Effect of Serum Fibrinogen, Total Stent Length, and Type of Acute Coronary Syndrome on 6-Month Major Adverse Cardiovascular Events and Bleeding After Percutaneous Coronary Intervention

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This study evaluated the relation between baseline fibrinogen and 6-month major adverse cardiovascular events (MACE) and bleeding after percutaneous coronary intervention (PCI). Three hundred eighty-seven subjects (65.6 ± 16.1 years, 69.5% men, 26.9% acute coronary syndrome [ACS]) who underwent PCI with baseline fibrinogen and platelet reactivity (VerifyNow P2Y12 assay, Accumetrics, San Diego, California) measured were enrolled. Fibrinogen (368.8 ± 144.1 vs 316.8 ± 114.3 mg/dl; p = 0.001), total stent length (TSL; 44.5 ± 25.0 vs 32.2 ± 20.1 mm; p <0.001), and ACS presentation (40.6% vs 23.9%; p = 0.005) were independently associated with 6-month MACE rates (17.8%: myocardial infarction 9.8%, rehospitalization for ACS 3.6%, urgent revascularization 3.6%, stroke 0.5%, and death 0.3%). Measures of platelet reactivity were not associated with 6-month MACE. After multivariate analysis, fibrinogen ≥280 mg/dl (odds ratio [OR] 2.60, 95% CI 1.33 to 5.11, p = 0.005), TSL ≥32 mm (OR 3.21, 95% CI 1.82 to 5.64, p <0.001), and ACS presentation (OR 2.58, 95% CI 1.45 to 4.61, p = 0.001) were associated with higher 6-month MACE. In 271 subjects receiving chronic P2Y12 inhibitor therapy, 6-month Thrombolysis In Myocardial Infarction bleeding after PCI was 7.0%, but no difference in fibrinogen level (338.3 ± 109.7 vs 324.3 ± 113.8 mg/dl, p = 0.60) stratified by Thrombolysis In Myocardial Infarction bleeding was observed. In conclusion, elevated serum fibrinogen, ACS presentation, and longer TSL are independently associated with higher 6-month MACE after PCI, whereas no association with on-thienopyridine platelet reactivity and 6-month MACE was observed. Post-PCI bleeding was not associated with lower fibrinogen level. **(Am J Cardiol 2016;117:1575−1581)**

Elevated serum fibrinogen is a risk factor for short- and long-term major adverse cardiovascular events (MACE) in patients with atherosclerotic heart disease.[1−10] We have previously reported an independent relation between elevated baseline serum fibrinogen level and periprocedural myocardial infarction (MI) in patients undergoing elective percutaneous coronary intervention (PCI) with clopidogrel pretreatment.[11] However, the relation between serum fibrinogen level and adverse bleeding events after PCI has not been previously studied. In cases of fibrinolysis after acute MI or noncardiac major hemorrhage, lower serum fibrinogen is an early marker for bleeding risk and a possible therapeutic target to improve outcomes.[12−14] In contemporary PCI with the use of potent anticoagulation and antiplatelet therapies, lower fibrinogen may serve as a marker predicting postprocedural bleeding. The present study was performed to determine the role of baseline fibrinogen level and on-thienopyridine platelet reactivity with 6-month MACE and bleeding events after PCI.

Methods

The study was approved by the Institutional Review Board of the University of California, San Diego. Patients with coronary artery disease who underwent successful PCI with stenting or balloon angioplasty alone from June 2006 to September 2012 with measurement of serum fibrinogen within 24 hours of PCI were included. Serum fibrinogen was obtained routinely as a part of previous observational studies performed during this time frame, which were designed to evaluate the role of fibrinogen and platelet reactivity in patients undergoing PCI. Subjects were 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. Subjects with ST-elevation MI within 72 hours before recruitment, age <18 years, or the use of glycoprotein IIb/IIIa inhibitor within 30 days before the index PCI were excluded. Among these subjects, those on chronic thienopyridine therapy

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≥7 days before the index PCI were also included for a secondary analysis of 24-hour and 6-month bleeding events.

Baseline serum laboratory measurements included complete blood count, creatinine, complete lipid panel, C-reactive protein, fibrinogen, and cardiac markers of ischemic injury (creatine kinase-MB, troponin I, and/or troponin T). Cardiac markers were measured every 6 to 8 hours after PCI until hospital discharge or up to 24 hours until cardiac biomarkers of ischemic injury had peaked. Platelet function testing was performed during PCI using the VerifyNow P2Y12 assay (Accumetrics, San Diego, California) 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-[result PRU/base PRU] × 100%),[15] was also reported as available.

A composite of MI, unplanned repeat revascularization, rehospitalization for suspected acute coronary syndrome (ACS), stroke, and death was defined as the MACE end spoint. Periprocedural MI was defined as CK-MB ≥threefold the 99% upper limit of normal within 24 hours after PCI, or increase >20% if the baseline values were elevated and stable or falling.[16] Six-month clinical events were determined by detailed medical record review and confirmed by at least 2 data abstractors. Thrombolysis In Myocardial Infarction (TIMI) bleeding (minimal, minor, or major bleeding) events 24 hours and 6 months after PCI were recorded.

The primary analysis was performed using a case-control design with 6-month MACE as the clinical end point. Secondary case-control analyses were performed using 24-hour and 6-month TIMI bleeding end points. Based on the results of our previous study, an evaluable sample size of 69 ischemic events was required to provide 80% power (1-sided alpha = 0.05) to detect a 52 mg/dl difference in fibrinogen between MACE outcome groups (361 vs 309 mg/dl; SD 109 mg/dl).[11]

Outcome events were compared against variables using the Student *t* tests or chi-square analyses as appropriate. Each outcome variable was then entered into a binary logistic multiple regression model with associated factors (univariate p value <0.05) and significant multiple variable relations reported. Interaction testing between significant variables associated with each outcome was also performed. Receiver-operator characteristic (ROC) curve analysis was used to determine the upper fibrinogen level with greatest summed sensitivity and specificity to predict events as appropriate.

Results

A total of 387 subjects (65.6 ± 16.1 years, men 69.5%) with a high prevalence of risk factors for cardiovascular disease and previous coronary revascularization were enrolled (Table 1). A significant proportion underwent urgent PCI (12.4% non−ST-elevation MI, 14.5% unstable angina) with the majority receiving drug-eluting stents (1.4 ± 0.7 lesions; 1.7 ± 1.0 stents/patient; 82.9% drug-eluting stents; 12.4% bare-metal stents).

The 6-month MACE rate after PCI was 17.8% (9.8% MI, 3.6% cardiac rehospitalization, 3.6% urgent revascularization, 0.5% stroke, and 0.3% death). Periprocedural MI alone occurred in 7.8% of subjects, whereas 0.8% had Academic Research Consortium definite stent thrombosis. Baseline subject characteristics, cardiac risk factors, co-morbidities, and pharmacotherapy were similar between those with and without 6-month MACE (Table 2). Serum fibrinogen level (368.8 ± 144.1 vs 316.8 ± 114.3 mg/dl; p = 0.001) and white blood cell count (8.1 ± 3.3 vs 7.2 ± 2.4 10^3 cells/L, p = 0.041) were higher in the 6-month MACE cohort, but other markers of systemic inflammation were similar between outcome groups. Platelet reactivity as measured with the VerifyNow P2Y12 assay was similar between cohorts with and without MACE.

Table 1
Study population baseline characteristics (n = 387)

Variable	
Age (years)	65.6 ± 16.1
Men	69.5%
Body mass index (kg/m^2)	28.6 ± 5.9
Past myocardial infarction	34.0%
Past coronary intervention	59.2%
Past coronary bypass	17.2%
Hypertension	91.1%
Hyperlipidemia	87.7%
Family history of cardiovascular disease	49.0%
Diabetes mellitus	42.6%
Smoker	15.6%
Ejection fraction	58.3 ± 12.4%
Acute coronary syndrome	26.9%

Subjects with 6-month MACE more commonly presented with ACS at the index PCI (ACS: 40.6% vs 23.9%; p = 0.005). More specifically, the prevalence of pre-PCI non−ST-elevation MI (20.3% vs 10.7%, p = 0.028) but not unstable angina (20.3% vs 13.2%, p = 0.150) was greater in those with 6-month MACE. In addition, greater vessel segments were treated (1.6 ± 0.9 vs 1.3 ± 0.6; p = 0.015) with more stents used (2.1 ± 1.4 vs 1.6 ± 0.9; p = 0.005) and longer stent length (44.5 ± 25.0 vs 32.3 ± 20.1 mm; p <0.001) in the cohort with higher 6-month MACE (Table 3). Procedural use of a glycoprotein IIb/IIIa inhibitor was more frequent and post-PCI use of clopidogrel slightly less frequent among those with higher 6-month MACE.

Multiple variable testing was performed using significant univariate factors (fibrinogen, white blood cell count, ACS indication, total stent length (TSL), total segments treated, stents per procedure, degree of pre-PCI stenosis, glycoprotein IIb/IIIa inhibitor use, and post-PCI clopidogrel use). Elevated serum fibrinogen (p = 0.011) and initial presentation with ACS (p = 0.004) remained significantly associated with 6-month MACE. Testing was repeated excluding total vessel segments and/or stent number, and significant relations between elevated serum fibrinogen (p = 0.013), initial ACS presentation (p = 0.004), and TSL (p <0.001) with 6-month MACE persisted. No 2- or 3-way interactions between these variables were identified.

ROC curve analysis showed fibrinogen ≥280 mg/dl (area 0.585; p = 0.032) and TSL ≥32 mm (area 0.658; p <0.001) to have maximum combined sensitivity and specificity for 6-month MACE. Kaplan−Meier analysis revealed