What to Do With Patients Receiving Long-Term Clopidogrel
Reload or Relax?

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It is difficult to recall a drug whose first dose has received as much attention as clopidogrel. Indeed, the current Clopidogrel Optimal Dose Usage to Reduce Recurrent Events (CURRENT-OASIS 7) clinical trial hopes to enroll 14,000 patients with acute coronary syndromes treated via invasive strategies to determine whether an initial 600-mg loading dose (LD) followed by 150 mg/d of clopidogrel for 1 week and 75 mg/d thereafter is superior to a 300-mg LD and a subsequent 75 mg/d dose. The basis for such a trial is to identify the dose of clopidogrel that will achieve rapid and maximal inhibition of platelet aggregation (IPA) in order to minimize the occurrence of spontaneous or procedural-related coronary thrombosis and have an acceptable incidence of significant bleeding.

Several reports have demonstrated that as compared with a 300-mg LD, a dose of 600 mg results in an earlier onset of inhibitory effect and substantially greater IPA, which results in a smaller proportion of clopidogrel “nonresponders” and patients with high posttreatment platelet reactivity.1,2 Furthermore, at least 2 randomized clinical trials have demonstrated improved clinical outcomes with a clopidogrel LD >300 mg. In the Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty (ARMYDA-2) trial, elective percutaneous coronary intervention (PCI) patients receiving pretreatment with a 600-mg LD of clopidogrel experienced fewer periprocedural myocardial infarctions than those treated with 300 mg clopidogrel, resulting in superior 30-day outcomes.3 In higher-risk PCI patients with non-ST-segment elevation acute coronary syndromes, a 600-mg LD of clopidogrel was superior to a 300-mg dose in terms of both inhibition of platelet aggregation and frequency of 1-month cardiovascular events.4 Evidence that even a 600-mg LD may be inadequate pretreatment for all PCI patients is exemplified in the Impact of Extent of Clopidogrel-Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rate (EXCELSIOR) study, which showed that the pre-PCI level of platelet aggregation is correlated with early outcomes after the procedure.5

A rationale exists to investigate if additional suppression of platelet function with even higher LDs of clopidogrel is achievable and clinically beneficial. To that end, the Intra-coronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect (ISAR-CHOICE) investigators compared the effects of 300-, 600-, and 900-mg clopidogrel on platelet function among stable patients scheduled for coronary angiography. At 4 hours, patients treated with both 600- and 900-mg doses demonstrated more IPA than the 300-mg dose group. No significant difference was found, however, between the 600- and 900-mg dose groups, although a review of individual patient IPA values reveals extensive overlap across all 3 groups. On the basis of their evaluation, ISAR-CHOICE investigators concluded that single doses >600 mg are not associated with any additional suppression of platelet activity, and that measured levels of clopidogrel metabolites indicate that this latter effect is related to impaired intestinal absorption of clopidogrel.6 The Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis (ALBION) trial investigators, on the other hand, in patients with non-ST-segment elevation acute coronary syndromes, found a 900-mg LD had an incremental benefit over lower LDs. Nonresponsiveness, defined as <10% of IPA at 6 hours, occurred in 46.4%, 20.7%, and 10.7% of patients who received 300-, 600-, and 900-mg LDs, respectively.7 A significant reduction in clinical events could not be demonstrated in this small trial. A recently published randomized trial in elective PCI patients assessed a 1200-mg clopidogrel LD. Greater platelet inhibition and fewer clopidogrel nonresponders were observed among patients receiving the 600-mg double bolus of clopidogrel 24 hours apart as compared with the conventional single 600-mg LD group.8

A related question of clopidogrel dosing involves patients who are already receiving a “maintenance” dose of clopidogrel. Would such patients benefit from a “booster dose” if they experienced a new acute clinical coronary event or were to have PCI performed? Support for this concept is based on recognition that maintenance clopidogrel therapy only modestly inhibits platelet aggregation. Published reports indicate that, on average, the magnitude of IPA for patients who receive a dose of 75 mg/d is ∼30% to 50%.9–11 Additional support that the maintenance dose may be inadequate in patients requiring nonemergency PCI is that those who exhibit high on-treatment ADP-induced platelet aggregation...
(>50%) are at increased risk for postprocedural ischemic events. Of patients with an ischemic event, 70% displayed high on-treatment platelet reactivity at baseline.9 Certainly, reloading on long-term maintenance therapy is an important scientific and clinical question, given the large number of patients currently receiving long-term clopidogrel therapy and the progressive and protracted course of coronary artery disease.

Two previous studies have attempted to determine the effects of administering an enhanced dose of clopidogrel on the background of long-term clopidogrel administration. In 2004, Kastrati and coworkers reported the effects of 600 mg of clopidogrel in 20 patients already receiving 75 mg/d.11 They observed that a 600-mg “reload” dose yielded further inhibition of platelet aggregation in addition to that achieved by the maintenance dose of 75 mg/d, from 52±14% to 33±12%. Furthermore, the recent ARMYDA-4 trial evaluated clinical outcomes among patients on long-term clopidogrel therapy who received either a clopidogrel 600-mg reload dose or placebo before PCI. For those patients who presented with acute coronary syndromes, the clopidogrel reload group experienced fewer myocardial infarctions by 30 days compared with those assigned to the reload with placebo group (Late Breaking Clinical Trials, SCAI-ACC12 Sessions, March, 2008. Available at: http://www.cardiosource.com/rapidnewssummaries/summary.asp?SumID=242.

We learn more about the antiplatelet effects of clopidogrel reloading in patients on long-term therapy in this issue of Circulation. Collet and colleagues report the findings of a randomized clinical trial that evaluated residual platelet aggregation (RPA) after administration of 900 mg of clopidogrel provided in 3 dosing strategies.12 Clopidogrel reloading was accomplished by either a single 900-mg dose followed 4 hours later with a placebo dose, or by split dosing with an initial bolus of 600 or 300 mg, followed 4 hours later by a second dose of 300 or 600 mg, respectively. Each patient had been treated with clopidogrel long term, the majority for a duration of >30 days. Approximately half of the study group presented with an acute coronary syndrome, nearly all underwent coronary angiography, and about half had PCI. Cardiac catheterization was delayed until completion of the study protocol. Troponin I levels were determined at baseline and after PCI, and clinical events were captured through 30 days.

The primary response variable was inhibition of RPA (IRPA), defined as the ratio of the difference between RPA at baseline and RPA after reloading over RPA at baseline. For example, if a patient receiving long-term clopidogrel therapy had a baseline RPA of 60% (IPA 40%) and an RPA of 30% after a reloading dose, their IRPA would be 50%. IRPA was determined at 4 hours after the initial reloading dose in order to compare the 900-mg dose with the lower LDs, and at 24 hours to determine whether differences in absorption or metabolism influenced the 900-mg loading regimen. Two analytical methods were used to evaluate platelet function: light transmission aggregometry (LTA) after induction with several concentrations of ADP, and the VerifyNow P2Y12 assay. An additional end point evaluated in this trial was “suboptimal response.” A suboptimal response to a mainte-
findings of this study with prior reports, particularly those with conflicting results, and also for placing this study in clinical context. Additionally, relative changes in platelet function, such as the IRPA end point, may be misleading in patients with a low baseline residual platelet reactivity that have minimal IRPA but a favorable clinical outcome.

The study fails to identify whether the 900-mg reloading dose is superior to lower doses according to nonresponder status. Prior studies support the concept that only patients with high residual platelet reactivity require reloading.5.9 In fact, guiding clopidogrel loading according to platelet function has been shown to improve outcomes in PCI patients that demonstrate clopidogrel “resistance,” which is defined as a vasodilator-stimulated phosphoprotein (VASP) index >50%. Patients with a VASP index >50% after the first 600-mg bolus of clopidogrel were randomized to the control group or the VASP-guided group. In the VASP-guided group, up to 3 additional boluses of 600 mg were given in 24-hour increments to achieve a VASP index <50%, which was obtained in 86% of patients. At 1 month follow-up, a lower rate of major adverse cardiac events was found in the VASP-guided group, and no difference in bleeding rates, which validates the strategy of guiding antiplatelet therapy based on platelet-function testing.14 Whether patients that receive VASP-guided therapy have similar outcomes to patients who are considered responders after the initial clopidogrel LD is unknown.

Given that it is possible to achieve nearly total IPA depending on the agent used and route of administration, what is the relationship between magnitude of IPA and clinical outcome? In the GOLD (Assessing Ultegra [AU]) study, for example, patients in the lowest quartile of platelet function inhibition experienced a significantly higher incidence of major adverse cardiac events.15 We know however, that not all patients require that high degree of platelet inhibition peri-PCI. For example, in the ISAR-REACT trial, abciximab (which achieves mean level of platelet inhibition 50%), which was obtained in 86% of patients. At 1 month follow-up, a lower rate of major adverse cardiac events was found in the VASP-guided group, and no difference in bleeding rates, which validates the strategy of guiding antiplatelet therapy based on platelet-function testing.14 Whether patients that receive VASP-guided therapy have similar outcomes to patients who are considered responders after the initial clopidogrel LD is unknown.

Similar results were seen in patients with diabetes mellitus in the Intracoronary Stenting and Antithrombotic Regimen: Is Abciximab a Superior Way to Eliminate Elevated Thrombotic Risk in Diabetics (ISAR-SWEET) study.17 With this information, it is hard to argue that higher LDs of clopidogrel are necessary for all comers. Conversely, in high-risk patients with non–ST-segment elevation acute coronary syndromes and elevated troponin levels who were undergoing PCI after pretreatment with 600 mg of clopidogrel, abciximab did reduce the risk of adverse events.18 These results may reflect higher levels of residual platelet aggregation in acute coronary syndrome patients receiving clopidogrel.19

Along the lines of dosing antiplatelet agents, what about the role of more potent platelet inhibitors such as prasugrel? The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation—Thrombolysis in Myocardial Infarction 44 (PRINCIPLE-TIMI 44) study showed significantly higher IPA among patients undergoing car-

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