EDITORIAL COMMENT

Diminishing Returns...and Too Many Choices...The Saga of Pharmacologic Therapy to Reduce the Complications of Percutaneous Coronary Intervention*

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Complications of percutaneous coronary intervention (PCI), and coronary stenting in particular, are well characterized. Death, myocardial infarction (MI), and the need for emergent or urgent repeat revascularization are all known possible outcomes of PCI (1). Thrombosis is a common mechanism in the development of each of these complications (2).

A number of pre-procedural treatment strategies using anti-thrombotic therapies have evolved in an attempt to lower the rate of complications related to performance of PCI. Pre-treatment with aspirin and unfractionated heparin is the bedrock of pharmacotherapy to lower procedural risk (3). In recent years, a number of new anti-thrombotic agents have been tested as pre-procedural treatments in conjunction with or as substitutes for aspirin and unfractionated heparin to minimize complications. Among these agents are the thienopyridines, ticlopidine (4), and clopidogrel (5,6); the platelet glycoprotein receptor IIb/IIIa inhibitors, abciximab (7–9), eptifibatide (10,11), and tirofiban (12); the low molecular weight heparins, enoxaparin (13,14), and dalteparin (15); and the direct thrombin inhibitor, bivalirudin (16,17). At least some clinical evidence supports the use of each of these agents as pre-treatment for the reduction of thrombosis-mediated PCI complications.

Ticlopidine and clopidogrel are accepted treatments to reduce the risk of sub-acute thrombosis when started soon after a stenting procedure (18–21). Because of its more favorable side effect profile, clopidogrel has become the accepted thienopyridine for clinical use in the post-stent setting (22). Whether there is additional benefit in reducing procedural complications by starting clopidogrel before the procedure has been the subject of two large randomized blinded trials, the Percutaneous Coronary Intervention-Clopidogrel in Unstable angina to prevent Recurrent Events (PCI-CURE) (5) and the Clopidogrel for the Reduction of Events During Observation (CREDO) (6) studies. In each study, patients were randomized to double-blind treatment with clopidogrel or placebo before PCI and again beginning 28 days after the procedure. However, from PCI to a day between 14 and 28 days after the procedure, all patients received open-label clopidogrel or ticlopidine because of the known benefit of these drugs in combination with aspirin for prevention of sub-acute thrombosis. The primary end point in the PCI-CURE trial was a composite of 30-day cardiovascular death, MI, and the need for urgent revascularization; this end point was reduced by 31% in patients assigned to clopidogrel treatment. In the CREDO trial, the primary end points were the composite of death, MI, and stroke at one year and the composite of death, MI, and urgent target vessel revascularization at 28 days. The one-year composite end point was significantly reduced by 27% with clopidogrel treatment. In order to focus on the question of benefit of clopidogrel pre-treatment and reduction of PCI-related procedural complications, it is necessary to evaluate short-term treatment effects. In the PCI-CURE 30-day trial data, the pre-treatment benefit with clopidogrel was limited to reduction of frequency of MI, with a trend toward benefit in need for urgent revascularization but no effect at all on cardiovascular death. In the CREDO trial, pre-treatment was not associated with a statistically significant reduction in the composite end point at the 28-day time point, although there was a trend toward benefit (p = 0.23). There were fewer events in each of the components of the composite end point (death, MI, and urgent revascularization) for pre-treated patients and an additional sub-group analysis looking at duration of pre-treatment indicated benefit for clopidogrel patients if they received the drug at least 6 h before the PCI but no benefit if <6 h elapsed between pre-treatment and the PCI.

We can add the study of van der Heijden et al. (23) in this issue of the Journal to the PCI-CURE and CREDO trial results. This current study used a randomized, non-blinded design to evaluate pre-treatment with clopidogrel in the setting of coronary stenting. Patients randomized to pre-treatment received 300 mg of clopidogrel three days before the procedure followed by 75 mg per day thereafter. Patients in the control group received 300 mg of clopidogrel immediately after the procedure followed by 75 mg per day. The pre-treatment interval in the current trial falls between the pre-treatment time interval used in the PCI-CURE and CREDO trial (median pre-treatment duration was 6 days) and the CREDO (3 to 24 h) trials. The control group of the current trial received a loading dose of clopidogrel early after stenting, unlike the control group patients in the CREDO trial, who received only the daily maintenance dose of clopidogrel early after the PCI procedure was completed. In the PCI-CURE trial, a loading dose strategy for clopidogrel or ticlopidine after PCI in the control group was not specified, only that these patients were treated with open-label drug for two to...
four weeks after the procedure. Using this study design, van der Heijden et al. (23) found no difference in the frequency of cardiac injury marker elevation between the two treatment groups. The current study is small in size, but there was no obvious benefit or detriment to administering clopidogrel before treatment when clinical end points were assessed.

How might one categorize the sum of the available randomized trial data regarding effectiveness of pretreatment with 300 mg of clopidogrel on procedural complications of PCI? One approach would be to categorize the results of each of the three trials as either “beneficial” or “no treatment effect” based on the overall 28- to 30-day data of each. This approach yields one trial being “beneficial” and two trials showing “no treatment effect.” The obvious limitations of this approach are: 1) equating the small size of van der Heijden et al trial, with the much–larger size of the other two trials; and 2) ignoring some of the nuances of the results of the two large trials. An alternate approach would be to combine the 28– to 30-day clinical outcome results of all three trials. A very informal “meta-analysis” of the published randomized data is as follows: (pretreatment vs. no pretreatment groups) total patients, 2,467 versus 2,510; death, 14 (0.6%) versus 17 (0.7%); MI, 81 (3.3%) versus 111 (4.4%); urgent revascularization, 35 (1.4%) versus 53 (2.1%). These numbers suggest to this reader a probable (in the legalistic sense) small benefit in prevention of procedural MI (on the order of preventing 1 MI event per 100 treated patients) and perhaps a possible small treatment effect on the prevention of urgent revascularization. It seems very unlikely that there is any effect on procedural death risk with pretreatment. Thus, the answer to the initially posed question appears to be that pretreatment with clopidogrel yields a result somewhere between the bounds of no detectable benefit and a small treatment benefit in the overall spectrum of clinical utility.

Recently, there has been interest in using a larger loading dose of clopidogrel for pretreatment, 600 mg. A study in PCI patients comparing this higher pre-treatment dose of clopidogrel with a historical cohort of patients pre-treated with ticlopidine reported a lower incidence of the composite end point of death, MI, and urgent revascularization in those receiving the high-dose clopidogrel load (24). A second study, the Intracoronary Stenting and Antithrombotic Regimen Rapid Early Action for Coronary Treatment study, included over 2,100 relatively low-risk patients undergoing PCI; all received the high-dose (600 mg) clopidogrel load before PCI and then were randomized to abciximab treatment or placebo (25). There was no apparent benefit to abciximab treatment being added to high loading dose clopidogrel in this study. Unfortunately, neither of these studies provides us with any information about the incremental benefit of the high loading dose clopidogrel regimen compared with either placebo or to the previously studied 300-mg loading dose regimen in the pre-treatment PCI setting.

Why clopidogrel pre-treatment fails to have a larger benefit may be explained by several different factors. Individual patient response to clopidogrel loading and maintenance dosing is variable (26,27). Between 20% and 30% of tested healthy subjects showed no significant inhibitory effect on measures of platelet reactivity after clopidogrel was started. There may be a genetic basis explaining the variability in individual response to clopidogrel dosing (28). Drug interactions may alter responsiveness to clopidogrel (29,30). Several recent in vitro studies of platelet reactivity have implicated an inhibitory effect of lipophilic 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on clopidogrel treatment effect. Clinical presentation may be another factor influencing treatment benefit. As van der Heijden et al. (23) note, there may be a larger treatment effect in patients presenting with ACS than those who have a more stable clinical presentation who present for elective PCI. Finally, the relative prevalence of complications of PCI affects the relative efficacy of clopidogrel (or any other treatment). With 30-day major adverse event rates less than 7.5% in the PCI settings being studied, the ability of any treatment to show a large effect is diminished. Because thrombosis most likely contributes mechanistically to only a part of these complications, the potential benefit of any anti-thrombotic therapy is further limited. Thus, the “return” on any new treatment offered in this setting is likely to be diminished based the relative low frequency of the complications with current conventional therapy.

If clopidogrel were the only novel anti-thrombotic therapy for the prevention of PCI procedural complications, then this whole discussion would have ended in the first paragraph because even a small treatment benefit would be worthwhile to many interventionalists. However, the coronary interventional community is literally inundated with anti-thrombotic treatment options that are being advocated as methods to reduce procedural complications. These options (aspirin in different dosages, bolus or weight adjusted heparin with or without activated clotting time monitoring, abciximab, epti-
setting; but the use of clopidogrel as a pre-treatment before PCI should be balanced against the increased risk of operative complications seen in patients receiving combined aspirin and clopidogrel compared with aspirin alone when coronary artery bypass surgery is performed (33), an infrequent but known possibility for patients being considered for PCI. Other interventionalists, however, may find one or more of the other pre-treatment choices having an impact on PCI procedural risk to be more compelling in their practice settings. The saga of defining optimal anti-thrombotic therapy to reduce PCI procedural risk continues.

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REFERENCES