Personalizing Oral Antiplatelet Therapy in PCI

A review of the current agents and choosing the right strategy for your patient.

BY HIREN PATEL, MD; ADAM BRESS, PharmD; AND ADHIR SHROFF, MD, MPH

Antiplatelet agents are a mainstay pharmacotherapy in percutaneous coronary interventions (PCIs) and acute coronary syndromes (ACS) because of their proven benefit in reduction and prevention of future ischemic cardiac complications. More than 600,000 PCIs are performed each year in the United States. Historically, clinicians were focused on preventing thrombotic complications with very aggressive anticoagulation regimens that led to high rates of bleeding complications.

As ischemic outcomes have become less common, more attention has been directed toward bleeding complications. Balancing bleeding risk and ischemic complications is a challenge to all clinicians who care for these patients. Given the prolonged duration of dual-antiplatelet therapy (DAPT), selection of an optimal regimen is even more relevant. In this article, all of the currently available oral antiplatelet agents are reviewed to allow the reader to identify the optimal regimen for their patients.

ANTIPLATELET AGENTS

Platelet activation and aggregation is a complex process with several promoters and inhibitors. Consequently, several antiplatelet agents are approved in the United States by the US Food and Drug Administration for use in the secondary prevention of ACS and after PCI. These agents can be broadly classified by their mechanism of action, including: cyclo-oxygenase (COX) inhibitors (aspirin), adenosine reuptake inhibitors (dipyrimadole), platelet phosphodiesterase inhibitors (cilostazol), and adenosine diphosphate (ADP) receptor inhibitors (ticlopidine, clopidogrel, prasugrel, and ticagrelor) (Figure 1).

Aspirin

Aspirin (acetylsalicylic acid [ASA]) has been the primary antiplatelet agent used for prevention of thrombotic complications in patients with ACS and PCI. By inhibiting production of thromboxane A2, which facilitates platelet aggregation, ASA reduces cardiac events after ACS and PCI. Current American Heart Association/American College of Cardiology (AHA/ACC) guidelines recommend initiating ASA in patients presenting with unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), or STEMI who are medically managed or selected to undergo PCI. Aspirin should be initiated as soon as possible after PCI.
hospital presentation, and be continued indefinitely in those who can tolerate it.6,7 The question still remains, what dose?

Optimal aspirin dose in the modern era. The dose of ASA to use after PCI remains uncertain, and practice patterns vary significantly. In the recently published PLATO study (discussed later), clinicians in the United States used higher (> 300 mg) maintenance doses of ASA compared to operators in other parts of the world (53.7% vs 1.7%). Several observational studies suggest that low-dose ASA (< 162 mg/d) is equally as effective as higher-dose ASA (> 300 mg/d) at protecting against stent thrombosis and that it decreases the risk of bleeding.8-11 Higher doses have little or no additional antiplatelet effect and are potentially more gastrotoxic.11 The highest quality evidence to date in helping answer this question comes from the CURRENT-OASIS 7 study, a multicenter, international, randomized, controlled trial that randomly assigned 25,000 patients with ACS and intended PCI to receive high-dose (300–325 mg/d) or low-dose (75–100 mg/d) maintenance ASA (as well as high-dose vs low-dose clopidogrel).12 This trial demonstrated no significant difference in the primary outcome at 30 days between the high-dose and low-dose ASA groups (Table 1). There was also no difference observed in the PCI subgroup (n = 17,260).13 Rates of major bleeding were similar; however, there was a significant increase in minor bleeding and gastrointestinal bleeding in the higher-dose ASA group.

A low-maintenance dose ASA strategy in ACS and PCI patients, when initiated immediately on presentation, is equally as effective as a high-dose strategy, while lowering bleeding risk. The current AHA/ACC 2012 UA/NSTEMI and 2011 STEMI/PCI guidelines support using a

### Table 1. Major Outcomes at 30 Days by Aspirin Dose in the Current-Oasis 7 Trial12

<table>
<thead>
<tr>
<th>Outcome</th>
<th>300–325 mg/d (N = 12,507)</th>
<th>75–100 mg/d (N = 12,579)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CV death, MI, or stroke (primary outcome)</td>
<td>530 (4.2)</td>
<td>549 (4.4)</td>
<td>0.97 (0.86–1.09)</td>
<td>.61</td>
</tr>
<tr>
<td>MI</td>
<td>253 (2)</td>
<td>261 (2.1)</td>
<td>0.97 (0.82–1.16)</td>
<td>.76</td>
</tr>
<tr>
<td>Stroke</td>
<td>70 (0.6)</td>
<td>59 (0.5)</td>
<td>1.19 (0.84–1.68)</td>
<td>.32</td>
</tr>
<tr>
<td>Recurrent ischemia</td>
<td>41 (0.3)</td>
<td>65 (0.5)</td>
<td>0.63 (0.43–0.94)</td>
<td>.02</td>
</tr>
<tr>
<td>All-cause death</td>
<td>273 (2.2)</td>
<td>314 (2.5)</td>
<td>0.87 (0.74–1.03)</td>
<td>.1</td>
</tr>
<tr>
<td>Safety</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding, study criteria</td>
<td>282 (2.3)</td>
<td>286 (2.3)</td>
<td>0.99 (0.84–1.17)</td>
<td>.9</td>
</tr>
<tr>
<td>Major bleeding, TIMI criteria</td>
<td>197 (1.6)</td>
<td>181 (1.4)</td>
<td>1.09 (0.89–1.34)</td>
<td>.39</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>618 (5)</td>
<td>551 (4.4)</td>
<td>1.13 (1.00–1.27)</td>
<td>.04</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>47 (0.4)</td>
<td>29 (0.2)</td>
<td>—</td>
<td>.04</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; MI, myocardial infarction; TIMI, thrombolysis in myocardial infarction.

Major bleeding, study criteria: Fatal or leading to a decrease in hemoglobin of 5 g/dL, or significant hypotension with the need for inotropes, or requiring surgery (other than vascular site repair), or symptomatic intracranial hemorrhage (ICH), or requiring transfusion of four or more units of red blood cells or equivalent whole blood. Significantly disabling, intracranial bleeding leading to significant loss of vision or bleeding requiring transfusion of two or three units of red blood cells or equivalent whole blood.

TIMI major bleeding: Defined as any ICH, fatal bleeding, cardiac tamponade or any clinically overt bleeding (including bleeding evident on imaging studies) associated with a decrease in hemoglobin of > 5 g/dL from baseline (accounting for the effect of transfusions on change in hemoglobin, defined as one unit of packed red blood cells [or 3% hematocrit] counting as a 1 g/dL hemoglobin decrease).

Minor bleeding: Defined as any other bleeding requiring modification of the drug regimen.
lower ASA maintenance dose strategy after PCI, giving it a class IIa (level of evidence B) recommendation.6,7

Dipyridamole
As a pyrimido-pyrimidine derivative phosphodiesterase inhibitor, dipyridamole acts by inhibiting the breakdown of cyclic adenosine monophosphate (cAMP). The subsequent increase in cAMP produces a vasodilatory effect and inhibits platelet aggregation. Dipyridamole has been evaluated in multiple randomized trials, and has demonstrated a 23% relative risk reduction for stroke in patients with a history of transient ischemic attack or stroke when given in combination with ASA.14 However, this benefit was not reflected in patients with a history of coronary or peripheral artery disease.15 There are currently no guideline recommendations to support the use of dipyridamole for use in post-UA/NSTEMI/STEMI and PCI patients specifically.6,7

Cilostazol
Cilostazol is a 2-oxoquinolone derivative that acts by selectively inhibiting phosphodiesterase type III, which in turn increases intracellular cAMP and results in inhibition of platelet aggregation and smooth muscle contraction causing vasodilation. Cilostazol is an intriguing add-on therapy in PCI because it has been shown to decrease platelet reactivity, reduce angiographic restenosis, and reduce cardiac events after PCI when given with ASA and clopidogrel in a primarily Asian population.16-18 An increase in headaches, diarrhea, dizziness, tachycardia, and palpitations was seen with this medication.19 Given the increase in the incidence of ventricular tachycardia, it is contraindicated in patients with heart failure. Based on recent AHA/ACC guidelines, there is no specific recommendation for the use of cilostazol in UA/NSTEMI/STEMI and PCI patients.

P2Y₁₂ RECEPTOR ANTAGONISTS
P2Y receptors are a class of purinergic receptors present in nearly every human tissue, exerting various functions when activated by nucleotides, such as adenosine diphosphate. A specific subset, the P2Y₁₂ receptor, when activated, results in platelet aggregation.20 Currently approved P2Y₁₂ inhibitors in the United States market include ticlopidine, clopidogrel, prasugrel, and ticagrelor. As an increasingly important class of medications, with the recent addition of two new agents, a more detailed review of their pharmacology, clinical data supporting their use, and shortcomings of each drug will be discussed.

Ticlopidine
Ticlopidine was the first P2Y₁₂ antagonist developed and FDA approved. Initially, it was approved for managing patients with ischemic stroke and peripheral vascular disease with claudication, where it demonstrated a significant improvement in walking distance and slowed progression of peripheral vascular disease. Later, in a placebo-controlled trial conducted in patients with unstable angina, ticlopidine administration resulted in a 46% relative risk reduction in vascular death or myocardial infarction at 6 months, thereby extending its use.21 Additionally, in a subsequent trial consisting of approximately 1,600 patients randomized to ticlopidine before PCI, a significant decrease in the incidence of the composite endpoint of death, myocardial infarction, or target vessel revascularization at 1 year was witnessed.22 The primary shortcoming of ticlopidine is its hematologic side effects, including neutropenia and thrombotic thrombocytopenic purpura. With the introduction of clopidogrel, which demonstrated a lower incidence of these effects, its use in patients with ACS and PCI was ultimately replaced.23 The 2007 and 2011 AHA/ACC guidelines for UA/NSTEMI gave a class I recommendation for clopidogrel (75 mg/d) or ticlopidine (250 mg twice daily) for post-UA/NSTEMI patients when ASA is contraindicated or not tolerated because of hypersensitivity or gastrointestinal intolerance.24 However, the updated 2012 AHA/ACC revision deleted this recommendation for ticlopidine from the guidelines.6 In the 2011 PCI guideline from ACCF/AHA/SCAI, the use of ticlopidine after PCI is no longer mentioned.7

Clopidogrel
Clopidogrel is the most commonly used P2Y₁₂ receptor antagonist to prevent vascular death in ACS/PCI patients, with more than 25 million prescriptions annually.25 It is a prodrug requiring bioconversion in the liver into its active metabolite, which then irreversibly binds the P2Y₁₂ receptor inhibiting platelet aggregation (Figure 2). Bioactivation occurs via a two-step process that involves several CYP450 isoenzymes, namely CYP2C19. Once administered, inhibition of platelet aggregation (IPA) of 20% can be seen at approximately 2 hours, with steady state inhibition being reached between day 3 and day 7 of daily administration (average IPA seen with 75 mg/d was 40%-60%).26 Once discontinued, platelet aggregation gradually returns to baseline after approximately 5 days (Table 2).26

Clinical data. Widespread use of clopidogrel in ACS began after the results demonstrated from the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial. This study showed a 20% relative risk reduction in cardiovascular death, nonfatal myocardial infarction, and stroke in UA/NSTEMI patients randomized to clopidogrel versus placebo, 20% of which were managed via PCI.27 In the analysis of PCI-treated patients in the CURE trial (PCI-CURE), clopidogrel was superior to standard treatment at 30 days (30% relative risk reduction in the primary endpoint) and up to 8 months.28 Until recent-
ly, ASA and clopidogrel has been the default regimen for all patients after PCI.

**Shortcomings of clopidogrel.** In addition to the 30% relative increased risk of major bleeding that was demonstrated in the CURE trial, several other major limitations of clopidogrel have been identified. Hepatic bioactivation of clopidogrel varies based on CYP2C19 genotype and drug interactions with other medications that interact with CYP2C19. Concomitant omeprazole administration has been shown to reduce the antiplatelet response of clopidogrel, but not with pantoprazole. The clinical impact of this drug-drug interaction remains in question. Finally, its irreversible binding is problematic in the acute setting when urgent cardiac surgery may be required. Notwithstanding these important limitations, clopidogrel remains one of the most commonly used medications in patients with ACS and urgent/elective PCI due to familiarity and lack of suitable options (until recently).

**Prasugrel**

Prasugrel was engineered to improve upon the limitations of clopidogrel. Like clopidogrel, it is a thienopyridine prodrug and an irreversible inhibitor of the P2Y12 receptor on the surface of the platelet. However, prasugrel undergoes a more efficient bioactivation (Figure 2), leading to a more rapid onset (IPA of 20% in approximately 20 minutes), higher potency (mean IPA approximately 80%), and minimal interpatient variability in response (Table 2). Unlike clopidogrel, prasugrel is not affected by variability in CYP2C19 loss-of-function alleles and the drug-drug interaction with omeprazole. These attributes make prasugrel an attractive alternative to clopidogrel, especially in patients who require fast and potent inhibition of platelet aggregation.

**Clinical data.** Clinical efficacy of prasugrel was tested in the TRITON-TIMI 38 trial, which randomized 13,608 patients with ACS undergoing planned PCI to prasugrel versus clopidogrel. A daily dose of 75 to 162 mg of ASA was recommended in the study. The TRITON-TIMI 38 trial demonstrated a 2.2% absolute risk reduction and a 19% relative risk reduction in the primary efficacy endpoint (cardiovascular death, myocardial infarction, stroke) with prasugrel (hazard ratio, 0.81; P < .001). However, a recent randomized study of prasugrel versus clopidogrel in ACS patients managed medically demonstrated no additional benefit with prasugrel over clopidogrel. Rates of major and minor bleeding were similar between both groups.

**Shortcomings of prasugrel.** The TRITON-TIMI 38 study demonstrated that prasugrel was associated with a significant increase in the rate of bleeding, notably TIMI major bleeding, CABG-related bleeding, and intracranial hemorrhage when compared to clopidogrel. Furthermore, elderly patients (> 75 years of age) and low-body-weight patients (< 60 kg) had increased risk of bleeding and experienced no net clinical benefit. A recent study conducted in low-body-weight patients demonstrated that by using a lower maintenance dosage of prasugrel (5 mg), the same degree of platelet reactivity was achieved without any significant increase in bleeding when compared to using a higher dose (10 mg) in high-body-weight patients, although the effectiveness and safety of the 5-mg dose have not been studied prospectively. Patients with a history of stroke also experienced a net harm with prasugrel, and therefore prasugrel is contraindicated in this patient group. Despite this subgroup of patients who experienced no net clinical benefit and/or worse outcomes, diabetics and those with ST elevation myocardial infarction showed a larger relative risk reduction for the primary outcome. Overall, prasugrel is a useful option in patients presenting with ACS undergoing primary PCI, taking care to avoid the at-risk subpopulations.

**Ticagrelor**

Unlike the other P2Y12 antagonists mentioned previously, ticagrelor is a non-thienopyridine, directly acting P2Y12 antagonist, making it a more potent and faster-acting drug than clopidogrel and potentially even prasugrel. These unique features result in faster onset, increased potency, a more consistent level of platelet inhibition, and lower interpatient variability (Figure 2). Within 30 minutes, a loading dose of ticagrelor is able to achieve a 40% IPA and roughly 80% IPA at 1 hour after this initial dose (Table 2). With its reversible platelet receptor binding, return of platelet function is quicker than with the
irreversible binding of clopidogrel and prasugrel.26

Clinical data. In the PLATO study, patients with ACS managed with or without PCI were randomized to ticagrelor or clopidogrel. The ticagrelor patients had a significantly lower rate of death from vascular causes, myocardial infarction, or stroke (hazard ratio, 0.84; \( P < .001 \)).39 The benefits were evident within the first 30 days, persisted for up to 360 days, and were evident regardless of clopidogrel pretreatment and whether patients had invasive or medical management. Most notable was a 1.4% absolute reduction in all-cause mortality. Also, patients who underwent CABG within 7 days of receiving ticagrelor experienced a 50% relative risk reduction in overall, as well as cardiovascular mortality, when compared to those who received clopidogrel.60

Shortcomings of ticagrelor. Although no significant difference in rates of major bleeding, TIMI major bleeding, or fatal/life-threatening bleeding were identified, the study did notice an increase in non–CABG-related major bleeding with ticagrelor (4.5% vs 3.8%; \( P = .03 \)). Overall, discontinuation of the study drug due to adverse events occurred more frequently with ticagrelor than with clopidogrel (7.4% vs 6%; \( P < .001 \)). Common adverse events demonstrated from the study included an increased rate of dyspnea (13.8% vs 7.8%), ventricular pauses (5.8% vs 3.6%), increase in serum uric acid levels (approximately 0.6), and a > 50% increase in serum creatinine levels (7.4%).

The study did not demonstrate a significant difference between ticagrelor and clopidogrel with respect to the primary efficacy endpoint in the North American cohort compared to the rest of the world.41 Statistical analysis revealed a potential interaction between ticagrelor and higher doses of ASA (\( \geq 300 \) mg), used more commonly in North America (53.6% in the United States compared to 1.7% with the rest of the world).

CURRENT GUIDELINES AND P2Y12 RECEPTOR ANTAGONISTS

The current AHA/ACC/SCAI PCI/STEMI and UA/NSTEMI guidelines have given class I recommendations to prasugrel, clopidogrel, and ticagrelor.6,7 These guidelines do not prioritize agents within this class. In the recently released guidelines from the European Society of Cardiology, the authors recommend prasugrel and ticagrelor as the first-line agents, and clopidogrel for only those patients unable to receive prasugrel or ticagrelor.42,43
When constructing a dual-antiplatelet regimen, the clinician is faced with the choice of multiple ASA doses and which P2Y<sub>12</sub> inhibitor to use. Based on current evidence, it is reasonable to use a lower maintenance dose of ASA (< 100 mg) to achieve the adequate antiplatelet inhibition while minimizing side effects in ACS or PCI patients. The most current AHA/ACC guidelines give a class IIA recommendation for using 81 mg of ASA daily post-PCI. Currently in the United States, clopidogrel, ticagrelor, and prasugrel all have a class I recommendation. However, the question still remains of who should get what? Since no direct comparisons among the newer agents have been made, we are not able to recommend wholesale transition from clopidogrel to these agents based on the limited data and experience with these newer agents. With that said, European guidelines have shown a preference for the newer agents over clopidogrel.

What is certain is that each clinician should become increasingly aware of the strengths and limitations of each agent and begin to individualize therapy accordingly. As clinical data for platelet activity and CYP2C19 genetic testing begin to emerge (to be covered in a future edition), further direction on “optimal therapy” will become clearer. Further complicating the risk/benefit discussion is the recent transition of clopidogrel to generic status, which will lead to substantial cost savings in the United States for clopidogrel over the newer agents.

<table>
<thead>
<tr>
<th>TABLE 2. PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES OF CLOPIDOGREL, PRASUGREL, AND TICAGRELOR&lt;sup&gt;26,44-46&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class</strong></td>
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<tr>
<td>Mechanism of action</td>
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<td>Metabolism</td>
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<td>IPA</td>
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<tr>
<td>Mean steady state inhibition</td>
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<td>Offset of action (days to IPA &lt; 20%)</td>
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**BALANCING RISK VERSUS BENEFITS: CHOOING THE RIGHT ANTIPLATELET STRATEGY**

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