ABSTRACT

Aims: Atherothrombotic events are influenced by systemic hypercoagulability and fibrinolytic activity. The present study evaluated thrombogenicity indices and their prognostic implications according to disease acuity.

Methods and Results: From the consecutive patients undergoing percutaneous coronary intervention (PCI), those with thrombogenicity indices (n=2,705) were grouped according to disease acuity (acute myocardial infarction [AMI] vs. non-AMI). Thrombogenicity indices were measured by thromboelastography (TEG). Blood samples for TEG were obtained immediately after insertion of the PCI sheath, and TEG tracing was performed within 4 hours post-sampling. Major adverse cardiovascular events (MACE, a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) were evaluated for up to 4 years. Compared to non-AMI patients, AMI patients had higher platelet-fibrin clot strength (maximal amplitude [MA]: 66.5±7.8 vs. 65.3±7.2 mm, P<0.001) and lower fibrinolytic activity (clot lysis at 30 minutes [LY_{30}]: 0.9±1.8% vs. 1.1±1.9%, P<0.001). Index AMI presentation was associated with MA (per 1-mm increase: odds ratio [OR] 1.024; 95% confidence interval [CI] 1.013-1.036; P<0.001) and LY_{30} (per 1% increase: OR 0.934; 95% CI 0.893-0.978; P=0.004). The presence of high platelet-fibrin clot strength (MA ≥68 mm) and low fibrinolytic activity (LY_{30}<0.2%) was synergistically associated with MACE occurrence. In the multivariable analysis, the combined phenotype of 'MA≥68 mm' and 'LY_{30} <0.2%' was a major predictor of post-PCI MACE in the AMI group (adjusted hazard ratio [HR] 1.744; 95% CI 1.135-2.679; P=0.011), but not in the non-AMI group (adjusted HR 1.031; 95% CI 0.499-2.129; P=0.935).

Conclusions: AMI occurrence is significantly associated with hypercoagulability and impaired fibrinolysis. Their combined phenotype increases the risk of post-PCI atherothrombotic event only in AMI patients. These observations may support individualized therapy that targets thrombogenicity for better outcomes in patients with AMI.

Structured Graphical Abstract final

Key Question

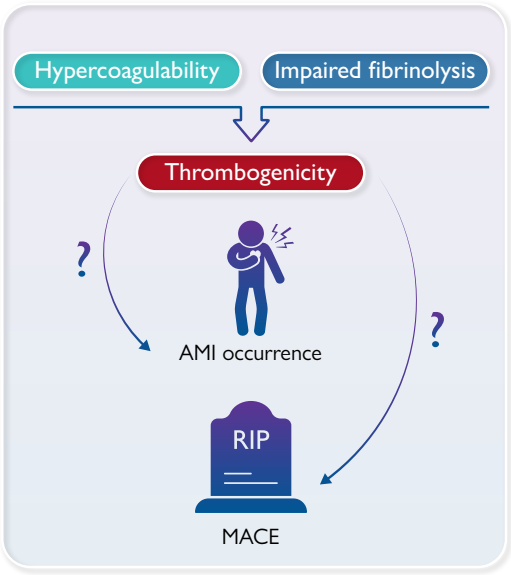
What is the association between thrombogenicity indexes and acute myocardial infarction (AMI) and their impact on long-term outcomes?

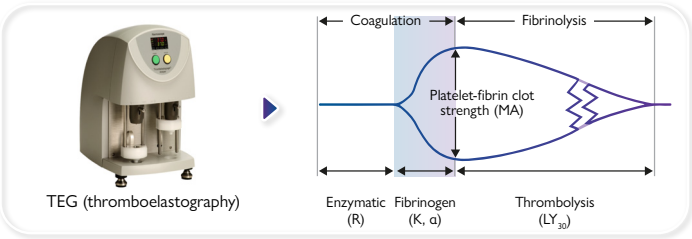
Key Finding

Elevated platelet-fibrin clot strength and impaired fibrinolysis were both independently associated with AMI occurrence. Among AMI patients the elevation of both biomarkers was associated with the highest risk of atherothrombotic events during follow up.

Take Home Message

Following percutaneous coronary intervention in AMI patients, individualized application of antithrombotic therapy according to thrombogenicity indexes may reduce the risk of atherothrombotic events.





PCI + TEG (n = 2,705)	AMI occurrence	4-year MACE
Hypercoagulability MA (per 1 mm increase)	OR 1.024 (p < 0.001)	HR 1.029 (p = 0.007)
Fibrinolysis LY_{30} (per1% increase)	OR 0.934 (p = 0.004)	HR 0.914 (p = 0.067)

4-year MACE	AMI (n = 1,294)	Non-AMI (n = 1,411)
Thrombogenicity (MA ≥ 68mm and LY_{30} < 0.2%)	HR 1.744 (p = 0.011)	HR 1.031 (p = 0.935)

Prognostic Impact of Hypercoagulability and Impaired Fibrinolysis in Acute Myocardial Infarction

Brief title: Association between thrombogenicity and AMI

Seung Hun Lee, MD, PhD[1†], Hyun Kuk Kim, MD, PhD[2†], Jong-Hwa Ahn, MD, PhD[3], Min Gyu Kang, MD, PhD[4], Kye-Hwan Kim, MD, PhD,[4] Jae Seok Bae, MD, PhD,[3] Sang Young Cho, MD,[3] Jin-Sin Koh, MD, PhD[4], Yongwhi Park, MD, PhD[3], Seok Jae Hwang, MD, PhD[4], Diana A Gorog, MD, PhD[5], Udaya S Tantry, PhD[6], Kevin P. Bliden, MBA[6], Paul A Gurbel, MD[6], Jin-Yong Hwang, MD, PhD[4], Young-Hoon Jeong, MD, PhD[7]

[1]Division of Cardiology, Department of Internal Medicine, Heart Center, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Republic of Korea;
[2]Department of Internal Medicine and Cardiovascular Center, Chosun University Hospital, University of Chosun College of Medicine, Gwangju, Republic of Korea;
[3]Department of Internal Medicine, Gyeongsang National University School of Medicine and Cardiovascular Center, Gyeongsang National University Changwon Hospital, Changwon, Republic of Korea;
[4]Department of Internal Medicine, Gyeongsang National University School of Medicine and Gyeongsang National University Hospital, Jinju, Republic of Korea;
[5]Postgraduate Medical School, University of Hertfordshire, Hertfordshire, United Kingdom.
[6]Sinai Center for Thrombosis Research and Drug Development, Sinai Hospital of Baltimore, Baltimore, MD, USA;
[7]Division of Cardiology, Chung-Ang University Gwangmyeong Hospital and Department of Internal Medicine, Chung-Ang University College of Medicine, Gwangmyeong, Republic of Korea

[†]**Contributed equally to this work.**

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Correspondence to:

Young-Hoon Jeong, MD, PhD, FAHA

CAU Thrombosis and Biomarker Center, Chung-Ang University Gwangmyeong Hospital, 110, Deokan-ro, Gwangmyeong 14353, Republic of Korea

Email: goodoctor@naver.com; younggoodoctor@gmail.com

Jin-Yong Hwang, MD, PhD

Division of Cardiology, Gyeongsang National University Hospital 79 Gangnam-ro, Jinju, Gyeongsangnam-do 52727, Republic of Korea

E-mail: angiojoy@gmail.com

ABSTRACT

Aims: Atherothrombotic events are influenced by systemic hypercoagulability and fibrinolytic activity. The present study evaluated thrombogenicity indices and their prognostic implications according to disease acuity.

Methods and Results: From the consecutive patients undergoing percutaneous coronary intervention (PCI), those with thrombogenicity indices (n=2,705) were grouped according to disease acuity (acute myocardial infarction [AMI] vs. non-AMI). Thrombogenicity indices were measured by thromboelastography (TEG). Blood samples for TEG were obtained immediately after insertion of the PCI sheath, and TEG tracing was performed within 4 hours post-sampling. Major adverse cardiovascular events (MACE, a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) were evaluated for up to 4 years. Compared to non-AMI patients, AMI patients had higher platelet-fibrin clot strength (maximal amplitude [MA]: 66.5±7.8 vs. 65.3±7.2 mm, P<0.001) and lower fibrinolytic activity (clot lysis at 30 minutes [LY_{30}]: 0.9±1.8% vs. 1.1±1.9%, P<0.001). Index AMI presentation was associated with MA (per 1-mm increase: odds ratio [OR] 1.024; 95% confidence interval [CI] 1.013-1.036; P<0.001) and LY_{30} (per 1% increase: OR 0.934; 95% CI 0.893-0.978; P=0.004). The presence of high platelet-fibrin clot strength (MA ≥68 mm) and low fibrinolytic activity (LY_{30}<0.2%) was synergistically associated with MACE occurrence. In the multivariable analysis, the combined phenotype of 'MA ≥68 mm' and 'LY_{30} <0.2%' was a major predictor of post-PCI MACE in the AMI group (adjusted hazard ratio [HR] 1.744; 95% CI 1.135-2.679; P=0.011), but not in the non-AMI group (adjusted HR 1.031; 95% CI 0.499-2.129; P=0.935).

Conclusions: AMI occurrence is significantly associated with hypercoagulability and impaired fibrinolysis. Their combined phenotype increases the risk of post-PCI atherothrombotic event only

in AMI patients. These observations may support individualized therapy that targets thrombogenicity for better outcomes in patients with AMI.

Clinical Trial Registration: Gyeongsang National University Hospital (GNUH) Registry, NCT04650529.

Key Words: hypercoagulability; fibrinolysis; acute myocardial infarction; atherothrombosis.

INTRODUCTION

Although contemporary cardiovascular (CV) treatments including revascularization and guideline-directed medical therapy have improved clinical outcomes in patients with atherosclerotic cardiovascular disease (ASCVD), its associated mortality rate remains unchanged and a considerable number of patients still suffer from recurrent CV events.[1] Abundant clinical evidence has supported the aggressive reduction of low-density lipoprotein cholesterol (LDL-C) in order to reduce CV events. Since achieving guideline-based recommended LDL-C levels fails to guarantee a significant reduction in ASCVD in many patients, further strategies may be required to adequately reduce the remaining CV risk.

Treatment guidelines recommend intensified anti-thrombotic treatment in patients with high-risk ischemic features, such as acute myocardial infarction (AMI) and poly-vascular disease,[2,3] based on the results of randomized controlled trials including the Dual Antiplatelet Therapy (DAPT), Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54), and Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trials.[4-6] This intensified regimen, i.e., the longer-term DAPT administration and the addition of vascular-dose rivaroxaban to aspirin, has significantly reduced the risk of atherothrombotic events compared with aspirin monotherapy, however, the risk of bleeding events has increased.

Following percutaneous coronary intervention (PCI), the activation of platelet and coagulation pathways followed by atherosclerotic vascular injury is fundamental to the development of acute and chronic CV events.[7] However, most post-PCI risk stratifications addressing anti-thrombotic agents have focused on antiplatelet strategy in addition to clinical and

procedural factors.[8,9] The lack of reliable laboratory tests for measuring the clot formation-lysis process leads to an underestimate of its effects on clinical prognosis. Therefore, we have an unmet need for reliable biomarkers or surrogates for this biological issue. For this purpose, there are several available candidates such as the global haemostasis assays which use native whole blood (e.g., thromboelastography [TEG], global thrombosis test [GTT]) or plasma (e.g., plasma turbidimetric assay).[10] The TEG assay uses citrated whole blood to measure clot formation under a low shear rate, whereas GTT uses a non-anticoagulated blood sample under a high shear rate. There have been conflicting results regarding the association between clinical outcomes and parameters from these haemostasis assays.[10-13]After PCI, the maximum amplitude (MA, platelet-fibrin clot formation) in the TEG assay has been mainly correlated with worse outcomes,[12] whereas lysis time (LT, fibrinolysis activity) in the GTT assay can predict clinical prognosis.[11]

To date, clinical evidence for the TEG assay has been modest in size and included selected patients with relatively short-term follow-ups. We sought to evaluate its clinical usefulness in a large-scale high-risk population that included ASCVD patients undergoing PCI by assessing: 1) thrombogenicity indices in patients who presented with and without AMI; and 2) the prognostic implications of thrombogenicity indices on long-term major adverse CV events (MACE) after PCI.

METHODS

Study Population

The study population was derived from the multicenter, prospective, observational Gyeongsang National University Hospital (G-NUH) registry (clinicaltrials.gov identifier, NCT04650529).[14] The G-NUH registry enrolled consecutive patients with significant coronary artery disease (CAD)

who underwent PCI in two distinct tertiary referral hospitals between January 2010 and November 2018, and included systematically evaluated multiple haemostatic, vascular, and physiologic parameters (**Figure 1**). From the 5,080 total patients, we included those who had undergone pre-PCI TEG measurement. A total of 2,375 patients were excluded due to duplicate patient data (readmission or staged procedure, n = 622), due to follow-up loss (n = 112), and a lack of TEG data, which included not available blood sampling (e.g., cardiogenic shock, n = 191), oral anticoagulation before sampling (n = 330), and off-hour visit (weekdays from 6 PM to 9 AM, weekends, and holidays) of technicians hired for haemostatic measurement (n = 1,120). There were no significant differences in the baseline characteristics between included and excluded patients (**Table S1**).

The Institutional Review Board of the respective hospitals approved the study protocol and waived the requirement for written informed consent for the access to an institutional registry. The study protocol was in accordance with the Good Clinical Practice Guidelines and the Declaration of Helsinki.

Patient Management and Procedures

Patients were treated according to standard practice at both hospitals, based on the current guidelines.[2,15-17] The choice of treatment strategy (stent implantation and medication choice) was left to the operator's discretion. All patients were recommended indefinite aspirin and clopidogrel or other $P2Y_{12}$ inhibitor treatment, such as prasugrel or ticagrelor. Treatment duration and choice of $P2Y_{12}$ inhibitor was left to the operator's discretion in accordance with the guidelines and the patients' individual bleeding risks as perceived by the treating physician.

Demographic features and CV risk factors were collected through patient interviews or by reviewing of medical records. During hospitalization, findings of coronary angiography and detailed procedural characteristics of PCI as well as information on discharge medications were collected.

Thromboelastography (TEG) Measurement

According to the prespecified protocol,[14] blood samples for TEG were drawn into Vacutainer tubes containing 3.2% trisodium citrate (Becton Dickinson, Franklin Lakes, NJ, USA) from the arterial sheath immediately after sheath insertion for coronary angiography, and TEG tracing was performed within 4 hours of sampling by a dedicated technician. Periprocedural heparin for the prevention of thrombosis was administered after blood sampling for TEG measurement. For haemostatic assessment, the TEG® 5000 Hemostasis Analyzer System (Haemonetics Corp, Braintree, MA, USA) with automated analytical software was used.[18] Briefly, 500 μL of citrated blood was mixed with kaolin by inversion, and 340 μL of the activated blood was then transferred to the reaction cup, to which 20 μL of 200 mmol/L calcium chloride was added. In heparin-pretreated cases, the classic TEG kit and the TEG kit with added heparinase (hTEG) were simultaneously used to evaluate the neutralizing effect of heparinase. A stationary pin was suspended into an oscillating cup that contained the whole blood sample. As the blood clots, it links the pin to the cup. Pin movement is converted into an electrical signal by a transducer and is interpreted by the computer which creates a tracing.

Reaction time (R, in minutes), a representative value of enzymatic clotting, is the time from the start of the sample run to the point of the initial clot formation corresponding to an amplitude of 2 mm of the TEG tracing. K (in minutes) is a measure of the time required to reach a 20 mm

clot strength from time point R. Angle (in degrees) is reflective of the fibrinogen activity and is the angle degree formed by the tangent line to the TEG tracing measure at the R time point. Kaolin-induced maximum amplitude (MA, in millimeters) represents the maximum platelet-fibrin clot strength (PFCS). LY_{30} is the percentage of the clot that has lysed 30 minutes after the MA time point and indicates the level of fibrinolytic activity.

Study Endpoint, Definitions, and Follow-up

The primary endpoint was the MACE, which was defined as a composite occurrence of CV death, spontaneous MI, and non-fatal stroke for up to 4 years after PCI. All endpoints were defined according to the Academic Research Consortium definitions.[19] All deaths were considered CV unless a definitive non-CV cause was identified. Spontaneous MI (or Type 1 MI) was defined as the recurrence of symptoms with the presence of electrocardiographic changes, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormalities in association with a rise in cardiac biomarker levels above the upper limit of normal. Peri-procedural MI was not included as a clinical outcome. Stroke was defined as evidence of a neurological deficit requiring hospitalization, with clinically documented brain lesions on computed tomography or magnetic resonance imaging confirmed by a neurologist. All clinical events were evaluated by an independent event adjudicating committee. Patients were routinely followed up by outpatient visits or by telephone at 1, 6, and 12 months after the index procedure, and annually thereafter.

Statistical Analysis

All categorical variables are presented as numbers and relative frequencies (percentage). Continuous variables are presented as means and standard deviations, or as medians with first and

third quartiles, according to their distribution, which has been checked by Kolmogorov-Smirnov test and a visual inspection of the Q-Q plots. Differences between groups were assessed using the chi-square test for categorical variables and the Student's *t*-test or the Mann-Whitney U test for continuous variables. For the multiple-group comparisons according to the MA and LY_{30}, continuous variables were tested using the analysis of variance to test for differences.

The optimal cut-off values of MA and LY_{30} associated with index MI presentation were calculated using receiver-operating characteristic (ROC) curves to maximize the sensitivity and specificity. To evaluate the clinical impact of MA and LY_{30} on the presence of index AMI, univariable and multivariable logistic regression analyses were performed. The multivariable model was constructed using all variables with a significance of $P < 0.1$ in the univariable analyses. The final multivariable model was constructed using backward elimination to identify the best Akaike's information criterion, and odds ratios (ORs) and 95% confidence intervals (CIs) were identified.

The associations between MA or LY_{30} as continuous variables and the risk of 4-year MACE were graphically presented with a restricted cubic spline with three degrees of freedom.[20] 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 hazard ratios (HRs) and 95% CIs. The assumption of proportionality was assessed graphically by the log-minus-log plot and was also tested by Schoenfeld residuals. Multivariable Cox proportional hazard models were constructed using variables with $P < 0.1$ in univariable analyses with backward elimination based on an information criterion. The final model included thrombogenicity, diagnosis of AMI, age, sex, current smoking, hypertension, diabetes mellitus, dyslipidaemia, chronic kidney disease, previous PCI, previous stroke, high sensitivity C-reactive protein (CRP)

level, potent $P2Y_{12}$ inhibitor, beta blocker, angiotensin blocker, and statin. The incremental prognostic value of TEG values was evaluated by comparing Harrell's c-index, category-free net reclassification index (NRI), and integrated discrimination index (IDI).

Statistical analyses were performed using SPSS version 25 for Windows (SPSS-PC, Chicago, IL, USA), and R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-tailed, and $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 2,705 patients were identified for the current analysis, and grouped into two cohorts: AMI (n = 1,294, 47.8%) and non-AMI (n = 1,411, 52.2%) (**Figure 1**). **Table 1** shows the baseline characteristics of the study population according to the index diagnosis of AMI. Patients who presented with AMI were older and had a higher incidence of current smoking, dyslipidaemia, and peripheral arterial disease than those without AMI. Conversely, the non-AMI group had a higher incidence of diabetes mellitus, hypertension, and previous PCI. Patients in the AMI group had higher levels of white blood cell count, haemoglobin and LDL-C, and a lower left ventricular ejection fraction.

Although there were no significant differences in procedural methods between the groups, AMI patients were treated with a fewer number of stents compared with non-AMI patients. The AMI group was more frequently treated with potent $P2Y_{12}$ inhibitors. Beta blockers, angiotensin receptor blockers, and statins were also more frequently prescribed in the AMI than in the non-AMI group.

Association Between Thrombogenicity Indices and Index Presentation of Disease

Table 2 shows TEG measurements according to the index presentation of disease acuity. PFCS was significantly higher in patients presenting with AMI (MA: 66.5 ± 7.8 vs. 65.3 ± 7.2 mm; $P < 0.001$). In addition, LY_{30} was significantly lower in the AMI group compared with the non-AMI group (0.9 ± 1.8 vs. 1.1 ± 1.9 mm; $P < 0.001$). When we stratified the AMI phenotype into ST-segment elevation vs. non-ST-segment elevation, patients with ST-segment elevation showed an enhanced thrombogenic property including a higher level of PFCS (MA: 67.1 ± 7.4 vs. 65.8 ± 8.3 mm; $P < 0.001$) than those with non-ST-segment elevation AMI (**Table S2**).

By multivariable analysis (**Table 3**), both MA (every 1 mm increase: OR, 1.024; 95% CI, 1.013-1.036; $P < 0.001$) and LY_{30} (every 1% increase: OR, 0.934; 95% CI, 0.893-0.978; $P = 0.004$) were independently associated with index AMI presentation, with a modest to good association (c-statistics = 0.69). **Figures S1** and **S2** show the optimal cut-offs of MA and LY_{30} for the index presentation of AMI, respectively. In the present analysis, 'MA ≥ 68 mm' indicated hypercoagulability phenotype and 'LY_{30} < 0.2%' indicated an impaired fibrinolysis phenotype. The AMI patients had a higher prevalence of hypercoagulability (44.9% vs. 35.4%; $P < 0.001$) and impaired fibrinolytic activity (53.7% vs. 42.9%; $P < 0.001$) compared with the non-AMI patients.

Prognostic Implications of Thrombogenicity Indices for Long-term MACE

As a continuous variable, MA was significantly associated with the MACE rate at 4 years (HR, 1.029; 95% CI, 1.008-1.051; $P = 0.007$) (**Figure 2A**). LY_{30} showed a numerical trend of a protective effect against 4-year MACE (HR, 0.914; 95% CI, 0.831-1.006; $P = 0.067$) (**Figure 2B**). When we compared clinical outcomes according to binary classification of MA (≥ 68 vs. < 68 mm)

and LY_{30} (< 0.2% vs. ≥ 0.2%), both hypercoagulability ('MA ≥ 68 mm': HR; 1.707; 95% CI, 1.265-2.305; *P* < 0.001) and impaired fibrinolytic activity ('LY_{30} < 0.2%': HR, 1.512; 95% CI, 1.118-2.045; *P* = 0.007) were associated with an increased risk of 4-year MACE (**Figure 3**). When considering the presence of hypercoagulability and impaired fibrinolytic activity simultaneously (**Table S3**), patients with 'MA ≥ 68 mm' and 'LY_{30} < 0.2%' (hypercoagulability with impaired fibrinolytic activity) had an increased risk of 4-year MACE (31.2% vs. 10.7%: adjusted HR, 1.781; 95% CI, 1.130-2.808; *P* = 0.012) compared with those with 'MA < 68 mm' and 'LY_{30} ≥ 0.2%' (normal coagulability and normal fibrinolytic activity) (**Figure 4** and **Table S4**).

The incremental prognostic value of thrombogenicity (hypercoagulability with impaired fibrinolytic activity) was compared with the clinical variable model. The final model, which included thrombogenicity, showed an increased discrimination and reclassification ability (c-index 0.756, *P* <0.001; NRI 0.701, *P* < 0.001; IDI 0.059, *P* < 0.001) (**Figure S3**).

Differential Impact of Thrombogenicity Indices According to Index Disease Acuity

There were several differences in the risk of 4-year MACE among the groups when classified by thrombogenicity indices and index disease acuity (overall log-rank *P* < 0.001) (**Figure 5**). Index AMI phenotype with heightened thrombogenicity ('MA≥68 mm'+'LY_{30}<0.2%') had the greatest risk of 4-year MACE. Heightened thrombogenicity did not increase the risk of MACE in non-AMI patients (HR, 1.031; 95% CI, 0.499-2.129; *P* = 0.935), whereas it did have a significant prognostic implication in AMI patients (HR, 1.744; 95% CI, 1.135-2.679; *P* = 0.011) (**Table 4**).

DISCUSSION

The current study is the largest analysis evaluating the relationship of hypercoagulability and impaired fibrinolysis by TEG assessment according to disease acuity, and its influence on long-term outcomes after PCI. The present analysis demonstrated that: 1) elevated levels of platelet-fibrin clot strength and low fibrinolysis activity measured by TEG were both independently associated with the index AMI presentation; and 2) each marker was significantly associated with worse clinical prognoses and their combined occurrence was associated with the highest risk of MACE in AMI patients undergoing PCI (Structured Graphical Abstract).

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The balance between prothrombotic and fibrinolytic factors is a key determinant in the development of ASCVD events.[21] In the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, thrombotic biomarkers, such as fibrinogen and factor VIII, were associated with a higher risk of ASCVD events, while fibrinolytic factors, such as oxidized phospholipid bound to plasminogen, were associated with a lower risk of ASCVD events, even after a multivariate analysis of traditional CV risk factors.[22] These assays, however, may not be appropriate for diagnosis and risk stratification in individual patients due to their variability and complexity.[23] Therefore, there have been efforts to use global haemostasis tests for measuring thrombosis and fibrinolysis in patients with CAD. Previous studies demonstrated that MA measured by TEG was correlated with the adenosine diphosphate (ADP)-induced platelet aggregation, coagulation factors (e.g., von Willebrand factor and fibrinogen), and inflammation markers (e.g., CRP and interleukin-8), which have been considered meaningful predictors of ASCVD development.[12,24-26] The results of the Thrombotic RIsk Progression (TRIP) study demonstrated that a distinct pathophysiological state of heightened platelet function, hypercoagulability and inflammation marks the presence of unstable ASCVD requiring intervention. In this study, a significant relationship was found between two important biologic markers, PFCS and CRP, as well as between them and other

biomarkers such as fibrinogen, von Willebrand factor, and plasminogen activator inhibitor (PAI)-1.[27] Patients with poly-vascular disease who have synchronous CAD and peripheral arterial disease had significantly higher MA and CRP levels compared with CAD patients with normal ankle-brachial indexes.[18]

Endogenous fibrinolysis may have a protective role in attenuating the occurrence of coronary events.[28-30] Saraf et al. showed that LT measured by GTT, a marker of endogenous thrombolysis, was prolonged in patients with acute coronary syndrome (ACS) compared to healthy patients.[31] In addition, AMI patients who presented with spontaneous ST-segment resolution before PCI had more rapid fibrinolytic activity than those who did not.[11] Sumaya et al. studied the clinical impact of plasma clot LT and maximum turbidity among ACS patients, and found that the resistance of fibrin clots to lysis was independently associated with adverse clinical events.[13]

Furthermore, both hypercoagulability and endogenous fibrinolysis were significant predictors of clinical outcomes in previous studies. Farag et al. showed that LT measured by GTT could identify the high ischemic phenotype in patients presenting with ST-segment elevation MI.[11] In their study, prolonged LT was highly predictive of recurrent MACE during a 1-year follow-up. Similarly, Jeong et al. evaluated the relationship between TEG MA and high platelet reactivity (HPR) in PCI-treated patients. A high MA was associated with a higher rate of HPR phenotype, and both parameters were associated with an increased risk of 2-year MACE.[32] Gurbel et al. investigated the prognostic implication of MA in CAD patients undergoing PCI.[33] 'MA > 69 mm' was a significant independent predictor of first ischemic events during their 3-year follow-up. Kang et al. evaluated the association between thrombogenicity and coronary microvascular dysfunction (CMD, defined as an index of microcirculatory resistance > 40 U) in AMI patients.[14] 'MA ≥ 68 mm' was significantly associated with post-procedural CMD in the culprit lesion, and

as well as with a higher rate of MACE. In the present study, we enrolled 2,705 patients who underwent pre-PCI global haemostasis profiling by TEG, and evaluated the clinical outcomes during a 4-year clinical follow-up. From our comprehensive analysis, we were able to confirm the close link of platelet-fibrin clot strength and endogenous fibrinolysis with the progression of ASCVD, and the differential impact of these markers on long-term atherothrombotic events according to the index disease acuity following PCI. In the current analysis, hypercoagulability and impaired fibrinolysis were associated with MACE in the AMI group, but not in the non-AMI group. AMI patients have a high-risk profile, which is associated with combined CV risks and comorbidities, as well as vulnerable blood property. The association between thrombogenicity and clinical events is likely closer in the AMI phenotype. Therefore, potent control of coagulation-fibrinolysis activity would be required in these patients to prevent the recurrence of atherothrombotic events.

However, interpreting the results from global haemostasis tests might require caution. Spinthakis et al. showed the difference in GTT and TEG measurements in evaluating fibrinolysis after anticoagulation treatment.[34] They found a discrepancy between the GTT and TEG parameters, namely, that the effect of apixaban on endogenous fibrinolysis was only observed with the GTT assay. In general, the GTT technique simulates high-shear circumstances, whereas the TEG technique assesses the global viscoelastic properties under low-shear circumstances.[30,34] Therefore, TEG measurement may have some limitations in the evaluation of the function of fibrinolysis among CAD patients.

The present study has demonstrated again that high-risk patients with diabetes, chronic kidney disease, and enhanced inflammation have high level of thrombogenicity, especially those presenting with both hypercoagulability and impaired endogenous fibrinolysis.[35-38] Interestingly,

thrombogenicity was found to be associated with long-term clinical outcomes after index PCI among AMI patients, even after guideline-directed medical therapy. These findings suggest that platelet-fibrin-plasmin interaction can be a future target for individualized therapy for improving the clinical outcomes in AMI patients. AMI patients with thrombogenicity might be the best anticoagulant therapy candidates when looking to maximize net benefit. Although other haemostasis assays have several limitations such as limited availability and the need for well-trained personnel,[13] TEG is a reliable test that has been in clinical practice for a long time. The updated TEG 6S system is fully automated with small variability,[39] and is relatively unbound by the requirement for ample personnel resources. Therefore, TEG may be a relevant modality for assessing the residual ischemic risk and stratifying the high-risk AMI patients after PCI in order to determine their long-term clinical prognoses.

Limitations

This study had several limitations. First, this was a prospective observational study. Although about 3,000 patients were consecutively enrolled in the current analysis, we could not exclude the possibility of selection bias or other systematic confounders. Concomitant medical therapies might have affected the clinical outcomes; however, this could not be fully evaluated in the current analysis since there were no significant differences in prescribed medications according to the thrombogenicity. Second, although we have reported relatively long-term clinical outcomes, the mean duration of follow-up was roughly 2 years. Third, our study is hypothesis-generating rather than confirmative. However, we believe that our findings regarding the cut-offs of this laboratory assay may present an important background for personalized antithrombotic therapy in future studies. Further research may be needed to establish the clinical usefulness of TEG measurement

in real-world practice. Fourth, it is known that external factors including lipid modification can affect endogenous clot characteristics.[40] To minimize these effects, blood sampling was timely performed on the same day of the PCI. However, we could not fully exclude the effects of these external factors on the TEG measurements. Fifth, the decision of performing PCI in stable CAD patients by the attending physician on the basis of imaging or invasive coronary physiologic tests for intermediate stenosis, which might not fully reflect the current practice. Sixth, there is a concern regarding whether the MA value obtained by the TEG is an actionable indicator. Several studies have already shown the relationship between the use of oral anticoagulants and the reduction of MA values,[41,42] which requires further laboratory evidence. Finally, we only collected clinically available laboratory data. Therefore, there is a possibility of missing crucial biomarkers affecting the TEG value and its prognostic implications.[13]

Conclusions

Heightened thrombogenicity evaluated by TEG-defined hypercoagulability and impaired fibrinolytic activity was associated with the occurrence of index AMI at the time of PCI. Despite guideline-recommended intensive medical therapy, heightened thrombogenicity was found to be an important predictor of long-term adverse clinical outcomes.

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None

Conflict of interest

Dr Jeong has received honoraria for lectures from AstraZeneca, Daiichi Sankyo, Sanofi-Aventis, and Han-mi Pharmaceuticals; and research grants or support from Yuhan Pharmaceuticals, Han-mi Pharmaceuticals, Sam-jin Pharmaceuticals, Biotronik, and U&I Corporation. The other authors report no conflicts of interest.

Data availability

Data will be shared on reasonable request to the corresponding author, if required.

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Figure Legends

Figure 1. Study Flow

Abbreviations: AMI = acute myocardial infarction; G-NUH = Gyeongsang National University Hospital; LY_{30} = percentage of the clot that has lysed 30 minutes after the time of maximum amplitude; MA = maximum amplitude; PCI = percutaneous coronary intervention; TEG = thromboelastography

Figure 2. Association Between MACE at 4 Years and TEG Parameters

Spline curves showed association between (A) MA or (B) LY_{30} and MACE at 4 years.
Abbreviations: CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiovascular events; other abbreviations as in Figure 1.

Figure 3. Comparison of 4-Year MACE According to TEG parameters

Comparison of cumulative incidence and Kaplan-Meier curves of MACE at 4 years according to (A) hypercoagulability and (B) impaired fibrinolytic activity.
Abbreviations as in Figures 1 and 2.

Figure 4. Comparison of 4-Year MACE According to Hypercoagulability and Impaired Fibrinolytic Activity

Comparison of cumulative incidence and Kaplan-Meier curves of MACE at 4 years according to the 3 groups classified by MA and LY_{30}; 1) MA <68 mm and LY_{30} ≥0.2%, 2) MA ≥68 mm or LY_{30} <0.2%; and 3) MA ≥68 mm and LY_{30} <0.2%.
Abbreviations as in Figures 1 and 2.

Figure 5. Comparison of 4-Year MACE According to Thrombogenicity and AMI Acuity

Comparison of cumulative incidence and Kaplan-Meier curves of MACE at 4 years according to the 4 groups by thrombogenicity and index AMI presentation.
Abbreviations as in Figures 1 and 2.

Structured Graphical Abstract

The association between thrombogenicity and AMI occurrence, and their prognostic implications for long-term cardiovascular outcomes were investigated.

Abbreviations: AMI = acute myocardial infarction; HR = hazard ratio; LY_{30} = percentage of the clot that has lysed 30 minutes after the time of maximum amplitude; MA = maximum amplitude; MACE = major adverse cardiovascular events; OR = odds ratio; PCI = percutaneous coronary intervention; TEG = thromboelastography.

Table 1

Table 1. Baseline Characteristics of Study Population

	Overall Population (N=2,705)	Non-AMI (N=1,411)	AMI (N=1,294)	*P* value
Age, years	65.1 ± 11.9	64.6 ± 11.0	65.6 ± 12.8	0.032
Men, n (%)	1,938 (71.6)	1,005 (71.2)	933 (72.1)	0.644
Body mass index, kg/m^2	24.3 ± 3.4	24.5 ± 3.3	24.0 ± 3.5	<0.001
Risk factors, n (%)				
Current smoking	813 (30.1)	308 (21.8)	505 (39.0)	<0.001
Diabetes mellitus	863 (31.9)	494 (35.0)	369 (28.5)	<0.001
Hypertension	1,429 (52.8)	794 (56.3)	635 (49.1)	<0.001
Dyslipidemia	1,459 (53.9)	665 (47.1)	794 (61.4)	<0.001
Chronic kidney disease	465 (17.2)	254 (18.0)	211 (16.3)	0.264
Peripheral arterial disease*	284 (12.3)	117 (9.9)	167 (14.9)	<0.001
Previous PCI	397 (14.7)	265 (18.8)	132 (10.2)	<0.001
Previous stroke	173 (6.4)	87 (6.2)	86 (6.6)	0.666
Laboratory findings				
LV ejection fraction, %	55.9 ± 9.5	58.3 ± 9.3	53.5 ± 9.1	<0.001
WBC, x 10^3/mm^3	9.0 ± 3.8	7.8 ± 3.1	10.3 ± 4.0	<0.001
Hemoglobin, g/dL	13.4 ± 2.0	13.1 ± 2.0	13.6 ± 2.0	<0.001
Platelet, x 10^3/mm^3	239.5 ± 69.7	233.4 ± 65.1	246.2 ± 74.0	<0.001
eGFR, mL/min/1.73 m^2	81.6 ± 29.6	81.5 ± 31.4	81.8 ± 27.5	0.833
Total cholesterol, mg/dL	177.9 ± 47.9	167.4 ± 46.0	189.2 ± 47.3	<0.001
LDL cholesterol, mg/dL	116.1 ± 41.5	106.8 ± 39.2	125.3 ± 41.7	<0.001
HDL cholesterol, mg/dL	45.5 ± 14.0	45.7 ± 13.1	45.3 ± 14.7	0.501
Triglyceride, mg/dL	161.0 ± 135.1	154.4 ± 97.3	167.5 ± 163.4	0.015
HbA1c, %	6.5 ± 1.4	6.5 ± 1.4	6.4 ± 1.3	0.557

hs-CRP, mg/dL	8.5 ± 29.0	7.6 ± 27.2	9.4 ± 30.5	0.123
Procedural characteristics				
AHA/ACC lesion: type B2/C	2,412 (89.1)	1,261 (89.4)	1,151 (88.9)	0.772
Multivessel disease, n (%)	1,332 (49.2)	691 (49.0)	641 (49.5)	0.799
Target lesion, n (%)				
- Left main coronary artery	69 (2.6)	42 (3.0)	27 (2.1)	0.179
- Left anterior descending artery	1510 (55.8)	841 (59.6)	669 (51.7)	<0.001
- Left circumflex artery	693 (25.6)	364 (25.8)	329 (25.4)	0.859
- Right coronary artery	953 (35.2)	462 (32.7)	491 (37.9)	0.005
Intracoronary imaging, n (%)	2,311 (85.4)	1,240 (87.9)	1,071 (82.8)	<0.001
- Intravascular ultrasound	2,259 (83.5)	1,217 (86.3)	1,042 (80.5)	
- Optical coherence tomography	52 (1.9)	23 (1.6)	29 (2.2)	
Treatment method, n (%)				0.059
- Drug-eluting stent	2,424 (89.6)	1,264 (89.6)	1,160 (89.6)	
- Bioresorbable scaffold	28 (1.0)	13 (0.9)	15 (1.2)	
- Bare metal stent	18 (0.7)	7 (0.5)	11 (0.9)	
- Drug-coated balloon	107 (4.0)	68 (4.8)	39 (3.0)	
- POBA	128 (4.7)	59 (4.2)	69 (5.3)	
Number of stent, n	1.5 ± 0.8	1.5 ± 0.8	1.4 ± 0.7	0.027
Total stent length, mm	36.8 ± 22.2	37.6 ± 23.4	36.0 ± 20.7	0.068
Stent diameter, mm	3.1 ± 0.5	3.1 ± 0.5	3.1 ± 0.5	0.436
Discharge medications, n (%)				
Aspirin	2,668 (98.6)	1,381 (97.9)	1,287 (99.5)	0.001
Type of $P2Y_{12}$ inhibitor				<0.001
- Clopidogrel	2,043 (75.5)	1,113 (78.9)	930 (71.9)	
- Prasugrel	169 (6.2)	85 (6.0)	84 (6.5)	

- Ticagrelor	465 (17.2)	192 (13.6)	273 (21.1)	
Beta blocker	1,549 (57.3)	596 (42.2)	953 (73.6)	<0.001
Angiotensin blocker	1,831 (67.7)	822 (58.3)	1,009 (78.0)	<0.001
Calcium channel blocker	223 (8.2)	161 (11.4)	62 (4.8)	<0.001
Statin	2,542 (94.0)	1,302 (92.3)	1,240 (95.8)	<0.001

Values are expressed as mean ± standard deviation or number (%).

* Overall, 2,200 patients had information about ankle-brachial index, and peripheral arterial disease was defined as ankle-branchial index ≤0.9 or >1.4

Abbreviations: ACC = American college of cardiology; AHA = American heart association; AMI = acute myocardial infarction; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; hs-CRP = high sensitivity C-reactive protein; LDL = low-density lipoprotein; LV = left ventricular; PCI = percutaneous coronary intervention; POBA = plain old balloon angioplasty; WBC = white blood count.

Table 2

Table 2. Thromboelastographic Measurements According to Index Presentation of Disease

	Overall Population (N=2,705)	Non-AMI (N=1,411)	AMI (N=1,294)	*P* value
R, min	6.7 ± 3.8	6.6 ± 3.2	6.8 ± 4.4	0.134
K, min	1.8 ± 1.6	1.7 ± 1.5	1.8 ± 1.8	0.160
Angle, degree	64.6 ± 12.2	65.0 ± 11.2	64.1 ± 13.3	0.077
MA, mm	65.9 ± 7.5	65.3 ± 7.2	66.5 ± 7.8	<0.001
MA ≥68 mm	1,081 (40.0)	500 (35.4)	581 (44.9)	<0.001
LY_{30}, %	1.0 ± 1.8	1.1 ± 1.9	0.9 ± 1.8	<0.001
LY_{30} <0.2%	1,301 (48.1)	606 (42.9)	695 (53.7)	<0.001

Values are expressed as mean ± SD or number (%).

Abbreviations: AMI = acute myocardial infarction; K = coagulation time; LY_{30} = percentage of the clot that has lysed 30 minutes after the time of maximum amplitude; MA = maximum amplitude; R = reaction time.

Table 3

Table 3. Predictors of Index AMI Presentation

	Univariable analysis		Multivariable analysis*	
	Odds ratio (95% CI)	***P* value**	**Odds ratio (95% CI)**	***P* value**
MA (every 1 mm increase)	**1.022 (1.011-1.032)**	**<0.001**	**1.024 (1.013-1.036)**	**<0.001**
LY_{30} (every 1% increase)	**0.922 (0.883-0.962)**	**<0.001**	**0.934 (0.893-0.978)**	**0.004**
Age (every 1 year increase)	1.007 (1.001-1.013)	0.031	1.023 (1.015-1.031)	<0.001
Body mass index (every 1 kg/m^2 increase)	0.951 (0.930-0.973)	<0.001	0.938 (0.914-0.962)	<0.001
Current smoking	2.292 (1.936-2.713)	<0.001	2.234 (1.853-2.693)	<0.001
Diabetes mellitus	0.741 (0.629-0.871)	<0.001	-	-
Hypertension	0.749 (0.644-0.871)	<0.001	-	-
Dyslipidemia	1.781 (1.528-2.076)	<0.001	1.703 (1.440-2.014)	<0.001
Previous PCI	0.491 (0.393-0.615)	<0.001	0.602 (0.475-0.764)	<0.001
Hemoglobin (every 1 g/dL increase)	1.129 (1.087-1.173)	<0.001	1.161 (1.107-1.217)	<0.001

Data are expressed as number of events (%). The c-statistics of multivariable model was 0.69.

* Multivariable logistic regression model was constructed using variables with P <0.1 in univariable analyses.

Abbreviations: AMI = acute myocardial infarction; CI = confidence interval; LY_{30} = percentage of the clot that has lysed 30 minutes after the time of maximum amplitude; MA = maximum amplitude; PCI = percutaneous coronary intervention.

Table 4

Table 4. Prognostic Implication of Thrombogenicity Indices According to Index Disease Acuity

	Cumulative incidence	Adjusted HR* (95% CI)	*P* value	Adjusted HR* (95% CI)	*P* value
MACE (Cardiovascular death, MI, Stoke)					
1. Non-AMI & No Thrombogenicity†	11.7% (54)	Reference			
2. Non-AMI & Thrombogenicity†	15.2% (13)	1.031 (0.499-2.129)	0.935		
3. AMI & No Thrombogenicity†	18.0% (66)	1.769 (1.173-2.669)	0.007	Reference	
4. AMI & Thrombogenicity†	45.7% (39)	2.451 (1.541-3.899)	<0.001	1.744 (1.135-2.679)	0.011
Cardiovascular death					
1. Non-AMI & No Thrombogenicity†	3.2% (22)	Reference			
2. Non-AMI & Thrombogenicity†	6.5% (7)	1.228 (0.446-3.378)	0.691		
3. AMI & No Thrombogenicity†	7.6% (24)	2.054 (1.053-4.007)	0.035	Reference	
4. AMI & Thrombogenicity†	7.6% (17)	4.032 (1.899-8.561)	0.001	2.062 (1.026-4.143)	0.042
MI					
1. Non-AMI & No Thrombogenicity†	3.9% (20)	Reference			
2. Non-AMI & Thrombogenicity†	2.1% (4)	0.360 (0.047-2.756)	0.325		
3. AMI & No Thrombogenicity†	11.6% (42)	3.302 (1.737-6.275)	<0.001	Reference	
4. AMI & Thrombogenicity†	31.7% (20)	4.430 (2.096-9.365)	<0.001	1.473 (0.828-2.623)	0.188
Stroke					
1. Non-AMI & No Thrombogenicity†	5.1% (14)	Reference			
2. Non-AMI & Thrombogenicity†	5.0% (3)	1.339 (0.372-4.823)	0.655		
3. AMI & No Thrombogenicity†	7.8% (14)	1.130 (0.486-2.626)	0.777	Reference	
4. AMI & Thrombogenicity†	13.8% (9)	1.837 (0.702-4.806)	0.215	2.281 (0.887-5.870)	0.087
BARC type 3 or 5 bleeding					
1. Non-AMI & No Thrombogenicity†	4.2% (26)	Reference			
2. Non-AMI & Thrombogenicity†	2.5% (4)	0.883 (0.297-2.626)	0.823		
3. AMI & No Thrombogenicity†	7.9% (28)	1.985 (1.044-3.776)	0.037	Reference	

4. AMI & Thrombogenicity†	5.3% (8)	1.261 (0.509-3.121)	0.616	0.622 (0.252-1.534)	0.302

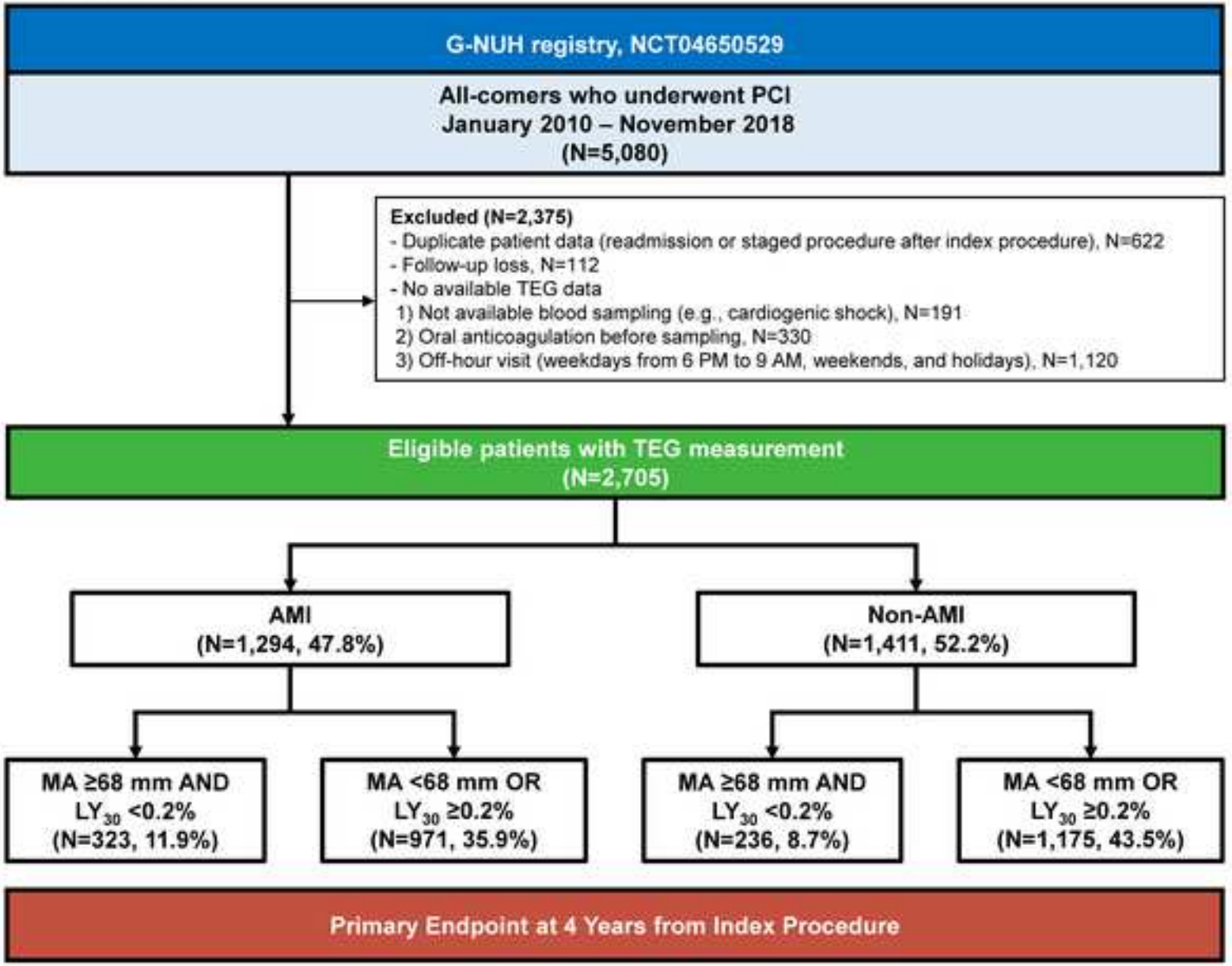
The cumulative incidence of clinical outcomes is presented as Kaplan-Meier estimates. The number of patients with specific events is also presented in parentheses.

* Multivariable analysis after adjusting for age, sex, current smoking, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, previous PCI, previous stroke, high sensitivity C-reactive protein level, potent $P2Y_{12}$ inhibitor, beta blocker, angiotensin blocker, and statin.

† Defined as MA ≥68 mm and LY_{30} <0.2%

Abbreviations: BARC = Bleeding Academic Research Consortium; CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac event; MI = myocardial infarction.

Figure 1. Study Flow



Primary Endpoint: A composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke

Figure 2

Click here to access/download;Figure;03_Figure 2.tiff

Figure 2. Association Between MACE at 4 Years and TEG Parameters

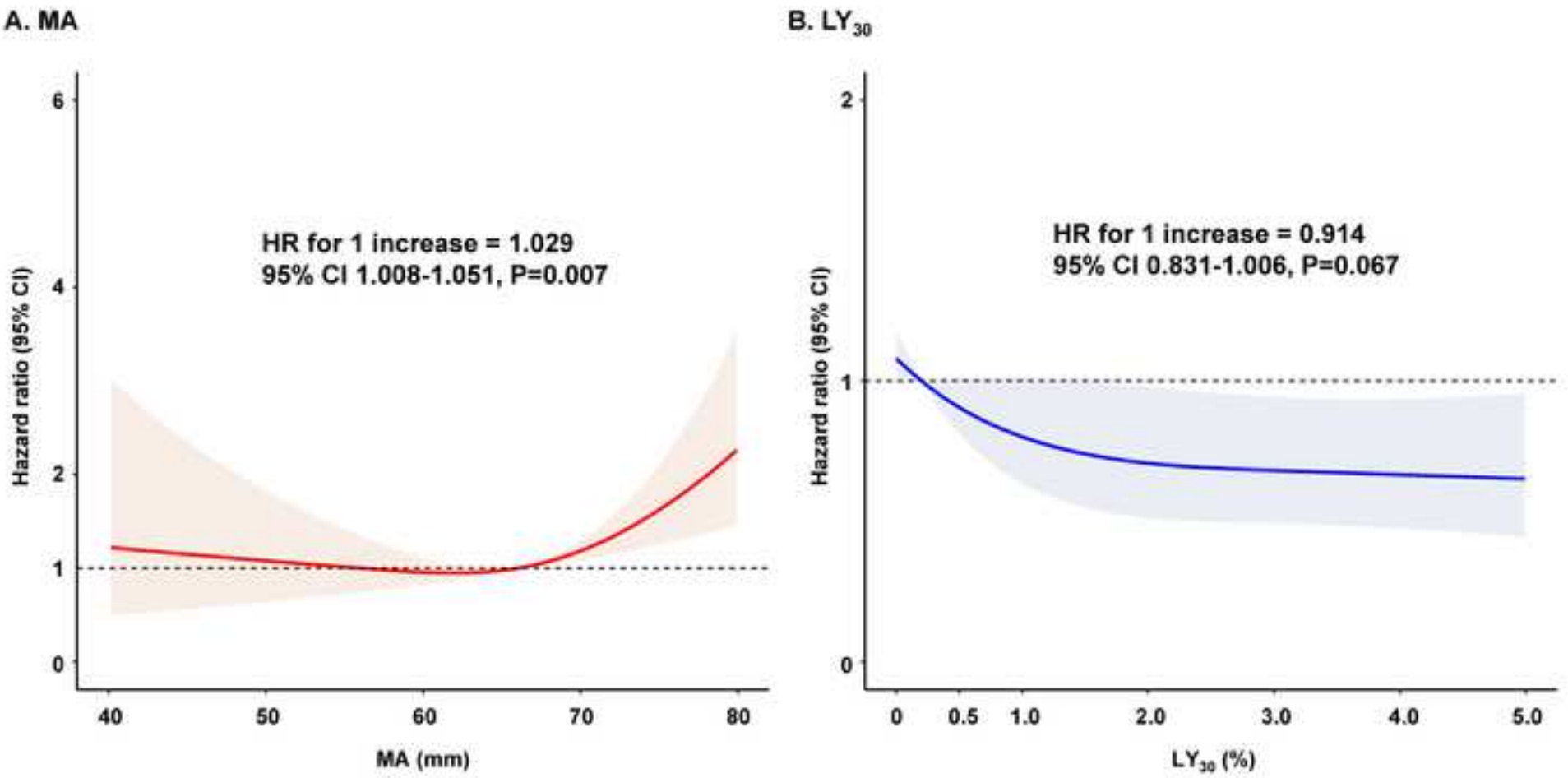


Figure 3

Figure 3. Comparison of 4-Year MACE According to TEG parameters

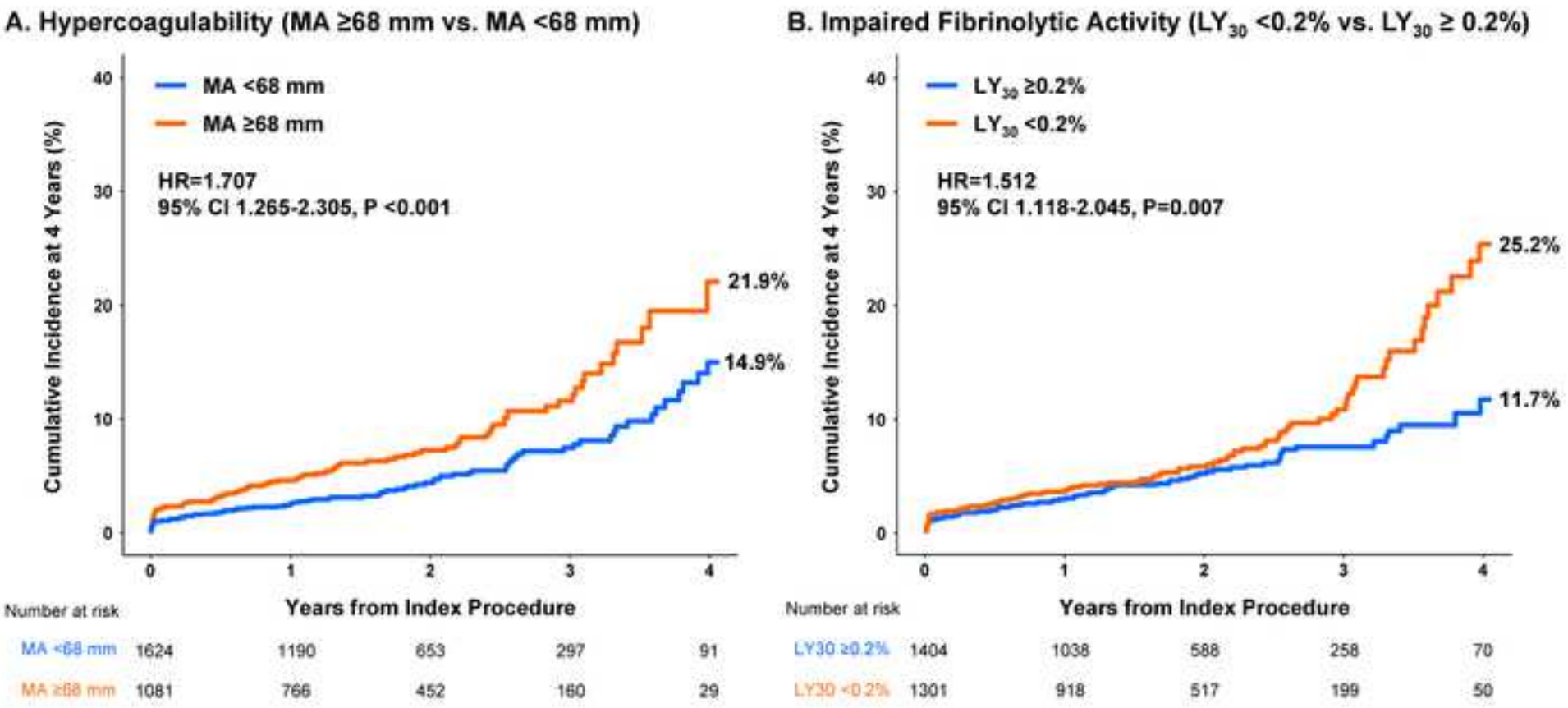


Figure 4. Comparison of 4-Year MACE According to Hypercoagulability and Impaired Fibrinolytic Activity

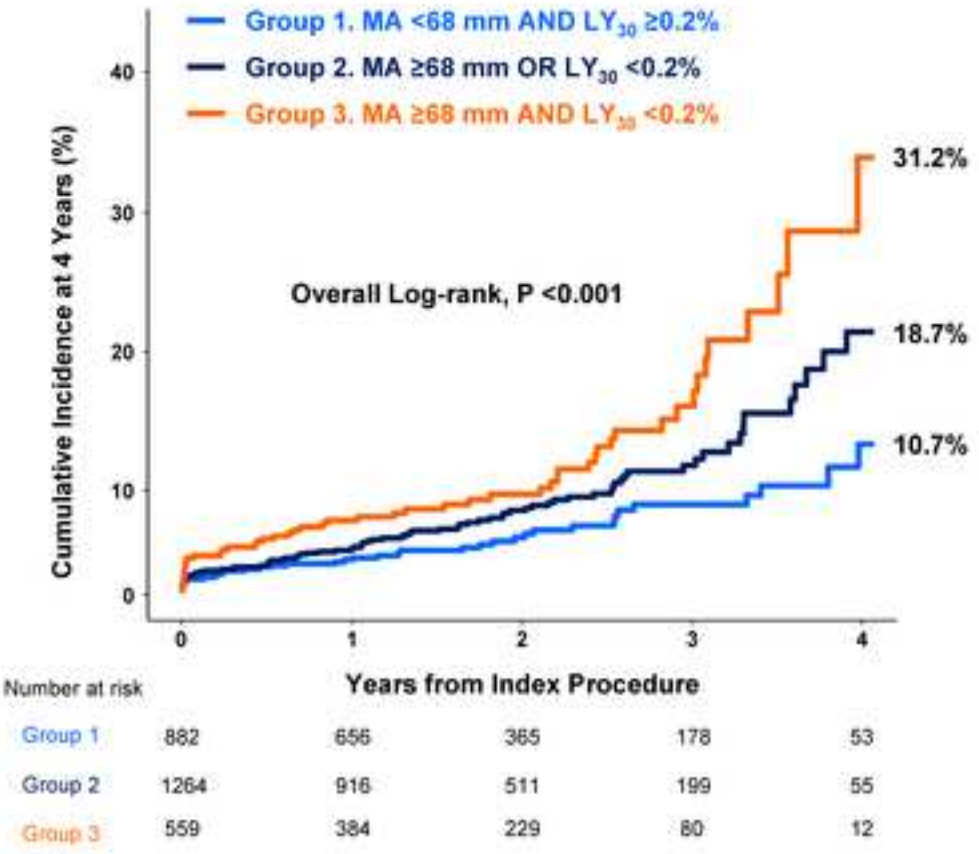
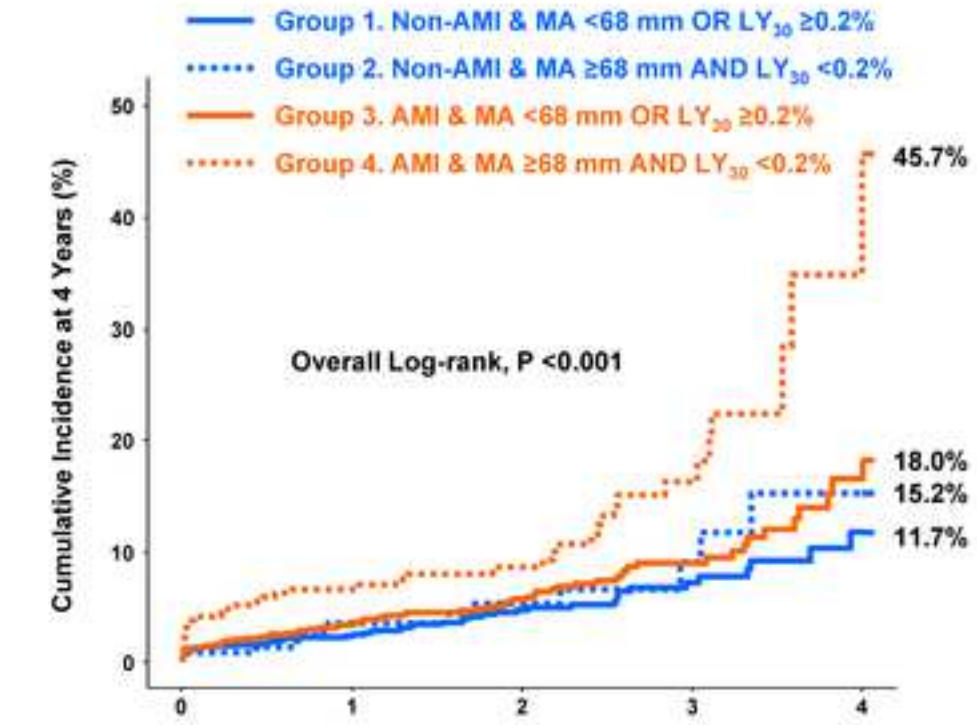


Figure 5. Comparison of 4-Year MACE According to Thrombogenicity and AMI Acuity



Number at risk					
Group 1	1175	835	448	179	57
Group 2	236	154	88	34	8
Group 3	971	737	428	198	51
Group 4	323	384	141	46	4

SUPPLEMENTAL MATERIAL

This appendix has been provided by the authors to give readers additional information about their work.

Supplemental Tables

Supplemental Figures

Table S1. Comparison of Baseline Characteristics Between Included and Excluded Patients

	Included (N=2,705)	Excluded (N=2,375)	*P* value
Age, years	65.1 ± 11.9	65.0 ± 11.8	0.708
Men, n (%)	1,938 (71.6)	1,686 (71.0)	0.628
Body mass index, kg/m^2	24.3 ± 3.4	24.3 ± 3.4	0.651
Acute myocardial infarction	1,294 (47.8)	1,128 (47.5)	0.829
Risk factors, n (%)			
Current smoking	813 (30.1)	710 (29.9)	0.925
Diabetes mellitus	863 (31.9)	774 (32.6)	0.623
Hypertension	1,429 (52.8)	1,265 (53.3)	0.778
Dyslipidemia	1,459 (53.9)	1,296 (54.6)	0.673
Chronic kidney disease	465 (17.2)	416 (17.5)	0.788
Peripheral arterial disease*	284 (12.3)	224 (11.8)	0.609
Previous PCI	397 (14.7)	345 (14.5)	0.911
Previous stroke	173 (6.4)	154 (6.5)	0.943
Laboratory findings			
LV ejection fraction, %	55.9 ± 9.5	56.0 ± 9.5	0.646
WBC, x 10^3/mm^3	9.0 ± 3.8	9.0 ± 3.7	0.913
Hemoglobin, g/dL	13.4 ± 2.0	13.4 ± 2.0	0.839
Platelet, x 10^3/mm^3	239.5 ± 69.7	239.0 ± 69.1	0.796
eGFR, mL/min/1.73 m^2	81.6 ± 29.6	80.9 ± 29.2	0.359
Total cholesterol, mg/dL	177.9 ± 47.9	177.7 ± 48.3	0.906
LDL cholesterol, mg/dL	116.1 ± 41.5	116.2 ± 41.9	0.885
HDL cholesterol, mg/dL	45.5 ± 14.0	45.5 ± 14.0	0.919
Triglyceride, mg/dL	161.0 ± 135.1	163.4 ± 124.9	0.532

HbA1c, %	6.5 ± 1.4	6.5 ± 1.4	0.688
hs-CRP, mg/dL	8.5 ± 29.0	8.7 ± 30.1	0.877
Procedural characteristics			
AHA/ACC lesion: type B2/C	2,412 (89.1)	2,113 (89.0)	0.855
Multivessel disease, n (%)	1,332 (49.2)	1,223 (51.5)	0.110
Target lesion, n (%)			
- Left main coronary artery	69 (2.6)	54 (2.3)	0.583
- Left anterior descending artery	1510 (55.8)	1,330 (56.0)	0.921
- Left circumflex artery	693 (25.6)	616 (25.9)	0.821
- Right coronary artery	953 (35.2)	842 (35.5)	0.892
Intracoronary imaging, n (%)	2,311 (85.4)	2,019 (85.0)	0.879
- Intravascular ultrasound	2,259 (83.5)	1,971 (83.0)	
- Optical coherence tomography	52 (1.9)	48 (2.0)	
Treatment method, n (%)			0.744
- Drug-eluting stent	2,424 (89.6)	2,148 (90.4)	
- Bioresorbable scaffold	28 (1.0)	17 (0.7)	
- Bare metal stent	18 (0.7)	14 (0.6)	
- Drug-coated balloon	107 (4.0)	90 (3.8)	
- POBA	128 (4.7)	106 (4.5)	
Number of stent, n	1.5 ± 0.8	1.5 ± 0.8	0.592
Total stent length, mm	36.8 ± 22.2	37.1 ± 22.6	0.706
Stent diameter, mm	3.1 ± 0.5	3.1 ± 0.5	0.704
Discharge medications, n (%)			
Aspirin	2,668 (98.6)	2340 (98.5)	0.842
Type of $P2Y_{12}$ inhibitor			0.288
- Clopidogrel	2,043 (75.5)	1,751 (73.7)	

- Prasugrel	169 (6.2)	145 (6.1)	
- Ticagrelor	465 (17.2)	457 (19.2)	
Beta blocker	1,549 (57.3)	1,370 (57.7)	0.784
Angiotensin blocker	1,831 (67.7)	1,604 (67.5)	0.932
Calcium channel blocker	223 (8.2)	170 (7.2)	0.164
Statin	2,542 (94.0)	2,223 (93.6)	0.622

Values are expressed as mean ± standard deviation or number (%).

* Overall, 4,201 patients had information about ankle-brachial index, and peripheral arterial disease was defined as ankle-branchial index ≤0.9 or >1.4.

Abbreviations: ACC = American college of cardiology; AHA = American heart association; AMI = acute myocardial infarction; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; hs-CRP = high sensitivity C-reactive protein; LDL = low-density lipoprotein; LV = left ventricular; PCI = percutaneous coronary intervention; POBA = plain old balloon angioplasty; WBC = white blood count.

Table S2. Thromboelastographic Measurements According to Index Presentation of Disease (STEMI vs. NSTEMI)

	Overall Population (N=1,294)	STEMI (712/1,294, 55.0%)	NSTEMI (582/1,294, 45.0%)	*P* value
Baseline (at presentation)				
R, min	6.8 ± 4.4	6.3 ± 4.0	7.4 ± 4.9	<0.001
K, min	1.8 ± 1.8	1.6 ± 1.5	2.0 ± 2.0	<0.001
Angle, degree	64.1 ± 13.3	65.8 ± 12.1	62.1 ± 14.3	<0.001
MA, mm	66.5 ± 7.8	67.1 ± 7.4	65.8 ± 8.3	<0.001
MA ≥68 mm	581 (44.9)	336 (47.2)	245 (42.1)	0.076
LY_{30}, %	0.9 ± 1.8	0.8 ± 1.7	0.9 ± 1.9	0.499
LY_{30} <0.2%	695 (53.7)	378 (53.1)	317 (54.5)	0.661

Values are expressed as mean ± SD or number (%).

Abbreviations: K = coagulation time; LY_{30} = percentage of the clot that has lysed 30 minutes after the time of maximum amplitude; MA = maximum amplitude; NSTEMI = non-ST-segment elevation acute myocardial infarction; R = reaction time; STEMI = ST-segment elevation acute myocardial infarction.

Table S3. Baseline Characteristics of Study Population According to Hypercoagulability and Impaired Fibrinolysis

	MA <68 mm and LY_{30} ≥0.2% (Group 1) (882/2,705, 32.6%)	MA ≥68 mm or LY_{30} <0.2% (Group 2) (1,264/2,705, 46.7%)	MA ≥68 mm and LY_{30} <0.2% (Group 3) (559/2,705, 20.7%)	*P* value
Age, years	63.3 ± 11.9	65.1 ± 11.8	68.1 ± 11.6	<0.001
Men, n (%)	686 (77.8)	890 (70.4)	362 (64.8)	<0.001
Body mass index, kg/m^2	24.4 ± 3.3	24.3 ± 3.4	24.0 ± 3.6	0.082
Index AMI presentation, n (%)	341 (38.7)	630 (49.8)	323 (57.8)	<0.001
Risk factors, n (%)				
Current smoking	277 (31.4)	378 (29.9)	158 (28.3)	0.442
Diabetes mellitus	242 (27.4)	418 (33.1)	203 (36.3)	0.001
Hypertension	431 (48.9)	675 (53.4)	323 (57.8)	0.004
Dyslipidemia	480 (54.4)	681 (53.9)	298 (53.3)	0.917
Chronic kidney disease	97 (11.0)	220 (17.4)	148 (26.5)	<0.001
Peripheral arterial disease*	71 (9.4)	125 (11.4)	88 (19.4)	<0.00
Previous PCI	139 (15.8)	192 (15.2)	66 (11.8)	0.092
Previous stroke	58 (6.6)	83 (6.6)	32 (5.7)	0.767
Laboratory findings				
LV ejection fraction, %	57.3 ± 8.9	55.9 ± 9.4	53.6 ± 10.1	<0.001
WBC, x $10^3/mm^3$	8.2 ± 3.4	9.2 ± 3.8	9.7 ± 4.1	<0.001
Hemoglobin, g/dL	13.7 ± 1.9	13.4 ± 2.0	12.7 ± 2.2	<0.001
Platelet, x $10^3/mm^3$	229.9 ± 61.3	241.0 ± 73.7	251.3 ± 71.1	<0.001
eGFR, mL/min/1.73 m^2	85.0 ± 27.3	82.7 ± 29.1	74.0 ± 32.7	<0.001
Total cholesterol, mg/dL	179.2 ± 48.7	177.1 ± 47.5	177.6 ± 47.6	0.593
LDL cholesterol, mg/dL	115.0 ± 40.8	116.4 ± 41.3	116.9 ± 43.2	0.661

HDL cholesterol, mg/dL	46.8 ± 13.9	44.8 ± 14.0	45.1 ± 13.7	0.005
Triglyceride, mg/dL	161.7 ± 131.1	163.5 ± 140.2	154.2 ± 129.2	0.411
HbA1c, %	6.4 ± 1.4	6.5 ± 1.4	6.6 ± 1.4	<0.001
hs-CRP, mg/dL	3.8 ± 13.1	8.4 ± 31.1	16.1 ± 38.3	<0.001
Procedural characteristics				
AHA/ACC lesion: type B2/C	772 (7.5)	1,139 (90.1)	501 (89.6)	0.154
Multivessel disease, n (%)	395 (44.8)	617 (48.8)	319 (57.1)	<0.001
Target lesion, n (%)				
- Left main coronary artery	23 (2.6)	34 (2.7)	12 (2.1)	0.788
- Left anterior descending artery	503 (57.0)	691 (54.7)	316 (56.5)	0.517
- Left circumflex artery	214 (24.3)	345 (27.3)	134 (24.0)	0.173
- Right coronary artery	298 (33.8)	438 (34.7)	217 (38.8)	0.126
Intracoronary imaging, n (%)	776 (88.0)	1,065 (84.3)	470 (84.1)	0.033
- Intravascular ultrasound	753 (85.4)	1,041 (82.4)	465 (83.2)	
- Optical coherence tomography	23 (2.6)	24 (1.9)	5 (0.9)	
Treatment method, n (%)				0.439
- Drug-eluting stent	797 (90.4)	1136 (89.9)	491 (87.8)	
- Bioresorbable scaffold	10 (1.1)	13 (1.0)	5 (0.9)	
- Bare metal stent	7 (0.8)	6 (0.5)	5 (0.9)	
- Drug-coated balloon	26 (2.9)	56 (4.4)	25 (4.5)	
- POBA	42 (4.8)	53 (4.2)	33 (5.9)	
Number of stent, n	1.4 ± 0.8	1.5 ± 0.7	1.5 ± 0.7	0.217
Total stent length, mm	36.1 ± 22.7	36.8 ± 21.7	38.2 ± 22.4	0.247
Stent diameter, mm	3.2 ± 0.5	3.1 ± 0.5	3.1 ± 0.5	0.015
Discharge medications, n (%)				
Aspirin	871 (98.8)	1247 (98.7)	550 (98.4)	0.842

Type of $P2Y_{12}$ inhibitor				0.538
- Clopidogrel	662 (75.1)	969 (76.7)	412 (73.7)	
- Prasugrel	59 (6.7)	68 (5.4)	42 (7.5)	
- Ticagrelor	153 (17.3)	211 (16.7)	101 (18.1)	
Beta blocker	469 (53.2)	759 (60.0)	321 (57.4)	0.007
Angiotensin blocker	585 (66.3)	858 (67.9)	388 (69.4)	0.466
Calcium channel blocker	88 (10.0)	96 (7.6)	39 (7.0)	0.067
Statin	822 (93.2)	1,193 (94.4)	527 (94.3)	0.496

Values are expressed as mean ± standard deviation or number (%).

* Overall, 2200 patients had information about ankle-brachial index, and peripheral arterial disease was defined as ankle-branchial index ≤0.9 or >1.4

Abbreviations: ACC = American college of cardiology; AHA = American heart association; AMI = acute myocardial infarction; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; hs-CRP = high sensitivity C-reactive protein; LDL = low-density lipoprotein; LV = left ventricular; LY_{30} = percentage of the clot that has lysed 30 minutes after the time of maximum amplitude; MA = maximum amplitude; PCI = percutaneous coronary intervention; POBA = plain old balloon angioplasty; WBC = white blood count.

Table S4. Comparison of Clinical Outcomes at 4 years According to Hypercoagulability and Impaired Fibrinolysis

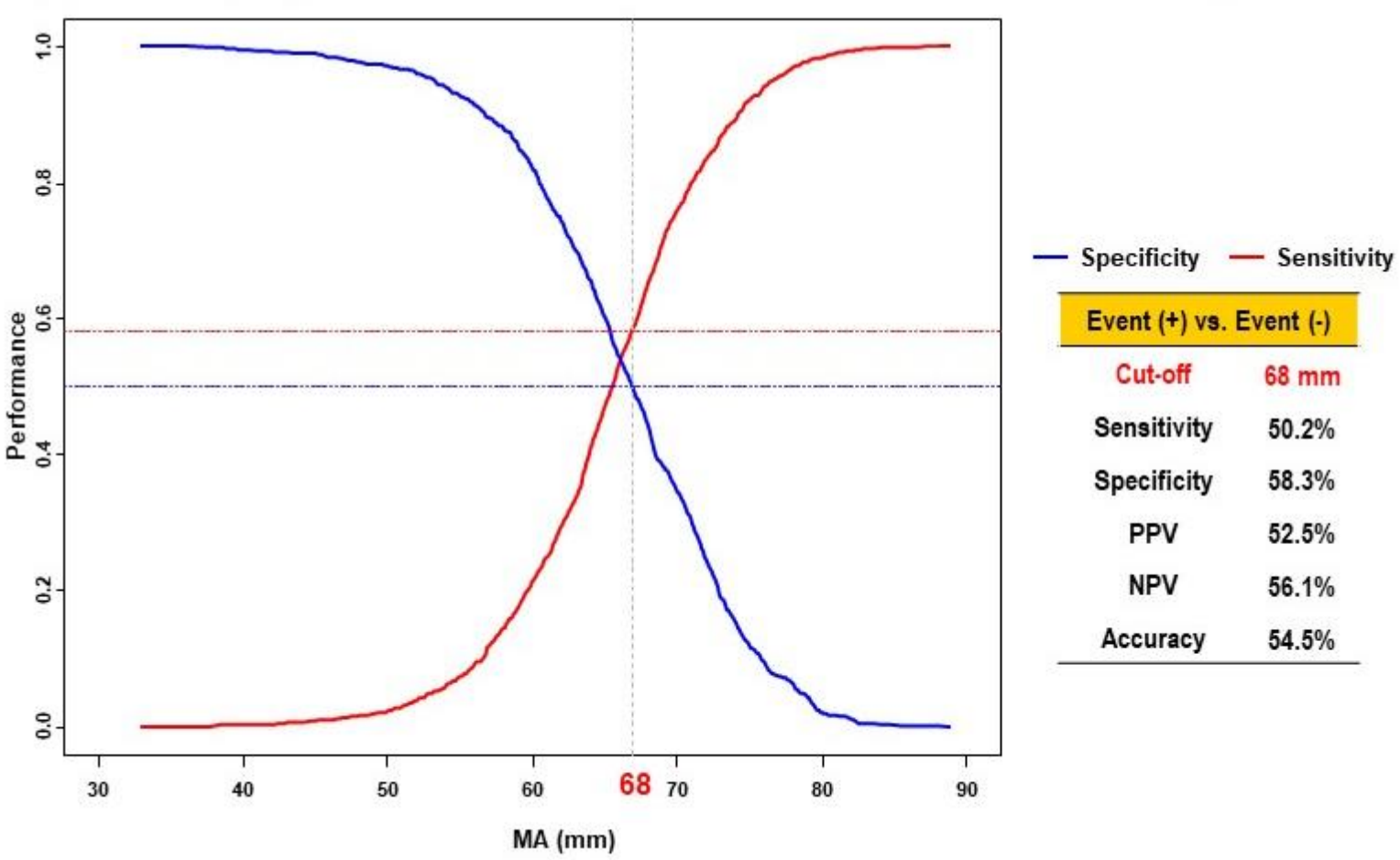
	Cumulative Incidence	Crude HR (95% CI)	*P* value	Adjusted HR* (95% CI)	*P* value
MACE (Cardiovascular death, MI, Stoke)					
1. MA <68 mm and LY_{30} ≥0.2%	10.7% (39)	Reference		Reference	
2. MA ≥68 mm or LY_{30} <0.2%	18.7% (81)	1.592 (1.085-2.334)	0.017	1.252 (0.833-1.883)	0.279
3. MA ≥68 mm and LY_{30} <0.2%	31.2% (52)	2.447 (1.612-3.713)	<0.001	1.781 (1.130-2.808)	0.012
Cardiovascular death					
1. MA <68 mm and LY_{30} ≥0.2%	5.1% (15)	Reference		Reference	
2. MA ≥68 mm or LY_{30} <0.2%	5.9% (31)	1.515 (0.818-2.808)	0.187	1.308 (0.655-2.613)	0.447
3. MA ≥68 mm and LY_{30} <0.2%	7.1% (24)	2.756 (1.443-5.264)	0.002	2.158 (1.028-4.531)	0.042
MI					
1. MA <68 mm and LY_{30} ≥0.2%	4.5% (19)	Reference		Reference	
2. MA ≥68 mm or LY_{30} <0.2%	11.0% (43)	1.744 (1.015-2.997)	0.044	1.317 (0.742-2.337)	0.347
3. MA ≥68 mm and LY_{30} <0.2%	16.8% (24)	2.325 (1.270-4.256)	0.006	1.562 (0.801-3.044)	0.190
Stroke					
1. MA <68 mm and LY_{30} ≥0.2%	7.3% (11)	Reference		Reference	
2. MA ≥68 mm or LY_{30} <0.2%	5.8% (17)	1.255 (0.587-2.685)	0.558	0.856 (0.387-1.896)	0.701
3. MA ≥68 mm and LY_{30} <0.2%	10.2% (12)	2.278 (0.999-5.196)	0.050	1.411 (0.589-3.381)	0.440
BARC type 3 or 5 bleeding					
1. MA <68 mm and LY_{30} ≥0.2%	4.8% (17)	Reference		Reference	
2. MA ≥68 mm or LY_{30} <0.2%	7.2% (37)	1.660 (0.934-2.950)	0.084	1.341 (0.702-2.562)	0.375
3. MA ≥68 mm and LY_{30} <0.2%	4.3% (12)	1.250 (0.595-2.610)	0.559	0.958 (0.422-2.174)	0.918

The cumulative incidence of clinical outcomes is presented as Kaplan-Meier estimates. The number of patients with specific events is also presented in parentheses.

* Multivariable analysis after adjusting for age, sex, diagnosis of acute myocardial infarction, current smoking, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, previous PCI, previous stroke, high sensitivity C-reactive protein level, potent $P2Y_{12}$ inhibitor, beta blocker, angiotensin blocker, and statin.

Abbreviations: BARC = Bleeding Academic Research Consortium; CI = confidence interval; HR = hazard ratio; LY_{30} = percentage of the clot that has lysed 30 minutes after the time of maximum amplitude; MA = maximum amplitude; MACE = major adverse cardiac event; MI = myocardial infarction.

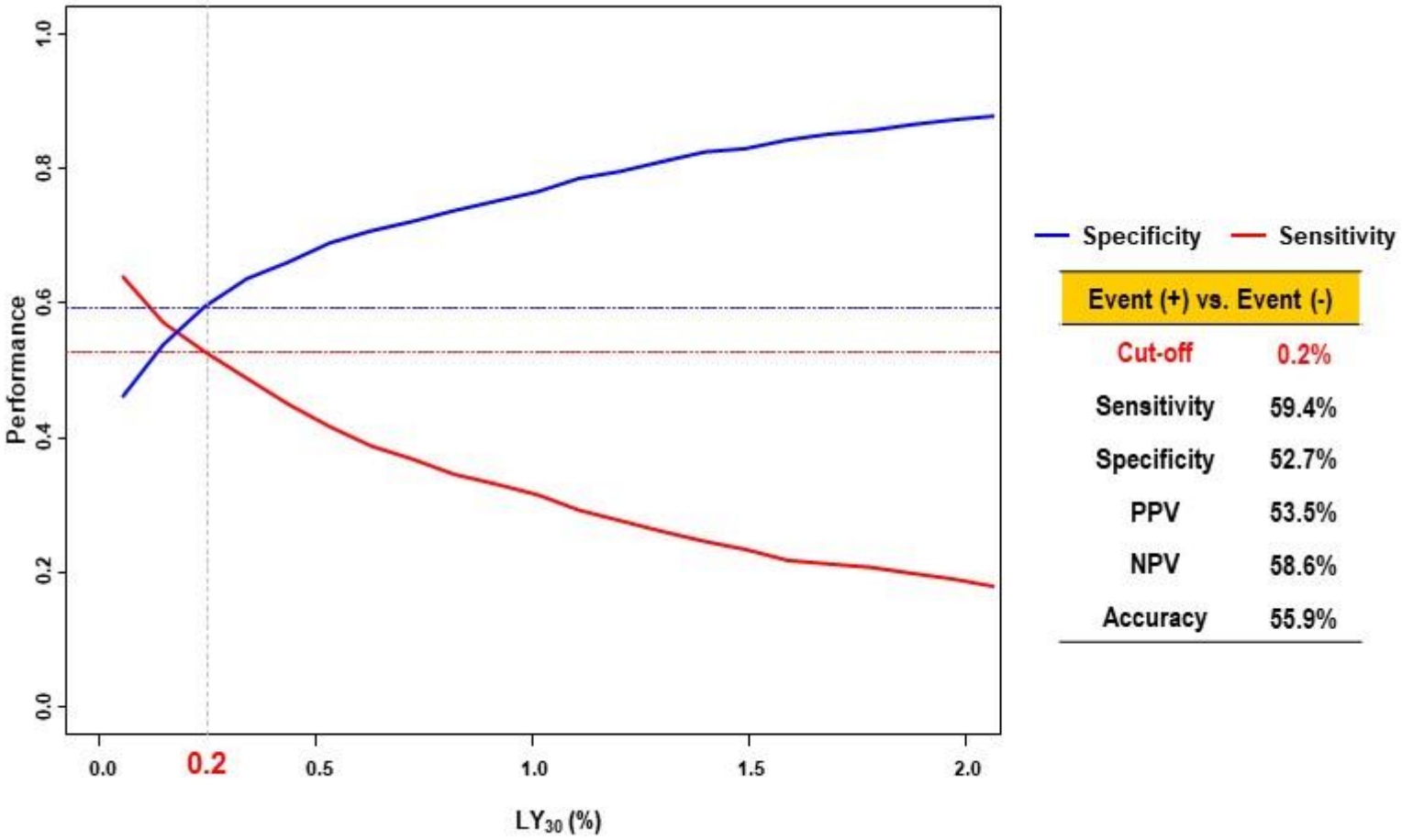
Figure S1. Determination of Cut-off Value of MA for Predicting Index AMI Presentation



The optimal cut-off value of MA for the occurrence of AMI was 68. Blue line shows specificity and red line shows sensitivity.

Abbreviations: AMI = acute myocardial infarction; MA = maximum amplitude; NPV = negative predictive value; PPV = positive predictive value.

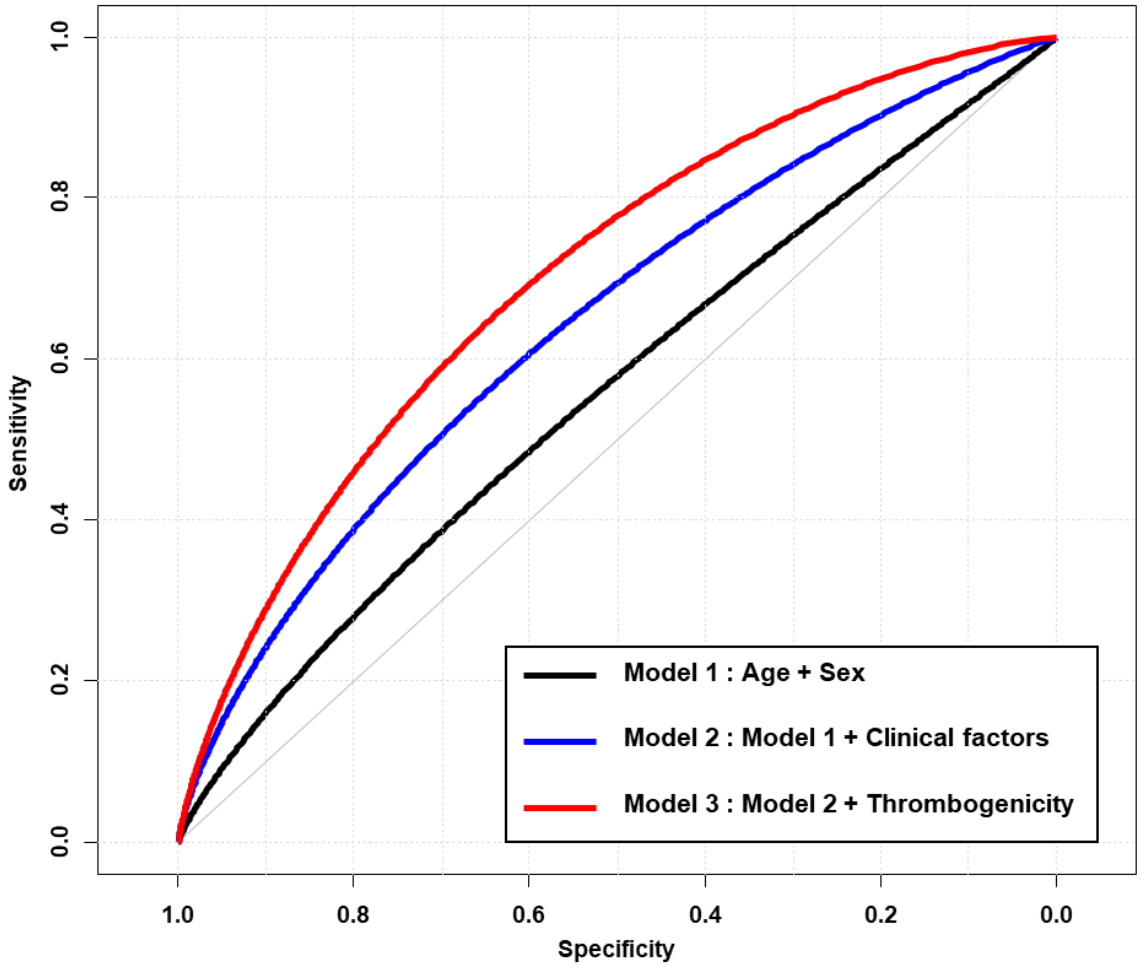
Figure S2. Determination of Cut-off Value of LY_{30} for Predicting Index AMI Presentation



The optimal cut-off value of LY_{30} for the occurrence of AMI was 0.2. Blue line shows specificity and red line shows sensitivity.

Abbreviations: AMI = acute myocardial infarction; LY_{30} = percentage of the clot that has lysed 30 minutes after the time of maximum amplitude; NPV = negative predictive value; PPV = positive predictive value.

Figure S3. Incremental Prognostic Value of Thrombogenicity for MACE Risk at 4 Years



Prediction Model	c-index (95% CI)	P value		NRI (95% CI)	P value	NRI (95% CI)	P value	IDI (95% CI)	P value	IDI (95% CI)	P value
Model 1	0.582 (0.527-0.637)	Reference		Reference				Reference			
Model 2	0.721 (0.674-0.768)	<0.001	Reference	0.496 (0.333-0.658)	<0.001	Reference		0.036 (0.024-0.048)	<0.001	Reference	
Model 3	0.756 (0.712-0.801)	<0.001	0.003	0.701 (0.543-0.858)	<0.001	0.481 (0.319-0.642)	<0.001	0.059 (0.042-0.076)	<0.001	0.023 (0.012-0.034)	<0.001

Prognostic values of models predicting 4-year MACE were compared using Harrell's c-index, NRI, and IDI. Model 1 included the clinical variables of age and sex. There was significant increase in discrimination and reclassification ability with addition of other clinical variables of hypertension, diabetes mellitus, dyslipidemia, current smoker, chronic kidney disease, previous PCI, previous stroke, high sensitivity C-reactive protein level, potent $P2Y_{12}$ inhibitor, beta blocker, angiotensin blocker, and statin (model 2). Model 3 with thrombogenicity (MA $\geq$68 mm and LY30 <0.2%) showed further increase in discrimination and reclassification ability for 4-year MACE. The incremental prognostic value of model 3 was consistent when compared with model 2.

Abbreviations: CI = confidence interval; LY_{30} = percentage of the clot that has lysed 30 minutes after the time of maximum amplitude; MA = maximum amplitude; MACE = major adverse cardiac event; NRI = net reclassification index; IDI = integrated discrimination index; PCI = percutaneous coronary intervention.

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