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ORIGINAL RESEARCH

Residual Cardiovascular Biomarkers After Medical Therapy and Their Prognostic Implications Following Percutaneous Coronary Intervention

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ABSTRACT

BACKGROUND Despite medical therapy, atherothrombotic events remain common in high-risk patients with coronary artery disease.

OBJECTIVES The purpose of this study was to evaluate the association between atherothrombotic biomarkers and outcomes in patients with coronary artery disease who are undergoing percutaneous coronary intervention (PCI).

METHODS Biomarkers including lipid profile (low-density lipoprotein cholesterol and triglycerides), inflammation (high-sensitivity C-reactive protein [hs-CRP]), platelet reactivity (P2Y12 reaction unit), and coagulation (fibrinogen) were measured on admission and at 1 month following medical therapy post-PCI (n = 2,789). The primary endpoint was major adverse cardiovascular events, defined as a composite of cardiovascular death, myocardial infarction, or stroke, occurring between 1 month and 4 years post-PCI.

RESULTS Biomarker levels decreased significantly (all P values ≤ 0.001), except for fibrinogen levels (329 ± 86 vs 359 ± 92 mg/dL; $P < 0.001$). The median follow-up of the participants was 2.2 years (IQR: 1.3-4.0 years). Covariate-adjusted HRs for the lowest to highest quartiles were 1.00 (referent) (95% CI), 1.37 (0.78-2.41), 1.89 (1.11-3.21), and 1.71 (1.01-2.91) for 1-month hs-CRP; and 1.00 (referent), 1.49 (0.83-2.67), 1.83 (1.03-3.26), and 2.47 (1.40-4.36) for 1-month fibrinogen. Among these biomarkers, hs-CRP and fibrinogen levels at 1 month showed the highest correlation (r = 0.426). After adjusting for covariates and biomarkers, the 1-month fibrinogen level was the strongest incremental predictor of major adverse cardiovascular event (HRs: 1.00 [referent], 1.45 [0.80-2.62], 1.65 [0.91-2.98], and 2.23 [1.20-4.12], $P < 0.001$).

CONCLUSIONS Among medically treated patients following PCI, elevated fibrinogen levels were associated with adverse outcomes. Further studies are warranted to clarify these associations and to determine whether adjunctive therapies can improve outcomes in this high-risk group. (Gyeongsang National University Hospital [GNUH] Registry; NCT04650529) (JACC Adv. 2026;5:102498) © 2026 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

ASCVD = atherosclerotic cardiovascular disease

CAD = coronary artery disease

CV = cardiovascular

hs-CRP = high-sensitivity C-reactive protein

LDL = low-density lipoprotein

MACE = major adverse cardiovascular event

MI = myocardial infarction

MT = medical therapy

PCI = percutaneous coronary intervention

PFT = platelet function test

PRU = P2Y12 reaction unit

Despite medical therapy (MT), a subset of patients with high-risk coronary artery disease (CAD) continues to experience atherothrombotic events.[1] Efforts to reduce residual atherothrombotic risk after percutaneous coronary intervention (PCI) have focused on targeting multiple implicated biological pathways. Recent large-scale randomized clinical trials have highlighted the pivotal roles of platelets, coagulation, lipids, and inflammation in recurrent atherothrombotic events, emphasizing their performance for long-term secondary prevention in high-risk patients with atherosclerotic cardiovascular disease (ASCVD).[2-7]

Intensive pharmacological strategies targeting low-density lipoprotein (LDL) cholesterol have significantly reduced ischemic outcomes.[8,9] However, ischemic events persist even when "low LDL-cholesterol levels" are achieved with maximally tolerated therapy. For instance, in the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk) trial, despite reducing the median LDL-cholesterol level to 30 mg/dL, atherothrombotic events occurred in 9.8% of patients during a 26-month follow-up period.[5]

Emerging evidence suggests that additional atherothrombotic CV risk is influenced by a combination of traditional CV risk factors and undefined individual risk-related mechanisms.[10,11] Therefore, a personalized approach that utilizes selected biomarkers may offer valuable insights for addressing residual atherothrombotic risk and guiding the use of targeted adjunctive pharmacotherapy. In this study, we evaluated the association between residual atherothrombotic biomarkers and recurrent atherothrombotic events in patients with CAD who underwent PCI.

METHODS

STUDY POPULATION. The study population was selected from the Gyeongsang National University Hospital registry (NCT04650529). This registry prospectively enrolled consecutive patients with significant CAD who underwent PCI at 2 tertiary referral hospitals (Jinju & Changwon) between January 2010 and November 2018, which evaluated available hemostatic, vascular, and physiologic parameters.[10] We excluded patients with non-CV conditions that could influence various forms of residual CV risk, including active infections, malignancies, or clinical evidence of autoimmune or systemic inflammatory diseases.

The Institutional Review Board approved the registry and waived the requirement for written informed consent. This study was conducted in accordance with Good Clinical Practice Guidelines and the principles of the Declaration of Helsinki.

PATIENT MANAGEMENT AND PROCEDURES. Patients were treated according to standard clinical practices based on the guidelines published during the study period.[12-15] The choice of treatment strategy (PCI strategy and choice of MT) was left to the physician's discretion. All patients were recommended indefinite aspirin and/or $P2Y_{12}$ inhibitor therapy. The treatment duration and choice of $P2Y_{12}$ inhibitor were determined by the treating physician in accordance with the guidelines and the patients' individual bleeding and ischemic risks, as perceived by the physician.

Baseline demographic characteristics, CV risk factors, angiographic and procedural details, and discharge medications were collected prospectively through patient interviews or review of medical records under the supervision of the principal investigator. Patients were routinely followed up through outpatient visits or telephone at 1, 6, and 12 months after the index procedure and annually thereafter. The study endpoints during the follow-up period were

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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.

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rigorously monitored by dedicated clinical research coordinators. All clinical events were reviewed based on source documents by an independent adjudication committee blinded to the laboratory data.

LABORATORY MEASUREMENTS. Laboratory assessments for residual CV risk were performed using the following biomarkers: lipid profile (LDL-cholesterol and triglycerides), inflammation (high-sensitivity C-reactive protein [hs-CRP]), coagulation (fibrinogen), and platelet reactivity (P2Y12 reaction unit [PRU], measured using the VerifyNow assay).[2-7,11,16]

Baseline biochemical assessments, except for the platelet function test (PFT), were performed using blood samples drawn from an antecubital vein upon arrival at the emergency department or general ward, and at the post-PCI 1-month (±1 week) follow-up visit. LDL-cholesterol, triglycerides, and hs-CRP were measured using a commercially available enzyme-linked immunosorbent assay on the UniCel DxC 800 Synchron Clinical System (Beckman Coulter, Inc). Fibrinogen was measured using the STAR Max (Diagnostica Stago, Inc).

PFT was performed using the commercially available VerifyNow PRUTest (Werfen), a whole-blood, point-of-care, turbidimetric-based optical detection assay.[17] The channel contains fibrinogen-coated polystyrene beads, 20 mmol/L adenosine diphosphate, and 22 nmol/L prostaglandin E1. The optical signal is reported as "PRU." Baseline blood samples were drawn into Vacutainer tubes containing 3.2% citrate from the arterial sheath immediately after insertion for coronary angiography. The baseline assay was performed at least 6 hours after loading with 600 mg of clopidogrel, at least 2 hours after loading with 180 mg of ticagrelor or 60 mg of prasugrel, or after at least 5 days of maintenance therapy with 75 mg of clopidogrel once daily. A follow-up PFT assay was conducted at 1 month using blood samples collected from the antecubital vein at least 2 hours after administering a maintenance dose of the $P2Y_{12}$ inhibitor.

STUDY ENDPOINTS AND DEFINITIONS. The primary endpoint was the occurrence of major adverse CV events (MACEs), defined as a composite of CV death, nonfatal myocardial infarction (MI), and nonfatal stroke, occurring between 1 month and 4 years post-PCI. We then evaluated the relationship between MACE and residual atherothrombotic CV risk, as indicated by biomarkers measured at 1 month.

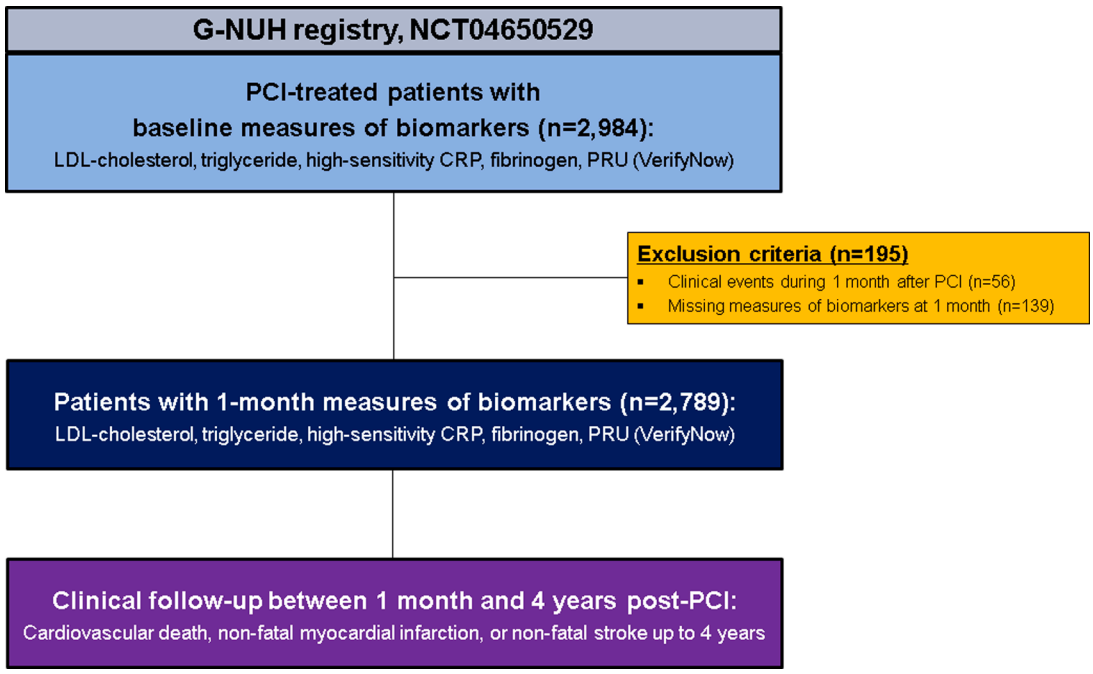
Risk stratification of biomarkers was determined based on a predefined high-risk phenotype and quartile category. The cutoffs for high-risk phenotypes were defined according to previous evidence and guidelines: "LDL-cholesterol ≥70 mg/dL,"[18,19] "triglyceride ≥150 mg/dL,"[19,20] "hs-CRP ≥2 mg/L,"[21] "fibrinogen >350 mg/dL,"[22] and "PRU >208."[23]

All endpoints were defined according to the Academic Research Consortium definitions.[24] All deaths were considered to be CV in origin unless a definite non-CV cause was identified. Spontaneous MI (type 1 MI) was defined as the recurrence of symptoms accompanied by electrocardiographic changes, imaging evidence of new loss of viable myocardium, or new regional wall motion abnormalities in conjunction with an increase in cardiac troponin values, with at least one value above the 99th percentile upper reference limit. Periprocedural MI was not considered a clinical outcome. Stroke was defined as the presence of a neurological deficit requiring hospitalization, with clinically documented lesions on brain computed tomography or magnetic resonance imaging, as confirmed by a neurologist.

STATISTICAL ANALYSIS. Continuous variables were reported as mean ± SD or as median (IQR). The Kolmogorov-Smirnov test was used to assess the normal distribution of continuous variables, with the Student's *t*-test or Mann-Whitney *U* test applied accordingly. Categorical variables were reported as absolute numbers and percentages and compared using the chi-square test or Fisher exact test.

Biomarker levels at baseline and 1-month follow-up were compared using a paired *t*-test. Spearman's correlation coefficients were used to determine relationships between the measured biomarkers. The associations between biomarkers (as continuous variables) and the risk of clinical events during the stabilized period (between 1 month and 4 years post-PCI) were graphically presented using a restricted cubic spline with 3 degrees of freedom. Cumulative event rates were estimated using the Kaplan-Meier method and compared using the log-rank test. A Cox proportional hazards regression model was used to calculate HRs and 95% CIs. The proportionality assumption was assessed graphically using a log-minus-log plot and tested using Schoenfeld residuals. Multivariable Cox proportional hazard "Model 1" was constructed using known CV covariates (index MI presentation, age, sex, body mass index, current smoking, hypertension, diabetes mellitus, chronic kidney disease, use of drug-eluting stent, multivessel PCI, potent $P2Y_{12}$ inhibitor, beta-blocker, angiotensin blocker, and statin). "Model 2" was built with the same CV covariates (Model 1) and measured biomarkers of residual risk (quartile category). Multiplicative interactions between 4th quartile fibrinogen and prespecified subgroups were

FIGURE 1 Study Flow



CRP = high-sensitivity C-reactive protein; GNUH = Gyeongsang National University Hospital; hs- LDL = low-density lipoprotein; PCI = percutaneous coronary intervention; PRU = P2Y12 reaction unit.

assessed by adding cross-product terms (exposure × subgroup) to the Cox proportional hazards models; Wald tests provided the *P* for interaction. A Cox model using restricted cubic splines was constructed with 4 knots located at the 5th, 35th, 65th, and 95th percentiles of each biomarker distribution. Areas under the receiver-operating characteristic curves were estimated as time-dependent measures at prespecified time horizons under the cumulative definition, using inverse probability of censoring weighting. The incremental prognostic value of hemostatic measurements was evaluated by comparing Harrell's C-index, category-free net reclassification index, and integrated discrimination index.

Statistical analyses were performed using SPSS version 25 for Windows (SPSS-PC) and R version 3.6.2 (R Foundation for Statistical Computing). All tests were 2-tailed, and a *P* value <0.05 was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS AND CLINICAL EVENTS. From the initial cohort with all measured biomarkers (n = 2,984), patients with a clinical event during the 1-month follow-up (n = 56) and those without biomarkers measured at 1 month (n = 139) were excluded. Therefore, the final cohort included 2,789 patients who underwent serial biomarker measurements (Figure 1). The median follow-up of the participants was 2.2 years (IQR: 1.3-4.0 years).

Baseline characteristics of the final cohort are shown in Table 1. The mean age was 65.7 years, and 72.6% (2,026/2,789) of patients were male. Approximately half of the patients initially presented with acute myocardial infarction (51.6%, 1,440/2,789), and the majority were treated with drug-eluting stent (90.6%, 2,528/2,789). PCI procedures were most frequently performed for lesions with high-risk phenotype (American Heart Association/American College of Cardiology lesion type B2/C; 89.0%, 2,482/2,789). Furthermore, most patients were discharged on MT.

Over the follow-up period, ranging from 1 month to 4 years post-PCI, a total of 118 MACEs (4.2%) were reported, including 21 CV deaths (0.8%), 65 nonfatal MIs (2.3%), and 32 nonfatal strokes (1.1%).

TEMPORAL CHANGES IN BIOMARKERS BETWEEN BASELINE AND 1-MONTH FOLLOW-UP. Biomarker levels, except for fibrinogen, were significantly

TABLE 1 Baseline Characteristics of the Study Population (N = 2,789)

Age, y	65.7 ± 11.8
Male, n (%)	2,026 (72.6%)
Body mass index, kg/m^2	24.4 ± 3.3
Index presentation	
Stable angina	1,026 (36.8%)
Unstable angina	323 (11.6%)
NSTEMI	734 (26.3%)
STEMI	706 (25.3%)
Risk factors, n (%)	
Diabetes mellitus	834 (29.9%)
Hypertension	1,423 (51.0%)
Dyslipidemia	1,496 (53.6%)
Chronic kidney disease	415 (14.9%)
Current smoking	918 (32.9%)
Previous history, n (%)	
Previous MI	146 (5.2%)
Previous PCI	362 (13.0%)
Previous CABG	22 (0.8%)
Previous stroke	160 (5.7%)
Laboratory findings	
LV ejection fraction, %	56.4 ± 9.1
WBC, x 10^3/mm^3	9.0 ± 3.6
Hemoglobin, g/dL	13.5 ± 1.9
Platelet, x 10^3/mm^3	238.7 ± 67.2
GFR (MDRD), mL/min/1.73 m^2	82.8 ± 27.4
HbA_{1c}, %	6.4 ± 1.3
Procedural characteristics	
AHA/ACC lesion: type B2/C	2,482 (89.0%)
Multivessel disease, n (%)	1,249 (44.8%)
Mutivessel PCI, n (%)	517 (18.5%)
Target lesion, n (%)	
Left main coronary artery	42 (1.5%)
Left anterior descending artery	1,309 (46.9%)
Left circumflex artery	552 (19.8%)
Right coronary artery	883 (31.7%)
Others	3 (0.1%)
Treatment method	
Drug-eluting stent	2,528 (90.6%)
Bioresorbable scaffold	61 (2.2%)
Bare metal stent	12 (0.4%)
Drug-coated balloon	101 (3.6%)
POBA	87 (3.1%)
Number of stents	1.0 [IQR: 1.0, 2.0]
Stent length, mm	36.8 ± 22.1
Stent diameter, mm	3.2 ± 0.5
Discharge concomitant medications, n (%)	
Aspirin	2,767 (99.2%)
Type of $P2Y_{12}$ inhibitor	2,763 (99.1%)
Clopidogrel	2004 (71.9%)
Prasugrel	154 (5.5%)
Ticagrelor	605 (21.7%)
Beta-blocker	1787 (64.1%)
Angiotensin blocker	2006 (71.9%)
Calcium-channel blocker	210 (7.5%)
Statin	2,661 (95.4%)
Proton pump inhibitor	2040 (73.1%)

Values are mean ± SD or n (%).

ACC = American College of Cardiology; AHA = American Heart Association; CABG = coronary artery bypass graft; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; LV = left ventricular; MDRD = modification of diet in renal disease; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; POBA = plain optimal balloon angioplasty; STEMI = ST-segment elevation myocardial infarction; WBC = white blood cell.

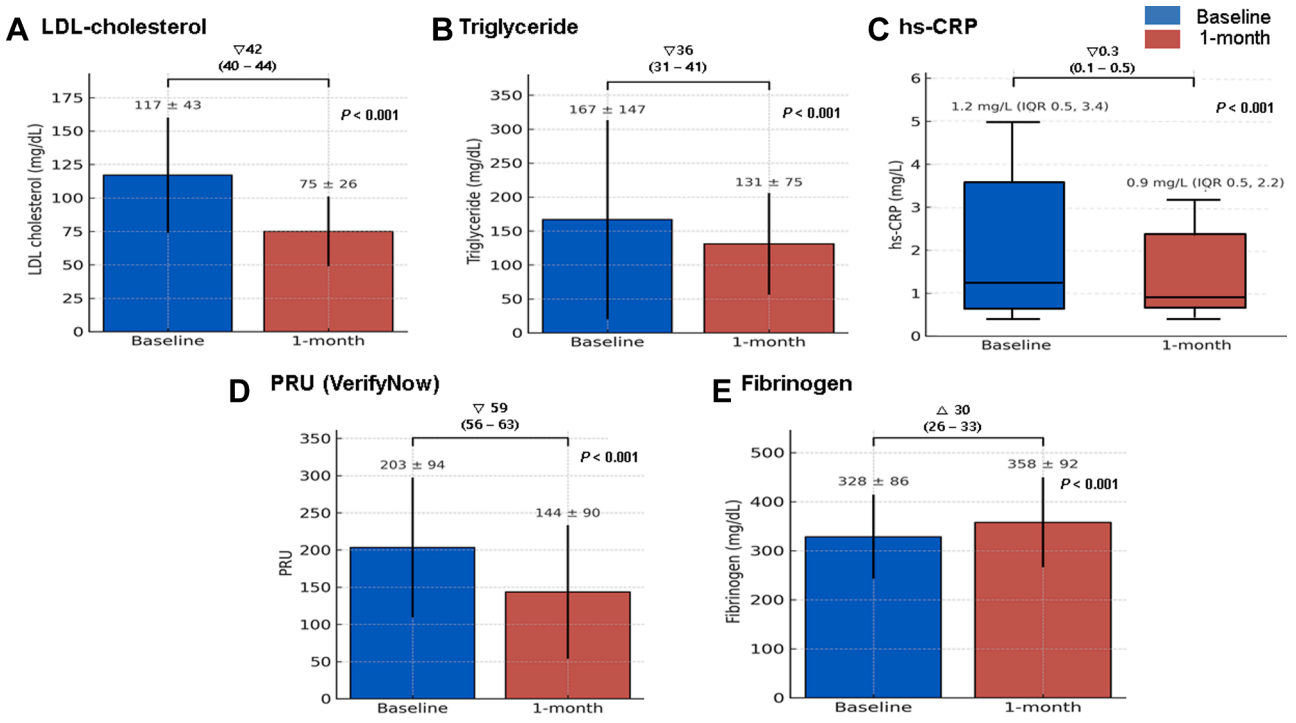
Continued in the next column

decreased during the first month of MT (all $P < 0.001$) (**Figure 2**). Between baseline and 1-month follow-up, LDL-cholesterol (117 ± 43-75 ± 26 mg/dL; ▽42 mg/dL), triglyceride (167 ± 147-131 ± 74 mg/dL; ▽36 mg/dL), and PRU levels (203 ± 94-144 ± 90; ▽59) all decreased. Despite a low baseline hs-CRP value (median: 1.2 mg/L [IQR: 0.5, 3.4]), there was a significant reduction at 1-month follow-up (median: 0.9 mg/L [IQR: 0.5, 2.2]; ▽0.3 mg/L). In contrast, fibrinogen levels showed a significant increase between baseline and 1-month follow-up (329 ± 86 to 359 ± 92 mg/dL; △30 mg/dL).

Table 2 shows the correlations between biomarkers measured after 1 month of medical treatment. LDL-cholesterol was weakly and positively correlated with triglycerides (r = 0.186; 95% CI: 0.150-0.221; $P < 0.001$), PRU (r = 0.134; 95% CI: 0.097-0.170; $P < 0.001$), and fibrinogen (r = 0.040; 95% CI: 0.003-0.077; $P = 0.033$) levels. Notably, the strongest correlation, albeit modest, was observed between the 1-month levels of hs-CRP and fibrinogen (r = 0.426; 95% CI: 0.395-0.456; $P < 0.001$) (Supplemental Figure 1). Conversely, a weak negative correlation was found between triglycerides and PRU (r = −0.057; 95% CI: −0.094 to −0.020; $P = 0.003$), whereas no significant correlation was observed between LDL cholesterol and hs-CRP (r = −0.014; 95% CI: −0.051 to 0.023; $P = 0.451$) or between PRU and fibrinogen (r = 0.020; 95% CI: −0.017 to 0.057; $P = 0.300$).

CLINICAL IMPACTS OF BASELINE BIOMARKER LEVELS ON LONG-TERM MACE. When clinical outcomes were compared based on the predefined cutoffs,[18-23] none of the 5 biomarkers measured at baseline showed a significant association with MACE occurring between 1 month and 4 years post-PCI (Supplemental Figure 2). In addition, no incremental associations were identified between the quartiles of these biomarkers and MACE occurring between 1 month and 4 years post-PCI (Supplemental Table 1).

FIGURE 2 Temporal Changes in Biomarkers Between Baseline and 1-Month Follow-Up



During the first month of medical therapy, all biomarker levels significantly decreased except fibrinogen. LDL-C (A), triglycerides (B), hs-CRP (C), and PRU (D) declined from baseline to 1 month, whereas fibrinogen (E) increased. Abbreviations as in Figure 1.

ASSOCIATIONS BETWEEN 1-MONTH BIOMARKER LEVELS AND LONG-TERM MACE. Restrictive spline curve models demonstrated that only hs-CRP (every 1 mg/L increase: HR: 1.009; 95% CI: 1.001-1.016; $P = 0.019$) and fibrinogen (every 10 mg/dL increase: HR: 1.002; 95% CI: 1.001-1.003; $P < 0.001$) measured at the 1-month follow-up were significantly associated with MACE occurrence (Supplemental Figure 3). Furthermore, the HRs of hs-CRP and fibrinogen were statistically significant when they exceeded the predefined cutoff values for high-risk phenotypes.[18-23]

Although the majority of patients adhered to the current MT strategy, a substantial portion of the cohort exhibited inadequate control of risk factors as indicated by biomarker levels (LDL-cholesterol ≥70 mg/dL, 53.2% [1,484/2,789]; triglycerides ≥150 mg/dL, 28.2% [786/2,789]; hs-CRP ≥2 mg/L, 27.6% [769/2,789]; PRU >208, 25.7% [718/2,789]; and fibrinogen >350 mg/dL, 46.3% [1,291/2,789]) (Figure 3). When clinical outcomes were compared according to these predefined high-risk phenotypes,[18-23] "fibrinogen >350 mg/dL" (adjusted HR: 1.386; 95% CI: 1.069-1.798; $P = 0.014$) and "hs-CRP ≥2 mg/L" (adjusted HR: 1.402; 95% CI: 0.944-2.082; $P = 0.094$) were associated with an increased risk of MACE during the period from 1 month to 4 years post-PCI. In contrast, high-risk phenotypes of the other biomarkers showed no significant associations with MACE.

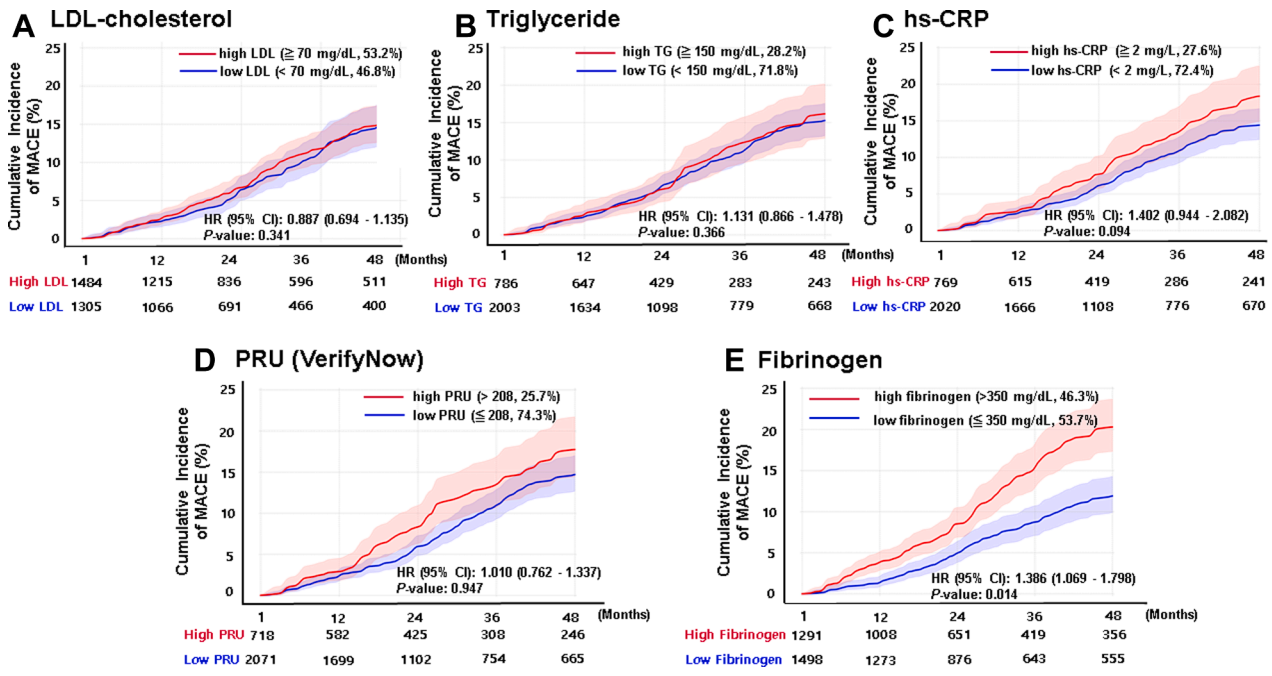
HRs FOR MACE ACCORDING TO QUARTILES OF 1-MONTH BIOMARKER LEVELS. Biomarkers were stratified into quartiles, and their clinical impact was

TABLE 2 Correlation Between Biomarkers Measured at 1-Month Follow-Up

	Triglyceride	hs-CRP	PRU	Fibrinogen
LDL-cholesterol	r = 0.186 $P < 0.001$	r = −0.014 $P = 0.451$	r = 0.134 $P < 0.001$	r = 0.040 $P = 0.033$
Triglyceride		r = −0.027 $P = 0.147$	r = −0.057 $P = 0.003$	r = 0.020 $P = 0.300$
hs-CRP			r = 0.074 $P < 0.001$	**r = 0.426** **$P < 0.001$**
PRU				r < 0.001 $P = 0.985$

hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; PRU = P2Y12 reaction unit.

FIGURE 3 Cumulative Rates of MACE: High-Risk Phenotypes of 1-Month Biomarker Levels



Adjustment was performed using known covariates such as index MI presentation, age, sex, body mass index, current smoking, hypertension, diabetes mellitus, chronic kidney disease, use of drug-eluting stents, multivessel PCI, potent $P2Y_{12}$ inhibitor, beta-blocker, angiotensin blocker, and statin. Among predefined high-risk phenotypes, elevated fibrinogen (>350 mg/dL) was significantly associated with higher MACE risk from 1 month to 4 years post-PCI, whereas other biomarkers were not. (A) LDL cholesterol, (B) Triglyceride, (C) hs-CRP, (D) PRU (verifynow), (E) Fibrinogen. MACE = major adverse cardiovascular event; MI = myocardial infarction; TG = triglyceride; other abbreviations as in **Figure 1**.

evaluated under the assumption of a linear effect across the distribution (**Table 3**). Supplemental Tables 2 to 6 present the baseline characteristics of the study population according to the quartile distribution of each biomarker. In the crude model, differences in HRs were observed across groups for LDL-cholesterol, hs-CRP, and fibrinogen levels (Supplemental Figure 4).

The covariate-adjusted HRs (95% CIs) for MACE (Model 1) across the quartiles of 1-month hs-CRP were as follows: 1.000 (reference), 1.369 (0.778-2.406; $P = 0.276$), 1.891 (1.112-3.214; $P = 0.019$), and 1.709 (1.005-2.906; $P = 0.048$) (**Figure 4A**, **Table 3**). The adjusted HRs (95% CIs) for MACE across 1-month fibrinogen levels were 1.000 (reference), 1.486 (0.828-2.667; $P = 0.184$), 1.830 (1.027-3.260; $P = 0.040$), and 2.472 (1.401-4.363; $P = 0.002$), corresponding to the quartile stratification. For 1-month LDL-cholesterol, only the second quartile demonstrated a significantly lower HR value compared to the first quartile (reference) (HR: 0.562; 95% CI: 0.324-0.975; $P = 0.040$). There were no significant differences in the HRs of triglyceride and PRU quartiles.

When the analysis was further adjusted for each of the biomarkers simultaneously (Model 2) (**Figure 4B**, **Table 3**), the observed HRs (95% CIs) for MACE across the quartiles of 1-month hs-CRP were attenuated and no longer statistically significant: 1.000 (reference), 1.170 (0.657-2.083; $P = 0.594$), 1.563 (0.902-2.710; $P = 0.111$), and 1.258 (0.704-2.250; $P = 0.439$). However, the HRs for MACE increased proportionally across the quartiles of 1-month fibrinogen levels: 1.000 (reference), 1.447 (0.800-2.617; $P = 0.222$), 1.648 (0.910-2.983; $P = 0.099$), and 2.225 (1.201-4.122; $P = 0.011$). Other biomarkers measured at 1 month did not show an increased association with MACE occurrence according to the quartiles. In addition, we evaluated the comparative HRs of MACE occurrence across subgroups based on 1-month fibrinogen levels (**Figure 5**). The 4th quartile of fibrinogen (>403 mg/dL) was associated with worse outcomes across subgroups compared with other quartiles (all $P_{interaction}$ values ≥ 0.136).

TABLE 3 Residual Risk Factors at 1 Month After PCI and MACE

	Crude HR (95% CI)	*P* Value	Model 1: Adjusted HR (95% CI)	*P* Value	Model 2: Adjusted HR (95% CI)	*P* Value
A. LDL cholesterol						
Quartile 1 (≦58 mg/dL)	1.000	-	1.000	-	1.000	-
Quartile 2 (59-71 mg/dL)	0.559 (0.327-0.956)	0.034	0.562 (0.324-0.975)	0.040	0.567 (0.326-0.988)	0.045
Quartile 3 (72-87 mg/dL)	0.660 (0.400-1.090)	0.105	0.745 (0.445-1.246)	0.262	0.674 (0.398-1.142)	0.142
Quartile 4 (>87 mg/dL)	0.797 (0.494-1.285)	0.352	0.954 (0.578-1.575)	0.854	0.879 (0.521-1.484)	0.629
B. Triglyceride						
Quartile 1 (≦84 mg/dL)	1.000	-	1.000	-	1.000	-
Quartile 2 (85-115 mg/dL)	1.284 (0.782-2.109)	0.322	1.410 (0.850-2.340)	0.183	1.438 (0.859-2.409)	0.167
Quartile 3 (116-157 mg/dL)	1.016 (0.607-1.701)	0.951	1.194 (0.700-2.038)	0.515	1.131 (0.651-1.965)	0.662
Quartile 4 (>157 mg/dL)	1.018 (0.599-1.728)	0.949	1.264 (0.718-1.039)	0.417	1.213 (0.673-2.185)	0.521
C. hs-CRP						
Quartile 1 (≦0.5 mg/L)	1.000	-	1.000	-	1.000	-
Quartile 2 (0.6-0.9 mg/L)	1.391 (0.794-2.436)	0.249	1.369 (0.778-2.406)	0.276	1.170 (0.657-2.083)	0.594
Quartile 3 (1.0-2.2 mg/L)	2.044 (1.215-3.438)	0.007	1.891 (1.112-3.214)	0.019	1.563 (0.902-2.710)	0.111
Quartile 4 (>2.2 mg/L)	2.027 (1.216-3.379)	0.007	1.709 (1.005-2.906)	0.048	1.258 (0.704-2.250)	0.439
D. PRU						
Quartile 1 (≦69)	1.000	-	1.000	-	1.000	-
Quartile 2 (70-152)	0.682 (0.379-1.226)	0.200	0.827 (0.418-1.637)	0.585	0.882 (0.442-1.760)	0.721
Quartile 3 (153-210)	1.107 (0.661-1.853)	0.699	1.167 (0.603-2.260)	0.646	1.160 (0.599-2.246)	0.659
Quartile 4 (>210)	0.915 (0.539-1.553)	0.741	0.790 (0.385-1.619)	0.519	0.859 (0.415-1.777)	0.682
E. Fibrinogen						
Quartile 1 (≦296 mg/dL)	1.000	-	1.000	-	1.000	-
Quartile 2 (297-344 mg/dL)	1.748 (0.985-3.101)	0.056	1.486 (0.828-2.667)	0.184	1.447 (0.800-2.617)	0.222
Quartile 3 (345-403 mg/dL)	1.969 (1.113-3.485)	0.020	1.830 (1.027-3.260)	0.040	1.648 (0.910-2.983)	0.099
Quartile 4 (>403 mg/dL)	3.272 (1.921-5.574)	<0.001	2.472 (1.401-4.363)	0.002	2.225 (1.201-4.122)	0.011

Model 1 (covariate-adjusted model): adjusted for index MI presentation, age, sex, body mass index, current smoking, hypertension, diabetes mellitus, chronic kidney disease, use of drug-eluting stent, multivessel PCI, use of potent $P2Y_{12}$ inhibitor, use of beta-blocker, angiotensin blocker, or statin at discharge. Model 2 (biomarker-adjusted model): adjusted for Model 1 + 1-month biomarkers of residual risks (LDL cholesterol, triglyceride, hs-CRP, PRU, and fibrinogen).

MACE = major adverse cardiovascular event; other abbreviations as in Tables 1 and 2.

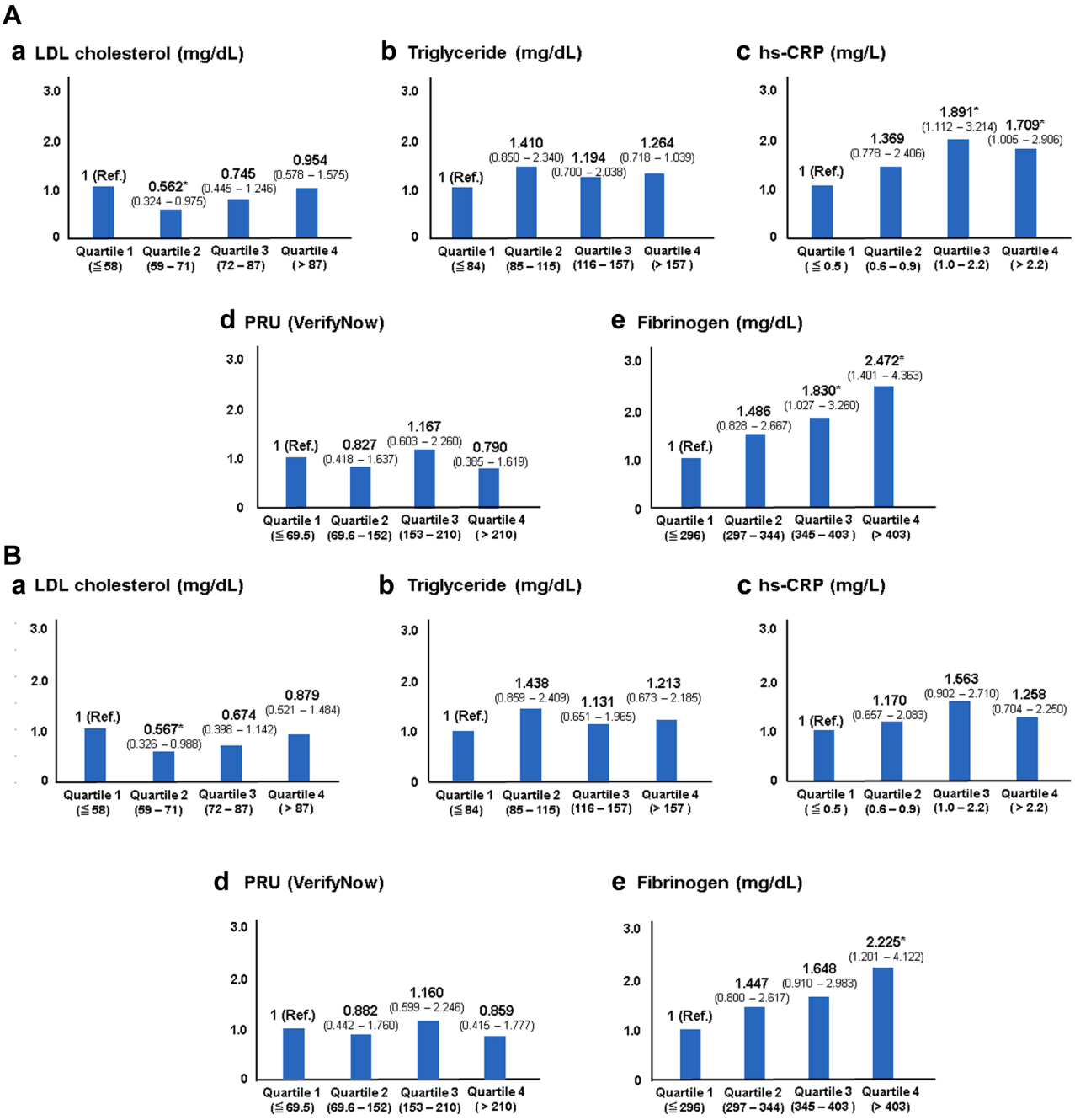
INCREMENTAL PROGNOSTIC VALUE OF HIGH FIBRINOGEN PHENOTYPE. The incremental prognostic value of a high fibrinogen phenotype (>350 mg/dL) measured 1-month post-PCI was evaluated against a clinical-variable model (**Figure 6**, Supplemental Figure 5). Incorporation of this phenotype into the conventional model improved reclassification (net reclassification index = 0.184; 95% CI: 0.001-0.366; $P = 0.049$) and discrimination (integrated discrimination index = 0.013; 95% CI: 0.005-0.025; $P = 0.026$).

DISCUSSION

To the best of our knowledge, this study is the first to demonstrate the independent prognostic implication of elevated fibrinogen levels in predicting long-term residual CV risks following PCI in patients receiving MT. The prognostic impacts of other residual risk factors, including lipid phenotype (LDL-cholesterol and triglyceride), inflammation (hs-CRP), and platelet function (PRU), were also evaluated. We identified a strong association between coagulation and inflammation, highlighting their critical roles in the development of post-PCI atherothrombotic events. The key findings are as follows: 1) even after 1 month of MT, high-risk phenotypes of residual risk biomarkers were frequently observed (25.7%∼53.2%); 2) residual risk biomarkers decreased significantly during MT, except for fibrinogen levels, which increased significantly (all P values < 0.001); 3) among residual risk biomarkers on MT, fibrinogen levels were significantly correlated with hs-CRP levels ($r = 0.426$; $P < 0.001$); and 4) high-risk phenotypes of fibrinogen and hs-CRP measured during MT were significantly associated with an increased risk of recurrent atherothrombotic events (**Central Illustration**). This study emphasizes the importance of dynamic assessment of residual CV risks (indicated by biomarkers) as potential tools for mitigating the long-term atherothrombotic risk in high-risk CAD patients.

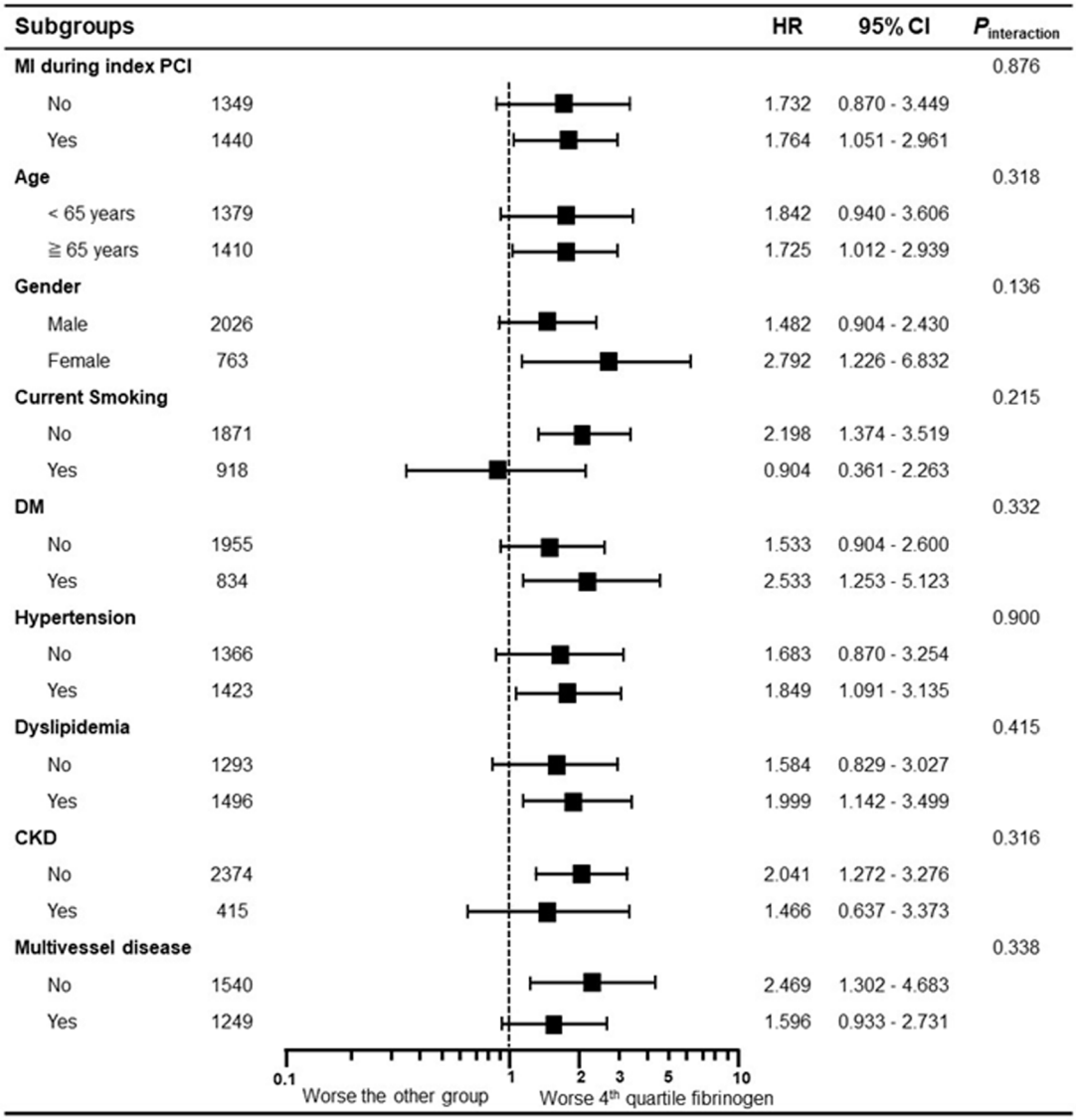
RESIDUAL CV RISKS FOR CV DISEASE. Over recent decades, aggressive MT for ASCVD has advanced markedly, improving recognition and treatment of

FIGURE 4 HRs for MACE Adjusted by CV Covariates and CV Covariates and 1-Month Biomarkers



(A) CV covariates; (B) CV covariates and 1-month biomarkers. Adjustment was performed using known covariates such as index MI presentation, age, sex, body mass index, current smoking, hypertension, diabetes mellitus, chronic kidney disease, use of drug-eluting stents, multivessel PCI, potent $P2Y_{12}$ inhibitor, beta-blocker, angiotensin blocker, and statin. CV = cardiovascular; other abbreviations as in Figures 1 and 3.

FIGURE 5 HRs for MACE Across Subgroups: 4th Quartile Fibrinogen vs Others

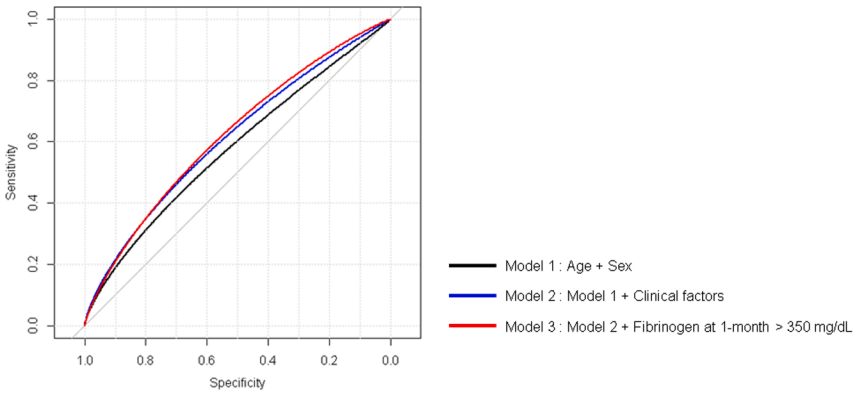


Adjustment was performed using known covariates such as index MI presentation, age, sex, body mass index, current smoking, hypertension, diabetes mellitus, chronic kidney disease, use of drug-eluting stents, multivessel PCI, potent $P2Y_{12}$ inhibitor, beta-blocker, angiotensin blocker, and statin. CKD = chronic kidney disease; DM = diabetes mellitus; other abbreviations as in Figures 1 and 3.

key risk factors—LDL-cholesterol, hypertriglyceridemia, glucose, inflammation, and heightened platelet reactivity.[2-7,10,11,16,21,25] LDL-cholesterol lowering with potent statins remains a cornerstone of primary and secondary prevention.[18,19] Benefits are further enhanced by the introduction of proprotein convertase subtilisin-kexin type 9 inhibitors. However, the absolute risk reductions observed in the clinical trials were modest at 1.5% and 1.6%, respectively, with ~10% experiencing recurrent CV events during the follow-up period.[5,26]

Inflammation markers (eg, hs-CRP, interleukin [IL]-1ß, and IL-6) are linked to atherosclerosis and adverse events. Adding anti-inflammatory therapy to standard care may reduce recurrent atherothrombotic events.[6,7,21,25] In patients with a history of MI,

FIGURE 6 **Incremental Prognostic Value of 1-Month Fibrinogen for MACE Occurrence**



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	0.567 (0.512 – 0.623)	Reference		Reference				Reference			
Model 2	0.616 (0.562 – 0.670)	0.021	Reference	0.065 (0.003 – 0.516)	0.042	Reference		0.039 (0.026 – 0.052)	<0.001	Reference	
Model 3	0.620 (0.666 – 0.673)	0.035	0.778	0.229 (0.045– 0.633)	0.017	0.184 (0.001 – 0.366)	0.049	0.058 (0.042 – 0.075)	<0.001	0.013 (0.005 – 0.025)	0.026

Prognostic values of models predicting 4-year major adverse cardiovascular event were compared using Harrell's C-index, net reclassification index, and integrated discrimination index. 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 index acute myocardial infarction presentation, body mass index, hypertension, diabetic mellitus, dyslipidemia, current smoking, chronic kidney disease, use of drug-eluting stent, multivessel PCI, potent $P2Y_{12}$ inhibitor, angiotensin blockade, and statin (Model 2). Model 3 with high fibrinogen phenotype (>350 mg/dL) at 1-month post-PCI showed further increase in discrimination and reclassification ability for 4-year major adverse cardiovascular event when compared with Model 2. IDI = integrated discrimination index; NRI = net reclassification index; other abbreviations as in **Figures 1 and 3**.

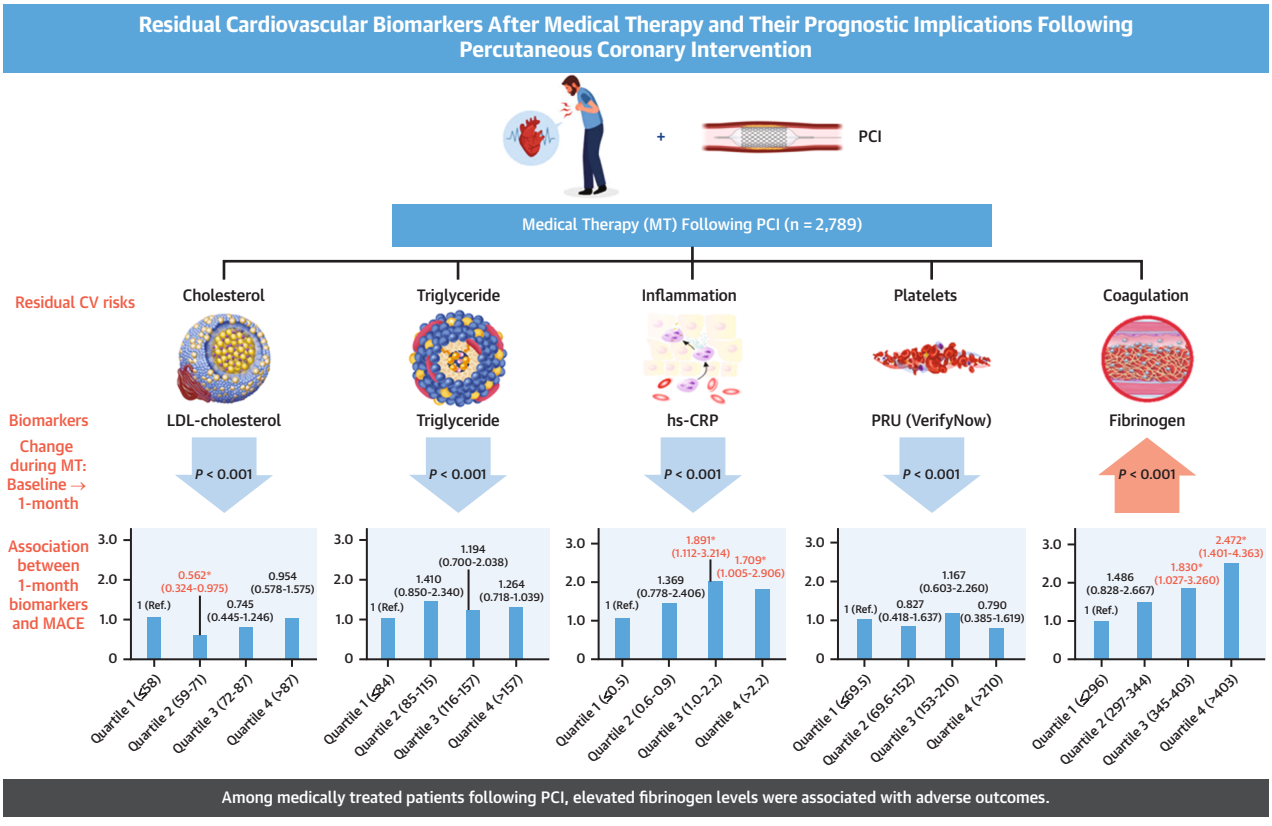
canakinumab, a direct IL-1ß inhibitor, lowered MACE and rehospitalization for heart failure, but increased neutropenia and fatal sepsis.[6] In contrast, low-dose colchicine therapy improved CV outcomes without a sepsis signal, yet uptake remains limited by mixed data and gastrointestinal/other adverse effects.[7] Further work is needed to define safe, cost-effective inflammation-targeted strategies beyond statins.

High platelet reactivity has long been a key risk factor for post-PCI ischemic events, largely shown in the clopidogrel era with early-generation stents. About 30% of Caucasians exhibit clopidogrel resistance, which is consistently linked to ischemic events.[23] Dual antiplatelet therapy based on potent $P2Y_{12}$ inhibitor vs clopidogrel reduced MACE but increased bleeding in acute coronary syndrome patients, and residual risk remains ~10%.[2,3] To address these limitations, recent studies have suggested de-escalation strategies—shorter dual antiplatelet therapy or less-potent agents—which show clinical benefit.[27,28] Overall, the benefit of intensive platelet inhibition appears greatest early in acute coronary syndrome patients with contemporary PCI and current MT.

CLINICAL SIGNIFICANCE OF THE THROMBO-INFLAMMATORY AXIS. Coagulation signaling drives atherosclerosis and thrombosis through promoting endothelial activation/dysfunction, smooth-muscle proliferation, inflammation, and foam-cell formation via protease-activated receptor.[29,30] Accordingly, targeted modulation of this pathway may slow plaque progression and reduce ischemic events.

The association between plasma fibrinogen and CV disease is supported by extensive laboratory and clinical evidence.[31-34] Fibrinogen may promote atherothrombosis through several biologic mechanisms[31,32]: 1) upregulation as an IL-6-driven acute-phase reactant; 2) serving as the principal ligand for activated platelet glycoprotein IIb/IIIa, thereby cross-linking platelets and stabilizing aggregates; 3) facilitating platelet-leukocyte crosstalk, enhancing a pro-inflammatory, procoagulant milieu; 4) generating dense, thin-fiber networks with small pores that are relatively resistant to fibrinolysis; 5) raising plasma viscosity by promoting red blood cell aggregation/rouleaux at low shear; and 6) engaging endothelial and immune receptors to amplify adhesion and inflammatory signaling.

CENTRAL ILLUSTRATION **Changes of Residual CV Risks During MT and Their Prognostic Implications After PCI**



Cho JH, et al. JACC Adv. 2026;5(2):102498.

MT = medical therapy; other abbreviations as in Figures 1, 3, and 4.

Moreover, this coagulation factor is recognized as an independent major risk factor for CV disease.[31,32] In the present study, fibrinogen levels were significantly elevated during MT after PCI, unlike other residual risk biomarkers. This high-risk phenotype is strongly associated with an increased risk of recurrent atherothrombotic events. Although this study is a hypothesis-generating observational study, it is consistent with previous research suggesting that incorporating fibrinogen measurement into routine CV risk assessments may improve the accuracy of predicting future CV events.[33,34] As a critical biomarker, fibrinogen may have a potential to guide personalized prevention strategies to reduce residual CV risks even during MT. Further research is needed to standardize fibrinogen measurement and determine whether fibrinogen-lowering therapies improve ASCVD outcomes.

Fibrinogen and hs-CRP are nonspecific hepatic acute-phase reactants induced via the same IL axis, playing crucial roles in the inflammation-coagulation cascade.[35] During inflammatory responses, fibrinogen rises and exerts pro-inflammatory effects, reinforcing the atherogenic profiles of both biomarkers.[33,34] We showed that thromboelastography-measured platelet-fibrin clot strength correlates closely with inflammation (ie, hs-CRP).[36] In addition, this study confirmed that these biomarkers continue to interact even during MT ($r = 0.426$, $P < 0.001$) (Supplemental Figure 1).

Inflammation, ischemia/hypoxia, and oxidative stress can stimulate IL-6 production. IL-6 in turn induces the liver to release acute phase reactants, such as CRP, fibrinogen, and plasminogen activator inhibitor-1.[33-36] Contrary to fibrinogen level, hs-CRP level showed a significant decrease after 1 month of

MT. Although fibrinogen is synthesized primarily in the liver, certain pathological or inflammatory conditions can also trigger its production in extrahepatic tissues. Local inflammation or injury may stimulate fibrinogen expression and release from epithelial cells (respiratory and intestinal tracts), endothelial cells (vascular system), vascular smooth muscle cells, fibroblasts (dermal and synovial tissues), and astrocytes/microglia in the brain. Therefore, fibrinogen levels after clinical events may be influenced not only by IL-6-mediated hepatic synthesis but also by production from other systems. Moreover, standard post-PCI regimens are not coagulation targeted.

DYNAMIC CHANGE OF RESIDUAL ATHEROTHROMBOTIC CV RISKS. A key finding of this study is the early post-PCI shift in biomarker levels; because MT alters baseline CV risk factors, dynamic biomarker assessment is essential for accurate long-term prognostication.[37] After 1 month of MT, LDL-cholesterol, triglycerides, hs-CRP, and PRU fell significantly from baseline, whereas fibrinogen increased. The independent link between a high-fibrinogen phenotype and outcomes suggests contemporary MT insufficiently targets coagulation pathways—and that doing so may reduce residual CV risk. In the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial, adding low-dose rivaroxaban to aspirin reduced thrombotic events but increased major bleeding, tempering the net benefit.[4] Factor XI inhibitors are a promising way to modulate coagulation with less bleeding, but a recent large trial showed asundexian 50 mg once daily led to more stroke/systemic embolism than apixaban in patients with atrial fibrillation at risk for stroke.[38] Further studies are needed to define optimal dosing and identify the patient populations most likely to benefit from Factor XI inhibitors.

LDL-CHOLESTEROL PARADOX. Intensive LDL-cholesterol lowering reduces ASCVD in a dose-dependent fashion.[5,39,40] The "LDL-cholesterol paradox" refers to the unexpected finding that, in certain populations, lower LDL-cholesterol levels are associated with similar or worse health outcomes compared to higher levels.[41,42] This paradox has been observed in older adults and patients with advanced heart failure, chronic inflammatory diseases, and malnutrition, where low levels may reflect poor overall health rather than offering protection against CV events.[43] Thus, CV risk assessment should weigh clinical context rather than LDL-cholesterol alone. Further study is needed to clarify the benefits and risks of prolonged exposure to pharmacologically very low LDL-cholesterol.

Recent studies suggest limited benefit from further lowering residual LDL-cholesterol even in high-risk patients.[44-46] In a large-scale registry involving ST-segment elevation MI patients (n = 44,563), LDL-cholesterol showed a J-shaped relationship with in-hospital mortality, with levels <75 mg/dL associated with higher risk.[44] In a pooled cohort of statin-treated patients with or at high ASCVD risk (n = 31,245), residual inflammatory risk predicted MACE (highest vs lowest hs-CRP quartile: adjusted HR: 1.31; 95% CI: 1.20-143; $P < 0.0001$), whereas residual LDL-cholesterol risk was neutral (highest vs lowest LDL-cholesterol quartile: adjusted HR: 1.07; 95% CI: 0.98-1.17; $P = 0.11$).[45] Consistent with prior reports, patients with very low LDL-cholesterol on MT (quartile 1: LDL-cholesterol ≦58 mg/dL) had modestly higher MACE than those with low LDL-cholesterol (quartile 2: 59 ≦ LDL ≦71 mg/dL) (HR: 1.764; 95% CI: 1.012-3.067; $P = 0.045$). This underscores the need for large, well-designed trials to define optimal LDL-cholesterol targets in low-intermediate-risk CAD, beyond the limits of current registries and observational studies.

STUDY LIMITATIONS. First, this retrospective analysis of a prospective registry is vulnerable to residual confounding despite adjustments; additionally, 6.5% of patients were excluded for missing data, which may bias results. Second, the long follow-up yielded few CV events—likely reflecting a stabilized East Asian cohort with lower event rates[36]—raising concerns about overfitting and limiting generalizability. Third, the optimal cadence for dynamic CV risk assessment in high-risk CAD is uncertain; a 1-month MT window may be too short to capture full biologic effects. Fourth, while fibrinogen's role as a standalone coagulation biomarker is debated, prior studies support its prognostic value for residual risk after PCI.[33-36] Finally, baseline biomarker-outcome associations during the stabilized phase were weak, warranting confirmation in large prospective studies.

CONCLUSIONS

In this cohort of medically treated PCI patients, elevated fibrinogen levels were associated with adverse outcomes. Studies are needed to understand these associations and determine whether additional therapies could benefit these high-risk patients.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In high-risk CAD patients undergoing PCI, dynamic monitoring of atherothrombotic biomarkers during MT is crucial for residual risk assessment. Thromboinflammatory axis was identified as a strong, independent predictor of recurrent atherothrombotic events. Identifying a fibrinogen phenotype could enhance clinical risk stratification, support closer surveillance, and inform timely intensification of targeted therapy, thereby personalizing secondary prevention in CAD patients.

TRANSLATIONAL OUTLOOK: Despite strong prognostic value, fibrinogen's therapeutic role remains undefined. Translational studies should test whether fibrinogen-lowering therapies reduce recurrent events in CAD patients during guideline-directed MT and resolve methodological hurdles—assay standardization and workflow integration—to enable routine risk stratification. Bridging prognostic evidence to therapy could advance precision care for atherothrombosis.

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KEY WORDS cardiovascular risk, coronary artery disease, fibrinogen, inflammation, lipid, platelet reactivity

APPENDIX For supplemental tables and figures, please see the online version of this paper.