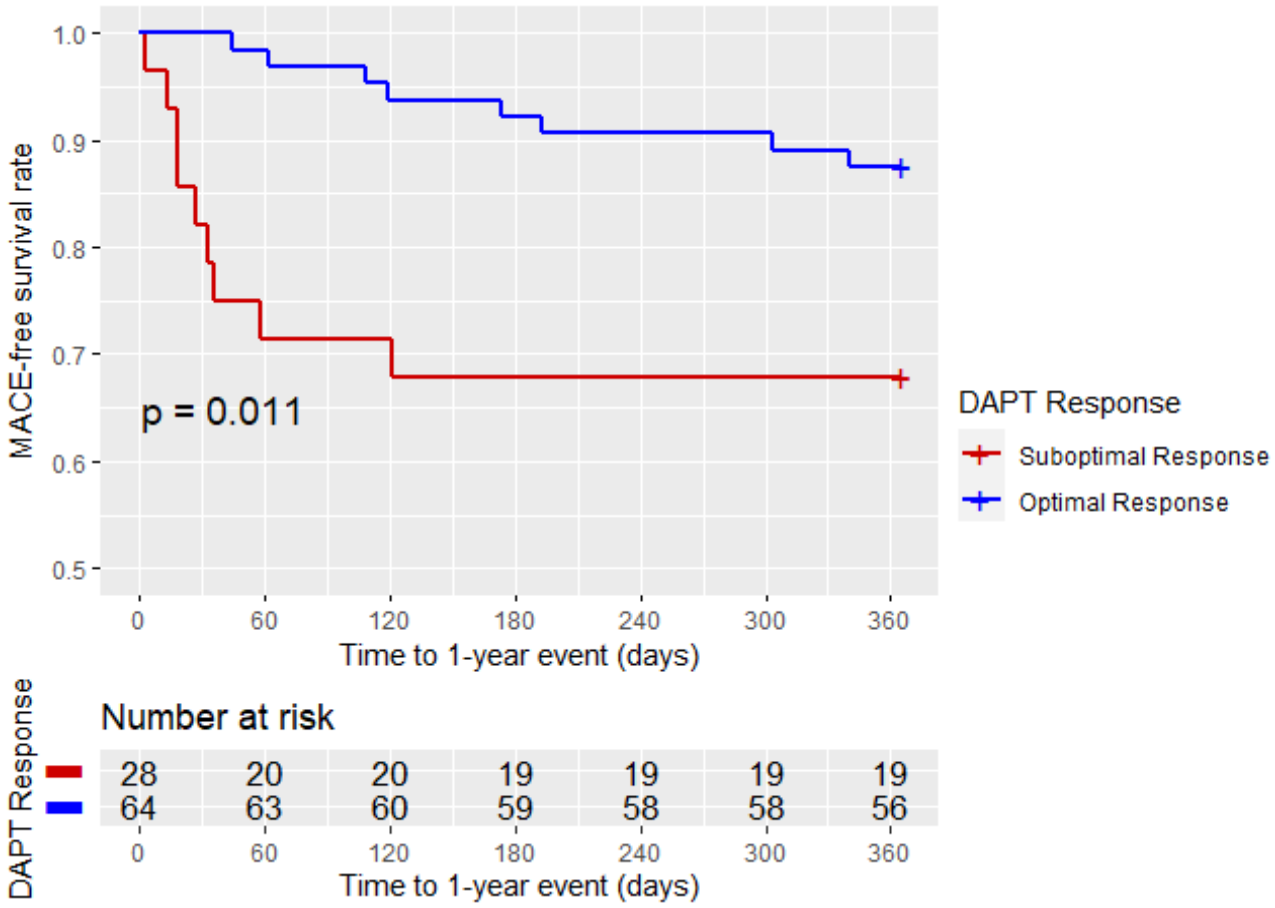
Multivariable binomial logistic regression model for predictors of LGE in patients treated with ticagrelor or prasugrel.

Figure S1. K-M Curve for 1-year clinical CHF and CV deaths.



Kaplan-Meier curve analysis with the accumulating events of heart failure and cardiovascular deaths on the y-axis (events) vs. time on the x-axis, stratified by MVO extent (upper 1\3 vs. lower 2\3). Log-rank p= 0.0006 (HR 7.3, 95% CI 1.9-26). MVO= microvascular obstruction.

Figure S2. K-M Curve for 1-year MACE Stratified by DAPT Response.



Kaplan-Meier curve analysis with the accumulating events on the y-axis (events) vs. time on the x-axis, stratified by DAPT response (Optimal vs. Suboptimal).

Log-rank p= 0.011 (HR 3.2, 95% CI 1.8-8.3)

DAPT- dual antiplatelet therapy. Suboptimal response- hypo-responsiveness to either aspirin or P2Y12 inhibitor.