

UC San Diego

UC San Diego Previously Published Works

Title

Elevated Baseline Serum Fibrinogen: Effect on 2-Year Major Adverse Cardiovascular Events Following Percutaneous Coronary Intervention

Permalink

<https://escholarship.org/uc/item/8kj677zz>

Journal

Journal of the American Heart Association, 6(11)

ISSN

2047-9980

Authors

Ang, Lawrence
Behnamfar, Omid
Palakodeti, Samhita
[et al.](#)

Publication Date

2017-11-01

DOI

10.1161/jaha.117.006580

Copyright Information

This work is made available under the terms of a Creative Commons Attribution-NonCommercial-NoDerivatives License, available at <https://creativecommons.org/licenses/by-nc-nd/4.0/>

Peer reviewed

Elevated Baseline Serum Fibrinogen: Effect on 2-Year Major Adverse Cardiovascular Events Following Percutaneous Coronary Intervention

Lawrence Ang, MD; Omid Behnamfar, MD; Samhita Palakodeti; Felice Lin, MD; Ali Pourdjabbbar, MD; Mitul P. Patel, MD; Ryan R. Reeves, MD; Ehtisham Mahmud, MD

Background—Elevated fibrinogen is associated with short-term major adverse cardiovascular events (MACE) after percutaneous coronary intervention, but the relation with late MACE is unknown.

Methods and Results—Baseline demographics and 2-year MACE were recorded among subjects undergoing nonemergent percutaneous coronary intervention. A total of 332 subjects (66.6 ± 19.5 years, 69.9% male, 25.3% acute coronary syndrome) were enrolled. Two-year MACE (periprocedural myocardial infarction 9.0%, rehospitalization 6.3%, revascularization 12.7%, non-periprocedural myocardial infarction 4.5%, stent thrombosis 0.9%, stroke 1.8%, and death 0.6%) were associated with higher fibrinogen (352.8 ± 123.4 mg/dL versus 301.6 ± 110.8 mg/dL; $P < 0.001$), longer total stent length (40.1 ± 25.3 mm versus 32.1 ± 19.3 mm; $P = 0.004$), acute coronary syndrome indication (38.7% versus 17.8%; $P < 0.001$), number of bare-metal stents (0.5 ± 1.1 versus 0.2 ± 0.5 ; $P = 0.002$), and stent diameter ≤ 2.5 mm (55.8% versus 38.4%, $P = 0.003$). No relation between platelet reactivity and 2-year MACE was observed. Fibrinogen ≥ 280 mg/dL (odds ratio [OR] 3.0, confidence interval [CI], 1.6–5.4, $P < 0.001$), total stent length ≥ 32 mm (OR 2.2, CI, 1.3–3.8, $P < 0.001$), acute coronary syndrome indication (OR 4.1, CI, 2.3–7.5, $P < 0.001$), any bare-metal stents (OR 3.2, CI, 1.6–6.1, $P < 0.001$), and stent diameter ≤ 2.5 mm (OR 2.0, CI, 1.2–3.5, $P = 0.010$) were independently associated with 2-year MACE. Following a landmark analysis excluding periprocedural myocardial infarction, fibrinogen ≥ 280 mg/dL remained strongly associated with 2-year MACE (37.0% versus 17.4%, log-rank $P < 0.001$).

Conclusions—Elevated baseline fibrinogen level is associated with 2-year MACE after percutaneous coronary intervention. Acute coronary syndrome indication for percutaneous coronary intervention, total stent length implanted, and use of bare-metal stents or smaller-diameter stents are also independently associated with 2-year MACE, while measures of on-thienopyridine platelet reactivity are not. (*J Am Heart Assoc.* 2017;6:e006580. DOI: 10.1161/JAHA.117.006580.)

Key Words: fibrinogen • major adverse cardiovascular events • percutaneous coronary intervention • platelet aggregation

Elevated serum fibrinogen level is associated with major adverse cardiovascular events (MACE) after percutaneous coronary intervention (PCI) for patients with both elective and urgent indications.^{1–3} Aside from being an acute phase reactant of inflammation, fibrinogen has crucial mechanistic roles in platelet crosslinking, platelet aggregation, and thrombus formation.⁴ Previously, it has been identified as a risk factor for both short- and long-term adverse cardiovascular events.^{5–14} More recently, elevated baseline fibrinogen

level has been reported to be associated with higher on-thienopyridine platelet reactivity, periprocedural myocardial infarction (MI), and combined MACE within 12 months of the index PCI.^{1–3,15} The present study was performed to determine whether a longer term adverse relationship between baseline serum fibrinogen level, on-thienopyridine platelet reactivity, and ischemic cardiovascular events exists in patients undergoing PCI for both elective or acute coronary syndrome (ACS) indications.

From the Division of Cardiovascular Medicine, San Diego Sulpizio Cardiovascular Center, University of California, La Jolla, CA.

Correspondence to: Ehtisham Mahmud, MD, Cardiovascular Medicine, UCSD Sulpizio Cardiovascular Center, 9434 Medical Center Dr, La Jolla, CA 92037-7784. E-mail: emahmud@ucsd.edu

Received May 4, 2017; accepted October 3, 2017.

© 2017 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Methods

Patient Selection

The study was approved by the Institutional Review Board of the University of California, San Diego and the requirement for informed written consent was waived. Data from patients with coronary artery disease who underwent successful PCI with stenting or balloon angioplasty alone and measurement of serum fibrinogen within 24 hours of PCI were retrospectively gathered

Clinical Perspective

What Is New?

- This study uniquely identifies baseline serum fibrinogen as a significant, independent risk factor for late major adverse cardiovascular events after percutaneous coronary intervention (PCI).
- The association between baseline fibrinogen level and cardiovascular events in the post-PCI context and extending to 2-year follow-up after index PCI are novel study contributions.
- Additional analyses uniquely highlight the independent association between serum fibrinogen and 1) objective, clinically relevant ischemic cardiovascular events, and 2) nonacute events occurring >24 hours after PCI.

What Are the Clinical Implications?

- Incorporation of fibrinogen level measurement may strengthen the ability of ischemic risk prediction strategies to identify individuals at higher risk of late major adverse cardiovascular events occurring 12 to 24 months after PCI.
- Individuals with elevated fibrinogen could potentially benefit from prolonged dual-antiplatelet therapy extended beyond 12 months after index PCI or potentially oral direct thrombin inhibitors.

from a PCI database and electronic medical record. All subjects had been pretreated with a thienopyridine for ≥ 7 days before PCI or received a loading dose of clopidogrel 600 mg or prasugrel 60 mg at least 2 hours before PCI. Those with ST-segment-elevation MI within 72 hours before recruitment, age <18 years, or use of intravenous glycoprotein IIb/IIIa inhibitor within 30 days before index PCI were excluded.

Measurements

Baseline subject characteristics, history of cardiovascular disease and comorbidities, serum laboratory measurements, procedural details, postprocedure cardiac marker levels, and 2-year MACE were recorded. Baseline serum laboratory measurements included complete blood count, creatinine, complete lipid panel, C-reactive protein, fibrinogen, and cardiac markers of ischemic injury (creatinine kinase-myocardial band, troponin I and/or troponin T) and were performed at the University of California, San Diego Medical Center. Cardiac markers of ischemic injury were measured every 6 to 8 hours following PCI until hospital discharge or up to 24 hours. Platelet function testing was performed during PCI using the VerifyNow P2Y12 assay (Accumetrics, San Diego, CA) with on-treatment platelet reactivity reported as “result” P2Y12 reaction units (PRU) and maximal platelet activation

using high-concentration thrombin receptor-activating protein reported as “base” PRU. Platelet inhibition or percent change in result PRU from baseline (calculated as $[1 - (\text{result PRU}) / (\text{base PRU})] \times 100\%$)¹⁶ was also reported as available. MACE included periprocedural MI (<24 hours after PCI: creatine kinase-myocardial band elevation at least 3-fold greater than the 99% upper limit of normal with normal baseline, or >20% rise from stable elevated baseline),¹⁷ nonperiprocedural MI (>24 hours after PCI) with or without concurrent ST-segment elevation, rehospitalization for a suspected ACS, unplanned repeat revascularization, definite stent thrombosis, transient ischemic attack, ischemic or hemorrhagic stroke, or any death.

Statistical Analysis

The study was performed using a nested case-control design and powered to detect a 52 mg/dL difference in mean fibrinogen level between outcome groups (361 mg/dL versus 309 mg/dL, overall SD 109 mg/dL) at 6 months, using α 0.05 and power 0.8. This analysis revealed that at least 69 outcome events were needed.¹ Collection of study data from eligible subjects was continued until 69 MACE events were recorded at 6 months, then enrollees had both 6-month and 2-year MACE events identified. Results from the combined 2-year MACE are reported.

Variables of interest were compared across MACE outcome groups using Student *t* tests or χ^2 analysis as appropriate. Significant continuous variables underwent receiver-operator characteristic curve analysis to determine cutoff values with greatest sum sensitivity and specificity in predicting events. Factors having significant univariate relationships with MACE ($P < 0.05$) were entered together into a binary logistic multiple regression model. Significant relationships and Kaplan-Meier event-free survival are reported. Interaction testing between significant variables was also performed.

Results

A total of 332 subjects were enrolled (mean age 66.6 ± 19.5 years, 69.9% men). The study population had a high prevalence of risk factors for cardiovascular disease (42.9% diabetes mellitus, 90.6% hypertension, 87.2% hyperlipidemia), and prior coronary revascularization (61.4% PCI, 17.0% coronary artery bypass grafting) (Table 1). The majority of subjects underwent elective PCI while a quarter of the study population had an urgent indication for index PCI (12.3% non-ST-segment-elevation MI, 13.0% unstable angina). An average of 1.4 ± 0.7 lesions were treated using 1.7 ± 1.1 stents (83.4% using drug-eluting stents, 16.3% using at least 1

Table 1. Study Population Baseline Characteristics

	Mean±SD or %
Age, y	66.6±19.5
Male sex, %	69.9
Body mass index, kg/m ²	28.6±5.9
Past MI, %	32.1
Past PCI, %	61.4
Past CABG, %	17.0
Hypertension, %	90.6
Hyperlipidemia, %	87.2
Family history of CVD, %	46.7
Diabetes mellitus, %	42.9
Smoking, %	14.4
LV ejection fraction, %	57.7±12.2
Acute coronary syndrome, %	25.3
NSTEMI, %	12.3
Unstable angina, %	13.0

CABG indicates coronary artery bypass grafting; CVD, cardiovascular disease; LV, left ventricular; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention.

bare-metal stent [BMS]) in each patient, though a small minority underwent balloon angioplasty alone (4.8%).

Two-year MACE after PCI occurred in 123 subjects (total events 35.8%: periprocedural MI alone 9.0%, rehospitalization for suspected ACS 6.3%, urgent revascularization 12.7%, non–ST-segment–elevation MI or ST-segment–elevation MI 4.5%, definite stent thrombosis 0.9%, transient ischemic attack or stroke 1.8%, all death 0.6%). Baseline subject characteristics, cardiac risk factors, comorbidities, and pharmacotherapy were compared between those with and without MACE (Table 2). Serum fibrinogen level (352.8±123.4 mg/dL versus 301.6±110.8 mg/dL, $P<0.001$) and white blood cell count (7.7±2.8 10^3 cells/dL versus 7.1±2.5 10^3 cells/dL, $P=0.024$) were higher in those with MACE, but other markers of systemic inflammation were similar between outcome groups (C-reactive protein: 1.2±2.7 mg/L versus 0.8±1.5 mg/L, $P=0.225$; platelet count: 228.3±89.8 10^3 cells/dL versus 215.4±65.5 10^3 cells/dL, $P=0.172$). Platelet reactivity measurements were similar between cohorts with and without MACE (base PRU: 330.0±58.7 versus 316.7±64.8, $P=0.633$; result PRU: 146.3±30.0 versus 167.1±102.7, $P=0.282$; platelet inhibition: 37.9±25.2% versus 37.1±26.4%, $P=0.893$; PRU >208: 42.9% versus 30.6%, $P=0.348$; PRU >230: 28.6% versus 27.8%, $P=0.949$; platelet inhibition <30%: 46.1% versus 45.7%, $P=0.959$). Those with 2-year MACE more commonly had a history of coronary artery bypass grafting (22.6% versus 13.9%, $P=0.046$), more often presented with ACS (38.7% versus 17.8%, $P<0.001$), but not non–ST-segment–elevation MI (16.0% versus 10.3%, $P=0.134$), at index PCI. In addition,

PCI in this cohort was more commonly performed within a coronary artery bypass graft (5.9% versus 1.4%, $P=0.039$) and was associated with greater total stent number (1.9±1.3 versus 1.6±0.9, $P=0.017$), total stent length (TSL) (40.1±25.3 mm versus 32.1±19.3 mm, $P=0.004$), total BMS number (0.5±1.1 versus 0.2±0.5; $P=0.002$), and total number of stents ≤2.5-mm diameter (0.9±1.1 versus 0.5±0.8, $P=0.002$) during PCI (Table 3). Glycoprotein IIb/IIIa inhibitor use was similar between outcome groups (17.8% versus 14.8%, $P=0.470$), while post-PCI use of prasugrel was low but more common among those with MACE (7.6% versus 2.8%, $P=0.046$).

Receiver-operator characteristic curve analysis showed fibrinogen level ≥280 mg/dL (area 0.613, $P<0.001$), TSL ≥32 mm (area 0.589, $P=0.009$), use of at least 1 BMS (area 0.578, $P=0.018$), use of at least 1 ≤2.5-mm diameter stent (area 0.592, $P=0.006$), and white blood cell count ≥ 5.6×10^3 cells/dL (area 0.585, $P=0.011$) to have maximum sensitivity and specificity in predicting occurrence of 2-year MACE.

Multiple variable testing was performed using significant univariate factors (fibrinogen ≥280 mg/dL, white blood cell count ≥ 5.6×10^3 cells/dL, prior coronary artery bypass grafting, ACS indication, bypass graft PCI, TSL ≥32 mm, at least 1 BMS used, at least 1 ≤2.5-mm diameter stent used, and post-PCI prasugrel use). Fibrinogen level ≥280 mg/dL ($P<0.001$), ACS indication ($P<0.001$), TSL ≥32 mm ($P=0.005$), use of a BMS ($P=0.001$), and use of a ≤2.5-mm diameter stent ($P=0.008$) remained significantly associated with occurrence of 2-year MACE, while other factors did not. No interactions between these significant variables were identified. Adjusted odds ratios (OR) for fibrinogen level ≥280 mg/dL (OR 3.0, confidence interval [CI], 1.6–5.4, $P<0.001$), ACS indication (OR 4.1, CI, 2.3–7.5, $P<0.001$), TSL ≥32 mm (OR 2.2, CI, 1.3–3.8, $P=0.005$), use of a BMS (OR 3.2, CI, 1.6–6.1, $P<0.001$), and use of a ≤2.5-mm stent (OR 2.1, CI, 1.2–3.5, $P<0.001$) are reported between these independent factors (Figure 1).

A post hoc analysis comparing these 5 factors and 2-year MACE excluding rehospitalization for ACS was performed, which showed persistent relationships for fibrinogen level ≥280 mg/dL ($P=0.004$), ACS indication ($P<0.001$), TSL ≥32 mm ($P<0.001$), and use of a BMS ($P=0.001$). This analysis was repeated excluding both rehospitalization for ACS and revascularization (without an inciting MI) from 2-year MACE, which demonstrated significant relationships between fibrinogen level ≥280 mg/dL ($P=0.018$), ACS indication ($P=0.002$), TSL ≥32 mm ($P=0.002$), and use of a BMS ($P=0.001$) with unequivocal adverse events (non–ST-segment–elevation MI /ST-segment–elevation MI, stent thrombosis, stroke/transient ischemic attack, and all-cause death).

Kaplan–Meier curve analysis showed increased 2-year MACE among those with fibrinogen ≥280 mg/dL (42.6%

Table 2. Clinical Characteristics Compared Between Subjects With and Without 2-Year MACE

	No Events (n=209)	MACE (n=123)	P Value
Age, y	65.8±11.7	68.1±28.5	0.397
Male sex, %	71.4	67.2	0.431
BMI, kg/m ²	29.0±6.0	28.0±5.7	0.141
Past PCI, %	59.4	65.0	0.325
Past CABG, %	13.9	22.6	0.046
Past MI, %	29.4	36.9	0.169
Diabetes mellitus, %	42.5	43.6	0.842
Hypertension, %	90.1	91.5	0.696
Hyperlipidemia, %	87.3	87.1	0.947
Family history, %	42.5	43.6	0.842
Smoking history, %	13.1	16.8	0.379
Medications			
Aspirin, %	87.6	86.7	0.818
Clopidogrel, %	65.9	67.8	0.723
Prasugrel, %	0.5	1.7	0.291
Statin, %	79.4	77.7	0.715
β-Blocker, %	65.6	69.6	0.457
ACE inhibitor/ARB, %	61.7	61.6	0.984
Nitrates, %	33.3	29.7	0.512
Calcium channel blocker, %	22.1	28.6	0.199
Anticoagulation, %	7.2	8.1	0.772
Laboratory values			
WBC, 10 ³ cells/dL	7.1±2.5	7.7±2.8	0.024
Hemoglobin, g/dL	12.9±1.6	12.7±1.6	0.309
Platelet, 10 ³ cells/dL	215.4±65.5	228.3±89.8	0.172
Creatinine, mg/dL	1.2±1.3	1.4±1.5	0.139
HbA1c, %	6.7±1.4	7.1±2.4	0.394
Total cholesterol, mg/dL	145.0±38.3	148.2±52.0	0.528
LDL, mg/dL	83.5±32.7	79.7±31.4	0.983
HDL, mg/dL	40.2±16.1	39.6±12.8	0.715
Triglyceride, mg/dL	120.0±82.3	149.7±271.7	0.250
Fibrinogen, mg/dL	301.6±110.8	352.8±123.4	<0.001
C-reactive protein, mg/L	0.8±1.5	1.2±2.7	0.225
Platelet reactivity (VerifyNow P2Y12 assay)			
Base PRU, PRU	316.7±64.8	330.0±58.7	0.633
Result PRU, PRU	167.1±102.7	146.3±30.0	0.282
Platelet inhibition, %	37.1±26.4	37.9±25.2	0.893

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MACE, major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; PRU, P2Y12 reaction unit; WBC, white blood cell.

versus 22.0%, log-rank $P<0.001$) (Figure 2). More specifically, fibrinogen ≥ 280 mg/dL was associated with increased MACE among those undergoing PCI for either elective indications

(35.4% versus 17.9%, log-rank $P=0.005$) or for an ACS (62.7% versus 36.0%, log-rank $P=0.023$) (Figure 3). A landmark survival analysis at 24 hours (excluding periprocedural MI

Table 3. Procedural Characteristics Compared Between Subjects With and Without 2-Year MACE

	Control (n=209)	MACE (n=123)	P Value
PCI indication			
Acute coronary syndrome, %	17.8	38.7	<0.001
NSTEMI, %	10.3	16.0	0.134
Unstable angina, %	7.5	22.7	<0.001
Procedural details			
Total segments treated	1.3±0.6	1.5±0.8	0.096
Stents per procedure	1.6±0.9	1.9±1.3	0.017
Total drug-eluting stents	1.5±1.0	1.5±1.2	0.978
Total bare-metal stents	0.2±0.5	0.5±1.1	0.002
Total small-caliber stents (2.0–2.5 mm)	0.5±0.8	0.9±1.1	0.002
Total stent length, mm	32.1±19.3	40.1±25.3	0.004
Pre-PCI stenosis, %	83.3±9.2	84.1±10.2	0.527
Post-PCI stenosis, %	1.4±4.4	3.0±10.7	0.127
LAD lesion, %	53.1	52.9	0.985
Bypass graft lesion, %	1.4	5.9	0.039
Chronic total occlusion lesion, %	4.2	2.5	0.548
Bivalirudin, %	84.3	80.5	0.383
Unfractionated heparin, %	16.7	24.6	0.083
Glycoprotein IIb/IIIa inhibitor, %	14.8	17.8	0.470
Post-PCI thienopyridine			
Clopidogrel, %	96.2	91.6	0.073
Prasugrel, %	2.8	7.6	0.046

LAD indicates left anterior descending artery; MACE, major adverse cardiovascular events; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention.

occurring <24 hours after PCI) showed significantly greater 2-year MACE in those with elevated fibrinogen (37.0% versus 18.3%, log-rank $P<0.001$) (Figure 4). The combined presence of any of the identified risk factors above was associated with a stepwise increase in MACE (0, 1, 2, 3, to 4 total risk factors: 8.3% versus 18.6% versus 31.2% versus 54.9% versus 84.6% 2-year MACE, log-rank $P<0.001$) (Figure 5).

Discussion

The current study demonstrates that higher baseline fibrinogen is an independent predictor of 2-year MACE after elective or urgent PCI, and is driven by objective, clinically relevant ischemic cardiovascular events, independent of periprocedural MI. Additionally, index PCI for an ACS, longer total implanted stent length, use of BMS, and use of small-caliber stents are also independent predictors of 2-year MACE, while measures of platelet reactivity using the VerifyNow P2Y12 assay are not. Post hoc analyses using objective, clinically relevant definitions of ischemic events as well as a 24-hour

landmark provide insight into the relation between baseline fibrinogen level and post-PCI MACE beyond prior reports at 6 and 12 months of follow-up.

Kaplan–Meier survival curves, based on the fibrinogen cutoff of 280 mg/dL, show early and persistent separation during 2-year follow-up after index PCI. A 24-hour landmark analysis demonstrates that this relation persists after excluding periprocedural MI. In fact, subjects with elevated baseline fibrinogen (≥ 280 mg/dL) had higher incidence of subsequent ACS hospitalization, revascularization, MI, definite stent thrombosis, stroke, or death beyond 24 hours after PCI. This relation between elevated fibrinogen and 2-year MACE also persisted when limiting the analysis to only include acute MI, stent thrombosis, stroke, and death in the 2-year end point (excluding both ACS rehospitalization and revascularization without an inciting MI). These findings highlight the potential role for elevated baseline fibrinogen level to identify those at higher risk of future ischemic events that are both of high clinical relevance and occurring relatively late (12–24 months after index PCI).

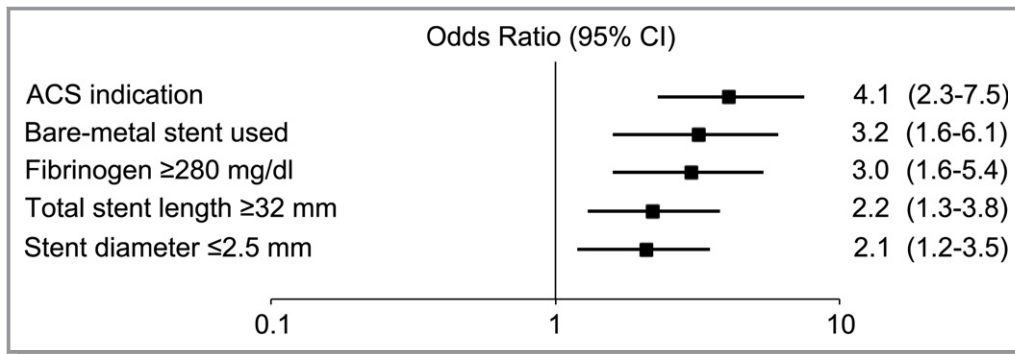


Figure 1. Factors associated with 2-year MACE after PCI. Adjusted odds ratios for 2-y MACE in the presence of associated factors during baseline PCI. ACS indicates acute coronary syndrome; CI, confidence interval; MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention.

The presence of other clinically relevant factors including ACS presentation, greater total stent length, use of BMS, and use of small-caliber stents were independently associated with 2-year MACE and suggested roles for baseline disease burden and procedural details on subsequent events regardless of fibrinogen level. In particular, the use of BMS may represent the use of smallest-diameter stents (2.0 mm) or presence of comorbidities warranting shorter dual antiplatelet therapy duration. Total stent length difference between

groups was also clinically relevant, representing greater underlying disease burden requiring multiple stents and more complex PCI procedures in those with subsequent MACE. The presence of multiple factors together with elevated fibrinogen level was associated with the greatest 2-year risk of MACE. An analysis of the GRAVITAS (Gauging Responsiveness With a VerifyNow P2Y12 Assay: Impact on Thrombosis and Safety) Trial also identified multiple significant covariates, notably ACS presentation and TSL, in predicting 6-month combined death, MI, and stent thrombosis after PCI for stable coronary artery disease or ACS.¹⁸ A post hoc analysis of the Dual Antiplatelet Therapy Study also identified multiple factors predicting late ischemic events, including MI at time of PCI and use of smaller-diameter stents, similar to the current study. However, the ability of these factors to predict late ischemic events 12 to 30 months after PCI remained limited with a c-statistic of 0.64 within a validation cohort.¹⁹ Elevated serum fibrinogen was not measured in these previous studies and has been identified by the current study to be a unique independent predictor of MACE up to 2 years after PCI. Furthermore, the current study highlights how elevated fibrinogen level augments the association of ACS presentation, longer total stent length, and small-diameter stent with 2-year MACE. Integrating serum fibrinogen level may help improve the performance of this late ischemia prediction model as well. If validated, serum fibrinogen could play a role in determining which patients could benefit from prolonged dual-antiplatelet therapy extended beyond 12 months after index PCI or potentially direct thrombin inhibitors.

Multiple mechanisms may explain the association between elevated fibrinogen level and long-term cardiovascular events in the current study population. Serum fibrinogen has a clear role in arterial thrombosis as a key component of platelet crosslinking and clot formation.⁴ Serum fibrinogen is produced and released in response to systemic inflammation, which can be present in those with more extensive cardiovascular risk factors and coronary heart disease, and further

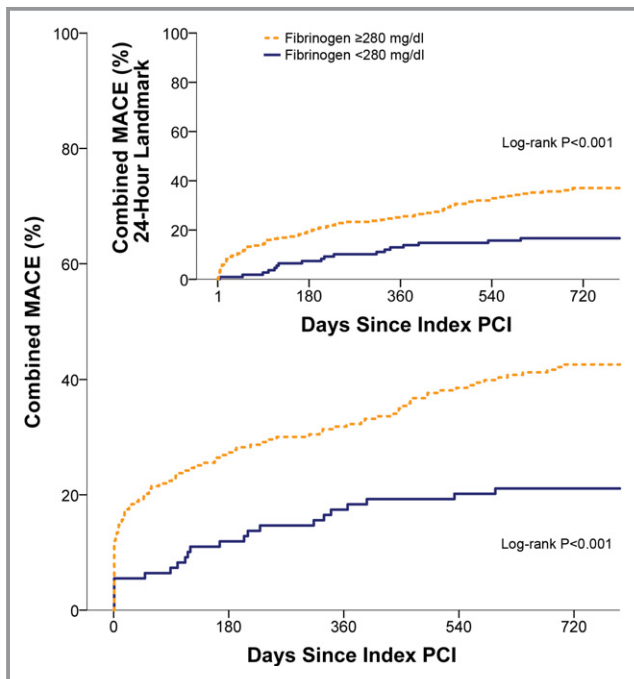


Figure 2. Elevated fibrinogen and 2-y MACE-free survival after PCI. Kaplan–Meier curves showing decreased 2-y MACE-free survival in the presence of fibrinogen level \geq 280 mg/dL before and after 24-h landmark analysis (inset). MACE indicates major adverse cardiovascular events; PCI, percutaneous coronary intervention.

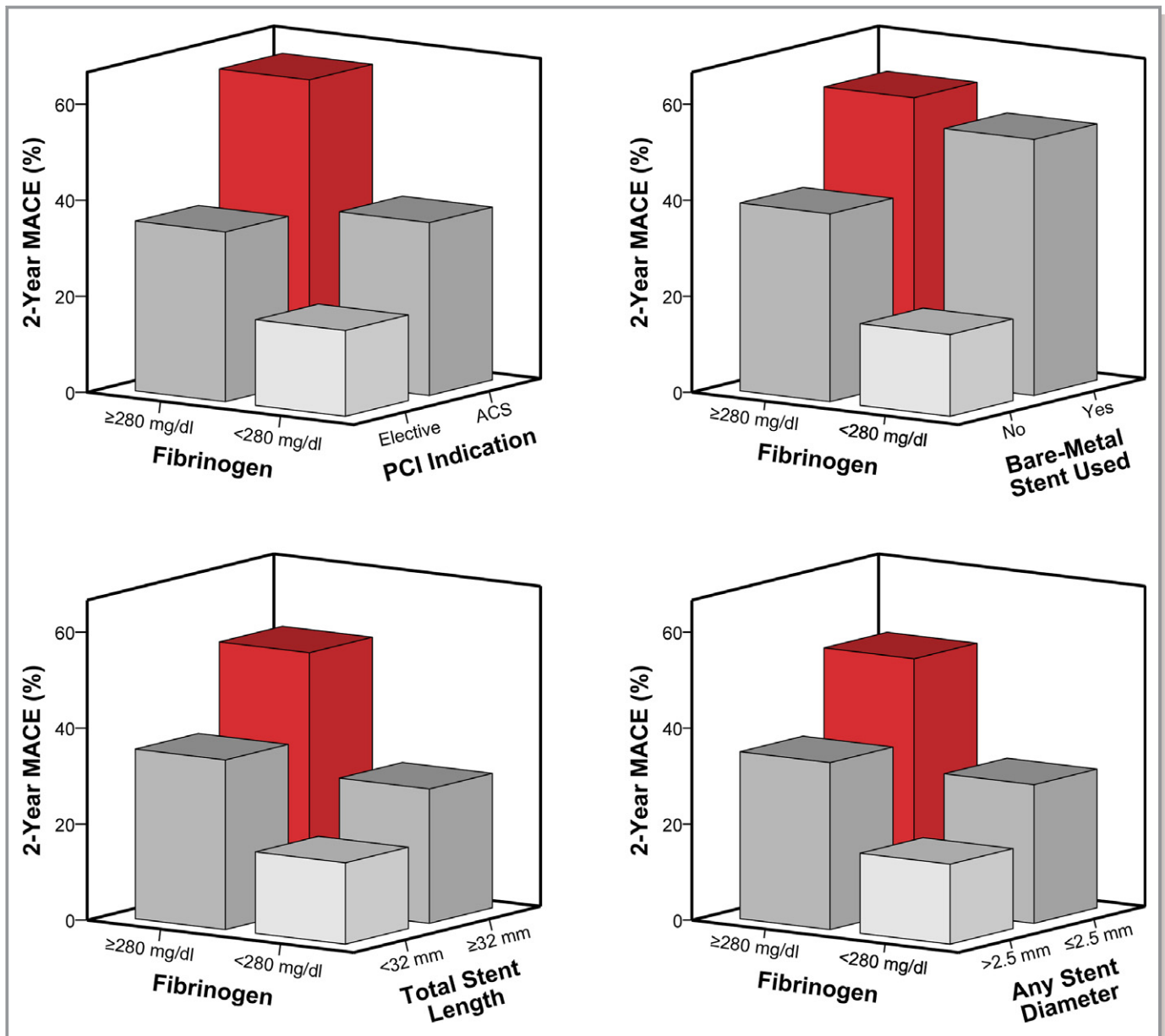


Figure 3. Elevated fibrinogen and 2-y MACE-free survival after PCI stratified by significant covariates. Bar graphs showing increased 2-y MACE in the presence of fibrinogen level ≥ 280 mg/dL, independent of other significant covariates. ACS indicates acute coronary syndrome; MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention.

manifested by acute clinical presentations. Platelet activation in these contexts can further contribute to release of intracellular fibrinogen stores, potentiate thrombus formation, and increase cardiovascular risk. The interplay between these mechanisms suggests a correlation between elevated fibrinogen level and increased cardiovascular events, but a direct causal link has not been established. Results of the current study showed that while elevated baseline fibrinogen level (≥ 280 mg/dL) is independently associated with 2-year MACE, it remains a nonspecific marker of events based on receiver-operator characteristic curve analysis (81.5% sensitivity,

39.0% specificity). We have previously reported that a higher fibrinogen level (≥ 345 mg/dL) was associated with periprocedural MI after PCI but also had limited specificity.¹ It is possible that a higher fibrinogen threshold predicts ischemic risk during PCI with administration of potent antiplatelet/anticoagulant therapy while a lower threshold might be associated with longer-term MACE. Furthermore, these identified cutoffs are within the normal range of the fibrinogen assay (150–400 mg/dL) and call into question whether a different range of normal values needs to be ascertained to better discriminate risk for patients with cardiovascular

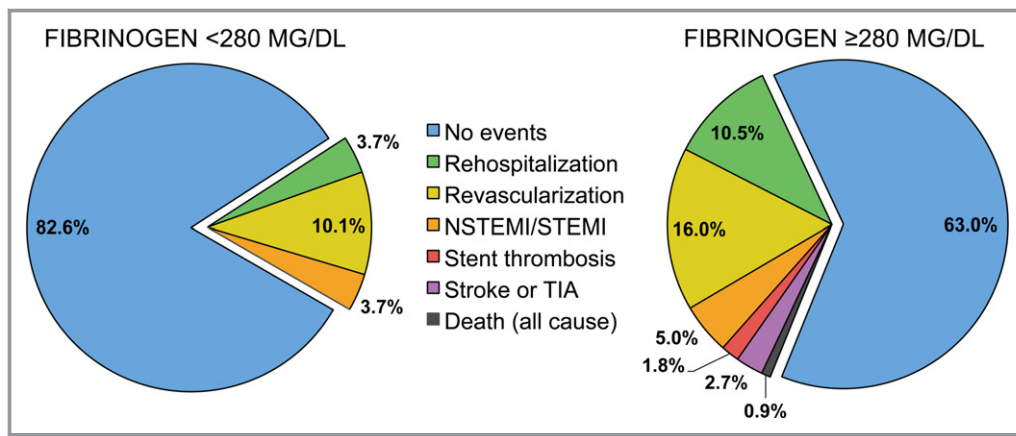


Figure 4. Elevated fibrinogen and 2-y MACE after PCI (24-h landmark analysis). Landmark analysis at 24 h (excluding biomarker-positive periprocedural MI after PCI) showing increased total MACE, and individual components of MACE, occurring between 24 h and 2 y after PCI in those with fibrinogen ≥ 280 mg/dL. MACE indicates major adverse cardiac events; MI, myocardial infarction; NSTEMI, non-ST-segment-elevation myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

disease or those undergoing PCI. A better understanding of other fibrinogen characteristics such as concentration variation with time or clinical contexts, isoform variability, posttranslational modifications, intracellular storage and release, and binding characteristics may further refine the relations between an elevated fibrinogen level and 2-year MACE after PCI.

Similar to the GRAVITAS Trial, results of the current study did not show a significant relationship between measures of platelet reactivity using the VerifyNow P2Y12 assay (including PRU and percent platelet inhibition values) and occurrence of MACE. The current study was specifically powered to detect a difference in fibrinogen level across outcome groups and may have been underpowered to also detect differences in platelet function measurements. Nevertheless, study results show that baseline fibrinogen level was more closely associated than platelet function with the occurrence of MACE at 2 years after PCI.

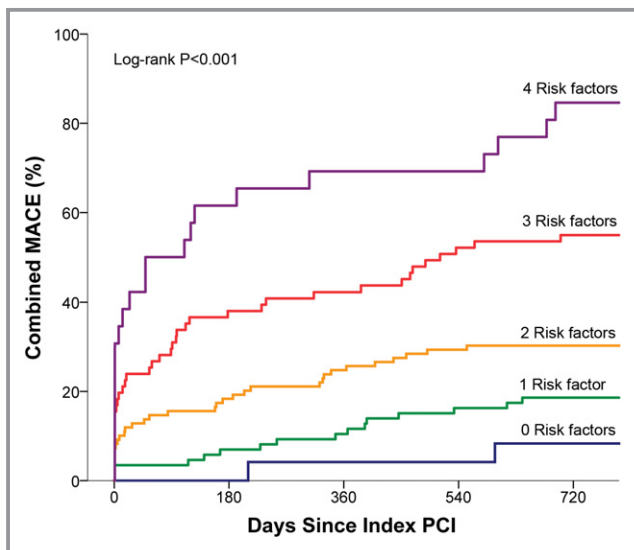


Figure 5. Kaplan–Meier curves show a stepwise increase in 2-y MACE (8.3% vs 18.6% vs 31.2%, vs 54.9% vs 84.6%, log-rank $P < 0.001$) in the presence of none (blue) or any combination of 1 (green), 2 (orange), 3 (red), or 4 (purple) previously identified risk factors: ACS indication for PCI, fibrinogen ≥ 280 mg/dL, use of a bare-metal stent, use of a ≤ 2.5 -mm diameter stent, and total stent length ≥ 32 mm. No subject had all 5 risk factors. ACS indicates acute coronary syndrome; MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention.

Limitations

This was a retrospective study and findings should be confirmed in a prospective manner. Post-PCI dual antiplatelet therapy and thienopyridine selection was determined at time of discharge after index procedure and may have been subsequently modified. Fibrinogen level was obtained at a single time point and variability in its level over time was not assessed. Platelet function test results were not available for all study subjects.

Conclusions

Elevated serum fibrinogen level (≥ 280 mg/dL) is independently associated with 2-year MACE after PCI, driven by objective, clinically relevant ischemic events. ACS indication for initial PCI, TSL ≥ 32 mm, use of stents ≤ 2.5 mm, and any BMS use during PCI are also independent predictors of 2-year MACE. The highest 2-year MACE is predicted by the presence of these factors together, while measures of on-thienopyridine platelet reactivity using the VerifyNow P2Y12 assay are not associated with 2-year MACE after PCI.

Disclosures

None.

References

- Ang L, Bin Thani K, Ilapakurti M, Lee MS, Palakodeti V, Mahmud E. Elevated plasma fibrinogen rather than residual platelet reactivity with clopidogrel is associated with an increased ischemic risk during elective percutaneous coronary intervention. *J Am Coll Cardiol*. 2013;61:23–24.
- Mahmud E, Ramsis M, Behnamfar O, Enright K, Huynh A, Kaushal K, Palakodeti S, Li S, Teh P, Lin F, Reeves R, Patel M, Ang L. Elevated serum fibrinogen is associated with 6-month major adverse cardiovascular events following percutaneous coronary intervention. *Am J Cardiol*. 2016;117:1575–1581.
- Mahmud E, Behnamfar O, Lin F, Reeves R, Patel M, Ang L. Elevated serum fibrinogen is associated with 12-month major adverse cardiovascular events following percutaneous coronary intervention. *J Am Coll Cardiol*. 2016;67:2556–2557.
- Ang L, Mahmud E. Monitoring oral antiplatelet therapy: is it justified? *Ther Adv Cardiovasc Dis*. 2008;2:485–496.
- Althoff TF, Fischer M, Langer E, Zeimer S, Baumann G. Sustained enhancement of residual platelet reactivity after coronary stenting in patients with myocardial infarction compared to elective patients. *Thromb Res*. 2010;125:190–196.
- Arnau Vives MA, Rueda Soriano J, Martínez Dolz LV, Osa Sáez A, Almenar Bonet L, Morillas Blasco P, Osca Asensi J, Quesada Carmona A, Sanjuán Mániz R, Palencia Pérez MA. Prognostic value of fibrinogen in patients admitted with suspected unstable angina and non-Q-wave myocardial infarction. *Rev Esp Cardiol*. 2002;55:622–630.
- Toss H, Lindahl B, Siegbahn A, Wallentin L; FRISC Study Group. Prognostic influence of increased fibrinogen and C-reactive protein levels in unstable coronary artery disease. Fragmin during Instability in Coronary Artery Disease. *Circulation*. 1997;96:4204–4210.
- Verheggen PW, de Maat MP, Cats VM, Haverkate F, Zwinderman AH, Kluft C, Bruschke AV. Inflammatory status as a main determinant of outcome in patients with unstable angina, independent of coagulation activation and endothelial cell function. *Eur Heart J*. 1999;20:567–574.
- Becker RC, Cannon CP, Bovill EG, Tracy RP, Thompson B, Knatterud GL, Randall A, Braunwald B. Prognostic value of plasma fibrinogen concentration in patients with unstable angina and non-Q-wave myocardial infarction (TIMI IIIB Trial). *Am J Cardiol*. 1996;78:142–147.
- Thompson SG, Kienast J, Pyke SD, Haverkate F, van de Loo JC; European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. *N Engl J Med*. 1995;332:635–641.
- Kannel WB, Wolf PA, Castelli WP, D'Agostino RB. Fibrinogen and risk of cardiovascular disease. The Framingham Study. *JAMA*. 1987;258:1183–1186.
- Meade TW, Mellows S, Brozovic M, Miller GJ, Chakrabarti RR, North WR, Haines AP, Stirling Y, Imeson JD, Thompson SG. Haemostatic function and ischemic heart disease: principal results of the Northwick Park Study. *Lancet*. 1986;2:533–537.
- Lee AJ, Lowe GD, Woodward M, Tunstall-Pedoe H. Fibrinogen in relation to personal history of prevalent hypertension, diabetes, stroke, intermittent claudication, coronary heart disease and family history: the Scottish Heart Health Study. *Br Heart J*. 1993;69:338–342.
- Fibrinogen Study Collaboration. Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: an individual participant meta-analysis. *JAMA*. 2005;294:1799–1809.
- Kavitha S, Sridhar MG, Satheesh S. Periprocedural plasma fibrinogen levels and coronary stent outcome. *Indian Heart J*. 2015;67:440–443.
- Valgimigli M, Campo G, de Cesare N, Meliga E, Vranckx P, Furgieri A, Angiolillo DJ, Sabatè M, Hamon M, Repetto A, Colangelo S, Bragaglia S, Parrinello G, Peroco G, Ferrari R; Tailoring Treatment With Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel (3T/2R) Investigators. Intensifying platelet inhibition with tirofiban in poor responders to aspirin, clopidogrel, or both agents undergoing elective coronary intervention: results from the double-blind, prospective, randomized Tailoring Treatment with Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel study. *Circulation*. 2009;119:3215–3222.
- Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *J Am Coll Cardiol*. 2007;50:2173–2195.
- Price MJ, Angiolillo DJ, Teirstein PS, Lillie E, Manoukian SV, Berger PB, Tanguay JF, Cannon CP, Topol EJ. Platelet reactivity and cardiovascular outcomes after percutaneous coronary intervention: a time-dependent analysis of the Gauging Responsiveness with a VerifyNow P2Y12 assay: Impact on Thrombosis and Safety (GRAVITAS) trial. *Circulation*. 2011;124:1132–1137.
- Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, Cohen DJ, Spertus JA, Steg PG, Cutlip DE, Rinaldi MJ, Camenzind E, Wijns W, Apruzzese PK, Song Y, Massaro JM, Mauri L; DAPT Study Investigators. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year and after percutaneous coronary intervention. *JAMA*. 2016;315:1735–1749.