In trying to explain how balloon angioplasty relieved coronary narrowing, Andreas Gruentzig often displayed a photograph of footprints in fresh snow. He proposed that balloon expansion resulted in gentle, uniform plaque compression. Subsequent histological examination in the porcine coronary model and of postmortem and ultrasound findings in humans indicated more traumatic effects of angioplasty, including deep medial fissuring and adventitial stretching. Such injury causes the release of potent substances from the arterial wall that have profound vasoactive and thrombotic effects. One early response is platelet activation and deposition over the injured arterial surface, creating the substrate for thrombosis. Stent implantation appears to be associated with even greater platelet activation than balloon angioplasty alone. Importantly, the magnitude of platelet activation is associated with an increased risk for adverse clinical events after coronary intervention.1

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Aspirin, administered as an agent to inhibit platelet activity, has been a standard component of the angioplasty protocol since the inception of the procedure. More recently, substantial evidence indicates that supplementing aspirin and unfractionated heparin with agents that antagonize the platelet glycoprotein (GP) IIb/IIIa receptor further reduces the incidence of abrupt coronary closure and the magnitude of periprocedural cardiac enzyme elevations and, in certain patient subsets, may enhance survival.2-6 To decrease the risk of stent thrombosis, practice guidelines call for augmented antiplatelet therapy (aspirin and a thienopyridine) for weeks to months after hospital discharge.

In this issue of *Circulation*, Patti et al7 extend our knowledge about antiplatelet therapy and percutaneous coronary intervention (PCI), particularly with regard to the impact of pretreatment clopidogrel dosage and the magnitude of treatment effect that can be achieved. These investigators administered either 300 or 600 mg of clopidogrel 4 to 8 hours before cardiac catheterization to 329 patients who were potential candidates for coronary revascularization. Excluded from this trial were patients with ST-elevation myocardial infarction (STEMI), those with an elevation of baseline creatine kinase-MB (CK-MB), and those already receiving clopidogrel. After diagnostic catheterization, 74 of the 329 patients did not undergo PCI, 44 were continued on medical therapy alone, and 30 (9.1%) of the original randomized cohort had coronary artery bypass grafting (CABG) rather than PCI. All remaining patients underwent PCI. Clopidogrel dose assignment was randomized, and the physicians performing PCI were blinded as to what dose each patient received. Other antiplatelet therapy included aspirin (100 mg daily) for all patients, and intravenous GP IIb/IIIa antagonists were administered to 13% of each group. Clopidogrel, 75 mg/d, was continued for at least 1 month after the procedure.

The PCI success rate was high. A stent was implanted in all but 2 patients, but only ≈25% received a drug-eluting stent. Multiple stent use was uncommon and total stent length was short, which suggests that the extent of coronary disease treated was not particularly complex. Furthermore, no treated lesion was located in a vein graft.

The primary end point of death, myocardial infarction (MI; defined as a postprocedural >3× rise in serum CK-MB) or target-vessel revascularization at 30 days, was 4% in the 600-mg group and 12% in the 300-mg group, the difference being significant (P=0.041). Because no patient died or required repeat revascularization during the 30 days of follow-up, all events within the composite end point were related to MI. Comparison of peak values of CK-MB, troponin, and myoglobin confirmed the differences in myocardial necrosis observed between the 2 groups. No additional data are provided in terms of electrocardiographic changes or symptoms reflective of MI among the study patients. Bleeding was infrequent and minor in severity.

On the basis of their findings, Patti et al7 conclude that pretreatment with 600 mg clopidogrel is safe, and compared with the 300-mg regimen, pretreatment “reduces periprocedural myocardial infarction and improves short-term prognosis in patients undergoing percutaneous revascularization.”

In attempting to determine the significance of this report, several questions come to mind. Was the study properly designed, executed, and analyzed to address the proposed scientific question? The answer is a definite “yes” for the types of patients studied. The trial was controlled and randomized, and the sample size was adequate for the end point of MI. There was good balance between the 2 groups in baseline and procedural features. Because no patient experienced death or repeat vessel revascularization, longer follow-up or enrollment of patients with more complex
coronary disease or unstable clinical status would be required to evaluate the effects of dose regimen on such clinical end points. In this regard, the authors’ conclusion that the 600-mg dose improved prognosis may be a bit of an overstatement.

Were the end points selected appropriate? Again, the answer is yes. Several pivotal trials have chosen this same composite of death, MI (as defined in this study) and target-vessel revascularization at 30 days, as the primary end point. Of interest is the magnitude of the treatment effect—a 75% reduction. The observed rates of the primary end point in this trial appear more extreme than might have been anticipated. For example, the 300-mg group had a primary end point rate of 12%, somewhat higher than that of 10.8% observed in the heparin-only arm of the Evaluation of Platelet IIb/IIIa Inhibitor for STENTing (EPISTENT) trial. In addition, the 600-mg group rate of 4% is lower than that observed with routine use of the GP IIb/IIIa antagonists abciximab (5.3% to 8.3%)12-13 or tiopronin (7.6%). An evaluation of the direct-acting antithrombin bivalirudin in conjunction with discretionary GP IIb/IIIa antagonist use revealed a rate of 7.6%. A clear explanation for these differences is not obvious, but they may most likely be due to the relatively small sample size of the present study. Although it is likely that a true difference exists between the 300-mg and 600-mg dosage regimens, it may not be as extreme as observed.

A substantial proportion of patients who routinely undergo PCI were not included in this trial, which limits our ability to generalize the findings. For example, we do not know whether these results apply to patients with vein graft disease, bifurcation, or long lesions. We would not necessarily expect any issues of safety with the 600-mg dosage in such patients, but the magnitude of effectiveness might certainly be less. Given the need for the 4- to 8-hour pretreatment period, it is understandable why patients with STEMI were excluded. The advantage of the 600-mg dose in inhibiting platelet aggregation more rapidly than the 300-mg dose may actually have special value for STEMI patients. Moreover, the recent finding that clopidogrel can augment the effects of thrombolytic therapy provides additional rationale for considering administering 600 mg clopidogrel as early as possible before performing primary PCI. The low proportion of drug-eluting stent use also limits our ability to generalize these findings to patients undergoing contemporary PCI.

Another relevant group of patients excluded were those already receiving clopidogrel. Because of the potent secondary prevention effects of clopidogrel, it is likely that patients presenting for PCI increasingly will have been treated with clopidogrel. Should these patients receive the 600-mg pretreatment regimen? According to work by Kastrati et al,12 the answer should be yes. These investigators demonstrated additional, significant inhibition of platelet aggregation when a 600-mg dose was administered to a group of 20 patients already receiving clopidogrel 75 mg daily for at least 1 month.

How do the findings of the present investigation relate to the report by Kastrati and coinvestigators, who first described the potential benefits of the 600-mg clopidogrel pretreatment regimen? In their trial, Kastrati et al gave each of the 2159 PCI patients studied 600 mg clopidogrel at least 2 hours before the procedure.13 Patients were then randomized to treatment with either abciximab or placebo. Using the same primary end point of death, MI, or target-vessel revascularization, these investigators observed a 4% event rate in both patient groups. The trial by Kastrati et al indicated that abciximab offered no additional benefit in the setting of clopidogrel pretreatment. The work by Patti et al further validates these findings and the potency of the 600-mg clopidogrel pretreatment dose regimen. Again, given the low use of GP IIb/IIIa receptor antagonists by Patti et al, such agents do not appear to be essential adjuncts to achieve these impressive treatment effects.

If 600 mg clopidogrel is to be recommended as routine pretreatment for potential PCI patients, then what is the impact of the qualification that the drug should be given 4 to 8 hours before the procedure? Such a requirement is easily accommodated when PCI is planned, although such cases are increasingly uncommon. More often, patients transition from a diagnostic procedure to an intervention without pause. Current practice guidelines indicate that routine clopidogrel treatment before diagnostic catheterization necessitates a substantial treatment delay for patients who are selected for CABG to avoid the risk of excessive perioperative bleeding. Such a concern is a substantial impediment for routine pretreatment with clopidogrel in clinical practice.

What is the absolute minimum time necessary for clopidogrel to be given in advance of PCI to achieve the benefits described by Patti et al? Perhaps peak platelet-inhibitory activity does not have to be present before PCI is performed. The results of the Clopidogrel for the Reduction of Events During Observation (CREDO) trial suggested that 6 to 15 hours may be the minimum pretreatment time required for efficacy, although the clopidogrel dose in CREDO was 300 mg.14,15 Kastrati et al13 demonstrated the efficacy of the 600-mg regimen with a 2-hour window. It was not the intent of Patti et al to investigate the influence of the duration of time between clopidogrel administration and the PCI procedure, but this issue would be a worthy objective for further investigation.

In addition to contributing to our knowledge about optimizing antiplatelet therapy for patients undergoing PCI, the study of Patti et al emphasizes the importance of evaluating drug dose. There are many instances in interventional cardiology in which a drug dose is critically important, but testing the effects of varying doses is extremely difficult. One example is the drug-eluting stent. Although there have been some trials comparing different rates of drug release, the majority of investigations have been performed with single-dose formulations wherein the only variable of drug dose relates to total stent length. Such a limitation results in difficulty in characterizing optimal efficacy and safety. In situations such as drug-eluting stents, the identification of legitimate surrogates to generate dose-ranging information may prove valuable.

With the information from Patti et al in hand, what can we reasonable conclude about antiplatelet therapy and PCI? First, augmenting aspirin with additional antiplatelet therapy reduces myocardial infarction after PCI. Second, according to the information currently available, if clopidogrel is selected, the
dose should be 600 mg and the drug should be administered at least 2 hours before PCI. Third, for the types of patients evaluated thus far, intravenous GP IIb/IIIa inhibitors appear unnecessary when clopidogrel has been administered. Fourth, if circumstances restrict clopidogrel pretreatment, intravenous GP IIb/IIIa is a reasonable alternative.

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