Standard- vs High-Dose Clopidogrel Based on Platelet Function Testing After Percutaneous Coronary Intervention
The GRAVITAS Randomized Trial

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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. 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 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.

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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.3-5 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, San Diego, California). Patients were classified as having high on-treatment reactivity if their VerifyNow P2Y12 reaction units (PRU) were greater than or equal to 230. We randomly assigned 5429 patients to receive 600 mg of clopidogrel or 75 mg daily for 1 year. The primary outcome was the composite of cardiovascular death, myocardial infarction, or stroke requiring admission to a hospital within 1 year.}

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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)
- 586 Randomly selected for observational cohort
- 2629 Excluded per study protocol
- 1109 Randomized to receive high-dose clopidogrel
  - 1056 Received intervention as randomized
  - 1 Did not meet inclusion criteria
  - 1 Patient decision
  - 1 Had protocol deviation
  - 1 Unknown reason
  - 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
  - 1109 Included in primary analysis
- 1105 Randomized to receive standard-dose clopidogrel
  - 1056 Received intervention as randomized
  - 13 Did not receive intervention
  - 5 Did not meet inclusion criteria
  - 8 Patient decision
  - 0 Lost to follow-up
  - 157 Discontinued intervention
  - 12 Had a cardiovascular event
  - 16 Had bleeding
  - 31 Had an adverse event
  - 98 Had other reasons
  - 1105 Included in primary analysis
- 586 Received standard-dose clopidogrel as assigned
  - 584 Received intervention as randomized
  - 2 Did not meet inclusion criteria
  - 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
  - 586 Included in primary analysis

PRU indicates P2Y12 reaction units.
conducted at 30 days and 6 months.

Aspirin treatment was required at on-treatment reactivity who were not
selected these patients over the course
of placebo followed by a dose of 75
mg and placebo tablet daily. A ran-
dom sample of patients without high
on-treatment reactivity was enrolled
and assigned to standard-dose clopi-
dogrel in a blinded fashion (placebo
loading dose followed by a dose of 75
mg and placebo tablet daily). A per-
muted 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
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 subse-
quent observational studies. The
primary efficacy variable was a com-
posite of death from cardiovascular
causes, nonfatal myocardial infar-
cction, or stent thrombosis. All deaths
were considered cardiovascular unless
an unequivocal noncardiovascular
cause could be established; hemor-
rhagic deaths were also considered to
be cardiovascular. Myocardial infarc-
tion followed the American College of
Cardiology definition. Stent throm-
bosis was defined as definite or prob-
able 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 com-
mittee blinded to treatment assign-
ment and independent of the trial
sponsor adjudicated all suspected pri-
mary 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 prin-
ciple. No imputation of missing data
was performed; patients lost to fol-
low-up were censored at the date of last
contact. Safety analyses were carried out
data from patients who had rece-
dwed at least 1 dose of the study drug.
Survival curves were generated by the
Kaplan-Meier method, and survival dif-
fferences between groups were com-
pared by the log-rank test stratified by
acute coronary syndromes. We esti-
imated 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 de-
tect 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 an-
ticipated event rate in the active con-
trol group was based on prospective,
observational studies of the relation-
ship between high on-treatment reac-
tivity and ischemic events. The
estimated relative risk reduction under-
lying the trial’s power calculation is greater than that of tra-
ditional megatrials, but we purpose-
fully selected the patients who would
be biologically most likely to have the
most powerful clinical response to the
intervention that was tested. This esti-
mate is also consistent with the treat-
ment effect observed in the placebo-
controlled trials of thienopyridine
therapy in patients undergoing coro-
nary intervention with bare metal
stents.

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 stan-
dard-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 with-
out high on-treatment reactivity.

Prespecified analyses included land-
mark analyses of the primary efficacy
end point in patients event-free at 30
days. The statistical analysis plan also
prespecified pharmacodynamic analy-
zes of the randomized groups that in-
cluded an assessment of the absolute
level of on-treatment reactivity, the
change in on-treatment reactivity, and
the rate of high on-treatment reactiv-
ity at 30 days and 6 months using the
Wilcoxon rank sum and χ2 tests. Anal-
yses 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 On-Treatment Reactivity, Randomized Comparison</th>
<th>Not High On-Treatment Reactivity, Observational</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High-Dose Clopidogrel (n = 1109)</td>
<td>Standard-Dose Clopidogrel (n = 1105)</td>
</tr>
<tr>
<td></td>
<td>Standard-Dose Clopidogrel (n = 586)</td>
<td>Standard-Dose Clopidogrel (n = 588)</td>
</tr>
<tr>
<td></td>
<td>P Value</td>
<td>P Value</td>
</tr>
<tr>
<td>Residual platelet reactivity at enrollment, median (25th percentile–75th percentile), PRU</td>
<td>282 (255–320)</td>
<td>283 (255–321)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>64.0 (10.5)</td>
<td>64.3 (10.5)</td>
</tr>
<tr>
<td>Sex, No./total No. (%)</td>
<td>Men 718/1109 (64.7)</td>
<td>723/1105 (65.4)</td>
</tr>
<tr>
<td>Body weight, median (range), kg</td>
<td>90.7 (42-220)</td>
<td>90.5 (45-193)</td>
</tr>
<tr>
<td>BMI, median (range)</td>
<td>31 (15-66)</td>
<td>31 (15-60)</td>
</tr>
<tr>
<td>White race, No./total No. (%)</td>
<td>993/1108 (89.6)</td>
<td>1009/1105 (91.3)</td>
</tr>
<tr>
<td>Medical history, No./total No. (%)</td>
<td>Diabetes mellitus 486/1109 (43.8)</td>
<td>518/1105 (46.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>943/1109 (85.0)</td>
<td>943/1105 (85.3)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>976/1109 (88.0)</td>
<td>958/1105 (86.7)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>163/1109 (14.7)</td>
<td>150/1105 (13.6)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>334/1109 (30.1)</td>
<td>315/1105 (28.5)</td>
</tr>
<tr>
<td>PCI</td>
<td>554/1109 (50.0)</td>
<td>501/1105 (45.3)</td>
</tr>
<tr>
<td>CABG surgery</td>
<td>233/1109 (21.0)</td>
<td>241/1105 (21.8)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>441/1099 (40.1)</td>
<td>456/1098 (41.5)</td>
</tr>
<tr>
<td>Indication for procedure, No./total No. (%)</td>
<td>Stable angina or ischemia 667/1109 (60.2)</td>
<td>664/1103 (60.2)</td>
</tr>
<tr>
<td>Non–ST-elevation ACS</td>
<td>269/1109 (24.3)</td>
<td>266/1103 (24.1)</td>
</tr>
<tr>
<td>ST-elevation MI</td>
<td>111/1109 (10.0)</td>
<td>113/1103 (10.2)</td>
</tr>
<tr>
<td>Pharmacotherapy at admission, No./total No. (%)</td>
<td>β-Blocker 736/1095 (67.2)</td>
<td>705/1092 (64.6)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>269/1095 (24.6)</td>
<td>267/1092 (24.5)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>506/1095 (46.2)</td>
<td>496/1092 (45.4)</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>215/1095 (19.6)</td>
<td>222/1092 (20.3)</td>
</tr>
<tr>
<td>Statin</td>
<td>854/1095 (78.0)</td>
<td>844/1092 (77.3)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>967/1109 (87.2)</td>
<td>984/1105 (89.0)</td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>327/1095 (29.9)</td>
<td>328/1092 (30.0)</td>
</tr>
<tr>
<td>Clopidogrel exposure at time of enrollment, No./total No. (%)</td>
<td>600-mg loading dose 591/1108 (53.3)</td>
<td>582/1092 (54.2)</td>
</tr>
<tr>
<td>75 mg/d &gt;7 d</td>
<td>429/1108 (38.7)</td>
<td>410/1094 (37.1)</td>
</tr>
<tr>
<td>Loading dose ≥300 mg, followed by 75 mg/d &lt;7 d</td>
<td>88/1108 (7.9)</td>
<td>112/1094 (10.1)</td>
</tr>
<tr>
<td>Procedural variables</td>
<td>Treated lesions per patient, mean (SD)</td>
<td>1.4 (0.6)</td>
</tr>
<tr>
<td>Stents per patient, mean (SD)</td>
<td>1.7 (1.0)</td>
<td>1.6 (1.0)</td>
</tr>
<tr>
<td>Total stented length, mean (SD), mm</td>
<td>29.6 (23.2)</td>
<td>29.3 (20.8)</td>
</tr>
<tr>
<td>Multivessel PCI, No./total No. (%)</td>
<td>192/1109 (17.3)</td>
<td>176/1104 (15.9)</td>
</tr>
<tr>
<td>Antithrombin use to support PCI, No./total No. (%)</td>
<td>Unfractionated heparin 427/1109 (38.6)</td>
<td>430/1104 (38.9)</td>
</tr>
<tr>
<td>Low-molecular-weight heparin</td>
<td>22/1109 (2.0)</td>
<td>29/1104 (2.6)</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>699/1109 (63.1)</td>
<td>703/1104 (63.7)</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, P2Y₁₂ reaction units; UA, unstable angina.

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

b Race was self-reported.

c Defined as smoker within previous 7 days.

d 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, 5429 patients from 83 sites in the United States and Canada were screened with platelet function testing 12 to 24 hours after PCI. Of these, 2214 (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.

Efficacy End Points
The rate of death from cardiovascular causes, nonfatal MI, or stent thrombosis was not different with high-dose compared with standard-dose clopidogrel in the patients with high on-treatment reactivity (25 [2.3%] vs 25 [2.3%]; hazard ratio [HR], 1.01; 95% confidence interval [CI], 0.58-1.76; P = .97; Table 2 and Figure 2). The event rates in the 2 groups after 30 days were not different by landmark analysis (20 [1.9%] vs 17 [1.6%]; HR 1.19; 95% CI, 0.62-2.27; P = .60).

In the secondary, observational comparison of patients with and without high on-treatment reactivity treated Table 2.

<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) 25 (2.3) 1.01 (0.58-1.76)</td>
<td>.97</td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>3 (0.3) 8 (0.7) 0.38 (0.10-1.43)</td>
<td>.14</td>
<td></td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>20 (1.8) 18 (1.6) 1.12 (0.59-2.12)</td>
<td>.72</td>
<td></td>
</tr>
<tr>
<td>Stent thrombosisc</td>
<td>5 (0.5) 8 (0.7) 0.63 (0.21-1.93)</td>
<td>.42</td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes or nonfatal myocardial infarction</td>
<td>23 (2.1) 25 (2.3) 0.93 (0.53-1.64)</td>
<td>.80</td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>7 (0.6) 10 (0.9) 0.70 (0.27-1.85)</td>
<td>.48</td>
<td></td>
</tr>
</tbody>
</table>

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

aPercentages are event rates from observed data.

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

cStent thrombosis was defined as definite or probable thrombosis, according to the Academic Research Consortium.

Figure 2. Cumulative Kaplan-Meier Estimates of the Time to the First Adjudicated Occurrence of the Primary Efficacy End Point

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.
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 (0.0%) 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 (\( P < .0001 \)) 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

| End Point | High On-Treatment Reactivity (n = 1109) | Not High On-Treatment Reactivity (n = 586) | HR for High On-Treatment Reactivity (95% CI) | \( P \) Value

| Death from cardiovascular causes, nonfatal myocardial infarction, or stent thrombosis | 25 (2.3) | 8 (1.4) | 1.68 (0.76-3.72) | .20
| Death from cardiovascular causes | 8 (0.7) | 3 (0.5) | 1.42 (0.38-5.38) | .60
| Nonfatal myocardial infarction | 18 (1.6) | 5 (0.9) | 1.93 (0.72-5.21) | .19
| Stent thrombosis\(^a\) | 8 (0.7) | 2 (0.3) | 2.16 (0.46-10.19) | .31
| Death from any cause | 10 (0.9) | 4 (0.7) | 1.34 (0.42-4.28) | .62

Abbreviations: CI, confidence interval; HR, hazard ratio.
\(^a\)Hazard ratios and \( P \) values were calculated with the log-rank test stratified by acute coronary syndromes status.
\(^b\)Stent thrombosis was defined as definite or probable thrombosis, according to the Academic Research Consortium.

### 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>End Point</strong></td>
<td><strong>No./Total No. (%) of Events for Patients With High On-Treatment Reactivity</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.
\(^a\)Compared with standard-dose clopidogrel in patients with high on-treatment reactivity.
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 after PCI.6,22 We found that compared with the standard maintenance dose of 75 mg daily, prolonged high-dose clopidogrel therapy in a population of patients with high on-treatment reactivity after PCI provided a modest pharmacodynamic effect but did not reduce the rate of death from cardiovascular causes, nonfatal myocardial infarction, or stent thrombosis.

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COMMENT
Pharmacodynamic studies have demonstrated wide interindividual variability in the platelet inhibitory response to clopidogrel, and observational studies have linked a poor pharmacodynamic response to cardiovascular events after PCI.6,22 We found that compared with the standard maintenance dose of 75 mg daily, prolonged high-dose clopidogrel therapy in a population of patients with high on-treatment reactivity after PCI provided a modest pharmacodynamic effect but did not reduce the rate of death from cardiovascular causes, nonfatal myocardial infarction, or stent thrombosis.

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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. 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 peri-procedural 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: Berger, Cannon, Angiolillo, Topol. Acquisition of Data: Price, Berger, Teirstein, Tanguay, Angiolillo, Spriggs, Puri, Robbins, Garratt, Bertrand, Stillblawer, 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, Spriggs, Puri, Robbins, Garratt, Bertrand, Stillblawer, Aragon, Stinis, Kandzari, Lee, Manoukian. Statistical analysis: Price. Obtained funding: Price, Topol. Study supervision: Price, Berger, Cannon, Tanguay, Teirstein, Topol.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Price reported receiving consulting fees from Bristol-Myers Squibb/sanofi-aventis; Daiichi Sankyo/Eli Lilly & Co; Accutemoetics, AstraZeneca, and Mediscure; 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 Squibbsanofi-aventis, Daiichi Sankyo/Eli Lilly & Co, GlaxoSmithKline, Abbott Vascular, and AstraZeneca. Drs. Price, Teirstein, and Topol reported no disclosures. Drs. Kandzari, Lee, and Grandi disclosed financial relationships with Abbott Vascular and Daiichi Sankyo/Eli Lilly & Co, and institutional support from Bristol-Myers Squibb and AstraZeneca.

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6. Price, Berger, Teirstein, Tanguay, Angiolillo, Topol, Schork, Spriggs, Puri, Robbins, Garratt, Bertrand, Stillblawer, Aragon, Stinis, Kandzari, Lee, Manoukian. Financial Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors reported that no potential conflicts of interest were disclosed.


