

ORIGINAL RESEARCH

Association and Prognostic Implications of “No-Reflow Phenomenon” and Hypercoagulability in Patients With ST-Segment Elevation Myocardial Infarction

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ABSTRACT

BACKGROUND Following percutaneous coronary intervention (PCI), the “no-reflow phenomenon” is associated with a worse outcome. However, it remains unclear how to prevent and treat this phenomenon during PCI.

OBJECTIVES This study aimed to evaluate the association between thrombogenicity profiles and “no-reflow phenomenon” during primary PCI in patients with ST-segment elevation myocardial infarction (STEMI).

METHODS From a real-world registry, we prospectively enrolled patients with STEMI who underwent primary PCI (n = 334). Thrombolysis In Myocardial Infarction flow grade was assessed at final angiography, and the “no-reflow phenomenon” was defined as Thrombolysis In Myocardial Infarction flow between 0 and 2. Thrombogenicity profiles were assessed with thromboelastography (TEG) and conventional hemostatic measurements.

RESULTS Thirty-seven patients (11.1%) showed no-reflow after primary PCI. High platelet-fibrin clot strength (P-FCS: ≥ 68 mm) measured by TEG was significantly associated with an increased risk of post-PCI “no-reflow phenomenon” (OR: 2.611; 95% CI: 1.220-5.584; $P = 0.010$). The risk stratification with “no-reflow phenomenon” and “high P-FCS phenotype” appeared to be additive to predict the risk of 3-year clinical event (log-rank $P < 0.001$ across the groups). Patients with both “no-reflow phenomenon” and high P-FCS had a higher risk of adverse clinical events compared with normal-reflow subjects with low P-FCS (adjusted HR: 6.654; 95% CI: 2.678-16.530; $P < 0.001$).

CONCLUSIONS This study demonstrated a close relationship between heightened thrombogenicity (assessed by TEG P-FCS) with “no-reflow phenomenon,” and their additive prognostic implications after primary PCI in STEMI patients. Effective control of clot strength may reduce the risk of “no-reflow phenomenon” and improve clinical outcomes in these patients. (Gyeongsang National University Hospital Registry [GNUH]; [NCT04650529](https://doi.org/10.1016/j.jacasi.2025.07.015)) (JACC Asia. 2025;■:■-■) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

aPTT = activated partial thromboplastin time

CV = cardiovascular

hs-CRP = high-sensitivity C-reactive protein

ECG = electrocardiogram

MA = maximal amplitude

MACE = major adverse cardiovascular event

MI = myocardial infarction

MIRI = myocardial ischemia-reperfusion injury

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PCI = percutaneous coronary intervention

P-FCS = platelet-fibrin clot strength

PRU = P2Y12 reaction unit

PT = prothrombin time

STEMI = ST-segment elevation myocardial infarction

TEG = thromboelastography

ST-segment elevation myocardial infarction (STEMI) is a critical medical emergency that carries high mortality and morbidity. This disease entity is caused by complete or near complete coronary artery occlusion, leading to myocardial ischemia and subsequent myocardial damage. Its pathophysiologic background is the interaction between atherosclerotic plaque formation, plaque rupture, and eventually occlusive thrombus formation.¹ Recent guidelines recommend primary percutaneous coronary intervention (PCI) as the initial treatment of STEMI.² However, the outcomes following primary PCI vary among patients and an optimal control of thrombotic milieu may be the most important determinant of long-term prognosis. The latter finding highlights the importance of identifying patients with a high thrombotic risk who may benefit from more intensive antithrombotic management after primary PCI.

Coronary “no-reflow phenomenon” was first described by Kloner et al³ in 1974 as a defective myocardial reperfusion due to a lack of coronary flow in the absence of mechanical obstruction. This phenomenon is characterized by angiographic evidence of slow or no antegrade epicardial flow and defined as TIMI flow grade <3. The coronary vascular damage and interactions among the endothelial cells, leucocytes, and platelets during myocardial ischemia play major roles in the absence of coronary flow after the removal of coronary obstruction.⁴ In addition, “no-reflow phenomenon” refers to the functional and structural alterations of the coronary microcirculation: distal atherothrombotic embolization, ischemic injury, reperfusion injury, and individual susceptibility to microvascular damage. Therefore, post-PCI no-reflow has been associated with an increase in infarct size, reduced left ventricular function, and long-term adverse clinical outcomes.

“No-reflow phenomenon” has been shown to be closely related to clinical (eg, age, smoking, dyslipidemia, renal failure, atrial fibrillation), procedure (eg, pre-PCI TIMI flow, high thrombotic burden, delayed presentation, high pressure inflation), and laboratory factors (eg, high-sensitivity C-reactive protein [hs-CRP], neutrophil-lymphocyte ratio).^{5,6} However, few experimental studies have evaluated the impact of hemostatic profiles (eg, platelet function test, global hemostasis test) on “no-reflow phenomenon” occurrence in patients presented with STEMI. The aim of this study was to evaluate the association between thrombogenicity profiles and post-PCI no-reflow, as well as their combined prognostic implications in these patients.

delayed presentation, high pressure inflation), and laboratory factors (eg, high-sensitivity C-reactive protein [hs-CRP], neutrophil-lymphocyte ratio).^{5,6} However, few experimental studies have evaluated the impact of hemostatic profiles (eg, platelet function test, global hemostasis test) on “no-reflow phenomenon” occurrence in patients presented with STEMI. The aim of this study was to evaluate the association between thrombogenicity profiles and post-PCI no-reflow, as well as their combined prognostic implications in these patients.

METHODS

PATIENT POPULATION. The study population was obtained from the GNUH (Gyeongsang National University Hospital) Registry (NCT04650529). This registry was a prospective, observational 2-center database that enrolled PCI-treated patients with significant coronary artery disease, and evaluated multiple hemostatic, vascular, and physiologic parameters if indicated.⁷ In this retrospective analysis, we enrolled STEMI patients who underwent uneventful primary PCI between January 2016 and December 2018, with available TIMI flow grade and thrombogenicity profiles.

Acute myocardial infarction (AMI) was defined as an acute myocardial injury with a rise and/or fall of cardiac troponins with 1 value above the 99th percentile and one of the following: 1) symptoms of cardiac ischemia; 2) electrocardiogram (ECG) showing new ischemic changes or pathological Q waves; and 3) loss of viable myocardium or wall motion abnormalities by imaging modalities. The presence of ST-segment elevation on a standard 12-lead surface ECG was determined at the time of visit to the emergency department. ST-segment elevation was defined based on the standard 12-lead ECG findings according to the current guideline: 1) an increase in ST-segment of more than 2 mm in 2 or more precordial leads; or 2) more than 1 mm in 2 or more limb leads.⁸

The inclusion criterion was timely primary PCI for the first-time STEMI that presented within the first 12 hours from the onset of symptoms, with standard pharmacologic therapy based on the current guidelines.² Exclusion criteria were as follows; 1) previous

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

Manuscript received October 31, 2024; revised manuscript received June 13, 2025, accepted July 2, 2025.

history of AMI; 2) fibrinolytic therapy; 3) current oral anticoagulant; 4) cardiogenic shock or NYHA functional class 4; and 5) noncardiac comorbidities with a life expectancy of less than 1 year.

Baseline demographic, angiographic, and procedural characteristics and clinical outcome data were prospectively collected. Patients were regularly followed up at 1, 6, and 12 months after the index procedure and then annually for 3 years. Additional information was acquired from medical records or telephone contact as needed. The institutional review board of the hospital approved the study protocol (GNUH 2020-04-026) and waived the requirement for written informed consent for access to an institutional registry. The study strictly adhered to the Good Clinical Practice Guidelines and the principles outlined in the Declaration of Helsinki.

PROCEDURES. After arrival at the emergency room, patients with suspected STEMI planned for primary PCI were treated with the conventional loading doses of aspirin and a P2Y₁₂ receptor inhibitor. For the periprocedural anticoagulation, unfractionated heparin was administered with dosage according to label instructions (100 IU/kg) after the insertion of the arterial sheath for coronary angiography. Glycoprotein IIb/IIIa inhibitor was allowed during the procedure at the discretion of attending interventionists for bailout cases (eg, high thrombotic burden, slow flow during the procedure).

All PCI procedures were performed in accordance with the standard technique.⁹ After an uneventful primary PCI, TIMI flow was evaluated at the final time of coronary angiography. All patients were treated with guideline-directed medical therapy.² Aspirin was continued indefinitely at a dose of 100 mg once daily, and a P2Y₁₂ inhibitor was recommended for at least 1 year following primary PCI.

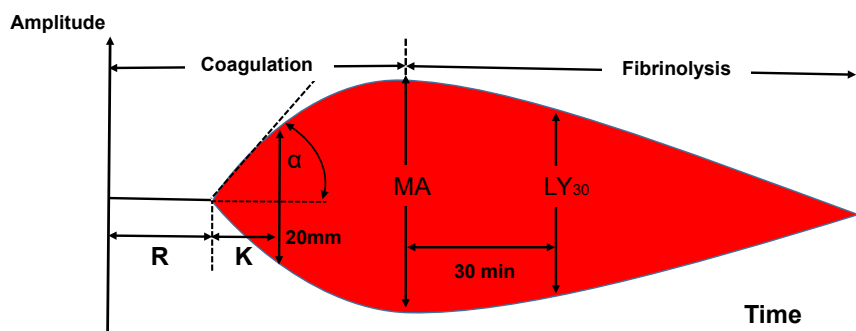
TIMI FLOW AND DEFINITION OF “NO-REFLOW PHENOMENON”. TIMI flow grade was defined according to use of TIMI flow classification: 1) grade 0: complete blockage with no contrast movement past the blockage site; 2) grade 1: some contrast flows past the lesion site but does not fully perfuse the entire area beyond the blockage; 3) grade 2: contrast flows to perfuse the areas beyond the blockage, but at a slower rate compared with the normal flow in the adjacent coronary artery; and 4) grade 3: full contrast perfusion in the areas beyond the blockage.¹⁰ “No-reflow phenomenon” was defined as abnormal epicardial coronary flow with TIMI flow grade between 0 and 2 after the removal of the coronary obstruction.¹¹ Final coronary angiography images following primary PCI were evaluated by 2

independent experienced interventional cardiologists blinded to the results of laboratory measures.

HEMOSTATIC MEASUREMENTS. As per the established protocol, an initial biochemical assessment was conducted on whole-blood samples immediately upon the patient's admittance to the emergency room. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured using an electrochemiluminescent immunoassay using an Elecsys 2010 instrument (Roche Diagnostics). The hs-CRP levels were determined using a commercially available enzyme-linked immunosorbent assay with the UniCel DxC 800 Synchron Clinical System (Beckman Coulter, Inc). In addition, fibrinogen levels were measured using the Clauss method with STA-Fibrinogen reagent (Diagnostica Stago) using the Stago STA-R Evolution hemostasis system. Additional biochemical measurements, including the blood chemistry profile, complete blood count, and lipid profile, were promptly conducted following the patient's arrival at the emergency room using standard laboratory assays.

Platelet function testing. Immediately after inserting the arterial sheath for coronary angiography, blood samples were promptly collected for platelet function analysis using the VerifyNow P2Y₁₂ assay (Accriva). The samples were precisely collected in citrate Vacuette tubes (Greiner Bio-One Vacuette North America, Inc.). This assay is a robust point-of-care, whole-blood, turbidimetric-based optical detection assay designed to accurately measure platelet aggregation in response to an agonist based on the innate ability of activated platelets to bind to fibrinogen.¹² The channel contains fibrinogen-coated polystyrene beads, 20 μmol/L adenosine diphosphate, and 22 nmol/L prostaglandin E1; the optical signal of this channel is reported as P2Y₁₂ reaction unit (PRU).

Thromboelastography. Immediately after the insertion of the arterial sheath for coronary angiography, blood samples for this global hemostasis test were collected using Vacutainer tubes containing 3.2% trisodium citrate (Becton-Dickinson). The samples were analyzed using the thromboelastography (TEG) 5000 Hemostasis Analyzer System (Haemonetics Corp), along with automated analytical software (Figure 1),¹³ This system provides measurements of the viscoelastic properties of a clot. To perform the test, 500 μL of citrated blood was mixed with kaolin by inversion. Then, 340 μL of the activated blood was transferred to a reaction cup, and 20 μL of 200 mM calcium chloride was added. In cases in which the patient was pretreated with heparin, a vial

FIGURE 1 TEG Measurement

Clot formation phase	TEG parameter	Explanation
Initial fibrin formation	R (reaction time)	Time from the initiation until the point where the clot begins to form
Rate of clot development	K (coagulation time)	Interval from the split of the test to the point where the fibrin cross-linking provides enough clot resistance to produce a 20 mm amplitude
	α (angle)	Angle formed by the slope of a tangent line traced from the R time to the K time: reflects rate of which the clot forms
Maximum clot strength	MA (maximum amplitude), P-FCS (platelet-fibrin clot strength)	Maximum amplitude of the clot dynamics (platelet-fibrin clot strength)
Clot lysis	LY ₃₀ (lysis time at 30 min)	Percentage of the clot that has lysed 30 min after the time of MA

The figure illustrates the key parameters of a thromboelastography (TEG) tracing, which are measured throughout the entire process of clot formation, stabilization, and dissolution. K = coagulation time; LY₃₀ = percentage of the clot that has lysed 30 minutes after the time of MA; MA = maximum amplitude; P-FCS = platelet-fibrin clot strength; R = reaction time.

containing heparinase was used to neutralize the effect of heparin. A stationary pin was suspended in an oscillating cup containing the whole-blood sample. As the blood clotted, it linked the pin to the cup. Pin movement was converted into an electrical signal by a transducer and was interpreted by the computer to create a tracing. The extent of platelet contribution to the clot strength through platelet-fibrin bonding directly influenced the pin movement's magnitude and the tracing's amplitude.

Reaction time (R, min) represents the initiation phase of enzymatic clotting, which is the time from the start of the sample run to the point of the first significant clot formation corresponding to a 2-mm reading on the TEG tracing. K measures the time to reach 20-mm clot strength from R. Angle (α) reflects fibrinogen activity, which is represented by the degrees of the angle formed by the tangent line to the TEG tracing measured at R. Kaolin-induced maximum amplitude (MA, mm) represents maximum platelet-fibrin clot strength (P-FCS) and is influenced by changes in fibrinogen, platelet count, and platelet function. Intra-assay and total precisions were 9% and 10%, respectively, with lower detection limit of 2 mm.

Previous studies have indicated that "high P-FCS phenotype" (MA ≥ 68 mm) was a major predictor for adverse atherothrombotic events following PCI in high-risk patients.^{7,13} LY₃₀ indicates the percentage of the clot that has lysed 30 minutes after the occurrence of MA and reflects the level of fibrinolytic activity.

ENDPOINTS AND DEFINITIONS. The primary endpoint was the incidence of "high P-FCS phenotype" between the no-reflow and normal-reflow groups.^{7,14} The secondary endpoints were: 1) other thrombogenicity profiles between the groups; and 2) prognostic implication of thrombogenicity indices on clinical events according to post-PCI reflow status.

A major adverse cardiovascular event (MACE) was defined as a composite of all-cause mortality, nonfatal myocardial infarction (MI), target-vessel revascularization, or rehospitalization due to heart failure.¹⁵ All-cause mortality included deaths from cardiovascular (CV) and non-CV causes during the follow-up. MI was defined as acute myocardial injury with a rise and/or fall of cardiac troponins, with one value above the 99th percentile and one of the following: 1) symptoms of cardiac ischemia; 2) ECG

showing either new ischemic changes or pathological Q waves; and 3) loss of viable myocardium or wall motion abnormalities by imaging modalities.⁸

STATISTICAL ANALYSIS. Based on a recent report, the incidence of the “no-reflow phenomenon” after primary PCI in STEMI patients was reported to be 10.9%.¹⁶ In a previous study, the incidence of “high P-FCS phenotype” in AMI patients was reported to be 47%.⁷ To achieve 80% power at the 5% level of significance, the total sample size required to detect the effect of “high P-FCS phenotype” on the “no-reflow phenomenon” in STEMI patients, with an estimated OR of 2.7, was at least 258, according to the Fleiss method.

The Kolmogorov-Smirnov test was conducted to assess the normal distribution of continuous variables. Continuous variables were presented as mean $\pm$ SD or median (IQR) as appropriate, whereas categorical variables were reported as frequencies and percentages. The analysis used the Student’s unpaired *t*-test for parametric continuous variables and the Mann-Whitney *U* test for nonparametric continuous variables. To compare categorical variables, the chi-square test or Fisher exact test was used as appropriate.

Cumulative event rates were estimated with the Kaplan-Meier method and compared using the log-rank test. A Cox proportional hazard regression model was used to calculate HRs and 95% CIs. For this model, proportional hazards assumption for “no-reflow phenomenon” and P-FCS phenotype was validated using the Schoenfeld residual method. Multivariable Cox proportional hazard models were constructed using key variables such as age (≥ 75 years old), sex, body mass index (≥ 25 kg/m²), hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, smoking, previous PCI, previous stroke, left ventricular ejection fraction $< 50\%$, infarct-related artery of left anterior descending artery, multivessel disease, aspiration thrombectomy, potent P2Y₁₂ inhibitor, beta blocker, angiotensin blockade, and statin. To further evaluate the relationship between “no-reflow phenomenon” and P-FCS value, we categorized P-FCS using both the quartiles and the optimal cutoff based on the receiver-operating characteristic (ROC) curve analysis. HRs for “no-reflow phenomenon” and P-FCS phenotype in relation to MACE were calculated. Subgroup analyses for the specific group were conducted as part of an exploratory data analysis.

Statistical analyses were performed using SPSS version 30.0 for Windows (SPSS-PC), and R version 4.3.3 (R Foundation for Statistical Computing). All

tests were 2-tailed, and $P < 0.05$ was considered statistically significant.

RESULTS

PATIENT CHARACTERISTICS. During the study period, 334 patients presented with STEMI and had the data regarding thrombogenicity indices and post-primary PCI TIMI flow grade. “No-reflow phenomenon” was observed in 37 patients (11.1%) (Figure 2). The no-reflow group exhibited lower pre-PCI TIMI flow ($P = 0.094$) and higher thrombus grade ($P = 0.063$) than the normal-reflow group (Table 1).

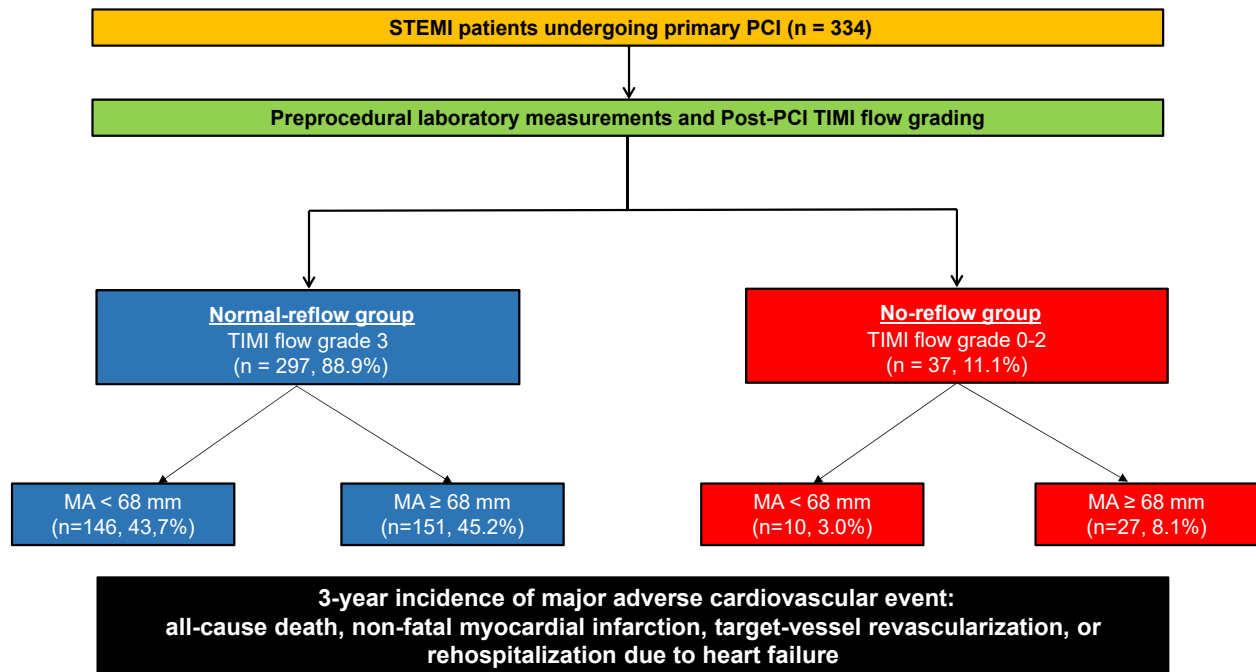
Patients with “no-reflow phenomenon” were older (69 ± 12 vs 63 ± 13 years; $P = 0.029$) compared with subjects with normal-reflow (Table 1). However, there were no significant differences with respect to clinical risk factors and concomitant medications between the groups. In addition, procedural and lesion characteristics were similar between the groups, except for higher rate of post-dilation in the no-reflow group (64.9% vs 44.8% ; $P = 0.021$).

CONVENTIONAL LABORATORY MEASUREMENTS. The no-reflow group showed higher levels of neutrophil-lymphocyte ratio (5.6 ± 4.4 vs 3.8 ± 3.3 ; $P = 0.004$), hs-CRP (5.2 ± 8.9 vs 2.9 ± 7.2 mg/L; $P = 0.078$), and NT-proBNP ($3,011 \pm 7,286$ vs $1,107 \pm 3,268$ pg/mL; $P = 0.006$) than the normal-reflow group (Table 2). Index levels of cardiomyocyte necrosis (ie, creatine phosphokinase-myocardial band, troponin I) were significantly greater in the no-reflow vs normal-reflow group. The other biochemical tests showed no significant differences between the groups.

HEMOSTATIC MEASUREMENTS. The no-reflow group had similar levels of platelet reactivity (258 ± 54 vs 272 ± 65 PRU; $P = 0.218$) and coagulation activity (eg, fibrinogen, prothrombin time [PT] and activated partial thromboplastin time [aPTT]) (all P values ≥ 0.258) compared with the normal-reflow group (Table 2). For TEG indexes, only P-FCS value was significantly higher in the no-reflow vs normal-reflow group (MA: 71.1 ± 4.9 vs 67.4 ± 8.3 mm; $P = 0.010$). Other TEG indices were not different between the groups.

DETERMINANTS OF “NO-REFLOW PHENOMENON”.

In a multivariable analysis, only 2 variables remained as significant independent predictors for “no-reflow phenomenon” occurrence: P-FCS (per 1-mm increase: OR: 1.065; 95% CI: 1.008-1.125; $P = 0.025$) and post-dilation (OR: 2.496; 95% CI: 1.146-5.437; $P = 0.021$) (Table 3).

FIGURE 2 Flow Diagram of the Study

A total of 334 patients with ST-segment elevation myocardial infarction (STEMI) who underwent primary percutaneous coronary intervention (PCI) were enrolled during the study period. Patients were categorized based on post-PCI TIMI flow grade and the level of maximum amplitude (MA) measured by thromboelastography. Clinical outcomes were tracked over a 3-year follow-up period.

The incidence of “no-reflow phenomenon” was proportionally increased across the quartile distribution of P-FCS (3.7% vs 9.5% vs 15.3% vs 15.6%; $P = 0.007$) (Figure 3A). In the ROC curve analysis, “MA ≥ 68 mm” was identified as the optimal cutoff of “high P-FCS phenotype” to predict “no-reflow phenomenon” (area under the curve, 0.644; 95% CI: 0.562-0.727; $P = 0.004$) (Figure 3B). “High P-FCS phenotype” was observed in 178 patients (53.3%); the risk of “no-reflow phenomenon” was higher in patients with “high P-FCS phenotype” (15.2%) than those with “normal P-FCS phenotype” (6.4%) (OR: 2.611; 95% CI: 1.220-5.584; $P = 0.010$).

CLINICAL OUTCOMES. All patients were followed up to 3 years. During this whole follow-up, 40 patients (12.0%) experienced a MACE occurrence, including 12 cases of death (3.6%), 5 cases of nonfatal MI (1.5%), 13 cases of target-vessel revascularization (3.9%), and 10 cases of rehospitalization due to heart failure (3.0%) (Table 4). The no-reflow group had a statistically increased risk of MACE compared with the

normal-reflow group (40.5% vs 8.4% at 3 years: HR: 5.824; 95% CI: 3.067-11.060; $P < 0.001$) (Figure 4A).

The risk stratification based on “no-reflow phenomenon” and “high P-FCS phenotype” was positively associated with the estimated extent of myocardial injury (Supplemental Table 1). This combined stratification was found to be additive to predict the rate of 3-year MACE (log-rank $P < 0.001$ across the groups) (Figure 4B). In a multivariate Cox proportional hazards regression analysis, the patients with both no-reflow and “high P-FCS phenotype” showed the highest risk of MACE compared with normal-reflow subjects with normal P-FCS (adjusted HR: 6.654; 95% CI: 2.678-16.530; $P < 0.001$). Presence of “high P-FCS phenotype” did not increase the risk of MACE occurrence in patients with normal-reflow (adjusted HR: 0.886; 95% CI: 0.379-2.075; $P = 0.781$), whereas this phenotype was significantly associated with an increased rate of MACE in individuals having no-reflow (adjusted HR: 2.566; 95% CI: 1.241-5.303; $P = 0.043$) (Table 5).

TABLE 1 Baseline Characteristics

	Total (N = 334)	Normal-Reflow Group (n = 297)	No-Reflow Group (n = 37)	P Value
Symptom onset-to-balloon time, min	210.5 ± 146	206.8 ± 148	240.3 ± 127.8	0.188
Age, y	64 ± 13	63 ± 13	69 ± 12	0.029
Female	72 (21.6)	64 (21.5)	8 (21.6)	0.992
Body mass index, kg/m ²	24.1 ± 3.4	24.1 ± 3.2	23.9 ± 4.1	0.602
Risk factor or past medical history				
Diabetes mellitus	77 (23.1)	69 (23.2)	8 (21.6)	0.826
Hypertension	131 (39.2)	118 (39.7)	13 (35.1)	0.589
Dyslipidemia	108 (32.3)	97 (32.7)	11 (29.7)	0.719
Smoking	147 (44)	132 (44.4)	15 (40.5)	0.652
Chronic kidney disease	4 (1.2)	3 (1.0)	1 (2.7)	0.376
Previous PCI	25 (7.5)	23 (7.7)	2 (5.4)	0.610
Previous stroke	11 (3.3)	8 (2.7)	3 (8.1)	0.082
Concomitant medications				
Aspirin	334 (100)	297 (100)	37 (100)	1.000
P2Y ₁₂ receptor inhibitor				0.696
Clopidogrel	305 (91.3)	270 (90.9)	35 (94.6)	
Ticagrelor	26 (7.8)	24 (8.1)	2 (5.4)	
Prasugrel	3 (0.9)	3 (1.0)	0 (0)	
Beta blocker	281 (84.1)	246 (82.8)	35 (94.5)	0.065
Angiotensin blockade	255 (76.3)	226 (76.1)	29 (78.4)	0.758
Statin	329 (98.5)	292 (98.3)	37 (100)	0.426
Proton pump inhibitor	275 (82.3)	245 (82.5)	30 (81.1)	0.832
Procedural characteristics				
Pre-PCI TIMI flow grade				0.094
TIMI flow grade 0	251 (75.1)	218 (73.4)	33 (89.2)	
TIMI flow grade 1	13 (3.9)	11 (3.7)	2 (5.4)	
TIMI flow grade 2	48 (14.4)	46 (15.5)	2 (5.4)	
TIMI flow grade 3	22 (6.6)	22 (7.4)	0 (0)	
Thrombus flow grade				0.063
Grade 1	17 (5.1)	17 (5.7)	0 (0)	
Grade 2	16 (4.8)	16 (5.4)	0 (0)	
Grade 3	25 (7.5)	25 (8.4)	0 (0)	
Grade 4	25 (7.5)	21 (7.1)	4 (10.8)	
Grade 5	251 (75.1)	218 (73.4)	33 (89.2)	
Post-PCI TIMI flow grade				<0.001
TIMI flow grade 0	1 (0.3)	0 (0)	1 (2.7)	
TIMI flow grade 1	3 (0.9)	0 (0)	3 (8.1)	
TIMI flow grade 2	32 (9.6)	0 (0)	33 (89.2)	
TIMI flow grade 3	298 (89.2)	297 (100)	0 (0)	
Infarct-related artery				0.607
Left main	2 (0.6)	0 (0)	2 (5.4)	
Left anterior descending	158 (47.3)	140 (47.1)	18 (48.6)	
Left circumflex	41 (12.3)	40 (13.5)	1 (2.7)	
Right coronary artery	133 (39.8)	117 (39.4)	16 (43.2)	
ACC/AHA lesion type B2/C	292 (87.4)	258 (86.9)	34 (91.9)	0.385
Multivessel disease	127 (38.0)	113 (38.0)	14 (37.8)	0.980
Aspiration thrombectomy	196 (58.7)	170 (57.2)	26 (70.3)	0.129
Bailout use of tirofiban	169 (50.6)	135 (45.5)	34 (91.9)	<0.001
Intervention method				0.438
Everolimus-eluting stent	238 (71.3)	212 (71.4)	26 (70.3)	
Zotalimus-eluting stent	52 (15.6)	48 (16.2)	4 (10.8)	
Sirolimus-eluting stent	44 (13.2)	37 (12.5)	7 (18.9)	
Number of stents, n	1.3 ± 0.5	1.2 ± 0.5	1.3 ± 0.6	0.289
Stent diameter, mm	3.2 ± 0.5	3.2 ± 0.5	3.3 ± 0.6	0.510
Stent length, mm	32 ± 16	32 ± 15	33 ± 17	0.599
Post-dilation	157 (47.0)	133 (44.8)	24 (64.9)	0.021

Values are n (%) or mean ± SD.

ACC = American College of Cardiology; AHA = American Heart Association; PCI = percutaneous coronary intervention.

TABLE 2 On-Admission Laboratory Measurements

	Total (N = 334)	Normal-Reflow Group (n = 297)	No-Reflow Group (n = 37)	P Value
WBC count, $\times 10^3/\text{mm}^3$	11.4 $\pm$ 4.0	11.4 $\pm$ 4.1	11.9 $\pm$ 3.7	0.444
Neutrophil, %	66.6 $\pm$ 15.6	65.7 $\pm$ 15.8	73.3 $\pm$ 12.7	0.006
Lymphocyte, %	26.5 $\pm$ 14.1	27.3 $\pm$ 14.2	19.6 $\pm$ 10.9	0.002
Neutrophil-lymphocyte ratio	4.0 $\pm$ 3.5	3.8 $\pm$ 3.3	5.6 $\pm$ 4.4	0.004
Hs-CRP, mg/L	3.1 $\pm$ 7.4	2.9 $\pm$ 7.2	5.2 $\pm$ 8.9	0.078
Hemoglobin, g/dL	13.9 $\pm$ 1.9	13.9 $\pm$ 1.9	14.3 $\pm$ 1.8	0.238
Platelet count, $\times 10^3/\text{mm}^3$	250 $\pm$ 91	250 $\pm$ 95	246 $\pm$ 54	0.767
Hemoglobin A1c, %	6.4 $\pm$ 1.2	6.4 $\pm$ 1.2	6.5 $\pm$ 1.3	0.532
GFR, mL/min/1.73 m ² (MDRD)	113 $\pm$ 47	114 $\pm$ 49	101 $\pm$ 33	0.121
Total cholesterol, mg/dL	197 $\pm$ 45	198 $\pm$ 45	194 $\pm$ 39	0.697
HDL cholesterol, mg/dL	44 $\pm$ 15	45 $\pm$ 15	42 $\pm$ 11	0.269
LDL cholesterol, mg/dL	134 $\pm$ 42	134 $\pm$ 42	134 $\pm$ 40	0.983
NT-proBNP, pg/mL	1318 $\pm$ 3949	1107 $\pm$ 3268	3011 $\pm$ 7286	0.006
CK-MB, ng/mL	18 $\pm$ 44	16 $\pm$ 38	35 $\pm$ 76	0.012
Troponin I, ng/mL	3.1 $\pm$ 7.3	2.8 $\pm$ 6.4	5.9 $\pm$ 12.5	0.016
LV ejection fraction, %	52 $\pm$ 8	53 $\pm$ 8	46 $\pm$ 10	<0.001
Platelet function assay				
VerifyNow, PRU	270 $\pm$ 64	272 $\pm$ 65	258 $\pm$ 54	0.218
Fibrinogen, mg/dL	318 $\pm$ 85	317 $\pm$ 83	332 $\pm$ 97	0.305
PT, s	13.3 $\pm$ 1.1	13.3 $\pm$ 1.2	13.4 $\pm$ 0.9	0.510
aPTT, s	37.6 $\pm$ 6.9	38.0 $\pm$ 7.7	34.6 $\pm$ 7.1	0.258
Thromboelastography (TEG)				
R, min	6.9 $\pm$ 8.3	7.1 $\pm$ 8.8	5.9 $\pm$ 2.2	0.427
K, min	2.1 $\pm$ 4.9	2.2 $\pm$ 5.1	1.4 $\pm$ 0.9	0.374
Alpha, angle	65.4 $\pm$ 14.7	65.3 $\pm$ 14.8	66.8 $\pm$ 12.1	0.571
P-FCS, mm	67.8 $\pm$ 8.1	67.4 $\pm$ 8.3	71.1 $\pm$ 4.9	0.010
LY ₃₀ , %	2.5 $\pm$ 11.1	2.7 $\pm$ 11.7	0.9 $\pm$ 1.6	0.366

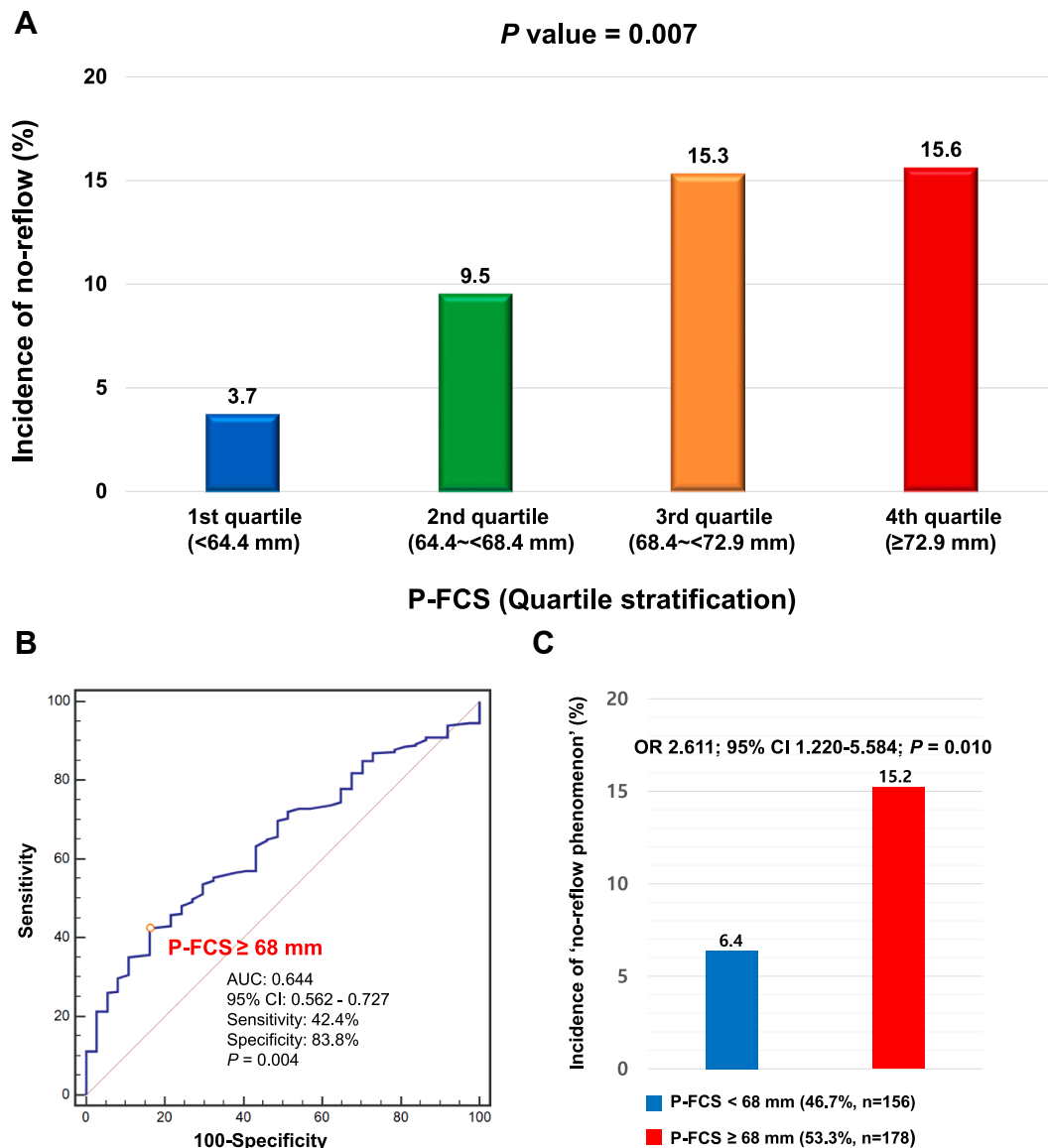
Values are mean $\pm$ SD.

aPTT = activated partial thromboplastin time; CK-MB = creatine phosphokinase-myocardial band; GFR = glomerular filtration rate; HDL = high-density lipoprotein; Hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; LV = left ventricle; LY₃₀ = percentage of the clot that has lysed after 30 min; MDRD = Modification of Diet in Renal Disease; NT-proBNP = N-terminal pro-B-type natriuretic peptide; P-FCS = platelet-fibrin clot strength; PRU = P2Y₁₂ reaction unit; PT = prothrombin time; WBC = white blood cell.

TABLE 3 Predictors of Coronary No-Reflow Phenomenon

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P Value	OR	95% CI	P Value
Age (per 1-year increase)	1.030	1.003-1.058	0.031	1.005	0.974-1.038	0.742
Previous stroke	3.187	0.807-12.590	0.098	4.591	0.993-21.234	0.051
Pre-PCI TIMI flow grade 0	2.990	1.026-8.708	0.036	1.164	0.00-91108.551	0.979
Post-dilation	2.276	1.116-4.643	0.024	2.496	1.146-5.437	0.021
Neutrophil-lymphocyte ratio (per 1-scale increase)	1.117	1.031-1.211	0.007	1.060	0.965-1.163	0.225
NT-proBNP (per 100-pg/mL increase)	1.007	1.001-1.013	0.018	1.000	1.000-1.000	0.075
Hs-CRP (per 1-mg/L increase)	1.026	0.993-1.060	0.118	-	-	-
CK-MB (per 1-ng/mL increase)	1.007	1.001-1.012	0.018	0.999	0.992-1.008	0.902
Troponin I (per 1-mg/mL increase)	1.044	1.009-1.081	0.013	1.049	0.992-1.109	0.092
P-FCS (per 1-mm increase)	1.068	1.016-1.122	0.010	1.065	1.008-1.125	0.025

PCI = percutaneous coronary intervention; other abbreviations as in [Tables 1 and 2](#).

FIGURE 3 Association Between P-FCS and "No-Reflow Phenomenon"

(A) Incidence of "no-reflow phenomenon" according to quartile stratification of P-FCS. (B) Receiver-operating characteristic curve analysis: the optimal cutoff of P-FCS for "no-reflow phenomenon." (C) Risk of "no-reflow phenomenon" according to P-FCS phenotype. AUC = area under the curve; ROC = receiver-operating characteristic; other abbreviation as in [Figure 1](#).

DISCUSSION

This study is the first analysis to demonstrate the impact of P-FCS on the occurrence of "no-reflow phenomenon" and its prognostic implications following primary PCI in patients presenting with STEMI ([Central Illustration](#)). The key findings of the

study are delineated as follows: 1) preprocedural P-FCS levels were significantly associated with the risk of "no-reflow phenomenon" (P-FCS ≥68 mm was identified to predict its risk by about 2.6-fold); 2) index levels of cardiomyocyte necrosis, coagulation (fibrinogen, aPTT, PT), platelet reactivity (VerifyNow), and inflammation (neutrophil-lymphocyte

TABLE 4 Three-Year Clinical Outcomes According to No-Reflow Phenomenon and P-FCS Phenotype

	Normal-Reflow & Normal P-FCS (n = 146)	Normal-Reflow & High P-FCS ^a (n = 151)	No-Reflow & Normal P-FCS (n = 10)	No-Reflow & High P-FCS (n = 27)	P Value
MACE	12 (8.2)	13 (8.6)	2 (20.0)	13 (48.1)	< 0.001
All-cause mortality	0 (0.0)	8 (5.3)	1 (10.0)	3 (11.1)	0.001
Nonfatal MI	2 (1.4)	2 (1.3)	0 (0.0)	1 (3.7)	0.518
Target-vessel revascularization	9 (6.2)	3 (2.0)	0 (0.0)	1 (3.7)	0.208
Readmission due to heart failure	1 (0.7)	0 (0.0)	1 (10.0)	8 (29.6)	< 0.001

Values are n (%). ^aHigh P-FCS indicates maximal amplitude ≥ 68 mm measured by thromboelastography.

MACE = major adverse cardiovascular event; other abbreviation as in Table 2.

ratio, hs-CRP) were not significantly associated with the occurrence of "no-reflow phenomenon"; 3) a combined risk stratification with "no-reflow phenomenon" and "high P-FCS phenotype" additively increased the prognostic power to predict 3-year MACE; and 4) prognostic implication of "high P-FCS phenotype" was particularly evident in cases of no-reflow phenomenon.

Myocardial ischemia-reperfusion injury (MIRI) is an independent aggravating factor that contributes to adverse cardiovascular events following myocardial ischemia, cardiac surgery, or circulatory arrest. Because of its significant clinical implications, MIRI has been the focus of extensive research. Notably, in experimental models, it can account for up to 50% of the final myocardial infarct size. Four distinct types of injury have been identified in the context of MIRI: 1) myocardial stunning; 2) the no-reflow phenomenon; 3) reperfusion arrhythmia; and 4) lethal reperfusion injury.¹¹

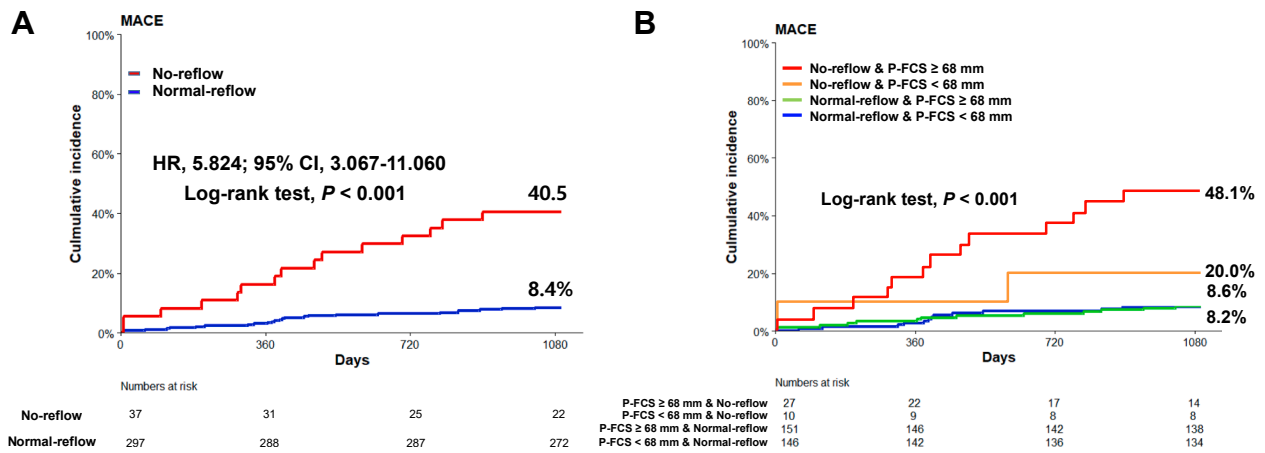
The current concept suggests that 2 mechanisms contribute to the occurrence of "no-reflow phenomenon." The first is the structural mechanism, characterized by microvascular damage caused by prolonged ischemia, along with edema and microvascular occlusion. In contrast, the functional mechanism involves the accumulation of neutrophils and platelets, along with the activation of the neurohormonal system, which results in microvascular spasm and distal micro-thrombotic embolization. Notably, the structural mechanism may be essentially irreversible, whereas the functional mechanism has the potential to be reversible.^{1,11}

Over the past 2 decades, numerous inflammatory and laboratory biomarkers, particularly those associated with the mechanism of "no-reflow phenomenon," have been investigated, yielding varying levels of diagnostic and prognostic accuracy.^{17,18} The primary objective of these studies has been to identify a diagnostic tool that could aid clinicians in preventing

and treating this phenomenon before primary PCI. In the present study, we found a strong correlation between P-FCS and "no-reflow phenomenon," whereas other biomarkers regarding cardiomyocyte necrosis, inflammation, coagulation, and platelet reactivity (eg, NT-proBNP, troponin I, creatine phosphokinase-myocardial band, hs-CRP, white blood cells, neutrophil-lymphocyte ratio, fibrinogen, PT, aPTT, VerifyNow) did not show any significant associations with "no-reflow phenomenon."

It remains uncertain which ex vivo thrombogenicity indices best reflect the in vivo thromboembolic cascade in a human's coronary vascular system. In this context, the present analysis offers valuable insights into this issue. Hemostasis is a finely regulated process involving numerous biochemical reactions that encompass both cellular elements and plasma proteins.¹⁹ Because routine hemostatic tests typically overlook these complex interactions and focus on evaluating a specific pathway, their ability to predict the clinical manifestation of thromboembolic events is likely to be quite limited.

The TEG assay is a whole-blood ex vivo assay that measures the dynamic viscoelastic properties of clot generation from the time of initial plasmatic thrombin generation to platelet-fibrin-dependent clot formation, clot strengthening, and finally to clot lysis.^{7,13} The TEG assay also provides comprehensive information on thrombin generation, the interaction between fibrinogen/fibrin and platelets to form a platelet-fibrin clot, the contribution of platelet counts and function, as well as fibrinogen level and activity to clot strength, and the stability of the clot. P-FCS values (MA measured by TEG) are affected by changes in fibrinogen level and activity, as well as platelet count and function. In addition, our previous reports suggested its close relationships with coagulation activity, fibrinogen level, hemoglobin, and platelet count.^{7,13,20} This finding may indicate that the TEG assay provides different precise results in

FIGURE 4 Kaplan-Meier Curves of 3-Year MACE

(A) Groups according to “no-reflow phenomenon.” (B) Groups divided by “high P-FCS phenotype” and “no-reflow phenomenon.” MACE = major adverse cardiovascular event; other abbreviation as in Figure 1.

evaluating “no-reflow phenomenon” compared with other conventional hemostatic measures.

Understanding the mechanism of the TEG assay and its clinical application in identifying a hypercoagulable state in high-risk patients (eg, STEMI) can help clinicians recognize patients who are more susceptible to consequent thrombotic events. In the present study, P-FCS levels measured by the TEG assay were able to identify patients at a high risk for the “no-reflow phenomenon” before the recanalization of the occluded coronary artery. In such cases, applying more intensive antithrombotic strategy (eg, intracoronary glycoprotein IIb/IIIa inhibitor) may improve clinical outcomes and help prevent the occurrence of “no-reflow phenomenon.”²¹ In addition, greater clot strength was associated with poorer

long-term clinical outcomes, suggesting that oral anticoagulant therapy may be beneficial for these high-risk patients.^{22,23} A recent study suggested that cangrelor pretreatment provided clinical benefits in improving post-PCI coronary flow in AMI patients, achieving a 96% rate of post-PCI TIMI flow grade 3.²⁴ However, our findings showed a weak association between the antiplatelet effect (as measured by PRU) and the “no-reflow phenomenon.” Thus, the impact of intravenous potent antiplatelet pretreatment on post-PCI coronary flow should be further evaluated in large-scale randomized clinical trials.

One of the proposed mechanisms for “no-reflow phenomenon” is coronary bed microvascular dysfunction. Our previous study found that “high P-FCS phenotype” (MA ≥ 68 mm) increased the risk of

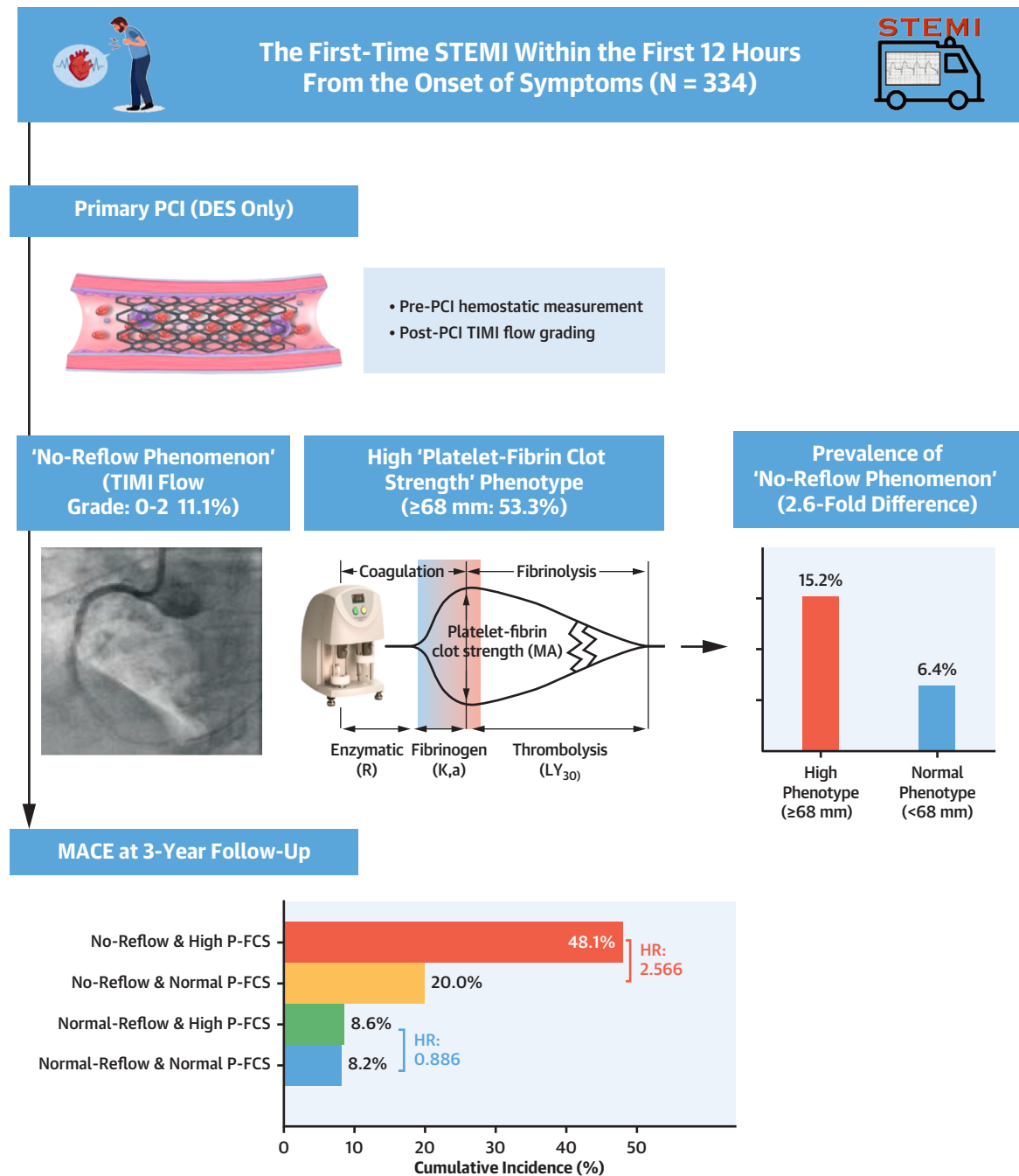
TABLE 5 HR for Clinical Outcomes According to Risk Groups

	Reference	Comparison	Unadjusted Model			Adjusted Model		
			HR	95% CI	P Value	HR	95% CI	P Value
MACE	Normal-reflow and normal P-FCS	Normal-reflow and high P-FCS ^a	1.050	0.479-2.301	0.904	0.886	0.379-2.075	0.781
		No-reflow and normal P-FCS	2.662	0.596-11.894	0.200	2.593	0.505-13.319	0.254
		No-reflow and high P-FCS	7.395	3.368-16.234	<0.001	6.654	2.678-16.530	<0.001
	Normal-reflow and high P-FCS	No-reflow and normal P-FCS	2.546	0.574-11.284	0.219	3.425	0.599-19.565	0.166
		No-reflow and high P-FCS	7.049	3.257-15.253	<0.001	8.225	3.220-21.009	<0.001
	No-reflow and normal P-FCS	No-reflow and high P-FCS	2.760	0.622-12.251	0.182	2.566	1.241-5.303	0.043

The model was adjusted with old age (≥ 75 years), male, obesity (body mass index ≥ 25 kg/m²), hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, smoking, previous PCI, previous stroke, left ventricular ejection fraction $< 50\%$, infarct-related artery of left anterior descending artery, multivessel disease, aspiration thrombectomy, potent P2Y₁₂ inhibitor, beta blocker, angiotensin blockade, and statin. ^aHigh P-FCS phenotype indicates maximal amplitude ≥ 68 mm measured by thromboelastography.

Abbreviations as in Tables 2, 3, and 5.

CENTRAL ILLUSTRATION Association Between Hemostatic Measurements and "No-reflow Phenomenon" Following Primary Percutaneous Coronary Intervention



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coronary microvascular dysfunction (CMD) by approximately 4-fold (OR: 4.35; 95% CI: 1.74-10.89; $P < 0.001$). In addition, patients with both "high P-FCS phenotype" and CMD had higher incidence of 3-year MACE compared with subjects with normal P-FCS and no CMD (HR: 5.58; 95% CI: 1.31-23.68; $P = 0.024$).²⁵ However, this previous study only included AMI patients with TIMI flow grade 3 having the result of Index of Microcirculatory Resistance, whereas the present study included a real-world STEMI cohort with available post-PCI TIMI flow. This emphasizes the role of the P-FCS value in predicting both microvascular and large epicardial coronary flow. These findings suggest a relation between P-FCS and overall coronary flow, as well as its potential to predict long-term clinical outcomes in high-risk patients.

The PLATO (Platelet Inhibition and Patient Outcomes) sub-study suggested the different relationship between thrombogenicity indices (measured by Multiskan FC turbidimetric assay) and adverse CV events in patients with acute coronary syndrome. After adjusting with prognostic biomarkers, the association with CV death remained significant for lysis time (HR: 1.20; 95% CI: 1.01-1.42; $P = 0.042$), but not for maximum turbidity.²⁶ The enrollment criteria of the PLATO trial encompassed intermediate and high-risk patients with acute coronary syndrome. In addition, only about 60% of patients were treated with stenting (bare-metal stent: ~40.0%) and approximately 10% of patients were treated with bypass graft surgery. Our study only enrolled STEMI patients treated with drug-eluting stent, and thrombogenicity indices were measured with TEG assay.

SELECTION OF ANTITHROMBOTIC REGIMENS. The present study demonstrated a close association between clot strength and the occurrence of the no-reflow

phenomenon following primary PCI in STEMI patients. Moreover, the presence of a high P-FCS phenotype was associated with a greater risk of adverse clinical events, particularly in patients with high-risk features such as the no-reflow phenomenon. At physiologic concentrations, both bivalirudin and heparin prolonged clotting time (R time) while maintaining stable clot strength (P-FCS) and fibrinolytic activity (LY₃₀); however, heparin demonstrated a steeper concentration-response curve compared with bivalirudin.²⁷ During elective stenting, the adjunctive use of eptifibatide with bivalirudin and clopidogrel significantly reduced P-FCS levels.²¹ In PCI-treated patients, dual antiplatelet therapy including clopidogrel was associated with a significantly longer R time compared with aspirin monotherapy (5.8 ± 1.3 vs 5.1 ± 1.1 minutes; $P = 0.017$), whereas no significant differences were observed in other TEG parameters.²⁸ In patients with atrial fibrillation, both direct oral anticoagulant and warfarin therapies resulted in prolonged clotting time (R time) and a modest reduction in clot strength (P-FCS) compared with aspirin monotherapy.²⁹ However, the impact of adding a direct oral anticoagulant to an antiplatelet regimen on TEG indices in the PCI setting requires further clinical and laboratory evidence.³⁰

STUDY LIMITATIONS. First, this study was based on a 2-center experience with a limited number of STEMI patients who exhibited heterogeneous demographics and treatments, reflecting the nature of this registry. Second, there is a significant concern regarding the clinical safety of potent P2Y₁₂ inhibitors compared with clopidogrel in East Asian patients presenting with AMI.³¹ As a result, the choice of antiplatelet treatment did not fully align with Western guidelines. Nonetheless, platelet reactivity levels did

CENTRAL ILLUSTRATION Continued

For patients presenting with first-time STEMI within the first 12 hours from the onset of symptoms ($n = 334$), hemostatic measurements including thromboelastography (TEG) were performed using preprocedural blood sampling. After primary PCI, TIMI flow grading was evaluated by 2 independent experienced interventional cardiologists blinded to the results of laboratory measures. The presence of "high P-FCS phenotype" (maximal amplitude by TEG ≥ 68 mm) significantly increased the risk of post-PCI "no-reflow phenomenon" (epicardial coronary flow with TIMI flow grade between 0 and 2) by 2.6-fold. The risk stratification based on "no-reflow phenomenon" and "high P-FCS phenotype" was found to be additive to predict the rate of 3-year MACE (log-rank $P < 0.001$ across the groups). Presence of "high P-FCS phenotype" did not increase the risk of MACE occurrence in patients with normal-reflow (adjusted HR: 0.886; 95% CI: 0.379-2.075; $P = 0.781$), whereas this phenotype was significantly associated with an increased rate of MACE in individuals having no-reflow (adjusted HR: 2.566; 95% CI: 1.241-5.303; $P = 0.043$). Effective control of P-FCS may reduce the risk of the "no-reflow phenomenon" and improve clinical outcomes in STEMI patients; this hypothesis warrants evaluation in large-scale clinical trials.

aPTT = activated partial thromboplastin time; CK-MB = creatine phosphokinase-myocardial band; CRP = C-reactive protein; DES = drug-eluting stent; MACE = major adverse cardiovascular event; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PCI = percutaneous coronary intervention; P-FCS = platelet-fibrin clot strength; PT = prothrombin time; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

not demonstrate any significant relationship with the risk of the "no-reflow phenomenon." Third, TEG indices might be changed over time according to the concomitant medications and patients' characteristics, which were not covered by our registry. Fourth, the study was underpowered to determine the definitive clinical impact of "no-reflow phenomenon" and "high P-FCS phenotype." In addition, the current hemostatic measurements were chosen based on the investigators' experience and current knowledge, which means other important hemostatic biomarkers related to "no-reflow phenomenon" may have been overlooked. Finally, although we aimed to enroll patients experiencing their first STEMI based on the current definition, there remains a possibility that some patients with silent MI and current findings suggestive of a prior MI may have been included.

CONCLUSIONS

This is the first study to demonstrate a close relationship between thrombogenicity indices assessed by the TEG assay (ie, high clot-strength phenotype) and the "no-reflow phenomenon" following reperfusion in STEMI patients. Moreover, combining risk stratification using the P-FCS phenotype and the "no-reflow phenomenon" may enhance risk assessment

and guide the application of potent antithrombotic therapies for high-risk patients in the future.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This research was supported by the Chung-Ang University Research Grants. The content is solely the responsibility of the authors and does not necessarily represent the official views of any funding agencies. The sponsors played no role in this study. There was no industry involvement in the design or conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review, and approval of the manuscript; or the decision to submit the manuscript for publication. Dr Gurbel has received grants and personal fees from Bayer HealthCare, Otitopic, Amgen, Janssen, and US WorldMeds; grants from Instrumentation Laboratory, Hikari Dx, Haemonetics, Medisure, and Idorsia Pharmaceuticals; and personal fees from UpToDate; and has patents "Detection of Restenosis Risk in Patients Issued" and "Assessment of Cardiac Health and Thrombotic Risk in a Patient." Dr Jeong has received honoraria for lectures from Daiichi-Sankyo, Sanofi-Aventis, Hanmi Pharmaceuticals, and Daewoong Pharmaceuticals; and research grants or support from Samjin Pharmaceuticals, Hanmi Pharmaceuticals, Yuhan Pharmaceuticals, Biotronik Korea, and U and I Corporation. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS acute myocardial infarction, cardiovascular event, clot strength, no-reflow phenomenon, percutaneous coronary intervention

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