ORIGINAL ARTICLE

High platelet reactivity is a predictor of left ventricular remodelling in patients with acute myocardial infarction

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Abstract

Aims   Acute myocardial infarction (AMI) is associated with left ventricular remodelling (LVR), which leads to progressive heart failure. Platelets play a pivotal role in promoting systemic and cardiac inflammatory responses during the complex process of myocardial wound healing or repair following AMI. This study aimed to investigate the impact of platelet reactivity immediately after primary percutaneous coronary intervention (PCI) on LVR in AMI patients with ST-segment (STEMI) and non-ST-segment elevation (NSTEMI).

Methods and results   This prospective, single-centre, observational study included 182 patients with AMI who underwent primary PCI (107 patient with STEMI and 75 patients with NSTEMI). Patients were administered a loading dose of aspirin plus prasugrel before the procedure, and platelet reactivity was assessed using the VerifyNow P2Y12 assay immediately after PCI. Echocardiography was performed before discharge and during the chronic phase (8 ± 3 months after discharge). LVR was defined as a relative ≥20% increase in left ventricular end-diastolic volume index (LVEDVI). LVR in chronic phase was found in 34 patients (18.7%) whose platelet reactivity was significantly higher than those without LVR (259.6 ± 61.5 and 213.1 ± 74.8 P2Y12 reaction units [PRU]; *P* = 0.001). The occurrence of LVR did not differ between patients with STEMI and patients with NSTEMI (21.5% and 14.7%; *P* = 0.33). The optimal cut-off value of platelet reactivity for discriminating LVR was ≥245 PRU. LVEDVI significantly decreased at chronic phase in patients without high platelet reactivity (<245 PRU) (from 49.2 ± 13.5 to 45.4 ± 15.8 mL/m^2; *P* = 0.02), but not in patients with high platelet reactivity (≥d245 PRU) (*P* = 0.06). Multivariate logistic analysis showed that high platelet reactivity was an independent predictor of LVR after adjusting for LVEDVI before discharge (odds ratio, 4.13; 95% confidence interval, 1.85–9.79).

Conclusions   High platelet reactivity measured immediately after PCI was a predictor of LVR in patients with AMI during the chronic phase. The role of antiplatelet therapy on inflammation in the myocardium is a promising area for further research.

Introduction

Although mortality after myocardial infarction (MI) has declined, the prevalence of post-MI heart failure (HF) continues to increase.[1] The development of the HF phenotype in these patients arises from a complex, progressive, molecular, and cellular transformation called 'left ventricular remodelling (LVR)'.[2] Moreover, some studies have shown that LVR that occurs after MI is related to long-term morbidity and mortality.[1] Therapeutic interventions such as early reperfusion therapy and optimal medical therapy with neurohormonal antagonists have been developed to reduce infarct size

and attenuate LVR development and progression.[3,4] However, a preventive strategy for LVR has not yet been established.

Platelets play a pivotal role in promoting systemic and cardiac inflammatory responses during the complex process of myocardial wound healing or repair following MI, which can cause LVR and cardiac rupture.[5,6] The REMODELLING (Role of Platelet Reactivity in LV Remodelling after ST-Segment Elevation Myocardial Infarction) trial first suggested a relationship between platelet reactivity 3 days after percutaneous coronary intervention (PCI) as well as the risk for subsequent LVR in patients with ST-segment elevation myocardial infarction (STEMI) during clopidogrel treatment.[6] Furthermore, the HEALING-AMI (High Platelet Inhibition with Ticagrelor to Improve Left Ventricular Remodelling in Patients With ST-Segment Elevation Myocardial Infarction) study showed ticagrelor, a potent oral P2Y12 inhibitor, was superior to clopidogrel for LVR after reperfusion of STEMI with primary PCI.[7] However, in these studies platelet reactivity was not assessed immediately after PCI, when platelet aggregation may have been increased by various invasions, including angioplasty.[8,9] Furthermore, little is known about the association between platelet reactivity and LVR in patients with non-ST-elevation myocardial infarction (NSTEMI), because previous studies have focused on patients with STEMI. In addition, no study has investigated the association between platelet reactivity immediately after PCI and evaluated structural changes in the LV using echocardiography.

Herein, the aim of this study is to investigate the impact of platelet reactivity immediately after primary PCI on LVR and echocardiographic changes in the chronic phase in patients with AMI, including STEMI and NSTEMI.

Methods

This prospective, single-centre, observational study was performed from January 2016 to June 2021. The study was approved by the ethics committee of Okayama City Hospital. All participants provided written informed consent prior to enrolment. All procedures were conducted in accordance with the Declaration of Helsinki and its amendments. This study was registered in the UMIN Clinical Trials Registry (UMIN-000029729).

Patient population

Patients who were hospitalized for STEMI or NSTEMI and who underwent primary PCI were prospectively enrolled. Definitions of STEMI and NSTEMI were determined according to appropriate guidelines.[9,10] Briefly, STEMI was diagnosed based on elevated levels of biomarkers for myocardial necrosis (including troponin T, troponin I, or creatine kinase muscle/brain), with ST-segment elevation of 1 mm or more in at least two contiguous ECG leads; NSTEMI was defined as elevated cardiac troponin I (cTnI) and symptoms of ischemia, without ST-segment elevation.

The exclusion criteria were as follows: (i) age <18 years; (ii) death during hospitalization; (iii) lack of platelet reactivity data; (iv) lack of appropriate echocardiographic data during hospitalization (cases in which the echocardiographic data were not appreciable for evaluation due to unclear images, or the images were not saved because of the use of portable ultrasonography); and (vi) cases with echo data outside the follow-up period (8 ± 3 months), or cases where echocardiographic follow-up was not performed.

The flow diagram of this study is presented in *Figure 1*. A total of 349 patients with AMI who underwent index PCI between January 2016 and June 2021 were identified from the hospital. After screening, 182 patients were included in the study. Platelet reactivity could not be measured in 36 patients because of hemodynamic instability or urgent treatment. Moreover, there were no available echocardiographic data in 32 patients, and 8 patients died during hospitalization. Therefore, these patients were excluded, and 273 patients remained in the initial cohort. Of these, appropriate echocardiographic data could not be acquired in 42 patients. Additionally, 49 patients could not undergo echocardiography within the designated period (8 ± 3 months) because of deterioration in activities or hospitalization in other institutions. The remaining 182 participants were enrolled in the study.

Procedure

All PCI procedures were performed according to standard techniques,[10] and the stent type was chosen by the operator after coronary angiography. We enrolled patients with AMI undergoing primary PCI for an infarct-related artery located in the proximal or midportion of a major epicardial coronary artery. In all cases, the loading doses of prasugrel (20 mg) and aspirin (200 mg) were administered in the cardiac catheter laboratory after diagnostic coronary angiography, and prasugrel (3.75 mg daily) and aspirin (100 mg daily) were subsequently administered as maintenance doses according to the guideline of the Japanese Circulation Society.[11] In most patients, dual antiplatelet therapy was continued for 6 months. At the discretion of the attending physician, certain patients were prescribed oral anticoagulants instead of aspirin, or were switched from prasugrel to clopidogrel at discharge, according to their co-morbidity or bleeding risk. All patients were treated with guideline-recommended optimal pharmacological therapy, including beta-blockers, angiotensin blockers, and statins.[3,10] Echocardiographic values during hospitalization and 8 ± 3 months after discharge were compared.

Figure 1 Flow diagram of this study. ACS, acute coronary syndrome; PRU, P2Y12 reaction. [Correction added on 16 November 2022, after first online publication: Figure 1 has been updated in this version.]
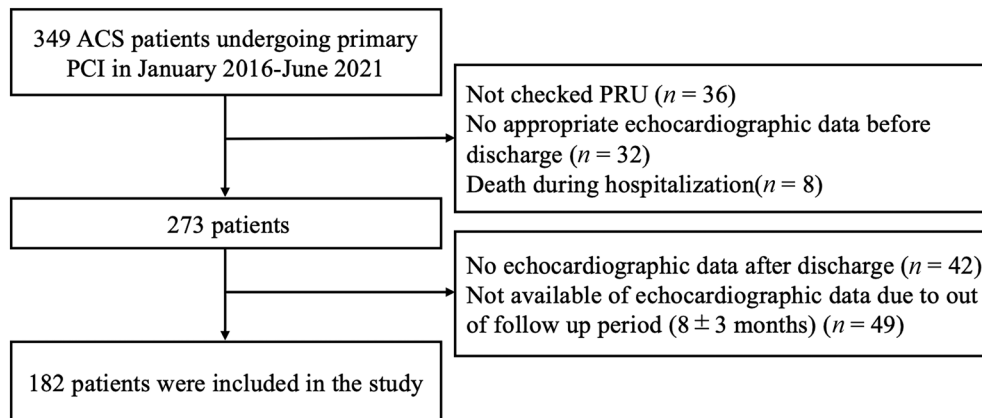
Echocardiographic measurement and definition of left ventricular remodelling

Echocardiographic images were obtained before discharge in accordance with current European and American guidelines.[12,13] Echocardiography was performed using commercially available equipment (EPIQ 7G Ultrasound System, Philips Japan, Tokyo, Japan) before discharge and at the follow-up visit. Echocardiographic recordings were performed by three experienced echocardiographers who were blinded to biomarker values. LV end-systolic and end-diastolic volume indices (LVESVI and LVEDVI, respectively) were calculated by dividing LVESV and LVEDV by body surface area, as the reference values of LV volumes are significantly influenced by body mass.[13] Left atrial (LA) volume was measured using the biplane method of disks using apical four- and two-chamber views at the LV end systole. The LA volume index (LAVI) was calculated by dividing the absolute LA volume by body surface area. Diastolic LV function was assessed by measuring the ratio between the peak mitral flow velocity in the early rapid filling phase (E) and the average peak early diastolic mitral annulus velocity (e'). Non-infarction-related segments were selected to obtain e'. The modified Simpson's rule was given priority in the measurement of LVEF, LVESVI, and LVEDVI, and the M mode was used when the measurement was not performed according to the modified Simpson's rule.

The LV remodelling index was calculated as the relative change in LVEDVI observed in the chronic phase compared with that at baseline. LVR was defined as a relative increase in LVEDVI $\geq$ 20%.[7] Patients were divided into LVR and non-LVR groups according to presence or absence of LVR in the chronic phase.

Laboratory measurement and assessment of platelet reactivity

Baseline biochemical assessments were performed before the index procedure. Platelet function in response to prasugrel was assessed using the VerifyNow P2Y12 assay (International Technidyne Corporation, Edison, NJ, USA), according to the manufacturer's instructions.[14] Blood samples were collected once per procedure from the artery immediately before sheath removal following PCI. VerifyNow P2Y12 is a whole-blood point-of-care assay that measures responsiveness to P2Y12 antagonists. The cartridge contained fibrinogen-coated polystyrene beads, 20 μM ADP, and 22 nM prostaglandin E1; the optical signal of this channel was reported as P2Y12 reaction units (PRU; range, 0–550).[15]

Statistical analysis

Categorical variables are presented as numbers (%). Normally distributed continuous variables are shown as the mean ± standard deviation and were compared between groups using Student's *t*-test. Continuous variables that were not normally distributed are shown as medians with interquartile ranges and were compared using the Mann–Whitney *U* test. The association between continuous variables was investigated using Pearson's correlation coefficient. Receiver operating characteristic curve analysis was performed to obtain an ideal cut-off for PRU to discriminate the presence of LVR, which was determined as the value providing the greatest sum of sensitivity and specificity. Univariate and multivariate logistic analyses were used to identify the significant factors associated with the primary endpoint. Multivariate

analysis was performed using variables with *P* values <0.05 in univariate analyses. Statistical significance was set at *P* value <0.05. All analyses were conducted using the SPSS version 21.0 software (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics and incidence of left ventricular remodelling

The demographic and clinical characteristics of patients are presented in *Table 1*. The mean age of the study population was 68.2 years, and 78.6% of patients were men. The prevalence of hypertension and diabetes was 67.6% and 33.0%, respectively. The follow-up duration was 7.2 ± 1.7 months. LVR was observed in 18.7%, or 34 cases. LVR occurred in 21.5% (*n* = 23) among 107 STEMI patients, and in 14.7% (*n* = 11) among 75 NSTEMI patients, with no statistically significant difference between patients with STEMI and NSTEMI (*P* = 0.332). There were no differences in age, sex, or blood pressure between the LVR and non-LVR groups. The LVR group had higher platelet reactivity (*P* = 0.001) than the non-LVR group, whereas laboratory characteristics, except for platelet reactivity, did not differ between the two groups.

In addition, there were no significant differences in comorbidities, PCI-related characteristics, or medication at discharge between the two groups. The proportion of patients with TIMI 3 did not differ between the two groups (*P* = 0.849). Regarding echocardiographic parameters, LVEDVI in the LVR group was significantly higher than that in the non-LVR group (*P* = 0.008), while there was no difference in other parameters, including LVMI, LVEF, LVESVI, LAVI, and E/e′, between these two groups.

Association of high platelet reactivity and changes in echocardiographic parameters

A Pearson's correlation analysis demonstrated that platelet reactivity at baseline was significantly associated with changes in LVEDVI (*r* = 0.23, *P* = 0.002), LVESVI (*r* = 0.17, *P* = 0.020), and LVMI (*r* = 0.15, *P* = 0.046). In contrast, LVEF (*r* = −0.11, *P* = 0.122), LAVI (*r* = 0.10, *P* = 0.184), and E/e′ (*r* = 0.08, *P* = 0.261), were not significantly associated. The optimal cut-off value of platelet reactivity for discriminating LVR by using receiver operating characteristic curve analysis was 244.5 PRU, with a sensitivity of 0.706 and a specificity of 0.655 (AUC: 0.689; 95% CI: 0.595 to 0.783). Therefore, we set the cut-off value for platelet reactivity that defined high platelet reactivity (HPR) as ≥245 PRU. HPR was found in 75 patients (41.2%) among all patients.

A comparison of echocardiographic parameters before discharge and during the chronic phase is shown in *Figure 2*. In the HPR group, LVEF was significantly increased in the chronic phase (58.3 ± 10.9% vs. 60.6 ± 11.6%; *P* = 0.013), while LVEDVI, LVESVI, LAVI, LVMI, and E/e′ did not change significantly. In contrast, in the non-HPR group, LVEF was increased significantly [60.3 ± 11.8 vs. 62.9 ± 11.5 (%); *P* = 0.005], and LVEDVI [49.2 ± 13.5 vs. 45.4 ± 15.8 (mL/m²); *P* = 0.020], LVESVI [20.0 ± 10.1 vs. 16.8 ± 8.8(mL/m²); *P* < 0.001], LAVI (28.0 ± 8.3 vs. 26.3 ± 9.1, *P* = 0.070), LVMI (106.9 ± 27.2 vs. 98.9 ± 27.4, *P* = 0.003), and E/e′ (13.4 ± 4.2 vs. 11.9 ± 3.8, *P* < 0.001), were significantly decreased.

Table 2 shows the change in echocardiographic parameters in patients with STEMI and NSTEMI. In patients with STEMI, LVEF was increased, and LVEDVI, LVESVI, and E/e′ were decreased significantly in the non-HPR group, while LVEF only improved in the HPR group. Similarly in patients with NSTEMI, LVESVI, LVMI, LAVI, and E/e′ were decreased significantly in the non-HPR group, while LVMI only decreased in the HPR group. However, LVEF did not improve significantly in both groups.

Impact of high platelet reactivity on left ventricular remodelling

The logistic analysis of the predictors of LVR is shown in *Table 3*. The univariate logistic analysis demonstrated that the presence of LVR was significantly associated with LVEDVI (odds ratio, 4.56; 95% confidence interval, 2.08–10.7; *P* < 0.001) and HPR (odds ratio, (0.95; 95% confidence interval, 0.92–0.99; *P* = 0.009). The multivariate logistic analysis also showed that the presence of LVR was significantly associated with LVEDVI (odds ratio, 0.96; 95% confidence interval, 0.92–0.99; *P* = 0.026) and HPR (odds ratio, 4.13; 95% confidence interval, 1.85–9.79; *P* < 0.001).

Discussion

To our knowledge, this is the first study to evaluate the association between platelet reactivity immediately after primary PCI with LVR and each echocardiographic parameter in patients with AMI, including STEMI and NSTEMI. We found that in patients with AMI, HPR (e.g. PRU ≥ 245) measured immediately after primary PCI was an independent predictor of LVR, with patients with HPR having an approximately 4.13-fold greater risk of LVR.

Previous studies have reported a negative impact of activated platelets on adverse cardiac events, suggesting that HPR is significantly and independently associated with cardiovascular death and major adverse coronary events in patients with acute coronary syndrome (ACS) undergoing PCI.[16,17] HPR was also a prognostic factor for cardiovascular events in patients with stable angina,[18–20] and a recent report also showed that HPR is associated with long-term mortality in

Table 1 Baseline characteristics

	All (n = 182)	LVR (n = 34)	Non-LVR (n = 148)	P-value
Age, years	68.2 ± 12.8	66.6 ± 12.4	68.6 ± 12.9	0.413
Male	143 (78.6)	27 (79.4)	116 (78.4)	1.000
Body mass index, kg/m^2	23.9 ± 3.8	23.3 ± 3.1	24.1 ± 3.9	0.258
SBP, mmHg	140.3 ± 37.9	138.8 ± 31.3	140.7 ± 39.4	0.794
DBP, mmHg	85.4 ± 24.5	86.7 ± 24.3	85.1 ± 24.6	0.730
Heart rate, /min	74.9 ± 22.9	77.0 ± 18.3	74.4 ± 23.8	0.542
Laboratory characteristics				
WBC, 10^3/mm^3	9.3 ± 3.1	9.5 ± 3.1	9.3 ± 3.1	0.693
Haemoglobin, g/dl	10.5 ± 4.7	9.6 ± 5.0	10.7 ± 4.6	0.209
Platelet, 10^3/mm^3	234.4 ± 87.9	221.7 ± 53.2	237.3 ± 94.0	0.354
eGFR, mL/min/1.73 m^2	64.7 ± 21.0	63.9 ± 19.5	64.9 ± 21.4	0.807
hsCRP, mg/L	0.19 (0.07–0.52)	0.2 (0.0–0.5)	0.2 (0.1–0.5)	0.279
HbA1c, %	6.4 ± 1.2	6.0 ± 0.5	6.5 ± 1.3	0.078
LDL-C, mg/dL	110.3 ± 36.5	110.8 ± 38.2	110.2 ± 36.3	0.935
Peak CPK, ng/mL	1780.3 ± 2134.4	2398.7 ± 2,561	1638.2 ± 2007.1	0.061
BNP, pg/mL	50.7 (14.3–154.4)	37.7 (15.5–129.7)	52.3 (14.3–161.8)	0.763
D-dimer, ng/mL	1.1 ± 1.8	1.2 ± 1.5	1.1 ± 1.9	0.777
Platelet reactivity, PRU	221.8 ± 74.6	259.6 ± 61.5	213.1 ± 74.8	0.001
Co-morbidities				
Hypertension	123 (67.6)	22 (64.7)	101 (68.2)	0.846
Dyslipidaemia	91 (50.0)	20 (58.8)	71 (48.0)	0.342
Diabetes mellitus	60 (33.0)	10 (29.4)	50 (33.8)	0.774
Chronic kidney disease	16 (8.8)	2 (5.9)	14 (9.5)	0.743
Smoking	100 (54.9)	18 (52.9)	82 (55.4)	0.945
PCI-related characteristics				
STEMI	107 (58.8)	23 (67.6)	84 (56.8)	0.332
Aspiration thrombectomy	118 (64.8)	24 (70.6)	94 (63.5)	0.562
PCPS/IABP	17 (9.3)	4 (11.8)	13 (8.8)	0.832
Multivessel disease	62 (34.3)	13 (39.4)	49 (33.1)	0.628
Infarct-related artery				0.805
LAD/Left main	109 (59.9)	22 (64.7)	87 (58.8)	
Left circumflex	26 (14.3)	4 (11.8)	22 (14.9)	
Right coronary	47 (25.8)	8 (23.5)	39 (26.4)	
Treatment for culprit lesion				0.506
Drug-eluting stent	169 (92.9)	30 (88.2)	139 (93.9)	
Drug coated balloon	10 (5.5)	3 (8.8)	7 (4.7)	
POBA	3 (1.6)	1 (2.9)	2 (1.4)	
Final TIMI grade after PCI				0.373
0	2 (1.1)	0 (0.0)	2 (1.4)	
1	0 (0.0)	0 (0.0)	0 (0.0)	
2	5 (2.7)	2 (5.9)	3 (2.0)	
3	175 (96.2)	32 (94.1)	143 (96.6)	
Medications at discharge				
Prasugrel	148 (81.3)	27 (79.4)	121 (81.8)	0.942
Clopidogrel	27 (14.8)	4 (11.8)	23 (15.5)	0.771
Aspirin	173 (95.1)	30 (88.2)	143 (96.6)	0.111
ACEI or ARB	138 (75.8)	26 (76.5)	112 (75.7)	1.000
Beta-blocker	136 (74.7)	26 (76.5)	110 (74.3)	0.967
MRA	30 (16.5)	5 (14.7)	25 (16.9)	0.957
Oral anticoagulants	15 (8.2)	4 (11.8)	11 (7.4)	0.629
Statins	171 (94.0)	32 (94.1)	139 (93.9)	1.000
Proton pump inhibitors	53 (29.1)	8 (23.5)	45 (30.4)	0.558
Echocardiographic parameters				
LVMI, g/m^2	106.8 ± 26.2	108.3 ± 26.1	100.4 ± 26	0.122
LAVI, mL/m^2	29.8 ± 9.5	29.8 ± 10.1	29.6 ± 6.8	0.909
E/e'	13.9 ± 4.7	13.9 ± 4.4	13.8 ± 5.8	0.976
LVEF, %	59.5 ± 11.5	60 ± 11.1	56.9 ± 12.8	0.153
LVEDVI, mL/m^2	47.6 ± 13.0	48.8 ± 12.8	42.3 ± 12.5	0.008
LVESVI, mL/m^2	19.71 ± 9.34	19.78 ± 8.93	19.38 ± 11.11	0.821

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CPK, creatine phosphokinase; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; hsCRP, high-sensitivity C-reactive protein; IABP, intra-aortic balloon pumping; LAD, left atrial dimension; LAVI, left atrial volume index; LDL-C, low-density lipoprotein cholesterol; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; LVMI, left ventricular mass index; MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; PCPS, percutaneous cardiopulmonary support; POBA, plain old balloon angioplasty; PRU, P2Y12 reaction units; WBC, white blood cell.
Data are presented as number (%), mean ± standard deviation, or median (25th–75th percentile).

Figure 2 Change in echocardiographic parameters in acute versus chronic phase, for HPR and non-HPR respectively (all cases; *n* = 182). (A) LVEF, (B) LVEDVI, (C) LVESVI, (D) LVMI, (E) LAVI, and (F) E/e'. HPR, high platelet reactivity; LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; LVMI, left ventricular mass index.
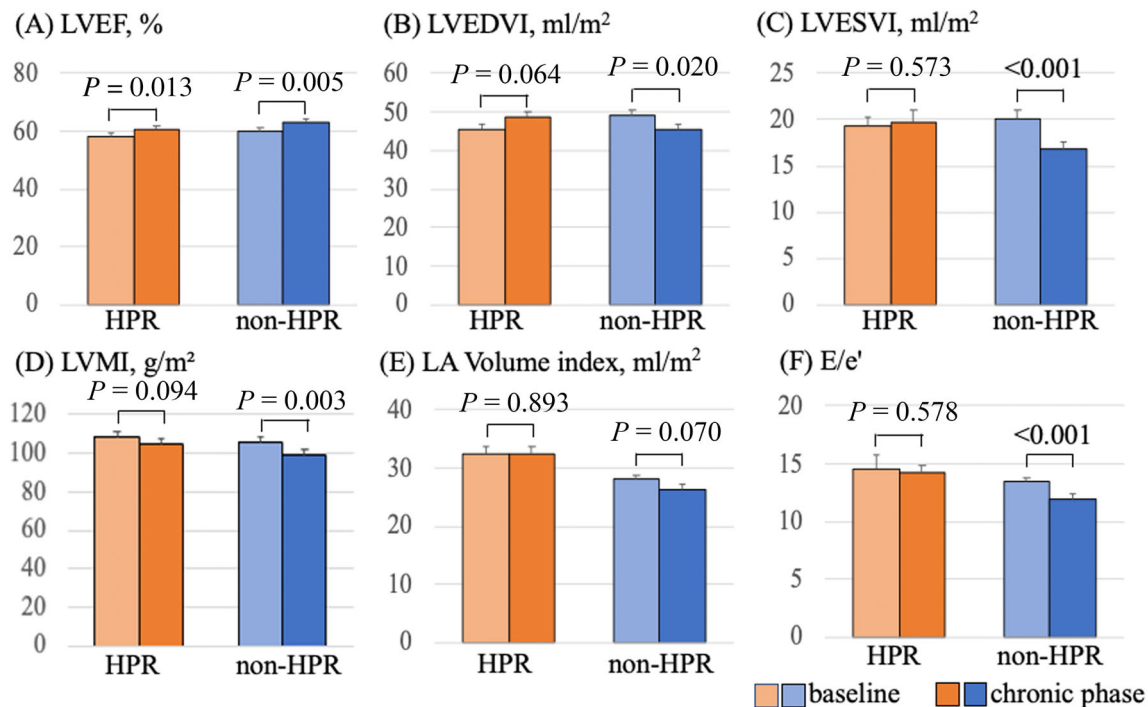
Table 2 Change in echocardiographic parameters in acute versus chronic phase, for HPR and non-HPR respectively

STEMI (*n* = 107)	HPR (*n* = 50)		*P*-value	Non-HPR (*n* = 57)		*P*-value
LVEF, %	57.3 ± 11.3	59.6 ± 11.6	0.046	56.4 ± 12.7	60.5 ± 11.5	<0.001
LVEDVI, mL/m^2	44.9 ± 9.8	48.8 ± 13.8	0.060	48.5 ± 15.3	43.7 ± 14.4	0.026
LVESVI, mL/m^2	19.4 ± 7.3	20.1 ± 9.9	0.558	22.0 ± 12.0	17.8 ± 10.5	0.002
LVMI, g/m^2	107.7 ± 24	106.7 ± 24.8	0.463	109.8 ± 31.7	102.1 ± 31	0.071
LAVI, mL/m^2	33.2 ± 9.9	33.0 ± 11.6	0.779	28.2 ± 9.2	26.9 ± 9.9	0.471
E/e'	14.4 ± 5.4	13.7 ± 6.3	0.384	13.5 ± 4.2	12.1 ± 4.4	0.015
NSTEMI (*n* = 75)	HPR (*n* = 25)		*P*-value	Non-HPR (*n* = 50)		*P*-value
LVEF, %	60.3 ± 10.1	62.6 ± 11.6	0.156	64.7 ± 9.0	65.6 ± 11.0	0.521
LVEDVI, mL/m^2	46.0 ± 15.5	47.9 ± 17.6	0.561	50.0 ± 11.3	47.3 ± 17.2	0.289
LVESVI, mL/m^2	18.9 ± 9.9	19.2 ± 14.6	0.874	17.8 ± 6.9	15.8 ± 6.2	0.043
LVMI, g/m^2	108.6 ± 26.9	100.4 ± 19.4	0.046	101.9 ± 20.6	95.3 ± 22.5	0.018
LAVI, mL/m^2	31.1 ± 11.8	30.9 ± 12.4	0.801	27.8 ± 7.4	25.6 ± 8.1	0.041
E/e'	14.8 ± 5.0	15.1 ± 7.0	0.751	13.3 ± 4.2	11.8 ± 3.0	0.001

HPR, high platelet reactivity; LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; LVMI, left ventricular mass index; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

patients with stable angina and ACS.[21] However, the effect of platelet reactivity after PCI on cardiac function in the chronic phase has not been fully investigated. The REMODELLING trial was the first to show the association between platelet activation and the LVR process in patients with STEMI and clopidogrel loading.[6] Our study adds new insights to the results of the REMODELLING trial by showing the relationship between HPR and LVR, with the difference that prasugrel was administered instead of clopidogrel and that both STEMI and NSTEMI were included. Moreover, the fact that low platelet reactivity immediately after PCI predicted preferable cardiac function in the chronic phase was a remarkable finding. Notably, this result was not limited to STEMI patients, but was also observed in those with NSTEMI in this study.

Table 3 Predictors of the presence of LVR

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
HPR ≥ 245 PRU	4.56	(2.08–10.7)	<0.001	4.13	(1.85–9.79)	<0.001
LVEDVI before discharge, per 1 mL/m^2	0.95	(0.92–0.99)	0.009	0.96	(0.92–0.99)	0.026
LVESVI before discharge, per 1 mL/m^2	1.00	(0.95–1.03)	0.820			
STEMI	1.59	(0.73–3.62)	0.247			
Body mass index, per 1 kg/m^2	0.94	(0.84–1.04)	0.257			
Peak CPK, per 1 U/mL	1.00	(1.00–1.00)	0.070			
hs-CRP, per 1 mg/L	0.89	(0.66–1.08)	0.400			
Aspirin	0.26	(0.06–1.11)	0.056			
Beta-blocker	1.12	(0.48–2.84)	0.795			
ACEI/ARB	1.04	(0.45–2.65)	0.922			
HbA1c, per 1%	0.66	(0.39–1.00)	0.084			
Platelet, per 10^3/mm^3	1.00	(0.99–1.00)	0.346			
D-dimer, per 1 ng/mL	1.03	(0.81–1.24)	0.776			

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CPK, creatine phospho-kinase; HbA1c, glycated haemoglobin; HPR, high platelet reactivity; hsCRP, high-sensitivity C-reactive protein; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; STEMI, ST-elevation myocardial infarction; PRU, P2Y12 reaction units.

Previous studies have shown that prasugrel and ticagrelor achieve platelet inhibition earlier and maintain it lower for a longer period than clopidogrel does.[22,23] The difference in the effect of prasugrel and ticagrelor on platelet reactivity remains unclear; however, both drugs seem to be superior to clopidogrel in lowering PRU effectively. In the HEALING-AMI study, platelet reactivity was measured before the PCI procedure (immediately after sheath insertion) in the acute phase, and was not found to be significantly different between the clopidogrel and ticagrelor groups.[7] However, that study suggested that PRU values at discharge and 30 days after PCI were significantly different between the two groups, and that ticagrelor was superior to clopidogrel for LVR. Both prasugrel and ticagrelor have been shown to sufficiently suppress platelet reactivity approximately 2 h after oral loading dose administration.[22] In addition, previous studies showed that cytochrome P-450 genetic variants did not affect inhibition of platelet aggregation in patients treated with prasugrel.[24,25] Meanwhile, platelet reactivity has been demonstrated to affected by PCI.[8,9,26] We also reported that an increase in platelet reactivity just after elective PCI was associated with increased risk of PCI-related myocardial infarction.[26] Additional studies showed that platelets are activated during PCI due to regional endothelial dysfunction caused by ischemia or by iatrogenic reasons.[8,9] Considering that high platelet activity influences the inflammatory status, we hypothesized that LVR may be affected by a condition with high platelet reactivity after PCI induced by both the acute myocardial infarction and the PCI procedure. Therefore, timing sample collection immediately after PCI should be appropriate for determining whether platelet function is effectively suppressed.

This study added new insights to the literature by including patients with NSTEMI and improved echocardiographic parameters in the chronic phase, regardless of STEMI or NSTEMI in non-HPR patients. However, LVEF and LVEDVI did not improve in patients with NSTEMI, regardless of platelet reactivity. One possible explanation for this is that the duration from the onset to PCI varied among patients with NSTEMI because some patients were not referred to the hospital soon after the onset. In such cases, CPK often peaked upon the patient's arrival at our hospital. In contrast, minimal cardiac injury is likely to be more common in NSTEMI than in STEMI cases. We considered this to be the main reason that LVEF did not improve in patients with NSTEMI, and there was no association between peak CPK value and the occurrence of LVR in this study. It has been reported that delayed reperfusion therapy is associated with LVR,[27] and it may be also associated with strong myocardial inflammation despite relatively low peak CPK values.

Regarding the underlying mechanisms between platelet reactivity and LVR, inflammation may have a critical role. The inflammatory response after an infarct event results in the formation of an extracellular matrix by fibroblasts, and persistent and exaggerated inflammatory responses after infarct events contribute to infarct expansion and LVR.[28,29] Platelets contribute to inflammatory responses through two fundamental mechanisms[5]: granular release of inflammatory mediators, such as serotonin, histamine, chemokines, cytokines, and MMPs2; and platelet-leukocyte interaction, contributing to activation of leukocytes and recruitment to inflamed tissues, which is mainly mediated by P-selectin/PSGL-1.[5,30] Treatment with a P2Y12 inhibitor suppresses the proportion of P-selectin-expressing platelets and inhibits platelet-leukocyte interactions.[5] It remains unclear whether suppressing platelet reactivity directly inhibits myocardial remodelling and improves patient prognosis, while several animal studies have suggested that P2Y12 inhibitors limit LVR myocardial infarct size and LVR progression.[5,31] In the present study, LVR was suppressed in patients without HPR and cardiac function was improved in the chronic phase, suggesting that platelet reactivity may be a marker of cardiac function

in the chronic phase. The increase in C-reactive protein, a marker of inflammation, was reported to be associated with the development of heart failure in patients after AMI,[32] although it cannot be a therapeutic target. The potential for potent P2Y12 inhibitors to suppress activated platelet reactivity, subsequent inflammation, and LVR, especially after PCI in patients with AMI, may be a new focus for chronic HF for which further studies are required.

Low platelet reactivity in the acute phase could predict less LVR development in the chronic phase and preferable cardiac function, which may explain the previously reported occurrence of cardiovascular events and poor prognosis in patients with HPR.[16–21] Therefore, HPR immediately after PCI may provide a reason for the earlier and more intensive administration of such medications, and for closer follow up, in order to prevent LVR. Moreover, it is important to suppress platelet reactivity as strongly as possible during PCI. Acute antiplatelet effects should be considered in the future as a novel approach to suppress myocardial remodelling in the chronic phase. P2Y12 inhibition against LVR may be a promising area for further research investigating factors that improve the prognosis of patients with AMI.

Limitations

First, this study involved a relatively small number of patients and was conducted at a single centre. In addition, patients with unstable hemodynamic condition on admission and no available echocardiographic data, as well as patients who died during hospitalization, were excluded. Therefore, it cannot be denied that selection bias has affected the results. Second, we only assessed platelet reactivity immediately after the PCI procedure and did not follow-up on residual platelet reactivity during treatment. However, a single measurement may not be sufficient to clarify the relationship between platelet reactivity and LVR. Hence, serial measurement of platelet reactivity are required to clarify the optimal timing of platelet reactivity. Third, we evaluated platelet reactivity using VerifyNow, although other tests to measure platelet function have also been developed.[33,34] Further study using additional tests will be needed to better understand the mechanistic background of platelet activity and LVR. Fourth, in this study, the impact of STEMI or NSTEMI on the association of HPR with LVR was not statistically significant, probably due to the limited number of LVR. To confirm this, larger studies are warranted. Finally, there were some cases in which adherence to pharmacological therapy could not be followed.

Given the above, further prospective studies with larger numbers of patients and longer follow-up periods are needed to confirm the findings of this study.

Conclusions

HPR immediately after PCI (platelet reactivity ≥245 PRU) was associated with the incidence of LVR in the chronic phase of AMI. Platelet reactivity in the acute phase may be a potential biomarker for predicting cardiac function in the chronic phase following an ischemic event. The role of antiplatelet therapy after ischemic events and its effect on inflammation in the myocardium are promising areas for further research.

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Conflict of interest

The authors declare no conflicts of interest regarding the materials presented in this article.

References

1. Heusch G, Libby P, Gersh B, Yellon D, Böhm M, Lopaschuk G, Opie L. Cardiovascular remodelling in coronary artery disease and heart failure. *Lancet*. 2014; **383**: 1933–1943.
2. Bhatt AS, Ambrosy AP, Velazquez EJ. Adverse Remodeling and reverse Remodeling after myocardial infarction. *Curr Cardiol Rep*. 2017; **19**: 71.
3. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P, ESC Scientific Document Group. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2018; **39**: 119–177.
4. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the Management of Heart Failure: A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Failure Society of America. *Circulation*. 2017; **136**: e137–e161.
5. Liu Y, Gao XM, Fang L, Jennings NL, Su Y, Q X, Samson AL, Kiriazis H, Wang XF, Shan L, Sturgeon SA, Medcalf RL, Jackson SP, Dart AM, du XJ. Novel role of platelets in mediating inflammatory responses and ventricular rupture or re-

modelling following myocardial infarction. *Arterioscler Thromb Vasc Biol.* 2011; **31**: 834–841.

6. Park Y, Tantry US, Koh JS, Ahn JH, Kang MG, Kim KH, Jang JY, Park HW, Park JR, Hwang SJ, Park KS, Kwak CH, Hwang JY, Gurbel PA, Jeong YH. Novel role of platelet reactivity in adverse left ventricular remodelling after ST-segment elevation myocardial infarction: The RE-MODELING trial. *Thromb Haemost.* 2017; **117**: 911–922.

7. Park Y, Koh JS, Lee JH, Park JH, Shin ES, Oh JH, Chun W, Lee SY, Bae JW, Kim JS, Kim W, Suh JW, Yang DH, Hong YJ, Chan MY, Kang MG, Park HW, Hwang SJ, Hwang JY, Ahn JH, Choi SW, Jeong YH, HEALING-AMI Investigators. Effect of Ticagrelor on left ventricular Remodeling in patients with ST-segment elevation myocardial infarction (HEALING-AMI). *JACC Cardiovasc Interv.* 2020; **13**: 2220–2234.

8. Alexopoulos D, Xenogiannis I, Vlachakis P, Tantry U, Gurbel PA. Peri-procedural platelet reactivity in percutaneous coronary intervention. *Thromb Haemost.* 2018; **118**: 1131–1140.

9. Prasad A, Herrmann J. Myocardial infarction due to percutaneous coronary intervention. *N Engl J Med.* 2011; **364**: 453–464.

10. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM, ESC Scientific Document Group. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* 2021; **42**: 1289–1367.

11. Kimura K, Kimura T, Ishihara M, Nakagawa Y, Nakao K, Miyauchi K, Sakamoto T, Tsujita K, Hagiwara N, Miyazaki S, Ako J, Arai H, Ishii H, Origuchi H, Shimizu W, Takemura H, Tahara Y, Morino Y, Iino K, Itoh T, Iwanaga Y, Uchida K, Endo H, Kongoji K, Sakamoto K, Shiomi H, Shimohama T, Suzuki A, Takahashi J, Takeuchi I, Tanaka A, Tamura T, Nakashima T, Noguchi T, Fukamachi D, Mizuno T, Yamaguchi J, Yodogawa K, Kosuge M, Kohsaka S, Yoshino H, Yasuda S, Shimokawa H, Hirayama A, Akasaka T, Haze K, Ogawa H, Tsutsui H, Yamazaki T, Japanese Circulation Society Joint Working Group. JCS 2018 guideline on diagnosis and treatment of acute coronary syndrome. *Circ J.* 2019; **83**: 1085–1196.

12. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: A report from the American Society of Echocardiography. Endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr.* 2010; **23**: 685–713.

13. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2015; **28**: 1–39.e14.

14. Valgimigli M, Campo G, de Cesare N, Vranckx P, Hamon M, Angiolillo DJ, Sabatè M, Ferrari F, Furgieri A, Tumscitz C, Repetto A, Colangelo S, Meliga E, Kubbajeh M, Parrinello G, Percoco G, Ferrari R. Tailoring treatment with tirofiban in patients showing resistance to aspirin and/or resistance to clopidogrel (3T/2R). Rationale for the study and protocol design. *Cardiovasc Drugs Ther.* 2008; **22**: 313–320.

15. Jeong YH, Bliden KP, Antonino MJ, Park KS, Tantry US, Gurbel PA. Usefulness of the VerifyNow P2Y12 assay to evaluate the antiplatelet effects of ticagrelor and clopidogrel therapies. *Am Heart J.* 2012; **164**: 35–42.

16. Marcucci R, Gori AM, Paniccia R, Giusti B, Valente S, Giglioli C, Buonamici P, Antoniucci D, Abbate R, Gensini GF. Cardiovascular death and nonfatal myocardial infarction in acute coronary syndrome patients receiving coronary stenting are predicted by residual platelet reactivity to ADP detected by a point-of-care assay a 12-month follow-up. *Circulation.* 2009; **119**: 237–242.

17. Marcucci R, Giusti B, Paniccia R, Gori AM, Saracini C, Valente S, Giglioli C, Parodi G, Antoniucci D, Gensini GF, Abbate R. High on-treatment platelet reactivity by ADP and increased risk of MACE in good clopidogrel metabolizers. *Platelets.* 2012; **23**: 586–593.

18. Viviani Anselmi C, Briguori C, Roncarati R, Papa L, Visconti G, Focaccio A, De Micco F, Latronico MV, Pagnotta P, Condorelli G. Routine assessment of on-clopidogrel platelet reactivity and gene polymorphisms in predicting clinical outcome following drug-eluting stent implantation in patients with stable coronary artery disease. *JACC Cardiovasc Interv.* 2013; **6**: 1166–1175.

19. Droppa M, Tschernow D, Müller KA, Tavlaki E, Karathanos A, Stimpfle F, Schaeffeler E, Schwab M, Tolios A, Siller-Matula JM, Gawaz M, Geisler T. Evaluation of clinical risk factors to predict high on-treatment platelet reactivity and outcome in patients with stable coronary artery disease (PREDICT-STABLE). *PLoS ONE.* 2015; **10**: e0121620.

20. Price MJ, Angiolillo DJ, Teirstein PS, Lillie E, Manoukian SV, Berger PB, Tanguay JF, Cannon CP, Topol EJ. Platelet reactivity and cardiovascular outcomes after percutaneous coronary intervention: A time-dependent analysis of the gauging responsiveness with a verifynow P2Y12 assay: Impact on thrombosis and safety (GRAVITAS) trial. *Circulation.* 2011; **124**: 1132–1137.

21. Lee SN, Moon D, Sung MK, Moon KW, Yoo KD. Impact of platelet reactivity on long-term prognosis in Korean patients receiving percutaneous coronary intervention. *Platelets.* 2019; **30**: 1030–1035.

22. Schnorbus B, Daiber A, Jurk K, Warnke S, Koenig J, Lackner KJ, Münzel T, Gori T. Effects of clopidogrel vs. prasugrel vs. ticagrelor on endothelial function, inflammatory parameters, and platelet function in patients with acute coronary syndrome undergoing coronary artery stenting: A randomized, blinded, parallel study. *Eur Heart J.* 2020; **41**: 3144–3152.

23. Liu Z, Tian R, Wang Y, Chen Q, Li J, Xu L, Zhang S. Platelet inhibition with ticagrelor versus clopidogrel in diabetic patients after percutaneous coronary intervention for chronic coronary syndromes. *Thromb Haemost.* 2020; **120**: 1221–1229.

24. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, Walker JR, Antman EM, Macias WL, Braunwald E, Sabatine MS. Cytochrome P450 genetic polymorphisms and the response to prasugrel relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. *Circulation.* 2009; **119**: 2553–2560.

25. Nakamura M, Isshiki T, Kimura T, Ogawa H, Yokoi H, Nanto S, Takayama M, Kitagawa K, Ikeda Y, Saito S. Optimal cut-off value of P2Y12 reaction units to prevent major adverse cardiovascular events in the acute periprocedural period: Post-hoc analysis of the randomized PRASFIT-ACS study. *Int J Cardiol.* 2015; **182**: 541–548.

26. Kawai Y, Miyoshi T, Nakamura K, Shokoku G, Yamamoto K, Ono T, Tokioka K, Ohe T, Ito H. Association between changes in platelet reactivity during elective percutaneous coronary intervention and periprocedural myocardial infarction: A pilot study. *J Cardiol.* 2019; **73**: 134–141.

27. Farag ESM, Al-Daydamony MM. Symptom-to-balloon time and myocardial blush grade are predictors of left ventricular remodelling after successful primary percutaneous coronary intervention. *Cardiovasc J Afr.* 2017; **28**: 186–190.

28. Westman PC, Lipinski MJ, Luger D, Waksman R, Bonow RO, Wu E, Epstein SE. Inflammation as a driver of adverse left ventricular Remodeling after acute myocardial infarction. *J Am Coll Cardiol.* 2016; **67**: 2050–2060.

29. Xie M, Burchfield JS, Hill JA. Pathological ventricular remodelling: Therapies: Part 2 of 2. *Circulation.* 2013; **128**: 1021–1030.

30. von Hundelshausen P, Weber C. Platelets as immune cells: Bridging inflammation and cardiovascular disease. *Circ Res*. 2007; **100**: 27–40.

31. Du XJ, Shan L, Gao XM, Kiriazis H, Liu Y, Lobo A, Head GA, Dart AM. Role of intramural platelet thrombus in the pathogenesis of wall rupture and intra-ventricular thrombosis following acute myocardial infarction. *Thromb Haemost*. 2011; **105**: 356–364.

32. Suleiman M, Khatib R, Agmon Y, Mahamid R, Boulos M, Kapeliovich M, Levy Y, Beyar R, Markiewicz W, Hammerman H, Aronson D. Early inflammation and risk of long-term development of heart failure and mortality in survivors of acute myocardial infarction: Predictive role of C-reactive protein. *J Am Coll Cardiol*. 2006; **47**: 962–968.

33. Consolo F, Pozzi L, Pieri M, Della Valle P, Redaelli A, D'Angelo A, Pappalardo F. Influence of different antithrombotic regimens on platelet-mediated thrombin generation in patients with left ventricular assist devices. *ASAIO J*. 2020; **66**: 415–422.

34. Consolo F, Sferrazza G, Motolone G, Contri R, Valerio L, Lembo R, Pozzi L, Della Valle P, De Bonis M, Zangrillo A, Fiore GB, Redaelli A, Slepian MJ, Pappalardo F. Platelet activation is a preoperative risk factor for the development of thromboembolic complications in patients with continuous-flow left ventricular assist device. *Eur J Heart Fail*. 2018; **20**: 792–800.