Impact of Platelet Reactivity on Clinical Outcomes After Percutaneous Coronary Intervention
A Collaborative Meta-Analysis of Individual Participant Data

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Objectives
The purpose of the study was to systematically evaluate the significance of platelet reactivity on clopidogrel treatment on adverse cardiovascular events using a collaborative meta-analysis using patient-level data for the VerifyNow P2Y12 assay (Accumetrics, San Diego, California).

Background
Clinical evidence has been controversial regarding the influence of clopidogrel on treatment platelet reactivity and ischemic outcomes.

Methods
MEDLINE, Scopus, and the Cochrane library databases were searched through January 2010. A database containing individual patient-level time-to-event data was generated from identified studies. The primary outcome of interest was a composite of death, myocardial infarction (MI), or stent thrombosis. Secondary outcomes included the incidence of: 1) death; 2) MI; and 3) stent thrombosis.

Results
A total of 6 studies with 3,059 patients was included. In each study, clopidogrel responsiveness was assessed using the same point-of-care assay after percutaneous coronary intervention. The primary endpoint occurred more frequently in higher quartiles of P2Y12 reaction unit (PRU) values: quartile I, 5.8%; quartile II, 6.9%; quartile III, 10.9%; quartile IV, 15.8% (p<0.001). Taking quartile I as referent, the hazard ratios (HRs) for the primary endpoint were as follows: quartile II, HR: 1.13 (95% confidence interval [CI]: 0.72 to 1.78; p=0.60); quartile III, HR: 1.82 (95% CI: 1.20 to 2.75; p=0.005); quartile IV, HR: 2.62 (95% CI: 1.78 to 3.87; p<0.001). On a continuous scale, every 10-U increase in PRU was associated with a significantly higher rate of the primary endpoint (HR: 1.04; 95% CI: 1.03 to 1.06; p<0.0001). According to receiver-operating characteristic curve analysis, a PRU value of 230 appeared to best predict death, MI, or stent thrombosis. Secondary outcomes included the incidence of: 1) death; 2) MI; and 3) stent thrombosis.

Conclusions
In this collaborative meta-analysis, the level of on-treatment platelet reactivity according to the P2Y12 assay is associated with long-term cardiovascular events after percutaneous coronary intervention, including death, MI, and stent thrombosis. (J Am Coll Cardiol 2011;58:1945–54) © 2011 by the American College of Cardiology Foundation
Dual antiplatelet therapy with aspirin and a thienopyridine is essential after percutaneous coronary intervention (PCI) with stent implantation (1,2), however, significant interindividual variability exists in clopidogrel-induced inhibition of platelet activation through the P2Y12 pathway. Several methods for assessment of on-clopidogrel treatment platelet reactivity have been developed (3). Although high on-treatment platelet reactivity has been associated with adverse cardiac events after PCI, the studies have had limited sample sizes, involved only single centers, and assessed only composite clinical endpoints. Therefore, we sought to investigate the relation of high on-treatment platelet reactivity with both composite and individual ischemic outcomes after PCI using a collaborative meta-analysis of patient-level data, and to derive a clinically meaningful cut-off platelet reactivity value to identify patients at risk of future ischemic events.

### Methods

**Literature search.** We identified published studies assessing platelet reactivity using uniform methodology with a commercially available, point-of-care, cartridge-based assay (VerifyNow P2Y12 assay, Accumetrics, San Diego, California). The search criteria used were key words, databases, and conference proceedings. Key words included the following in various combinations: platelet reactivity, clopidogrel, and VerifyNow. The databases searched included MEDLINE (1966 through January 2010), Scopus (1980 through January 2010), and the Cochrane Library (1993 through January 2010). We also searched conference proceedings of the American College of Cardiology, American Heart Association, Transcatheter Cardiovascular Therapeutics, and European Society of Cardiology for “late breaking” presentations from 2005 to 2009. The references of review articles, meta-analysis, and evidence-based guidelines were reviewed by 2 authors (S.S.B. and G.D.) (1,2,4). We did not use language restriction in the search.

**Study selection.** To be included in this analyses studies needed to meet the following criteria: 1) use the VerifyNow P2Y12 test to assess platelet reactivity; 2) report the timing of assay performance in relation to PCI and clopidogrel loading; 3) report outcomes for death and myocardial infarction (MI); and 4) report at least 30-day follow-up. Articles meeting the inclusion criteria were selected for further analysis. The investigators of the identified studies were contacted, and each agreed to provide patient-level data.

**Study outcomes and data collection.** The primary endpoint of this study was the composite of death, MI, or stent thrombosis from the index PCI. The endpoints were defined according to the individual study protocols. Secondary endpoints included each 1 of the above components of the primary endpoint.

An electronic form containing the data elements to be completed for the patient-level meta-analysis was sent to all the principal investigators of the identified studies. Individual patient-level data were provided for all 6 trials identified. The data requested for each enrolled patient included the date of the procedure, diabetes mellitus status, event status (including death, MI, or stent thrombosis), age, sex, hypertension status, dyslipidemia, type of clinical presentation, stent type, and date of last follow-up. Any queries were resolved, and the respective study investigators verified the final database entries.

**PCI and antiplatelet management.** All interventions were performed according to local standards. The type of stent implanted was left to the discretion of the operator in all studies. All patients received 1 clopidogrel loading dose of 300 to 600 mg followed by a daily dose of 75 mg. Aspirin, 100 to 325 mg orally, was administered post-procedure. Anticoagulation therapy with either heparin or bivalirudin was at the discretion of the operator.

**Platelet reactivity assessment.** The time of blood withdrawal for P2Y12 testing was at the time of PCI in patients pre-treated with clopidogrel or at least 1 day after the clopidogrel loading dose. A uniform testing method for clopidogrel responsiveness was selected to eliminate the variability in assessment of platelet reactivity by different hematologic assays. Platelet reactivity testing to clopidogrel therapy was performed using the VerifyNow P2Y12 assay (Accumetics). This method has been approved for human use by the U.S. Food and Drug Administration. This assay is a turbidimetry-based optical detection device that measures platelet-induced aggregation in a system containing fibrinogen-coated beads. The P2Y12 assay contains 20 μM ADP, as the platelet agonist, and 22 nmol prostaglandin E1, to reduce the contribution of ADP binding to P2Y12 receptors. The instrument measures platelet-induced aggregation of the beads as an increase in light and expresses the results as P2Y12 reaction units (PRU).

**Statistical methods.** Categorical variables were compared by the chi-square test or Fisher exact test. Continuous variables are reported as mean ± SD and were compared by unpaired t tests. For variables that were not normally distributed (e.g., PRU quartiles), the Wilcoxon test was...
used for comparing 2 groups, and the Kruskal-Wallis for >2 groups (e.g., PRU values between studies).

Time-to-event data are reported and displayed using the Kaplan-Meier method, with comparisons between groups performed using the log-rank test. Cumulative survival curves by PRU quartiles were constructed by the Kaplan-Meier method. Quartiles II, III, and IV were compared to quartile I with the log-rank test. In the survival analyses, adjustments for multiple comparisons were performed by applying the Sidák correction to the raw p values (5). Analyses were truncated at 2 years of follow-up because of the small number of patients with available data thereafter. Cox proportional hazards models were also generated for the primary efficacy and safety outcomes. The proportionality assumption was tested using log(−log) plots and Schoenfeld residuals; the assumption was satisfied by both tests.

A landmark analysis was used to determine if there were long-term differences in the primary endpoint between groups with normal versus high on-treatment platelet reactivity after excluding periprocedural events. In this analysis, all patients with events within the first 3 days after PCI were excluded.

Logistic regression was used to generate a receiver-operating characteristic curve for the PRU values and the primary endpoint. The area under the curve (AUC) or c-statistic was determined from this model, as was the optimal cutpoint; the latter was determined by the PRU value that maximized the following relationship: sensitivity − (1 − specificity). Model goodness of fit was tested and satisfied by the Hosmer-Lemeshow goodness-of-fit test. The robustness of the PRU threshold value was also assessed in sensitivity analyses. The cohort was randomly divided into a derivation and validation dataset, with 50% of the sample distributed to each dataset. In the derivation dataset, bootstrap estimates (sampling with replacement) of the PRU threshold were calculated for 100 iterations, yielding the best average cutoff and 95% confidence interval (CI). For estimates of standard errors and normal approximation CI, 100 bootstrap replications are generally adequate. Next, Kaplan-Meier failure estimates and hazard ratios (HR) were calculated using the PRU threshold in the derivation and validation cohorts.

The increased discriminative value of platelet function testing was further examined using net reclassification improvement (NRI) and integrated discrimination improvement (IDI) (6). The NRI was calculated by assessing the net improvement in risk classification. This method requires that there exist a priori risk categories. In the absence of well-established risk categories, we used 0% to 4%, 5% to 10%, and >10% for the risk of the composite endpoint of death, MI, or stent thrombosis (Online Appendix).

Subgroups for further analyses were specified a priori and included age, sex, diabetes status, stent type, and acute coronary syndrome presentation. The Cochrane Q statistic and the I² statistic were used to assess the heterogeneity across trials. A Cochrane Q statistic with a p value ≤0.1 was considered significant. The I² statistic was used to measure the consistency among trials with values of 25%, 50%, and 75% showing, respectively, low, moderate, and high heterogeneity. A funnel plot was used to assess for the presence of publication and other reporting biases by plotting the standard error against the log risk ratio. Using Egger's regression method, we examined the association between the study size and estimated treatment (7).

The p value threshold for statistical significance was set at 0.05. Analyses were conducted by S.S.B in Stata 10.1 (Stata Corp., College Station, Texas) and SAS version 9.2 (SAS Institute, Cary, North Carolina). The study was performed in accordance to the recommendations set forth by the QUOROM (Quality of Reporting of Meta-Analysis) and the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) work groups (8,9).

Results

Eight studies were identified, and 6 were included in the pooled analysis. Follow-up in 1 study was limited to in-hospital events, and therefore it did not meet inclusion criteria (10). We also excluded 1 study where testing was performed in an unspecified time frame shortly after oral clopidogrel loading dose was administered (11). The authors of all 6 studies that met inclusion criteria provided patient-level data for analysis (12–17). Data on death and MI were available from all 6 studies; stent thrombosis data were available from 5 of the studies. Data were collected prospectively in each of the studies included. Endpoints were adjudicated by an independent endpoints committee in 2 of the studies (12,17). When studies included treatment arms or groups treated with antiplatelet therapies other than clopidogrel and aspirin, we only included patients receiving the combination of clopidogrel and aspirin (13,14).

Study characteristics are shown in Table 1. The age of the cohort was 66 ± 10 years, 68% were male, 24% were diabetic, 74% had hypertension, 64% had dyslipidemia, and 20% were smokers. The time of blood withdrawal for P2Y12 testing was at the time of PCI in patients pre-treated with clopidogrel or at least 1 day after the clopidogrel loading dose. The distribution of PRU values by study and quartile is shown in Figure 1. The mean platelet reactivity of the full cohort was 196.5 ± 84.5 PRU and the median was 200 PRU (interquartile range [IQR]: 121 PRU). The median values were qualitatively comparable between studies, except for the study by Campo et al. (13), which had the lowest median PRU value (p < 0.001). Quartile I represents patients with the lowest on-treatment platelet reactivity, whereas quartile IV represents patients with the highest on-treatment platelet reactivity. In the full study cohort, the mean PRU values for quartiles I to IV were 84.5 ± 37.3, 171 ± 18.7, 229.7 ± 16.7, and 301 ± 32.9, respectively (p
The median PRU values were 92 (IQR: 57), 172 (IQR: 33), 229 (IQR: 28), and 294 (IQR: 49), respectively (p < 0.001). The PRU range for quartiles I to IV were <138, 138 to 200, 201 to 258, and >258, respectively.

Heterogeneity and small study effects. Before performing the pooled analysis, we assessed heterogeneity across studies. There was no evidence for heterogeneity between studies by either the Cochrane Q statistic (p = 0.56) or the I² statistic (I² = 0%). Also, visual inspection of the funnel plot did not reveal asymmetry in the studies (Online Fig. 1). In support, Egger’s regression test was not statistically significant for a small study effect or publication bias (p = 0.62).
Main outcomes. The long-term clinical outcomes for the primary composite endpoint of death, MI, or stent thrombosis are shown in Figure 2. Multiple pair-wise comparisons were performed, taking quartile I as referent. All pair-wise comparisons were adjusted for multiple testing as previously described. The event rates were similar between quartiles I and II (p = 0.97). However, the event rates in quartiles III and IV were significantly greater compared to quartile I (p = 0.02 and p < 0.001, respectively). The HRs for the primary endpoint for quartiles II, III, and IV compared to quartile I were 1.13 (95% CI: 0.72 to 1.78), 1.82 (95% CI: 1.20 to 2.75), and 2.62 (95% CI: 1.77 to 3.87), respectively. When PRU values were analyzed on the continuous scale, there remained a statistically significant association. There was a 4% increase in the primary endpoint for every 10-unit increase in PRU (HR: 1.04; 95% CI: 1.03 to 1.06; p < 0.0001).

The rate of death was not significantly different across PRU quartiles, although the highest rate of death occurred in quartile IV (Fig. 3A). The pair-wise comparisons, taking quartile I as referent, were not significantly different for quartile II (p = 0.97), quartile III (p = 0.92), and quartile IV (p = 0.30). The HRs for mortality for quartiles II, III, and IV compared to quartile I were 0.84 (95% CI: 0.39 to 1.81), 1.24 (95% CI: 0.62 to 2.50), and 1.67 (95% CI: 0.85 to 3.23), respectively.

The rate of MI differed significantly between quartiles (Fig. 3B). The pair-wise comparison, taking quartile I as referent, was similar for quartile II (p = 0.78), but the event rate was significantly greater in quartile III (p = 0.007) and quartile IV (p < 0.001). The HRs for MI for quartiles II, III, and IV compared to quartile I were 1.34 (95% CI: 0.78 to 2.30), 2.23 (95% CI: 1.36 to 3.64), and 2.93 (95% CI: 1.82 to 4.71), respectively.

The rate of stent thrombosis by PRU quartile is shown in Figure 3C. The event rate was significantly greater in quartile IV compared to quartile I, 3.4% versus 0.4%, respectively (p = 0.002). However, there was no significant difference between quartile II (p = 0.67) and quartile III (p = 0.59) compared to quartile I. The corresponding HRs for quartiles II, III, and IV, taking quartile I as referent, were 3.26 (95% CI: 0.68 to 15.69), 3.11 (95% CI: 0.65 to 14.96), and 7.48 (95% CI: 1.72 to 32.52), respectively.

Threshold analysis. Using logistic regression, a receiver-operating characteristic curve was able to distinguish between patients with and without subsequent ischemic events (AUC: 0.61; 95% CI: 0.57 to 0.65; p < 0.001). The optimal cut-off value to predict death, MI, or stent thrombosis was a PRU value of 230, with corresponding sensitivity, specificity, positive predictive value, and negative predictive values of 55%, 65%, 11%, and 95%, respectively. Patients with PRU values ≥230 were categorized as having high on-treatment platelet reactivity, and patients with values <230 as having normal on-treatment platelet reactivity. There were no differences in patients with or without high on-treatment platelet reactivity for female sex (36% vs. 39%; p = 0.11), hypertension (32% vs. 38%; p = 0.22), dyslipidemia (37% vs. 37%; p = 0.92), or an acute coronary syndrome (36% vs. 38%; p = 0.54). However, diabetes was significantly more frequent among subjects with high on-treatment platelet reactivity, 30% versus 21% (p < 0.001).
The Kaplan-Meier curve for the composite primary endpoint of death, MI, or stent thrombosis is shown in Figure 4A. Patients with high on-treatment platelet reactivity had a significantly higher event rate for the primary endpoint, 14.7% versus 7.0% (p < 0.001); the corresponding HR for the high versus normal on-treatment platelet reactivity was 2.10 (95% CI: 1.62 to 2.73; p < 0.0001) (Table 2). When effects on individual endpoints were examined, a PRU value ≥230 was associated with a significantly higher rate of mortality (HR: 1.66; 95% CI: 1.03 to 2.68; p = 0.04), MI (HR: 2.04; 95% CI: 1.51 to 2.76; p < 0.001), and stent thrombosis (HR: 3.11; 95% CI: 1.50 to 6.46; p = 0.002).

In sensitivity analyses, we divided the cohort into derivation and validation datasets. Using the derivation dataset, the bootstrap (sampling with replacement) analysis comprising 100 iterations yielded a PRU threshold value similar to the main analysis; the average best PRU cutoff was 231 (95% CI: 190 to 272) (Online Table 1). In the derivation dataset, the Kaplan-Meier failure rate among subjects above the 231 threshold was 14.1% compared to 7.1% among...
subjects below the cutoff (p = 0.0001); the corresponding HR was 2.07 (95% CI: 1.50 to 2.86; p < 0.001) (Online Fig. 2). The performance of the PRU threshold was then evaluated in the validation dataset. The Kaplan-Meier failure estimate for the event rate remained qualitatively unchanged; it was 14.8% for patients above the threshold and 7.3% for patients below the threshold (p = 0.0002); the HR was 2.00 (95% CI: 1.38 to 2.91; p < 0.001) (Online Fig. 3).

The net discrimination improvement was also determined for the PRU threshold value of 230 as well as PRU quartiles. The net discrimination improvement was 0.23 in both analyses (p < 0.001). The IDI was also similar for both PRU variables; in both analyses, the IDI was 0.01 (p < 0.001). Reclassification tables are provided in the Online Appendix.

**Subgroup analysis.** The event rates for pre-specified subgroups of sex, age, diabetes, and clinical presentation were also determined (Table 3). High on-treatment platelet reactivity was associated with higher rates of death, MI, or stent thrombosis for men and women, for patients ages >65 years or <65 years, and for persons with or without an acute coronary syndrome presentation. However, for diabetes, assessment of platelet reactivity was associated with a significantly higher event rate in the cohort without diabetes only. The HR for subjects with high versus normal on-treatment platelet reactivity was 2.49 (95% CI: 1.84 to 3.39; p < 0.0001) for nondiabetic patients and 1.30 (95% CI: 0.79 to 2.15; p = 0.32) for diabetic patients (p interaction = 0.03).

In post-hoc analyses, we investigated the relationship between type of stent and adverse cardiovascular outcomes. For the composite primary endpoint of death, MI, or stent thrombosis, the HR for high versus normal on-treatment reactivity for patients treated with bare metal stents or drug-eluting stents was 2.49 (95% CI: 1.44 to 4.32; p = 0.001) and 2.27 (95% CI: 1.57 to 3.03; p < 0.001), respectively.

**Sensitivity and influence analysis.** Because peri-procedural MI was included in certain studies, we performed a sensitivity analysis where all events in the first 3 days after PCI were censored. In this 3-day landmark analysis, the results were qualitatively similar to those in the main analysis. The rate of the composite primary endpoint was significantly greater in the high on-treatment platelet reactivity group, 10.1% versus 1.5% (HR: 3.08; 95% CI: 1.32 to 7.16; p = 0.009) for quartile II, 1.75 (95% CI: 1.04 to 2.95; p = 0.035) for quartile III, and 2.15 (95% CI: 1.31 to 3.52; p = 0.003) for quartile IV. For patients with a PRU value ≥230 versus <230, the results were also similar to the main analysis; the HR for death, MI, or stent thrombosis for PRU ≥230 versus <230 was 1.83 (95% CI: 1.27 to 2.62; p = 0.001).

**Discussion**

We performed a patient-level pooled meta-analysis of 6 prospective studies that quantified on-clopidogrel platelet reactivity with a uniform methodology in patients undergoing PCI. The principal finding of our study is that higher on-treatment platelet reactivity measured using the VerifyNow P2Y12 assay was predictive of long-term ischemic events.

**Main outcomes.** We observed a higher event rate of the composite primary endpoint of death, MI, or stent thrombosis for increasing levels of on-treatment platelet reactivity through 2 years of follow-up. Importantly, the highest quartile of PRU values (i.e., highest level of on-treatment platelet reactivity), was also associated with a significant increase in the individual rates of nonfatal MI and stent thrombosis. The event rate for the primary endpoint in the highest quartile of PRU values was significantly greater compared to the lowest quartile, 15.8% versus 5.8% (HR: 2.62; 95% CI: 1.77 to 3.87; p < 0.001). Quartile III was also associated with a higher rate of death, MI, and stent thrombosis when compared to quartile I (p = 0.005). For the primary or secondary endpoints, there were no significant differences between quartiles I and II. Therefore, our observations support a threshold effect for the relationship between on-treatment reactivity and ischemic events after PCI. We identified a potential cut-off value of a PRU >230 for high on-treatment platelet reactivity and the composite endpoint of death, MI, or stent thrombosis after PCI using receiver-operator characteristics curve analysis.

**Stent thrombosis.** Stent thrombosis remains a vexing problem associated with a high rate of morbidity and mortality after PCI. In both the quartile and threshold analysis using the 230 PRU cut-off, we observed a significantly higher rate of stent thrombosis in persons with higher on-treatment platelet reactivity. The stent thrombosis rate using the threshold value of 230 PRU was 3.0% vs. 1.0%; the corresponding HR was 3.11 (95% CI: 1.50 to 6.46; p = 0.002). A similar observation was made in a smaller cohort study using ADP mediated platelet aggregation. In that study, non-responsiveness to clopidogrel was associated with a HR of 3.08 (95% CI: 1.32 to 7.16; p = 0.009) for stent thrombosis (18). The ability of a single antiplatelet aggregation assessment after PCI to predict stent thrombosis may have important clinical implications.

**Sensitivity analyses and subgroups.** We performed a landmark analysis in an attempt to better understand the importance of platelet P2Y12 reactivity testing after PCI with respect to longer-term outcomes. There remained a significant...
association between on-treatment platelet reactivity and long-term out-of-hospital ischemic events when events during the first 3-days after PCI were excluded. This observation further supports the relationship between high on-treatment platelet reactivity identified around the time of PCI and the risk of long-term adverse cardiovascular events.

We performed several pre-specified subgroup analyses to determine whether the effect of high on-treatment reactivity was consistent across the population studied. We observed similar rates of the composite of death, MI, or stent thrombosis for subjects >65 or ≤65 years of age, for women and men, for the presence of or absence of an acute coronary syndrome presentation, and for patients treated with drug-eluting or bare metal stents. Interestingly, we observed a potential interaction in the diabetic subgroup. Quantifying platelet reactivity after PCI appeared significantly predictive in patients without diabetes but did not reach statistical significance in patients with diabetes. That raises the questions of whether risk stratification with platelet function testing may be especially important for patients without diabetes; this potential interaction warrants further investigation in future studies.

**Threshold analyses.** The threshold PRU value of 230, obtained using the full cohort, is associated with an increase in death, MI, and stent thrombosis after PCI. To assess the robustness of this value, the full cohort was divided into derivation and validation datasets. The PRU threshold from this analysis, 231, was qualitatively similar to the 230 cutoff. The composite primary outcome was validated internally using the derivation dataset by sampling with replacement for 100 iterations. External validation was performed using the validation cohort. Kaplan-Meier failure rates and corresponding HRs were similar in the derivation and validation cohorts, supporting the PRU threshold identified.

Despite the statistical significance and consistency of these findings, the AUC or c-statistic of the assay used was modest. The AUC in the component studies ranged from 0.61 to 0.80, and in the pooled analysis, it was 0.61. Receiver-operating characteristic curve analysis is frequently used to describe diagnostic test performance, with the AUC being indicative of the discriminatory ability of the test in question compared to a gold standard (19). Whereas diagnostic tests used to identify patients with a specific disease often have high AUCs, tests used to identify patients at risk of having a clinical endpoint (like that examined in the present study) often have modest AUCs. Prognostication frequently involves estimating risk or the probability of a future event, adding a stochastic element, distinguishing this task from diagnosis (20). Methods are not well developed for time to event data; therefore, AUC values from predictive models should be interpreted cautiously (21). For comparison, in a comprehensive assessment by the Agency for Health Care Quality and Research the AUC for B-type natriuretic peptide (BNP) and NT-proBNP were 0.57 to 0.88 across several studies, not notably different from the AUC range observed using the VerifyNow P2Y12 assay in

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### Table 2

**Event Rates According to On-Treatment Platelet Reactivity Status**

<table>
<thead>
<tr>
<th>On-Treatment Platelet Reactivity, n/N (%)</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRU ≤230</td>
<td>PRU &gt;230</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death/MI/stent thrombosis</td>
<td>124/1,133 (11.1)</td>
<td>103/1,908 (7.0)</td>
<td>2.10 (1.62–2.73)</td>
</tr>
<tr>
<td>Death</td>
<td>33/1,133 (4.5)</td>
<td>34/1,908 (2.5)</td>
<td>1.66 (1.03–2.68)</td>
</tr>
<tr>
<td>MI</td>
<td>92/1,133 (10.3)</td>
<td>78/1,908 (5.2)</td>
<td>2.04 (1.51–2.76)</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>26/625 (3.8)</td>
<td>14/1,087 (1.5)</td>
<td>3.11 (1.50–6.46)</td>
</tr>
</tbody>
</table>

*n = number of events; N = number of subjects per group; % = rates are Kaplan-Meier estimates.

### Table 3

**Selected Subgroup Analysis by On-Treatment Platelet Reactivity Status**

<table>
<thead>
<tr>
<th>Death/MI/Stent Thrombosis</th>
<th>On-Treatment Platelet Reactivity, n/N (%)</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>p Value†</th>
<th>p Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>87/748 (16.2)</td>
<td>70/1,324 (7.1)</td>
<td>2.37 (1.73–3.24)</td>
<td>&lt;0.0001</td>
<td>0.27</td>
</tr>
<tr>
<td>Female</td>
<td>37/385 (12.1)</td>
<td>33/601 (6.4)</td>
<td>1.73 (1.08–2.78)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Age &gt;65 yrs</td>
<td>77/697 (14.6)</td>
<td>64/1,022 (8.4)</td>
<td>1.84 (1.32–2.56)</td>
<td>0.003</td>
<td>0.20</td>
</tr>
<tr>
<td>Age ≤65 yrs</td>
<td>47/436 (14.7)</td>
<td>39/904 (5.5)</td>
<td>2.56 (1.69–4.00)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Diabetes, yes</td>
<td>32/346 (13.1)</td>
<td>26/401 (10.9)</td>
<td>1.30 (0.79–2.15)</td>
<td>0.32</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes, no</td>
<td>92/787 (15.3)</td>
<td>74/1,522 (6.2)</td>
<td>2.49 (1.84–3.39)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Acute coronary syndrome, yes</td>
<td>16/144 (11.1)</td>
<td>11/256 (4.3)</td>
<td>2.97 (1.37–6.45)</td>
<td>0.006</td>
<td>0.64</td>
</tr>
<tr>
<td>Acute coronary syndrome, no</td>
<td>92/743 (12.4)</td>
<td>64/1,232 (5.2)</td>
<td>2.47 (1.79–3.40)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

*n = number of events; N = number of subjects per group; % = rates are Kaplan-Meier estimates. †The p value is for treatment comparisons within the subgroup. ‡The p value is testing the treatment × subgroup interaction estimates. Abbreviations as in Table 2.
the present study (22). Foregoing an attempt at a dichotomous separation, there remains a strong relationship between PRU values on the continuous scale and the primary endpoint. The rate of death, MI, or stent thrombosis increased by 4% for every 10-U increase in PRU (p < 0.0001); and there was a strong association observed using the 230 PRU cut-off with the "hard" clinical endpoints of death, nonfatal MI, and stent thrombosis, with an absolute risk difference of 7.7%. Also, both IDI and NRI support quantifying platelet reactivity; NRI improved classification for a net of 23% of subjects.

**Future directions.** Several antiplatelet strategies may potentially be used in patients with high on-treatment platelet reactivity (23–26). The GRAVITAS (Gauging Responsiveness With A VerifyNow Assay—Impact on Thrombosis and Safety) trial showed that increasing the clopidogrel maintenance dose from 75 mg to 150 mg daily did not lower ischemic events among low-risk subjects with high-on-treatment platelet reactivity; interestingly, bleeding events were also similar between groups (27). The event rate of 2.3% in both groups was considerably lower than predicted (5%); therefore, the trial was underpowered for the composite primary endpoint of death, MI, or stent thrombosis. In aggregate, these observations suggest very low risk patients were enrolled. Because stable patients after PCI were included in the GRAVITAS study, the event rates from our landmark analysis provide insight into the anticipated event rates. In the landmark analysis, the event rates at 180 days in the normal and high on-treatment platelet reactivity groups were 2.5% and 3.8%, respectively; this finding suggests the expected event rate of 5% and anticipated 50% relative risk reduction in the GRAVITAS trial was somewhat optimistic. A lower than expected event rate has also lead to the termination of the TRIGGER–PCI (Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) trial. In the present study, the greatest separation of the Kaplan–Meier curve was observed beyond 180 days; before 180 days, there was considerable overlap in the 95% CIs. These observations suggest that future trials will need to recruit larger cohorts, extend follow-up, or both. In summary, additional intervention trials are required to better understand how platelet function testing can be integrated into the treatment of patients undergoing PCI, including in the acute coronary syndrome setting where prasugrel is indicated. In the absence of such data, recommendations for routine testing are not possible.

**Study limitations.** In the present study, data regarding CYP2C19 genotype were not available; therefore, the impact of genotype on platelet function and clinical outcomes could not be assessed. Also, we were not able to assess bleeding complications because this outcome was not consistently included in the trials we included in our analysis. Bleeding complications are very important with respect to mortality risk; however, their clinical importance in relation to oral antiplatelet therapy has been recognized after completion of the studies we analyzed (28).

**Conclusions**

The results of this study show that high on-treatment platelet reactivity around the time of PCI is associated with long-term cardiovascular events including death, MI, and stent thrombosis. These findings were consistently observed in landmark, sensitivity, and influence analyses. Also, using the P2Y\textsubscript{12} point-of-care assay, a PRU value of ≥230 was associated with higher rates of death, MI, or stent thrombosis. Future randomized controlled trials investigating the role of oral antiplatelet therapy guided by P2Y\textsubscript{12} reactivity testing will provide insights into effective therapeutic interventions for patients with high on-treatment platelet reactivity.

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**REFERENCES**


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APPENDIX

For supplementary data, please see the online version of this article.