editorial

Antiplatelet Therapy After Percutaneous Coronary Intervention

Should Another Regimen Be “TAPT?”

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Current guidelines recommend dual antiplatelet therapy (DAPT) that includes aspirin and the platelet P2Y12 ADP receptor antagonist clopidogrel after percutaneous coronary intervention (PCI). These recommendations are based on data that DAPT with the P2Y12 inhibitors clopidogrel reduces major adverse cardiac events after PCI in stable angina and acute coronary syndrome (ACS) patients when compared with aspirin, or aspirin in combination with warfarin.1 Despite treatment with DAPT, patients with ACS undergoing PCI are at elevated risk for recurrent ischemic events compared with stable angina patients in part because of increased platelet thrombotic activity in ACS. In addition, there is considerable interindividual variability in the degree of platelet inhibition achieved by clopidogrel, and high residual platelet activity in the setting of clopidogrel therapy (hyporesponsiveness) is associated with adverse cardiovascular (CV) events after PCI. Clopidogrel hyporesponsiveness is related to a variety of clinical and genetic factors that alter pharmacokinetics, and diabetes, congestive heart failure (CHF), and obesity are associated with reduced efficacy. Clopidogrel is a prodrug that requires conversion by the hepatic cytochrome P450 system (CYP) to an active metabolite, and it can take up to 6 hours for clopidogrel to have maximal effect after the loading dose. Genetic polymorphisms that reduce CYP activity result in decreased hepatic metabolism of clopidogrel. Among persons treated with clopidogrel, carriers of specific reduced function CYP2C19 alleles have impaired clopidogrel conversion, significantly lower levels of active metabolite, diminished platelet inhibition, and higher rates of adverse CV events and stent thrombosis after PCI.2 The prevalence of CYP2C19 polymorphisms ranges from 30% to 60% depending on ethnicity.2,3 Medications that inhibit CYP activity also reduce clopidogrel conversion, and some proton pump inhibitors (PPI) that reduce CYP function (eg, omeprazole) diminish clopidogrel metabolite levels and efficacy measured by platelet function testing. The interaction between clopidogrel and PPIs is currently controversial. Early observational studies suggested increased adverse CV events in patients taking clopidogrel and a PPI; however, analysis of patients treated with clopidogrel in randomized trials including TRITON TIMI-38 and COGENT demonstrated no association between PPI use and risk of adverse CV events.4,5 These findings highlight the point that biological interaction measured with platelet function testing may not always predict clinical interactions that affect CV outcomes.

Clopidogrel hyporesponsiveness can be partially overcome by increasing the dose, and several studies have demonstrated that high loading doses (600 or 900 mg) shorten the onset of action, reduce interindividual variability, and improve early outcomes without increasing bleeding.6,7 Short-term use of high dose therapy benefited patients with ACS treated with PCI in the CURRENT OASIS 7 study. In OASIS 7, patients given a 600 mg loading dose and 150 mg daily 7 days before switching to standard dosing (75 mg daily) had improved 30 day CV outcomes with no evidence of increased bleeding compared with patients treated with standard therapy (300 mg load, 75 mg daily).8 Clopidogrel hyporesponders can be identified by platelet function testing with light transmittance aggregometry or with similar technologies such as the Affymetrix VerifyNow P2Y12 test. Although increased dosing (600 mg load and/or 150 mg daily) improves clopidogrel efficacy in hyporesponsive patients, the antiplatelet effects achieved under these conditions remain nonuniform, and a considerable number of patients continue to show inadequate platelet inhibition.9 Randomized studies are underway to evaluate whether there is a clinical benefit to identifying clopidogrel hyporesponders by platelet function testing so that they can be treated with high maintenance dose therapy (high-MD, 150 mg daily).10

Triple antiplatelet therapy (TAPT) provides another potential option for addressing clopidogrel hyporesponsiveness and providing more uniform and potent platelet inhibition. In this issue of Circulation: Cardiovascular Interventions, investigators from the ACCEL-AMI study explore the antiplatelet effect of TAPT compared with both standard and high-MD DAPT with clopidogrel in patients with acute myocardial infarction (AMI) undergoing PCI.11 TAPT combines aspirin, clopidogrel, and cilostazol, a selective inhibitor of type-3 phosphodiesterase, which is approved by the FDA for treatment of intermittent claudication. Cilostazol works synergistically with clopidogrel to inhibit platelet aggregation by increasing platelet cAMP; and in the OPTIMUS-2 study,
cilostazol augmented platelet aggregation when added to DAPT after PCI.\textsuperscript{12} In addition to its platelet actions, cilostazol causes vasodilation, inhibits smooth muscle proliferation, and reduces intimal hyperplasia after endothelial injury. In clinical studies, cilostazol lessens bare metal and drug-eluting stent restenosis.\textsuperscript{13,14} Retrospective analysis of ST-segment elevation patients treated with PCI revealed that compared with DAPT, TAPT was associated with reduced in hospital cardiac death (adjusted odds ratio, 0.52; 95% CI, 0.32 to 0.84; \(P=0.007\)) and reduced major adverse CV outcomes at 8 months (adjusted odds ratio, 0.74; 95% CI, 0.58 to 0.95; \(P=0.019\)).\textsuperscript{15} Prospective analyses of patients with ACS similarly demonstrated that compared with DAPT, TAPT reduced incidence of adverse CV events (10.3% versus 15.1%; \(P=0.011\)) and decreased stent thrombosis.\textsuperscript{17} In all of these studies, TAPT did not seem to increase the risk of bleeding. Given multiple cellular sites of action, clinical benefit of cilostazol could be related to biological effects on thrombosis, restenosis, and endothelial dysfunction.

The primary goal of the ACCEL-AMI study was to determine whether the benefit of TAPT in previous clinical investigations could result from enhanced inhibition of ADP-induced platelet activation. The study prospectively randomized 90 patients with AMI undergoing PCI to 1 of 3 groups: standard DAPT, clopidogrel 75 mg daily; high-MD DAPT, clopidogrel 150 mg daily; and TAPT, clopidogrel 75 mg daily, cilostazol 100 mg twice daily. Platelet reactivity was assessed by conventional light transmittance aggregometry and by the VerifyNow P2Y\textsubscript{12} assay before the administration of the study regimen and at 30-day follow-up. At 30-day follow-up, percent change in the inhibition of ADP-stimulated platelet aggregation in the TAPT arm was 42.4%, which was significantly higher compared with 6.0% in the standard group, and 19.1% in the high-MD group (\(P<0.001\)). Percent changes of P2Y\textsubscript{12} reaction unit showed similar enhancement with 43.0% percent change inhibition in the TAPT group compared with 10.6% in the standard group and 30.7% in the high-MD group (\(P<0.001\)). Furthermore, TAPT resulted in a significant reduction in the number of patients who met criteria for clopidogrel hyporesponsiveness defined as \(>50\%\) maximal ADP-stimulated platelet aggregation. Although ACCEL-AMI was underpowered to assess bleeding outcomes, no major bleeding events were observed in any group, and the incidence of minor bleeding was similar across treatments. These findings demonstrate that in patients with AMI who are treated with PCI, TAPT has greater antiplatelet effect compared to DAPT with standard- or high-MD clopidogrel. The results further suggest that clinical benefit of TAPT seen in earlier trials could be derived from augmented inhibition of ADP-induced platelet activation.

Hyporesponsiveness does not seem to be a problem with next generation P2Y\textsubscript{12} antagonists that are more potent, have faster onset of action (<1 hour), and have minimal interindividual variability. Several of these new inhibitors are being evaluated in clinical trials, and the thienopyridine prasugrel was recently approved for use by the FDA as an alternative to clopidogrel in patients with ACS undergoing PCI. Common functional CYP genetic variants do not affect prasugrel active drug metabolite levels, and prasugrel provides more uniform and more potent inhibition of platelet aggregation compared with clopidogrel. In patients with ACS undergoing PCI, prasugrel (60 mg load, 10 mg daily) reduced CV events compared to clopidogrel (300 mg load, 75 mg daily); however, this reduction was accompanied by increased risk of major bleeding.\textsuperscript{18} Ticagrelor is another promising next generation reversible P2Y\textsubscript{12} inhibitor with rapid onset and more potent platelet inhibition compared with clopidogrel. In patients with ACS undergoing PCI, ticagrelor (180 mg load, 90 mg twice daily) compared to clopidogrel (300 to 600 mg load, 75 mg daily), significantly reduced CV events without increasing the overall risk of major bleeding.\textsuperscript{19} Results with more potent P2Y\textsubscript{12} agents such as prasugrel and ticagrelor highlight the tension between efficacy and safety in striving to reduce ischemic events while minimizing bleeding.

The ACCEL-AMI Study needs to be considered in the context of recent results with next generation P2Y\textsubscript{12} inhibitors. To date, TAPT has only been evaluated in patients with ACS. In addition, blinded, randomized clinical trials evaluating TAPT efficacy and safety in patients undergoing PCI are not available, and data from such trials will be required to make definitive conclusions about the relative clinical performance of TAPT compared with clopidogrel, prasugrel, and newer agents such as ticagrelor. With regard to the safety of TAPT, although adjunctive cilostazol does not seem to increase bleeding, several drugs in the type-3 phosphodiesterase inhibitor class cause decreased survival in patients with class III to IV CHF, and the FDA currently recommends that cilostazol not be used in patients with CHF of any severity.\textsuperscript{20} A large percentage of patients treated with PCI have a history of CHF, and clinical studies have not examined the effect of TAPT on indices of CHF severity in PCI patients. Despite the superiority of TAPT in inhibiting platelet activation compared with high-MD clopidogrel, we should remain cautious about extrapolating platelet function data as proof of clinical efficacy. This point was demonstrated by the experience with clopidogrel and PPIs, where biological effects seen during platelet function testing have not translated into adverse ischemic outcomes in clinical trials (discussed earlier). Also, the optimal treatment duration for adjunctive cilostazol in PCI patients is unclear because length of therapy has varied from 1 month to 6 months in studies evaluating TAPT efficacy.\textsuperscript{16,17} So, where might TAPT fit into the currently available regimens for antiplatelet therapy following PCI? Although strategies to identify clopidogrel hyporesponders so that antiplatelet therapy can be intensified are under evaluation,\textsuperscript{16} TAPT has potential to benefit patients who do not achieve optimal platelet inhibition on standard or high-MD clopidogrel. The question remains, however, whether clopidogrel hyporesponders are best treated with adjunctive cilostazol or with more potent P2Y\textsubscript{12} inhibitors such as prasugrel. Because of its antirestenotic effect, TAPT might also be useful in treating patients at high risk for restenosis due to clinical or procedural factors such as diabetes, long segments of artery stenting, or use of bare metal stents.

The results of the ACCEL-AMI study demonstrating improved platelet inhibition with TAPT are provocative and coupled with evidence of improved ischemic outcomes in early clinical studies, there is mounting data that TAPT may
be a viable antithrombotic regimen for select patient subsets following PCI. Further study in randomized clinical trials powered to assess CV outcomes and bleeding will be required to draw more definitive conclusions about the clinical efficacy of TAPT compared with DAPT with clopidogrel, prasugrel, or other next generation P2Y12 inhibitors.

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References

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