Effect of Clopidogrel Pretreatment Before Percutaneous Coronary Intervention in Patients With ST-Elevation Myocardial Infarction Treated With Fibrinolytics
The PCI-CLARITY Study

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PLATELET ACTIVATION PLAYS A critical role both in spontaneous coronary artery thrombosis due to atherosclerotic plaque rupture and in thrombotic complications following percutaneous coronary intervention (PCI) with coronary artery stenting. For that reason, aspirin is part of the standard treatment given to patients with coronary artery disease, including those undergoing PCI.1

Dual antiplatelet therapy following PCI, using a combination of a P2Y12 adenosine diphosphate receptor blocker (such as ticlopidine or clopidogrel) and aspirin, further reduces platelet activation and thrombotic and ischemic complications.2-4 However, the optimal time...

For editorial comment see p 1271.
the initiation of clopidogrel has been debated. Specifically, the benefit of routine clopidogrel pretreatment started hours to days before PCI compared with treatment given at the time of PCI in high-risk patients with acute coronary syndromes remains incompletely defined, and hence current guidelines do not universally recommend pretreatment.1,5,6

In the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)—Thrombolysis in Myocardial Infarction (TIMI) 28 trial, patients with ST-segment elevation myocardial infarction (STEMI) receiving a fibrinolytic were randomized on presentation to receive clopidogrel (including a loading dose) or placebo.7 Per protocol, all patients were to undergo angiography after 2 to 8 days, and this design created the opportunity to study clopidogrel pretreatment given in a standardized fashion. Accordingly, PCI-CLARITY was a prespecified test of the hypothesis that in patients undergoing PCI after initial pharmacological therapy for STEMI, clopidogrel pretreatment hours to days before PCI is superior to clopidogrel treatment initiated at the time of PCI in preventing major adverse cardiovascular events.

METHODS

Patient Population

The PCI-CLARITY study was a planned subanalysis of patients undergoing PCI who were randomized to receive clopidogrel or placebo at presentation in the CLARITY-TIMI 28 trial.7 As described previously,8 men and women 18 to 75 years of age were eligible for inclusion if they had all of the following: onset of ischemic discomfort at rest 12 hours or less prior to randomization and lasting longer than 20 minutes; ST-segment elevation at least 0.1 mV in at least 2 contiguous limb leads or at least 0.2 mV in at least 2 contiguous precordial leads; or left bundle-branch block not known to be old; and planned treatment with a fibrinolytic, an anticoagulant (if receiving a fibrin-specific lytic), and aspirin. Excluded from the main CLARITY-TIMI 28 trial were patients (1) treated with clopidogrel within 7 days prior to enrollment or in whom treatment with clopidogrel or a glycoprotein IIb/IIIa (GpIIb/IIIa) inhibitor before angiography was planned; (2) who had contraindications to fibrinolysis; (3) in whom there was the intention of performing angiography within 48 hours in the absence of a new clinical indication; (4) with cardiogenic shock; (5) who had undergone prior coronary artery bypass grafting; or (6) weighing 67 kg or less who had received more than 4000 U bolus or weighing more than 67 kg who had received more than 5000 U bolus of unfractionated heparin, or who had received greater than standard doses of low-molecular-weight heparin.

The main study protocol was approved by the relevant institutional review boards, and written informed consent was obtained from all patients. Patients were enrolled at 319 sites in 23 countries from February 2003 through October 2004.

Procedures

Patients were randomized in a 1:1 ratio to receive either clopidogrel (300 mg loading dose, then 75 mg once daily) or placebo in a double-blind fashion. The loading dose was to be given within 45 minutes (and optimally within 10 minutes) of the start of fibrinolytic therapy. Patients were to receive study medication daily up to and including the day of coronary angiography.

All patients were to be treated with a fibrinolytic (selected by the treating physician), aspirin (recommended dose of 150-325 mg on the first day and 75-162 mg daily thereafter), and, for those receiving a fibrin-specific lytic, heparin for 48 hours. The recommended unfractionated heparin dosing was 60 U/kg intravenous bolus (maximum 4000 U) followed by an infusion at 12 U/kg/h (maximum 1000 U/h).9 Use of low-molecular-weight heparin at established doses instead of unfractionated heparin and use of heparin in patients receiving streptokinase was at the discretion of the treating physician.

Coronary angiography was required by protocol in all patients and was to be performed 48 to 192 hours after starting the study medication to determine patency of the infarct-related artery. Angiography before 48 hours was permitted only if clinically indicated.8 Percutaneous coronary intervention was done at the discretion of the local investigator. For patients who underwent coronary stenting, it was recommended that open-label clopidogrel be administered after the diagnostic angiogram with a loading dose of at least 300 mg, followed by 75 mg daily. Use of a GpIIb/IIIa inhibitor was not permitted before coronary angiography unless clinically indicated, but was allowed after the diagnostic coronary angiogram was obtained.

Patients were followed up for clinical outcomes and adverse events during their index hospitalization. Patients undergoing PCI were to have creatine kinase (CK)-MB measured 3 times over the 24 hours following PCI to ensure systemic monitoring for post-PCI MI. Telephone follow-up was performed 30 days after randomization to assess for clinical outcomes or adverse events, which were verified using medical records. Follow-up was complete in 1862 (99.9%) of the 1863 patients who underwent PCI.

Outcomes

The primary efficacy outcome for this analysis was the composite of cardiovascular death, recurrent MI, or stroke from PCI to 30 days after randomization. Secondary outcomes included recurrent MI or stroke before PCI and the composite of cardiovascular death, recurrent MI, or stroke from randomization to 30 days. Recurrent MI within 24 hours after a PCI was prospectively defined as needing to meet one of the following 3 criteria: (1) CK-MB value (or total CK value if CK-MB not available) of at least 3× upper limit of normal and, if the pre-PCI CK-MB (or total CK) value was greater than the upper limit of normal, both an increase by at least 50% over the previous value and documentation that the CK-MB (or total CK-MB) value was greater than the upper limit of normal.
CK) value was decreasing prior to the suspected recurrent MI; or (2) development of new, abnormal Q waves in 2 or more contiguous leads; or (3) pathological findings of an acute MI thought to be distinct from the qualifying MI.8 The primary safety outcome for this analysis was the rate of TIMI major or minor bleeding10 from PCI to 30 days after randomization. All ischemic and any clinically significant bleeding events were adjudicated by an independent clinical events committee that was blinded to treatment assignment.

Statistical Analysis
All efficacy analyses were based on the intention-to-treat principle. For patients who underwent more than 1 PCI, the first PCI was counted as the index procedure. For patients who underwent more than 1 PCI, the first PCI was counted as the index procedure. For patients who underwent more than 1 PCI, the first PCI was counted as the index procedure. For comparing baseline characteristics, differences in continuous variables were analyzed using t tests, and differences in categorical variables were analyzed using the Fisher exact test. Efficacy outcome analyses were performed using a logistic regression model that included terms for treatment group, type of fibrinolytic, initial type of heparin, infarct location, and a propensity score for PCI. A propensity score allows for adjustment for potential selection bias when comparing the effect of randomized treatment allocation within a subset of patients.11,12 The propensity score was constructed by applying a forward selection algorithm with an inclusion P value threshold of <.05 to a logistic regression model predicting PCI in the entire trial cohort and containing candidate baseline variables that included demographics, country, traditional cardiovascular risk factors, prior cardiac disease and procedures, cardiac medications, time to presentation, initial vital signs, infarct location, type of lytic, initial type of heparin, and treatment allocation. The final propensity score included terms for country, race (self-reported), prior MI, prior PCI, systolic blood pressure and heart rate at presentation, time from symptom onset to administration of fibrinolytic, type of fibrinolytic, and type of initial heparin. (For this trial there will be a substudy funded by the National Institutes of Health [NIH], and collection of data on race is an NIH requirement.) Time-to-first-event curves were generated using the Kaplan-Meier method and were compared using a Cox proportional hazards model with the same covariates as used in the logistic regression model. The proportional hazards assumption was confirmed by checking the Schoenfeld residuals. Safety outcomes were analyzed according to the treatment actually received by each patient, and rates were compared using the Fisher exact test.

A meta-analysis of the results of the PCI-CLARITY, PCI-Clopidogrel in Unstable angina to prevent Recurrent Events (PCI-CURE),13 and Clopidogrel for the Reduction of Events During Observation (CREDO)14 studies was performed. Summary data on the rates of cardiovascular death and MI were abstracted from the publications of the other 2 trials and verified by the trial sponsors. Odds ratios (ORs) and 95% confidence intervals (CIs) for the effect of clopidogrel pretreatment vs no pretreatment on the incidence of MI before PCI and cardiovascular death or MI up to 30 days following PCI were calculated for each trial. The results from trials were combined using a random-effects model that used weighting based on inverse variance.15 Between-trial heterogeneity was assessed using χ² tests. All statistical analyses were performed using Stata/SE, version 8.2 (StataCorp LP, College Station, Tex).

RESULTS
Overall, 1863 (53.4%) of the 3491 patients enrolled in the CLARITY-TIMI 28 trial underwent PCI during the index hospitalization. The rates of PCI...
were equivalent in the 2 treatment arms. Thus, of 1863 patients who underwent PCI, 933 (50.1%) had been randomized to receive clopidogrel and 930 (49.9%) had been randomized to receive placebo at the time of initial presentation (Figure 1). The 2 treatment groups were well-matched with regard to baseline characteristics (Table 1), with no statistically significant differences. Seventy-nine percent of patients received a fibrin-specific lytic, and the remainder received streptokinase. Ninety-nine percent of patients received aspirin and 89% received heparin.

The median number of days from initiation of the study drug to PCI was 3 days (Table 2). Immediately prior to PCI, the infarct-related artery was patent in 806 patients (86.9%) in the clopidogrel pretreatment arm and in 748 patients (80.8%) in the placebo arm (P < .001). Following PCI, 99% of patients in both groups had a patent infarct-related artery. Approximately one third of patients received a GpIIb/IIIa inhibitor at the time of PCI, and 95% of patients received a stent. Slightly more than three quarters of patients received a loading dose of an open-label thienopyridine at the time of PCI, and 90% of patients received a maintenance dose of an open-label thienopyridine after PCI.

Pretreatment with clopidogrel significantly reduced the rate of cardiovascular death, recurrent MI, or stroke over time (Figure 2). The effect of clopidogrel pretreatment on reducing cardiovascular death and ischemic events after PCI was consistent across a wide range of important subgroups (Figure 3). Specifically, in terms of baseline characteristics, clopidogrel pretreatment was beneficial regardless of patient age, sex, presence of diabetes mellitus, or infarct location. The benefit of pretreatment was also similar whether patients underwent PCI urgently for recurrent ischemia or electively, and irrespective of the timing of PCI relative to randomization. The benefit was also consistent regardless of the pre-

### Table 1. Baseline Characteristics and Treatment of Patients*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Clopidogrel Pretreatment (n = 933)</th>
<th>No Pretreatment (n = 930)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>57.7 (10.0)</td>
<td>56.9 (10.1)</td>
<td>.08</td>
</tr>
<tr>
<td>Age ≥65 y</td>
<td>276 (29.6)</td>
<td>250 (26.9)</td>
<td>.20</td>
</tr>
<tr>
<td>Male sex</td>
<td>757 (81.1)</td>
<td>765 (82.3)</td>
<td>.55</td>
</tr>
<tr>
<td>White</td>
<td>869 (93.1)</td>
<td>860 (92.5)</td>
<td>.59</td>
</tr>
<tr>
<td>Hypertension</td>
<td>365 (39.5)</td>
<td>399 (43.3)</td>
<td>.10</td>
</tr>
<tr>
<td>Hypertension</td>
<td>344 (41.2)</td>
<td>328 (43.0)</td>
<td>.73</td>
</tr>
<tr>
<td>Current smoker</td>
<td>480 (51.5)</td>
<td>469 (50.7)</td>
<td>.75</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>133 (14.5)</td>
<td>149 (16.3)</td>
<td>.30</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>82 (8.9)</td>
<td>71 (7.7)</td>
<td>.40</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>54 (5.4)</td>
<td>48 (5.2)</td>
<td>.61</td>
</tr>
<tr>
<td>Anterior MI</td>
<td>345 (37.0)</td>
<td>379 (40.8)</td>
<td>.10</td>
</tr>
<tr>
<td>Time from symptom onset to start of fibrinolytic, median (IQR), h</td>
<td>2.4 (1.7-3.8)</td>
<td>2.3 (1.6-3.5)</td>
<td>.12</td>
</tr>
</tbody>
</table>

| Fibrinolytic                          |                                  |                           |         |
|---------------------------------------|                                  |                           |         |
| Fibrin-specific                       | 737 (79.0)                       | 733 (78.8)                | .96     |
| Non–fibrin-specific                   | 196 (21.0)                       | 197 (21.2)                |         |
| Initial aspirin                       | 919 (98.5)                       | 917 (98.6)                | >.99    |
| Initial heparin†                      |                                  |                           |         |
| Unfractionated heparin                | 508 (54.5)                       | 493 (53.0)                | .50     |
| Low-molecular-weight heparin          | 283 (30.3)                       | 276 (29.7)                |         |
| Both                                  | 43 (4.6)                         | 57 (6.1)                  |         |
| Neither                                | 99 (10.6)                        | 104 (11.2)                |         |

* Abbreviations: IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention.

** Data are presented as number and percentage unless otherwise indicated. Denominators are based on available data for each characteristic.

† Initial heparin includes any heparin given immediately before and during the first 2 hours postrandomization.

### Table 2. Percutaneous Coronary Intervention (PCI) Characteristics†

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Clopidogrel Pretreatment (n = 933)</th>
<th>No Pretreatment (n = 930)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from randomization to PCI, median (IQR), d</td>
<td>3.2 (1.7-5.5)</td>
<td>2.9 (0.5-5.2)</td>
<td>.003</td>
</tr>
<tr>
<td>Infarct-related artery patency (TIMI flow grade 2 or 3) Before PCI</td>
<td>806/928 (86.9)</td>
<td>748/926 (80.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>After PCI</td>
<td>734/744 (98.7)</td>
<td>759/768 (98.6)</td>
<td>.82</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa use</td>
<td>288 (31.1)</td>
<td>310 (33.5)</td>
<td>.27</td>
</tr>
<tr>
<td>Loading dose of open-label thienopyridine given at time of PCI</td>
<td>888 (96.2)</td>
<td>884 (96.1)</td>
<td>.92</td>
</tr>
<tr>
<td>Coronary artery stenting</td>
<td>832 (89.3)</td>
<td>836 (89.9)</td>
<td>.71</td>
</tr>
</tbody>
</table>

** Abbreviations: IQR, interquartile range; TIMI, Thrombolysis In Myocardial Infarction.

† Denominators are based on available data for each characteristic.
dominant type of heparin the patient received while awaiting angiography and whether a GPIIb/IIIa inhibitor or a loading dose of open-label clopidogrel was given at the time of PCI.

Prior to undergoing PCI, treatment with clopidogrel significantly reduced the rate of recurrent MI or stroke (37 [4.0%] vs 58 [6.2%]; adjusted OR, 0.62 [95% CI, 0.40-0.95]; P = .03) (Table 3 and Figure 2). Overall, when the events before and after PCI are considered as a whole (Table 3), pretreatment with clopidogrel significantly reduced the incidence of cardiovascular death, recurrent MI, or stroke through 30 days (70 [7.5%] vs 112 [12.0%]; adjusted OR, 0.59 [95% CI, 0.43-0.81]; P = .001; number needed to treat = 23).

There was no significant excess in the rates of TIMI major bleeding (0.5% vs 1.1%), TIMI minor bleeding (1.4% vs 0.8%), or the combination (2.0% vs 1.9%) following PCI in those who received clopidogrel pretreatment compared with those who did not (Table 4). In addition, among patients who received a GPIIb/IIIa inhibitor during PCI, the rate of TIMI major or minor bleeding was no higher in those who had received clopidogrel pretreatment (2.1% [6/283]) than in those who did not receive pretreatment (2.9% [9/307]) (P = .36).

**COMMENT**

Our study demonstrates that pretreatment with clopidogrel before PCI significantly reduced by 46% the odds of cardiovascular death, recurrent MI, or stroke within 30 days following PCI. This benefit was seen in patients with STEMI treated with fibrinolytics who subsequently underwent PCI on average 3 days later, but with a consistent benefit regardless of the time from initiation of pretreatment to PCI. Moreover, benefits were seen regardless of whether patients received a GPIIb/IIIa inhibitor at the time of PCI or whether patients received a loading dose of open-label clopidogrel at the time of PCI. Despite the more intensive antiplatelet therapy, there was no significant excess in TIMI major or minor bleeding.

Clopidogrel is a prodrug that is metabolized in the liver by the cytochrome P450 system into its active form.16 In the absence of a loading dose,
it takes approximately 3 to 5 days for the antiplatelet effects of 75 mg of clopidogrel daily to reach steady state. The use of a 300- to 600-mg loading dose, even in the setting of long-term therapy, greatly accelerates that process and allows substantial platelet inhibition to be achieved after several hours.17,18 However, in the setting of PCI, platelet activation is immediate19 and therefore may be incompletely suppressed if clopidogrel is initiated only at the time of PCI. In platelet aggregation studies, compared with a loading dose at the time of PCI, pretreatment with clopidogrel resulted in greater suppression of markers of platelet activation after PCI.20 Mehta and the PCI-CURE Investigators demonstrated that in patients with non–ST-elevation acute coronary syndromes undergoing PCI, pretreatment with clopidogrel reduced the risk of MI before PCI by 32% and the risk of cardiovascular death or MI after PCI to 30 days by 34%.13 Importantly, though, as the trial was conducted at sites that took a less aggressive approach toward cardiac catheterization, the median time to PCI was 10 days. Subsequent analyses suggested a consistent benefit among those undergoing PCI within 2 days vs after 2 days.21 Nonetheless, questions were raised about potential imbalances between treatment groups because the performance of angiography was at the discretion of the treating physician and not mandated by the trial protocol.22

The CREDO trial provided additional important data on the value of clopidogrel pretreatment in patients undergoing planned, elective PCI.14 In that study, Steinhubl and colleagues demonstrated that clopidogrel pretreatment was associated with a trend to a reduction in the odds of death or MI through 28 days after PCI. Analysis by the duration of pretreatment found that patients in whom clopidogrel was initiated at least 6 hours prior to PCI had a 38.6% reduction in events with a strong trend toward statistical significance (P = .051). Of note, however, following PCI all patients received only 75 mg of open-label clopidogrel. Therefore, in the CREDO trial, patients who did not receive clopidogrel pretreatment never received a loading dose of clopidogrel, which does not reflect current practice patterns.23

The PCI-CLARITY study builds on these prior studies in several important ways. First, we studied patients with STEMI and showed a benefit with clopidogrel pretreatment in these patients who are at the highest risk for early recurrent ischemic events. Clopidogrel thus appears to be an important component to include in a pharmacoinvasive approach toward cardiac catheterization, the median time to PCI was 10 days. Subsequent analyses suggested a consistent benefit among those undergoing PCI within 2 days vs after 2 days.21 Nonetheless, questions were raised about potential imbalances between treatment groups because the performance of angiography was at the discretion of the treating physician and not mandated by the trial protocol.22

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sive approach to patients with STEMI.24-27 Second, we evaluated a broad range of durations of pretreatment from less than 6 hours to 8 days and showed a consistent benefit of clopidogrel pretreatment across this range of pretreatment durations. Of note, although the maximal effect of clopidogrel on platelet inhibition may not occur until 6 or more hours after a 300-mg loading dose,28,29 some degree of platelet inhibition can be measured as early as 90 minutes.30 Prior studies have shown that the degree of platelet inhibition at the time of PCI is strongly related to the likelihood of major adverse cardiovascular events following PCI.31 Our findings suggest that in the setting of an acute coronary syndrome with heightened platelet activation32 and PCI causing immediate and further platelet activation,33,34 even relatively brief durations of pretreatment with clopidogrel before PCI may translate into improved patient outcomes. Third, we showed a benefit with clopidogrel pretreatment regardless of whether a standard loading dose of clopidogrel was administered in the cardiac catheterization laboratory at the time of PCI. Fourth, we showed a benefit with clopidogrel pretreatment regardless of GpIIb/IIIa inhibitor use peri-PCI in patients with acute coronary syndromes. This finding is supported by results from non-randomized comparisons in registries and in the Do Tirofiban and ReoPro Give Similar Efficacy Outcome (TARGET) and Randomized Evaluation in Percutaneous coronary intervention Linking Angiomax to reduced Clinical Events (REPLACE) trials,35-38 and builds on a similar observation made in the setting of elective PCI in CREDO and non-ST-elevation acute coronary syndromes in PCI-CURE.13,14

Interestingly, in the PCI-CLARITY study, the event curves following PCI continued to diverge over time despite almost all patients in both treatment groups receiving open-label clopidogrel following PCI, an observation also seen in PCI-CURE.13 This observation suggests that the beneficial effect of clopidogrel may extend beyond just prevention of platelet aggregation and myocyte necrosis during the procedure. By blocking the P2Y12 receptor, clopidogrel inhibits platelet activation and thus may have more widespread effects on endothelial cells, leukocytes, and inflammation.39 For example, clopidogrel has been shown to blunt expression of both P-selectin and CD40 ligand,20,40 the former of which contributes to platelet-leukocyte aggregation and the latter of which can trigger an inflammatory response in endothelial cells.41,42 To that end, thienopyridine pretreatment has been shown to attenuate the rise in C-reactive protein immediately after PCI43 and to decrease the need for target vessel revascularization over 1 year.44

In terms of implications of PCI-CLARITY for clinical practice, for every 100 patients undergoing PCI in whom a strategy of clopidogrel pretreatment is adopted, approximately 2 MIs would be prevented before PCI and an additional 2 cardiovascular deaths, MIs, or strokes would be prevented after PCI to 30 days. Overall, only 23 patients would need to be pretreated with

### Table 4. Safety Outcomes*

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Clopidogrel Pretreatment (n = 923)</th>
<th>No Pretreatment (n = 918)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major or minor bleeding</td>
<td>18 (2.0)</td>
<td>17 (1.9)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>5 (0.5)</td>
<td>10 (1.1)</td>
<td>.21</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>13 (1.4)</td>
<td>7 (0.8)</td>
<td>.26</td>
</tr>
</tbody>
</table>

*Safety outcomes were analyzed according to the treatment actually received by each patient. Bleeding events were categorized according to the Thrombolysis in Myocardial Infarction criteria.

### Figure 4. Meta-analysis of Clopidogrel Pretreatment in Percutaneous Coronary Intervention (PCI)

**A** Myocardial Infarction Before PCI

<table>
<thead>
<tr>
<th>Source</th>
<th>Events, No./Total (%)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI-CURE,13,14 2001</td>
<td>47/1313 (3.6)</td>
<td>0.70 (0.48-1.02)</td>
<td></td>
</tr>
<tr>
<td>CREDO,14 2002</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>PCI-CLARITY</td>
<td>37/933 (4.0)</td>
<td>0.63 (0.41-0.97)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>84/2246 (3.7)</td>
<td>0.67 (0.50-0.89)</td>
<td>P = .005</td>
</tr>
</tbody>
</table>

**B** Cardiovascular Death or Myocardial Infarction After PCI to 30 Days

<table>
<thead>
<tr>
<th>Source</th>
<th>Events, No./Total (%)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI-CURE,13,14 2001</td>
<td>38/1313 (2.9)</td>
<td>0.65 (0.43-0.98)</td>
<td></td>
</tr>
<tr>
<td>CREDO,14 2002</td>
<td>54/9000 (6.0)</td>
<td>0.83 (0.57-1.21)</td>
<td>P = .26</td>
</tr>
<tr>
<td>PCI-CLARITY</td>
<td>31/933 (3.3)</td>
<td>0.60 (0.38-0.96)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>123/3146 (3.9)</td>
<td>0.71 (0.56-0.89)</td>
<td>P = .004</td>
</tr>
</tbody>
</table>

Individual trial and combined results for the effect of clopidogrel pretreatment on myocardial infarction before PCI (panel A) or cardiovascular death or myocardial infarction after PCI up to 30 days (panel B). The squares indicate the unadjusted odds ratios (ORs) and the size of each square reflects the statistical weight of a trial in calculating the OR; the horizontal lines indicate the 95% confidence intervals (CIs). Tests for heterogeneity: \( \chi^2 = 0.11, P = .74 \) (panel A); \( \chi^2 = 1.37, P = .51 \) (panel B). CREDO indicates Clopidogrel for the Reduction of Events During Observation; PCI-CLARITY, PCI-Clopidogrel as Adjunctive Reperfusion Therapy; PCI-CURE, PCI-Clopidogrel in Unstable angina to prevent Recurrent Events. Ellipses indicate not applicable.
clopidogrel to prevent 1 cardiovascular death, MI, or stroke. This benefit with pretreatment is achieved when compared with the current practice in which patients receive a loading dose of clopidogrel at the time of PCI and a maintenance dose thereafter. Thus in 100 patients, 4 major cardiovascular events can be avoided simply by the use of 1 to 3 doses of clopidogrel before PCI.

Taken together, the PCI-CURE and CREDO studies, and now PCI-CLARITY, demonstrate a clear and consistent benefit with clopidogrel pretreatment for PCI (FIGURE 4). The significant reduction in adverse cardiovascular events before PCI suggests that a strategy of clopidogrel pretreatment should be initiated as soon as possible. Accordingly, even if clopidogrel is not given at presentation, once the decision is made to proceed with angiography, and hence possible PCI, initiation of pretreatment will maximize the benefit. The consistency of benefit of clopidogrel pretreatment across the spectrum from stable coronary artery disease to STEMI, and regardless of patient demographics or the use of a GpIIb/IIa inhibitor at the time of PCI, should help encourage widespread incorporation of clopidogrel pretreatment into cardiology clinical pathways.

In terms of safety, we saw no increase in TIMI major or minor bleeding in PCI-CLARITY. This observation is similar to the findings in the PCI-CURE study, in which the rates of major bleeding were 1.6% in the clopidogrel treatment arm and 1.4% in the placebo treatment arm. These data, coupled with observations on the efficacy and safety of initiating clopidogrel even in patients who ultimately proceed to coronary artery bypass grafting, suggest that rather than waiting for angiography, an empirical strategy of early clopidogrel pretreatment begins as soon as possible in patients with acute coronary syndromes, only a small minority of whom will need to undergo surgery, will be of the greatest benefit in preventing cardiovascular events. Potential limitations of this study merit consideration. Percutaneous coronary intervention was performed at the discretion of the treating physician and was a postrandomization event. However, angiography was mandated in the CLARITY-TIMI 28 trial and was carried out in all but 4% of surviving patients. This design should have minimized any potential bias, and, in fact, in PCI-CLARITY, the rates of both angiography and PCI were identical in the 2 treatment arms. Moreover, we included a propensity score in our multivariable analyses to minimize any potential bias, although we recognize that residual confounding could still exist. Furthermore, we performed a sensitivity analysis in which we examined the magnitude of benefit of clopidogrel pretreatment in the setting of both urgent and elective PCI and found no difference. Our results do not apply to all STEMI patients undergoing PCI, as patients in the CLARITY-TIMI 28 trial were required to be treated with a fibrinolytic, which can lead to platelet activation and thus possibly enhance the benefit of more intensive antplatelet therapy. However, the benefit of clopidogrel pretreatment that we found was similar in magnitude to the benefit seen in patients with non–ST-elevation acute coronary syndromes and in patients undergoing elective PCI.

In conclusion, we found that in high-risk patients with STEMI treated with fibrinolytic therapy, a strategy of clopidogrel pretreatment significantly reduced the incidence of cardiovascular death and ischemic complications both before and after PCI without a significant increase in major or minor bleeding. These data add further support to the early use of clopidogrel in STEMI and the broader strategy of clopidogrel pretreatment in patients undergoing PCI.

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Author Contributions: Dr Sabatine 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.

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