Influence of hypercoagulability and impaired fibrinolysis on occurrence of acute myocardial infarction and combined prognostic implication following percutaneous coronary Interventions

Brief title: Association between thrombogenicity indices and AMI occurrence

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ABSTRACT

Background: The underlying mechanisms of atherothrombosis comprise plaque disruption and subsequent thrombus formation, which can be modulated with systemic thrombogenicity and fibrinolytic activity. We thus sought to compare thrombogenicity indices and its prognostic implication according to the type of disease.

Methods: CAD patients undergoing percutaneous coronary intervention (PCI) were classified depending on their index clinical presentation (acute myocardial infarction [AMI] vs. non-AMI) (n=2,705). Thrombogenicity indices were measured with thromboelastography (TEG®). Major adverse cardiovascular events (MACEs) were defined as a composite of CV death, non-fatal MI, or non-fatal stroke.

Results: Compared with non-MI patients (n=1,411, 52.1%), MI patients (n=1,294, 47.9%) showed higher platelet-fibrin clot strength (PFCS) (maximum 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). AMI phenotype was significantly associated with the levels of MA (per 1 mm increase: OR: 1.024; 95% CI: 1.013-1.036; *P*<0.001) and LY30 (per 1 mm increase: OR: 0.934; 95% CI: 0.893-0.978; *P*=0.004), respectively. High PFCS (MA≥68 mm) and low fibrinolytic activity (LY30<0.2%) synergistically increased the risk of MACE. In multivariable analysis, the combined phenotype of $PFCS_{high}$ and $LY30_{low}$ was a major predictor of MACE occurrence in the AMI group (adjusted HR: 1.732; 95% CI: 1.145-2.619; *P*=0.009), but not in the non-AMI group (adjusted HR: 1.103; 95% CI: 0.955-2.031; *P*=0.752) ($P_{interaction}$=0.0xx).

Conclusion: AMI occurrence is significantly associated with hypercoagulability and impaired fibrinolysis. In addition, the combined phenotype increases the risk of atherothrombotic event only in AMI patients. These observations may support the clinical application of anticoagulant treatment in patient presented with AMI.

Trial Registration: ClinicalTrials.gov: NCT04650529.

Keywords: thrombosis; fibrinolysis; acute myocardial infarction; anticoagulant.

INTRODUCTION

Although contemporary cardiovascular treatments including revascularization and medical therapy have improved clinical outcomes in patients with atherosclerotic cardiovascular disease (ASCVD), the mortality rate from ischemic heart disease unchanged and about 5% of patients suffered from recurrent cardiovascular events each year.(1)

Treatment guidelines recommended intensified anti-thrombotic treatment in stabilized patients with high-risk ischemic features such as acute myocardial infarction (AMI) and poly-vascular disease,(2,3) based on the results of the 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) trial.(4-6). This kind of intensified regimen including longer-term DAPT, and addition of ticagrelor or rivaroxaban to aspirin significantly reduced major adverse cardiovascular and cerebrovascular events compared with aspirin monotherapy, but the risk of bleeding events increased in accordance with ischemic benefits.

Activation of platelet and coagulation cascade followed by disruption of atherosclerotic plaque is fundamental to development of acute vascular events.(7) However, most risk stratification systems for selection of anti-thrombotic therapy have only focused on patients' clinical and procedural factors.(8,9) Endogenous hypercoagulability and impaired fibrinolysis was associated with poor prognosis in patients after AMI in previous studies.(10,11) Nevertheless, most studies included relatively small numbers and selected patients with short-term follow-up. Therefore, we sought to evaluate 1) differences in thrombogenicity indices between patients

presented with and without AMI; and 2) prognostic implication of thrombogenicity indices in predicting the long-term prognosis after percutaneous coronary intervention (PCI).

METHODS

Study Population

Study population was derived from multicenter and prospective Gyeongsang National University Hospital (GNUH) registry.(12) The GNUH registry enrolled all consecutive patients with significant coronary artery disease (CAD) who underwent PCI in two distinct hospitals, Jinju GNUH and Changwon GNUH, from January 2010 to November 2018. For the present study, we selected patients who had pre-PCI global hemostasis profile data measured by thromboelastography (TEG)-5000. A total of 2,705 patients were included in the current analysis, and they were grouped into two groups: AMI (n=1,294) and non-AMI (n=1,411) groups (**Figure 1**).

The Institutional Review Board of the hospitals approved the study protocol and waived the requirement for written informed consent for access to an institutional registry. The study protocol was in accordance with the Good Clinical Practice Guidelines and the Declaration of Helsinki (clinicaltrials.gov identifier, NCT04650529).

Patient Management and Procedures

Patient treatment was performed according to the standard practice. The choice of treatment strategy, type, diameter, and length of stents, or the use of medications were left to the operator's discretion. All patients were recommended to be given aspirin indefinitely plus clopidogrel or

other potent antiplatelet agents, such as prasugrel or ticagrelor. Treatment duration and choice of $P2Y_{12}$ inhibitors prescribed was left to operator's discretion in accordance with the guidelines and patients' individual bleeding risk.

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

Thromboelastography (TEG) Measurement

According to the predetermined protocol,(12) blood samples for TEG were drawn into Vacutainer tubes containing 3.2% trisodium citrate (Becton Dickinson, Franklin Lakes, NJ, USA), immediately after the arterial sheath insertion for coronary angiography. For hemostatic assay, the TEG® 5000 Hemostasis Analyzer System (Haemonetics Corp, BrainTree, MS, USA) with automated analytical software, which provides measurements of the viscoelastic properties of a clot, was used.(13) Briefly, 500 μL of citrated blood is mixed with kaolin by inversion, and 340 μL of the activated blood is then transferred to a reaction cup, to which 20 μL of 200 mmol/L calcium chloride is added. In heparin-pretreated cases, a vial containing heparinase is used to neutralize the heparin effect. A stationary pin is suspended into an oscillating cup that contains 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 to create a tracing. The degree of platelet contribution to the clot strength through platelet-fibrin bonding directly influences the magnitude of pin movement and the amplitude of the tracing.

Reaction time (R, in minutes), a representative of the initiation phase of enzymatic clotting, is the time from the start of the sample run to the point of the first significant clot formation corresponding to an amplitude of 2 mm reading on the TEG tracing. K (in minutes) is a measure of the time to reach 20-mm clot strength from R. Angle (in degrees) is reflective of fibrinogen activity and is the degrees of the angle formed by the tangent line to TEG tracing measure at R. Kaolin-induced maximum amplitude (MA, in millimeters) represents the maximum platelet-fibrin clot strength. Although blood sampling was performed after pre-treatment of dual antiplatelet agents including aspirin and $P2Y_{12}$ inhibitors, it is known that clot strength and fibrinolysis measured by the present system have not been affected. LY_{30} indicates the percentage of the clot that has lysed 30 minutes after the time of maximal amplitude and indicates the level of fibrinolytic activity. After discharge from index procedure, patients were recommended to perform follow-up TEG. However, the follow-up TEG was not mandatory, since it was not covered by national health insurance.

Study Endpoint, Definitions, and Follow-up

The primary endpoint was major adverse cardiovascular events (MACE) defined as a composite of cardiovascular death, spontaneous MI, and non-fatal stroke at 4 years. All deaths were considered cardiovascular unless a definitive non-cardiovascular cause was identified. Spontaneous MI was defined as the recurrence of symptoms, 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, and periprocedural MI was not included as a clinical outcome. Stroke was defined as evidence of neurological deficit requiring hospitalization and with clinically documented lesions on brain

computed tomography or magnetic resonance imaging confirmed by a neurologist. All endpoints were defined according to the Academic Research Consortium definitions.(14) All clinical events were evaluated by an independent event adjudicating committee. Patients were routinely followed up by outpatient visits or telephone contact at 1, 6, and 12 months after the index procedure, and annually thereafter. Mean duration of follow-up was 666.1 days.

Statistical Analysis

All categorical variables were presented as numbers and relative frequencies (percent) and continuous variables as means and standard deviations or medians with first and third quartiles, according to their distribution, which was checked by Kolmogorov-Smirnov test and visual inspection of Q-Q plots. Differences between groups were assessed using chi-square for categorical variables and Student's t-test or Mann-Whitney test for continuous variables. For comparison of serial changes of MA and LY_{30}, we performed paired t-test. For the multiple group comparisons according to the MA and LY_{30}, continuous variables were tested using the analysis of variance to test differences. Post-hoc analyses were not performed.

The optimal cut-off values of MA and LY_{30} to predict for occurrence of AMI were calculated to maximize the product of sensitivity and specificity using receiver operating characteristic curves. To evaluate the clinical impact of MA and LY_{30} on the occurrence of 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 final model included the variables of MA, LY_{30}, age, body mass index, dyslipidemia, current smoker, previous PCI, and initial hemoglobin level.

The associations between MA or LY_{30} as continuous variables and the risk of 4-year MACE were graphically presented with restricted cubic spline with 3 degrees of freedom.(15) 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 using backward elimination based on an information criterion. The final model included age, sex, diagnosis of AMI, hypertension, diabetes mellitus, chronic kidney disease, and previous PCI.

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

Table 1 shows the baseline characteristics of study population according to the diagnosis of AMI or not. Patients who presented with AMI were older than those without AMI (65.6±12.8 years vs. 64.6±11.0 years, P=0.032). AMI group showed higher incidence of current smoker and dyslipidemia than non-AMI group; conversely, non-AMI group showed higher incidence of diabetes mellitus, hypertension, and previous PCI than AMI group. On laboratory findings,

patients in AMI group had higher white blood cell count (10.3±4.0 x10^3/mm^3 vs. 7.8±3.1 x10^3/mm^3, P<0.001) and low-density lipoprotein cholesterol level (125.3±41.7 mg/dL vs. 106.8±39.2 mg/dL, P<0.001) than those in non-AMI group.

Although there was no significant difference in treatment methods including drug-eluting stents between 2 groups, AMI patients were treated with less number and shorter stent length compared with non-AMI patients. AMI group was more frequently treated with potent $P2Y_{12}$ inhibitors than non-AMI group. Rates of using beta blocker, angiotensin blockade, and statin were also higher in the AMI group than non-AMI group.

Association Between Thrombogenicity Indices and AMI Occurrence

Table 2 shows TEG parameters according to presentation with AMI or not. Among the parameters for thrombogenicity, MA was significantly higher in the patients with AMI than those with non-AMI. LY_{30} was significantly lower in the AMI group compared with non-AMI group**.** **Supplementary Figure 1** and **Supplementary Figure 2** demonstrated the optimal cut-offs of MA and LY_{30} for predicting occurrence of AMI, respectively. In the present study, MA ≥68 mm indicated hypercoagulability and LY_{30} <0.2% indicated impairment of fibrinolytic activity. Approximately half of the AMI patients showed significantly higher incidence of hypercoagulability (44.9% vs. 35.4%, P<0.001) and impaired fibrinolytic activity (53.7% vs. 42.9%, P<0.001), compared with non-AMI patients.

After index procedure, a total of 776 patients were followed-up with measurement of TEG parameters at mean 82.0 days from the initial examination. Even after stabilization from AMI events and guideline-directed medical therapy, the AMI group still showed significantly higher level of MA than the non-AMI group. When we compared serial change in MA, there was no

significant difference in MA between baseline and follow-up stages (baseline 65.9±7.5 mm vs. follow-up 66.1±7.6%; paired t-test, P=0.210) (**Supplementary Figure 3**). Conversely, although the proportion of impaired fibrinolytic activity was higher in AMI group at both baseline and follow-up stages, the difference in LY_{30} between AMI and non-AMI group was not more significant at follow-up TEG. Compared with baseline, the LY_{30} was significantly improved (baseline 1.0±1.8% vs. follow-up 1.2±2.1%; paired t-test, P=0.023), and this change was mainly driven among AMI patients rather than non-AMI patients.

By multivariable logistic regression 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 independent predictors of AMI occurrence with modest to good prediction power (c-statistics=0.69).

Prognostic Implication of Thrombogenicity Indices

As continuous variable, MA was significantly associated with the risk of MACE at 4 years (HR 1.029, 95% CI 1.008-1.051, P=0.007) (**Figure 2**). Although LY_{30} showed a numerical trend of protective effect from 4-year MACE, however, it was not statistically significant (HR 0.914, 95% CI 0.831-1.006, P=0.067). When we compared clinical outcomes of binary classification of MA (≥68 mm vs. <68 mm) and LY_{30} (<0.2% vs. ≥0.2%), both hypercoagulability (HR 1.707, 95% CI 1.265-2.305, P<0.001) and impaired fibrinolytic activity (HR 1.512, 95% CI 1.118-2.045, P=0.007) were associated with an increased risk of 4-year MACE, respectively (**Figure 3**). Considering the hypercoagulability and impaired fibrinolytic activity simultaneously, only patients with MA ≥68 mm and LY_{30} <0.2% (hypercoagulability plus impaired fibrinolytic activity) were showed an increased risk of 4-year MACE (31.2% vs. 10.7%; adjusted HR 1.788, 95% CI 1.159-2.760,

P=0.009) compared to those with MA <68 mm and LY_{30} ≥0.2% (no hypercoagulability and no impaired fibrinolytic activity) (**Figure 4** and **Supplementary Table 2**)

Differential Impact of Thrombogenicity Indices According to the Type of Disease

When we compared clinical outcomes according to the 4 groups classified by thrombogenicity and AMI, there was significant difference in the risk of 4-year MACE among the groups (overall log-rank P<0.001) (Figure 5). AMI patients with thrombogenicity had an increased risk of 4-year MACE compared to non-AMI patients without thrombogenicity (adjusted HR 2.359, 95% CI 1.541-3.611, P<0.001) or AMI patients without thrombogenicity (adjusted HR 1.732, 95% CI 1.145-2.619, P=0.009).

DISCUSSION

The current study evaluated the prognostic implication of hypercoagulability and impaired fibrinolysis after PCI. First, both elevated level of platelet-fibrin clot strength and low percentage of lysis measured by TEG were independent predictors of AMI presentation among the patients with significant CAD. Second, each property was significantly and complementarily associated with clinical prognosis during 4 years of follow-up after PCI.

The balance between thrombotic and fibrinolytic factors is one of the key determinants of development of ASCVD events.(16) Thrombotic biomarkers such as fibrinogen and factor VIII were associated with the higher risk of ASCVD events, while fibrinolytic factor like oxidized phospholipid plasminogen was associated with the lower risk of ASCVD events even after multi-variate analysis of the traditional risk factors in the Multi-Ethnic Study of Atherosclerosis (MESA)

trial cohort. These factorial assays, however, are not appropriate to use for diagnosis and risk stratification in the individual patient because of their variability and complexity.(17) Therefore, there has been several efforts to use global tests for 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 including von Willebrand factor and fibrinogen, and inflammation markers such as C-reactive protein (CRP), interlukin-8, which have been considered as meaningful predictors of ASCVD development.(18-21). Poly-vascular disease patients, who have simultaneously CAD and peripheral artery disease, showed significant higher MA and CRP level compared with CAD patients with normal ankle-brachial index.(13) Timely endogenous fibrinolysis has a protective role against devastating coronary vascular events.(22-24) Previous studies from the group of Gorog et al. have shown that endogenous lysis time (LT) was prolonged in ACS patients compared with healthy control subjects.(25) AMI Patients with spontaneous ST-segment resolution before PCI had more rapid fibrinolysis than those without.(10)

In the present analysis, both platelet-fibrin clot strength and percentages of lysis expressed by MA and LY_{30} in TEG were independent predictors of AMI presentation. About 30% of total population were performed follow-up TEG within 6 months. Level of MA was not significantly different regardless of AMI presentation, but level of LY_{30} was significantly increased at stabilized period. This improvement of endogenous fibrinolysis was more prominently occurred in patients with AMI. Our hypothesis about this finding is that platelet-fibrin clot strength might be associated with the atheroma burden and its progression,(26) and impaired fibrinolysis might be the determinants of development of vascular events and related with its severity.

Both endogenous fibrinolysis and hyper-coagulation were significant predictors of MACE in previous studies. Jeong et al. evaluated the relationship between MA and high on treatment platelet reactivity (HPR) in 197 PCI-treated patients. High level of MA was associated with HPR, and both parameters showed an increased risk for MACE during 2-years follow-up.(27) Gurbel et al. investigated the prognostic implication of MA in 225 PCI-treated patients.(28) MA > 69mm was a significant independent predictors of first ischemic events during the 3-year follow-up. Kang et al. evaluated the association between thrombogenicity and coronary microvascular dysfunction (CMD) in 116 patients with AMI.(12) CMD was defined as index of microcirculatory resistance >40 U measured by thermos-dilution method using coronary pressure wire. MA ≥68 mm significantly increased the risk of post-procedural CMD in culprit lesion, and it is translated into higher rate of MACE. Farag et al. showed that LT measured by the global thrombosis test (GTT) could identify high cardiovascular risk patients with AMI.(10) In this study, LT was measured in 496 patients with ST-segment elevation myocardial infarction at the time of admission, discharge, and 30-days follow-up. Baseline LT prolonged more than 2500 seconds was highly predictive of recurrent MACE during 1-year follow-up. The present study enrolled 2,705 consecutive patients who had pre-PCI global hemostasis profile data and 4-year clinical follow-up. Platelet-fibrin clot strength and endogenous impaired fibrinolysis were significantly and complementarily associated with recurrent MACE during 4-year follow-up after PCI.

LIMITATION

There were several limitations in this study to be addressed. First, this study 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.

Second, although we have reported the clinical outcomes at 4 years, the mean duration of follow-up was about 2 years. Third, it should be note that this study is closed to hypothesis generating study rather than a confirmative study. Namely, our findings could not provide solid evidence for considering anticoagulation based on MA or LY_{30} values. Fourth, we reported the serial changes between baseline and follow-up TEG parameters, however, only about 30% of patients performed follow-up tests due to limitation of medical cost problems.

CONCLUSION

Thrombogenicity, including hypercoagulability and impaired fibrinolytic activity by TEG, was associated with the occurrence of AMI. After PCI, the thrombogenicity was related to an increased risk of long-term clinical outcomes, even though guideline-directed medical therapy was given. There was differential impact of thrombogenicity on the prognosis that was more evident among AMI patients.

Figure Legends

Figure 1. Study Flow

Abbreviations: AMI = acute myocardial infarction; GNUH = 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 Figure 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 Figure 1 and 2.

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

Comparison of cumulative incidence and Kaplan-Meier curves of MACE at 4 years according to the 4 groups by thrombogenicity and AMI.

Abbreviations as in Figure 1 and 2.

Supplementary Figure 1. Determination of Cut-off Value of MA for Predicting Occurrence of AMI

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.

Supplementary Figure 2. Determination of Cut-off Value of LY_{30} for Predicting Occurrence of AMI

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.

Supplementary Figure 3. Comparison of MA and LY_{30} Between Baseline and Follow-up

Serial changes of MA (upper panel) and LY_{30} (lower panel) were compared between baseline and follow-up among (A) total population, (B) AMI, and (C) non-AMI patients. Boxes represent 25th to 75th percentile; line represent median; and point represent mean.

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

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