Platelet activation and aggregation are key contributors to the pathophysiology of acute coronary syndromes (ACS) and to ischemic complications of percutaneous coronary intervention (PCI), including spontaneous and periprocedural myocardial infarction (MI) and stent thrombosis. Platelets adhere to the site of vascular injury (whether spontaneous with ACS or iatrogenic with PCI). This initial adherence is followed by activation, which includes shape change and secretion of various procoagulant, proinflammatory, and vasoconstrictive secondary messengers, including ADP, thromboxane A2, and serotonin. Among the effects of these messengers is further activation of platelets, resulting in a feedback loop and explosive amplification of activation. ADP in particular interacts with puranergic receptors (P2Y1 and P2Y12) to amplify and sustain this activation. In addition to shape change and secretion, platelet activation leads to the exposure of glycoprotein IIb/IIIa integrin receptors, which allows for cross-linking of platelets and fibrinogen to form platelet aggregates. Local vasoconstriction and inflammation, combined with the accumulation and embolization of platelet aggregates, result in thrombosis, ischemia, and infarction.

With this pathophysiology, it is not surprising that antiplatelet agents play a key role in the prevention of ischemic complications of ACS and PCI. Three key classes of antiplatelet agents play major roles in the management of patients with these conditions: aspirin, intravenous glycoprotein IIb/IIIa integrin receptor antagonists, and thienopyridine antiplatelet agents. Aspirin inhibits the cyclooxygenase enzyme, a key mediator of arachadonic acid metabolism, resulting in a decrease in the production of proinflammatory and procoagulant mediators, including thromboxane A2, and has been demonstrated to reduce ischemic events in the setting of ST-elevation and non-ST-elevation ACS. The glycoprotein IIb/IIIa integrin receptor antagonists block platelet aggregation by interfering with the formation of platelet fibrinogen crosslinks and have also been demonstrated to improve clinical outcomes of selected patients with ACS, especially those at high risk of recurrent ischemic events and those being managed with an invasive (coronary angiography directed) strategy of care.

The thienopyridine class of antiplatelet agents has three members: ticlopidine, clopidogrel, and the subject of this review, prasugrel. All three...
drugs are prodrugs, orally inactive, and require metabolism to an active metabolite. The active metabolite of the thienopyridine binds irreversibly to the P2Y12 receptor, blocking the binding of ADP, and thereby inhibiting platelet activation and aggregation.\(^1\) Ticlopidine, the first-generation thienopyridine was initially developed and tested in patients with previous transient ischemic attack or stroke.\(^12,13\) The major utility of ticlopidine, however, was as a component of dual antiplatelet therapy in combination with aspirin for patients with PCI and intracoronary stents.\(^14-17\) The utility of this agent was shown in a series of trials comparing dual antiplatelet therapy to aspirin plus an oral anticoagulant.\(^14,15\) The utility of ticlopidine, however, was limited by the need to take the drug twice daily, and by issues with tolerability, including gastrointestinal distress and, most importantly, rare but severe hematological side effects, such as bone marrow aplasia,\(^18\) which required frequent monitoring. As such, the clinical use of ticlopidine is largely historical. However, the results of studies of ticlopidine in cardiovascular disease set the stage for the use of the second-generation thienopyridine, clopidogrel, in cardiovascular disease, including ACS and PCI.

Clopidogrel plus aspirin dual antiplatelet therapy has become the standard of care for the support of patients undergoing PCI with stenting regardless of the indication for PCI.\(^19\) In the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS)\(^20\) comparing ticlopidine plus aspirin to clopidogrel (with or without a loading dose) plus aspirin in patients with stenting, clopidogrel was found to have a significantly better safety/tolerability profile, but no difference between the two agents was observed in recurrent ischemic events.

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial compared clopidogrel plus aspirin with aspirin alone in patients with non-ST-elevation ACS\(^21\) and observed an improvement in minor bleeding outcomes and an increase in minor bleeding events. Of the patients enrolled in the CURE trial who underwent PCI, reported as the PCI-CURE,\(^22\) analysis demonstrated 30% relative reduction in the key composite end point of cardiovascular death, MI, and urgent revascularization.\(^22\) On the basis of these and other studies, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend dual antiplatelet therapy with aspirin and clopidogrel in patients with ACS for up to 1 year regardless of treatment strategy (medical, PCI, or surgery).\(^5\)

Patients with ST-segment elevation MI (STEMI) were not included in the CURE trial but also have strong clinical trial evidence for the use of dual antiplatelet therapy, including aspirin and clopidogrel. In the Clopidogrel as Adjunctive Reperfusion Therapy—Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28) trial, subjects with STEMI receiving fibrinolytic therapy were randomized to dual antiplatelet therapy with aspirin or to aspirin alone. The composite end point of death, MI, or an occluded infarct-related artery was reduced by 36%, which was highly statistically significant, without an observed increase in major bleeding or a difference in intracranial hemorrhage.\(^23\) The results of CLARITY-TIMI 28 were complemented by the report of the Clopidogrel and Metoprolol in Myocardial Infarction Trial—Second Chinese Cardiac Study (COMMIT-CCS 2),\(^24\) a large simple trial with more than 45,000 subjects enrolled within 24 hours of MI and allocated to clopidogrel daily plus aspirin or aspirin alone until hospital discharge. Clopidogrel resulted in a 0.9% absolute reduction in death, which was statistically significant.\(^24\) These studies together have resulted in the recommendation by national guidelines committees for the use of clopidogrel in patients with STEMI treated medically with or without fibrinolytic therapy.\(^3\)

**PHARMACOLOGIC LIMITATIONS OF CLOPIDOGREL**

Despite the profound successes of clopidogrel alone and in combination with aspirin for patients with ACS and those undergoing PCI, there are pharmacologic limitations of this agent.\(^25\) The antiplatelet effects of clopidogrel have a delayed onset and substantial variability among patients. With a growing number of studies using a variety of measures linking poor antiplatelet response to clopidogrel and in turn to adverse clinical outcomes, particularly coronary ischemia and stent thrombosis,\(^26-29\) an interest has emerged in the development of antiplatelet therapy that is more intensive than that offered with clopidogrel.

One such agent, prasugrel, a third-generation thienopyridine, is the focus of this review.

**PHARMACOLOGY AND EARLY PHASE CLINICAL STUDIES OF PRASUGREL**

Like ticlopidine and clopidogrel, prasugrel is a prodrug that requires activation (Fig. 1) to form an active metabolite with platelet inhibitory properties.\(^30\) Prasugrel is metabolized in a two-step process, including initial activation by plasma esterases followed by a single cytochrome P-450 (CYP)-dependent step.\(^31\) In contrast, clopidogrel is largely inactivated by plasma esterases before a two-step CYP-dependent activation.\(^31\) These
metabolic disparities appear to underlie the key pharmacodynamic differences: quicker onset, greater potency, and greater consistency of anti-platelet activity with prasugrel compared with clopidogrel. In healthy subjects, prasugrel has been demonstrated to be approximately 10-fold more potent (on a milligram basis) than clopidogrel as measured by ADP-induced platelet aggregation (IPA). Ten milligrams of prasugrel achieved higher levels of platelet inhibition than 75 mg of clopidogrel, both alone and in combination with aspirin. A key early-phase study of prasugrel included a crossover design of healthy subjects receiving both prasugrel 60 mg and clopidogrel 300 mg in random order and separated by a washout period. As early as 30 minutes, and throughout the follow-up period, higher levels of IPA were observed with prasugrel, with maximum IPA of 79%, compared with 35% with clopidogrel. In addition to higher overall levels, there was less variability in response to prasugrel and, in contrast to clopidogrel, no patients with an IPA less than 20% (a level of inhibition that cannot reliably be differentiated from placebo). As would have been predicted by the metabolic differences, substantially greater concentrations of the active metabolite of prasugrel were observed compared with the active metabolite of clopidogrel.

In results similar to those for healthy subjects, prasugrel was demonstrated to achieve higher levels of IPA in patients with stable coronary artery disease. In this study, 101 subjects with coronary artery disease were randomized to standard-dose clopidogrel (300-mg loading dose followed by 75 mg daily) or one of four dose regimens of prasugrel (40-mg loading dose followed by 5 mg daily; 40-mg loading dose followed by 7.5 mg daily; 60-mg loading dose followed by 10 mg daily; or 60-mg loading dose followed by 15 mg daily). Greater levels of IPA and fewer predefined poor responders (<20% IPA) were observed in patients receiving either 40- or 60-mg loading doses. In the maintenance phase, both 10-mg and 15-mg doses of prasugrel achieved higher IPA and had fewer poor responders than did clopidogrel. Though no significant differences were observed for bleeding events, bruising and bleeding tended to be higher in the prasugrel 15-mg treatment arm.

The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation—Thrombolysis in Myocardial Infarction 44 (PRINCIPLE-TIMI 44) trial extended the pharmacodynamic comparison of prasugrel and clopidogrel in two important ways. First, the study compared prasugrel (60-mg loading dose followed by 10 mg daily) to higher loading- and maintenance-dose clopidogrel (600-mg loading dose followed by 150 mg daily) and, second, this comparison was performed in patients with coronary artery disease undergoing cardiac catheterization with PCI if coronary anatomy was suitable. Two hundred one subjects were enrolled and randomized to receive either 60 mg of prasugrel or 600 mg of clopidogrel pretreatment before cardiac

![Prasugrel and clopidogrel structure and metabolism. E, esterases; C, cytochrome-P450.](image-url)
catheterization in the loading-dose phase of the study. Patients who received PCI entered the maintenance-dose phase, which was a two-period crossover study of 10 mg of prasugrel versus 150 mg of clopidogrel daily, with the initial treatment corresponding to the loading-dose assignment. The primary end point of the loading-dose phase, IPA at 6 hours, was higher in the prasugrel arm 75% versus 32% (P < .0001). The greater antiplatelet effects were apparent at 30 minutes and persisted through 24 hours. In addition, the effects were consistent across a broad range of platelet-function measures. At 6 hours, 27% of clopidogrel-treated patients and none of the prasugrel-treated patients had IPA less than 20%, a predefined measure of poor response. Though the absolute differences were less, a highly significant difference in IPA was also observed in the maintenance phase with mean IPA of 61% with prasugrel compared with 46% with clopidogrel (P < .0001).34

CLINICAL EVALUATION

Early-phase evaluations of prasugrel established the pharmacologic differences between prasugrel and clopidogrel outlined above: that prasugrel resulted in more rapid, more consistent, and more complete inhibition of ADP-mediated platelet aggregation. Though several studies had suggested that IPA was related to clinical outcomes,35,36 no one had shown that the pharmacologic advantages of prasugrel translated to improved clinical outcomes. The Joint Utilization of Medications to Block Platelets Optimally—Thrombolysis in Myocardial Infarction 26 (JUMBO-TIMI 26) trial was a randomized, dose-ranging safety study of prasugrel compared with clopidogrel in 904 patients with coronary artery disease undergoing planned elective or urgent PCI.37 Patients were randomized to standard-dose clopidogrel or three loading- and maintenance-dose regimens of prasugrel (40-mg loading dose followed by 7.5 mg daily; 60-mg loading dose followed by 10 mg daily; 60-mg loading dose followed by 15 mg daily). The primary end point of the study was the combination of thrombolysis in myocardial infarction (TIMI) major or minor bleeding. All treatment arms had low rates of bleeding. However, the composite end point tended to be higher in prasugrel-treated patients (1.7% versus 1.2%, hazard ratio 1.42 [0.40–5.08]), and no difference was observed in major bleeding.37 Though not powered for clinical events, major adverse clinical events tended to be lower with prasugrel (7.2% versus 9.4%, P = .31) driven primarily by a trend toward less MI (5.7% versus 7.9%, P = .23). Though no clear trend was seen among the doses of prasugrel studied for major or minor bleeding, less severe bleeding episodes tended to be more frequent with the highest dose of prasugrel, which aided in the choice of doses (prasugrel 60-mg loading dose and 10-mg maintenance dose) for the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38).38

The TRITON-TIMI 38 trial was, therefore, designed with two key aims: to evaluate a novel drug and to test a scientific concept. The trial was thus designed to answer two questions: (1) Is prasugrel (60-mg loading dose followed by 10 mg daily) safe and effective for the reduction of major ischemic events in patients with ACS undergoing PCI compared with standard-dose clopidogrel (300-mg loading dose followed by 75 mg daily)? and (2) Does a thienopyridine dose regimen (in this case prasugrel 60-mg loading dose followed by 10 mg daily), which is known to achieve higher and more consistent levels of platelet aggregation than standard-dose clopidogrel, reduce ischemic events? TRITON-TIMI 38 (Fig. 2) was designed to be a trial of patients undergoing PCI. Therefore, the inclusion criteria were designed so...
that all patients would undergo PCI. So, 13,608 patients were enrolled with one of the following: (1) moderate- to high-risk unstable angina–non-STEMI with coronary anatomy known to be suitable for PCI, (2) planned primary PCI for STEMI (regardless of known coronary anatomy), or (3) following medical therapy for STEMI with coronary anatomy known suitable for PCI. Key exclusion criteria were high risk for bleeding and prior thienopyridine use within the previous 5 days. Unlike many previous studies of anticoagulants, there were no exclusions for advanced age or renal dysfunction. Patients were treated with study medications for a minimum of 6 months and a maximum of 15 months. The primary end point of the trial was the composite of cardiovascular death, nonfatal MI, and nonfatal stroke.

In TRITON-TIMI 38, randomization to prasugrel resulted in a highly significant reduction in ischemic events with prasugrel as measured by the primary end point (9.9% versus 12.1%, hazard ratio 0.81 [0.73–0.90], P = .0004) (Fig. 3). This included similar reductions in events likely related to the loading dose (within 3 days: 4.7% versus 5.6%, hazard ratio 0.82, P = .01) and the maintenance dose (after 3 days: 5.6% versus 6.9%, hazard ratio 0.80, P = .003). The reduction in the primary end point was primarily driven by a substantial reduction in fatal or nonfatal MI (7.4% versus 9.7%, hazard ratio 0.76, P < .001). However, stroke was neutral and cardiovascular death (2.1% versus 2.4%, hazard ratio 0.89, P = .31) tended to favor prasugrel. These reductions in ischemic events were similar to those noted in the CURE study comparing clopidogrel to placebo.

Perhaps the most striking finding in the TRITON-TIMI 38 study was the efficacy of prasugrel in the reduction of stent thrombosis (ST). Stent thrombosis events were serious with nearly 90% of patients experiencing death or MI associated with the stent thrombosis event. Stent thrombosis was reduced overall by more than 50% with prasugrel (1.1% versus 24%, hazard ratio 0.48, P < .0001). The reduction in stent thrombosis was robust with respect to stent thrombosis definition, stent type (bare metal or drug-eluting stents), timing, and across several key clinical characteristics.

As with previous studies of antiplatelet agents, more potent inhibition of platelet aggregation with prasugrel resulted in more bleeding than with standard-dose clopidogrel. The key safety end point of non–coronary artery bypass graft–related TIMI major bleeding was increased with prasugrel (2.4% versus 1.8%, hazard ratio 1.32; P = .03). This increase in bleeding was consistent across several definitions of bleeding, including major plus minor (5.0% versus 3.8%, hazard ratio 1.31, P = .002), and included significant increases in rare but serious events, including life-threatening bleeding (1.4% versus 0.9%, P = .01) and fatal bleeding (0.4% versus 0.1%, P = .002).

To weigh the benefits of improved ischemic outcomes against the risks of higher rates of bleeding, a net clinical outcome (net clinical benefit) was calculated using the prespecified definition of all-cause death, nonfatal MI, nonfatal stroke, and nonfatal TIMI major bleed. This calculation favored prasugrel overall (12.2% versus 13.9%, hazard ratio 0.87, P = .004), a finding that was robust to multiple net benefit end points, including...

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**Fig. 3.** Primary Results of TRITON-TIMI 38.

the addition of less severe bleeding. In a post hoc effort to identify patients for whom the net benefit did not favor prasugrel, we identified two subgroups with a neutral benefit (the reduction of ischemic events was balanced by the increase in major bleeding): the elderly (≥75 years) and those with low body weight (<60 kg). We also identified a single major subgroup where the net outcome was worse with prasugrel: patients with a history of prior stroke or transient ischemic attack. Patients without these features had a greater relative net benefit of prasugrel compared with clopidogrel (10.2% versus 12.5%, hazard ratio 0.80, P < .001, P interaction = 0.006) than those who had at least one of these (20.2% versus 19.0%, hazard ratio 1.07, P = .43).

LESSONS LEARNED

The study of prasugrel compared with clopidogrel outlined above has significant implications both for the management of patients with ACS and those undergoing PCI, and for the understanding of the role of the platelet activation and aggregation in the clinical outcomes of these patients. In TRITON-TIMI 38, despite an active comparison with standard-dose clopidogrel, an extremely effective medication, prasugrel demonstrated superiority in the reduction of ischemic events, including MI and stent thrombosis. In addition to the benefits seen, an increase in hemorrhagic complications, including severe bleeding was observed with prasugrel. For the significant majority of patients enrolled, without specific features (prior stroke or transient ischemic attack, advanced age, or low body weight) the balance of safety and efficacy favored prasugrel treatment. In addition to offering implications for prasugrel specifically, TRITON-TIMI 38 served as a “proof of concept” study. This trial is the first adequately powered clinical trial to show that an agent (or a dose of an agent) that achieves higher and more consistent levels of IPA than standard-dose clopidogrel results in improved ischemic outcomes. These results serve as support for the growing body of literature that relates laboratory measures of platelet function, and the variability of response, to clopidogrel and to clinical outcomes. Some have criticized TRITON-TIMI 38 for the use of a 300-mg loading dose of clopidogrel, stating that 600 mg is the standard of care. In fact, before TRITON-TIMI 38, the frequent use of higher-dose clopidogrel was based on pharmacodynamic studies and small clinical trials with few end points. Until the definitive trial of clopidogrel dosing (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events—Optimal Antiplatelet Strategy for Interventions 7 [CURRENT-Oasis 7]) is reported, the TRITON-TIMI trial stands as the single greatest support for the use of higher-dose clopidogrel in clinical practice. Though 600 mg of clopidogrel has substantially less antiplatelet effect than the prasugrel dose in TRITON-TIMI 38, 600 mg of clopidogrel has greater antiplatelet effect than 300 mg and therefore may have a portion of the benefits observed with prasugrel. Had TRITON-TIMI 38 not shown a reduction in ischemic events, it would have been difficult to expect a less potent thienopyridine dose regimen to improve outcomes compared with standard dosing. In addition, these data support the continued development of potent antiplatelet agents for the reduction of cardiovascular events.

REMAINING QUESTIONS

While the evaluation of prasugrel to date has answered several important questions about the safety and efficacy of the drug and has provided support for the importance of intensive platelet inhibition in ACS and PCI, it has also raised several more questions for both the clinician and the platelet biologist. First, which aspect of the pharmacologic profile of prasugrel is most important for the improvement in outcomes: the speed of onset, the level of inhibition on a population basis, or the consistency of inhibition? Is the same aspect of the profile responsible for the excess bleeding? In each case (both for safety and efficacy), can we use clinical features or laboratory measures (biomarkers, genetics, platelet function testing) to better identify the patients who are most likely to benefit with the least harm from intensive antiplatelet therapy to better target therapy on an individual basis? Will prasugrel result in improved outcomes with adequate safety in patients with ACS treated medically (this question is being evaluated in the ongoing Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes [TRILOGY] study)? Studies will address additional question that the prasugrel experience has raised. Can the results of TRITON-TIMI 38 be replicated with the lesser difference in antiplatelet effect obtained by the use of higher-dose clopidogrel? This will be addressed by CURRENT-Oasis 7. Will blocking the P2Y12 receptor with nonthienopyridine antiplatelet agents with different pharmacologic profiles, such as cangrelor or AZD6140, have similar effects to prasugrel? Cangrelor is being evaluated in the ongoing Clinical Trial Comparing Cangrelor to Clopidogrel in Subjects Who Require Percutaneous Coronary Intervention (CHAMPION PCI). AZD6140 is being studied in the Platelet Inhibition and Patient
Outcomes (PLATO) study. Will antiplatelet agents that target other platelet receptors, such as the PAR-1 receptor, improve clinical outcomes. The ongoing Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events—Thrombolysis in Myocardial Infarction (TRA 2P–TIMI 50) and Trial to Assess the Effects of SCH530348 in Preventing Heart Attack and Stroke in Patients with Acute Coronary Syndromes (TRACER) will address this question. Other questions remain: What is the role of platelet function testing in the future of patient management? Will there come a time that antiplatelet therapy will be tailored not only to patient risk, but also to respond to a single agent or a series of agents?

SUMMARY

Platelet activation and aggregation play key roles in the management of ischemic complications of ACS and PCI. Dual antiplatelet therapy with aspirin and the thienopyridine clopidogrel has become the standard of care for prevention of such complications. Prasugrel, a novel thienopyridine antiplatelet agent, has been demonstrated to have favorable pharmacologic properties including rapid onset and potent and consistent inhibition of platelet aggregation. When compared directly against clopidogrel in the TRITON-TIMI 38 trial, prasugrel resulted in significant reductions in ischemic events including MI and stent thrombosis, but with more bleeding. Prasugrel shows promise for improvements in patient care, for better understanding of platelet biology, and for more helpful evaluations of antiplatelet therapy.

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