Relationship of Platelet Reactivity With Bleeding Outcomes During Long-Term Treatment With Dual Antiplatelet Therapy for Medically Managed Patients With Non-ST-Segment Elevation Acute Coronary Syndromes

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Background—The relationship between “on-treatment” low platelet reactivity and longitudinal risks of major bleeding dual antiplatelet therapy following acute coronary syndromes remains uncertain, especially for patients who do not undergo percutaneous coronary intervention.

Methods and Results—We analyzed 2428 medically managed acute coronary syndromes patients from the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial who had serial platelet reactivity measurements (P2Y12 reaction units; PRUs) and were randomized to aspirin + prasugrel versus aspirin + clopidogrel for up to 30 months. Contal’s method was used to determine whether a cut point for steady-state PRU values could distinguish high versus low bleeding risk using 2-level composites: Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) severe/life-threatening or moderate bleeding, Exploratory analyses used 3-level composites that incorporated mild and minimal GUSTO and TIMI events. Continuous measures of PRUs (per 10-unit decrease) were not independently associated with the 2-level GUSTO (adjusted hazard ratio [HR], 1.01; 95% CI, 0.96–1.06) or TIMI composites (1.02; 0.98–1.07). Furthermore, no PRU cut point could significantly distinguish bleeding risk using the 2-level composites. However, the PRU cut point of 75 differentiated bleeding risk with the 3-level composites of GUSTO (26.5% vs 12.6%; adjusted HR, 2.28; 95% CI, 1.77–2.94; P<0.001) and TIMI bleeding events (25.9% vs 12.2%; adjusted HR, 2.30; 95% CI, 1.78–2.97; P<0.001).

Conclusions—Among medically managed non-ST-segment elevation acute coronary syndromes patients receiving prolonged dual antiplatelet therapy, PRU values were not significantly associated with the long-term risk of major bleeding events, suggesting that low on-treatment platelet reactivity does not independently predict serious bleeding risk.


Key Words: DAPT • hemorrhage • platelet

Clinical practice guidelines recommend dual antiplatelet therapy (DAPT) with aspirin+a P2Y12 inhibitor for at least 12 months for patients with acute coronary syndromes (ACS), given the consistent benefits of DAPT demonstrated in large randomized trials.1,2 Although P2Y12 inhibitors have been shown to reduce ischemic events, there has been a consistent

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Accompanying Figure S1 and Tables S1 through S4 are available at http://jaha.ahajournals.org/content/5/11/e003977/DC1/inline-supplementary-material-1.pdf

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signal of increased bleeding with DAPT treatment compared with aspirin monotherapy, and with DAPT regimens that include more-potent P2Y12 inhibitors (prasugrel and ticagrelor) compared with clopidogrel.3–5 These latter observations may indicate that enhanced platelet inhibition is associated with increased bleeding risk.

Given the consistent association of bleeding events with an increased risk of subsequent mortality and other ischemic outcomes, the focus of DAPT treatment is shifting toward finding the optimal risk/benefit balance for patients with ACS to mitigate the risk of major bleeding while maintaining a significant reduction of ischemic events.6 In this regard, past studies have suggested that patients undergoing percutaneous coronary intervention (PCI) who have a robust response to a P2Y12 inhibitor (termed low on-treatment platelet reactivity [LPR] to ADP) have a higher risk of long-term bleeding events following the procedure.7,8 Based on the results of these observational studies, a therapeutic window concept for P2Y12 receptor reactivity, in which a cut-off value for high on-treatment platelet reactivity and LPR to ADP associated with post-PCI ischemic and bleeding event risk, has been recently proposed.9 However, the relationship of platelet reactivity measurements and LPR with long-term bleeding risk in patients with ACS treated with DAPT and managed without revascularization has not been prospectively evaluated.

We analyzed data from the Platelet Function Substudy (PFS) of the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial to evaluate the relationship between measurements of platelet reactivity and the longitudinal risks of predominantly spontaneous bleeding events among medically managed patients with unstable angina/non-ST-segment elevation myocardial infarction (UA/NSTEMI); collectively referred to as non-ST-segment elevation acute coronary syndrome, or NSTE ACS) who were treated with DAPT (aspirin+clopidogrel vs aspirin+prasugrel) for up to 30 months and to determine whether a threshold of LPR could be established that significantly delineated bleeding risk.

Methods

Study Population

The study design and results of the TRILOGY ACS trial have been described.10,11 TRILOGY ACS was a double-blind, active-controlled, randomized trial in high-risk patients with NSTE ACS who were managed medically without planned revascularization. Participants had at least 1 of 4 enrichment criteria (age ≥60 years, diabetes mellitus, past myocardial infarction [MI], or past coronary revascularization at least 30 days before index ACS hospitalization). Patients with a history of transient ischemic attack/stroke, renal failure requiring dialysis, or concomitant oral anticoagulant treatment were excluded. The TRILOGY ACS study was approved by regulatory authorities in all participating countries and by participating sites’ institutional review boards. All participants provided written informed consent.

In the overall trial, 9326 participants at 966 sites in 52 countries were enrolled. Patients were randomly assigned to prasugrel or clopidogrel therapy in a double-blind, double-dummy fashion. The daily prasugrel maintenance dose was 10 mg in participants <75 years of age and 5 mg for study participants ≥75 years of age or who weighed <60 kg. The daily clopidogrel maintenance dose was 75 mg for all patients. Concomitant daily treatment with aspirin was strongly recommended, with low-dose aspirin strongly recommended. Treatment duration was up to 30 months, with a median treatment duration of 15 months and a median follow-up of 17 months.10 Patients who required treatment with an oral anticoagulant (OAC) were excluded, and the study drug was stopped if a patient required treatment with an OAC during follow-up.

Platelet Function Substudy Protocol

A total of 25 countries participated in the TRILOGY ACS PFS.12 All patients randomized into the main trial were included in the PFS at participating sites in those countries. The VerifyNow P2Y12 assay (Accriva Diagnostics, San Diego, CA) was used to assess platelet reactivity to ADP measured in P2Y12 reaction units (PRUs) to the randomized therapy, as previously described.12 Sites were instructed to collect samples only for those patients taking blinded study drug. Platelet reactivity was assessed at baseline; at 2 hours after first dose of study drug; at 30 days; and at 3, 6, 12, 18, 24, and 30 months after randomization, independent of the occurrence of a bleeding event. Patients with at least 1 valid PRU measurement at 30 days or later were included in the analysis. Previous analyses from the TRILOGY ACS PFS demonstrated little inter- and intraindividual changes in serial PRU values over time.12

Study Endpoints

All bleeding endpoints were prespecified in the trial protocol and were prospectively ascertained.10,11 An independent cardiovascular adjudication committee adjudicated all suspected bleeding endpoints using the TIMI (Thrombolysis In Myocardial Infarction) bleeding classification scale. Bleeding endpoints were determined algorithmically from case report form data elements using the GUSTO (Global Use Strategies to Open Occluded Coronary Arteries) classification scale. Among participants who received at least 1 dose of study drug during the “at-risk” interval of actual study drug

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treatment through 7 days after study drug discontinuation, non–coronary artery bypass graft (CABG)-related bleeding events were classified by the GUSTO bleeding scale as GUSTO severe/life-threatening, moderate, or mild bleeding, and by the TIMI bleeding scale as major, minor, or minimal, as previously defined. The primary analyses used the 2-level composite GUSTO and TIMI bleeding endpoints (GUSTO severe/life-threatening or moderate bleeding; TIMI major or minor bleeding), given that we chose to focus upon consequential and clinically meaningful bleeding events that typically result in hospitalization. Further exploratory analyses extended to the 3-level composite bleeding endpoints for each classification scale (GUSTO severe/life-threatening, moderate, or mild bleeding; TIMI major, minor, or minimal bleeding), given the potential effects of mild/minimal bleeding events on study drug compliance. All bleeding analyses included only the 9240 patients who received at least 1 dose of the study drug.

Statistical Analysis

For this analysis, the “steady-state” PRU values were defined as those occurring at 5 days postrandomization, given that the first 2 PRU measurements obtained (at baseline and 2 hours following first study drug administration) did not reflect steady-state PRU values that would only be expected to occur after at least 5 days of treatment with maintenance doses of prasugrel or clopidogrel (there was no “reloading” of clopidogrel and prasugrel at the time of randomization for the 95% of patients who had been receiving clopidogrel before randomization). To account for events that occurred between 5 and 30 days postrandomization, we assumed that the 30-day PRU value (the next value assessed after the 2-hour value per the study protocol) represented “steady-state treatment” at 5 days (when it was impractical to require patients to have an additional study visit solely for PRU measurement). Missing PRU values with a valid value after day 30 were used as the PRU value at 5 days (backward imputation). Forward imputation was used for patients randomized to clopidogrel who were already taking clopidogrel at home and had missing PRU values at 30 days or later (patient exclusions and imputation details are contained in Figure S1).

Baseline characteristics were compared by tertiles of steady-state PRU values to demonstrate how patient clinical characteristics differed by 3 categories of PRU response to the randomized study drug (clopidogrel vs prasugrel). Continuous variables are presented as medians and interquartile ranges. Categorical variables are presented as counts and percentages. Differences in baseline characteristics were tested among tertiles of steady-state PRU values. Continuous variables were compared using ANOVA when the assumption of normality was satisfied; otherwise, the Kruskal–Wallis test was used. Categorical variables were compared using the chi-square test when cell frequencies were sufficient; otherwise, an exact test was used. Kaplan–Meier plots for the bleeding endpoints by PRU tertiles were analyzed for the 2-level composite bleeding endpoints.

To determine whether a PRU cut point existed that distinguished between high- and low-risk bleeding patients, we used the method of Contal and O’Quigley. This method considers all possible observed values of steady-state PRU values and derives a standardized score statistic that can be used to test the null hypothesis that all observed values have equally likely risks of bleeding using the 2-level composites of GUSTO severe/life-threatening or moderate bleeding and TIMI major or minor bleeding. This test was used to determine whether the cut point that maximizes the score value is statistically different from other cut points with similar score values. However, given results from a past study that only demonstrated associations with clopidogrel metabolizer genotypic variants and composite bleeding outcomes that incorporated mild bleeding events, we also separately performed analyses for PRU cut points that incorporated the 3-level composite bleeding endpoints for each classification scale (GUSTO severe/life-threatening, moderate, or mild bleeding; and TIMI major, minor, or minimal bleeding) to comprehensively assess the relationship between PRU values and bleeding risk. As a result, 4 separate PRU cut points were determined.

To explore the unadjusted relationship between PRU values and bleeding outcomes, we grouped individuals according to the PRU value that maximized the score statistic regardless of whether it was a significant cut point. We then used these groups to create Kaplan–Meier plots of the cumulative distribution function and used the log-rank test to determine whether the survival functions (for bleeding endpoints) differed significantly between the groups. This testing procedure was analyzed completely separately for each of the 2- and 3-level composite GUSTO and TIMI bleeding composite outcomes (as previously described) to determine whether each of the 4 derived PRU cut points could reliably distinguish high versus low bleeding risk using the different composite outcomes from both bleeding classification scales.

To account for potential imbalances in baseline characteristics, we derived Cox proportional hazards models to assess the adjusted association between steady-state PRU values and time to first bleed using the GUSTO and TIMI bleeding composite endpoints, as previously described. Based upon previous analyses, we chose to use the following variables for adjustment: weight, age, clopidogrel stratum at time of randomization, aspirin dose category, time from randomization to treatment start, sex, disease classification, Killip class, previous peripheral arterial disease, previous peptic ulcer disease, systolic blood pressure, baseline hemoglobin, baseline...
creatinine, baseline (prerandomization) PRU values, and con-
comitant beta-blocker use. Additionally, we included a
variable unique to TRILOGY ACS (use of angiography before
randomization) given a previous analysis that demonstrated
higher rates of bleeding for patients who underwent angiog-
raphy before randomization. To explore the relationship
between steady-state PRU and time to first bleeding event, we
constructed a series of models to evaluate the relationship
between steady-state high versus low PRU values using the
cut points we derived and PRU values (in a continuous
fashion) with the 2- and 3-level GUSTO and TIMI composite
bleeding endpoints. We also analyzed the adjusted risks of
bleeding in a restricted population of patients aged <75 years
who were included in the primary efficacy analysis population
of the overall TRILOGY ACS trial given that an exploratory
treatment regimen (prasugrel 5 mg/day vs clopidogrel 75 mg/day) was studied in the elderly population (age ≥75 years). Also, we performed a sensitivity analysis to evaluate the interactions between day 5 PRU values and randomized treatment with respect to bleeding outcomes.

All statistical tests were performed at a significance level of
0.05. All analyses were performed using SAS (version 9.3; SAS
Institute Inc., Cary, NC) and R (version 2.14.1; R Foundation
for Statistical Computing, Vienna, Austria) software by statisticians
at the Duke Clinical Research Institute (Durham, NC), with an
independent copy of the database. Dr Roe, the principal
investigator for the TRILOGY ACS trial, had full access to all the
data in the study and takes responsibility for the integrity of the
data and the accuracy of the data analyses.

Results

Platelet Function Substudy Participation

Among 9326 patients enrolled in TRILOGY ACS, 2690 (28%)
were initially enrolled in the PFS. After database lock, it was
determined that 13 of these patients were inaccurately listed
as included in the PFS at randomization and 126 did not have
a valid PRU measurement recorded, leaving a total of 2564
patients. Among the patients who received at least 1 dose of
study drug, 2428 (26% of the total population) had a valid PRU
measurement recorded at 30 days (for imputation of day 5
PRU results), and these patients were included in our analysis
(Figure S1).

As previously published, the baseline clinical characteris-
tics and efficacy (ischemic) outcomes were similar for
patients who did versus did not participate in the PFS, and
bleeding composite outcomes were also similar. Frequen-
cies of GUSTO severe/life-threatening or moderate bleeding
events and TIMI major or minor bleeding events were lower
for patients who did versus did not participate in the PFS
(Table S1).

Baseline Characteristics

Among the 2428 participants included in this analysis,
baseline characteristics stratified by tertiles of baseline PRU
values are shown in Table 1. Compared with participants in
the middle and highest tertiles, participants in the lowest PRU
tertile (PRU <105) were younger; more likely to be male; less
likely to have diabetes mellitus; had higher body weight,
higher baseline hemoglobin levels, and higher baseline
creatinine clearance values; had a lower median Global
Registry of Acute Coronary Events (GRACE) risk score; more
commonly received the prasugrel 10-mg dose; and had the
lowest median baseline PRU values assessed at the time of
randomization before the first dose of study drug was
administered (when ≈95% of the participants were being
treated for the index ACS event with prerandomization
clopidogrel). More elderly patients (≥75 years) and those
with low body weight (<60 kg) were present in the highest
PRU tertile (PRU >211), likely attributed to the use of a lower
dose of prasugrel (5 mg) for these key subgroups. Baseline
characteristics by the PRU cut point of <75 are detailed in
Table S2.

Unadjusted Bleeding Outcomes

Using the 2-level composite bleeding endpoints for the
primary analyses, 28 GUSTO severe/life-threatening or
moderate bleeding events and 39 TIMI major or minor
bleeding events not related to CABG occurred from
randomization through the end of study follow-up. Starting
at the landmark of 5 days postrandomization (the starting
point for this analysis that corresponds with the steady-
state day 5 PRU values), there were 27 GUSTO severe/life-
threatening or moderate bleeding events and 37 TIMI major
or minor bleeding events not related to CABG that were
included in these analyses. Gastrointestinal bleeding was
the most common location for both GUSTO and TIMI
bleeding events (Table 2). Bleeding event curves through
30 months by PRU tertiles overlapped during the first 12
months. The highest rates of bleeding through 30 months
were observed for the middle PRU tertile (PRU 106–211) for both GUSTO and TIMI 2-level composite
bleeding events (Figure 1A and 1B).

Using the 3-level composite bleeding endpoints, there
were 297 GUSTO severe/life-threatening, moderate, or mild
bleeding events and 290 TIMI major, minor, or minimal
bleeding events, with bleeding locations shown in Table S3.

PRU Cut Points to Define Bleeding Risk

Using the method of Contal and O’Quigley, the best PRU cut
points identified for GUSTO severe/life-threatening or
Table 1. Baseline Characteristics Stratified by Tertiles of P2Y<sub>12</sub> Reaction Unit (PRU) Values

<table>
<thead>
<tr>
<th>Variable</th>
<th>Day 5 PRU Tertiles</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>PRU ≤105 (n=817)</td>
<td>PRU 106 to 211 (n=803)</td>
<td>PRU &gt;211 (n=808)</td>
<td>P Value</td>
<td></td>
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<tr>
<td>Demographics</td>
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<tr>
<td>Age, y*</td>
<td>63 (57, 70)</td>
<td>66 (59, 73)</td>
<td>67 (60, 75)</td>
<td>&lt;0.001</td>
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<tr>
<td>≥75 y (%)</td>
<td>84/817 (10.3)</td>
<td>167/803 (20.8)</td>
<td>217/808 (26.9)</td>
<td>&lt;0.001</td>
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<tr>
<td>Female sex (%)</td>
<td>277/817 (33.9)</td>
<td>293/803 (36.5)</td>
<td>376/808 (46.5)</td>
<td>&lt;0.001</td>
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<tr>
<td>Weight, kg*</td>
<td>76.0 (65.8, 87.5)</td>
<td>75.0 (64.2, 87.0)</td>
<td>74.0 (62.3, 85.0)</td>
<td>0.002</td>
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<tr>
<td>&lt;60 kg (%)</td>
<td>86/817 (10.5)</td>
<td>139/803 (17.3)</td>
<td>149/808 (18.4)</td>
<td>&lt;0.001</td>
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<tr>
<td>Disease classification (%)</td>
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<tr>
<td>NSTEMI</td>
<td>555/817 (67.9)</td>
<td>524/803 (65.3)</td>
<td>545/808 (67.5)</td>
<td>0.476</td>
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<tr>
<td>History (%)</td>
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<tr>
<td>Diabetes mellitus (%)</td>
<td>270/816 (33.1)</td>
<td>291/801 (36.3)</td>
<td>341/808 (42.2)</td>
<td>&lt;0.001</td>
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<tr>
<td>Past MI</td>
<td>375/810 (46.3)</td>
<td>343/802 (42.8)</td>
<td>340/801 (42.4)</td>
<td>0.224</td>
<td></td>
<td></td>
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<tr>
<td>Past PCI</td>
<td>225/815 (27.6)</td>
<td>220/801 (27.5)</td>
<td>199/805 (24.7)</td>
<td>0.335</td>
<td></td>
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<tr>
<td>Past CABG</td>
<td>100/817 (12.2)</td>
<td>111/803 (13.8)</td>
<td>132/806 (16.4)</td>
<td>0.054</td>
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<tr>
<td>Past PAD</td>
<td>42/804 (5.2)</td>
<td>37/790 (4.7)</td>
<td>50/790 (6.3)</td>
<td>0.337</td>
<td></td>
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<tr>
<td>Past atrial fibrillation</td>
<td>51/802 (6.4)</td>
<td>76/791 (9.6)</td>
<td>78/791 (9.9)</td>
<td>0.021</td>
<td></td>
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<tr>
<td>Past heart failure (%)</td>
<td>148/808 (18.3)</td>
<td>168/795 (21.1)</td>
<td>166/801 (20.7)</td>
<td>0.313</td>
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<tr>
<td>Past peptic ulcer disease (%)</td>
<td>50/809 (6.2)</td>
<td>51/800 (6.4)</td>
<td>39/802 (4.9)</td>
<td>0.371</td>
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<tr>
<td>Baseline risk assessment</td>
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<tr>
<td>Systolic BP, mm Hg*</td>
<td>127 (115, 138)</td>
<td>127 (116, 139)</td>
<td>130 (120, 140)</td>
<td>0.14</td>
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<tr>
<td>Killip class II to IV (%)</td>
<td>80/817 (9.8)</td>
<td>83/803 (10.3)</td>
<td>120/807 (14.9)</td>
<td>0.002</td>
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<tr>
<td>GRACE risk score*</td>
<td>115 (42, 201)</td>
<td>122 (54, 189)</td>
<td>126 (59, 205)</td>
<td>&lt;0.001</td>
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<tr>
<td>Creatinine, mg/dL*</td>
<td>1.0 (0.8, 1.2)</td>
<td>1.0 (0.8, 1.2)</td>
<td>1.0 (0.8, 1.2)</td>
<td>0.548</td>
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<tr>
<td>CrCl, mL/min*</td>
<td>80.5 (61.3, 104.2)</td>
<td>73.9 (56.2, 97.8)</td>
<td>68.9 (51.1, 91.8)</td>
<td>&lt;0.001</td>
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<tr>
<td>Hemoglobin, g/dL*</td>
<td>14.0 (13.1, 15.1)</td>
<td>13.8 (12.8, 14.9)</td>
<td>13.2 (12.2, 14.1)</td>
<td>&lt;0.001</td>
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<td>Prerandomization procedures (%)</td>
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<tr>
<td>Angiography performed</td>
<td>334/817 (40.9)</td>
<td>313/803 (39.0)</td>
<td>295/808 (36.5)</td>
<td>0.193</td>
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<td>Medications at randomization (%)</td>
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<td>Aspirin, daily dose, mg</td>
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<td>&lt;100</td>
<td>325/817 (39.8)</td>
<td>343/803 (42.7)</td>
<td>300/808 (37.1)</td>
<td>0.073</td>
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<tr>
<td>100 to 250</td>
<td>361/817 (44.2)</td>
<td>353/803 (44.0)</td>
<td>394/808 (48.8)</td>
<td>0.091</td>
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<tr>
<td>&gt;250</td>
<td>59/817 (7.2)</td>
<td>59/803 (7.3)</td>
<td>56/808 (6.9)</td>
<td>0.946</td>
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<tr>
<td>Beta-blocker</td>
<td>645/817 (78.9)</td>
<td>620/803 (77.2)</td>
<td>606/808 (75.0)</td>
<td>0.166</td>
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<tr>
<td>ACE-I/ARB</td>
<td>571/817 (69.9)</td>
<td>582/803 (72.5)</td>
<td>603/808 (74.6)</td>
<td>0.102</td>
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<tr>
<td>Statin</td>
<td>682/817 (83.5)</td>
<td>657/803 (81.8)</td>
<td>662/808 (81.9)</td>
<td>0.618</td>
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<tr>
<td>Proton pump inhibitor</td>
<td>164/817 (20.1)</td>
<td>210/803 (26.2)</td>
<td>193/808 (23.9)</td>
<td>0.014</td>
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<td>Randomization-specific information</td>
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<td></td>
</tr>
<tr>
<td>Clopidogrel stratum (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>No prerandomization clopidogrel</td>
<td>35/817 (4.3)</td>
<td>38/803 (4.7)</td>
<td>40/808 (5.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel started in-hospital; continued to randomization</td>
<td>578/817 (70.7)</td>
<td>516/803 (64.3)</td>
<td>537/808 (66.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home clopidogrel continued to randomization</td>
<td>204/817 (25.0)</td>
<td>249/803 (31.0)</td>
<td>231/808 (28.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
moderate bleeding events (PRU <106) and TIMI major or minor bleeding events (PRU <46) for the primary analyses did not significantly distinguish longitudinal bleeding risks using these 2-level bleeding composite endpoints (Figure 2A and 2B). For the exploratory analyses, the separately determined PRU cut points that maximized the score statistic were <75 both for the 3-level composite of GUSTO severe/life-threatening, moderate, or mild bleeding events (unadjusted bleeding rates=26.5% for PRU values <75 vs 12.6% for PRU values ≥75) and for the 3-level composite of TIMI major, minor, or minimal bleeding events (unadjusted bleeding rates=25.9% vs 12.2%, respectively). Bleeding event curves distinguished by this cut point of <75 PRU (using the 3-level composite bleeding endpoints) separated early and continued to separate during the trial follow-up period (Figure 2C and 2D).

### Adjusted Bleeding Outcomes

For the primary analyses, no significant association was found between continuous measures of PRU (per 10-unit decrease) with the adjusted risk of the 2-level composites of GUSTO severe/life-threatening or moderate bleeding or with TIMI major or minor bleeding (Table 3). For the exploratory analyses, using the 3-level GUSTO and TIMI composite bleeding endpoints that incorporated GUSTO mild and TIMI minimal bleeds, respectively, there was a significant increase in bleeding risk with continuous measures of PRU (per 10-unit decrease).

When the derived LPR cut points of PRU <46 for TIMI bleeding and PRU <106 for GUSTO bleeding were analyzed for the primary analyses, there was no significant association with the adjusted risk of the 2-level composites of GUSTO severe/life-threatening or moderate bleeding for PRU values below versus above the LPR cut point, and there was a marginally significant association with the adjusted risk of TIMI major or minor bleeding. For the exploratory analyses, there was an association with PRU values below versus above the LPR cut point of 75 for both the adjusted risks of the 3-level composites of GUSTO severe/life-threatening, moderate, or mild bleeding and for the TIMI major, minor, or minimal bleeding. Similar adjusted results were observed in the sensitivity analysis of the restricted population of patients aged <75 years (Table S4). Additional modeling showed no significant interactions between day 5 PRU values, randomized treatment, and bleeding outcomes.

### Discussion

These hypothesis-generating findings demonstrate no clear relationship between LPR and the longitudinal risks of serious bleeding events (using both the GUSTO and TIMI bleeding classification scales) among patients with NSTEMI ACS who were managed without revascularization and treated with

---

### Table 1. Continued

<table>
<thead>
<tr>
<th>Variable</th>
<th>Day 5 PRU Tertiles</th>
<th>PRU ≤105 (n=817)</th>
<th>PRU 106 to 211 (n=803)</th>
<th>PRU &gt;211 (n=808)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized to prasugrel (%)</td>
<td>643/817 (78.7)</td>
<td>359/803 (44.7)</td>
<td>200/808 (24.8)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Prasugrel 5-mg dose†</td>
<td>98/643 (15.2)</td>
<td>156/359 (43.5)</td>
<td>102/200 (51.0)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Baseline, pre-randomization PRU*</td>
<td>181 (120, 250)</td>
<td>215 (163, 274)</td>
<td>273 (219, 315)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CABG, coronary artery bypass grafting; CrCl, creatinine clearance; GRACE, Global Registry of Acute Coronary Events; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PRU, P2Y12 reaction unit.

*Median (25th, 75th percentiles).
†Percentage of the overall patient group from each PRU tertile who received the prasugrel 5 mg/day maintenance dose.

### Table 2. Distribution of Bleeding Locations for the Primary Analyses (2-Level Bleeding)

<table>
<thead>
<tr>
<th>Location</th>
<th>GUSTO Severe/Life-Threatening or Moderate Bleeding</th>
<th>TIMI Major or Minor Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Hematuria</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>No site identified</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Subdural hematoma</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Surgical incision site</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Urethral</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vaginal</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Vascular access site</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>37</td>
</tr>
</tbody>
</table>

GUSTO indicates Global Use of Strategies to Open Occluded Coronary Arteries; TIMI, Thrombolysis In Myocardial Infarction.
prolonged DAPT for up to 30 months. Only when mild/minimal events were incorporated into composite bleeding endpoints was an association with low PRU values and bleeding risk demonstrated. Frequency of TIMI major or minor bleeding over 30 months was low (1.5%), however, and bleeding was primarily gastrointestinal in origin.

**Figure 1.** Cumulative Kaplan–Meier (KM) estimates of Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) severe/life-threatening (LT) or moderate (A) and Thrombolysis In Myocardial Infarction (TIMI) major or minor (B) bleeding events by P2Y₁₂ reaction unit (PRU) tertiles of distribution.
This is the first large study that evaluated the 5-mg prasugrel dose used to mitigate bleeding risk and the relationship of PRU values with bleeding risk in patient populations that are vulnerable and eligible for this dose (ie, those with low body weight and the elderly). However, our findings highlight how clinical characteristics associated with...
bleeding risk strongly influence platelet response to P2Y<sub>12</sub> inhibitors and thus may confound any potential relationship between PRU values and risks of serious bleeding events. In the current study, patients in the lowest PRU tertile (PRU ≤ 105) were younger, had higher body weight, and had higher baseline creatinine clearance and hemoglobin values—all factors that are known to be associated with a lower risk of short- and intermediate-term bleeding among patients with ACS.19–23 Whereas patients in the lowest PRU tertile were more likely to be randomized to prasugrel and receive the prasugrel 10-mg maintenance dose (as expected from our previous evaluation of the PFS data according to randomized treatment assignment), the unadjusted risks of GUSTO severe/life-threatening or moderate and TIMI major or minor bleeding were highest among patients in the middle PRU tertile (PRU 106–211). Additionally, we have separately shown that elderly patients (≥75 years) from the TRILOGY ACS study population had a 2- to 3-fold increased risk of both
Table 3. Adjusted Associations of GUSTO and TIMI Composite Bleeding Definitions With Continuous PRU Distributions and the Derived Cut Points for Low Versus High Platelet Reactivity in All Patients

<table>
<thead>
<tr>
<th></th>
<th>Adjusted HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUSTO severe/life-threatening or moderate non-CABG bleeding</td>
<td>1.01 (0.96–1.06)</td>
<td>0.82</td>
</tr>
<tr>
<td>Continuous day 5 PRU (per 10-unit decrease)</td>
<td>0.68 (0.25–1.87)</td>
<td>0.46</td>
</tr>
<tr>
<td>Dichotomous (&lt;106) day 5 PRU (LPR vs HPR)*</td>
<td>2.30 (1.72–3.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GUSTO severe/life-threatening, moderate, or mild non-CABG bleeding</td>
<td>1.04 (1.02–1.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Continuous day 5 PRU (per 10-unit decrease)</td>
<td>2.35 (1.00–5.52)</td>
<td>0.05</td>
</tr>
<tr>
<td>Dichotomous (&lt;46) day 5 PRU (LPR vs HPR)*</td>
<td>2.34 (1.74–3.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIMI major or minor non-CABG bleeding</td>
<td>1.02 (0.98–1.07)</td>
<td>0.37</td>
</tr>
<tr>
<td>Continuous day 5 PRU (per 10-unit decrease)</td>
<td>2.35 (1.00–5.52)</td>
<td>0.05</td>
</tr>
<tr>
<td>Dichotomous (&lt;46) day 5 PRU (LPR vs HPR)*</td>
<td>2.34 (1.74–3.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIMI major, minor, or minimal non-CABG bleeding</td>
<td>1.04 (1.02–1.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Continuous day 5 PRU (per 10-unit decrease)</td>
<td>2.35 (1.00–5.52)</td>
<td>0.05</td>
</tr>
<tr>
<td>Dichotomous (&lt;46) day 5 PRU (LPR vs HPR)*</td>
<td>2.34 (1.74–3.14)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass graft; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; HPR, high platelet reactivity; HR, hazard ratio; LPR, low platelet reactivity; PRU, P2Y12 reaction unit; TIMI, Thrombolysis In Myocardial Infarction.

*The 4 derived cut points to determine bleeding risk were separately determined for each of the 2- and 3-level TIMI and GUSTO composite bleeding outcomes.

GUSTO and TIMI bleeding (using 2-level bleeding composite endpoints) when treated with either clopidogrel 75 mg/day or prasugrel 5 mg/day, as compared to younger patients.24 The underlying factors associated with increased bleeding risks for elderly patients are likely multifactorial (lower body weight, lower baseline creatinine clearance, and lower hemoglobin values compared to younger patients) and inter-related, but we observed similar findings in our adjusted analysis of the relationship of PRU values with bleeding risks when elderly patients were excluded. We previously observed that elderly patients had a less-robust PRU response to clopidogrel 75 mg daily compared to younger patients, so older age may be a much stronger contributor to bleeding risk irrespective of on-treatment PRU response to a P2Y12 inhibitor.12 Finally, our study is the first large study that included both a third-generation P2Y12 inhibitor (prasugrel) and clopidogrel when assessing the association of bleeding risk with PRU values. Further investigation is therefore needed to ascertain how interactions between clinical characteristics, the dose/type of P2Y12 inhibitor chosen for an individual patient, and on-treatment PRU values influence serious bleeding rates.

In contrast to the medically managed population studied in TRILOGY ACS, observational studies in patients treated with PCI have suggested that LPR during DAPT treatment may be associated with major bleeding risk.7–9,25,26 A prospective, randomized trial that leveraged bedside PRU monitoring to inform antiplatelet treatment decisions did not confirm this relationship, but findings from the ADAPT-DES prospective registry demonstrated an inverse relationship between high platelet reactivity (PRU >208) and clinically relevant bleeding in patients undergoing PCI.23,27,28 After successful PCI, lower platelet reactivity on clopidogrel was an independent predictor of postdischarge bleeding, and these bleedings had a strong relationship with mortality at the 2-year follow-up point.23 Another recent study in a cohort of patients who underwent elective PCI suggested that LPR provided incremental predictive value for bleeding events through 30 days compared with a bleeding risk score.29 Although the influence of platelet reactivity on bleeding risk may differ for patients who undergo PCI versus ACS patients who are managed without revascularization, the primary 2-level composite bleeding events in TRILOGY ACS occurred infrequently and were primarily spontaneous and unrelated to cardiovascular procedures. The present analysis from TRILOGY ACS thus provides novel evidence for the relationship of platelet reactivity measurements with bleeding risk for ACS patients treated with DAPT who did not undergo PCI.

Limitations

A number of limitations to our analysis should be noted. First, PRU values were missing across all time periods, and multiple imputation techniques were used to account for missing values. The back-imputation technique used to estimate day 5 PRU values requires assumptions about the stability of drug effects and steady state at 5 days postbaseline that may not be accurate. Second, the number of serious bleeding events was small, so this study was underpowered to determine whether there was a significant difference in bleeding risk using the 2-level composite GUSTO and TIMI bleeding outcomes. However, this is the largest platelet function substudy that has been embedded within a randomized clinical trial comparing post-ACS DAPT regimens beyond clopidogrel, so it is unlikely that a larger study will be conducted in the future to capture more-serious bleeding events. Third, the frequencies of GUSTO severe/life-threatening or moderate bleeding events and TIMI major or minor bleeding events were lower for patients who did versus did not participate in the PFS. These findings could be attributed to regional differences in the reporting and/or querying of suspected bleeding events that were further confounded by...
the choice of countries that participated in the PFS, but we were not able to investigate these potential assumptions. Finally, we did not analyze how clopidogrel metabolizer genomic variants influenced the relationship of bleeding risk with DAPT treatment in this analysis because we chose to focus solely upon the relationship of platelet reactivity measurements (regardless of genomic status and type/dose of P2Y₁₂ inhibitor used).

Conclusions

Among NSTE ACS patients managed without revascularization and receiving prolonged DAPT treatment, PRU values were not significantly associated with long-term serious bleeding risk. These hypothesis-generating results suggest that LPR does not independently predict the risk of serious bleeding during the period of DAPT treatment post-ACS.

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Disclosures

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References


Supplemental Material
Figure S1. Consort diagram demonstrating patient flow and PRU imputation approaches

9326 pts with UA or NSTEMI randomized in TRILOGY ACS to receive clopidogrel or prasugrel

2690 agree to participate in PFS

2564 included PFS

2558 safety population

2033 valid PRU values at Day 30 (i.e., Day 5)

525 missing PRU values at Day 30 (i.e., Day 5)

373 of these invalid observations have a valid PRU value after Day 30 (back-imputed)

395 of these invalid observations have a valid PRU value after Day 30 (back-imputed) or were on clopidogrel at home and randomized to clopidogrel with a PRU measurement before Day 30

2428 FINAL sample size used in this analysis

2426 landmarked analysis (5 day) GUSTO severe/LT moderate bleeding (non-CABG)

2425 landmarked analysis (5 day) TIMI major/minor bleeding (non-CABG)

6 ITT but not safety population
Table S1. Bleeding event rates by participation in the PFS*

<table>
<thead>
<tr>
<th></th>
<th>Included in PFS (N=2428)</th>
<th>Not Included in PFS (N=6812)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUSTO severe/life-threatening or moderate bleeding (%)</td>
<td>1.83%</td>
<td>3.63%</td>
</tr>
<tr>
<td>TIMI major or minor bleeding (%)</td>
<td>2.24%</td>
<td>3.81%</td>
</tr>
</tbody>
</table>

*Kaplan-Meier estimates of bleeding rates through 30 months

PFS, Platelet Function Sub-Study
Table S2. Baseline characteristics stratified by PRU values

<table>
<thead>
<tr>
<th>Demographics</th>
<th>PRU &lt;75 (N=601)</th>
<th>PRU ≥75 (N=1827)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>62.0 (56.0, 69.0)</td>
<td>66.0 (60.0, 74.0)</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Female sex</td>
<td>212/601 (35.3)</td>
<td>734/1827 (40.2)</td>
<td>0.033</td>
</tr>
<tr>
<td>White race</td>
<td>388/601 (64.6)</td>
<td>1120/1827 (61.3)</td>
<td>0.153</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76.0 (66.7, 87.5)</td>
<td>75.0 (63.0, 86.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>403/601 (67.1)</td>
<td>1221/1827 (66.8)</td>
<td>0.919</td>
</tr>
<tr>
<td>Killip class II-IV</td>
<td>52/601 (8.7)</td>
<td>231/1826 (12.7)</td>
<td>0.008</td>
</tr>
<tr>
<td>Time from FMC to treatment start, hrs</td>
<td>99.8 (54.9, 157.8)</td>
<td>108.9 (63.0, 160.9)</td>
<td>0.211</td>
</tr>
<tr>
<td>CV risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>179/536 (33.4)</td>
<td>503/1640 (30.7)</td>
<td>0.238</td>
</tr>
<tr>
<td>Hypertension</td>
<td>480/598 (80.3)</td>
<td>1508/1823 (82.7)</td>
<td>0.174</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>318/541 (58.8)</td>
<td>1011/1699 (59.5)</td>
<td>0.765</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>190/600 (31.7)</td>
<td>712/1825 (39.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Current/recent smoking</td>
<td>118/594 (19.9)</td>
<td>322/1808 (17.8)</td>
<td>0.261</td>
</tr>
<tr>
<td>Prior peptic ulcer disease</td>
<td>38/596 (6.4)</td>
<td>102/1815 (17.8)</td>
<td>0.494</td>
</tr>
<tr>
<td></td>
<td>PRU &lt;75 (N=601)</td>
<td>PRU ≥75 (N=1827)</td>
<td>P-value</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------------</td>
<td>------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Angiography performed</td>
<td>252/601 (41.9)</td>
<td>690/1827 (37.8)</td>
<td>0.069</td>
</tr>
<tr>
<td>CV disease history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>282/595 (47.4)</td>
<td>776/1818 (42.7)</td>
<td>0.044</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>170/599 (28.4)</td>
<td>474/1822 (26.0)</td>
<td>0.256</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>72/601 (12.0)</td>
<td>271/1825 (14.8)</td>
<td>0.080</td>
</tr>
<tr>
<td>Prior PAD</td>
<td>28/590 (4.7)</td>
<td>101/1794 (5.6)</td>
<td>0.410</td>
</tr>
<tr>
<td>Prior atrial fibrillation</td>
<td>33/589 (5.6)</td>
<td>172/1795 (9.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>Prior chronic heart failure</td>
<td>110/593 (18.5)</td>
<td>372/1811 (20.5)</td>
<td>0.293</td>
</tr>
<tr>
<td>Baseline labs and measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRACE risk score</td>
<td>114.0 (42.0, 201.0)</td>
<td>123.0 (54.0, 205.0)</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.0 (0.8, 1.1)</td>
<td>1.0 (0.8, 1.2)</td>
<td>0.094</td>
</tr>
<tr>
<td>CrCL, mL/min</td>
<td>82.3 (62.5, 105.6)</td>
<td>71.8 (54.0, 94.7)</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>127.0 (115.0, 138.0)</td>
<td>129.0 (118.0, 140.0)</td>
<td>0.334</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>68.0 (61.0, 75.0)</td>
<td>70.0 (62.0, 76.0)</td>
<td>0.068</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>14.0 (13.0, 15.1)</td>
<td>13.5 (12.5, 14.6)</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Concomitant medications at</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PRU &lt;75 (N=601)</td>
<td>PRU ≥75 (N=1827)</td>
<td>P-value</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------------</td>
<td>------------------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>randomization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily dose &lt;100 mg</td>
<td>233/601 (38.8)</td>
<td>735/1827 (40.2)</td>
<td>0.526</td>
</tr>
<tr>
<td>Daily dose 100-250 mg</td>
<td>266/601 (44.3)</td>
<td>842/1827 (46.1)</td>
<td>0.435</td>
</tr>
<tr>
<td>Daily dose &gt;250 mg</td>
<td>43/601 (7.2)</td>
<td>131/1827 (7.2)</td>
<td>0.990</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>476/601 (79.2)</td>
<td>1395/1827 (76.4)</td>
<td>0.150</td>
</tr>
<tr>
<td>ACE-I/ARB</td>
<td>419/601 (69.7)</td>
<td>1337/1827 (73.2)</td>
<td>0.100</td>
</tr>
<tr>
<td>Statin</td>
<td>502/601 (83.5)</td>
<td>1499/1827 (82.0)</td>
<td>0.408</td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>121/601 (20.1)</td>
<td>446/1827 (24.4)</td>
<td>0.032</td>
</tr>
<tr>
<td><strong>Randomization specific information</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel strata</td>
<td></td>
<td></td>
<td>0.014</td>
</tr>
<tr>
<td>1</td>
<td>24/601 (4.0)</td>
<td>89/1827 (4.9)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>433/601 (72.0)</td>
<td>1198/1827 (65.6)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>144/601 (24.0)</td>
<td>540/1827 (29.6)</td>
<td></td>
</tr>
<tr>
<td>Randomized treatment</td>
<td>503/601 (83.7)</td>
<td>699/1827 (38.3)</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Duration of clopidogrel use before treatment start, hrs</td>
<td>108.3 (62.8, 149.3)</td>
<td>107.9 (65.0, 156.6)</td>
<td>0.794</td>
</tr>
<tr>
<td>Age ≥75 yrs</td>
<td>41/601 (6.8)</td>
<td>427/1827 (23.4)</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Weight &lt;60 kg</td>
<td>50/601 (8.3)</td>
<td>324/1827 (8.3)</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td></td>
<td>PRU &lt;75 (N=601)</td>
<td>PRU ≥75 (N=1827)</td>
<td>P-value</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------------</td>
<td>------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Prasugrel maintenance 5 mg</td>
<td>54/503 (10.7)</td>
<td>302/699</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td></td>
<td>(43.2)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Baseline PRU values</td>
<td>179.0 (115.0,</td>
<td>238.0 (179.0,</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td></td>
<td>249.0)</td>
<td>295.0)</td>
<td>1</td>
</tr>
</tbody>
</table>

Data are presented as medians (25th, 75th percentiles) or n/N (%).

ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BP, blood pressure; CAD, coronary artery disease; CABG, coronary artery bypass graft; CrCl, creatinine clearance; CV, cardiovascular; FMC, first medical contact; GRACE, Global Registry of Acute Coronary Events; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PFS, Platelet Function Substudy; PRU, P2Y12 reaction unit; NSTEMI, non-ST-segment elevation myocardial infarction.
Table S3. Distribution of bleeding locations for the exploratory analyses (3-level bleeding)

<table>
<thead>
<tr>
<th>Location</th>
<th>GUSTO severe/life-threatening or moderate or mild bleeding</th>
<th>TIMI major or minor or minimal bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>47</td>
<td>50</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>63</td>
<td>59</td>
</tr>
<tr>
<td>Hematuria</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Intraocular</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>No site identified</td>
<td>9</td>
<td>.</td>
</tr>
<tr>
<td>Other</td>
<td>132</td>
<td>136</td>
</tr>
<tr>
<td>Subdural hematoma</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Surgical incision site</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Urethral</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Vaginal</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Vascular access site</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>297</strong></td>
<td><strong>290</strong></td>
</tr>
</tbody>
</table>

GUSTO indicates Global Use of Strategies to Open Occluded Coronary Arteries; TIMI, Thrombolysis In Myocardial Infarction.
Table S4. Adjusted associations of GUSTO and TIMI composite bleeding definitions with continuous PRU Distributions and the derived cut-points for low vs. high platelet reactivity restricted to patients aged <75 years

<table>
<thead>
<tr>
<th></th>
<th>Adjusted HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GUSTO severe/life-threatening or moderate non-CABG bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous day 5 PRU (per 10-unit decrease)</td>
<td>1.01 (0.95–1.06)</td>
<td>0.85</td>
</tr>
<tr>
<td>Dichotomous (&lt;106) day 5 PRU (LPR vs. HPR)</td>
<td>0.61 (0.20–1.84)</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>GUSTO severe/life-threatening, moderate, or mild non-CABG bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous day 5 PRU (per 10-unit decrease)</td>
<td>1.04 (1.03–1.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dichotomous (&lt;75) day 5 PRU (LPR vs. HPR)</td>
<td>2.19 (1.61–2.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>TIMI major or minor non-CABG bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous day 5 PRU (per 10-unit decrease)</td>
<td>1.02 (0.98–1.07)</td>
<td>0.35</td>
</tr>
<tr>
<td>Dichotomous (&lt;46) day 5 PRU (LPR vs. HPR)</td>
<td>1.99 (0.81–4.90)</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>TIMI major, minor, or minimal non-CABG bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous day 5 PRU (per 10-unit decrease)</td>
<td>1.04 (1.03–1.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dichotomous (&lt;75) day 5 PRU (LPR vs. HPR)</td>
<td>2.21 (1.62–3.02)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CABG, coronary artery bypass graft; CI, confidence interval; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; HPR, high platelet reactivity; HR, hazard ratio; LPR, low platelet reactivity; PRU, P2Y₁₂ reaction unit; TIMI, Thrombolysis In Myocardial Infarction.