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Early and Sustained Dual Oral Antiplatelet Therapy Following Percutaneous Coronary Intervention

A Randomized Controlled Trial

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ASPIRIN IS A CORNERSTONE OF therapy for patients undergoing coronary intervention. Its use is considered a standard of care before the procedure and lifelong following revascularization. Adding to aspirin a short course (2-4 weeks) of an adenosine diphosphate (ADP) P2Y₁₂ receptor antagonist (ticlopidine or clopidogrel) leads to even greater protection from thrombotic complications following a percutaneous coronary intervention (PCI) with a stent.¹⁻⁴ However, the optimal timing for the initiation of clopidogrel and aspirin, as well as their duration of treatment following a PCI procedure, remains unknown.

The results of multiple observational and nonrandomized studies suggest that treating patients with an ADP receptor antagonist prior to a planned PCI may provide additional, incremental benefit beyond that provided by aspirin, and even beyond that of glycoprotein (Gp) IIb/IIIa antagonists.⁵⁻⁷

Despite the consistency of this observation, patient or procedural characteristics may have biased the results in

Context Following percutaneous coronary intervention (PCI), short-term clopidogrel therapy in addition to aspirin leads to greater protection from thrombotic complications than aspirin alone. However, the optimal duration of combination oral antiplatelet therapy is unknown. Also, although current clinical data suggest a benefit for beginning therapy with a clopidogrel loading dose prior to PCI, the practical application of this therapy has not been prospectively studied.

Objectives To evaluate the benefit of long-term (12-month) treatment with clopidogrel after PCI and to determine the benefit of initiating clopidogrel with a preprocedure loading dose, both in addition to aspirin therapy.

Design, Setting, and Participants The Clopidogrel for the Reduction of Events During Observation (CREDO) trial, a randomized, double-blind, placebo-controlled trial conducted among 2116 patients who were to undergo elective PCI or were deemed at high likelihood of undergoing PCI, enrolled at 99 centers in North America from June 1999 through April 2001.

Interventions Patients were randomly assigned to receive a 300-mg clopidogrel loading dose (n=1053) or placebo (n=1063) 3 to 24 hours before PCI. Thereafter, all patients received clopidogrel, 75 mg/d, through day 28. From day 29 through 12 months, patients in the loading-dose group received clopidogrel, 75 mg/d, and those in the control group received placebo. Both groups received aspirin throughout the study.

Main Outcome Measures One-year incidence of the composite of death, myocardial infarction (MI), or stroke in the intent-to-treat population; 28-day incidence of the composite of death, MI, or urgent target vessel revascularization in the per-protocol population.

Results At 1 year, long-term clopidogrel therapy was associated with a 26.9% relative reduction in the combined risk of death, MI, or stroke (95% confidence interval [CI], 3.9%-44.4%; $P=.02$; absolute reduction, 3%). Clopidogrel pretreatment did not significantly reduce the combined risk of death, MI, or urgent target vessel revascularization at 28 days (reduction, 18.5%; 95% CI, -14.2% to 41.8%; $P=.23$). However, in a prespecified subgroup analysis, patients who received clopidogrel at least 6 hours before PCI experienced a relative risk reduction of 38.6% (95% CI, -1.6% to 62.9%; $P=.051$) for this end point compared with no reduction with treatment less than 6 hours before PCI. Risk of major bleeding at 1 year increased, but not significantly (8.8% with clopidogrel vs 6.7% with placebo; $P=.07$).

Conclusions Following PCI, long-term (1-year) clopidogrel therapy significantly reduced the risk of adverse ischemic events. A loading dose of clopidogrel given at least 3 hours before the procedure did not reduce events at 28 days, but subgroup analyses suggest that longer intervals between the loading dose and PCI may reduce events.

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Author Affiliations, Financial Disclosures, and a List of the CREDO Investigators are listed at the end of this article.

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favor of pretreatment. More definitive data regarding the benefit of pretreatment with clopidogrel were recently reported in the subset of 2658 patients undergoing PCI as part of a larger trial of combined antiplatelet therapy for acute ischemic heart disease, the PCI-Clopidogrel in Unstable angina to prevent Recurrent Events (PCI-CURE) study.⁸ However, the duration of pretreatment (a median of 10 days) as well as other factors make these results hard to extrapolate and logistically difficult to apply to patients undergoing elective PCI.

The most appropriate duration of dual antiplatelet therapy following PCI has not been prospectively studied, to our knowledge. The current standard of 4 weeks is relatively arbitrary, and while adequate for preventing most cases of stent thrombosis, this duration is not necessarily consistent with the duration of heightened risk for complications following a PCI or the long-term risk for thrombotic events throughout the vasculature.⁹⁻¹¹ The PCI-CURE study⁸ has provided the best data to date regarding the benefit of continuing clopidogrel and aspirin beyond 4 weeks after PCI, with patients taking clopidogrel for a mean of 9 months (maximum, 1 year) experiencing an overall 31% relative reduction in the risk of cardiovascular death, myocardial infarction (MI), and stroke.

The CREDO (Clopidogrel for the Reduction of Events During Observation) trial was designed to evaluate the efficacy and safety of clopidogrel therapy for 1 year and the efficacy and safety of a loading dose of clopidogrel prior to elective PCI.

METHODS

Study Population

Patients potentially eligible for enrollment were identified at participating US and Canadian sites among patients referred for a planned PCI or coronary angiogram and were approached about participation by the site investigator and nurse coordinator. Patients were considered eligible for enrollment in the study if they had symptomatic coro-

nary artery disease with objective evidence of ischemia (eg, symptoms of angina pectoris, positive stress test results, or dynamic electrocardiographic [ECG] changes); were referred for PCI, or thought to be at high likelihood for requiring PCI with either stent placement with or without conventional balloon angioplasty or another revascularization device; were at least 21 years old; provided informed consent before randomization; and agreed to comply with all protocol-specified procedures.

Major exclusion criteria included contraindications to antithrombotic/antiplatelet therapy; greater than 50% stenosis of the left main coronary artery; failed coronary intervention in the previous 2 weeks; coronary anatomy not amenable to stent placement; persistent ST elevation within 24 hours prior to randomization; planned staged interventional procedure; and administration of the following medications prior to randomization: GpIIb-IIIa inhibitor within 7 days, clopidogrel within 10 days, or thrombolytics within 24 hours.

All patients provided written informed consent, and the institutional review board at each participating center approved the protocol.

Randomization and Blinding

Patients were randomly assigned to groups using a prospective randomization schedule. The randomization was performed in blocks of 2 and stratified by center. When a patient was ready to be randomized, the site dispensed a drug package that contained a unique 4-digit random number; this number was entered on the case report form and provided an identifier of the treatment assigned. After investigators satisfactorily completed screening procedures, obtained informed consent, and reviewed all inclusion and exclusion criteria, patients were entered into the study and received study drug (clopidogrel or matching placebo). A patient was considered to be randomized upon opening of the study medication. The study was conducted on a double-blind basis: investigators were blind to treat-

ment allocation from randomization until the end of the study period.

Interventions

Following randomization, and 3 to 24 hours prior to PCI, patients received either a 300-mg loading dose of clopidogrel or matching placebo. All patients also received 325 mg of aspirin.

Immediately after the PCI procedure was completed, both groups received 75 mg/d of clopidogrel and 325 mg/d of aspirin through day 28. After 28 days and until the end of the study period, the pretreatment group continued to receive 75 mg/d of clopidogrel, whereas the no-pretreatment group received matching placebo. Both groups continued to receive standard therapy including aspirin (81-325 mg/d, at the discretion of the investigator) until the end of the 12-month treatment period.

Twenty percent of all patients could be prespecified at the time of randomization to receive a GpIIb-IIIa receptor antagonist (primarily abciximab) at the time of PCI. Bail-out GpIIb-IIIa inhibitor use was allowed for all patients at the discretion of the physician performing PCI.

Follow-up assessment was performed on days 2, 28, 60, 180, 270, and 365 following randomization.

Outcomes

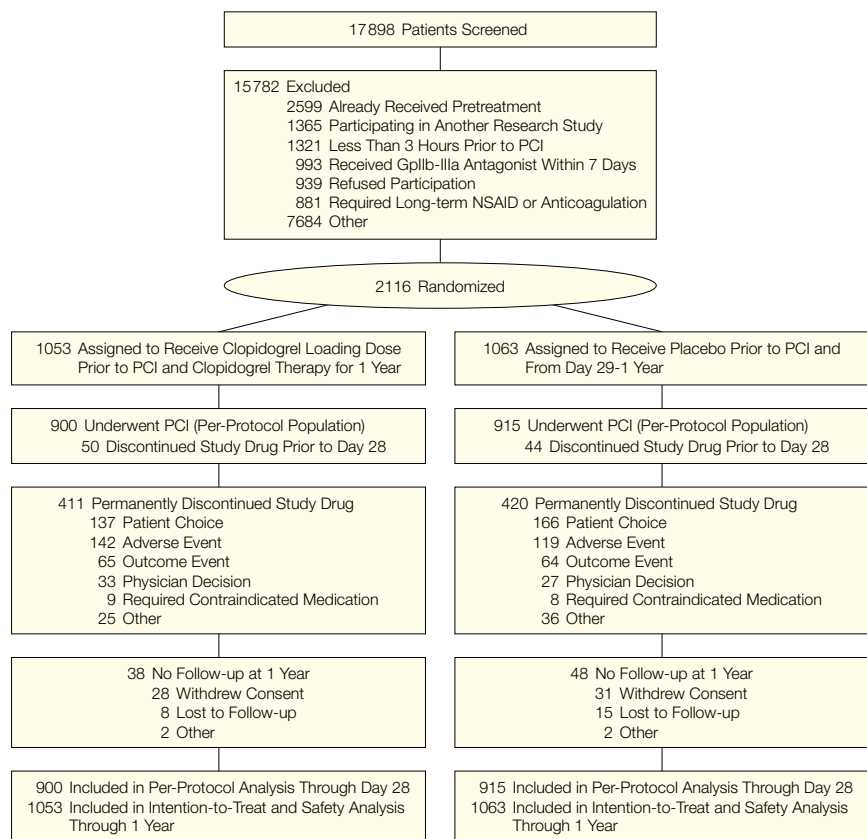
The primary 1-year outcome was the composite of death, MI, and stroke in the intent-to-treat population. The primary outcome of interest at 28 days was the composite of death, MI, or urgent target vessel revascularization in the per-protocol population, which included all randomized patients who underwent PCI. Prespecified secondary analyses included the individual components of the composite end points, administration of clopidogrel less than 6 hours or at least 6 hours before PCI, and the need for target vessel revascularization or any revascularization at 1 year.

Death was defined as mortality from any cause (cardiovascular or noncardiovascular). Cardiovascular death was defined as any death with a clear cardio-

vascular (including hemorrhagic) or unknown cause. Only deaths due to a clear and documented nonvascular cause were documented as nonvascular. Acute Q-wave MI was defined as the presence of a new significant Q wave with a duration of at least 0.04 seconds or a depth equal to one fourth of the corresponding R-wave amplitude in 2 or more contiguous leads. A periprocedural non-Q-wave MI was defined as the elevation of the serum levels of creatine kinase (CK) or CK-MB isoenzyme to at least 3 times the upper limit of normal in 2 samples collected at different sampling times, with an increase of at least 50% over the previous trough level. In patients undergoing elective coronary artery bypass graft (CABG) surgery, postsurgical MI was defined as the elevation of CK or CK-MB isoenzyme to at least 5 times the upper limit of normal. The criteria for postdischarge or repeat Q-wave MI were the same as for acute Q-wave MI. Postdischarge non-Q-wave MI was defined as the elevation of CK or CK-MB isoenzyme at least twice the upper limit of normal in 2 samples collected at different sampling times. Stroke was defined as a new focal neurologic deficit of vascular origin lasting at least 24 hours. Stroke was further classified as an intracranial hemorrhage, ischemic infarction (if a computed tomographic or magnetic resonance imaging scan was available), or of uncertain cause. Urgent target vessel revascularization was defined as CABG initiated within 24 hours of the index procedure due to an inadequate or unstable result of the index procedure, even if ongoing myocardial ischemia was not present; repeat PCI or CABG of the target vessel initiated within 1 week of (re)hospitalization for acute MI or unstable angina; or repeat PCI or CABG of the culprit vessel initiated within 24 hours of the last episode(s) of ischemia. Any revascularization was defined as any peripheral revascularization or PCI or CABG performed on any coronary vessel.

All potential events were identified by site investigators or through screen-

Figure 1. Flow of Participants Through the Trial



PCI indicates percutaneous coronary intervention; Gp, glycoprotein; and NSAID, nonsteroidal anti-inflammatory drug.

ing of protocol-specified ECGs and laboratory tests, blinded to treatment assignment. An independent clinical events committee, also blinded to treatment assignment, adjudicated all outcome events, and all analyses were based on the committee's classification of the end points.

Secondary end points focused on safety and included the incidence of major bleeding events and of early discontinuation of study drugs at 28 days and 1 year. Bleeding was defined as major, minor, or insignificant using a modification of the Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria. Major bleeding was defined as intracranial bleeding or bleeding associated with a decrease in hemoglobin of more than 5 g/dL (or, when hemoglobin values were not available, a

hematocrit decrease of at least 15%). Hematocrit and hemoglobin measurements were adjusted for any packed red blood cell (PRBC) or whole blood transfusions between baseline and posttreatment hemoglobin measurements, with the number of units of PRBC and whole blood combined being added to the change in hemoglobin level. Three times the number of units of PRBCs and whole blood combined was added to the change in hematocrit. Bleeding that met the criteria for major bleeding events but was associated with a surgical procedure (eg, CABG) was also considered separately from other bleeding.

Statistical Methods

Based on a projected 1-year event rate of 20% for the composite of death, MI, or any revascularization, and using a

2-sided α level of .05, a study with 1814 patients would have 80% power to detect a 25% relative risk reduction (RRR). The planned sample size was increased by 10% to allow for patients randomized but lost to follow-up, giving a total overall sample size of 2000 patients. The expected rate of the primary end point in the placebo group at 28 days was 13.4%, based on the event rate seen in the EPISTENT trial in patients who underwent PCI but did not receive ticlopidine prior to the intervention.⁶ Based on the 28-day event rate of 8.9% in EPISTENT patients who began ticlopidine therapy prior to the procedure, and the likely impact of suboptimal initiation of ticlopidine before intervention, the estimated 28-day event rate in the clopidogrel pretreated arm was 7.5%.

All hypothesis tests were performed using 2-sided tests at the 5% signifi-

cance level. The 28-day efficacy outcome was analyzed in the per-protocol population, which constituted all randomized patients who underwent PCI at the time of initial angiography. The per-protocol population was studied to evaluate the specific effect of clopidogrel therapy administered before PCI. All other analyses were in the intent-to-treat population, which included all patients as randomized.

For time-to-event variables, Kaplan-Meier estimates were used and the groups were compared with a log-rank test. Relative risk reductions and associated 95% confidence intervals (CIs) were estimated from the Cox proportional hazards model. The same method was used to investigate a number of population subgroups that were prespecified at the time of protocol development: diabetes, sex, timing of load-

ing dose (3 to <6 hours, 6 to <12 hours, and 12 to 24 hours prior to PCI), GpIIb-IIIa antagonist use, clinical diagnosis (acute coronary syndrome or not), and treatment (stent or not).

Incidence of bleeding was compared using the Fisher exact test. Analyses were performed with SAS version 6.12 (SAS Institute Inc, Cary, NC).

RESULTS

Between June 1999 and April 2001 in 99 centers in the United States and Canada, 2116 patients who were to undergo a planned PCI or were deemed at high likelihood to undergo PCI were enrolled into the study (FIGURE 1). Baseline demographics in the 2 treatment groups were well matched, although there was less use of statins and calcium channel blockers in the clopidogrel arm (TABLE 1). By design, the majority of patients enrolled underwent PCI following initial angiogram—86% in both groups.

28-Day End Point

Procedural characteristics of patients undergoing PCI at the time of initial angiogram (per-protocol population) were similar in the 2 groups, although the use of GpIIb-IIIa antagonists was more common in the pretreatment cohort (TABLE 2). The mean duration between study drug loading dose and PCI was 9.8 hours. Fifty-one percent of patients received their loading dose between 3 and less than 6 hours before their PCI and 49% between 6 and 24 hours prior to PCI.

Among patients undergoing PCI, pretreatment with a clopidogrel loading dose was associated with a nonsignificant 18.5% relative reduction in the combined end point of death, MI, or urgent target vessel revascularization at 28 days (6.8% pretreatment vs 8.3% no pretreatment; 95% CI, -14.2% to 41.8%; $P = .23$) (FIGURE 2A). For each component of the combined end point there were fewer events in patients receiving clopidogrel pretreatment (pretreatment vs no pretreatment: death, 0 vs 4; MI, 52 vs 60; urgent target vessel revascularization, 9 vs 12; total, 61 vs 76).

Table 1. Baseline Demographics*

	Clopidogrel (n = 1053)	Placebo (n = 1063)	P Value
Age, mean (SD), y	61.5 (11.2)	61.8 (11.0)	.45
White race, No. (%)	929 (88.2)	951 (89.5)	.92
Women, No. (%)	309 (29.3)	297 (27.9)	.50
Weight, mean (SD), kg	87.8 (18.3)	87.7 (18.5)	.95
Body mass index >30, No. (%)	455 (43.2)	468 (44.0)	.73
Risk factors, No. (%)			
Previous myocardial infarction	353 (33.5)	366 (34.4)	.68
Previous stroke	67 (6.4)	74 (7.0)	.60
Peripheral vascular disease	102 (9.7)	109 (10.3)	.72
Diabetes	290 (27.5)	270 (25.4)	.26
Hypertension	710 (67.4)	740 (69.6)	.28
Smoking (within past year)	339 (32.2)	313 (29.4)	.16
Family history of heart disease	437 (41.5)	456 (42.9)	.54
Hyperlipidemia	780 (74.1)	800 (75.3)	.55
Baseline medications, No. (%)			
Aspirin	315 (29.9)	315 (29.6)	.92
β -Blocker	664 (63.1)	696 (65.5)	.26
Statin	563 (53.5)	609 (57.3)	.08
ACE inhibitor	347 (33.0)	364 (34.2)	.55
Calcium channel blocker	268 (25.5)	312 (29.4)	.05
Treatment after initial angiogram, No. (%)			
PCI	902 (85.6)	916 (86.2)	.96
Medical therapy	87 (8.3)	81 (7.6)	
CABG	41 (3.9)	42 (4.0)	
Indication for PCI, No. (%)			
Recent myocardial infarction	151 (14.3)	139 (13.1)	.74
Unstable angina	553 (52.5)	564 (53.1)	
Stable angina and other	345 (32.8)	349 (32.8)	

*PCI indicates percutaneous coronary intervention; ACE, angiotensin-converting enzyme; and CABG, coronary artery bypass grafting. Body mass index is calculated as the weight in kilograms divided by the square of height in meters.

Results were similar when the 28-day end point was analyzed in the intent-to-treat population (6.2% vs 7.8%; RRR, 20.9%; $P = .15$).

When the per-protocol population was analyzed based on the prespecified time-to-treatment intervals of 3 to 6 hours, 6 to 12 hours, and 12 to 24 hours prior to the PCI, an important interaction was noted in the duration of pretreatment and the degree of protection from adverse cardiac events. Among the 893 patients receiving their loading dose of study medication 3 to less than 6 hours prior to PCI, no benefit of clopidogrel pretreatment was found (RRR, -13.4%; 95% CI, 29.8% to -83.3% $P = .60$). On the other hand, in the 230 patients treated 6 to less than 12 hours prior to PCI and in the 621 patients treated 12 to 24 hours before PCI, the relative reduction in the combined end point was 35.5% (95% CI, 73.3% to -55.6%; $P = .32$) and 40.1% (95% CI, 67.6% to -10.7%; $P = .09$), respectively. Therefore, among patients in whom study drug was initiated at least 6 hours prior to PCI, those randomized to clopidogrel experienced a 38.6% relative reduction in the combined end point that was of borderline statistical significance (95% CI, -1.6% to 62.9%; $P = .051$) (Figure 2B). To ensure that this finding was not due to some systematic difference in the populations, the background characteristics of these patients were examined and found to be similar regardless of the timing of the pretreatment (all $P > .30$). This benefit of early pretreatment, and the lack of benefit with less than 6 hours of pretreatment, appeared similar among all important subgroups (FIGURE 3A and B).

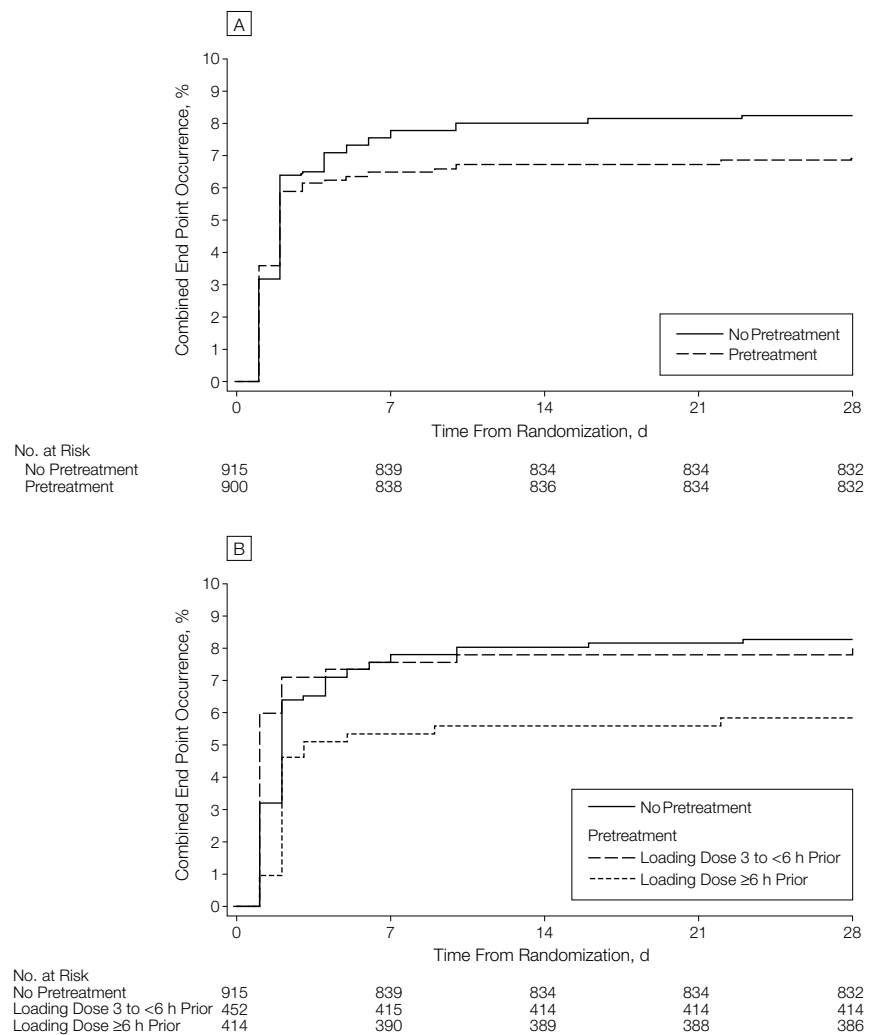
Patients treated with a GpIIb-IIIa antagonist, either specified at the time of randomization to receive GpIIb-IIIa at the time of PCI or receiving one during the procedure as “bail-out” therapy, were another important prespecified subgroup. Of the per-protocol population, 45% received a GpIIb-IIIa antagonist; approximately half were specified at the time of randomization and half as “bail-out” therapy. Among the 991 patients who did not receive a GpIIb-IIIa antagonist, clopidogrel pretreatment did not signifi-

Table 2. Procedural Characteristics (Per-Protocol Population)*

	Pretreatment (n = 900)	No Pretreatment (n = 915)	P Value
Successful PCI (<50% residual stenosis), No. (%)	870 (97.2)	875 (96.5)	.42
Received ≥1 stent, No. (%)	807 (89.7)	808 (88.3)	.37
No. of stents per patient, mean (SD)	1.5 (0.8)	1.5 (0.8)	.30
Total stent length per patient, mean (SD), mm	24.4 (16.2)	23.5 (14.7)	.24
Any atherectomy, No. (%)	58 (6.4)	62 (6.8)	.78
Balloon angioplasty only, No. (%)	53 (5.9)	69 (7.5)	.19
GpIIb/IIIa antagonist use, No. (%)	427 (47.4)	396 (43.3)	.08
Prespecified	217 (24.1)	208 (22.7)	.51
Bail-out	210 (23.3)	188 (20.6)	.16
Peak in-laboratory ACT, mean (SD), s	281 (76)	283 (82)	.60

*PCI indicates percutaneous coronary intervention; Gp, glycoprotein; and ACT, activated clotting time.

Figure 2. Combined End Point Results at 28 Days for Clopidogrel vs Placebo



Data are shown as occurrence of death, myocardial infarction, or urgent target vessel revascularization at 28 days (per-protocol population) in A, the treatment and control arms and B, in the treatment arm divided into those pretreated 3 to 6 hours before and at least 6 hours before percutaneous coronary intervention, along with the control arm.

cantly influence the occurrence of the combined end point (6.4% pretreated vs 6.7% no pretreatment; $P = .81$). However, a trend toward benefit was suggested in patients who did receive a GpIIb-IIIa antagonist and were randomized to clopidogrel pretreatment, with a 30% relative reduction in events (7.3% pretreated vs 10.3% no pretreatment but receiving a GpIIb-IIIa antagonist; $P = .12$), with similar benefit irrespective of the timing of GpIIb-IIIa antagonist use. Again, as in the overall per-protocol population, the degree of benefit of clopidogrel pretreatment among patients receiving and not receiving GpIIb-IIIa inhibitors appeared to be influenced by the timing of pretreatment (Figure 3).

Overall, clopidogrel pretreatment at 28 days did not significantly increase major or minor bleeding (TABLE 3). Minor bleeding increased nonsignificantly in patients who also received a GpIIb-IIIa antagonist (2.8% pretreatment vs 1.0% no pretreatment; $P = .08$). Importantly, there were no fatal bleeds or intracranial hemorrhages. Nearly all major bleeding events were associated with invasive procedures (either the index PCI or CABG) in both groups.

1-Year End Point

A total of 63% of patients in the clopidogrel group and 61% of patients in the control group completed the full 1-year course of study drug. The primary rea-

sons for cessation of study drug are listed in Figure 1.

For the entire study population, randomization to long-term treatment was associated with a 26.9% reduction in the relative risk of the combined end point of death, MI, and stroke at 1 year (95% CI, 3.9%-44.4%; $P = .02$) (FIGURE 4). A similar level of benefit was found in the individual components of this end point, although individual outcomes were not significant (TABLE 4). The degree of benefit was similar among all subgroups, although several were not significant (FIGURE 5). Treatment randomization did not appear to influence the rate of target vessel revascularization or any other revascularization during the follow-up period. Among patients not undergoing PCI there were a total of 18 primary outcome events: 7 in those randomized to clopidogrel and 11 in those randomized to placebo.

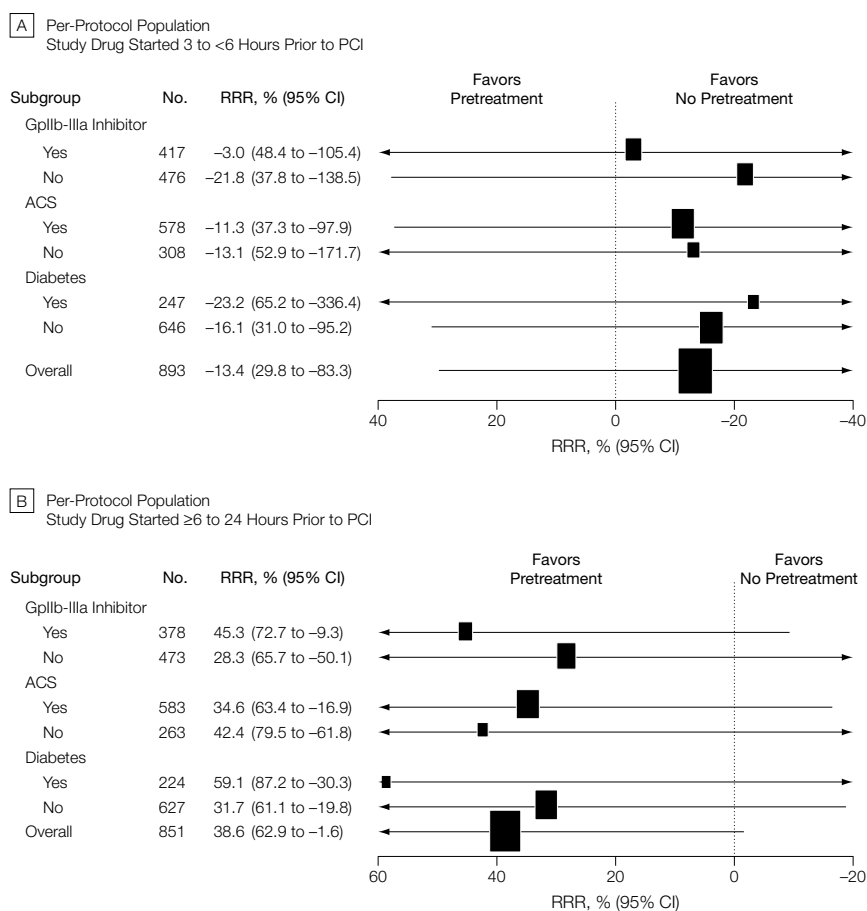
In the intent-to-treat population, a relative reduction of 19.7% in the combined end point of death, MI, and stroke was achieved by 28 days in those randomized to a clopidogrel loading dose (95% CI, -13.3% to 43.1%; $P = .21$). Although the treatment effect from day 29 until the end of follow-up at 1 year was not a prespecified analysis, continued treatment with clopidogrel beyond 4 weeks was associated with a further RRR of 37.4% in the combined end point (95% CI, 1.8%-60.1%; $P = .04$).

Patients treated with clopidogrel for 1 year experienced a trend toward an increase in major bleeding (8.8% clopidogrel vs 6.7% placebo; $P = .07$). Approximately two thirds of all major bleeds occurred in patients undergoing CABG, with all such patients experiencing a high incidence of major bleeds (Table 3).

COMMENT

This study is the first randomized trial, to our knowledge, to assess optimal initiation and duration of dual antiplatelet therapy with an ADP-receptor antagonist and aspirin in a population undergoing elective revascularization. Our major finding is that continuation of dual antiplatelet therapy with clopidogrel and aspirin for at least 1 year, in-

Figure 3. 28-Day Primary End Point in Key Subgroups for Clopidogrel vs Placebo



Study cohort divided into A, those pretreated less than 6 hours before percutaneous coronary intervention (PCI) and B, those pretreated at least 6 hours before PCI (per-protocol population). Gp indicates glycoprotein; ACS, acute coronary syndrome; and CI, confidence interval. The sizes of the data markers are proportional to the population size.

stead of the current standard of 2 to 4 weeks, leads to a statistically and clinically significant reduction in major thrombotic events. Although the data from this trial do not directly support the routine administration of a 300-mg loading dose of clopidogrel between 3 and 24 hours prior to PCI (the 18.5% reduction in adverse events did not reach statistical significance), the data suggest that when a 300-mg loading dose can be administered more than 6 hours before PCI it may well offer substantial benefit. Furthermore, the long-term combination of aspirin and clopidogrel was relatively safe and the efficacy extended to a large population of patients who undergo elective percutaneous coronary revascularization.

The potential benefit of pretreatment prior to PCI has been recognized for a number of years based on the results of a number of retrospective and nonrandomized analyses.⁵⁻⁷ Despite the lack of rigorous data supporting pretreatment with clopidogrel, this practice has become commonplace, as highlighted in this study by clopidogrel pretreatment being the single most common reason for a screened patient being ineligible for study enrollment. Patients enrolled in CURE who underwent PCI and who were randomized to receive clopidogrel experienced a significantly lower incidence of adverse cardiovascular events at both 30 days and at a mean of 9 months, but pretreatment was given for a median of 10 days.⁸ In CREDO, although pretreatment with clopidogrel 3 to 24 hours before PCI did not improve outcomes, those who received pretreatment more than 6 hours before did have fewer events, supporting the hypothesis that pretreatment with clopidogrel that is of adequate duration or dose to provide its full antiplatelet effects does provide substantial protection from the acute thrombotic complications associated with PCI. Although some early studies suggested that near maximal effects of clopidogrel could be achieved within 3 hours of a 300-mg loading dose,¹² more recent studies have found that 6 hours or longer is needed with a

300-mg dose, or larger loading doses in the range of 450 to 600 mg may be necessary to achieve maximal effects more rapidly.¹³⁻¹⁵

The apparent benefit of pretreatment, specifically those pretreated more than 6 hours prior to the procedure, showed a similar pattern among all subgroups. Surprisingly, patients treated with a GpIIb-IIIa receptor antagonist experienced a relative benefit even greater than in those not receiving one. This finding, which needs to be confirmed, highlights the importance of inhibiting platelet activation, as achieved with clopidogrel and aspirin, even in the setting of near-complete inhibition of platelet aggregation via GpIIb-IIIa antagonists. No conclusions can be drawn from CREDO regarding the potential concomitant benefit of adding a GpIIb-IIIa antagonist to patients already ad-

equately pretreated with clopidogrel, but this important question is currently being addressed in the Intracoronary Stenting and Antithrombotic Regimen—Rapid Early Action for Coronary Treatment (ISAR-REACT) trial, in which patients pretreated with a 600-mg loading dose of clopidogrel are randomly assigned to abciximab or placebo.¹⁶ Nonetheless, the results of our trial, smaller single-center trials, and those of a recent large comparative trial of GpIIb-IIIa antagonists strongly suggest a complementary role of parenteral GpIIb-IIIa inhibition with dual oral antiplatelet in the setting of PCI, without a concomitant increase in the risk of major bleeding.^{7,17}

The long-term risk for thrombotic events in patients following PCI has not always been fully appreciated. Primary emphasis has been on the prevention of

Table 3. Safety End Points for Clopidogrel vs Placebo*

	Patients, No. (%)		P Value
	Clopidogrel (n = 1053)	Placebo (n = 1063)	
1-Year Intent-to-Treat Population			
Major bleeding			
Any	93 (8.8)	71 (6.7)	.07
Nonprocedural	13 (1.2)	8 (0.8)	.28
Procedural	81 (7.7)	63 (5.9)	.12
CABG	63	55	
Non-CABG	18	8	
Minor bleeding			
Any	56 (5.3)	59 (5.6)	.84
Nonprocedural	7 (0.7)	8 (0.8)	>.99
Procedural	50 (4.7)	52 (4.9)	.92
CABG	24	30	
Non-CABG	26	22	
28-Day Intent-to-Treat Population			
Major bleeding			
Any	50 (4.7)	38 (3.6)	.19
Nonprocedural	1 (0.1)	3 (0.3)	.62
Procedural	49 (4.7)	35 (3.3)	.11
GpIIb-IIIa (per-protocol population only)			
Yes (n = 823)	9 (2.1)	9 (2.3)	>.99
No (n = 991)	11 (2.3)	7 (1.3)	.34
Minor bleeding			
Any	33 (3.1)	24 (2.3)	.23
Nonprocedural	3 (0.3)	1 (0.1)	.37
Procedural	30 (2.9)	23 (2.2)	.33
GpIIb-IIIa (per-protocol population only)			
Yes (n = 823)	12 (2.8)	4 (1.0)	.08
No (n = 991)	8 (1.7)	9 (1.7)	>.99

*CABG indicates coronary artery bypass grafting; Gp, glycoprotein.

procedural complications and thrombosis of the treated vessel and attempts to minimize restenosis. However, once a patient has developed a coronary stenosis sufficiently severe to require revascularization, the atherosclerotic burden throughout the arterial system can already be considered extensive and the subsequent risk for death, MI, or stroke heightened. Importantly, the risk of patients with a high C-reactive protein level at baseline for subsequent major events, including death, has been well docu-

mented in recent studies of coronary intervention.¹⁸ Clopidogrel, coadministered with aspirin, has been shown to markedly reduce the risk associated with an elevated baseline C-reactive protein level prior to PCI.¹⁹ These results are consistent with the important role platelets play in the inflammatory system^{20,21} and the potential for agents such as clopidogrel that diminish many of the consequences of platelet activation, not just aggregation.²² Accordingly, the benefit of combined therapy in reducing the

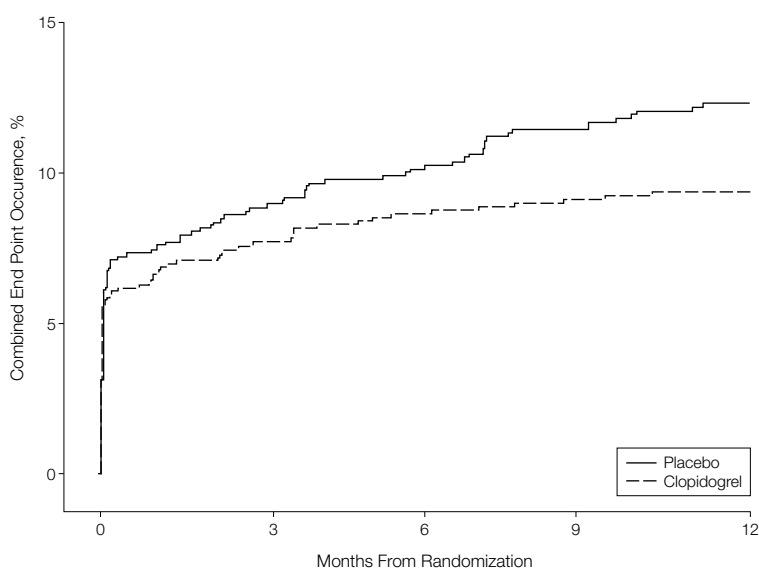
events of death, stroke, or MI may reflect a more potent anti-inflammatory effect as compared with aspirin monotherapy.

The results of our study support the recent CURE trial findings and expand the benefit of prolonged clopidogrel and aspirin to a more stable, less acutely ill population.²³ The timing of this benefit emphasizes the risk of major thrombotic events in this population and highlights the need for improved long-term protection. The CREDO trial could not assess whether clopidogrel and aspirin treatment beyond 1 year would continue to reduce risk, but the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial, which will include more than 15 000 high-risk but stable patients, with a mean anticipated follow-up of 42 months, will definitively establish whether clopidogrel (in addition to low-dose aspirin) should be continued beyond 1 year.²⁴

Despite the clear benefit of clopidogrel and aspirin for preventing thrombotic events, the risk of spontaneous bleeding was not significantly affected. Although a trend toward an increase in major bleeding was identified in patients receiving long-term clopidogrel, the majority of this was CABG-related, in which the incidence of major bleeding was high in both groups. Further evaluation of any correlation between the timing of study drug discontinuation and bleeding incidence will help identify the optimal dosing regimen prior to invasive procedures. Also, recent analysis from the CURE trial identified an important correlation between increasing aspirin dose and the risk of major bleeds, without an increase in efficacy, suggesting that better adherence to lower aspirin doses can also help minimize bleeding risk.²⁵

There are several aspects of the current trial that limit the ability to draw specific conclusions regarding the potential benefit of clopidogrel pretreatment and the true risk reduction associated with long-term therapy. Despite the suggestion of a relationship be-

Figure 4. Combined End Point Results at 1 Year for Clopidogrel vs Placebo



No. at Risk					
Clopidogrel	1053	931	920	909	901
Placebo	1063	929	910	881	863

Data are shown as occurrence of death, myocardial infarction, or stroke at 1 year. The relative risk reduction for clopidogrel compared with placebo is 26.9% (95% confidence interval, 3.9%-44.4%; $P=.02$).

Table 4. One-Year Clinical Outcomes for Clopidogrel vs Placebo*

End Point	Patients, No. (%)		RRR, % (95% CI)
	Clopidogrel (n = 1053)	Placebo (n = 1063)	
Death, MI, stroke	89 (8.5)	122 (11.5)	26.9 (3.9 to 44.4)
Death, MI	84 (8.0)	111 (10.4)	24.0 (-0.9 to 42.7)
Death	18 (1.7)	24 (2.3)	24.6 (-38.9 to 59.1)
MI	70 (6.6)	90 (8.5)	21.7 (-7.1 to 42.7)
Stroke	9 (0.9)	12 (1.1)	25.0 (-77.9 to 68.4)
Revascularization			
Any TVR	139 (13.2)	144 (13.5)	3.2 (-22.2 to 23.3)
Urgent TVR	21 (2.0)	23 (2.2)	8.1 (-66.1 to 49.1)
Any revascularization	225 (21.4)	223 (21.0)	-1.6 (-22.3 to 15.5)

*RRR indicates relative risk reduction; MI, myocardial infarction; and TVR, target vessel revascularization.

tween the duration of pretreatment and treatment effect, the size of the subgroups prevents the establishment of definitive conclusions and recommendations regarding pretreatment. Also, due to the relatively high proportion of patients who discontinued both clopidogrel and placebo prior to the completion of the full year of follow-up, it is possible that the risk reduction associated with long-term clopidogrel in this population may have been underestimated. Finally, because patients were not rerandomized after 28 days of therapy, it is not completely possible to separate the treatment benefit of long-term therapy from that of pretreatment, although it is difficult to postulate an influence of pretreatment on late thrombotic events that are not associated with the treated coronary lesion.

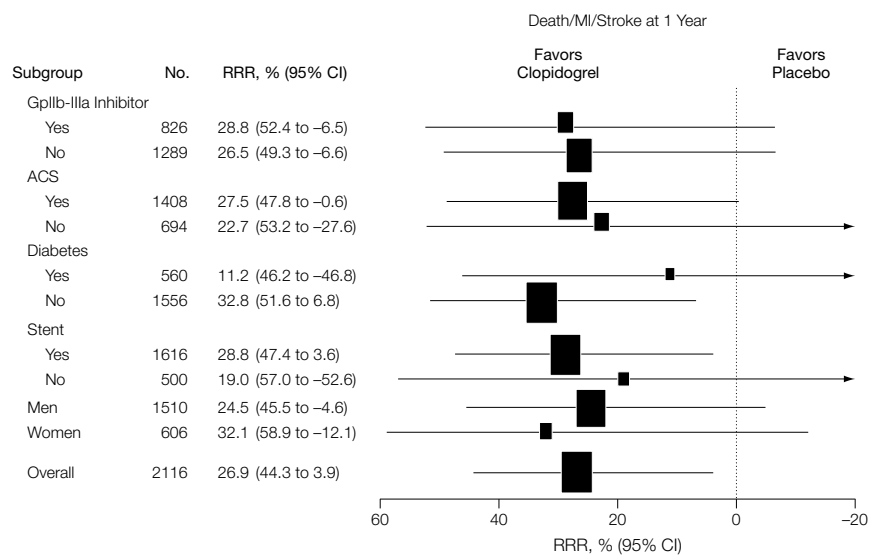
In conclusion, the results of the CREDO trial indicate that in patients undergoing PCI, the continuation of clopidogrel and aspirin therapy for 1 year leads to a significant reduction in irreversible atherothrombotic events compared with treatment for only 4 weeks. Although a 300-mg loading dose of clopidogrel administered more than 3 hours prior to the procedure was not significantly better than administration of clopidogrel without a loading dose immediately after the procedure, the subgroup analysis of patients treated at least 6 hours prior to PCI suggested a significant reduction in periprocedural major adverse cardiac events, with or without the concomitant use of a GpIIb-IIIa antagonist.

A detailed description of the study methodology and patient flow is available at <http://rctbank.ucsf.edu/Presenter?552>. The RCT Presenter site is not maintained by JAMA.

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Figure 5. One-Year Primary End Point in Key Subgroups for Clopidogrel vs Placebo



Results of combined end point of death, myocardial infarction (MI), and stroke at 1 year. Gp indicates glycoprotein; ACS, acute coronary syndrome; and CI, confidence interval. The sizes of the data markers are proportional to the population size.

board for Bristol-Myers Squibb/Sanofi-Synthelabo; and Dr Topol is a consultant to Bristol-Myers Squibb/Sanofi-Synthelabo.

Author Contributions: Dr Steinhubl had full access to all of the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Steinhubl, Topol.
Acquisition of data: Mann, Fry, DeLago, Wilmer.
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Data Management: Alex Boddy of Sanofi-Synthelabo provided data support and aided in the management of the blinded data.

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CORRECTIONS

Incorrect Data in Tables and Figures: In the Original Contribution entitled "Early and Sustained Dual Oral Antiplatelet Therapy Following Percutaneous Coronary Intervention" published in the November 20, 2002, issue of THE JOURNAL (2002;288:2411-2420), there were incorrect numbers in several tables and figures. In Table 1 on page 2414, the data for statin use should have read 563 (53.5%) for clopidogrel and 609 (57.3%) for placebo, with a *P* value of .08. In the top half (1-year data) of Table 3 on page 2417, numbers of clopidogrel patients for CABG and non-CABG bleeding should have read 63 and 18, respectively. In the bottom half (28-day data) of Table 3, data for any major bleeding should have read 50 (4.7%) for clopidogrel and 38 (3.6%) for placebo, with a *P* value of .19. Data for nonprocedural major bleeding should have read 3 (0.3%) for placebo, with a *P* value of .62. Data for procedural major bleeding should have read 49 (4.7%) for clopidogrel and 35 (3.3%) for placebo, with a *P* value of .11. Data for any minor bleeding should have read 33 (3.1%) for clopidogrel and 24 (2.3%) for placebo, with a *P* value of .23. Data for procedural minor bleeding should have read 30 (2.9%) for clopidogrel and 23 (2.2%) for placebo, with a *P* value of .33.

In Table 4 on page 2418, for the outcomes of death or MI, clopidogrel data should have been 84 (8.0%). For the outcome of MI, clopidogrel data should have read 70 (6.6%), placebo should have read 90 (8.5%), and the RRR (95% CI) should have been 21.7 (-7.1 to 42.7). For stroke, placebo should have read 12 (1.1%) and the RRR (95% CI) should have been 25.0 (-77.9 to 68.4). Under "revascularization," any TVR data should have read 139 (13.2%) for clopidogrel, 144 (13.5%) for placebo, and the RRR (95% CI) should have been 3.2 (-22.2 to 23.3). Data for any revascularization should have read 225 (21.4%) for clopidogrel and the RRR (95% CI) should have been -1.6 (-22.3 to 15.5).

In Figure 3, panel B, the number of patients for ACS "yes" should have been 583 and the RRR (95% CI) should have been 34.6 (63.4 to -16.9). In Figure 5, the number of patients for ACS "yes" should have been 1408 and the RRR (95% CI) should have been 27.5 (47.8 to -0.6).

None of these corrections substantively affects the results or conclusions of the article.

Incorrect Wording: In The Patient-Physician Relationship article entitled "Health-Related Quality of Life Assessments and Patient-Physician Communication: A Randomized Controlled Trial" published in the December 18, 2002, issue of THE JOURNAL (2002;288:3027-3034), there was incorrect wording and data in a table. The title of Table 2 that read "Patients' Health-Related Quality of Life (HRQL) at Fourth-Visit Consultations" should read "Fourth-Visit Consultations Discussing Health-Related Quality of Life (HRQL)." Also in Table 2 in the "Physical" type of functioning row under the "Intervention" column that read "76 (73)" should have read "29 (28)" and the "Role" type of function row under the "Intervention" column that read "28 (27)" should have read "68 (66)." The differences between the control and intervention groups for those domains remain statistically nonsignificant.

Incorrect Link: In the Instructions for Authors published in the January 1, 2003, issue of THE JOURNAL (2003;289:104-110), the link for the STARD flow diagram and checklist was incorrect. On page 108, under "Reports of Diagnostic Tests," the link should have read <http://www.clinchem.org/cgi/content/full/49/1/1>. The correct link appears in the Instructions for Authors online at <http://www.jama.com>.

Author Name Misspelled and Incorrect Affiliations: In the Research Letter entitled "Humming, Nitric Oxide, and Paranasal Sinus Obstruction" published in the January 15, 2003, issue of THE JOURNAL (2003;289:302-303), the name of the second author was misspelled. Rather than "Maniscalco," the name should have been spelled "Maniscalco." Also, Dr Lundblad is affiliated not with the Department of Surgical Science, but with the Department of Otorhinolaryngology; and Dr Weitzberg is affiliated not with the Department of Otorhinolaryngology, but with the Department of Anesthesiology and Intensive Care.

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