**Prasugrel**

**A New Antiplatelet Drug for the Prevention and Treatment of Cardiovascular Disease**

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**Abstract:** Prasugrel, trade name Effient, is an investigational new antiplatelet drug currently under review for clinical use by the Food and Drug Administration. It is a thienopyridine analog with a structure similar to that of clopidogrel and ticlopidine. Thienopyridine derivatives inhibit platelet aggregation induced by adenosine diphosphate by irreversibly inhibiting the binding of adenosine diphosphate to the purinergic P2Y₁₂ receptor on the platelet surface. Prasugrel has been shown to be a potent antiplatelet agent with a faster, more consistent, and greater inhibition of platelet aggregation compared with clopidogrel. It is debatable, however, how effectively these pharmacologic benefits will translate to clinical benefits. The results of the large TRITON-TIMI 38 trial, which compared prasugrel and clopidogrel in patients with acute coronary syndrome who were scheduled to receive coronary stents, demonstrated a significant reduction in ischemic events, including stent thrombosis, with prasugrel, but with an increased risk of major bleeding. The exact role of prasugrel in the management of ischemic heart disease is still being defined, but the risk:benefit ratio will likely play a major role in directing the best place for therapy with this new agent.

**Key Words:** prasugrel, antiplatelet agents, cardiovascular disease, P2Y₁₂ inhibition

*(Cardiology in Review 2008;16: 314–318)*

Prasugrel, trade name Effient, is an investigational new antiplatelet drug that is being developed by Daiichi Sankyo Co., Ltd. and Ube Industries Ltd., along with its US partner Eli Lilly & Co. It is currently being reviewed by the US Food and Drug Administration for clinical approval. Prasugrel is a thienopyridine analog with a structure similar to that of clopidogrel and ticlopidine (Fig. 1). Thienopyridine derivatives inhibit platelet aggregation induced by adenosine diphosphate (ADP) by irreversibly inhibiting the binding of ADP to the purinergic P2Y₁₂ receptor on the platelet surface. In 1991, ticlopidine was the first drug in this family to be approved, but due to its higher incidence of adverse reactions, such as neutropenia, abnormal liver function, and thrombotic thrombocytopenic purpura, along with its slower maximal inhibition of platelet aggregation, it has been largely replaced by clopidogrel in clinical practice. Clopidogrel, approved for use in the United States in 1997, is used in the secondary prevention of myocardial infarction, stroke, and peripheral artery disease due to the results of the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events trial. It has also become a part of the standard therapy for patients after percutaneous coronary intervention (PCI) and stent placement. Although clopidogrel therapy has many proven clinical benefits, there are several shortcomings of clopidogrel, such as the interpatient variability in antiplatelet effects, delayed inhibition of platelet aggregation, and the occurrence of secondary thrombotic events. Thus, there has been a need for the development of new antiplatelet therapies, such as prasugrel, in an attempt to overcome such shortcomings.

**MECHANISM OF ACTION**

Prasugrel [2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno(3,2-c)pyridine] has been shown to be a potent ex vivo inhibitor of the Gₛ-linked P2T receptor on rat platelets in an irreversible manner. This study also showed that prasugrel produced a specific and dose-related inhibition of ex vivo ADP-induced platelet aggregation that developed rapidly. When compared with clopidogrel and ticlopidine in this study, a single oral administration of prasugrel in rats was reported to be approximately 10 times more potent in antiaggregatory efficacy than that of clopidogrel and up to 100 times more potent than ticlopidine. Although the duration of inhibition of platelet aggregation of prasugrel and clopidogrel was similar, prasugrel had a more rapid onset of antiaggregatory action in rat platelets. Although the precise mechanism responsible for the rapid onset of prasugrel could not be determined, it was hypothesized that it may be due to prasugrel being more rapidly metabolized to its active hepatic metabolite, R-99224, [(2Z)-1-[2-cyclopropyl [2-fluoro phenyl]-2-o xoethyl]-4-mercapto-3-piperidinyldiene] which inhibits the in vitro aggregation of rat
platelets. A subsequent study of genetically altered mice showed prasugrel to selectively inhibit the binding of ADP to the purinergic P2Y12 receptor on the platelet surface, thereby inhibiting ADP-mediated platelet aggregation.

In humans, clopidogrel, which is also inactive in vitro, requires in vivo hepatic metabolism through the cytochrome P450-dependent pathway to form an intermediate metabolite (2-oxo-clopidogrel) that is hydrolyzed to generate the highly active metabolite. This pathway requires 2 cytochrome P450-dependent oxidative steps to generate the thiol-containing active metabolite, which in turn irreversibly binds to the P2Y12 receptor via cysteine residues. In contrast, prasugrel is rapidly deesterified to R-95913, which is then converted to R-138727 via cytochrome P450 metabolism. This compound has the same chemical structure as R-99224, the active metabolite of prasugrel found in rats. This requires only 1 cytochrome P450-dependent oxidative step, which is more efficient and may account for the more rapid onset seen with prasugrel.

**PHARMACODYNAMICS**

The effects of prasugrel are time and dose dependent with a single, oral 40–60 mg loading dose (LD) producing rapid and consistent inhibition of ADP-stimulated platelet aggregation, with a near-maximal effect seen in healthy volunteers 60–90 minutes after dosing. This effect is maintained for at least 24 hours, reflecting the irreversible nature of platelet inhibition. A single ascending dose study in healthy subjects showed that a LD of 30 or 75 mg produced a 57–59% mean inhibition of platelet aggregation 2 hours post dose, which was maintained throughout the subsequent 22 hours. A multiple oral dose study demonstrated that the inhibition of platelet aggregation induced by prasugrel reached a steady state by 2–4 days after initiation of daily dosing and was maintained throughout the dosing period with full recovery of platelet aggregation occurring between 48 hours and 7 days after discontinuation of dosing.

For comparison, previous studies have characterized clopidogrel as having a ceiling effect in healthy subjects, of approximately 40% inhibition of platelet aggregation after a single oral 400 mg dose detected 2 hours after dosing and remaining relatively stable for up to 48 hours. Steady state inhibition is achieved in 2–4 hours when a 75 mg maintenance dose is given after a 300 or 600 mg LD.

**PHARMACODYNAMICS OF PRASUGREL VERSUS CLOPIDOGREL IN HEALTHY SUBJECTS**

Studies were subsequently done to compare prasugrel and clopidogrel in healthy subjects. When LD’s of prasugrel and clopidogrel were compared, a 60 mg LD of prasugrel resulted in a faster and greater inhibition of platelet aggregation, along with less intersubject variability compared with the standard 300 mg LD of clopidogrel in the absence of concurrent aspirin therapy. A maximal plateau effect was observed approximately 1 hour after administration of prasugrel compared with about 4 hours after the administration of clopidogrel. This study also showed that the magnitude of platelet inhibition was higher at any point during the 24-hour period after administration of clopidogrel. When combined with 325 mg of aspirin, a LD of prasugrel 60 mg showed a greater level of platelet inhibition, approximately 60%, as opposed to a LD of 300 mg clopidogrel and 325 mg of aspirin, which only showed approximately a 35% inhibition of platelet aggregation in healthy subjects. When maintenance dosages of prasugrel and clopidogrel were compared, both 10 and 20 mg dosages of prasugrel showed a greater level of platelet inhibition compared with the standard 300 mg LD of clopidogrel in the absence of concurrent aspirin therapy. 

![Chemical structures of prasugrel, clopidogrel, and ticlopidine and their active metabolites.](image-url)
daily doses of prasugrel achieved steady-state inhibition more quickly and consistently than did clopidogrel 75 mg in healthy subjects, with a mean inhibition of platelet aggregation of 71% with prasugrel 10 mg compared with 37% with clopidogrel 75 mg. However, this study also showed that prasugrel produced a greater prolongation of bleeding time (3.5 times placebo) at the end of the 10-day study compared with clopidogrel (1.4 times placebo). For comparison, bleeding time prolongation with aspirin has previously been reported as 1.5 times. Similar results were seen in studies comparing prasugrel and clopidogrel in patients with stable coronary artery disease and in patients with planned PCI in the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation—Thrombolysis In Myocardial Infarction 44 (PRINCIPLE-TIMI 44) trial.39

**PRASUGREL AS A THERAPEUTIC AGENT**

Dual antiplatelet therapy with aspirin plus a thienopyridine has proved to be a useful combination for the prevention of acute and subacute thrombosis after PCI. Data from the Clopidogrel to Reduce Events During Observation (CREDO) trial suggest that long term (ie, 1 year) clopidogrel plus aspirin therapy can significantly reduce the risk of major vascular events after PCI compared with aspirin alone, although this data also showed that a 300 mg LD of clopidogrel must be given at least 6 hours before PCI, and perhaps as much as 15 hours, to reduce periprocedural events. However, because of the fact that some patients planned for PCI may need coronary artery bypass surgery (CABG) instead, there is a reluctance in current clinical practice to give clopidogrel before the coronary anatomy has been defined and a decision regarding the need for PCI or CABG has been made due to the risk of major bleeding events from clopidogrel therapy seen in CABG.

Because of the faster, more consistent, and greater inhibition of platelet aggregation seen with prasugrel compared with the standard 300 mg LD of clopidogrel, a study was conducted in patients undergoing elective or urgent PCI in the United States and Canada, called the Joint Utilization of Medications to Block Platelets Optimally—Thrombolysis In Myocardial Infarction (JUMBO-TIMI 26) trial. This study was a phase 2, randomized, dose ranging, double-blind safety trial of prasugrel versus clopidogrel in 904 patients undergoing elective or urgent PCI at 80 sites. Patients were randomly assigned to either the standard 300 mg LD of clopidogrel along with a maintenance dose of 75 mg daily or of 3 prasugrel regimens: low dose (40 mg LD followed by 7.5 mg daily), intermediate dose (60 mg LD followed by 10 mg daily), or high dose (60 mg LD followed by 15 mg daily). The primary end point was non-CABG-related “significant hemorrhage” at 30 days, defined as the composite of TIMI major and minor hemorrhage. Additional efficacy end points included death, MI, stroke, recurrent myocardial ischemia requiring hospitalization, and clinical target vessel thrombosis. Results from this study showed no difference in the rate of clinically significant (TIMI major plus minor) non-CABG-related bleeding between patients treated with prasugrel and those treated with clopidogrel, although modest increases associated with prasugrel could not be ruled out due to the lower-than-expected bleeding rates in both treatment groups. This study also showed a trend toward fewer ischemic events with prasugrel, with an acceptable safety profile. The results of this trial served as the foundation for the subsequent TRITON-TIMI 38 trial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibition with prasugrel—Thrombolysis In Myocardial Infarction (TRITON-TIMI 38).

The TRITON-TIMI 38 trial was designed to compare the efficacy and safety of prasugrel and clopidogrel in PCI-treated acute coronary syndrome (ACS) patients. The study was a phase 3, randomized, double-blinded, multinational, parallel group, clinical trial. The study enrolled 13,608 patients from 707 sites in 30 countries with moderate-to-high risk ACS undergoing scheduled PCI, including those with unstable angina or non–ST-elevation MI and ST-elevation MI. Patients were randomly assigned to either prasugrel 60 mg LD followed by 10 mg daily or clopidogrel 300 mg LD followed by 75 mg daily for up to 15 months. The primary end point was the time of the first event of cardiovascular death, MI, or stroke. The results showed that treatment of patients with ACS, across the full spectrum of such syndromes, with prasugrel as compared with clopidogrel, resulted in a significant absolute reduction (2.2%) and a relative reduction (19%) of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (12.1% for clopidogrel vs. 9.9% for prasugrel; P < 0.001). The rates of ischemic events and stent thrombosis were also reduced with prasugrel as compared with clopidogrel. However, as may have been expected, prasugrel was associated with a significant increase in the rate of bleeding compared with clopidogrel, with a relative increase of 32% in non-CABG-related TIMI major bleeding (2.4% vs. 1.8%; P = 0.03). In addition, prasugrel treatment also resulted in more life-threatening TIMI major hemorrhages (1.4%, vs. 0.9%; P = 0.01) and fatal bleeds (0.4% vs. 0.1%; P = 0.002). Interestingly, patients with a history of stroke or transient ischemic attack, those who were elderly (age ≥75), and those with a body weight <60 kg were found to generally benefit less from prasugrel with greater absolute levels of bleeding.

Furthermore, this study showed that for patients with moderate-to-high risk ACS undergoing scheduled PCI, including those with unstable angina or non–ST-elevation MI and ST-elevation MI, that for every 1000 patients treated with prasugrel as compared with clopidogrel, 23 myocardial infarctions would be prevented with an increase in 6 non-CABG-related TIMI major hemorrhages. In other words, the number of patients needed to be treated with prasugrel compared with clopidogrel to prevent 1 event of cardiovascular death, MI, or stroke in a 15-month period is 46, and the number of patients needed to be treated with prasugrel as compared with clopidogrel to result in an excess non-CABG-related TIMI major hemorrhage is 167.

Similar to aspirin, there is also a variability in the antiplatelet response to clopidogrel. The relative antiplatelet effects of higher doses of clopidogrel than those used in...
TRITON-TIMI 38 in patients undergoing PCI were compared with those of prasugrel in the PRINCIPLE-TIMI 44 trial. In this study the antiplatelet effects of prasugrel 60 mg LD followed by a 10 mg/d maintenance dose were compared with a clopidogrel 600 mg LD followed by a 150 mg/d maintenance dose. Greater inhibition of platelet aggregation at all time points measured from 30 minutes to 24 hours was observed in patients receiving prasugrel compared with high LD clopidogrel. During the maintenance dose phase, greater inhibition of platelet aggregation was also seen in those subjects receiving prasugrel compared with high maintenance dose clopidogrel. The trial was not powered statistically for clinical endpoints. Bleeding tended to be more frequent with prasugrel, although no significant differences were observed.

Based on the results of TRITON-TIMI 38, it seems that greater antiplatelet efficacy with drug therapy may be associated with additional clinical benefit on thrombotic events, but with an increased risk of bleeding. Future research studies may require individualized antiplatelet therapy regimens based on point-of-care testing of platelet function, similar to what is done with monitoring of prothrombin times in patients receiving warfarin, so as to maximize benefit of this treatment while minimizing risk. As with warfarin, too much anticoagulant activity with antiplatelet drugs, resulting in bleeding, will counteract the potential benefits of these antithrombotic treatments.

CURRENT STATUS
Prasugrel is currently an investigational drug in the United States. It was submitted for approval to the Food and Drug Administration in December 2007 for the treatment of ACS patients who will receive PCI. At the time of this writing, FDA action on the prasugrel application is expected on September 26, 2008. In the meantime, the phase 3 TRILOGY ACS (Targeted platelet Inhibition to Clarify the Optimal StrategY to medicallY manage ACS) trial is currently underway. TRILOGY ACS is a multicenter, double-blind, randomized, controlled trial of approximately 10,000 patients with ACS who will receive medical management without planned revascularization. This study will compare the safety and efficacy of prasugrel and clopidogrel in reducing the risk of cardiovascular death, heart attack, or stroke.

Other ongoing and planned trials include the SWAP study, the ACAPULCO study, and the OPTIMUS-3 study. The ongoing SWAP study is a multicenter randomized, active controlled trial designed to assess the impact of prasugrel after a switch from clopidogrel compared to clopidogrel on various parameters of platelet function. The ACAPULCO study will compare pharmacodynamic differences between high LD and maintenance doses of clopidogrel and standard doses of prasugrel in patients with ACS who are undergoing PCI. The OPTIMUS-3 study will compare standard doses of prasugrel with high LD and maintenance doses of clopidogrel in patients with type 2 diabetes and coronary artery disease.

REFERENCES


