

# Improving outcomes in patients undergoing percutaneous coronary intervention: role of prasugrel

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**Abstract:** Dual oral antiplatelet therapy, aspirin plus thienopyridine, has permitted a rapid increase in the use of coronary intervention procedures. Clopidogrel is the thienopyridine of choice for dual antiplatelet therapy in patients treated with percutaneous coronary intervention. However, there are two issues with clopidogrel: (1) clopidogrel's antiplatelet activity is delayed because the drug needs to be metabolized into its active form and (2) variability in patient response to clopidogrel has been demonstrated. To overcome these shortcomings of clopidogrel, new more potent inhibitors of P2Y<sub>12</sub> receptors, which have a more rapid onset of action have been introduced for clinical evaluation. This article is a nonexhaustive review of the literature and concentrates on prasugrel, a third-generation, oral thienopyridine. The purpose is to summarize the current knowledge about the benefits and risks of prasugrel and to outline the most prudent strategies for the drug's clinical use.

**Keywords:** P2Y<sub>12</sub> receptors, prasugrel, oral thienopyridine, dual oral antiplatelet therapy

## Introduction

Recognition that activation of platelets, rather than the coagulation pathway, increases the risk of stent-associated thrombosis<sup>1</sup> has led to the strategy of platelet inhibition with a combination of antiplatelet drugs with complementary mechanisms of action as an adjuvant therapy for percutaneous coronary intervention (PCI). Complementary and independent mechanisms, irreversible inhibition of the thromboxane A<sub>2</sub>, adenosine diphosphate (ADP) and glycoprotein IIb/IIIa platelet recruitment pathways, have produced cumulative decreases in thrombotic events with acceptable bleeding risks following stent implantation.<sup>2</sup>

Dual oral antiplatelet therapy, aspirin plus thienopyridine, has permitted a rapid increase in the use of coronary intervention procedures. PCIs have become the most commonly performed coronary revascularization procedures, accounting for approximately 60% of all revascularizations.<sup>3,4</sup> Therefore, optimizing the outcome after the procedure through the use of adjunctive antiplatelet therapy, which provides maximum protection against thrombosis without increasing the risk of bleeding, can have a substantial impact on cardiovascular morbidity and mortality.

## Thienopyridines

Thienopyridine derivatives irreversibly modify platelet P2Y<sub>12</sub> receptors by covalently binding to cysteine residues of the receptor.<sup>5</sup> The proportion of ADP receptors sensitive to the effects of thienopyridines is limited to 60%–70%.<sup>6</sup> Currently there are two equally effective thienopyridines,<sup>7,8</sup> ticlopidine and clopidogrel, available

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for clinical use. Clopidogrel is better tolerated and more convenient to use (once-daily dosing) compared to ticlopidine.<sup>7</sup> As a result, clopidogrel has almost replaced ticlopidine as the thienopyridine of choice for dual antiplatelet therapy in patients treated with PCI.<sup>9</sup> Clopidogrel decreases the incidence of coronary stent thrombosis; additionally it has been approved and has proven beneficial in the reduction of myocardial infarction, stroke, and vascular death in patients with atherosclerotic vascular disease.<sup>10</sup> Beyond its anti-aggregation effect, clopidogrel decreases the expression of activated platelet-dependent inflammatory markers such as the CD40 ligand (a potent stimulus of vascular inflammation) and CD62 P-selectin in patients undergoing PCI.<sup>11,12</sup>

## Clopidogrel limitations

Clopidogrel is an inactive prodrug of thienopyridine, which needs to be metabolized by the hepatic cytochrome P450 enzymes (CYP450) into the active compound.<sup>13</sup> However, only a small percentage of administered clopidogrel is metabolized by CYP450. The majority of clopidogrel is hydrolyzed to an inactive derivative that accounts for 85% of the clopidogrel-related compounds circulating in plasma.<sup>14</sup> The need for metabolization delays the blocking of P2Y<sub>12</sub> platelet receptors and thus, the drug's antiplatelet activity. Additionally, patient variability to clopidogrel has been demonstrated and shown to follow a typical bell-shaped or normal curve distribution.<sup>15,16</sup> The variable inhibition of platelet aggregation (IPA) observed with clopidogrel seems to result from lower exposure to the active metabolite.<sup>17</sup> Therefore, all factors that influence drug absorption<sup>18</sup> and metabolic activation (ie, CYP450 activity)<sup>19,20</sup> can affect drug effectiveness.

In the clopidogrel-efficacy curve, a relation between the pre- and post-treatment platelet reactivity index was found.<sup>21</sup> Clopidogrel's capacity to inhibit platelet ADP-induced platelet activation was found to be limited. This can be partially explained by the greater proportion of low responders to clopidogrel in patients with diabetes who have enhanced platelet reactivity.<sup>20,22</sup> Therefore, the degree of platelet suppression after clopidogrel was lower in patients undergoing PCI, for acute coronary syndrome, than in patients with stable coronary artery disease.<sup>21,23,24</sup>

Patients on clopidogrel therapy with lower responsiveness to clopidogrel had an increased rate of recurrent cardiovascular events.<sup>25,26</sup> The best antiplatelet effects occurred at loading doses of 600 mg and maintenance doses of 150 mg a day.<sup>27</sup> Nonresponsiveness to high loading doses has also been reported in clinical studies. One of the largest of these studies

(N = 804) reported that "nonresponsiveness" to a clopidogrel 600 mg loading dose was a strong independent predictor of stent thrombosis in patients receiving drug-eluting stents.<sup>28</sup>

To overcome shortcomings of clopidogrel, new more potent inhibitors of P2Y<sub>12</sub> receptors, with a more rapid onset of action have been introduced for clinical evaluation, these include: prasugrel, cangrelor, and AZD 6140.

## Prasugrel Drug characteristics

Prasugrel is also a prodrug and must be converted to an active form before binding irreversibly to the P2Y<sub>12</sub> receptor and inhibiting platelet aggregation for the life of the platelet. Prasugrel is rapidly absorbed and extensively metabolized. Prasugrel is quickly hydrolyzed to pharmacologically inactive thiolactone (R-95913).<sup>29,30</sup> Thiolactone (R-95913) is further metabolized (oxidized) by intestinal and hepatic CYP-450 enzymes, which leads to formation of the active metabolite. In humans, renal excretion accounts for approximately 70% prasugrel metabolites.<sup>29,30</sup> The antiplatelet effects of prasugrel are time- and dose-dependent.

## Onset of action and antiplatelet efficacy

Conversion of clopidogrel to its active metabolite is a 2-step, CYP450-dependent process.<sup>14</sup> However, prasugrel requires only one CYP450-dependent oxidative step to generate the thiol-containing active metabolite.<sup>30</sup> This difference may underlie the more rapid metabolic conversion and onset of action of prasugrel compared with clopidogrel.<sup>31</sup> The active metabolite of prasugrel was detected in plasma within 15 min of dosing and reached a maximum plasma concentration approximately 30 min after dosing.<sup>29,31</sup>

In a randomized, crossover, ex vivo study, healthy subjects received a single loading dose of prasugrel (60 mg) or clopidogrel (300 mg).<sup>31</sup> Inhibition of platelet aggregation with prasugrel was evident after 15 min. Platelet inhibitory effects of a 60 mg loading dose of prasugrel 30 min after administration was greater than the maximum antiplatelet effects of clopidogrel 12 hours after a 300 mg loading dose.

In patients with stable atherosclerosis, prasugrel (60 mg loading dose) achieved quicker and greater inhibition of ADP-induced platelet aggregation, compared to a 600 mg loading dose of clopidogrel.<sup>17</sup> The difference in the IPA between clopidogrel and prasugrel was observed in as little as 30 min following drug administration. Within 30 minutes, prasugrel had achieved antiplatelet effects superior to the maximum antiplatelet effects attained by 600 mg of clopidogrel over the 24-hour long observation period.

The data from the PRINCIPLE-TIMI 44 (Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation- Thrombolysis in Myocardial Infarction)<sup>32</sup> study extend the results to patients undergoing cardiac catheterization for planned percutaneous coronary intervention. This trial compared the same dose regimen of prasugrel with high-dose clopidogrel (600 mg loading dose and 150 mg/d maintenance dose). Substantially and statistically significant greater platelet inhibition with prasugrel was observed at all time points studied during the loading dose and maintenance dose phases. Prasugrel was more potent and consistent in comparison to clopidogrel in the PCI setting.

The active metabolites of prasugrel and clopidogrel have similar potency at the platelet level.<sup>33</sup> The greater potency of prasugrel to inhibit platelet P2Y<sub>12</sub> receptors in patients with coronary artery disease, compared with clopidogrel, has been linked to more efficient generation of prasugrel's active metabolite, to higher peak plasma levels and greater exposure of platelets to the active metabolite.<sup>17,31</sup>

### Inter-individual variability

Studies including patients with coronary artery disease have documented inter-individual variability relative to clopidogrel's capacity to inhibit platelet aggregation.<sup>15,16,34</sup> A substantial proportion (24%<sup>35</sup> nonresponders with the clopidogrel 300 mg and 11% nonresponders with the clopidogrel 600 mg)<sup>34</sup> of the patients undergoing elective PCI were evaluated as nonresponders to clopidogrel treatment. The proportion of patients, with limited clopidogrel efficacy, was even higher in patients with acute myocardial infarction.<sup>36</sup> The percentage of prasugrel nonresponders, in patients with stable coronary artery disease (using the same definition for nonresponse; IPA < 20% in response to 20 μM ADP), was only 3% after the 40 and 60 mg doses of prasugrel.<sup>37</sup> A crossover study in healthy, aspirin-free subjects demonstrated that all individuals who responded poorly to the clopidogrel 300 mg achieved robust platelet inhibition when switched to prasugrel.<sup>31</sup>

### Translation of prasugrel benefits into the clinical outcomes

The degree of suppression of platelet activity achieved through the use of antithrombotic agents should be balanced against the risk of atherothrombotic events.<sup>38</sup> Accordingly the target population for prasugrel includes patients at high risk of thrombo-occlusive events:

- patients undergoing PCI for STE myocardial infarction,

- patients at risk of stent thrombosis and patients after stent thrombosis,
- diabetics undergoing PCI,
- patients with the presence of genetic variants related to nonresponsiveness to clopidogrel.

### Patients undergoing PCI for STE myocardial infarction

The TRITON-TIMI 38 (TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibition with prasugrel)<sup>39</sup> found that in patients with acute coronary syndromes scheduled for PCI, prasugrel (60 mg loading dose and a 10 mg daily maintenance dose), compared with approved doses of clopidogrel (300 mg loading dose and a 75 mg daily maintenance dose), yielded significantly reduced rates of ischemic events. The primary efficacy end point (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) occurred in 12.1% of patients receiving clopidogrel and 9.9% of patients receiving prasugrel ( $p < 0.001$ ). There were also significant reductions in the prasugrel group relative to rates of (i) myocardial infarction (9.7% for clopidogrel vs 7.4% for prasugrel;  $p < 0.001$ ), (ii) urgent target-vessel revascularization (3.7% vs 2.5%;  $p < 0.001$ ), and (iii) stent thrombosis (2.4% vs 1.1%;  $p < 0.001$ ). Death from cardiovascular causes and overall mortality did not differ significantly between treatment groups. However, this clinical benefit was accompanied by a significant increase in the risk of serious bleeding with prasugrel. Major bleeding was observed in 2.4% of patients receiving prasugrel and in 1.8% of patients receiving clopidogrel ( $p = 0.03$ ). In addition, the prasugrel group showed an increased rate of life-threatening bleeding (1.4% vs 0.9%;  $p = 0.01$ ) and fatal bleeding (0.4% vs 0.1%;  $p = 0.002$ ). A post hoc analysis of the study data identified three subgroups that had greater bleeding risk than the overall studied population: (i) patients with a history of stroke or transient ischemic attack, (ii) age  $\geq 75$  years, and (iii) body weight < 60 kg.

TRITON-TIMI 38 was designed to compare clopidogrel with prasugrel in patients undergoing PCI over the entire spectrum of acute coronary syndrome with moderate-to-high-risks. Montalescot and colleagues<sup>40</sup> recently published a prespecified analysis from the subgroup with STE myocardial infarctions. Patients with STE myocardial infarction underwent primary PCI within 12 hours of symptom onset or secondary PCI within 14 days of myocardial infarction for ongoing or recurrent ischemia or as part of a routine invasive strategy.<sup>39</sup> The significant reduction in primary ischemic endpoint with prasugrel was consistent with that in the population with unstable angina or non-STE

myocardial infarction. At 30 days, 6.5% of patients in the prasugrel arm had met the primary endpoint compared with 9.5% in the clopidogrel arm ( $p = 0.0017$ ). Cardiovascular death ( $p = 0.0469$ ) and all causes of death ( $p = 0.0445$ ) were also significantly reduced with prasugrel. After 15 months, rates of myocardial infarction and stent thrombosis remained significantly reduced with prasugrel. Differences in all-cause and cardiovascular deaths between the groups lost statistical significance. The benefit from the more intensive platelet inhibitory effects associated with prasugrel was more pronounced in patients at higher risk. Patients with anterior myocardial infarctions had significantly ( $p = 0.0003$ ) lower incidence of primary endpoint with prasugrel (9.8%) compared with clopidogrel (16.3%). In individuals with nonanterior myocardial infarctions, treatment effects did not differ with regard to the primary endpoint (9.9% clopidogrel vs 10.1% prasugrel;  $p = 0.8749$ ). In the subgroup with STE myocardial infarctions, no difference was reported between prasugrel and clopidogrel in thrombolysis in myocardial infarction (TIMI) major bleeding, life-threatening bleeding or intracranial hemorrhage. Prasugrel was associated with a significantly increased risk for TIMI major bleeding after coronary artery bypass graft surgery at 15 months, compared with clopidogrel (18.8% vs 2.7%;  $p = 0.0033$ ).

No randomized studies have been identified that compared prasugrel with clopidogrel 600 mg in patients with acute coronary syndromes. The ongoing TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) study<sup>41</sup> is comparing the tolerability and efficacy of a reduced dose of prasugrel (30 mg loading dose, 5 mg/d maintenance dose) with those of clopidogrel (300 mg loading dose, 75 mg/d maintenance dose) in reducing the risk of cardiovascular death, heart attack, or stroke in patients with an acute coronary syndrome who are to be medically managed without planned revascularization.

## Patients at risk of stent thrombosis and patients after stent thrombosis

Despite combined antiplatelet therapy, stent thrombosis persists at a rate of 0.5%–2% in elective interventions, and up to 6% in patients with acute coronary syndromes.<sup>42</sup> In cases of immediate reperfusion therapy by means of emergency PCI, patients with stent thrombosis have progressed to a major myocardial infarction, with a consequential significant decline in left ventricular function – a strong negative predictor of long-term survival.<sup>42–45</sup> Clinical and angiographic predictors of stent thrombosis have been identified; the most important predictors

involved a poor post-procedural result such as inadequate stent expansion, residual dissection, and inappropriate IPA.<sup>43,44</sup> Therefore, improvement in stenting techniques and proper IPA represent variable of causal importance. Unfortunately, patient-related factors including diabetes mellitus, extent of coronary artery disease, and renal failure are not modifiable.

In the TRITON-TIMI 38, the overall mortality rate for patients with stent thrombosis was 26%.<sup>45</sup> In the same study, prasugrel, compared with the approved dose of clopidogrel, reduced the rate of stent thrombosis by 52% ( $p < 0.001$ ). The reduction in stent thrombosis was consistent across multiple subgroups with respect to baseline characteristics (age, sex, acute coronary syndrome presentation, creatinine clearance, diabetes, or previous myocardial infarction) and treatment characteristics (glycoprotein IIb/IIIa use, stent length, and presence of bifurcation stenting). The greatest absolute benefits were seen in patients at higher risk for stent thrombosis, such as those with longer stents, bifurcation stents, impaired kidney function, and diabetes. Similar benefits of prasugrel were also seen in patients who received loading doses of study drugs before PCI (0.83% vs 2.23%;  $p = 0.002$ ) or after the start of the procedure (1.24 vs 2.39%;  $p < 0.0001$ ).

Prasugrel reduced early (1.56% vs 0.64%;  $p < 0.001$ ) as well as late (0.82% vs 0.49%;  $p = 0.035$ ) stent thrombosis in patients with acute coronary syndromes treated with either bare metal or drug-eluting stents.<sup>45</sup> As the TRITON results demonstrate, the reduction in stent thrombosis by prasugrel should be weighed against its increased bleeding risk. However, subgroup analyses of the study<sup>39,45</sup> found no increased bleeding risk with prasugrel, compared with clopidogrel, in patients at increased risk of stent thrombosis, such as diabetic patients and those with STE myocardial infarction. Recommendation of prasugrel for patients at high risk of stent thrombosis and in patients after stent thrombosis would be a very prudent strategy.

## Diabetics undergoing PCI

Diabetes mellitus had an independent adverse effect on clinical outcomes in patients with coronary artery disease.<sup>39,47,48</sup> Diabetic patients have been shown to be poor responders to clopidogrel.<sup>20,49,50</sup> Moreover, a high clopidogrel loading dose (600 mg) has been unable to satisfactorily inhibit platelet reactivity in diabetics undergoing elective PCI.<sup>20,51</sup> Prasugrel treatment (60 mg loading dose) resulted in a significantly lower proportion of diabetic patients with weak inhibition of ADP induced platelet activation, compared with 600 mg of clopidogrel.<sup>51</sup> The relationship between insufficient inhibition of platelet reactivity in diabetic patients,



on dual antiplatelet therapy, and a greater risk of adverse cardiovascular events has been demonstrated.<sup>50</sup>

Subgroup analysis from the TRITON-TIMI 38<sup>52</sup> reports that the composite of cardiovascular death, myocardial infarction, and stroke, was significantly reduced with prasugrel, among subjects without diabetes mellitus (9.2% vs 10.6%;  $p = 0.02$ ), and even more significantly in patients with diabetes mellitus (12.2% vs 17.0%;  $p < 0.001$ ), particularly in those taking insulin (14.3% vs 22.2%;  $p = 0.009$ ). Although TIMI major hemorrhage was increased among subjects without diabetes mellitus on prasugrel (2.4%) vs clopidogrel (1.6%);  $p = 0.02$ ), the rates were similar among subjects with diabetes mellitus (2.6% vs 2.5%;  $p = 0.81$ ). In diabetic patients, the rate of TIMI major or minor bleeding was observed in 5.3% with prasugrel and 4.3% with clopidogrel ( $p = 0.13$ ). Therefore, the net clinical benefit with prasugrel was greater for patients with diabetes than for patients without diabetes (8% vs 26%). The greater platelet inhibition among patients with diabetes results in improved outcomes.

## Patients with genetic variants related to nonresponsiveness to clopidogrel

Focusing on the relationship between genetics and therapy efficacy, could provide clinical advances, mostly for drugs with observed high inter-individual efficacy variability and life-threatening consequences resulting from inefficacy of these drugs. From this point of view, clopidogrel is an ideal candidate for pharmacogenetic studies which target the genetics behind clopidogrel inefficacy.

A significant reduction in clopidogrel antiplatelet effectiveness, linked to the PIA2 polymorphism, has been found. A 600 mg loading dose of clopidogrel failed to acceptably inhibit platelet reactivity in patients with stable coronary artery disease undergoing elective PCI who were positive for this polymorphism.<sup>53</sup>

Genetic variants of CYP450 have been linked to a reduced exposure to the active drug metabolite, less platelet inhibition, and less protection from recurrent ischemic events in persons receiving clopidogrel.<sup>54,55</sup> In patients with acute coronary syndromes treated with clopidogrel, the presence of CYP 2C19 reduced-function allele was associated with adverse clinical outcomes, including an increased death rate from cardiovascular causes, myocardial infarction, or stroke, especially among patients undergoing PCI.<sup>54,55</sup> Notably, the rate of stent thrombosis was three times greater than that among noncarriers.<sup>55</sup>

The contribution of genetic testing relative to routine clinical practice remains unclear. Therefore, CYP 2C19 reduced-function allele carriers are an optimal target population for the study of new antithrombotic regimens, which includes prasugrel, the efficacy of which is unaffected by variability in CYP2C19 isoenzymes.<sup>56</sup>

## Conclusion

The degree of suppression of platelet activity achieved through the use of antithrombotic agents should be balanced against the risk of atherothrombotic events. Prasugrel, in comparison to clopidogrel, is a more potent inhibitor of P2Y12 receptors, and has a more rapid onset of action. Accordingly the target population for prasugrel should include patients at high risk of thrombo-occlusive events, eg, patients undergoing percutaneous coronary intervention for STE myocardial infarction, patients at risk of stent thrombosis or patients after stent thrombosis, diabetics undergoing PCI, or patients with the presence of genetic variants related to nonresponsiveness to clopidogrel.

The Committee for Medicinal Products for Human Use of the European Medicines Agency issued a positive opinion and recommended approval of prasugrel. Thereafter, the European Commission granted marketing approval of prasugrel (Efient, Lilly/Daiichi Sankyo) for the prevention of atherothrombotic events in patients with acute coronary syndromes undergoing PCI.<sup>57</sup> Prasugrel will be marketed in European countries as early as April 2009. The initial, worldwide, launch of prasugrel took place in the UK. A positive nod from the US Food and Drug Administration is expected soon.<sup>58</sup>

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