

Practice Tips and Frequently Asked Questions

A Midday Symposium, *Optimizing Oral Antiplatelet Therapy in Acute Coronary Syndrome*, was presented at the 45th ASHP Midyear Clinical Meeting and Exhibition in Anaheim, California, on December 7, 2010. Attendees at the symposium submitted questions about unresolved issues and controversies that were later addressed by Paul P. Dobesh, Pharm.D., in a live webinar on March 2, 2011, and serve as the basis of the frequently asked questions in this e-newsletter. Dr. Dobesh serves as chair of this educational initiative. Other elements of the initiative include an on-demand activity approved for two hours of continuing pharmacy education (CPE) and faculty podcast interviews. These can be accessed through the initiative web portal at www.ashpadvantage.com/optimize.

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Practice Changes Related to Oral Anticoagulant Therapy in Acute Coronary Syndrome

When pharmacists participate in educational activities, what do they do with their new knowledge? Here are some of the changes in practice that participants in the 2010 Midyear Symposium, "Optimizing Oral Antiplatelet Therapy in Acute Coronary Syndrome," reported in a survey about two months after the symposium:

- Consider more patient factors, such as diabetes, when recommending oral antiplatelet therapy.
- Monitor patients receiving clopidogrel more closely to consider alternative therapy.
- Question use of aspirin 325 mg vs. aspirin 81 mg daily.
- Evaluate new oral antiplatelet agents for formulary consideration.
- Evaluate omeprazole as the single formulary option for proton pump inhibitors (PPIs).
- Recommend pantoprazole as the PPI of choice for patients on concomitant clopidogrel and PPI therapy.
- Continue to evaluate studies on new and emerging oral antiplatelet agents.
- Develop recommendations for platelet function testing.
- Incorporate genetic information into care of patients with acute coronary syndrome.

In addition, almost 80% of respondents indicated that they were able to discuss antiplatelet therapy more effectively with physician and pharmacist colleagues after participating in the symposium.

If these practice changes piqued your interest and you want to learn more about this topic, go to the initiative web portal at www.ashpadvantage.com/optimize.

Frequently Asked Questions

This e-newsletter features frequently asked questions (FAQs) addressed by the faculty pertaining to laboratory testing of platelet function and genotype in patients receiving clopidogrel and emerging oral antiplatelet therapies. FAQs pertaining to current information about interactions between the thienopyridine clopidogrel and proton pump inhibitors and the role of prasugrel in treating patients with acute coronary syndrome (ACS) are described in a [previous e-newsletter](#). Prasugrel is a newer thienopyridine with greater potency than clopidogrel that became available in 2009.

Question: What is the role of platelet function testing in the use of clopidogrel in patients with ACS?

There is considerable interpatient variability in platelet inhibition in response to clopidogrel, a P2Y₁₂ receptor antagonist.¹ The variability in response to clopidogrel as measured by platelet function tests correlates with clinical outcomes in patients undergoing percutaneous coronary intervention (PCI).^{2,3}

Several assays are available to test platelet function, including light transmission aggregometry, vasodilator-stimulated phosphoprotein (VASP) phosphorylation, and the VerifyNow P2Y12 assay. A threshold for high on-treatment reactivity that may be associated with adverse clinical events has been established for each assay, although there is some uncertainty about the optimal threshold. The platelet function test that best predicts clinical outcomes in patients with ACS is not known. The VerifyNow P2Y12 assay is the most convenient test, although it is expensive. None of the assays measures *in vivo* platelet function or is ideal. Most of the assays are used only in the clinical trial setting.

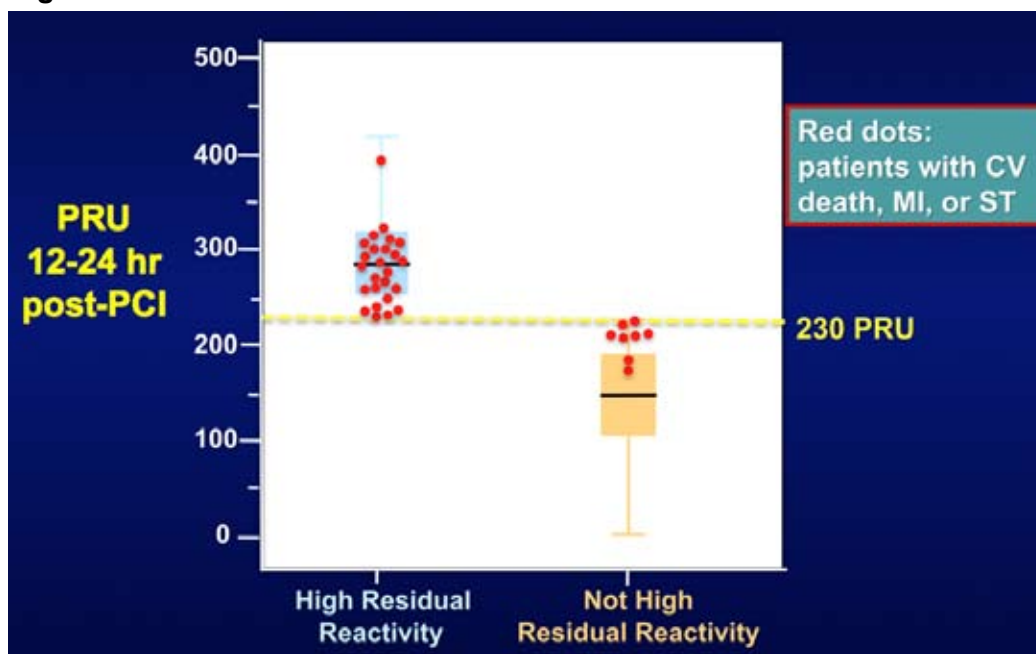
Platelet function testing has been used in the research setting to individualize dosing of clopidogrel in patients undergoing PCI and stent placement. In theory, the use of a clopidogrel dosage that is larger than the standard dosage in patients with high on-treatment reactivity (i.e., nonresponders) could improve clinical outcomes by decreasing platelet reactivity. In a randomized, controlled study of 419 patients undergoing PCI, VASP-guided clopidogrel dosing with additional loading doses given to maintain platelet reactivity below the threshold for high on-treatment reactivity was compared with standard dosing of clopidogrel.⁴ A lower rate of stent thrombosis was observed with VASP-guided dosing than with standard dosing. It should be noted, however, that while guided dosing improved antiplatelet response in many patients, 8% of the VASP-guided group remained nonresponders even after receiving up to 4 loading doses of clopidogrel 600 mg over 4 days (2400 mg total).

In the GRAVITAS study, the VerifyNow P2Y12 assay was used to guide clopidogrel dosing 12-24 hours after successful PCI with drug-eluting stent implantation in 2800 patients.⁵ The 2214 nonresponders with high residual platelet reactivity (defined as platelet reactivity units >230) were randomly assigned to continue to receive clopidogrel 75 mg/day (standard therapy) or an additional clopidogrel 600-mg loading dose followed by 150 mg/day (tailored therapy). Standard therapy also was provided to 586 responders without high residual platelet reactivity. After 6 months of follow up, the incidence of a composite end point of cardiovascular death, myocardial infarction (MI), or stent thrombosis was 2.3% in both nonresponder groups and 1.4% in the responder group. The differences between groups were not significant. There also were no significant differences between the two nonresponder groups in bleeding. The percentage of patients with persistently high platelet reactivity after 30 days was significantly reduced from baseline in both nonresponder groups.

Based on trials with alternative antiplatelet agents that produce a more consistent and robust antiplatelet response when compared with clopidogrel (e.g., prasugrel, ticagrelor), the use of the larger clopidogrel dosage in nonresponders receiving tailored therapy was expected to reduce the risk for the composite end point compared with standard therapy in nonresponders by decreasing platelet reactivity. Several possible explanations have been offered for the unexpected findings.⁵⁻⁷ The inclusion of patients with stable coronary artery disease undergoing elective PCI (80%) might have influenced the results because they are at lower risk for thrombosis than are patients with ACS. In addition, the

threshold for clopidogrel response might have been too high to identify patients at risk for thrombosis (Figure 1).⁵ The use of a lower threshold to identify nonresponders or a lower target for antiplatelet response might have resulted in a lower incidence of the composite end point in the nonresponders receiving tailored therapy compared with nonresponders receiving standard therapy.

Figure 1. GRAVITAS Results: CV Events and Post-PCI PRU⁵



CV = cardiovascular, MI = myocardial infarction, PCI = percutaneous coronary intervention, PRU = platelet reactivity units, ST = stent thrombosis

Several clinical trials are under way to further explore the impact on clinical outcomes of using platelet function testing with the VerifyNow P2Y12 assay to guide treatment with clopidogrel or prasugrel in various patient populations. One of these, the Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel (TRIGGER-PCI) study, was comparing the efficacy and safety of prasugrel and clopidogrel in patients with high platelet reactivity after a 600-mg clopidogrel loading dose and successful implantation of a drug-eluting stent,⁸ but it was stopped early due to low event rates and the unlikely possibility of seeing any difference between the groups.⁹ The TRIGGER-PCI trial had the same limitation as GRAVITAS by enrolling only low-risk patients and not patients with ACS. Event rates in TRIGGER-PCI were on course to be lower than those in GRAVITAS.

Question: What is the role of genetic testing in patients receiving clopidogrel?

Clopidogrel is a prodrug that undergoes a two-step activation process, and both steps take place within the liver.¹⁰ Although multiple enzymes may take part in clopidogrel activation, cytochrome P450 (CYP) 2C19 is a key enzyme in both steps. There is genetic variability in CYP2C19 and an increased risk for cardiovascular events in patients with ACS who are poor metabolizers of clopidogrel compared with patients with normal CYP2C19 function.^{11,12}

Tests are available to assess a patient's CYP2C19 genotype, and, theoretically, knowledge of genotype might help predict which patients will have a suboptimal antiplatelet response to clopidogrel and be at risk for clinical events. However, it has been demonstrated that CYP2C19 polymorphisms account for only about 12% of the variability in response to clopidogrel.¹³ Other variables involved with clopidogrel response include clinical factors (e.g., advanced age, high body mass index, low levels of high-density lipoprotein cholesterol, high triglyceride levels, diabetes), as well as other polymorphisms.^{13,14}

A genetic polymorphism in paraoxonase-1 (PON1) recently was reported.¹⁵ Based on initial evidence, it is

possible that polymorphism in the PON1 gene could play a much larger role than CYP2C19 polymorphism in clopidogrel variability. This suggests that PON1 genotyping could potentially be useful together with CYP2C19 genotyping in predicting response to clopidogrel and clinical outcomes. Additional research is needed to clarify the role of PON1 polymorphism in variability in clopidogrel response.

A boxed warning about the diminished effectiveness of clopidogrel in poor metabolizers of the drug appears in the Food and Drug Administration (FDA)-approved labeling.¹² A clinical alert from the American College of Cardiology (ACC) and American Heart Association (AHA) notes that the labeling does not mandate, require, or recommend genetic testing, thereby allowing for flexibility in clinical decisions.¹⁶ Moreover, the evidence base currently is not sufficient to recommend routine genetic or platelet function testing, according to the ACC and AHA clinical alert. There is debate about this conclusion, however, and some health systems are routinely testing all patients receiving clopidogrel. Nevertheless, pharmacists should investigate the availability of assays for genetic and platelet function testing in their institutions and consider the impact of test results on clinical decision making, patient care, and costs. If such tests are used, plans should be made for how the test results will be applied in clinical practice.

Question: Given what we know about platelet function and genetic testing, what do you foresee as possible strategies for optimizing oral antiplatelet therapy in patients with ACS?

A variety of strategies might be used to optimize oral antiplatelet therapy in patients with ACS. The strategies can include increasing the clopidogrel dosage or switching to a more potent P2Y₁₂ inhibitor, and they may or may not include platelet function or genetic testing. Table 1 outlines several possible clinical scenarios and strategies for oral antiplatelet therapy in patients with ACS based on what we have learned from clinical studies. Risk stratification of patients with ACS may be performed to identify patients at high risk for thrombosis in whom a double clopidogrel dose or a more potent antiplatelet agent is warranted, although the risk of bleeding also should be taken into consideration. The increased risk of bleeding must be weighed against the need for greater platelet inhibition in determining when to use prasugrel instead of clopidogrel.

Table 1. Possible Clinical Scenarios and Strategies for Oral Antiplatelet Therapy in Patients with ACS^a

| Scenario | Strategy | Exceptions |
|-----------------|--|---|
| 1 | All patients receive standard-dose clopidogrel | None |
| 2 | Most patients receive double-dose clopidogrel | Patients at high risk of bleeding receive standard-dose clopidogrel |
| 3 | Most patients receive standard-dose clopidogrel | Patients at high risk of thrombosis ^b receive prasugrel (or ticagrelor in the future) |
| 4 | Most patients receive standard-dose clopidogrel | Patients at high risk of thrombosis ^b receive double-dose clopidogrel |
| 5 | Most patients receive prasugrel (or ticagrelor in the future) | Patients at high-risk of bleeding on prasugrel (history of TIA or stroke, age ≥ 75 years old, weight < 60 kg) receive standard-dose clopidogrel Or Patients with potential contraindications or cautions with ticagrelor (asthma, gout, bradycardia, high-dose aspirin?) receive standard-dose clopidogrel. |
| 6 | Patients with “normal” on-treatment platelet reactivity or “normal” CYP2C19 status receive standard-dose clopidogrel | Patients with high on-treatment platelet reactivity or CYP2C19 polymorphism receive predetermined alternative management strategy |

ACS = acute coronary syndrome, STEMI = ST-segment elevation myocardial infarction, TIA = transient ischemic attack

^aThe strategies and exceptions listed in this table are theoretical and have not been validated through clinical trials.

^bPatients with diabetes or STEMI are at high risk for thrombosis.

In the TRITON-TIMI 38 study comparing prasugrel and clopidogrel in patients with ACS undergoing planned PCI, prasugrel was significantly more effective than clopidogrel for reducing the risk of death from cardiovascular causes, nonfatal MI, or nonfatal stroke.^{17,18} The benefit was greatest in patients with diabetes or ST-segment elevation MI, which are known risk factors for thrombosis.¹⁸ However, an increased risk of bleeding was associated with prasugrel use primarily in patients 75 years of age or older, weighing less than 60 kg, or with a history of stroke or transient ischemic attack.¹⁷ For this reason, prasugrel use is contraindicated in patients with a history of stroke or transient ischemic attack, the drug generally is not recommended in patients 75 years of age or older (unless they have diabetes or ST-segment elevation myocardial infarction [STEMI]), and, although it has not been prospectively tested in a clinical trial, a reduced dosage (5 mg once daily instead of 10 mg once daily) should be considered for patients weighing less than 60 kg, according to the FDA-approved labeling.¹⁹

The cost-effectiveness of using prasugrel and emerging antiplatelet therapies with greater potency will be a consideration in selecting a strategy for oral antiplatelet therapy in patients with ACS. Definitive studies demonstrating both positive clinical outcomes and the cost-effectiveness of strategies for using test results to guide antiplatelet therapy in patients with high on-treatment platelet reactivity or a CYP2C19 polymorphism need to be conducted. Platelet function and genetic testing probably will not be used routinely in health systems until after results from such studies become available. The availability of generic forms of clopidogrel in 2012 may increase the use of platelet function and genetic testing, the cost of which will offset some of the savings in drug cost.

Question: What new oral antiplatelet therapies for the treatment of ACS might become available in the near future?

The thienopyridines clopidogrel and prasugrel are adenosine diphosphate P2Y₁₂ receptor antagonists. Ticagrelor, a reversible oral non-thienopyridine with a greater potency and a more rapid onset of antiplatelet effect than clopidogrel, currently is under investigation for FDA approval.²⁰ In the pivotal multicenter, randomized, double-blind, Platelet Inhibition and Patient Outcomes (PLATO) study, ticagrelor 180 mg followed by 90 mg twice daily was significantly more effective than clopidogrel 300-600 mg followed by 75 mg/day for reducing the risk of cardiovascular death, MI, and stroke (the primary end point) in more than 18,000 patients with ACS with or without ST-segment elevation.²¹ At the end of 12 months the primary endpoint was significantly reduced by 16% with the use of ticagrelor compared with clopidogrel (9.8% vs. 11.7%). There was no significant difference between the two treatments in the incidence of total major bleeding, but the risk of major bleeding not related to coronary artery bypass graft (CABG) surgery (e.g., fatal intracranial bleeding) was significantly higher in the ticagrelor group (4.5%) than in the clopidogrel group (3.8%).

FDA declined to approve ticagrelor in December 2010, presumably because of a lack of demonstrated benefit in a subset of 1413 PLATO participants in the United States.²² These findings may reflect the use of large aspirin dosages in the United States, other differences between U.S. and non-U.S. patient populations, other confounding variables, or chance.^{23,24} The agency requested additional analyses of data from the PLATO study, and these data were submitted to the agency in early February 2011. A decision about approval of the drug is expected from FDA in July 2011.²⁵

Additional antiplatelet agents that target novel receptors are also in development. Existing antiplatelet agents target one of several pathways for platelet activation or aggregation that lead to thrombosis. Inhibition of the protease activated receptor-1 (PAR-1) for thrombin has been shown to inhibit thrombin-mediated platelet activation.²⁶ Thrombin is one of the most potent activator of platelets, and inhibition of thrombin's action on platelets holds the promise of increased efficacy when used with existing agents. Furthermore, inhibition of thrombin at the PAR-1 receptor also may allow for increased efficacy without an increased risk of bleeding. This positive risk-benefit profile may be possible as thrombin is not integral to the initial functions of platelets in hemostasis (platelet adhesion, formation of a platelet plug). Rather, thrombin is key in the later steps of large-scale activation and aggregation. Inhibition of the PAR-1 receptor may then allow for key steps to occur in vascular hemostasis but interrupt the process of pathologic thrombus formation.

Vorapaxar, a selective oral PAR-1 inhibitor that targets thrombin-induced platelet activation, has been the subject of a primary prevention study known as TRACER involving approximately 13,000 patients with NSTEMI ACS and a secondary prevention study known as TRA-2P (or TIMI 50) with approximately 26,500 patients with a history of MI, ischemic stroke, or peripheral vascular disease.²⁷ The TRACER study has been discontinued, and participants in TRA-2P with a history of stroke will discontinue vorapaxar because the drug was shown to increase the risk of intracranial hemorrhage in patients with a history of stroke.²⁸

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Share Your Ideas

After participating in this educational initiative, have you come up with a unique approach to optimizing oral antiplatelet therapy at your institution that might be helpful to your colleagues? Share your ideas for how to incorporate into practice the concepts learned through this initiative. Send your ideas by e-mail to support@ashpadvantage.com (put "Optimize ACS" in the subject line).



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For complete information about educational activities that are part of this initiative, visit www.ashpadvantage.com/optimize. There is no charge for the activities, and ASHP membership is not required.

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