Optimal Timing for the Initiation of Pre-Treatment With 300 mg Clopidogrel Before Percutaneous Coronary Intervention

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OBJECTIVES
This study sought to determine the optimal timing of a 300-mg clopidogrel loading dose before percutaneous coronary intervention (PCI) in patients enrolled in the Clopidogrel for the Reduction of Events During Observation (CREDO) trial.

BACKGROUND
A loading dose of clopidogrel before a PCI has become relatively commonplace, although the data supporting this practice are limited and sometimes conflicting.

METHODS
Patients were randomized to receive either 300 mg clopidogrel or a matching placebo administered a minimum of 3 h and a maximum of 24 h before PCI. The primary 28-day combined end point was death, myocardial infarction, or urgent target vessel revascularization. Linear splines were used to summarize the effect of the time of pre-treatment as a continuous variable.

RESULTS
A total of 1,762 patients were evaluated. For patients randomized to placebo, there was no relationship between the duration of pre-treatment and the occurrence of the primary end point, whereas longer durations of pre-treatment in patients randomized to clopidogrel were associated with improved outcomes. The event rates diverged maximally at 24 h. The difference in outcomes between placebo and clopidogrel pre-treated patients was not significant until ≥15 h pre-treatment, with a 58.8% (p = 0.028) reduction in the primary end point in patients pre-treated with clopidogrel ≥15 h compared with placebo.

CONCLUSIONS
When a 300-mg loading dose of clopidogrel is used, little benefit is obtained compared with just 75 mg at the time of the PCI when the treatment duration is <~12 h. In patients pre-treated for longer durations, the optimal duration seems to approach 24 h. (J Am Coll Cardiol 2006;47:939–43) © 2006 by the American College of Cardiology Foundation

Although the clinical benefit of the early initiation of thienopyridine treatment for the prevention of periprocedural thrombotic complications in patients undergoing percutaneous coronary intervention (PCI) has yet to be definitively proven in placebo-controlled clinical trials, the volume of data supporting such a benefit has led to its widespread acceptance into clinical practice (1–5). However, the optimal duration of pre-treatment remains unclear, especially with the commonly used 300-mg dose. Much of this confusion centers around the wide variability in duration of pre-treatment—ranging from hours to days—reported in clinical studies supporting the benefit of pre-treatment.

Ex-vivo determination of the degree of inhibition of adenosine diphosphate–induced platelet aggregation using light transmission aggregometry has been most commonly used to identify the pharmacodynamics of clopidogrel, with the time between treatment initiation and the achievement of maximal inhibition of platelet aggregation assumed to reflect the time required to achieve maximal clinical efficacy. Based on several of these studies, it was therefore initially thought that 300 mg given at least three hours before a PCI would supply maximal, or at least near maximal, clinical benefit (6,7). However, in the Clopidogrel for the Reduction of Events During Observation (CREDO) trial, in which patients were randomized to 300 mg clopidogrel or matching placebo, no significant difference in the 28-day combined end point of death, myocardial infarction (MI), or urgent target vessel revascularization (UTVR) was observed (5). Subsequent analysis using pre-specified durations of pre-treatment of 3 to 6 h, 6 to 12 h, or 12 to 24 h before PCI found that only those patients pre-treated with clopidogrel for >6 h experienced a decrease in event rates compared with placebo, with a 37% relative risk reduction in the 28-day end point that was not quite statistically significant (p = 0.051). Based on these clinical data and ex vivo aggregometry, six hours of pre-treatment with 300 mg of clopidogrel has been suggested to be adequate to achieve the full clinical benefit of this loading dose.

The goal of this study was to examine the duration of pre-treatment with clopidogrel as a continuous variable and identify the optimal duration of pre-treatment with a 300-mg loading dose of clopidogrel in terms of the occurrence of ischemic complications.

METHODS
The CREDO trial methodology has been published in detail elsewhere (5). Briefly, the CREDO trial enrolled...
2,116 patients (1,053 assigned to clopidogrel and 1,063 to placebo) referred for planned PCI or likely to require PCI. Several important exclusion criteria were an ST-segment elevation MI within 24 h, a planned staged procedure, treatment with a platelet glycoprotein (GP) IIb/IIIa antagonists within 7 days, or clopidogrel or ticlopidine within 10 days. The present analysis includes only those 1,815 patients who underwent a PCI shortly after enrollment, during the index catheterization.

All patients were randomized to a 300-mg clopidogrel oral loading dose or to matching placebo 3 to 24 h pre-procedure in a double-blind fashion. The use of GP IIb/IIIa antagonists was at the discretion of the operator but could only be pre-specified at the time of enrollment or given as bail-out during the PCI procedure. Both groups were treated with clopidogrel 75 mg and aspirin 325 mg daily for 28 days after the PCI. The present analysis is only of the relationship between duration of pre-treatment and outcome at 28 days.

The 28-day end points. The primary end point was the composite of death, MI, or UTVR at 28 days, the definitions of which have been previously published (5). Major bleeding was defined as intracranial bleeding or bleeding associated with a decrease in hemoglobin of more than 5 g/dl. All outcome events were adjudicated by a blinded Clinical Events Committee.

Statistical analysis. Categorical variables are displayed as frequencies and percentages, and comparisons were made with chi-square testing. Continuous variables appear as medians with interquartile ranges and were compared using Wilcoxon rank-sum tests. Kaplan-Meier methods are used in time-to-event analyses. Linear splines were used to summarize the effect of time of pre-treatment. It created two independent regression lines from a linear regression model that were joined at one point, or knot, because the slopes of the time of pre-treatment changed direction at that knot. Statistical analyses were performed with SAS version 8.2 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Of 2,116 patients randomized, 1,815 underwent PCI during their index procedure. The timing of study drug treatment was able to be analyzed in 1,762 of these 1,815 patients, and they comprise the study population. The mean duration of pre-treatment was 9.8 h. As previously reported, randomization to clopidogrel pre-treatment was associated with a non-significant 18.5% relative risk reduction in the 28-day combined end point (5).

Among the patients randomized to placebo, no relationship was found between the duration of pre-treatment and the occurrence of the primary 28-day combined end point of death, MI, or UTVR (Fig. 1). On the other hand, patients randomized to receive a 300-mg loading dose of clopidogrel had a strong relationship between the duration of pre-treatment and occurrence of the primary end point. Unexpectedly, no separation between the placebo and treatment arm curves was seen until after 10 to 12 h of pre-treatment, and this difference did not become statistically significant until after 15 h of pre-treatment. The log odds of the 28-day combined end point continued to decrease out to the maximal duration of pre-treatment in this study, 24 h.

Pertinent baseline and procedural characteristics in patients randomized to placebo, patients randomized to clopidogrel pre-treatment whose therapy was initiated <15 h before PCI, and patients randomized to clopidogrel pre-treatment whose therapy was initiated ≥15 h before PCI are shown in Table 1. No significant differences were noted except for less use of GP IIb/IIIa antagonists in those patients pre-treated with clopidogrel ≥15 h compared with those pre-treated <15 h.

The incidence of the 28-day end point was similar in those patients randomized to the placebo arm and those randomized to the clopidogrel arm who had therapy initiated <15 h before PCI (Fig. 2). The relative risk reduction in those pre-treated with clopidogrel from ≥15 h compared with the placebo arm was 58.8% (p = 0.028). This relative risk reduction associated with ≥15 h of clopidogrel pre-treatment before PCI was unchanged when only those patients in the placebo (n = 206) and treatment (n = 202) arms who had been pre-treated ≥15 h were compared (9.7% vs. 3.5%; relative risk reduction, 66.6%; 95% confidence interval, 19.2% to 86.2%; p = 0.011). When all pertinent baseline and procedural characteristics were evaluated in a multivariate analysis, clopidogrel pre-treatment for ≥15 h

### Abbreviations and Acronyms

- GP = glycoprotein
- MI = myocardial infarction
- PCI = percutaneous coronary intervention
- UTVR = urgent target vessel revascularization

**Figure 1.** Relationship between the duration of study drug treatment before percutaneous coronary intervention and log odds of the primary combined end point of death, myocardial infarction (MI), and urgent target vessel revascularization (UTVR). **Dotted line** = placebo; **Solid line** = clopidogrel.
remained a significant predictor of the 28-day end point (odds ratio, 0.72; p = 0.043).

Glycoprotein IIb/IIIa inhibitors were used in ~45% of all patients, and at similar rates in those randomized to placebo and to active treatment. Whether or not a patient received a GP IIb/IIIa antagonist did not significantly influence the benefit of clopidogrel pre-treatment for <15 h (p value for interaction = 0.90), although the relative risk reduction associated with prolonged clopidogrel pre-treatment tended to be greater in those patients who did not receive a GP IIb/IIIa antagonist (Fig. 3).

The incidence of major and minor bleeding at 28 days was not significantly different between the placebo arm, those patients pre-treated <15 h, and those patients pre-treated ≥15 h (Table 2).

**DISCUSSION**

The results of this analysis from the CREDO trial have important clinical implications and call into question some long-held assumptions regarding the optimal use of thienopyridines in the setting of a PCI.
It is not exactly known what percentage of patients undergoing a non-urgent PCI are currently pre-treated with clopidogrel. During the CREDO trial, the single most common reason for a potentially eligible patient being excluded from randomization was the desire of the patient’s physician to pre-treat with a thienopyridine. Recent data from the CRUSADE registry, which include only acute coronary syndrome patients, confirm that the use of early clopidogrel is increasing over the last several years (8). Our findings suggest that many pre-treated patients are not receiving any protection from PCI-related thrombotic events if they are receiving 300 mg clopidogrel ≤12 h before the procedure, and may require at least 24 h of pre-treatment to achieve maximal protection.

One intriguing finding from this analysis is the apparent discrepancy between ex vivo studies of the pharmacodynamics of a clopidogrel loading dose and the timing of its clinical benefit. In one of the most extensive studies to date of the pharmacodynamics of a 300-mg loading dose of clopidogrel, 15 different measures of platelet function were studied in 100 patients, 75 of whom received 300 mg clopidogrel between 3 and 24 h before a PCI and 25 patients who received 75 mg at the time of the procedure (6). Patients receiving a loading dose achieved similar levels of platelet inhibition pre-PCI, irrespective of timing of the loading dose that was not matched by those patients who received 75 mg at the time of PCI until 5 days after the PCI procedure. Other pharmacodynamic studies of 300 mg clopidogrel have for the most part mirrored these results, with the majority of platelet inhibition, although not maximal inhibition, being achieved within the first three to six hours of treatment (9,10).

Although it is clear that the clinical benefit of all antiplatelet agents, including aspirin, thienopyridines, and the GP IIb/IIIa antagonists (parenteral and oral), cannot solely be predicted by their ability to inhibit agonist-induced platelet aggregation, platelet aggregometry is still considered the gold standard for identifying the pharmacodynamic properties of antiplatelet agents. However, we are aware of no other measure of the antiplatelet (or any other) effects of clopidogrel that mimic the clinical findings described here. Further studies might elucidate other potential effects of thienopyridines not related to their direct effect on the platelet P2Y12 receptor that could possibly follow a pharmacodynamic course more consistent with the clinical findings from this study. Decreases in monocyte and endothelial tissue factor activity (11,12), endothelial passivation (13,14), vascular smooth cell effects (15), or anti-inflammatory effects, some possibly related to direct effects on lymphocytes (16), are some possible mechanisms that may better correlate with the clinical data.

A second interesting finding from this analysis was that when adequate pre-treatment was not achieved, the dose of clopidogrel used seemed to have little impact on 28-day event rates. Surprisingly, patients receiving 300 mg clopidogrel, even when given up to 10 h before the PCI, had identical outcomes as did those patients who received only 75 mg at the time of the PCI. When the interventional cardiologists switched from routinely using ticlopidine to using clopidogrel in patients with stents, one reason was the ability to achieve a more rapid onset of action with a 300-mg loading dose. It was assumed that this faster onset after stenting would lead to fewer adverse events. We did not find this to be the case in the CREDO trial. Our findings are consistent with those found in the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS) trial, the only blinded trial of ticlopidine versus clopidogrel (75 mg and 300 mg) in stent-treated patients (17).

In a recent analysis of the Intracoronary Stenting and Antithrombotic Regimen—Rapid Early Action for Coronary Treatment (ISAR-REACT) trial, in which all patients received a 600-mg loading dose of clopidogrel between 2 and 24 h before PCI, no relationship was found between the duration of pre-treatment and clinical events (18). Although there was no clopidogrel-placebo arm in this study, these results suggest that unlike with a 300-mg loading dose, a 600-mg loading dose is able to achieve its maximal clinical benefit within 2 h. This faster onset of action of a 600-mg loading dose compared with 300 mg would help explain the lower event rates in a recent trial comparing these two loading regimens initiated 4 to 8 h before a PCI (19).

**Study limitations.** This is a post-hoc analysis of a prospective, randomized, blinded trial. Although a post-hoc analysis is the only manner in which the duration of pre-treatment can be analyzed as a continuous variable, which adds considerable power to the analysis and allows one to identify the point at which the curves begin to separate, it also raises the possibility of a finding attributable to chance. Beyond the broad limits of 3 to 24 h before a planned PCI, the actual duration of pre-treatment was at the discretion of the operator. However, because treatment was blinded and the decision regarding when the study drug should be initiated was made before the patients received the study drug, unaccounted-for biases would be unlikely to have influenced the results and conclusions of this study.

### Table 2. 28-Day Bleeding Events

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 915)</th>
<th>Clopidogrel Pre-Treatment &lt;15 h (n = 645)</th>
<th>Clopidogrel Pre-Treatment ≥15 h (n = 202)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding, n (%)</td>
<td>16 (1.7)</td>
<td>15 (2.3)</td>
<td>3 (1.5)</td>
<td>0.64</td>
</tr>
<tr>
<td>Minor bleeding, n (%)</td>
<td>13 (1.4)</td>
<td>14 (2.2)</td>
<td>4 (2.0)</td>
<td>0.52</td>
</tr>
</tbody>
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CONCLUSIONS

These data suggest that when a 300-mg loading dose of clopidogrel is used, little benefit is obtained compared with just 75 mg of clopidogrel at the time of the PCI when treatment duration is $\leq 12$ h before the procedure. In those patients pre-treated for longer durations, the optimal duration is still not clear, but seems to approach 24 h. Based on these results, along with the results of the analysis from the ISAR-REACT trial (18), for pre-treatment with a clopidogrel loading dose to be of any benefit before a PCI it should be initiated at least 15 to 24 h beforehand if a dose of 300 mg is used. In situations in which longer durations of pre-treatment are not possible, 600 mg may be used when given at least two hours before PCI.

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REFERENCES


