

# ANTIPLATELET THERAPY FOR ACUTE CORONARY SYNDROMES

## Current Issues and Controversies



## Updates in Cardiology for Nurse Practitioners and Physician Assistants

Volume 1, Number 2



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#### Target Audience

Nurse practitioners (NPs) and physician assistants (PAs) specializing in cardiology.

#### Activity Goal

To familiarize NPs and PAs in cardiology practices with current issues and controversies in the use of antiplatelet therapies for the secondary prevention of ischemic events in patients with acute coronary syndromes (ACS), including drug resistance, drug interactions, optimal dosing and duration of treatment, and bleeding risks.

#### Learning Objectives

After completing this activity, participants should be better able to:

- Explain the possible mechanisms of resistance to aspirin and clopidogrel based on current clinical evidence.
- Define the drug interactions with aspirin and clopidogrel that may attenuate their effectiveness for preventing ischemic events.
- Differentiate the bleeding risks associated with aspirin, clopidogrel, and prasugrel.
- Formulate treatment plans for secondary prevention of ACS events based on current guidelines on the optimal dosing and duration for antiplatelet therapy.

#### Accreditation Information

The University of Nebraska Medical Center College of Nursing Continuing Nursing Education is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity is provided for 1.0 contact hour under ANCC criteria.

Provided for 1.2 contact hours under Iowa Provider #78. Provider approved by the California Board

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This program has been reviewed and is approved for a maximum of 1.0 hour of AAPA Category I CME credit by the Physician Assistant Review Panel.

Approval is valid for one year from the issue date of August 23, 2010. Participants may submit the self-assessment at any time during that period.

This program was planned in accordance with AAPA's CME Standards for Enduring Material Programs and for Commercial Support of Enduring Material Programs.

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The estimated time to complete this activity is 1 hour.

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*Acute coronary syndromes (ACS)* is an umbrella term that includes both acute myocardial infarction (MI) and unstable angina (UA).

Although the treatment of ACS has improved dramatically over the last 3 decades, it continues to be a significant contributor to morbidity and mortality. ACS is responsible for ~1.4 million hospitalizations (~730,000 primary and ~630,000 secondary) annually in the United States.<sup>1</sup> An estimated 18% of men and 23% of women ≥40 years of age die within 1 year of their first MI.<sup>1</sup> In addition, ACS is associated with a significant healthcare burden. The total healthcare utilization cost during the first year of new-onset ACS is a staggering \$309 million, 72% of which is attributable to hospitalizations.<sup>2</sup> The high rates of reinfarction and mortality as well as the high healthcare cost associated with ACS hospitalization make it a major public health concern that necessitates increased efforts to prevent recurrent events and improve patient outcomes.

Antiplatelet agents are a cornerstone of ACS management. Current guidelines recommend dual antiplatelet therapy for secondary prevention of ACS.<sup>3-6</sup> The optimal duration of treatment, optimal dosing regimen, drug resistance, drug-drug interactions, and bleeding risks associated with antiplatelet agents, however, have not been clearly defined.

This issue of *Antiplatelet Therapy for Acute Coronary Syndromes* reviews current issues and controversies surrounding the use of antiplatelet therapy for the management of ACS. Case-based expert commentary on practical clinical considerations is provided by Mori J. Krantz, MD, FACC, FACP, and Julie A. Davey, MSN, RN, APRN, BC.

### Antiplatelet Therapy for Secondary Prevention of ACS

Platelet activation and aggregation play important roles in the pathogenesis of cardiac ischemic events after spontaneous plaque disruption in ACS or mechanical disruption of coronary artery plaques caused by percutaneous coronary intervention (PCI), a focal intervention for

stabilization of the ruptured plaque.<sup>7,8</sup> The use of coronary stents has resulted in a reduced need for recurrent target vessel revascularization but has increased the risk of acute and subacute thrombosis of the instrumented vessel.<sup>9</sup> Thus, systemic antiplatelet therapy is essential for inhibiting the atherothrombotic process to reduce the risk of secondary thrombotic events. Aggressive implementation of dual antiplatelet therapy has significantly decreased rates of adverse cardiovascular (CV) events, such as death, MI, stroke, in-stent thrombosis, and repeat revascularization in patients with ACS.<sup>3-5</sup>

### Optimal Duration of Therapy

The combination of aspirin and a thienopyridine (clopidogrel or prasugrel) is currently the standard of care for secondary prevention of ACS. Evidence-based management guidelines recommend aspirin in all patients with ACS who do not have a contraindication to its use and clopidogrel as an alternative to or in conjunction with aspirin in a large subset of patients with ACS.<sup>3-5</sup> It is not recommended for primary prevention of ACS. (See *Primary Prevention With*

*Aspirin?* page 3) Generally, full-dose aspirin (325 mg/d) is used in the United States during the peri-MI period, followed by lifelong, low-dose (81-165 mg/d) therapy. In patients with ST-segment elevation MI (STEMI) for whom PCI is planned, the American College of Cardiology (ACC)/American Heart Association (AHA) 2009 Joint STEMI/PCI Focused Updates recommend the use of clopidogrel or prasugrel in combination with aspirin.<sup>6</sup>

Despite widespread use of dual antiplatelet therapy, the optimal duration of use is unknown. While low-dose aspirin is recommended indefinitely for patients with ACS without contraindications to its use, clopidogrel<sup>3-6</sup> and prasugrel<sup>6</sup> are recommended for use *ideally for at least 1 year* after intracoronary stent implantation, irrespective of the type of stent (bare metal stent [BMS] or drug-eluting stent [DES]).

Long-term dual antiplatelet therapy appears to be particularly important for reducing the risk of stent thrombosis, MI, and death in patients who have undergone stent implantation. However, there is little clinical evidence recommending dual antiplatelet therapy beyond 1 year. Based on the results of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38), which evaluated prasugrel and clopidogrel for up to 15 months,<sup>12</sup> the ACC/AHA 2009 Joint STEMI/PCI Focused Updates state that clopidogrel or prasugrel *may be considered* beyond 15 months in patients who have received DES implantation.<sup>6</sup> Although the benefits of clopidogrel and prasugrel are likely to continue with longer duration of treatment, data from randomized controlled trials supporting use of clopidogrel or prasugrel beyond 1 year in patients with

## Primary Prevention With Aspirin?

The clinical efficacy of aspirin in reducing risk of serious vascular events (nonfatal MI, nonfatal stroke, or vascular death) in patients who have had occlusive vascular disease is well established. However, the benefits of aspirin for primary prevention have not been clearly demonstrated.<sup>10</sup>

A recent meta-analysis of 6 primary prevention trials of aspirin comprising 95,000 individuals at low average risk reported<sup>11</sup>:

- A 12% proportional reduction in serious vascular events with aspirin vs control (0.51% vs 0.57% control per year,  $P = .0001$ )
- No net effect on stroke reduction with aspirin vs control (0.20% vs 0.21% per year,  $P = .4$ : hemorrhagic stroke 0.04% vs 0.03%,  $P = .05$ ; other stroke 0.16% vs 0.18% per year,  $P = .08$ )
- No significant difference in vascular mortality between aspirin and control (0.19% vs 0.19% per year,  $P = .7$ )

The cardioprotective benefits of aspirin were offset by significantly increased major GI and extracranial bleeds (0.10% vs 0.07% per year, aspirin vs control;  $P < .0001$ ). Thus, the administration of aspirin for primary prevention is of uncertain net value as the reduction in occlusive events needs to be weighed against any increase in major bleeds.<sup>11</sup>

In the absence of conclusive evidence, universal prescription of aspirin for primary prevention in adults may be unnecessary, and care should be individualized taking into account bleeding and CV disease risk. Clinicians need to emphasize the importance of proven CV disease risk-reduction strategies to their at-risk patients, such as blood pressure and low-density lipoprotein cholesterol control, for risk reduction.<sup>10</sup>

DES are limited. A recent analysis of combined data from 2 randomized trials failed to show a significant reduction in ischemic events from longer term clopidogrel therapy in patients with DES, despite the well-established risk of *very late* (>12 months) in-stent thrombosis associated with DES implantation.<sup>13</sup>

Some clinicians, however, suggest continuing dual antiplatelet therapy, even indefinitely, if the patient has no severe side effects, because there is no evidence indicating the risk of stent thrombosis terminates at 12 months after stent implantation.<sup>14</sup> To determine the optimal duration of long-term dual antiplatelet therapy (aspirin plus a second antiplatelet agent) and assess the safety and effective-

ness of dual antiplatelet therapy after DES implantation, a large-scale, collaborative, double-blind, randomized, controlled, clinical trial, the Dual Antiplatelet Therapy (DAPT) Study, is underway.<sup>15</sup>

Another consideration regarding optimal duration of antiplatelet therapy is the possibility of a rebound effect after clopidogrel treatment is stopped. A retrospective cohort study of patients with ACS ( $N = 3137$ ) discharged on clopidogrel therapy reported a significantly higher rate of all-cause mortality or acute MI during the first 90 days (vs 91-180 days) after stopping clopidogrel.<sup>16</sup> This effect was seen among all subpopulations studied—patients who received shorter or longer courses of clopidogrel treat-

ment, patients with or without diabetes, medically treated patients, and PCI-treated patients, especially those who had BMS implantation (Table 1).

Until data from DAPT become available, clinicians need to rely on their judgment and preferences and their patients' preferences when deciding whether to continue dual antiplatelet therapy beyond the current guideline recommendations.

## Optimal Doses Aspirin

Doses of aspirin used for secondary prevention vary, typically ranging from 75 to 1500 mg/d. The 2002 Antiplatelet Trialists' Collaboration meta-analysis of randomized trials of antiplatelet regimens in high-risk patients showed the proportional reduction in risk appears to be similar with aspirin doses of 75 to 150 mg, 160 to 325 mg, and 500 to 1500 mg.<sup>17</sup> Most guidelines recommend aspirin doses between 162 and 325 mg/d (high dose) at the time of an index event and 1 to 6 months after stent placement, followed by 75 to 162 mg/d (low dose) indefinitely for secondary prevention.<sup>3-5</sup> However, the comparative efficacy and safety of low-dose versus high-dose aspirin has not been fully elucidated in the context of dual antiplatelet therapy.

A subgroup analysis of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, showed that the addition of increasing doses of aspirin ( $\leq 100$  mg, 101-199 mg, and  $\geq 200$  mg) to clopidogrel did not result in increased efficacy (combined incidence of CV death, MI, or stroke), but did increase the risk of major bleeding.<sup>18</sup> In addition, a pooled analysis of more than 20,000 patients with UA or acute MI from the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb and Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor

Suppression Using Integrelin Therapy (PURSUIT) trials reported no difference in the incidence of death but, potentially, less frequent MI and more frequent stroke among patients discharged while receiving higher aspirin doses ( $\geq 150$  mg), compared with patients receiving lower aspirin doses ( $< 150$  mg) (Figure 1).<sup>19</sup>

## Clopidogrel

The optimal loading dose of clopidogrel has not been established. Although results of clinical trials evaluating clopidogrel loading doses greater than 300 mg have been generally favorable,<sup>20-22</sup> data have been insufficient for guidelines to make definite dose recommendations. The ACC/AHA STEMI/PCI Focused Updates recommend a clopidogrel loading dose of at least 300 to 600 mg.<sup>6</sup>

Questions regarding optimal aspirin and clopidogrel dosing were addressed by the recently completed Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events—Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS) 7 trial. This trial compared a high-dose clopidogrel regi-

men (600-mg loading dose on day 1, followed by 150 mg once daily on days 2 to 7, followed by 75 mg once daily on days 8-30) with a standard clopidogrel dosing regimen (300-mg loading dose on day 1, followed by 75 mg once daily on days 2-30) in patients with ACS managed with an early invasive strategy.<sup>23</sup> CURRENT-OASIS 7 also evaluated high-dose (300-325 mg/d) versus low-dose (75-100 mg/d) aspirin administered for 29 days following a 300-mg or greater dose on day 1. The primary efficacy outcome was death from CV causes, MI, or stroke up to day 30 (composite end point). The primary safety outcome was major bleeding, defined as severe bleeding plus other major bleeding at day 30.

Overall, higher-dose clopidogrel had no significant effect on outcomes versus standard clopidogrel dosing.<sup>24</sup> In the subgroup of patients undergoing PCI, there was a 15% statistically significant reduction in the primary composite end point of death from CV causes, MI, or stroke with high-dose clopidogrel, compared with the standard dose. A 42% relative risk reduction (RRR) in stent thrombosis

among patients who received the high dose also was seen.

The improved efficacy was partially offset by the increased bleeding risk observed with the higher-dose clopidogrel regimen. Rates of major and severe bleeding were significantly higher in patients receiving high-dose versus low-dose clopidogrel (major bleeding: 1.6% vs 1.1%,  $P = .006$ ; severe bleeding: 1.1% vs 0.8%,  $P = .034$ ). The higher bleeding rates, however, were not associated with an increase in intracerebral hemorrhage or fatal bleeds. Using high-dose versus low-dose aspirin did not appear to influence safety or efficacy. The lowest rates of primary composite outcome and stent thrombosis were observed among those patients randomized to the high-dose aspirin and high-dose clopidogrel treatment arm.<sup>24</sup>

Although this trial established a potential role for high-dose clopidogrel in ACS patients receiving PCI, it did not answer the question of an optimal dose for aspirin since there were no differences in outcome by dose. Given that higher doses of aspirin are associated with an increased risk of bleeding without clinical benefit, it would be judicious to use lower doses of aspirin for secondary prevention.

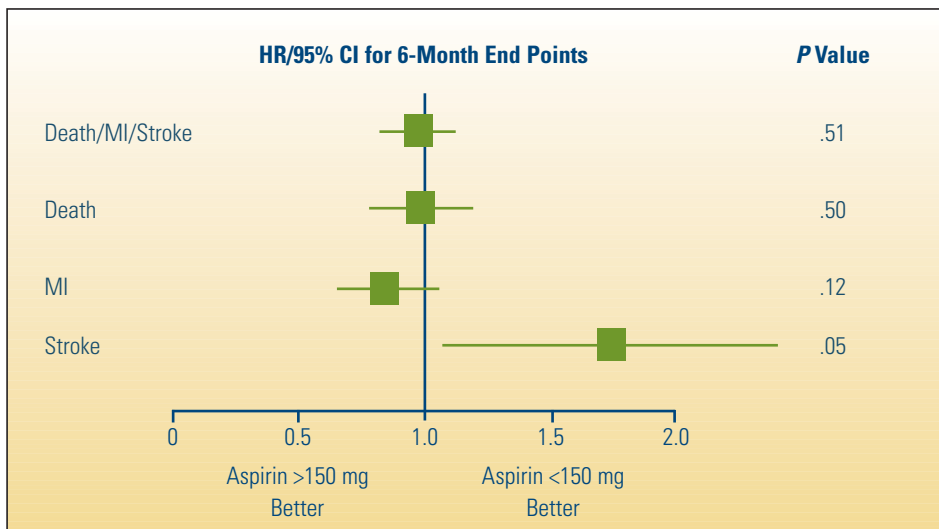
**Table 1. Death or Acute MI After Stopping Clopidogrel<sup>a</sup>**

Group	Patients (n)	Adjusted Incidence Rate Ratio (95% CI)
Medically treated	1568	1.98 (1.46-2.69)
Clopidogrel $\leq 90$ d	312	2.13 (1.36-3.32)
Clopidogrel $\leq 180$ d	530	2.20 (1.49-3.26)
Clopidogrel $\leq 270$ d	751	2.00 (1.41-2.85)
Clopidogrel $> 270$ d	817	1.79 (0.96-3.34)
Diabetes	376	2.37 (1.34-4.19)
No diabetes	1192	1.75 (1.22-2.52)
Acute MI outcome only	158	2.39 (1.50-3.82)
Treated with PCI	1568	1.82 (1.17-2.83)
BMS	984	2.14 (1.23-3.74)

<sup>a</sup>Multivariate analysis comparing periods of 0 to 90 days with 91 to 180 days after stopping treatment. With permission from Ho PM, et al. Copyright © 2008 American Medical Association. All rights reserved.<sup>16</sup>

## Prasugrel

Based on the results of TRITON-TIMI 38, a loading dose of 60 mg is recommended for patients undergoing PCI.<sup>6,12</sup> A daily dose of 10 mg is recommended when prasugrel is used with aspirin for long-term dual antiplatelet therapy.<sup>6</sup> According to the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation (PRINCIPLE)—TIMI 44 trial, both the 60-mg loading dose and the 10-mg maintenance dose of prasugrel produce greater platelet inhibition than a higher-than-standard-dose regimen (600-mg loading dose and 150-mg



**Figure 1. Aspirin dose did not impact the postdischarge 6-month composite outcome (death, nonfatal MI, or stroke) in patients with UA or acute MI from the GUSTO IIb and PURSUIT trials; however, an increased risk of stroke was seen with the higher aspirin dose.** (HRs are for the matched propensity analysis used to adjust for baseline imbalances.) CI = confidence interval. Reprinted from Quinn MJ, et al, Copyright 2004, with permission from Elsevier.<sup>19</sup>

maintenance dose) of clopidogrel, but this trial was not powered to study clinical end points.<sup>25</sup> A 5-mg maintenance dose of prasugrel is suggested for patients with a body weight <60 kg, in whom the risk of prasugrel-related bleeding is increased, but the effectiveness and safety of this dose has not been established.<sup>6</sup>

### Resistance to Antiplatelet Agents Aspirin

Despite the proven efficacy of aspirin in reducing vascular events, 10% to 20% of patients have recurrent vascular events within 5 years of the initial event.<sup>26</sup> These patients have been labeled *aspirin-resistant* or *aspirin nonresponders*, but a proportion of these patients actually represents cases of treatment failure. Aspirin blocks the synthesis of only 1 platelet agonist (thromboxane A<sub>2</sub> [TXA<sub>2</sub>]), leaving other mediators of platelet activation—including adenosine diphosphate, thrombin, and collagen—unaltered and continuing to activate platelets. Consequently, not all vascular events are preventable with aspirin. For this reason, dual antiplatelet therapy is recommended for secondary prevention of ACS.

Some patients, however, require a higher dose of aspirin than what is normally recommended to achieve the expected antiplatelet effect, as measured by inhibition of platelet function or inhibition of platelet TXA<sub>2</sub> synthesis.<sup>27-29</sup> These patients exhibit aspirin resistance in that their platelets are not affected in the same way or are affected differently from the platelets of patients who seem to benefit from aspirin therapy (ie, aspirin-sensitive patients).<sup>30</sup> Two meta-analyses have shown an association between laboratory-measured aspirin resistance and a higher risk of recurrent CV events.<sup>30,31</sup> In both studies, about 30% of patients were labeled as aspirin-resistant based on laboratory tests. Regardless of the laboratory assay used for classification, patients who were aspirin-resistant (compared with those who were aspirin-sensitive) had about a 4-fold increased risk of nonfatal and fatal CV, cerebrovascular, or vascular events while taking aspirin.<sup>30,31</sup>

However, these meta-analyses have important limitations, including: variability in the incidence of aspirin resistance (ranging between 5%-65%, depending on

the assay used and other variables); small sample sizes (n = 14-488); low number of adverse clinical events, which limited the statistical power of the studies; occurrence of noncompliance as a confounding variable; and possibility of reporting bias for studies with positive outcomes.<sup>32</sup>

Confounding the issue of aspirin resistance further is the possibility that aspirin resistance may, in part, be unrelated to aspirin but may rather result from underlying platelet hyper-reactivity that is present before the initiation of aspirin therapy.<sup>33</sup> In addition, other causes of aspirin resistance have been identified including: drug interactions; underdosing; poor absorption; accelerated platelet turnover with introduction into the bloodstream of newly formed, drug-unaffected platelets; stress-induced generation of cyclooxygenase (COX)-2 in platelets; single nucleotide polymorphisms in COX-1 and/or other molecules; and bypass of platelet COX-1 by endothelial cell or monocyte COX-1 and/or inducible COX-2.<sup>34,35</sup> Thus, both the mechanism(s) and clinical relevance of aspirin resistance, as defined by platelet aggregation measurements, remain to be established.

### Clopidogrel

Approximately 15% to 25% of patients treated with clopidogrel do not achieve adequate levels of platelet inhibition and are classified as clopidogrel-resistant.<sup>36</sup> Clopidogrel resistance may be attributed to gene polymorphisms of the liver enzyme *CYP2C19* or drug-drug interactions (see *Drug Interactions*, page 6).<sup>37,38</sup>

Clopidogrel is a prodrug that needs to be metabolized to its active form in the liver. Metabolism occurs via the *CYP2C19* or *CYP3A* enzymes.<sup>39</sup> Genetic polymorphisms of *CYP2C19* modulate clopidogrel pharmacokinetics and pharmacodynamics.<sup>37</sup> Compared with persons

with no *CYP2C19* variant allele, persons carrying 1 or 2 *CYP2C19* loss-of-function alleles have been shown to have lower plasma concentrations of the active metabolite of clopidogrel and a decrease in the antiplatelet effect of clopidogrel in ex vivo aggregation tests.<sup>37</sup>

There are several known loss-of-function alleles of *CYP2C19*—\*2, \*3, \*4, \*5, \*6, \*7, and \*8. The *CYP2C19*\*2 and \*3 alleles have no functional metabolism of clopidogrel. These 2 alleles account for most of the reduced-function alleles in patients of Caucasian (85%) and Asian (99%) descent classified as poor metabolizers. A patient with 2 loss-of-function alleles will have poor metabolizer status. An estimated 2% to 14% of the popula-

tion are poor metabolizers, depending on their racial background.<sup>40</sup> Patients with ACS who are carrying the *CYP2C19* loss-of-function alleles and receiving clopidogrel have been shown to have a higher rate of subsequent CV events (death from any cause, nonfatal stroke, or MI) than those who do not carry the defective alleles.<sup>39,41,42</sup>

In March 2010, the US Food and Drug Administration (FDA) issued a boxed warning about the reduced effectiveness of clopidogrel in patients who are poor metabolizers of clopidogrel. The FDA informed healthcare professionals that tests are available to identify genetic differences in *CYP2C19* function and they should consider the use of other antiplatelet medica-

tions or alternative dosing strategies for clopidogrel in patients identified as poor metabolizers.<sup>40</sup> In June 2010, the ACC and AHA issued a clinical alert on the reduced effectiveness of clopidogrel in poor metabolizers with recommendations for practice (Table 2).<sup>43</sup> At present, routine genetic polymorphism and platelet function testing are not recommended, given the lack of data indicating that this strategy improves clinical outcomes.

## Drug Interactions Aspirin With NSAIDs

The effects of aspirin are attenuated when administered concomitantly with traditional NSAIDs, such as ibuprofen and naproxen, and this interaction contributes to aspirin resistance. Ibuprofen and naproxen interfere with aspirin's irreversible inactivation of platelet COX-1 by competing for a common docking site within the COX channel (arginine-120) to which aspirin binds with weak affinity before irreversible acetylation of serine-529.<sup>44</sup> The FDA has issued a statement that ibuprofen (400 mg) can interfere with the antiplatelet effect of low-dose aspirin (81 mg/d), potentially rendering aspirin less effective when used for secondary prevention of MI and stroke.<sup>45</sup> Healthcare professionals and patients should be aware of this interaction between aspirin and ibuprofen that leads to reduced effectiveness, which is beyond a greater propensity for gastrointestinal (GI) bleeding.

## Clopidogrel With PPIs

In patients receiving antiplatelet therapy, proton pump inhibitors (PPIs) commonly are used for GI bleeding prophylaxis.<sup>3,46</sup> Because PPIs are metabolized via the *CYP2C19* or *CYP3A* enzymes in the liver, there is a concern that PPIs may reduce clopidogrel's antiplatelet effects when PPIs are coadministered with clopidogrel.<sup>47,48</sup> In patients with

**Table 2. Reduced Effectiveness of Clopidogrel in Poor Metabolizers: ACC/AHA Recommendations for Practice**

1. Adherence to ACC/AHA guidelines on antiplatelet therapy remain the foundation for therapy; careful clinical judgment is required to assess clopidogrel response variability for an individual patient
2. Clinicians must be aware that genetic variability in CYP enzymes can alter clopidogrel metabolism and its inhibition of platelet function
3. The specific impact of genetic polymorphisms on clinical outcome remains to be determined
4. Information on the predictive value of pharmacogenomic testing is limited; issues of specific test selection and reimbursement must be considered
5. Routine genetic or platelet function testing is not presently recommended because of insufficient evidence. Before initiating clopidogrel therapy, clinicians may consider genetic testing to determine whether a patient is predisposed to poor clopidogrel metabolism if the risk of a poor outcome is moderate or high
6. Therapeutic alternatives for patients who experience an adverse event while taking clopidogrel (in the absence of medication compliance issues) include:
  - Switching to prasugrel
  - Increasing the dose of clopidogrel (eg, to 150 mg/d)
  - Considering functional testing of platelets
7. Alternatives for high-risk patients who respond poorly to standard loading and maintenance doses of clopidogrel include:
  - Increasing clopidogrel loading dose (to 600 mg or 600 mg twice over 2 h)
  - Increasing maintenance dose of clopidogrel to 150 mg/d
  - Switching to prasugrel
  - Adding cilostazol to standard doses of aspirin and clopidogrel<sup>a</sup>
  - Using cilostazol alone<sup>a</sup>

*NOTE:* the risk-benefit ratios for safety and efficacy for each of these strategies remains to be determined.

<sup>a</sup>Follow-up platelet function testing might be considered to ensure adequate platelet inhibition. Holmes Jr DR, et al.<sup>43</sup>

ACS, concomitant use of PPIs and clopidogrel has been reported to increase the risk of adverse outcomes (all-cause mortality, rehospitalization for ACS, or reinfarction) compared with those who did not take PPIs.<sup>38,49</sup>

Late in 2009, the FDA issued a warning stating that patients who take clopidogrel should avoid using the PPI omeprazole because it reduces the antiplatelet activity of clopidogrel by about 50%.<sup>50</sup> However, conflicting results from several recent studies have provoked dissension in opinion regarding the clinical significance of the potential clopidogrel and PPI interaction on CV outcomes.

A recent analysis of the 2 randomized trials, TRITON-TIMI 38 and PRINCIPLE-TIMI 44, assessed the association between PPI use and measures of platelet function and clinical outcomes in patients treated with clopidogrel or prasugrel.<sup>51</sup> The analysis revealed no association between PPI use and risk of CV death, MI, or stroke. The authors concluded that current data do not support the need to avoid the concomitant use of PPIs in patients receiving clopidogrel or prasugrel.

Only 1 randomized controlled trial has compared the PPI omeprazole with placebo in patients receiving clopidogrel. The Clopidogrel and the Optimization of Gastrointestinal Events (COGENT) trial reported no difference in risk of CV events or MI between the treatment groups. However, rates of GI-related events were reduced in the combination therapy group.<sup>52</sup>

A study using data from the Guthrie PCI registry found no increased risk of CV outcomes in patients taking concomitant PPI and dual antiplatelet therapy (clopidogrel and aspirin) after PCI.<sup>53</sup> Among patients taking omeprazole or esomeprazole with dual antiplatelet therapy, use of either of the PPIs was associated with sta-

tistically similar rates of major adverse CV events compared with no PPI use.<sup>53</sup>

A retrospective cohort study of ~21,500 patients hospitalized for MI, coronary artery revascularization, or UA reported a lower incidence of hospitalization in concurrent clopidogrel and PPI users and no increase in the incidence of serious CV events.<sup>54</sup> The adjusted incidence of hospitalization for gastroduodenal bleeding in concurrent clopidogrel and PPI users was 50% lower than in nonusers (hazard ratio [HR] 0.50 [95% confidence interval (CI), 0.39-0.65]). The HR associated with concurrent PPI use for risk for serious CV disease was 0.99 (CI, 0.82-1.19). Among concurrent PPI users, pantoprazole and omeprazole accounted for 62% and 9% of PPI use, respectively.<sup>54</sup>

In contrast to these studies, a recent retrospective cohort study of patients enrolled in a multistate insurance plan reported that patients who were discharged from the hospital after MI or coronary stent placement and treated with

clopidogrel plus a PPI had a 93% higher risk of rehospitalization for MI ( $P = .03$ ) and a 64% higher risk of rehospitalization for MI or coronary stent placement ( $P = .005$ ) than patients receiving clopidogrel alone. An increased risk of rehospitalization for MI or coronary stent placement also was observed in the subgroup of patients receiving clopidogrel plus pantoprazole ( $P = .008$ ).<sup>55</sup> Similarly, a retrospective study that followed patients for 1 year after stent placement for index hospitalization for acute MI also reported higher rates of readmission for acute MI in patients discharged on clopidogrel and a PPI than in patients discharged on clopidogrel alone.<sup>56</sup> In aggregate, the impact of PPIs on CV disease event rates in the setting of dual antiplatelet therapy remains a subject of uncertainty.

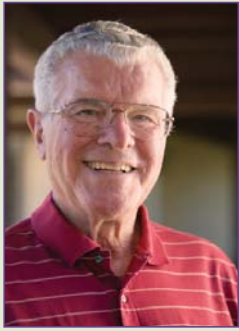
### Bleeding Risks With Antiplatelet Agents

Management of ACS through the use of combined pharmacotherapies and invasive

**Table 3. Prasugrel Versus Clopidogrel in Patients With Moderate- to High-Risk ACS: Efficacy and Safety Outcomes From TRITON-TIMI 38**

Efficacy Outcomes	Prasugrel (n = 6813)	Clopidogrel (n = 6795)	HR for Prasugrel (95% CI)	P Value
Death from CV causes, nonfatal MI, or nonfatal stroke, n (%)	643 (9.9)	781 (12.1)	0.81 (0.73-0.90)	<.001
Death from CV causes, n (%)	133 (2.1)	150 (2.4)	0.89 (0.70-1.12)	.31
Nonfatal MI, n (%)	475 (7.3)	620 (9.5)	0.76 (0.67-0.85)	<.001
Nonfatal stroke, n (%)	61 (1.0)	60 (1.0)	1.02 (0.71-1.45)	.93
Safety Outcomes	Prasugrel (n = 6741)	Clopidogrel (n = 6716)	HR for Prasugrel (95% CI)	P Value
Non-CABG-related TIMI major bleeding	146 (2.4)	111 (1.8)	1.32 (1.03-1.68)	.03
Life-threatening bleeding	85 (1.4)	56 (0.9)	1.52 (1.08-2.13)	.01
Fatal bleeding	21 (0.4)	5 (0.1)	4.19 (1.58-11.11)	.002
Nonfatal bleeding	64 (1.1)	51 (0.9)	1.25 (0.87-1.81)	.23

HR = hazard ratio. Wiviott SD, et al.<sup>12</sup>



## CASE: 80-Year-Old Man With ACS Managed With PCI

An 80-year-old man presents for a post-discharge follow-up. He was hospitalized 2 weeks earlier after presenting to the emergency department with complaints

of chest pressure. His medical history is significant for coronary artery disease (CAD), hypertension, and hyperlipidemia. Six months ago he had undergone BMS placement to the right coronary artery (RCA) for treatment of UA. He had received clopidogrel plus aspirin for 1 month post-PCI. During his recent hospitalization, he underwent cardiac catheterization, which demonstrated a patent stent in the RCA and a focal 40% stenosis of the left anterior descending artery as well as luminal irregularities in the circumflex artery. He did not require repeat PCI and was managed medically. He is feeling well and denies chest discomfort, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, palpitations, and/or syncope.

### Physical Findings

- General appearance: well developed, well nourished; no acute distress
- Blood pressure: 130/75 mm Hg; pulse: 88 beats/min; respirations: 12 breaths/min; afebrile
- Neck: no carotid bruits or jugular venous distention; carotid upstroke brisk, 2+ bilaterally

procedures has led to significant improvements in outcomes, but also to an increased risk of bleeding. This increased bleeding risk is seen with all currently available antiplatelet agents, and the risk increases with combination therapy. A meta-analysis of 18 randomized trials comprising 129,000 patients that compared the bleeding risks of combination versus single antiplatelet therapy reported an approximate 40% to 50% increase in risk of major and minor bleeding in patients treated with combination therapy.<sup>57</sup>

### Clopidogrel

Data from the CURE trial showed a 20% RRR in the incidence of major ischemic

events in patients with ACS without ST-segment elevation who were treated with clopidogrel plus aspirin compared with aspirin alone, with an absolute risk reduction of 2.1% (11.4% to 9.3%). But the combination of clopidogrel and aspirin also led to a 1% absolute risk increase in major or life-threatening bleeds.<sup>58</sup>

### Prasugrel

In patients with ACS, prasugrel was more effective than clopidogrel in preventing CV death, MI, and stroke; however, major bleeding rates were higher in the prasugrel group (Table 3).<sup>12</sup> Although prasugrel has been shown to be more effective than clopidogrel in preventing ischemic events

- Lungs: clear to auscultation bilaterally; no adventitious breath sounds
- Heart: regular rate and rhythm; S<sub>1</sub> and S<sub>2</sub> appreciated; no murmur, rub, gallop
- Peripheral vasculature: no edema noted; peripheral pulses 2+ throughout
- Abdomen: soft, nondistended, nontender; bowel sounds present throughout; no organomegaly or palpable masses noted
- Neurologic findings: alert and oriented; no focal deficits noted

### Current Medications

- Lisinopril 10 mg/d
- Simvastatin 40 mg/d
- Aspirin 81 mg/d
- Metoprolol 25 mg twice daily
- Omeprazole 20 mg/d

*For an expert opinion, read the following Case Commentary by Mori J. Krantz, MD, FACC, FACP, and Julie A. Davey, MSN, RN, APRN, BC.*

### Commentary

MJK: An important consideration in this case is the notion that patients with BMS require only 30 days of adenosine diphosphate receptor-antagonist therapy postprocedure. Clinicians should be aware that this recommendation applies primarily to patients with stable angina treated with elective PCI to prevent postprocedure in-stent thrombosis. This patient, however, presented initially with ACS and therefore

in patients with STEMI undergoing primary PCI (with or without stents), the rate of serious bleeding in patients requiring emergency coronary artery bypass grafting (CABG) was higher in the prasugrel group.<sup>59</sup> Thus, prasugrel is contraindicated in patients with active pathologic bleeding. It also is contraindicated in patients with a history of transient ischemic attack (TIA) or stroke and in patients age  $\geq 75$  years unless they are at high risk of a recurrent event (eg, because of diabetes or other risk factors).<sup>60</sup>

### Balancing Risks and Benefits

Increased bleeding is consistently related to adverse outcomes in patients with

should receive 1 year of dual antiplatelet therapy. The ACC/AHA guidelines make no distinction between UA and acute MI with regard to duration of dual antiplatelet therapy after hospitalization for ACS. Although patients with elevated cardiac biomarkers are at higher risk, especially those with STEMI, all ACS patients should optimally receive dual antiplatelet therapy for at least 1 year.

**JAD:** This patient has established CAD that required percutaneous intervention. Aggressive medical management is warranted for this patient to prevent future ischemic events. The prevalence of ACS and its impact on morbidity, mortality, and healthcare costs worldwide make it a true public health issue. As healthcare providers, nurse practitioners (NPs) and physician assistants (PAs) play a crucial role in the treatment of ACS patients. It is our responsibility to ensure that patients are receiving the appropriate care based on current evidence. We must keep abreast of the evolving literature and clinical practice guidelines to achieve this goal. While the optimal antiplatelet regimen and dosing of antiplatelet agents is not “black and white,” the use of these agents is clearly of great importance in the prevention of secondary CV events. NPs and PAs should treat each patient on a case-by-case basis, balancing the risk of bleeding with the benefit of ischemic prevention.

The occurrence of resistance to antiplatelet agents sheds some light on the treatment failure and recurrent events we witness in clinical practice. This emerging body of evidence may soon change practice guidelines and allow an individual’s medication regimen to be tailored to their unique genetic profile.

ACS and those undergoing PCI.<sup>61,62</sup> In 1 meta-analysis, major bleeding conferred a 5-fold higher risk of death within 30 days of an ACS event.

Certain patient characteristics (advanced age, higher serum creatinine, prior stroke, renal insufficiency) have been associated with increased risk of bleeding. A further increased risk of major bleeding exists for PCI patients who are older, female, hypertensive, or anemic; and those who have ST-segment deviation or renal failure.<sup>62</sup>

Achieving optimal outcomes in patients with ACS requires the ability to balance the risk of ischemic events with bleeding risk. Assessment of baseline

hemorrhagic risk, selecting an appropriate antiplatelet/antithrombotic regimen, procedural modifications, and careful

observation have been described as crucial measures in minimizing bleeding complications in ACS.<sup>63</sup>

The concomitant use of PPIs and clopidogrel has become a significant issue for patients and clinicians. Although the evidence is not conclusive, we must make ourselves aware of the issues and current data surrounding this subject. Providers must use this evidence-based data to make appropriate clinical recommendations while simultaneously educating their patients. Patients depend on us and our knowledge to provide them with the best care possible.

## Treatment Decision

After a review of the patient’s current medical regimen, the decision is that he would benefit from long-term dual antiplatelet therapy for secondary prevention of ACS. Options for a second antiplatelet agent include clopidogrel and prasugrel. Given the patient’s age, prasugrel is not an optimal choice because of the increased risk of bleeding in this patient population. Therefore, clopidogrel 75 mg/d is prescribed for at least 12 months.

However, because the patient is taking omeprazole, the potential for decreased efficacy with concomitant clopidogrel must be considered before treatment begins. The patient denies a history of gastroesophageal reflux disease, GI bleeding, or peptic ulcer disease. He states he was given omeprazole during his hospitalization and a prescription on discharge, but is not sure why. A review of his hospital records indicates omeprazole was prescribed solely for GI prophylaxis. Given the potential decreased efficacy of clopidogrel with concomitant use of omeprazole, the best treatment option is to discontinue omeprazole as there is no clear indication for its use.

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## PCE Takeaways

- Dual antiplatelet therapy is recommended for all patients with ACS.
  - The optimal duration of dual antiplatelet therapy for secondary prevention of ACS is unknown; guidelines recommend aspirin indefinitely and clopidogrel or prasugrel for at least 12 months after ACS presentation.
  - The optimal dose of antiplatelet agents for all ACS patients has not been defined.
  - The effects of aspirin are attenuated when administered concomitantly with NSAIDs.
  - FDA has warned against using clopidogrel with omeprazole to avoid reduced antiplatelet activity.
  - Prasugrel is more effective than clopidogrel at reducing risk of recurrent ACS events, but is more likely to cause major bleeding, including fatal bleeding.
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