Standard- vs High-Dose Clopidogrel Based on Platelet Function Testing After Percutaneous Coronary Intervention

The GRAVITAS Randomized Coronary Trial

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For editorial comment see p 1136.

Context High platelet reactivity while receiving clopidogrel has been linked to cardiovascular events after percutaneous coronary intervention (PCI), but a treatment strategy for this issue is not well defined.

Objective To evaluate the effect of high-dose compared with standard-dose clopidogrel in patients with high on-treatment platelet reactivity after PCI.

Design, Setting, and Patients Randomized, double-blind, active-control trial (Gauging Responsiveness with A VerifyNow assay—Impact on Thrombosis And Safety [GRAVITAS]) of 2214 patients with high on-treatment reactivity 12 to 24 hours after PCI with drug-eluting stents at 83 centers in North America between July 2008 and April 2010.

Interventions High-dose clopidogrel (600-mg initial dose, 150 mg daily thereafter) or standard-dose clopidogrel (no additional loading dose, 75 mg daily) for 6 months.

Main Outcome Measures The primary end point was the 6-month incidence of death from cardiovascular causes, nonfatal myocardial infarction, or stent thrombosis. The key safety end point was severe or moderate bleeding according to the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) definition. A key pharmacodynamic end point was the rate of persistently high on-treatment reactivity at 30 days.

Results At 6 months, the primary end point had occurred in 25 of 1109 patients (2.3%) receiving high-dose clopidogrel compared with 25 of 1105 patients (2.3%) receiving standard-dose clopidogrel (hazard ratio [HR], 1.01; 95% confidence interval [CI], 0.58-1.76; P = .97). Severe or moderate bleeding was not increased with the high-dose regimen (15 [1.4%] vs 25 [2.3%]; HR, 0.59; 95% CI, 0.31-1.11; P = .10). Compared with standard-dose clopidogrel, high-dose clopidogrel provided a 22% (95% CI, 18%-26%) absolute reduction in the rate of high on-treatment reactivity at 30 days (62%; 95% CI, 59%-65% vs 40%; 95% CI, 37%-43%; P < .001).

Conclusions Among patients with high on-treatment platelet reactivity after PCI with drug-eluting stents, the use of high-dose clopidogrel compared with standard-dose clopidogrel did not reduce the incidence of death from cardiovascular causes, nonfatal myocardial infarction, or stent thrombosis.

Trial Registration clinicaltrials.gov Identifier: NCT00645918

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Pharmacokinetic and pharmacodynamic studies have demonstrated wide interindividual variability in the concentration of active metabolite and in the magnitude of platelet inhibition achieved by recommended loading and maintenance doses of clopidogrel.\(^3\)\(^4\) Although some of this variability is due to genetic polymorphisms that affect the functional activity of the CYP2C19 enzyme, most cannot be explained by genotype or other clinical characteristics.\(^6\)\(^7\)

Several studies have suggested that patients with high on-treatment platelet reactivity while receiving clopidogrel are at an increased risk of cardiovascular events after PCI, including stent thrombosis.\(^8\) We conducted the Gauging Responsiveness with A VerifyNow assay—Impact on Thrombosis And Safety (GRAVITAS) trial to determine whether high-dose clopidogrel is superior to standard-dose therapy for the prevention of cardiovascular events after PCI in patients with high on-treatment reactivity according to a point-of-care platelet function assay.

**METHODS**

**Trial Design**

GRAVITAS was a multicenter, randomized, double-blind, active-control trial. The details of the study design have been published previously.\(^9\) Patient flow is shown in [Figure 1](#). An independent data and safety monitoring board monitored the trial and had access to the unblinded data. 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 Population**

Patients were eligible to be enrolled if they had undergone PCI with 1 or more drug-eluting stents for the treatment of stable coronary artery disease or non-ST-elevation acute coronary syndromes. Race and ethnicity were self-identified. A protocol amendment during the conduct of the study allowed for the enrollment of patients with ST-elevation myocardial infarction. Major exclusion criteria included the use of periprocedural glycoprotein IIb/IIIa inhibitors, the planned future use of oral anticoagulant therapy, and bleeding prior to platelet function measurement. Patients were also excluded if they did not receive a clopidogrel regimen around the time of PCI that ensured that they were near to or at their steady state level of inhibition at the time of platelet function measurement. Specifically, 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 less than 7 days, they must have received a loading dose of 300 mg or more at the time that clopidogrel was initiated. Patients could not receive an additional loading dose prior to assessment of platelet function.

**Study Procedures**

Platelet function was measured with the VerifyNow P2Y12 test (Accumetrics, Inc, San Diego, California)

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**Figure 1. Trial Profile**

- **5429 Patients assessed by VerifyNow P2Y12 test**
  - 2214 Had high on-treatment reactivity (PRU ≥ 230)
  - 3215 Did not have high on-treatment reactivity (PRU < 230)

- **2214 Randomized**
  - 1109 Randomized to receive high-dose clopidogrel
    - 1036 Received intervention as randomized
    - 1 Did not receive intervention
    - 11 Patient decision
    - 1 Had protocol deviation
    - 1 Unknown reason
  - 105 Randomized to receive standard-dose clopidogrel
    - 1006 Received intervention as randomized
    - 13 Did not receive intervention
    - 5 Did not meet inclusion criteria
    - 8 Patient decision

- **3215 Did not have high on-treatment reactivity (PRU < 230)**
  - 586 Randomly selected for observational cohort
  - 2629 Excluded per study protocol

- **1109 Included in primary analysis**
  - 2 Lost to follow-up
  - 176 Discontinued intervention
    - 6 Had a cardiovascular event
    - 19 Had bleeding
    - 42 Had an adverse event
    - 108 Had other reasons

- **105 Included in primary analysis**
  - 0 Lost to follow-up
  - 157 Discontinued intervention
    - 12 Had a cardiovascular event
    - 16 Had bleeding
    - 31 Had an adverse event
    - 96 Had other reasons

- **586 Received standard-dose clopidogrel as assigned**
  - 2 Lost to follow-up
  - 78 Discontinued intervention
    - 2 Had a cardiovascular event
    - 14 Had bleeding
    - 22 Had an adverse event
    - 40 Had other reasons

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PRU indicates P2Y\(_{12}\) reaction units.
San Diego, California) 12 to 24 hours after PCI. This test has been previously described in detail. In brief, this test measures adenosine diphosphate-induced platelet agglutination as an increase in light transmission and uses a proprietary algorithm to report values in P2Y12 reaction units (PRU). A higher PRU result reflects greater P2Y12-mediated reactivity. Specialized software developed for the trial encrypted the platelet function results to maintain double blinding. Study drug assignment was performed centrally by an interactive voice-response system. The clopidogrel and placebo were in tablet form and identical in appearance. Patients with high on-treatment platelet reactivity according to the platelet function test 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 prescribed as a loading dose of placebo followed by a dose of 75 mg and placebo tablet daily. A random sample of patients without high on-treatment reactivity was enrolled and assigned to standard-dose clopidogrel in a blinded fashion (placebo loading dose followed by a dose of 75 mg and placebo tablet daily). A permuted block design was used to select these patients over the course of the trial. Patients without high on-treatment reactivity who were not selected by the interactive voice-response system were not followed up. Aspirin treatment was required at a dose of 75 to 162 mg daily. Study visits and platelet function testing with the VerifyNow P2Y12 test were conducted at 30 days and 6 months.

**End Points**

High on-treatment reactivity was defined as 230 PRU or higher. This cutoff was chosen because it was similar to the cutoff suggested by a prior observational study that used receiver-operating characteristic (ROC) curve analysis to identify the level of on-treatment reactivity that provided the maximal sensitivity and specificity for the prediction of major adverse cardiovascular events after PCI. The cutoff is also consistent with the suggested cutoffs derived by ROC curve analyses in several subsequent observational studies. The primary efficacy variable was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or stent thrombosis. All deaths were considered cardiovascular unless an unequivocal noncardiovascular cause could be established; hemorrhagic deaths were also considered to be cardiovascular. Myocardial infarction followed the American College of Cardiology definition. Stent thrombosis was defined as definite or probable according to the Academic Research Consortium definitions. The key safety end point was severe or moderate bleeding according to the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) definition. All potential events were identified by site investigators. A clinical events committee blinded to treatment assignment and independent of the trial sponsor adjudicated all suspected primary efficacy end points.

**Statistical Analysis**

Efficacy comparisons were performed on the basis of the time to the first event according to the intention-to-treat principle. No imputation of missing data was performed; patients lost to follow-up were censored at the date of last contact. Safety analyses were carried out on data from patients who had received at least 1 dose of the study drug. Survival curves were generated by the Kaplan-Meier method, and survival differences between groups were compared by the log-rank test stratified by acute coronary syndromes. We estimated that, assuming an event rate of 5% in patients with high on-treatment reactivity treated with standard-dose clopidogrel and a withdrawal rate of 10%, 2200 patients with high on-treatment reactivity (1100 in each group) would provide 80% power to detect a 50% relative risk reduction in the rate of the primary efficacy variable at the 2-sided .05 significance level. This would translate into the expectation of 68 events to have 82% power. The anticipated event rate in the active control group was based on prospective, observational studies of the relationship between high on-treatment reactivity and ischemic events. The event rate was further supported by the results of a large observational study reported after the trial began enrollment. The estimated relative risk reduction underlying the trial’s power calculation is greater than that of traditional megatrials, but we purposefully selected the patients who would be biologically most likely to have the most powerful clinical response to the intervention that was tested.

The principal secondary analysis was an observational comparison of the rate of the primary efficacy variable among the patients with and without high on-treatment reactivity treated with standard-dose clopidogrel. We estimated that 583 patients would provide 80% power at the 2-sided .05 significance level based on the assumptions above and an event rate of 2% in patients without high on-treatment reactivity.

Prespecified analyses included landmark analyses of the primary efficacy end point in patients event-free at 30 days. The statistical analysis plan also prespecified pharmacodynamic analyses of the randomized groups that included an assessment of the absolute level of on-treatment reactivity, the change in on-treatment reactivity, and the rate of high on-treatment reactivity at 30 days and 6 months using the Wilcoxon rank-sum and χ² tests. Analyses were performed with SAS version 9.1.3 (SAS Institute Inc, Cary, North Carolina).
Table 1. Baseline Clinical and Procedural Characteristics of the Study Patients, According to Treatment Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>High-Dose Clopidogrel (n = 1109)</th>
<th>Standard-Dose Clopidogrel (n = 1105)</th>
<th>P Value</th>
<th>Standard-Dose Clopidogrel (n = 586)</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residual platelet reactivity at enrollment,</td>
<td>282 (255-320)</td>
<td>283 (255-321)</td>
<td>.98</td>
<td>151 (105-191)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>median (25th percentile–75th percentile),</td>
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<tr>
<td>PRU</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>64.0 (10.5)</td>
<td>64.3 (10.5)</td>
<td>.46</td>
<td>61.9 (10.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex, No./total No. (%)</td>
<td>718/1109 (64.7)</td>
<td>723/1105 (64.5)</td>
<td>.73</td>
<td>470/586 (80.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Body weight, median (range), kg</td>
<td>90.7 (42-220)</td>
<td>90.5 (45-193)</td>
<td>.82</td>
<td>88.0 (38-167)</td>
<td>.01</td>
</tr>
<tr>
<td>BMI, median (range)</td>
<td>31 (15-66)</td>
<td>31 (15-60)</td>
<td>.75</td>
<td>29 (12-69)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>White race, No./total No. (%)</td>
<td>993/1108 (89.6)</td>
<td>1009/1105 (91.3)</td>
<td>.23</td>
<td>543/586 (92.7)</td>
<td>.64</td>
</tr>
<tr>
<td>Medical history, No./total No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>486/1109 (43.8)</td>
<td>518/1105 (46.9)</td>
<td>.15</td>
<td>170/586 (29.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>943/1109 (85.0)</td>
<td>943/1105 (85.3)</td>
<td>.84</td>
<td>450/586 (76.8)</td>
<td>.001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>976/1109 (88.0)</td>
<td>958/1105 (86.7)</td>
<td>.35</td>
<td>496/586 (84.5)</td>
<td>.21</td>
</tr>
<tr>
<td>Current smoker&lt;sup&gt;c&lt;/sup&gt;</td>
<td>163/1109 (14.7)</td>
<td>150/1105 (13.6)</td>
<td>.45</td>
<td>120/586 (20.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>334/1109 (30.1)</td>
<td>315/1105 (28.5)</td>
<td>.41</td>
<td>189/586 (32.3)</td>
<td>.11</td>
</tr>
<tr>
<td>PCI</td>
<td>554/1109 (50.0)</td>
<td>501/1105 (45.3)</td>
<td>.03</td>
<td>268/586 (45.7)</td>
<td>.88</td>
</tr>
<tr>
<td>CABG surgery</td>
<td>233/1109 (21.0)</td>
<td>241/1105 (21.8)</td>
<td>.65</td>
<td>109/586 (18.6)</td>
<td>.12</td>
</tr>
<tr>
<td>Renal insufficiency&lt;sup&gt;d&lt;/sup&gt;</td>
<td>441/1099 (40.1)</td>
<td>456/1098 (41.5)</td>
<td>.50</td>
<td>159/584 (27.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cognitive status</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Stable angina or ischemia</td>
<td>667/1109 (60.2)</td>
<td>664/1103 (60.2)</td>
<td>.57</td>
<td>325/586 (55.5)</td>
<td>.41</td>
</tr>
<tr>
<td>UA without ST-segment depression or elevated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>biomarker levels</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Non–ST-elevation ACS</td>
<td>111/1109 (10.0)</td>
<td>113/1103 (10.2)</td>
<td>.65</td>
<td>65/586 (11.1)</td>
<td>.01</td>
</tr>
<tr>
<td>UA with ST depression</td>
<td>56/1109 (5.0)</td>
<td>58/1103 (5.3)</td>
<td>.28</td>
<td>58/586 (9.8)</td>
<td>.001</td>
</tr>
<tr>
<td>ST-elevation MI</td>
<td>6/1109 (0.5)</td>
<td>2/1103 (0.2)</td>
<td>.52</td>
<td>2/586 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Pharmacotherapy at admission,</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No./total No. (%)</td>
<td></td>
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<tr>
<td>β-Blocker</td>
<td>736/1095 (67.2)</td>
<td>705/1092 (64.6)</td>
<td>.19</td>
<td>373/584 (63.9)</td>
<td>.78</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>269/1095 (24.6)</td>
<td>267/1092 (24.5)</td>
<td>.95</td>
<td>101/584 (17.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>506/1095 (46.2)</td>
<td>496/1092 (45.4)</td>
<td>.71</td>
<td>258/584 (44.2)</td>
<td>.63</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>215/1095 (19.6)</td>
<td>222/1092 (20.3)</td>
<td>.68</td>
<td>90/584 (15.4)</td>
<td>.01</td>
</tr>
<tr>
<td>Statin</td>
<td>854/1095 (78.0)</td>
<td>844/1092 (77.3)</td>
<td>.69</td>
<td>424/584 (72.6)</td>
<td>.03</td>
</tr>
<tr>
<td>Aspirin</td>
<td>967/1109 (87.2)</td>
<td>984/1105 (89.0)</td>
<td>.18</td>
<td>510/586 (87.0)</td>
<td>.22</td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>327/1095 (29.9)</td>
<td>328/1092 (30.0)</td>
<td>.92</td>
<td>115/584 (19.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Clopidogrel exposure at time of enrollment,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No./total No. (%)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>600-mg loading dose</td>
<td>591/1109 (53.3)</td>
<td>582/1092 (52.7)</td>
<td>.19</td>
<td>306/586 (52.9)</td>
<td></td>
</tr>
<tr>
<td>75 mg/d × 7 d</td>
<td>429/1108 (38.7)</td>
<td>410/1094 (37.1)</td>
<td>.19</td>
<td>221/586 (37.7)</td>
<td>.97</td>
</tr>
<tr>
<td>Loading dose ≥300 mg, followed by 75 mg/d × 7</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>88/1108 (7.9)</td>
<td>112/1094 (10.1)</td>
<td>.97</td>
<td>59/586 (10.1)</td>
<td></td>
</tr>
<tr>
<td>Procedural variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated lesions per patient, mean (SD)</td>
<td>1.4 (0.6)</td>
<td>1.4 (0.7)</td>
<td>.19</td>
<td>1.4 (0.7)</td>
<td>.28</td>
</tr>
<tr>
<td>Stents per patient, mean (SD)</td>
<td>1.7 (1.0)</td>
<td>1.6 (1.0)</td>
<td>.23</td>
<td>1.6 (1.0)</td>
<td>.25</td>
</tr>
<tr>
<td>Total stented length, mean (SD), mm</td>
<td>29.6 (23.2)</td>
<td>29.3 (20.8)</td>
<td>.90</td>
<td>29.6 (19.2)</td>
<td>.29</td>
</tr>
<tr>
<td>Multivessel PCI, No./total No. (%)</td>
<td>192/1109 (17.3)</td>
<td>176/1104 (15.9)</td>
<td>.39</td>
<td>86/586 (14.7)</td>
<td>.49</td>
</tr>
<tr>
<td>Antithrombin use to support PCI,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No./total No. (%)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>427/1109 (38.6)</td>
<td>430/1094 (38.3)</td>
<td>.86</td>
<td>218/586 (37.2)</td>
<td>.48</td>
</tr>
<tr>
<td>Low-molecular-weight heparin</td>
<td>22/1109 (2.0)</td>
<td>29/1094 (2.6)</td>
<td>.32</td>
<td>7/1104 (1.2)</td>
<td>.05</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>699/1109 (63.1)</td>
<td>703/1094 (63.7)</td>
<td>.79</td>
<td>382/586 (65.2)</td>
<td>.54</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; ACS, acute coronary syndromes; BMI, body mass index, which is calculated as weight in kilograms divided by height in meters squared; CABG, coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention; PRU, P2Y<sub>12</sub> reaction units; UA, unstable angina.

<sup>a</sup>P value for the comparison of patients with or without high platelet reactivity assigned standard-dose clopidogrel.

<sup>b</sup>Race was self-reported.

<sup>c</sup>Defined as smoker within previous 7 days.

<sup>d</sup>Renal insufficiency was defined as a calculated creatinine clearance of less than 60 mL per minute as determined by the Cockcroft-Gault equation.
RESULTS
Between July 2008 and April 2010, 5,429 patients from 83 sites in the United States and Canada were screened with platelet function testing 12 to 24 hours after PCI. Of these, 2,214 (40.8%) had high on-treatment reactivity and were randomly assigned to either high-dose or standard-dose clopidogrel (Figure 1). The treatment groups were generally well balanced with regard to baseline demographic, clinical, and procedural characteristics (Table 1). An additional 586 patients without high on-treatment reactivity were selected at random and assigned to treatment with standard-dose clopidogrel. Demographic and clinical characteristics were similar between patients who were or were not selected, except more patients with prior myocardial infarction were in the selected cohort (189 [32%] vs 711 [27%], P=.01). As shown in Table 1, there were several differences in the baseline demographics, medical history, and concomitant medications of the selected patients without high on-treatment reactivity compared with the patients in the randomized groups with high on-treatment reactivity. Clopidogrel exposure prior to enrollment was similar across all 3 treatment groups. Four patients (0.1%) were lost to follow-up.

### Table 2. Major Efficacy and Safety End Points at 6 Months in Randomized Patients With High On-Treatment Platelet Reactivity

<table>
<thead>
<tr>
<th>End Point</th>
<th>No. (%) of Patients Taking Clopidogrel</th>
<th>HR for High-Dose Clopidogrel (95% CI)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from cardiovascular causes, nonfatal myocardial infarction, or stent thrombosis (primary end point)</td>
<td>25 (2.3)</td>
<td>1.01 (0.58-1.76)</td>
<td>.97</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>3 (0.3)</td>
<td>0.38 (0.10-1.43)</td>
<td>.14</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>20 (1.8)</td>
<td>1.12 (0.59-2.12)</td>
<td>.72</td>
</tr>
<tr>
<td>Stent thrombosisc</td>
<td>5 (0.5)</td>
<td>0.63 (0.21-1.93)</td>
<td>.42</td>
</tr>
<tr>
<td>Death from cardiovascular causes or nonfatal myocardial infarction</td>
<td>23 (2.1)</td>
<td>0.93 (0.53-1.64)</td>
<td>.80</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>7 (0.6)</td>
<td>0.70 (0.27-1.85)</td>
<td>.48</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

*bPercentages are event rates from observed data.

*cHazard ratios and P values were calculated with the log-rank test stratified by acute coronary syndromes status.

The primary end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or stent thrombosis. Data were analyzed according to the intention-to-treat principle.

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with standard-dose clopidogrel, the rate of death from cardiovascular causes, nonfatal MI, or stent thrombosis was numerically greater in the patients with high on-treatment reactivity than in those without high on-treatment reactivity, but this difference did not reach statistical significance (25 [2.3%] vs 8 [1.4%]; HR, 1.68; 95% CI, 0.76-3.72; P = .20; Table 3 and Figure 2). Landmark analysis at 30 days also demonstrated a greater, but not significant, risk of events in patients with high on-treatment reactivity (17 [1.6%] vs 4 [0.7%]; HR, 2.27; 95% CI, 0.76-6.74; P = .13).

Safety End Points

The frequencies of bleeding events are shown in Table 4. Intracranial hemorrhage occurred in none of the patients with high on-treatment reactivity randomly assigned to high-dose clopidogrel, in 2 patients (0.2%) with high on-treatment reactivity randomly assigned to standard-dose clopidogrel, and in 1 patient (0.2%) without high on-treatment reactivity treated with standard-dose clopidogrel. The rate of discontinuation of study drug due to GUSTO severe or moderate bleeding was similar across all 3 groups: 8 patients (0.7%), 11 patients (1.0%) and 6 patients (1.0%), respectively.

Pharmacodynamic Outcomes

The pharmacodynamic effect of the study drug in patients randomly assigned to high-dose or standard-dose clopidogrel according to the intent-to-treat principle is illustrated in Figure 3. The level of on-treatment reactivity decreased significantly over the first 30 days in both groups, from 283 PRU (interquartile range [IQR], 255-321 PRU) to 250 PRU (IQR, 206-298 PRU) with standard-dose clopidogrel (P < .001) and from 282 PRU (IQR, 255-320 PRU) to 211 PRU (IQR, 155-262 PRU) with high-dose clopidogrel (P < .001). The reduction in on-treatment reactivity at 30 days and at 6 months after randomization was significantly greater with high-dose than with standard-dose clopidogrel (80 PRU; IQR, 37-128 PRU vs 37 PRU; IQR, 1-79 PRU; P < .0001 and 85 PRU; IQR, 37-138 PRU vs 44 PRU; IQR, 3.5-91 PRU; P < .001, respectively). High-dose clopidogrel led to an absolute 22% (95% CI, 18%-26% and 24%, 95% CI, 20%-28%) lower rate of high on-treatment reactivity (ie, PRU ≥ 230) compared with standard-dose clopidogrel at 30 days and 6 months (40%; 95% CI, 37%-43% vs 62%; 95% CI, 59%-65%; P < .001 and 36%; 95% CI, 33%-39%)

### Table 3. Major Efficacy and Safety End Points at 6 Months for the Nonrandomized Comparison of Patients With or Without High On-Treatment Platelet Reactivity Treated With Standard-Dose Clopidogrel

<table>
<thead>
<tr>
<th>End Point</th>
<th>High On-Treatment Reactivity (n = 1109)</th>
<th>Not High On-Treatment Reactivity (n = 586)</th>
<th>HR for High On-Treatment Reactivity (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from cardiovascular causes, nonfatal myocardial infarction, or stent thrombosis</td>
<td>25 (2.3)</td>
<td>8 (1.4)</td>
<td>1.68 (0.76-3.72)</td>
<td>.20</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>8 (0.7)</td>
<td>3 (0.5)</td>
<td>1.42 (0.38-5.38)</td>
<td>.60</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>18 (1.6)</td>
<td>5 (0.9)</td>
<td>1.93 (0.72-5.21)</td>
<td>.19</td>
</tr>
<tr>
<td>Stent thrombosis§</td>
<td>8 (0.7)</td>
<td>2 (0.3)</td>
<td>2.16 (0.46-10.19)</td>
<td>.31</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>10 (0.9)</td>
<td>4 (0.7)</td>
<td>1.34 (0.42-4.28)</td>
<td>.62</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.
§Percentages are event rates from observed data.
### Table 4. Bleeding Events at 6 Months by GUSTO Criteria

<table>
<thead>
<tr>
<th>Clopidogrel Use</th>
<th>Standard-Dose Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No./Total No. (%) of Events for Patients With High On-Treatment Reactivity</strong></td>
<td><strong>No./Total No. (%) of Events for Patients Without High On-Treatment Reactivity</strong></td>
</tr>
<tr>
<td><strong>End Point</strong></td>
<td><strong>High Dosage</strong></td>
</tr>
<tr>
<td>Severe or moderate bleeding (key safety end point)</td>
<td>15/1095 (1.4)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>133/1109 (12)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; HR, hazard ratio.

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affected by genetic variation of the CYP2C19 enzyme. The clinical impact of prasugrel in patients with high reactivity while receiving clopidogrel is currently being examined in an ongoing clinical trial (clinicaltrials.gov, NCT00910299).

The relative benefit of high-dose clopidogrel may also have been diluted by the decrease in the frequency of high on-treatment reactivity in both randomized groups over the initial 30 days after PCI. High on-treatment reactivity measured 12 to 24 hours after PCI resolved at the 30-day follow-up in 38% of the patients randomly assigned to standard-dose clopidogrel. A possible explanation for this decrement in reactivity in the post-PCI period may be that early high on-treatment reactivity is a manifestation of poststenting platelet activation in a subset of patients.

Several potential mechanisms may explain the lack of a beneficial treatment effect with high-dose clopidogrel. The possibility that on-treatment platelet reactivity is not a modifiable risk factor for thrombotic events after PCI cannot be excluded. However, under-treatment may explain our findings because high-dose clopidogrel resulted in only a modest reduction in the level of on-treatment reactivity and in the rate of high on-treatment reactivity compared with standard-dose clopidogrel. This observation is consistent with previous smaller studies demonstrating that clopidogrel 150 mg daily provides only a moderate increase in platelet inhibition above that provided by 75 mg daily in patients with high on-treatment reactivity, and that heightened platelet reactivity persists in a large proportion of patients. Carriers of a reduced function CYP2C19 allele are at greater risk for high on-treatment platelet reactivity while taking clopidogrel, and higher-dose clopidogrel may have only a marginal pharmacodynamic effect in these patients, especially in homozygotes. It is possible that other more potent inhibitors of platelet aggregation may have been beneficial. Prasugrel has a strong and consistent pharmacodynamic effect in clopidogrel nonresponders and is not affected by genetic variation of the standard dose.

The relative benefit of high-dose clopidogrel suggests that rather than prescribing a fixed, higher dose of clopidogrel based on a single post-PCI platelet function test, a strategy of repeated platelet function testing may have merit, and this hypothesis should be explored further.

The duration of treatment with high-dose maintenance clopidogrel in the present trial is substantially longer than previously examined. We found that treatment with a 6-month post-PCI regimen of high-dose clopidogrel did not appear to be accompanied by an excess of severe or moderate bleeding events or intracranial hemorrhage compared with a standard-dose regimen. This clinical finding is consistent with our pharmacodynamic observation that high-dose clopidogrel provided only a modest amount of incremental platelet inhibition in patients with high on-treatment reactivity. The Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events—Seventh Organization to Assess Strategies in Ische-

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mic Syndromes (CURRENT-OASIS 7) trial evaluated a 600-mg clopidogrel loading dose followed by 7 days of 150 mg of clopidogrel in patients with acute coronary syndromes not selected by platelet function testing and found an increased risk of bleeding that required blood transfusion. 38 The discordant findings between that study and GRAVITAS may in part be explained by differences in the study populations: in the current trial, we enrolled patients with high on-treatment reactivity and excluded those with major bleeding around the time of the index PCI, while CURRENT-OASIS 7 enrolled patients prior to PCI without regard to the level of on-treatment reactivity.

Although GRAVITAS is the largest randomized trial to date of individualized antiplatelet therapy based on ex vivo platelet function testing, the desired power of our primary analysis was reduced because we observed only 50 events, yet anticipated 68 events to have greater than 80% power to detect a 50% relative risk reduction with our intervention. A treatment effect of high-dose clopidogrel therefore cannot be excluded.

Our trial has several limitations. Although eligible to be enrolled, few patients in the trial had high-risk acute coronary syndromes (biomarker-positive non–ST-elevation and ST-elevation myocardial infarction); accordingly, the results may not apply to such patients. We measured platelet reactivity and assigned study drug after PCI, and therefore could not assess the effectiveness of high-dose clopidogrel in reducing the incidence of periprocedural myocardial infarction. Our therapeutic intervention was a higher, fixed dose of clopidogrel, rather than a strategy of iterative-dose adjustment to “normalize” platelet reactivity to a specific target. The baseline characteristics of patients with and without high on-treatment reactivity differed greatly, as noted in previous, smaller studies. 7,39-41 We did not adjust our analyses for these differences because of the large number of independent variables compared with the relatively small number of events. 42 Therefore, the current study cannot address whether on-treatment reactivity is an independent predictor of thrombotic risk. 14

In conclusion, high-dose clopidogrel for 6 months in patients with high on-treatment platelet reactivity 12 to 24 hours after PCI with drug-eluting stents did not reduce the rate of death from cardiovascular causes, nonfatal myocardial infarction, or stent thrombosis compared with standard-dose clopidogrel. The results of GRAVITAS do not support a uniform treatment strategy of high-dose clopidogrel in patients with high on-treatment reactivity identified by a single platelet function test after PCI. Alternative treatment strategies incorporating platelet function testing merit further investigation.

Author Contributions: Dr Price had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Price, Berger, Cannon, Angiolillo, Topol. Acquisition of Data: Price, Berger, Teirstein, Tanguay, Angiolillo, Spurges, Puri, Robbins, Garratt, Bertrand, Stillabower, Aragon, Manoukian. Analysis and Interpretation of the data: Price, Berger, Cannon, Teirstein, Angiolillo, Schork, Topol. Drafting of the manuscript: Price. Critical revision of the manuscript for important intellectual content: Price, Berger, Cannon, Teirstein, Tanguay, Angiolillo, Topol, Schork, Spurges, Puri, Robbins, Garratt, Bertrand, Stillabower, Aragon, Manoukian. Statistical analysis: Price, Schork. Obtained funding: Price, Topol. Study supervision: Price, Berger, Cannon, Tanguay, Teirstein, Topol.

Conflict of Interest Disclosures: All authors have completed and submitted the ICME Form for Disclosures of Potential Conflicts of Interest. Dr Price reported receiving consulting fees from Bristol-Myers Squibb/sanofi-aventis, Daiichi Sankyo/Eli Lilly & Co, Accumetrix, AstraZeneca, and Medici; speakers fees from Daiichi Sankyo/Eli Lilly & Co; and grant support from Bristol-Myers Squibb/sanofi-aventis. Dr Tanguay reported receiving consulting and speakers fees from Bristol-Myers Squibb/sanofi-aventis, Daiichi Sankyo/Eli Lilly & Co, GlaxoSmithKline, Abbott Vascular, and AstraZeneca and speakers fees from Boehringer Ingelheim. Dr Angiolillo reported receiving consulting fees from Bristol-Myers Squibb/sanofi-aventis, Daiichi Sankyo/Eli Lilly & Co, AstraZeneca, The Medicines Company, Portola, Novartis, Medice, Accumetrix, Arena Pharmaceuticals, and Merck; and speakers fees from Bristol-Myers Squibb/sanofi-aventis and Daiichi Sankyo/Eli Lilly & Co; Dr Garratt reported receiving consulting fees from The Medicines Company; speakers fees from Boston Scientific, The Medicines Company, sanofi-aventis, Daiichi Sankyo/Eli Lilly & Co, Medtronic, and Abbott Vascular; and serving on the advisory board of Boston Scientific. Dr Aragon reported receiving consulting and speakers fees from The Medicines Company, and speakers fees from Bristol-Myers Squibb/sanofi-aventis. Dr Kandzari reported receiving consulting and speakers fees from Daichi Sankyo/Eli Lilly & Co. Dr Lee reported receiving consulting fees from Bristol-Myers Squibb/sanofi-aventis. Dr Cannon reports receiving consulting fees from Bristol-Myers Squibb/sanofi-aventis, Alynlam, and Novartis and grant support from Intekrin Therapeutics; and serving on the advisory board for GlaxoSmithKline and Merck. Dr Topol reported receiving consulting fees from Bristol-Myers Squibb/sanofi-aventis and Daiichi Sankyo/Eli Lilly & Co. The other authors reported no disclosures.

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Role of the Sponsor: The executive committee, consisting of both academic members and nonvoting representatives of the sponsor, designed and oversaw the conduct of the trial. The sponsor coordinated the data management with a contract research organization (Synteract, Carlsbad, California). Bristol-Myers Squibb/sanofi-aventis had no role in the design and management of the trial or in the analysis of the data.


Previous Presentation: This study was presented as a late-breaking clinical trial at the American Heart Association Scientific Sessions, Chicago, Illinois, November 16, 2010.

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