EDITORIAL COMMENT

Platelet Inhibition Strategies in Percutaneous Coronary Intervention

Competition or Coopetition?

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Over the past two and a half decades, a remarkable series of tools, technologies, and techniques have been created, developed, and refined for the performance of percutaneous coronary intervention (PCI). A constant over time, however, has been the therapeutic framework of enlargement of the luminal dimensions of diseased coronary vessels as the hallmark of PCI. Within this construct, an obligatory disruption of the integrity of the vascular endothelium and other vessel components is produced. An inherent and inevitable consequence of PCI is, thus, the creation of a local environment conducive to thrombosis.

In parallel with developments in the technology of PCI has been the detailed elucidation of platelet physiology, coupled with a deeper understanding of the role of the platelet in the thrombosis cascade (1,2). The complexities of the platelet can be distilled into several overlapping functions: adhesion, activation, secretion, and aggregation. In the setting of PCI, numerous clinical trials have established the independent efficacies of agents that target the platelet, namely aspirin, the thienopyridines, and platelet glycoprotein (GP) IIb/IIIa receptor blockers (3–8). Classified by their respective targets, aspirin inhibits platelet activation via the irreversible acetylation of cyclooxygenase and consequent suppression of the synthesis of thromboxane A2, a potent platelet stimulant. The thienopyridines (ticlopidine and clopidogrel) also irreversibly inhibit platelet activation, albeit via a different pathway, blockade of the P2Y1 type adenosine diphosphate (ADP) receptor (9). Adenosine diphosphate modulates the change of the GP IIb/IIia receptor from an inactive, inert state to a ligand receptive conformation. The platelet GP IIb/IIia receptor antagonists inhibit platelet aggregation via blockade of the RGD-specific binding site for fibrinogen and other adhesion molecules to the IIb/IIia integrin on platelets (10). Since activation is a prerequisite to secretion and aggregation, both aspirin and the thienopyridines (partially) inhibit these functions; conversely, GP IIb/IIia blockade indirectly reduces platelet secretion by reducing platelet mass while having little direct effect on platelet activation.

Rather than clarifying the landscape, clinical trials of antiplatelet therapies have led to a bewildering array of uncertainties regarding the appropriate selection, timing, and duration of the various treatment options. Although there is universal acceptance of aspirin as a mainstay of treatment, less certain are the answers about clopidogrel and the GP IIb/IIIa antagonists. With respect to clopidogrel therapy as an adjunct to contemporary PCI, the key remaining questions include the following. First, what is the optimal timing of the initiation of thienopyridine therapy relative to the start of a PCI procedure—along with the corollary question, is ad hoc treatment (i.e., on the catheterization table during a “cath possible” case) as good as several hours (or days) of pretreatment? Second, what is actually being accomplished with clopidogrel pretreatment—again with a corollary question, is post-treatment (after PCI) effective in preventing subacute stent thrombosis? Third, can a thienopyridine be used as a substitute for a GP IIb/IIIa integrin antagonist (and vice versa), or are these agents complementary and best used concurrently? Fourth, what is the appropriate loading dose of clopidogrel, particularly in the ad hoc situation? And fifth, how long should clopidogrel be administered after the procedure?

In this issue of the Journal, Chan et al. (11) have addressed the first three of these key questions. A series of post hoc analyses of the 4,809-patient TARGET (Do Tirofiban and ReoPro Give Similar Efficacy Outcomes Trial) study of tirofiban versus abciximab in stent PCI (12) were conducted, incorporating statistical approaches to adjust and account for differences among groups. The key findings have a high degree of relevance to the practice of contemporary stent PCI.

With respect to the first question (timing of clopidogrel relative to intervention), outcomes of patients were improved with the administration of a 300-mg loading dose of clopidogrel when given at any time before the PCI procedure (including just before the procedure) relative to the subgroup that had clopidogrel started after PCI. In this report, the majority (57%) of patients who were pretreated received drug within 2 h of PCI, with only 16% of pretreated patients having received clopidogrel >6 h before PCI. The benefit of >6 h of pretreatment was marginal relative to treatment for <6 h, suggesting a slight, but perhaps still meaningful, additional advantage to a longer period of pretreatment before PCI.

The crucial point of the analysis is that benefit is greatest when clopidogrel is started before PCI. This is consistent with both the pathophysiology of PCI (wherein a relatively inert blood vessel is abruptly converted into a prothrombotic milieu) and the rapid bioavailability of the active metabolite of clopidogrel, generally within minutes of drug adminis-
tination (13–15). Delaying treatment until after PCI has been completed (i.e., after activation of the thrombosis cascade) would seem somewhat imprudent, particularly because administration even in an ad hoc fashion is not especially difficult. Coupled with the known liabilities of clopidogrel treatment vis-à-vis the excessive rates of bleeding in the patient undergoing coronary artery bypass surgery, (16,17), this would argue for pretreatment of patients posted for elective PCI who have already undergone diagnostic catheterization, and for the ad hoc treatment of “cath possible” patients who may (or may not) subsequently undergo PCI.

These data are thus both congruous and expand upon the results of the recent PCI-CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) and CREDO (Clopidogrel for the Reduction of Events During Observation) trials (6,16). In these studies, patients undergoing PCI were randomized to treatment with clopidogrel for either several days (PCI-CURE) or 3 to 24 h (CREDO) before PCI and were found to have 30% (p = 0.03) and 18.5% (p = 0.23) relative risk reductions in the composite of death, myocardial infarction (MI), or urgent target vessel revascularization (TVR) to 28 days, respectively, compared with those started on clopidogrel after PCI. The unique contribution of the current work is the efficacy observed in the large group of patients treated within 0 to 2 h before PCI, a group heretofore left unstudied in randomized clinical trials. This compelling observation speaks to the absence of a specific trial addressing the question of ad hoc treatment; a randomized clinical trial comparing >6 h of treatment versus ad hoc treatment (perhaps with 300 mg vs. 600 mg dosing schedules) would seem to be in order to verify these post hoc findings.

A mild damper on the pro forma conclusions to the first question relates to the second question (characterization of the benefits of clopidogrel treatment). In the mid 1990s, the wholesale substitution of thienopyridine therapy for warfarin anticoagulation after stent PCI was driven largely by reductions in bleeding and subacute stent thrombosis (18–21). However, most of the efficacy of pretreatment with clopidogrel in the current study was in reducing death or MI. There were no reported differences in rates of urgent TVR between the pretreatment and post-treatment groups, suggesting that subacute stent thrombosis is an infrequent event that can be suppressed by administration of clopidogrel as long as it is started around the time (either before or immediately following) of PCI. If the goal is thus to simply prevent subacute stent thrombosis, the timing of clopidogrel administration would appear to be less relevant provided a 300-mg loading dose is administered shortly after PCI. However, this would be obviating the potential benefits of reducing death or MI simply as a matter of convenience and would overall seem ill advised.

Finally, the third question (the relative contributions of clopidogrel and platelet GP IIb/IIIa blockade to reducing ischemic complications) can be inferentially approached by examining the current study in the context of the existing literature. Pretreatment with clopidogrel provided additional efficacy to patients already receiving a GP IIb/IIIa inhibitor in the TARGET trial. The converse was addressed in two other studies, the Evaluation of IIb/IIIa Platelet Inhibition for Stenting (EPISTENT) and the ESPRIT (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy) trials. In these trials, improvements in outcomes were seen with adjunctive treatment with abciximab or eptifibatide compared with placebo, even in the presence of ticlopidine (EPISTENT) or clopidogrel (ESPRIT) (22,23). In particular, in the 2,064-patient ESPRIT stent PCI study, an additional 35% (p = 0.003) relative risk reduction in the composite end point of death, MI, and urgent TVR at 30 days was observed with eptifibatide treatment with concurrent thienopyridine administration. These observations should thus help put to rest the ongoing debate about whether to consider thienopyridine and platelet GP IIb/IIIa blockade as therapeutic competitors or synergistic collaborators in favor of strategies that use these agents in a concomitant fashion. This is in accordance with our current understanding of the physiology of platelets and the pharmacology of the antiplatelet agents. Platelet activation, inhibited by thienopyridine therapy, is not affected by platelet GP IIb/IIIa blockade, and platelet aggregation, suppressed by blockade of the platelet GP IIb/IIIa integrin, is only modestly inhibited by thienopyridine therapy. Even with platelet GP IIb/IIIa blockade, secretion of vasoactive humors and proinflammatory cytokines can occur; conversely, even with inhibition of the ADP receptor with thienopyridine therapy, platelet aggregation can occur. The body of evidence thus argues for a complementary, rather than competitive role for antiplatelet therapies. To borrow a term coined by the founder of the Novell Corporation, Ray Noorda, this would be an example of “coopetition,” both at the pharmacologic and drug industry levels. Although this is admittedly an inferential deduction that demands formal testing in randomized clinical trials, available data would suggest that outcomes are best optimized by combining aspirin, thienopyridine, and GP IIb/IIIa antagonist therapies in patients undergoing stent PCI.

Answers to queries four (optimizing the loading dose) and five (duration of treatment) are not addressed in this report, but need to be mentioned to complete the list of pertinent questions relevant to the positioning of clopidogrel as an adjunct to PCI. Provocative data suggest that further optimization of the loading dose may be possible (24), whereas the PCI-CURE and CREDO trials suggest that continued therapy to one year is of particular benefit in patients following PCI, a benefit even greater than that imparted to patients managed with medical therapy alone (5,6).

In conclusion, there is a compelling and consistent literature that argues for the use of triple antiplatelet therapy including aspirin, clopidogrel, and platelet GP IIb/IIIa
inhibitors in the setting of stent PCI. This broad approach to inhibiting the platelet at several different loci is effective in improving the prothrombotic environment created during PCI while diminishing the inflammatory response associated with platelet activation. Triple therapy remains safe and is associated with a lower incidence of subacute stent thrombosis, periprocedural MI, TVR, and death. Based on the current report along with a compilation of previous work, prudent specific recommendations concerning clopidogrel include the following:

1. Clopidogrel should be started as early as possible (>6 h) before PCI when the anatomy has been defined and the patient is scheduled for elective PCI.

2. Clopidogrel should be started in an ad hoc fashion before PCI (but after diagnostic catheterization) in “cath possible” patients.

3. Both GP IIb/IIIa antagonists and clopidogrel should be used together and started before PCI, particularly in higher risk patients; neither is a complete substitute for the other.

4. Still more information is needed about the optimum loading dose of clopidogrel preprocedure; a minimum of 300 mg is recommended, with up to 600 mg appearing reasonable.

5. Clopidogrel treatment should be continued for up to one year after PCI.

The platelet remains a “black box” that is incompletely understood; unfortunately, there remain patients with theoretically adequate antiplatelet therapy who develop thrombosis. Although we have learned much in the recent years about how to improve our management of patients in the periprocedural timeframe, more investigation with appropriately designed and sized trials will be required to definitively answer the remaining questions and further refine treatment algorithms.

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REFERENCES


