Review of Prasugrel for the Secondary Prevention of Atherothrombosis

Sarah A. Spinler, PharmD, FCCP, BCPS, and Catherine Rees, BHB, BA

ABSTRACT

BACKGROUND: The role of platelets in atherothrombotic disease is well established, and antiplatelet therapy is now recommended for the short- and long-term management of patients with acute coronary syndromes (ACS), with and without percutaneous coronary intervention (PCI). The thienopyridine clopidogrel is accepted as a key component of antiplatelet management and is recommended in current treatment guidelines as add-on therapy to aspirin in secondary prevention to reduce coronary risk in patients with ACS and/or following PCI. The FDA Cardiovascular and Renal Drugs Advisory Committee met on February 3, 2009, and recommended approval of prasugrel, but with guidance to physicians about increased risk in low-weight or elderly patients and avoidance of use (a) around coronary artery bypass graft (CABG) or other surgical or invasive procedures and (b) in patients with prior or current stroke or transient ischemic attack (TIA).

OBJECTIVE: To review the published literature examining primarily the clinical efficacy and safety of prasugrel in ACS patients.

METHODS: The PubMed database was searched for English language studies involving the use of prasugrel in human subjects published up to April 2009 using the keyword “prasugrel.” The review focused on randomized, controlled trials with clinical end points. Abstracts from recent scientific meetings (up to November 2008) were also searched for relevant studies, as was the FDA briefing document prepared in advance of the advisory committee meeting on February 3, 2009.

RESULTS: Of the 124 published papers identified, 28 pertained to research in human subjects: 21 on prasugrel pharmacology and 7 with clinical end points. In the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction (PRINCIPLE-TIMI) 44 trial, a cross-over study of laboratory-determined platelet activity, prasugrel produced significantly greater inhibition of platelet aggregation than clopidogrel after both loading dose (74.8% vs. 31.8% at 6 hours, P < 0.001) and maintenance dose (day 14: 61.3% vs. 46.1%, P < 0.001) in patients with stable coronary artery disease (CAD). In the only end point outcomes study (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction [TRITON-TIMI 38]), there was a significant reduction in adverse cardiac outcomes in patients with ACS treated with prasugrel, 94% of whom received at least 1 coronary stent. The incidence of the primary composite end point of cardiovascular death, nonfatal MI, or nonfatal stroke was 9.9% in the prasugrel group versus 12.1% in the clopidogrel group (hazard ratio = 0.81, 95% CI = 0.73-0.90, P = 0.001). However, the risk of major bleeding event was significantly greater with prasugrel versus clopidogrel, and prasugrel appeared to be of net clinical harm in patients with a history of stroke/TIA. The FDA reviewer recommended that prasugrel use be discouraged in patients aged 75 years or older or those with a history of stroke/TIA.

CONCLUSION: Available data suggest that prasugrel offers potential as an alternative to clopidogrel with greater efficacy but with increased bleeding risk in patients with ACS who receive PCI. Data are not yet available to define the efficacy and risk-benefit profile of prasugrel in patients not undergoing PCI.

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What is presently known about this subject from this review

• Dual antiplatelet therapy with clopidogrel and aspirin significantly reduces the risk of an adverse outcome after acute coronary syndromes (ACS). Dual antiplatelet therapy is not recommended for primary prevention in patients without symptomatic cardiovascular disease.
• In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 trial, 13,608 patients with moderate-to-high risk ACS with scheduled percutaneous coronary intervention (PCI) showed prasugrel superior to clopidogrel at a median follow-up of 14.5 months. The occurrence of the primary end point (combined outcome of death from cardiovascular causes, nonfatal myocardial infarction [MI], or nonfatal stroke) was 9.9% of prasugrel patients versus 12.1% for clopidogrel (HR = 0.81, 95% CI = 0.73-0.90, P < 0.001) but with increased risk of bleeding. Major bleeding not related to coronary artery bypass graft (CABG) occurred in 2.4% of patients receiving prasugrel versus 1.8% of patients receiving clopidogrel (HR = 1.32, 95% CI = 1.03-1.68, P = 0.03). The rate of life-threatening bleeding was 1.4% for prasugrel versus 0.9% for clopidogrel (P = 0.01), and fatal bleeding was 0.4% for prasugrel versus 0.1% for clopidogrel (P = 0.002).
• Based on the TRITON-TIMI 38 trial results, Schafer et al. (2009) reported that 24 cardiovascular end points would be prevented at the cost of 10 additional bleeding events for every 1,000 patients treated with prasugrel instead of clopidogrel, a risk-benefit profile found acceptable by the FDA Cardiovascular and Renal Drugs Advisory Committee at its meeting on February 3, 2009.
• In post-hoc analyses, 3 subgroups of patients were identified in TRITON-TIMI 38 in whom prasugrel was associated with either no net clinical benefit or net harm. There was no clinical benefit from prasugrel versus clopidogrel in ACS patients with scheduled PCI who (a) had a body weight below 60 kg or (b) were aged 75 years or older, and there was net harm in those with a history of stroke or transient ischemic attack (TIA; HR = 1.54, 95% CI = 1.02-2.32, P = 0.004).
• In TRITON-TIMI subgroup analyses, incidence of the primary composite cardiovascular end point for prasugrel compared with clopidogrel at 15 months was 10.0% versus 12.4% in patients with ST segment elevation MI (STEMI; P = 0.002), 9.2% versus 10.6% in patients without diabetes (P = 0.02), 12.2% versus 17.0% in patients with diabetes (P < 0.001), 10% versus 12% in patients with a stent (P < 0.001), 10% versus 12% in patients with bare-metal stent (P = 0.003), and 9% versus 11% in patients with drug-eluting stent (P = 0.019).
Antiplatelet therapy has been shown to significantly reduce the risk of serious vascular events in high-risk patients, including those with a prior acute ischemic event. The long-term use of antiplatelet agents is thus a key component of secondary prevention measures following acute coronary syndromes (ACS).

Platelets play a fundamental role in the pathophysiology of unstable angina and acute myocardial infarction (MI) as plaque rupture is followed by adhesion, activation, and aggregation of platelets, and formation of a coronary thrombus. Platelet activation also plays a role in the development of secondary ischemia following an initial ACS event and is more pronounced following intracoronary stent implantation than after coronary balloon angioplasty alone. Secondary ischemia, which may include MI and stroke, is a significant hazard for patients who have already experienced an acute event.

Some of the strongest evidence available for long-term prevention of adverse cardiac events in patients with coronary disease pertains to the use of aspirin. Current treatment guidelines from the American College of Cardiology (ACC) recommend that aspirin therapy be continued indefinitely for secondary prevention of ischemic events following ACS, with the thienopyridine clopidogrel to be added for up to 12 months for the majority of patients with unstable angina, non-ST segment elevation MI (NSTEMI), or ST segment elevation MI (STEMI) or longer in the case of patients receiving drug-eluting stents (Table 1). At the time that this review was completed (May 2009), there were 2 thienopyridines (ticlopidine and clopidogrel) approved by the U.S. Food and Drug Administration (FDA) for use in patients with ACS.

On February 3, 2009, a new thienopyridine, prasugrel, was recommended for approval as an addition to aspirin for patients with ACS by the FDA Cardiovascular and Renal Drugs Advisory Committee. This article reviews the published data on the pharmacologic and clinical profile of prasugrel. The purpose is to describe what is known about prasugrel from the published literature and the FDA review compared with the current standard of add-on antiplatelet therapy (clopidogrel) in the United States.

Current Recommendations for Thienopyridines as Add-On Antiplatelet Therapy

Briefly, dual antiplatelet therapy with aspirin and a thienopyridine for at least 1 year is now recommended for all patients with non-ST segment elevation ACS with or without stents at hospital discharge. Ticlopidine was used in the past for prevention of subacute stent thrombosis, but the adverse effects of the drug (principally rash and diarrhea, but also the potential for neutropenia [reported in approximately 2.4% of patients]) limit its utility. Therefore, clopidogrel, which lacks the adverse effect of neutropenia, has become the most commonly prescribed thienopyridine.

While effective in the prevention of atherothrombotic disease, there are risks and trade-offs associated with long-term antiplatelet therapy, since all antiplatelet agents carry an increased risk of bleeding. The absolute benefits of aspirin therapy have been found to substantially outweigh its risks in moderate- to high-risk patients (those with a 3% or greater annual risk of a vascular event), however. A meta-analysis of 4 primary prevention trials indicated that aspirin is safe and worthwhile when the annual risk of coronary events is 1.5% or more. Furthermore, benefits were found to greatly outweigh hazards in patients with chronic stable angina, prior MI, or unstable angina in an analysis of randomized trial data. The benefit in terms of number needed to be treated (NNT) to avoid 1 event per year ranged from 20 to 100, compared with the number needed to harm (NNH) of 500 to 1,000 to cause 1 major gastrointestinal bleeding event each year.

When a second antiplatelet agent is added to aspirin, the bleeding risk may be increased. Therefore, the overall risk-benefit profile of dual antiplatelet therapy in patients with ACS, including those undergoing coronary artery bypass grafting (CABG), should be considered. Of note, a post-hoc analysis of the subgroup of patients with prior ischemic events in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study suggests that the increase in bleeding risk with dual antiplatelet therapy versus aspirin alone occurs predominantly during the first few months of treatment and decreases after 12 months.

Methods

Literature searches were conducted by one author (Rees), and the results confirmed by the lead author (Spinler), in August 2008 and April 2009 using the keyword “prasugrel” for publications indexed on the National Library of Medicine’s PubMed database. No lower date limit was set, and all studies that were identified through August 2008 were evaluated for inclusion in this review. The search identified 125 published papers, of which 29 were studies involving the use of prasugrel in human subjects. Forty-six publications were discarded on the basis that they were news items (15) or general reviews of antiplatelet therapy (31). Bibliographies from prasugrel-specific reviews (9 identified) or comments/editorials/letters to the editor (24 identified) were scanned for papers that may not have been identified in our search. Relevant information regarding limitations of current data was extracted from these papers, but they were not otherwise considered for inclusion. Similarly, in vitro/ex vivo (11 papers) or animal studies (6) were excluded from this review.

The 28 prasugrel reports involving research in humans comprised 21 pharmacology reports and 7 reports with clinical end points. The phase II studies included: (1) the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction (PRINCIPLE-TIMI) 44 trial, a cross-over study of laboratory-
determined platelet activity that had safety and antiplatelet activity end points, and (2) the Joint Utilization of Medications to Block Platelets Optimally-Thrombolysis in Myocardial Infarction (JUMBO-TIMI) 26 trial,22 a dose-ranging study with safety end points. There were 6 published articles that reported the primary and secondary results of 1 large phase III efficacy and safety study called Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI) 38,23-28

The studies were selected for this review with a focus on comparative data from randomized, controlled studies relating to the pharmacological and/or clinical properties of prasugrel, and data/commentary from the FDA review document were also included.12 However, in order to place the prasugrel data into context within current clinical practice, comparative information on the pharmacologic and clinical profile of clopidogrel from smaller studies was also identified via PubMed.

**Pharmacology and Pharmacokinetics**

Thienopyridines block the ADP P2Y12 receptor on platelets and offer additive effects when given with aspirin because of their differing but complementary mechanism of action. Like clopidogrel, prasugrel is a thienopyridyl prodrug. It is metabolized to the active platelet-inhibiting compound R-138727, which has specific affinity for the P2Y12 ADP receptor. The pharmacokinetic properties of prasugrel and clopidogrel have been investigated in several studies and are summarized in Table 2.12,29-42 In contrast to clopidogrel,31-45 genetic variants in CYP 2C19 genes have not been shown to affect the antiplatelet response to prasugrel.30

**Drug-Drug Interactions**

Although the activation/metabolism of both prasugrel and clopidogrel involves some of the same CYP enzyme systems, the potential for pharmacokinetic interactions differs between prasugrel and clopidogrel. For example, competition for CYP 3A4 may explain why the antiplatelet effect of clopidogrel is reduced when given concomitantly with atorvastatin or dihydropyridine calcium channel blockers (CCBs).46-47 Concomitant administration of dihydropyridine CCBs and clopidogrel also increased the risk of an adverse cardiovascular outcome (adjusted hazard ratio

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**TABLE 1** Antiplatelet Therapy Recommendations for Patients With ACS

<table>
<thead>
<tr>
<th>AHA/ACC Recommendations</th>
<th>ACCP Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unstable Angina and NSTEMI</strong></td>
<td></td>
</tr>
<tr>
<td>Without stenting</td>
<td>Clopidogrel 300-600 mg (loading) then 75 mg per day for at least 1 month and ideally for longer than 1 year</td>
</tr>
<tr>
<td>Bare-metal stent</td>
<td>Clopidogrel 300-600 mg (loading) then 75 mg per day for at least 1 month</td>
</tr>
<tr>
<td>Drug-eluting stent</td>
<td>Clopidogrel 300-600 mg (loading) then 75 mg per day for at least 1 year</td>
</tr>
</tbody>
</table>

**STEMI**

<table>
<thead>
<tr>
<th>PCI with stenting</th>
<th>Clopidogrel (generally 600 mg) then 75 mg per day</th>
<th>Aspirin 160-325 mg (loading) then 75-100 mg per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bare-metal stent</td>
<td>PCI = percutaneous coronary intervention; NSTEMI = non-ST segment elevation myocardial infarction; STEMI = ST segment elevation myocardial infarction.</td>
<td>PCI = percutaneous coronary intervention; NSTEMI = non-ST segment elevation myocardial infarction; STEMI = ST segment elevation myocardial infarction.</td>
</tr>
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**ACC = American College of Cardiology, ACCP = American College of Chest Physicians; ACS = acute coronary syndromes; AHA = American Heart Association; PCI = percutaneous coronary intervention; NSTEMI = non-ST segment elevation myocardial infarction; STEMI = ST segment elevation myocardial infarction.**

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[HR] = 3.5, 95% CI = 1.4-8.6, \( P = 0.005 \) vs. patients not taking CCBs). However, post-hoc analyses from 2 large clinical trials of clopidogrel reported no such increased risk with atorvastatin.48,49

No such interactions have been reported for prasugrel, although 1 patient taking atorvastatin in 1 of the phase III studies with prasugrel developed elevated liver enzymes after 3 doses of prasugrel.12 Since this reaction could have occurred with atorvastatin in the absence of prasugrel, the FDA did not recommend any label warnings about this combination.12

Exposure to proton pump inhibitors (PPIs), which are substrates for an inhibitor of CYP2C19,50 has also been associated with a significantly increased risk of acute MI among clopidogrel users in prescription database analyses (1.38% incidence of MI in 1 year in clopidogrel users not taking a PPI compared with 3.08% incidence in clopidogrel users with low PPI exposure based on prescription adherence and 5.03% in clopidogrel users with high PPI exposure; \( P < 0.05 \)).51 as well as in a Veterans Health Administration database.52 Compared with placebo, omeprazole but not pantoprazole or esomeprazole appears to reduce the antiplatelet effect of clopidogrel.53,54 However, preliminary unpublished data were reported in May 2009 that suggested that there may be a class effect in the interaction of clopidogrel with PPIs: omeprazole, lansoprazole, esomeprazole, and pantoprazole use was associated with an increased risk of major adverse cardiac events over 12 months, compared with patients who did not have a PPI pharmacy claim.55 This conclusion was derived from an analysis of pharmacy and medical claims in the Medco Solutions database for 9,862 patients who received a PPI, compared with 6,828 patients who did not receive a PPI following a percutaneous coronary intervention (PCI). The Society for Cardiovascular Angiography and Interventions issued a statement on May 6, 2009, supporting the use of other agents such as histamine-2 blockers rather than PPIs for dual antiplatelet therapy, reserving PPIs for selected patients at highest risk of bleeding.56 One open-label pharmacokinetics trial suggested that lansoprazole may have less impact on the antiplatelet effect associated with prasugrel compared with clopidogrel.57 However, there are no data from prospective randomized trials to substantiate the clinical impact of the interaction of clopidogrel with PPIs, and it is not yet known if prasugrel has a clinically significant interaction with PPIs.

### Antiplatelet Activity

The antiplatelet profile of prasugrel has been extensively described in studies of healthy volunteers and patients,29,31,35,58,59,60 and direct pharmacodynamic comparisons with clopidogrel as part of clinical trials have confirmed the differing antiplatelet efficacy of these 2 thienopyridine agents.21,61,62 Prasugrel produced significantly greater inhibition of platelet aggregation than clopidogrel after both loading and maintenance doses in 2 clinical trials of patients with stable coronary artery disease (CAD)46 or planned PCI in the PRINCIPLE-TIMI 44 trial (with a loading dose of clopidogrel 600 mg).21 It is not yet known how the differences in antiplatelet activity between prasugrel and clopidogrel are related to end point clinical outcomes.

### Clinical Profile of Prasugrel

Two phase II studies, JUMBO-TIMI 2622 and PRINCIPLE-TIMI 44,23 evaluated the safety and antiplatelet profile of prasugrel. The results from these studies suggested that it was feasible to evaluate prasugrel in phase III studies.

Table 3 presents the clinical end point data from TRITON TIMI 38, a phase III trial.23 The TRITON TIMI 38 study was a
randomized, double-blind trial involving 13,608 patients with moderate- to high-risk ACS with scheduled PCI. Patients received either prasugrel (60 mg loading dose and 10 mg per day maintenance) or clopidogrel (300 mg loading dose and 75 mg per day maintenance), both in addition to aspirin, for 6 to 15 months (median 14.5 months). The primary efficacy end point was a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke. The key safety end point was non-CABG major bleeding.²³

The primary composite efficacy end point was reported in 643 of 6,813 patients (9.9%) receiving prasugrel, compared with 781 of 6,795 (12.1%) clopidogrel recipients (hazard ratio [HR] = 0.81, 95% CI = 0.73-0.90, P < 0.001). There were also reductions with prasugrel relative to clopidogrel in several individual efficacy end points, notably rates of nonfatal MI, urgent target vessel revascularization, and stent thrombosis (Table 2).²³ The difference in clinical end points between the treatment groups was mainly attributable to a reduction in non-fatal MI (Table 2); overall mortality rates did not differ significantly between the 2 treatment groups.

Five prespecified secondary analyses of TRITON TIMI 38 have been published.²⁴-²⁸ Three examined patient subgroups—sten recipients,²⁷ patients with STEMI,²⁸ and patients with diabetes—²⁹—and 2 examined end points—recurrent events²³ and early/late events.²⁴

In all 3 TRITON patient subgroup analyses, prasugrel was
associated with a significant reduction in the primary composite end point of cardiovascular death, nonfatal MI, or nonfatal stroke, relative to clopidogrel (Figure 1).26–28 The between-group treatment difference in the primary end point was most marked in the subgroup of patients with diabetes mellitus; the NNT to prevent 1 primary end point event was 21 in those with diabetes compared with 71 in those without diabetes.26 The benefit was seen in both insulin-treated and non-insulin-treated diabetic patients, with a NNT of 13 to prevent 1 primary end point in the insulin-treated cohort and 26 in the non-insulin-treated cohort of patients with diabetes for prasugrel relative to clopidogrel.26

Although there was a significant benefit with prasugrel relative to clopidogrel in the overall subgroup of STEMI patients (10.0% vs. 12.4% incidence of the primary composite end point, HR = 0.79, 95% CI = 0.65–0.97, P = 0.022), the benefit was primarily limited to the subgroup receiving secondary PCI (defined as PCI between 12 hours and days after the onset of MI symptoms).28 The between-group treatment difference did not reach statistical significance in those undergoing primary PCI (defined as occurring less than 12 hours from onset of MI symptoms): prasugrel 10.2% versus clopidogrel 11.6%; HR = 0.87, 95% CI = 0.68–1.11, P = 0.266. The NNT to prevent 1 primary end point event was 41 in the overall STEMI subgroup for prasugrel relative to clopidogrel and 21 in STEMI patients undergoing secondary PCI.28

The incidence of the primary composite end point was significantly reduced with prasugrel relative to clopidogrel in the overall stent population (9.7% vs. 11.9%, P < 0.001), as well as in the subgroups of patients with drug-eluting stents only (9.0% vs. 11.1%, P = 0.019) and those with bare-metal stents only (10.0% vs. 12.2%, P = 0.020).27 Rates of definite or probable stent thrombosis were also lower with prasugrel than with clopidogrel in the overall stent population (1.13% vs. 2.35%, P < 0.001),27 in the STEMI cohort (1.6% vs. 2.8%, P = 0.023),28 and in the subgroups with only bare-metal stents (1.27% vs. 2.41%, P = 0.009) and only drug-eluting stents (0.84% vs. 2.31%, P < 0.001).27 The effects of prasugrel on stent thrombosis were consistent, regardless of the type of drug-eluting stent (sirolimus- or paclitaxel-eluting).27

The 2 subanalyses of end points demonstrated a benefit of prasugrel relative to clopidogrel during the periprocedural period (after loading doses) and long term (during maintenance dosing)28 and in the prevention of recurrent events.25 Prasugrel significantly reduced the occurrence of MI during the first 3 days (periprocedural period) relative to clopidogrel (4.27% vs. 5.24%, HR = 0.81, 95% CI = 0.70–0.95, P = 0.008), as well as during the maintenance dosing period from day 3 to the end of the trial (3.40% vs. 4.79%, HR = 0.69, 95% CI = 0.58–0.83, P < 0.001).28 Significant reductions were also seen in early and late occurrences of stent thrombosis and urgent target vessel revascularization. During the first 3 days, the incidence of stent thrombosis was 0.33% with prasugrel versus 0.67% with clopidogrel (HR = 0.49, 95% CI = 0.29–0.82.
ST segment elevation. The results of this trial showed that statistically significant reductions in clinical end points with clopidogrel were accompanied by significant increases in bleeding risk. However, the benefit-risk ratio favored treatment, with an NNT of 48 to prevent 1 primary cardiovascular event and NNH of 100 to cause major bleeding.

It is not surprising that prasugrel, which has more potent antiplatelet effects than clopidogrel, may cause increased bleeding in clinical use. The phase II PRINCIPLE-TIMI 44 study, in which the primary end point was antiplatelet activity, included 201 patients undergoing PCI who were randomized to prasugrel at a loading dose of 60 mg then 14 days of maintenance therapy with 10 mg per day or clopidogrel 600 mg then 150 mg per day. After 14 days, patients crossed over to the alternate antiplatelet agent. During the loading dose and pre-crossover phase, 19 of 102 (18.6%) patients receiving prasugrel and 14 of 99 (14.1%) randomized to clopidogrel had any type of bleeding event (not significant). Prior to crossover, 2 patients (2.0%) in the prasugrel group experienced a thrombosis in myocardial infarction (TIMI) minor bleeding episode compared with no patients in the clopidogrel group. After crossover, 4 patients who received clopidogrel followed by prasugrel experienced a hemorrhagic adverse event (TIMI major or minor bleeding) compared with no patients

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$P=0.006$, and the incidence of target vessel revascularization was 0.54% versus 0.83% (HR=0.66, 95% CI=0.43-0.99, $P=0.047$). From day 3 to the end of the trial, the corresponding incidence of stent thrombosis was 0.80% versus 1.74% (HR=0.45, 95% CI=0.32-0.64, $P<0.001$) and of target vessel revascularization 1.94% versus 2.97% (HR=0.65, 95% CI=0.52-0.82, $P<0.001$). In addition to the patients experiencing a first event (cardiovascular death, nonfatal MI, or stroke) reported in the primary TRITON results, 58 patients in the prasugrel group and 115 patients in the clopidogrel group experienced a second event ($P<0.001$). When both the first and recurrent events were considered, the overall incidence of the primary composite end point in TRITON was 701 in the prasugrel group and 896 in the clopidogrel group (rate ratio [RR]=0.79, 95% CI=0.71-0.87, $P<0.001$).

Safety Profile of Prasugrel

The clinical benefits of any antiplatelet drug must be balanced against the potential for bleeding events. This is shown by experience from past clinical trials with oral agents such as aspirin and clopidogrel and with GPIIb/IIIa inhibitors. For example, in the Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial, 12,562 patients were randomized to placebo or to clopidogrel in addition to aspirin for 3 to 12 months for ACS without ST segment elevation. The results of this trial showed that statistically significant reductions in clinical end points with clopidogrel were accompanied by significant increases in bleeding risk. However, the benefit-risk ratio favored treatment, with an NNT of 48 to prevent 1 primary cardiovascular event and NNH of 100 to cause major bleeding.

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$P=0.006$, and the incidence of target vessel revascularization was 0.54% versus 0.83% (HR=0.66, 95% CI=0.43-0.99, $P=0.047$). From day 3 to the end of the trial, the corresponding incidence of stent thrombosis was 0.80% versus 1.74% (HR=0.45, 95% CI=0.32-0.64, $P<0.001$) and of target vessel revascularization 1.94% versus 2.97% (HR=0.65, 95% CI=0.52-0.82, $P<0.001$). In addition to the patients experiencing a first event (cardiovascular death, nonfatal MI, or stroke) reported in the primary TRITON results, 58 patients in the prasugrel group and 115 patients in the clopidogrel group experienced a second event ($P<0.001$). When both the first and recurrent events were considered, the overall incidence of the primary composite end point in TRITON was 701 in the prasugrel group and 896 in the clopidogrel group (rate ratio [RR]=0.79, 95% CI=0.71-0.87, $P<0.001$).
who received prasugrel followed by clopidogrel. No TIMI major bleeding events were observed through day 29 of this study.21

Another phase II study, JUMBO-TIMI 26, was designed primarily to assess prasugrel safety.22 In this study, 904 patients undergoing elective or urgent PCI were randomized to standard therapy with clopidogrel (loading dose of 300 mg with 75 mg per day maintenance dosage) or to 1 of 3 prasugrel regimens (loading dose of 40 or 60 mg followed by maintenance with 7.5, 10, or 15 mg per day).22 The primary clinical end point was clinically significant (TIMI major and minor) non-CABG-related bleeds at 30 days.22 There were no significant differences between clopidogrel and prasugrel in terms of clinically significant bleeding and nonsignificant higher rates of minor and minimal bleeding in patients treated with prasugrel, particularly at the highest dosage.22 There were 3 deaths in the high-dose (15 mg per day) prasugrel group and none in the clopidogrel arm. The authors note that the incidence of bleeding in the clopidogrel arm of the study was lower than expected, rendering the study underpowered to detect statistically significant differences in bleeding rates between the treatment groups; therefore, more pertinent safety information can be derived from the TRITON study, which was larger and had longer follow-up.

The reduction in ischemic events with prasugrel observed in TRITON-TIMI 38 was not associated with a reduction in overall mortality and was associated with increases in rates of non-CABG-related major bleeding compared with clopidogrel (2.4% vs. 1.8%; HR = 1.32, 95% CI = 1.03-1.68, P = 0.03).23 CABG-related major bleeding events occurred in 24 prasugrel recipients (13.4%) and 6 clopidogrel recipients (3.2%; HR = 4.73, 95% CI = 1.90-11.82, P < 0.001).23 On February 3, 2009, the FDA advisory committee recommended that prasugrel not be the drug of choice in patients for whom CABG is anticipated.2 Twenty-one patients in the prasugrel group (0.4%) and 5 in the clopidogrel group (0.1%) had a fatal hemorrhage (P = 0.002).21 All fatal bleeding events in the clopidogrel group were intracranial, compared with 9 fatal intracranial hemorrhages in the prasugrel group; 5 fatal gastrointestinal hemorrhages, 2 each from puncture sites, surgical sites, and retroperitoneal locations; and one intra-abdominal hemorrhage.21 The published subgroup analyses from TRITON TIMI 38 showed generally similar rates of non-CABG-related major TIMI bleeding (the primary safety end point) between prasugrel and clopidogrel.24-28 The only subgroup in which a statistically significant difference in this end point was the non-diabetic cohort (prasugrel 2.4% and clopidogrel 1.6%; HR = 1.43, 95% CI = 1.07-1.91, P = 0.02).28 This was also the largest patient subgroup, which suggests that the other subgroups were underpowered to detect statistically significant differences in this parameter. The rates of non-CABG major bleeding in the TRITON-TIMI 38 study and subgroup analyses are shown in Figure 2.

As is common practice in newer clinical trials comparing 2 antithrombotic agents, a net clinical benefit was calculated in TRITON TIMI 38, comparing the combined rate cardiovascular efficacy outcomes with adverse events (both ischemic and bleeding events). Overall, prasugrel was associated with a net clinical benefit (combination of clinical efficacy and nonfatal major bleeding events) in 13.9% of patients compared with 12.2% of clopidogrel recipients (P = 0.004). In the main study, the NNT for prasugrel was 46 to prevent 1 primary efficacy end point during 15 months of treatment, relative to clopidogrel, and the NNH was 167 to cause 1 non-CABG-related TIMI major bleeding event for prasugrel relative to clopidogrel (Table 4).23 However, post-hoc analysis identified 3 subgroups of patients from TRITON-TIMI 38 in whom prasugrel was associated with either no net clinical benefit or net harm. There was no clinical benefit from prasugrel versus clopidogrel in ACS patients with scheduled PCI who (a) had a body weight below 60 kg or (b) were aged 75 years or older, and there was net harm in those with a history of stroke or transient ischemic attack (TIA; HR = 1.54, 95% CI = 1.02-2.32, P = 0.004).23

Patients with a history of cerebrovascular events had no evidence of benefit from prasugrel and showed a significant interaction (P = 0.02) between such a history and degree of net clinical benefit of prasugrel as opposed to clopidogrel. For example, the net clinical benefit (incidence of the primary composite efficacy end point plus the primary safety end point of non-CABG-related major bleeding) was 23.0% with prasugrel versus 16.0% with clopidogrel in patients with a history of stroke/TIA (HR = 1.54, 95% CI = 1.02-2.32, P = 0.04). However, in those without such history, the corresponding net clinical benefit rates were 11.8% for prasugrel versus 13.8% for clopidogrel (HR = 0.84, 95% CI = 0.76-0.93, P < 0.001), suggesting a significant risk of harm from prasugrel among patients with a history of cerebrovascular events (n = 518) in TRITON-TIMI 38 compared with significant benefit among those with no history of stroke or TIA (n = 13,090).23 Additionally, the risk of another stroke in patients with a history of stroke/TIA was high in TRITON-TIMI 38: 17 of 262 (6.5%) patients in the prasugrel group with stroke history had a stroke during follow-up compared with 3 of 256 (1.2%) patients in the clopidogrel group (HR = 5.64, 95% CI = 1.65-19.3, P = 0.002). The TRITON-TIMI 38 study population did not include patients with a history of hemorrhagic stroke or an ischemic stroke within 3 months of enrollment (these patients were excluded),67 so this was a relatively low stroke-risk population. On the basis of these findings, the FDA advisory committee recommended that prasugrel be contraindicated in patients with a history of stroke/TIA.22

There was also a significant interaction between the presence or absence of any of the 3 risk factors (age 75 years or older, weight less than 60 kg, or history of stroke/TIA) and the degree of net clinical benefit of prasugrel relative to clopidogrel (P = 0.006).23 These findings add to generalized concerns about the risks of antiplatelet therapy in patients with a history of cerebrovascular disease. Among the elderly and those with low body weight, neither net benefit nor net harm was observed. The risk of a fatal or
intracranial hemorrhage was higher in patients aged 75 years and older receiving prasugrel compared with clopidogrel. Fatal hemorrhage occurred in 9 of 891 prasugrel recipients aged 75 years or older (1.0%) compared with 1 of 894 clopidogrel recipients in this age group (0.1%); the corresponding rates of intracranial hemorrhage were 7 (0.8%) and 3 (0.3%), respectively. Coupled with the modest clinical benefits of prasugrel in patients aged 75 years or older, these data prompted the FDA advisory committee to suggest that prasugrel use should be discouraged in this age group. Thus, identification of patients at higher risk of bleeding events and attention to discontinuation of therapy before surgery may help to guide therapeutic decisions and optimize outcomes.

An evaluation of the relative contribution of the loading and maintenance phases on events in TRITON-TIMI 38 suggests that excess major bleeding with prasugrel occurred mainly in the maintenance phase. The authors of that study suggested maintenance dosage reduction in high-risk patients as a potential strategy to minimize bleeding events, although the efficacy of lower maintenance doses have not been studied. Dose-ranging studies have found that, compared with [loading] maintenance doses of clopidogrel [300 mg] 75 mg per day, inhibition of platelet aggregation was not significantly greater with prasugrel [loading] maintenance doses of [20 mg] 5 mg per day or [30 mg] 7.5 mg per day but was significantly (p<0.05) greater for prasugrel [loading] maintenance doses of [40 mg] 7.5 mg per day, [60 mg] 10 mg per day, and [60 mg] 15 mg per day. While no data are currently available on the impact of such dosages on clinical events, the Targeted Platelet Inhibition to clarify the Optimal straGeY to medically manage Acute Coronary Syndromes (TRILOGY ACS) study should provide some insight. This study aims to determine the relative safety and efficacy of prasugrel [loading] maintenance doses [30 mg] 10 mg per day or [30 mg] 5 mg per day) versus clopidogrel ([300 mg] 75 mg per day) in patients with non-ST segment elevation ACS not undergoing PCI.

The currently available data on prasugrel indicate that it is effective when used in combination with aspirin, in reducing the risk of adverse cardiovascular outcomes in patients with ACS undergoing PCI, at the expense of an increased risk of major bleeding events. It would appear that the clinical differences between prasugrel and clopidogrel may be related to differences in pharmacokinetic and pharmacodynamic properties, including in vivo antiplatelet effects, although this has yet to be confirmed. The NNT to prevent 1 primary outcome event with prasugrel compared with clopidogrel in TRITON TIMI 38 is 46, and the NNH for prasugrel compared with clopidogrel is 167, showing a net clinical benefit. The benefit appears to be greatest in patients with diabetes mellitus but controversial in patients aged 75 years or older or who weigh less than 60 kg and with net harm in patients with a history of TIA/stroke.

**Limitations**

Currently, the clinical benefits of prasugrel are derived from a single study (TRITON TIMI 38), albeit a large and robust one. Further studies are needed to clarify the clinical profile of prasugrel in other patient groups, such as those with ACS who are medically managed. The results from the TRILOGY ACS study (NCT00699998) will provide insight into this issue. Similarly, the TRITON study included few patients of African descent, and the effect of prasugrel did not appear superior to clopidogrel in this subgroup. The TRITON population also included a very small number of Asian patients, but a phase III study is planned in this group (NCT00830960) that will provide efficacy information for this patient subgroup. Other subgroups under-represented in TRITON are those with chronic kidney disease...
(only 12% of the population had creatinine clearance <60 mL per minute)\textsuperscript{12} or severe hepatic impairment (excluded),\textsuperscript{67} both of which predispose patients with increased bleeding risk, so the efficacy and safety of prasugrel in these groups has not been clearly established. Further clarification on the risk-benefit of prasugrel compared with clopidogrel in patients aged 75 years or older is also required.

The clopidogrel loading dose used in the TRITON study was 300 mg. The 600 mg loading dose has been shown to be more effective than the 300 mg dose in reducing clinical end points after PCI, without a significant increase in major or minor bleeding events.\textsuperscript{69} While the PRINCIPLE study indicated a significantly greater acute (6-hour) antiplatelet effect with prasugrel 60 mg versus clopidogrel 600 mg,\textsuperscript{21} the impact of the 2 agents at these dosages on clinical events has not been assessed in an adequately powered randomized trial.

Clopidogrel is indicated for use in combination with aspirin for patients with recent MI, ischemic stroke, or symptomatic peripheral arterial disease, based on the results of the CAPRIE (clopidogrel versus aspirin in patients at risk of ischemic events) international clinical trial.\textsuperscript{70} However, it is not yet known whether prasugrel has clinical benefits in other groups of patients with atherothrombotic disease, outside of the ACS population undergoing PCI that was studied in TRITON. Certainly, based on the TRITON data in patients with a history of stroke or TIA, a clinical trial in the secondary prevention after acute ischemic stroke would present considerable challenges.

Another unanswered question relates to whether the bleeding risk associated with prasugrel can be ameliorated by using a lower maintenance dose and whether a lower maintenance dose will provide adequate antiplatelet effect to translate into a benefit. The TRILOGY ACS study, which is using maintenance prasugrel dosages of 5 or 10 mg (after a loading dose of 30 mg) may answer this question.\textsuperscript{68} However, the TRILOGY ACS population comprises medically managed patients; therefore, the results may not be applicable to a post-PCI population.

For formulary managers, a key question will be the relative cost-effectiveness of prasugrel and clopidogrel. Although both short- and long-term clinical outcomes favored prasugrel in the TRITON study,\textsuperscript{13,24} there was an excess of major bleeding with prasugrel that occurred principally during maintenance therapy.\textsuperscript{29} In fact, the benefit-risk of prasugrel is greatest during the first 12 days of therapy, when the difference between the prevention of ischemic end points and occurrence of bleeding end points is greatest.\textsuperscript{12,71} Therefore, relative cost-effectiveness should be established in both the acute care and community care settings, taking into account all clinical outcomes, including bleeding. Careful patient selection will also likely be a feature of formulary access to prasugrel, limiting its use to where a clear benefit was shown in the TRITON-TIMI 38 study.\textsuperscript{71}

### Conclusions

The thienopyridine antiplatelet agents are effective in reducing the risk of a second ischemic event in patients with atherothrombotic disease. The thienopyridine clopidogrel is now recommended as dual therapy with aspirin in secondary prevention for patients with both ST segment and non–ST segment ACS, including those undergoing PCI. Prasugrel is a novel thienopyridine with a faster onset of action and more potent antiplatelet effect than older agents. It has shown superiority over the currently accepted standard (clopidogrel) in reducing the risk of the composite end point of cardiovascular death, nonfatal MI, and nonfatal stroke in patients who undergo PCI following ACS at standard dosages, as well as reducing the risk of the component end points of nonfatal MI, urgent target- vessel revascularization, and stent thrombosis. The greatest benefit appears to be in patients with diabetes mellitus. However, the enhanced antiplatelet activity and greater efficacy seen with prasugrel in clinical trials has been accompanied by increased bleeding risk. The FDA advisory committee voted unanimously for the approval of prasugrel in February 2009 but with guidance to physicians about increased risk in low-weight or elderly patients and avoidance of use (a) around CABG or other surgical or invasive procedures and (b) in patients with prior or current stroke or TIA. Identification of patients at higher risk of bleeding events and attention to discontinuation of therapy before surgery may help to guide therapeutic decisions and optimize outcomes including the benefit-risk ratio.

### Authors

SARAH A. SPINLER, PharmD, FCCP, BCPS (AQ Cardiology), is Professor of Clinical Pharmacy, Department of Pharmacy Practice and Pharmacy Administration, University of the Sciences in Philadelphia, Philadelphia, Pennsylvania. CATHERINE REES, BHB, BA, is a senior medical writer at Adis Communications.

**AUTHOR CORRESPONDENCE:** Sarah A. Spinler, PharmD, FCCP, BCPS, University of the Sciences in Philadelphia, Department of Pharmacy Practice and Pharmacy Administration, 600 S. 43rd St., Philadelphia, PA 19104. Tel.: 215.596.8576; Fax: 215.596.8586; E-mail: s.spinle@usp.edu

### DISCLOSURES

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Rees performed the majority of data collection and writing of the initial draft, and both authors shared equally in the revision.
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