Platelet Reactivity and Cardiovascular Outcomes After Percutaneous Coronary Intervention

A Time-Dependent Analysis of the Gauging Responsiveness With a VerifyNow P2Y12 Assay: Impact on Thrombosis and Safety (GRAVITAS) Trial

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Background—In the Gauging Responsiveness With A VerifyNow P2Y12 Assay: Impact on Thrombosis and Safety (GRAVITAS) trial, 6 months of high-dose clopidogrel did not reduce cardiovascular events compared with standard-dose clopidogrel in patients with high on-treatment platelet reactivity (OTR) after percutaneous coronary intervention, defined as OTR ≥230 P2Y12 reaction units according to the VerifyNow P2Y12 platelet function test. The aim of this analysis was to examine the relationship between outcomes and OTR over the course of the trial.

Methods and Results—OTR was measured at 12 to 24 hours and 30±7 days after percutaneous coronary intervention. Cox proportional hazards models with OTR as a time-varying covariate were used to determine the association between OTR and the primary end point of cardiovascular death, myocardial infarction, and stent thrombosis. Of the 2800 enrolled patients, 2796 (99.98%) had evaluable platelet function data. OTR <208 P2Y12 reaction units was significantly associated with a lower risk of the primary end point at 60 days (hazard ratio, 0.18; 95% confidence interval, 0.04 to 0.79; P=0.02) and at 6 months (hazard ratio, 0.43; 95% confidence interval, 0.23 to 0.82; P=0.01). After adjustment for other significant predictors of outcome, OTR <208 P2Y12 reaction units remained independently associated with the primary end point at 60 days (hazard ratio, 0.23; 95% confidence interval, 0.05 to 0.98; P=0.047) and tended to be associated at 6 months (adjusted hazard ratio, 0.54; 95% confidence interval, 0.28 to 1.04; P=0.065).

Conclusions—In the GRAVITAS trial, achievement of on-clopidogrel reactivity <208 P2Y12 reaction units at 12 to 24 hours after percutaneous coronary intervention or during follow-up was associated with a lower risk for cardiovascular events. The efficacy of an individualized strategy to target a level of OTR below this threshold merits investigation.


Key Words: clopidogrel ▪ platelets ▪ randomized controlled trial ▪ stent thrombosis ▪ thrombosis

The pharmacodynamic effect of clopidogrel varies substantially among individuals.1–5 Numerous single-center, observational studies have demonstrated an association between the level of on-treatment reactivity at a single time point during clopidogrel therapy and the risk of cardiovascular events after percutaneous coronary intervention (PCI).3,4,6–18 Several of these studies have suggested “optimal” cutoffs to identify high-risk patients.4 The Gauging Responsiveness With a VerifyNow P2Y12 Assay: Impact on Thrombosis and Safety (GRAVITAS) trial tested a strategy of a fixed regimen of high-dose clopidogrel (600 mg followed by 150 mg daily for 6 months) in patients with high on-treatment reactivity (defined as ≥230 P2Y12 reaction units [PRU] according to the VerifyNow P2Y12 test). This strategy of a fixed higher dose, regardless of the achieved level of platelet inhibition, did not reduce cardiovascular death, myocardial infarction, and stent thrombosis after PCI compared with standard-dose clopidogrel (75 mg daily). The use of platelet function testing and individualized, adjusted dosing of clopidogrel according to an achieved level of platelet inhibition has shown promise in pilot studies.19,20 Therefore, we sought to explore the relationship between platelet reactivity while patients were receiving clopidogrel and the risk of subsequent cardiovascular events in the GRAVITAS trial.

Clinical Perspective on p 1137

Methods

Patient Population
GRAVITAS enrolled patients who had undergone PCI with 1 or more drug-eluting stents for the treatment of stable coronary artery disease or...
acute coronary syndrome (ACS) at 83 sites in the United States and Canada. If the patient had no prior exposure to clopidogrel, a dose of 600 mg had to have been administered no later than 2 hours after PCI. Patients already treated with clopidogrel must have received 75 mg daily for at least 7 days or, if <7 days, they must have received a loading dose of ≥300 mg at the time that clopidogrel was initiated. Patients already treated with clopidogrel could not receive an additional loading dose before assessment of platelet function. The other inclusion and exclusion criteria have been described previously.21,22 The trial was approved by the institutional ethics committee of each participating institution as well as by the appropriate national ethics committees. All patients provided written informed consent.

### Study Procedures

Platelet function was measured with the VerifyNow P2Y12 test 12 to 24 hours and 30±7 days after PCI. This test has been described previously in detail.21 In brief, this test measures ADP-induced platelet agglutination as an increase in light transmittance and utilizes a proprietary algorithm to report values in PRU. A higher PRU result reflects greater P2Y12-mediated platelet reactivity. Specialized software developed for the trial encrypted the platelet function test results to maintain double blinding. Study drug assignment was performed centrally by an interactive voice-response system. Study visits were conducted at 30 days and 6 months.

### Trial Enrollment and Study Drug Allocation

A total of 2214 patients with high on-treatment reactivity (≥230 PRU) while receiving clopidogrel therapy were randomly assigned in a 1:1 fashion to a regimen of high-dose or standard-dose clopidogrel. High-dose clopidogrel was given as a total first-day dose of 600 mg followed thereafter by a dose of 150 mg daily for 6 months; standard-dose clopidogrel was given as a loading dose of placebo followed by a dose of 75 mg and placebo tablet daily. A random sample of 586 patients without high on-treatment reactivity was enrolled with the use of a permuted block design and assigned to standard-dose clopidogrel in a blinded fashion (placebo loading dose followed by a dose of 75 mg and placebo tablet daily). Aspirin treatment was required at a dose of 75 to 162 mg daily. The baseline demographic and clinical characteristics of the treatment groups have been described previously.22

### End Points

#### Pharmacodynamic End Points

High on-treatment reactivity was prospectively defined as on-treatment reactivity ≥230 PRU. The rationale for this cutoff has been described previously.21 In this analysis, a second, post hoc cutoff of 208 PRU was also examined. This cutoff was identified as a predictor of death, myocardial infarction, and stroke at 1 year after elective PCI by the multicenter Tailoring Treatment With Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel (3T/2R) study.24

The Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel (TRIGGER PCI) randomized clinical trial (NCT00910299), which began enrollment after GRAVITAS had started, used this cutoff to identify patients at risk for ischemic events.

#### Clinical End Points

The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, and stent thrombosis. A clinical events committee blinded to treatment assignment and independent of the trial sponsor adjudicated all suspected primary end points.

### Statistical Analysis

Patients from all 3 study arms of GRAVITAS were pooled for this analysis given the overall lack of treatment effect of high-dose clopidogrel on clinical outcomes.22 Cox proportional hazards regression was used to test the association between the predefined cutoff values for on-treatment reactivity and outcomes, with on-treatment reactivity used as a time-varying covariate. Proportional hazards assumptions were evaluated with the use of Schoenfeld residuals. Patients without a platelet function measurement within the protocol-defined window of 30±7 days were censored at 37 days unless they had withdrawn from the study or had a cardiovascular event on or before day 37. Models were built for the association between on-treatment reactivity and outcome at 60 days after PCI (ie, 30 days after the platelet function test performed at 30-day follow-up) and for the association between on-treatment reactivity and outcome at 6 months. Multivariate time-dependent Cox regression analyses were further performed to adjust for clinical and procedural characteristics associated with outcome. The following candidate predictors were assessed: age, gender, body mass index, prior myocardial infarction, prior PCI, prior coronary artery bypass grafting, prior stroke or transient ischemic attack, history of diabetes mellitus, history of hypertension, history of hyperlipidemia, creatinine clearance ≤60 mL/min, number of lesions treated, multivessel PCI, periprocedural clopidogrel regimen, total stent length, ACS presentation, and use of a proton-pump inhibitor, β-blocker, calcium channel blocker, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or statin. Covariates that were associated with outcome at an α<0.05 level of significance were included as fixed covariates in the multivariate model. Categorical variables are reported as counts (percentages), and continuous variables are reported as mean±SD where appropriate. A cutoff of P<0.05 was determined a priori as the level to determine statistical significance. Analyses were performed with SAS version 9.2 (SAS Institute Inc, Cary, NC).

### Results

A total of 5429 patients were screened with platelet function testing 12 to 24 hours after PCI. Among the 5427 patients with available results, 3213 patients (59.2%) had on-treatment reactivity <230 PRU, and 2737 patients (50.4%) had on-treatment reactivity ≥208 PRU. A total of 2796 of the 2800 patients (99.98%) enrolled in GRAVITAS and followed on the study drug had evaluable platelet function data and were included in this analysis (Figure). None of the 4 patients without platelet function data experienced a primary end point event. Platelet function was repeated within the protocol-specified follow-up window in 2553 patients (91.3%) (median, 31 days; interquartile range, 28 to 34 days). Four patients (0.14%) were lost to follow-up.

#### Pharmacodynamic Effect of High- and Standard-Dose Clopidogrel

Among patients with high on-treatment reactivity (≥230 PRU) at enrollment, platelet function at 30-day follow-up was avail-
able in 1011 patients (91.2%) randomly assigned to high-dose clopidogrel and 1013 patients (91.7%) randomly assigned to standard-dose clopidogrel. On-treatment reactivity <208 PRU at 30 days was identified in 489 patients (48.4%) in the high-dose clopidogrel group compared with 261 patients (25.8%) in the standard-dose clopidogrel group (P<0.001).

Clinical Outcomes and On-Treatment Reactivity as a Time-Varying Covariate
When treated as a time-varying covariate, on-treatment reactivity <230 PRU was not associated with a lower risk of the primary end point at 60 days (hazard ratio [HR], 0.62; 95% confidence interval [CI], 0.25 to 1.51; P=0.30) and at 6 months after PCI (HR, 0.71; 95% CI, 0.41 to 1.23; P=0.22). On-treatment reactivity <208 PRU was significantly associated with a lower risk of the primary end point at 60 days (HR, 0.18; 95% CI, 0.04 to 0.79; P=0.02) and at 6 months (HR, 0.43; 95% CI, 0.23 to 0.82; P=0.01). The significantly lower risk associated with on-treatment reactivity <208 at 6 months was still apparent when all patients were censored at last contact irrespective of the timing or availability of repeat platelet function testing (HR, 0.44; 95% CI, 0.22 to 0.83; P=0.01). The primary end point occurred in 12 patients (1.0%) achieving an on-treatment reactivity <208 PRU compared with 46 patients (2.7%) achieving an on-treatment reactivity ≥208 PRU.

Clinical, Procedural, and Lesion Characteristics and Clinical Outcome
Other variables significantly associated with cardiovascular death, myocardial infarction, and stent thrombosis on univariate analysis included prior myocardial infarction (HR, 2.58; 95% CI, 1.54 to 4.31; P<0.001), prior PCI (HR, 1.85; 95% CI, 1.09 to 3.15; P=0.02), prior coronary artery bypass grafting (HR, 2.30; 95% CI, 1.36 to 3.92; P=0.002), history of diabetes mellitus (HR, 2.86; 95% CI, 1.66 to 4.96; P<0.001), creatinine clearance <60 mL/min (HR, 1.74; 95% CI, 1.04 to 2.93; P=0.04), β-blocker use at discharge (HR, 2.80; 95% CI, 1.20 to 6.51; P=0.02), total stented length in millimeters (HR, 1.01; 95% CI, 1.00 to 1.02; P=0.01), and ACS presentation (HR, 1.75; 95% CI, 1.02 to 2.98; P=0.04).

Adjusted Models for the Association Between On-Treatment Reactivity and Cardiovascular Risk
After adjustment for the other significant correlates of outcome, on-treatment reactivity <208 remained significantly associated with a lower risk of cardiovascular death, myocardial infarction, and stent thrombosis at 60 days (HR, 0.23; 95% CI, 0.05 to 0.98; P=0.047). There was a strong trend toward a lower adjusted risk of the primary end point at 6 months as well (HR, 0.54; 95% CI, 0.28 to 1.04; P=0.065) (Tables 1 and 2). The association between on-treatment reactivity <230 PRU and the primary end point at 60 days or at 6 months was not significant after adjustment (HR, 0.75; 95% CI, 0.30 to 1.87; P=0.53; and HR, 0.88; 95% CI, 0.50 to 1.56; P=0.67, respectively).

Discussion
A broad set of data has demonstrated an association between platelet reactivity on clopidogrel and cardiovascular events after PCI. Several prospective observational studies have proposed optimal cutoffs for on-treatment reactivity to identify high-risk patients.1,7,13,14,25 The GRAVITAS trial demonstrated that in patients with on-treatment reactivity ≥230 PRU after PCI, a fixed regimen of high-dose clopidogrel had a variable and modest pharmacodynamic effect and did not reduce the risk of cardiovascular death, myocardial infarction, and stent thrombosis compared with standard-dose clopidogrel. Furthermore, the 6-month cardiovascular event rate in the cohort of patients with on-treatment reactivity <230 at 12 to 24 hours after PCI was numerically lower but not significantly different compared with patients with on-treatment reactivity ≥230 PRU treated with standard-dose clopidogrel.22 The primary finding of the present analysis is that in GRAVITAS, on-treatment reactivity <208 PRU after PCI or during follow-up was significantly and independently associated with a reduced risk of cardiovascular events. This observation has important implications regarding the prognostic utility of platelet function testing and the identification of clinically effective strategies for individualized P2Y12 antagonist therapy in PCI patients.

Table 1. Influence of Covariates on Cardiovascular Death, Myocardial Infarction, and Stent Thrombosis At 60 Days in the Final Cox Multivariate Regression Model

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Adjusted HR</th>
<th>95% CI</th>
<th>P</th>
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</thead>
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<tr>
<td>On-treatment reactivity &lt;208 PRU</td>
<td>0.23</td>
<td>0.05</td>
<td>0.98</td>
</tr>
<tr>
<td>ACS presentation</td>
<td>3.95</td>
<td>1.83</td>
<td>8.53</td>
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<tr>
<td>Diabetes mellitus</td>
<td>2.49</td>
<td>1.10</td>
<td>5.64</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>2.16</td>
<td>0.94</td>
<td>4.93</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>1.92</td>
<td>0.87</td>
<td>4.23</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>1.76</td>
<td>0.74</td>
<td>4.16</td>
</tr>
<tr>
<td>Creatinine clearance &lt;60</td>
<td>1.48</td>
<td>0.69</td>
<td>3.18</td>
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<tr>
<td>β-Blocker at discharge</td>
<td>1.27</td>
<td>0.42</td>
<td>3.85</td>
</tr>
<tr>
<td>Total stented length, mm</td>
<td>1.01</td>
<td>1.01</td>
<td>1.02</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence interval; PRU, P2Y12 reaction unit; ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; and PCI, percutaneous coronary intervention.

Table 2. Influence of Covariates on Cardiovascular Death, Myocardial Infarction, and Stent Thrombosis At 6 Months in the Final Cox Multivariate Regression Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td>On-treatment reactivity &lt;208 PRU</td>
<td>0.54</td>
<td>0.28</td>
<td>1.04</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
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<td>1.10</td>
<td>4.35</td>
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<tr>
<td>β-Blocker at discharge</td>
<td>2.12</td>
<td>0.89</td>
<td>5.05</td>
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<tr>
<td>ACS presentation</td>
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<td>3.53</td>
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<tr>
<td>Prior myocardial infarction</td>
<td>1.86</td>
<td>1.06</td>
<td>3.28</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>1.80</td>
<td>1.04</td>
<td>3.11</td>
</tr>
<tr>
<td>Creatinine clearance &lt;60</td>
<td>1.52</td>
<td>0.89</td>
<td>2.57</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>1.45</td>
<td>0.81</td>
<td>2.61</td>
</tr>
<tr>
<td>Total stented length, mm</td>
<td>1.01</td>
<td>1.01</td>
<td>1.02</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence interval; PRU, P2Y12 reaction unit; ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; and PCI, percutaneous coronary intervention.
Prior studies have examined the relationship between platelet reactivity and clinical outcome with a single assessment of platelet function. However, on-treatment reactivity varies over time,\textsuperscript{1,2,22} and the pharmacodynamic effect of higher-dose clopidogrel regimens may differ greatly among individuals with high on-treatment reactivity while receiving standard-dose clopidogrel.\textsuperscript{26–30} The present analysis incorporated the dynamic characteristics of platelet reactivity by evaluating on-treatment reactivity as a time-varying covariate. We observed that when assessed in this fashion, on-treatment reactivity <230 PRU was not significantly associated with the risk of the primary end point, consistent with the primary results of the trial. However, achievement of on-treatment reactivity <208 PRU was significantly and independently associated with a markedly lower risk of the primary end point at 60-day follow-up (adjusted HR, 0.23; 95% CI, 0.05 to 0.98; \(P=0.047\)). The significant association between on-treatment reactivity <208 PRU and outcome at 6 months was modestly attenuated after adjustment for other risk factors associated with adverse outcome (HR, 0.53; 95% CI, 0.28 to 1.04; \(P=0.06\)). These findings support the independent prognostic value of serial platelet function testing after PCI. The attenuation in the association between reactivity and clinical outcome over longer-term follow-up could be due to ongoing variability in reactivity that weakened the relationship between the reactivity measured at 30-day follow-up and the actual reactivity at later time points. In addition, it has been suggested that platelet inhibition has greatest influence on cardiovascular events in the early post-PCI period.\textsuperscript{11} The influence of other clinical characteristics associated with longer-term outcome on the risk related to on-treatment reactivity also cannot be excluded.

Approximately one half of the 5427 patients screened in GRAVITAS would be identified as at high risk according to the cutoff we found to be independently associated with a lower risk of cardiovascular events at 30 days.\textsuperscript{22} Consistent with our findings, a prior observational study of 802 patients treated with clopidogrel 600 mg before elective coronary stent placement reported that ADP-induced platelet aggregation before PCI above the median of the study population was a significant predictor of 30-day major adverse cardiac events, driven primarily by events within 48 hours of the procedure.\textsuperscript{11} Therefore, it appears that platelet function testing can identify a substantial proportion of clopidogrel-treated patients who present with low-risk clinical scenarios (ie, stable coronary artery disease) but are at higher risk for both periprocedural and postdischarge ischemic events.

A large proportion of patients with high on-treatment reactivity treated with either standard- or high-dose clopidogrel after PCI did not achieve the level of on-treatment reactivity that we found to be associated with a lower risk of cardiovascular events. Although patients with high on-treatment reactivity after PCI treated with clopidogrel 75 mg daily displayed a decrement in platelet reactivity over the ensuing 30 days,\textsuperscript{22} we observed that only 1 in 4 such patients achieved the level of on-treatment reactivity associated with decreased event rates; this level was achieved in slightly less than half of the patients treated with clopidogrel 150 mg daily. This supports the hypothesis that an insufficient overall pharmacodynamic response may have been responsible for the lack of clinical effectiveness observed with high-dose clopidogrel in the GRAVITAS trial. Prasugrel provides more consistent and powerful antagonism of the P2Y\textsubscript{12} receptor and substantially increases inhibition in healthy volunteers who are clopidogrel nonresponders.\textsuperscript{12,31} A randomized pharmacodynamic study demonstrated that switching patients after an ACS from clopidogrel to prasugrel resulted in levels of on-treatment reactivity well below the threshold associated with risk in the present study.\textsuperscript{34} The TRIGGER-PCI trial was designed to evaluate the impact of prasugrel compared with standard-dose clopidogrel therapy among elective PCI patients with high on-treatment reactivity while receiving clopidogrel with a cutoff of \(\geq 208\) PRU, which in the present study was shown to be predictive of outcomes in GRAVITAS. However, the trial was halted prematurely because of the low number of events accrued in the trial. Very large sample sizes will be required to adequately power randomized clinical trials of individualized antiplatelet therapy after PCI for patients with stable coronary artery disease, given the low overall event rates in these patients despite the hazard associated with high on-treatment reactivity while patients are receiving clopidogrel. Moreover, the therapeutic window may be especially narrow in these patients, and therefore the potential ischemic benefit provided by such intensified therapy must be weighed carefully against the risk of bleeding.\textsuperscript{15}

An individualized antiplatelet strategy based on serial platelet function testing merits investigation. First, our findings emphasize the impact of platelet function over time on cardiovascular risk. Second, high-dose clopidogrel successfully reduced on-treatment reactivity to a level associated with lower cardiovascular risk in 48% of patients with high on-treatment reactivity after PCI, suggesting that this dose may provide ischemic benefit in some patients. Proof of principle for the clinical efficacy of serial platelet function testing to target a level of on-treatment reactivity was demonstrated by 2 small, randomized trials using iterative clopidogrel loading doses guided by vasodilator-stimulated phosphoprotein phosphorylation analysis.\textsuperscript{19,20} Cardiovascular event rates at 30 days were significantly lower in patients who achieved a platelet reactivity index \(<50\%\) before PCI compared with those who did not. Approximately 50% of patients achieved a platelet reactivity index \(<50\%\) after the first clopidogrel loading dose, similar to the frequency of adequate on-treatment reactivity (\(<208\) PRU) in the 5427 patients screened in GRAVITAS with the VerifyNow P2Y12 test, the results of which correlate strongly with vasodilator-stimulated phosphoprotein.\textsuperscript{35,36}

This study has several limitations. Although the analysis of outcomes stratified by the achievement of on-treatment reactivity \(<230\) PRU was prespecified, we chose post hoc to assess a cutoff of 208 PRU on the basis of findings of a recent study\textsuperscript{24} and the use of this cutoff in the TRIGGER-PCI trial, which began after GRAVITAS started enrollment. The analysis that censored patients at 60-day follow-up was not prespecified; however, this time point provided another 30-day interval after the per-protocol 30-day platelet function test and is consistent with a clinically practical approach to serial platelet function testing (ie, interval risk between office visits). Few patients in the trial had high-risk ACS;\textsuperscript{22} and therefore our results may not apply to such patients, although in the present study we observed...
that ACS presentation was associated with clinical outcomes and therefore adjusted for this covariate in multivariate analyses. We may not have been able to detect a significant association between on-treatment reactivity <230 PRU and clinical outcomes because of the lower than expected rate of the primary end point in the trial.22 Inherent to the study design of GRAVITAS, patients with lower levels of on-treatment reactivity were underrepresented in the enrolled population, which also may have limited our ability to detect significant associations between particular levels of on-treatment reactivity and clinical outcomes. Although our findings need to be confirmed, we believe that these data support the hypothesis that on-treatment reactivity is associated with adverse events and suggest the need for properly designed, prospective therapeutic studies using on-treatment reactivity to guide clinical decision making.

In conclusion, achievement of on-treatment reactivity <208 PRU while patients are receiving clopidogrel at 12 to 24 hours or at 30 days after PCI was a significant and independent predictor of cardiovascular death, myocardial infarction, and stent thrombosis in the GRAVITAS trial. This finding supports the prognostic utility of serial platelet function testing in patients undergoing PCI. Because a strategy of fixed-dose clopidogrel 150 mg daily decreases reactivity below this threshold in a minority of patients with high on-treatment reactivity, the safety and efficacy of alternative approaches targeting a level of reactivity below this threshold merit further investigation.

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Disclosures

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