Clinical Implications of Percutaneous Coronary Intervention–Clopidogrel in Unstable angina to prevent Recurrent Events (PCI-CURE) Study
A US Perspective

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The long-term use of both aspirin and clopidogrel for patients with an acute coronary syndrome was analyzed in the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. In that trial, 12 562 patients with an acute coronary syndrome were randomly assigned to receive aspirin and clopidogrel or aspirin and placebo for a period of no more than 1 year. The results of the trial after a mean duration of follow-up of 9 months revealed an approximately 20% relative reduction in the risk of vascular death, myocardial infarction, and stroke. There were 2658 patients (21%) who underwent percutaneous coronary intervention (PCI) in the CURE trial a median of 10 days after enrollment. This was decided not by study protocol but by physician preference, which was influenced by the therapy to which patients were randomized; among these patients, the reduction in events (cardiovascular death, myocardial infarction [MI], or an urgent repeat revascularization procedure) from the PCI procedure through 30 days was an absolute 1.9% (6.4% versus 4.5%), which was a relative reduction of 30% (P<0.03). From the time of PCI through the remainder of follow-up, there was an absolute reduction in cardiovascular (CV) death and MI of 2% (8.0% versus 6.0%), which was a relative risk reduction of 25% (P=0.047).

Although dual antiplatelet therapy with clopidogrel and aspirin is often considered to be of benefit only in patients treated with stents, an interesting finding in PCI-CURE was that pretreatment and continued therapy with clopidogrel appeared to be as beneficial among the 19% of patients who did not receive a coronary stent as among the 81% of patients who did. There had not previously been evidence of benefit from thienopyridines use among patients undergoing PCI without stent placement, although it seems logical that there might be.

Applicability to US Practice
There are several features of the analysis of PCI in the CURE trial that make extrapolation to the general practice of PCI in the United States difficult. First, the study prohibited medical centers from participation, including a great many in the United States that performed PCI in the majority of patients with an acute coronary syndrome. Why such centers were excluded was not specified, but regardless of the reason, that clearly makes the application of the results of the PCI-CURE trial to medical centers which do perform PCI in the majority of the cases problematic. Second, the use of platelet glycoprotein IIb/IIIa inhibitors in the 72 hours before study entry was prohibited. Because such drugs are far more frequently used in the United States, that exclusion criteria also poses a difficulty in applying the results of the PCI-CURE trial more generally. Another difference between the CURE study and United States practice patterns is the fact that more than 70% of patients undergoing PCI in the United States receive a platelet glycoprotein (GP) IIb/IIIa inhibitor at the time of the procedure, and this percentage is even greater in acute coronary syndrome (ACS) patients; yet, the use of these drugs during PCI in the CURE trial was uncommon (23.7%).

In view of these issues, what findings from the PCI-CURE analysis can be used to help guide patient treatment? The study attempts to address 2 issues that physicians must deal with in every patient undergoing PCI in their practice: when a thienopyridine should be started and how long it should be continued after the procedure.

Pretreatment With a Clopidogrel
The beneficial effects of pretreatment with a thienopyridine before PCI have been reported in several studies, although none were randomized comparisons. In the PCI-CURE analysis, all patients in the aspirin and clopidogrel arm had been pretreated with clopidogrel for a median of 10 days, whereas the majority of patients in the aspirin and placebo arm received no pretreatment, although 25% did receive an open-label thienopyridine before PCI. The frequency of death or MI in the 30 days after PCI was significantly less among patients who had been pretreated than in those who had not (4.4% versus 2.8%, a relative risk reduction of 34%; P=0.04). Importantly, unlike all recent PCI trials of GP IIb/
Duration of Therapy With Clopidogrel

The other major issues addressed regarding the most appropriate duration of therapy with clopidogrel after the procedure are slightly less subject to bias. Because no patient in the aspirin alone arm received clopidogrel for more than 30 days after PCI and all patients in the aspirin and clopidogrel arm did receive it for the duration of the study (a median of 8 additional months), analysis of the frequency of adverse events during this time period can shed light on the most appropriate duration of clopidogrel after PCI. After 30 days and until the end of follow-up, continued clopidogrel treatment was associated with a 21% relative reduction in the frequency of cardiovascular death and MI in the 2 groups compared with placebo, representing an absolute 0.8% fewer deaths or MIs (3.1% versus 3.9%, \( P = \text{NS} \)). Thus, 125 patients must be treated to reduce the frequency of this end point, which was primarily driven by nonfatal MI in 1 patient. When one considers that the difference was driven entirely by a difference in MI rather than death, the results are not overwhelming and significantly impact cost-effectiveness. This finding could have been anticipated by prior studies, which revealed very low event rates in relatively well patients who undergo a successful PCI procedure and who are treated with a thienopyridine for even just 2 weeks, and certainly in those treated for 4 weeks.9–12 However, there are clearly subsets of patients who are at a markedly increased risk of thrombotic events long-term after a PCI, and often at sites in the vascular bed other than the treated site; we believe such patients are more likely to benefit from long-term dual antiplatelet therapy than the general population of PCI patients. Such patients include those with diabetes mellitus and chronic renal failure, patients with multivessel disease and particularly diffuse disease who have a relatively large atherosclerotic burden even after a successful PCI procedure treated the culprit vessel, patients with old vein grafts, patients with multiple events while on aspirin, and those peripheral and cerebrovascular disease. Such patients are at a markedly increased risk compared with patients without these characteristics and are, we believe, much more likely to derive the greatest absolute benefit from prolonged antiplatelet therapy than patients without these characteristics.

Remaining Unanswered Questions

Procedure-Related Bleeding Risk

The PCI-CURE analysis identified no significant increase in major or minor bleeding associated with clopidogrel pretreatment in patients who underwent a percutaneous revascularization, even in the minority of patients also treated with a GPIIb/IIIa antagonist. However, when clopidogrel is started, it is typically unknown what method of revascularization will be best for the individual patient. In fact, on the basis of the results of recent randomized trials, the proportion of ACS patients who undergo early angiography and subsequently require a surgical revascularization is not trivial. In the Treat angina with Aggrastat and determine Costs of Therapy with Invasive or Conservative Strategies (TACTICS-TIMI 18) and FRagmin during InStability in Coronary artery disease (FRISC II) trials, in patient populations similar to that in CURE but in whom early angiography was allowed, 32% to 45% of patients who were revascularized underwent CABG as their primary mode of therapy.13,14 Therefore, a remaining important issue is the problem associated with the early treatment of ACS patients with clopidogrel before diagnostic coronary angiography is performed. Several previous observational studies have suggested that if a patient undergoes bypass surgery while on therapy with a thienopyridine and
aspirin, the risk of major complications and the need for blood products is significantly increased. In 2 single-center observational studies,\textsuperscript{15,16} the risk of reoperation for bleeding was reported to be 5- to 10-fold higher in patients on clopidogrel and aspirin. However, even though reported observational studies have tried to adjust for differences between patients that went to surgery while on therapy, there is undoubtedly bias in such analyses. The best data about the risk of coronary artery bypass grafting (CABG) while on a thienopyridine are from the CURE trial itself.\textsuperscript{1} In the CURE trial, patients who received clopidogrel any time within the 5 days before surgery had a relative 50% increase in the risk of major or life threatening bleeding, which is an absolute increase of 3%. It is entirely likely that if the therapy were continued until the day of or prior to surgery, the risk would have been higher. American medical centers whose practice patterns are such that patients undergo coronary angiography very soon after admission and, if coronary angiography reveals surgical anatomy, send their patients to surgery within a day or two, will not have the opportunity to derive the same benefit from a longer duration of pretreatment and will likely run an even higher risk of bleeding than the 50% increase in risk of major or life threatening bleeding seen in the CURE study.

Therefore, a reasonable approach to minimizing bleeding risks or treatment delays, an approach we suggest might be to withhold clopidogrel pretreatment before diagnostic angiography in patients at increased risk of requiring CABG, particularly if angiography will be performed after minimal delay. Such patients would include those with known multivessel disease shown by prior angiograms (particularly if they were not to be amenable to PCI but were amenable to surgery), those with known borderline left main disease, and those with diabetes mellitus or with chronic renal failure; these are patient groups in whom PCI appears to be associated with a much higher risk than CABG. Also, patients with old vein grafts and those with peripheral and cerebrovascular disease are much more likely to require CABG than patients without any of these characteristics. Note that the list of patients more likely to require CABG is similar to the list of patients most likely to benefit from long-term treatment with clopidogrel after a successful PCI procedure.

As it is likely that only a small percentage of ACS patients actually require an emergent surgical revascularization, another strategy for minimizing bleeding would be to delay surgery for at least 5 days in patients already receiving clopidogrel. However, as a large proportion of such patients would have to remain hospitalized awaiting surgery, the additional cost of such a strategy may be prohibitive at many institutions.

Use With GPIIb/IIIa Antagonists

Perhaps the most important questions facing the interventional cardiologist regarding clopidogrel pretreatment, which are unanswered by the PCI-CURE trial, are whether pretreatment with clopidogrel remains beneficial if a platelet GPIIb/IIIa inhibitor is administered, or visa versa, and whether the benefit of aspirin plus clopidogrel plus a GPIIb/IIIa antagonist is additive without an unacceptable bleeding risk. The results of the Evaluation of Platelet IIb/IIIa Inhibitor for STENTing (EPISTENT) Trial analysis suggested that pretreatment was no longer beneficial in reducing adverse events at 30 days when the IIb/IIIa inhibitor abciximab was used; however, the duration of pretreatment with the slower-onset ticlopidine was unknown and likely short.\textsuperscript{6} On the other hand, the results of the do Tirofiban (Aggrastat) And ReoPro Give similar Efficacy outcomes Trial (TARGET) suggested that event rates were lower among patients pretreated with clopidogrel even when all patients received a GPIIib/IIIa antagonist.\textsuperscript{7} However, both the EPISTENT and TARGET trials were not designed to answer the question about the benefit of pretreatment with a thienopyridine among patients receiving a GPIIib/IIIa inhibitor, and therefore the optimal use of a GPIIib/IIIa antagonist when a patient has already received clopidogrel, or of clopidogrel in a patient already receiving a GPIIib/IIIa antagonist, remains unclear.

Ongoing Trials

The Clopidogrel for Reduction of Events During Observation (CREDO) trial is directly designed to answer many of the above questions, avoiding many of the limitations from which the PCI-CURE trial suffers. This trial is designed to determine whether more complete platelet inhibition with a thienopyridine at the time of a percutaneous revascularization procedure is beneficial, as well as the most effective duration of clopidogrel treatment in patients after a percutaneous revascularization. In the CREDO trial, more than 2100 patients in whom a percutaneous revascularization (with or without a stent) was planned were randomly assigned to receive a 300 mg loading dose of clopidogrel 3 to 24 hours before the procedure or a 75 mg/d dose of clopidogrel (which is equivalent in speed of action to the old most-studied regimen of a ticlopidine 500 mg loading dose) immediately before the procedure. Importantly, 400 patients were prespecified at the time of randomization to receive abciximab during the PCI procedure. Patients assigned to the 300 mg loading dose received 75 mg/d of clopidogrel for 1 year with aspirin. Patients assigned to clopidogrel without a loading dose received 75 mg/d of clopidogrel for only 4 weeks, followed by placebo with aspirin for 11 months. The results of the trial will be announced this year and will help further define the role of combination antiplatelet therapy in the PCI population.

In the Intracoronary Stenting and Antithrombotic Regimen–Rapid Early Action for Coronary Treatment (ISAREACT) study, patients who had symptoms of coronary artery disease and scheduled to undergo coronary angiography and who are extremely unlikely to require CABG within days of angiography will receive a loading dose of 600 mg clopidogrel at least 2 hours before the procedure; those with insulin-dependent diabetes mellitus and those with a positive biomarker are excluded. Patients receiving this large dose of clopidogrel before their procedure will then be randomized to receive either abciximab and reduced dose heparin or standard dose heparin and placebo. The primary end point of the study is the composite rate of death, MI, and urgent target vessel revascularization within 30 days; secondary end points
include the incidence of major and minor bleeding complications, as well as indices of restenosis after 6 months.

**Conclusion**

As a retrospective (although prospectively designed) analysis of a very large randomized ACS trial, the PCI-CURE study provides strong, consistent support for the benefit of clopidogrel pretreatment in patients undergoing a PCI. However, because of the limitations discussed above, its results cannot be considered definitive proof of the degree of benefit, especially when attempting to apply these results to the treatment of ACS patients in the US, where early angiography and GPIIb/IIIa antagonist use is the norm. The development of an integrative strategy for optimizing early antiplatelet therapies in patients undergoing a PCI, with or without ACS, awaits the results of the CREDO and ISAR-REACT trials. The benefit of continuing clopidogrel and aspirin therapy for the long term in ACS patients does not seem to be diminished if a patient undergoes a PCI, but the cost-effectiveness of such a generalized strategy will continue to be debated. The ability to identify those patients most likely to derive the greatest benefit from chronic dual antiplatelet therapy will be critical for this to be optimized.

**References**

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