New P2Y\textsubscript{12} Inhibitors

Marco Cattaneo, MD

Adenosine diphosphate (ADP) plays a key role in the genesis of physiological platelet-rich hemostatic plugs and of pathological arterial thrombi.\textsuperscript{1} The transduction of the ADP signal involves its interaction with 2 platelet receptors, the \(G\text{\textsubscript{q}}\)-coupled P2Y\textsubscript{1} receptor and the \(G\text{\textsubscript{i}}\)-coupled P2Y\textsubscript{12} receptor, which belong to the family of purinergic P2 receptors. Concomitant activation of both the \(G\text{\textsubscript{q}}\) and \(G\text{\textsubscript{i}}\) pathways by ADP is necessary to elicit normal platelet aggregation.\textsuperscript{2} In addition to its role in ADP-induced platelet aggregation, P2Y\textsubscript{12} (Figure 1) also mediates the potentiation of platelet secretion induced by strong agonists, which is independent of the formation of large aggregates and thromboxane A\textsubscript{2} synthesis;\textsuperscript{3} the stabilization of thrombin-induced platelet aggregates;\textsuperscript{4} shear-induced platelet aggregation;\textsuperscript{5} and the inhibition of the antiplatelet effects of the natural regulator of platelet function, prostacyclin.\textsuperscript{6} In contrast to P2Y\textsubscript{1}, P2Y\textsubscript{12} has a very selective tissue distribution, making it an attractive molecular target for therapeutic intervention. Indeed, P2Y\textsubscript{12} is the target of efficacious antithrombotic agents.\textsuperscript{1}

Thienopyridines

**First- and Second-Generation Thienopyridines: Ticlopidine and Clopidogrel**

Ticlopidine and clopidogrel (Figure 2) are prodrugs that need to be converted in vivo by the hepatic cytochrome P-450 (CYP) enzymatic pathway to active metabolites, which covalently bind to P2Y\textsubscript{12} by forming a disulfide bond with cysteine residues, thereby irreversibly inhibiting the receptor.\textsuperscript{1} Because of the toxicity of ticlopidine (neutropenia, thrombotic thrombocytopenic purpura),\textsuperscript{7} ticlopidine has been almost completely replaced by clopidogrel in clinical practice.

Despite its proven antithrombotic efficacy, clopidogrel lacks some important features of the ideal antithrombotic agent (Table 1). Its main drawbacks are the following: (1) Its antiplatelet effects are delayed as a consequence of the need for metabolism of the prodrug (a maximum plateau of inhibition of P2Y\textsubscript{12} is observed 4 to 5 days after daily administration of 75 mg clopidogrel\textsuperscript{1}); (2) there is substantial interindividual variability in platelet inhibition, which is due mostly to interindividual differences in the extent of metabolism of the prodrug;\textsuperscript{1} and (3) its ability to irreversibly inhibit P2Y\textsubscript{12} may be a problem for patients who need to undergo coronary bypass (CABG) surgery because clopidogrel treatment within 4 to 5 days of the procedure is associated with increased blood loss, reoperation for bleeding, increased transfusion requirements, and prolonged intensive care unit and hospital stays.\textsuperscript{8} Although the delayed onset of action of clopidogrel can be reduced to 3 to 5 hours by giving patients a loading dose of 300 to 600 mg, the solutions for the other 2 problems appear more difficult.

The high interindividual variability of the response is a clinically relevant issue; it has been demonstrated that poor responders are not adequately protected from major adverse cardiac events (MACEs).\textsuperscript{4} Several studies showed that about one third of treated patients do not display inhibition of P2Y\textsubscript{12}-dependent platelet function; this condition, which is known as clopidogrel resistance, is in most instances associated with loss-of-function mutations of CYP\textsubscript{5,6} and may be exacerbated by negative interference with common adjunctive medications. Among the drugs shown to negatively interfere with clopidogrel, proton-pump inhibitors have received considerable attention;\textsuperscript{9} however, a recent subanalysis of the results of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) (see later) showed that the use of proton-pump inhibitors concomitantly with thienopyridines was not associated with increased incidence of MACEs.\textsuperscript{8}

**Tailored Treatment Is Not the Ideal Solution for Clopidogrel Resistance**

Tailored treatment of patients, based on the results of platelet function tests, has been proposed to solve the problem of clopidogrel resistance. Not only does this approach not meet one of the main requirements for the ideal antithrombotic agent (Table 1), but it cannot yet be recommended in daily clinical practice because the best laboratory method to monitor the effects of clopidogrel on platelet function still needs to be identified, standardized (in both preanalytical and analytical variables), and validated in the clinical setting. In addition, preliminary experiments of tailored clopidogrel treatment gave results that are incompletely satisfactory. For instance, Bonello et al.	extsuperscript{10} recently identified patients with acute coronary syndrome (ACS) scheduled for percutaneous coronary intervention (PCI) who were considered resistant to a loading dose of 600 mg clopidogrel on the basis of the results of the phosphorylation of vasodilator-stimulated phos-
The phosphoprotein (VASP) assay, which specifically explores the function of platelet P2Y12. These patients were randomized to undergo VASP-guided additional loading doses of 600 mg clopidogrel until they reached adequate inhibition of P2Y12 function or to no further treatment (control group). Some patients in the VASP-guided group achieved this goal after repeated clopidogrel doses, but 10% of them were still resistant after a total of 2400 mg clopidogrel (32 pills) (Figure 3).9,10 Although the rate of MACEs9 or stent thrombosis10 at 30 days was lower in the VASP-guided group than in the control group, it is clear that the tailored treatment approach is far from ideal because it is cumbersome, time consuming, expensive, and most important, not effective in all patients. In addition, it is unknown whether resistant patients who eventually did display an adequate response to the drug after many loading doses of clopidogrel will maintain a satisfactory inhibition of platelet function when given the much lower daily maintenance doses of clopidogrel that are administered after the loading dose and for several months thereafter. This concern is substantiated by the results of another study that showed how difficult it may be to override clopidogrel resistance by increasing the maintenance doses of the drug. Some patients were still resistant to maintenance doses of 300 mg clopidogrel daily,11 which could not be continued because of the occurrence of severe side effects (stomach discomfort and joint pain).11 It was only after the administration of regular maintenance doses of prasugrel (see later) that these patients exhibited adequate inhibition of P2Y12-dependent platelet function.11 Therefore, because tailored treatment with clopidogrel appears less promising than expected, it is far from an ideal strategy to solve the problem of clopidogrel resistance. Hence, new P2Y12 antagonists that are able to induce predictable and adequate inhibition of platelet function in all patients are necessary.

**Prasugrel, a New Thienopyridine**

Prasugrel is a new thienopyridine, with much more rapid and consistent inhibitory effects on platelet aggregation than clopidogrel. Its distinctive chemical structure permits conversion to its active metabolite with less dependence on CYP en-

![Figure 1. Central role of P2Y12 in platelet aggregation. ADP, by interacting with P2Y12, a 7-transmembrane receptor that is coupled to the inhibitory G protein Gi, induces platelet aggregation and amplifies the aggregation response that is induced by other agonists or by ADP itself, interacting with its other platelet receptor, P2Y1. In addition, P2Y12 stabilizes the platelet aggregates and amplifies the secretion of platelet dense granules stimulated by secretion-inducing agonists (which are coupled to Gq). Although P2Y12 is coupled to inhibition of adenylyl cyclase (AC) through Gi, this function does not appear to be directly related to P2Y12-mediated platelet activation. However, it could have important implications in vivo, where platelets are exposed to the inhibitory prostaglandin PG12 (prostacyclin), which inhibits platelet aggregation by increasing platelet cAMP through activation of AC mediated by Gs. Inhibition of AC by P2Y12 counteracts the inhibitory effect of prostacyclin, thereby favoring the formation of platelet aggregates in vivo. Green arrow indicates activation; red line, inhibition; blue line, amplification; and dotted black line, secretion.

![Figure 2. Chemical structures of clopidogrel, prasugrel, and their active metabolites.](http://circ.ahajournals.org/Downloaded from)

![Figure 3. Effects of each additional loading dose of 600 mg clopidogrel in clopidogrel-resistant patients in the VASP-guided group (see text for details). Reproduced from Bonello et al10 with permission from Elsevier. Copyright 2009 Elsevier.)

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the Ideal Antithrombotic Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictable pharmacodynamic profile, making monitoring unnecessary</td>
</tr>
<tr>
<td>Rapid onset</td>
</tr>
<tr>
<td>Rapid offset* (and/or availability of an antidote)</td>
</tr>
<tr>
<td>No interaction with adjunctive medicines commonly used</td>
</tr>
<tr>
<td>Potent antithrombotic effect</td>
</tr>
<tr>
<td>Low risk</td>
</tr>
<tr>
<td>Low cost</td>
</tr>
<tr>
<td>Easy administration</td>
</tr>
</tbody>
</table>

*For safety reasons, a drug with rapid offset is generally preferable to a drug with long-lasting effects; however, theoretically, the use of the latter might minimize the negative effects of poor compliance.
zymes than clopidogrel (Figure 2). Consequences of the different metabolism of prasugrel compared with that of clopidogrel are the following: (1) fast appearance of its active metabolite in circulating blood within 15 minutes of dosing, which reaches maximal plasma concentration at ~30 minutes; (2) higher mean area under the concentration-time curve of the active metabolite of prasugrel 60 mg than that of clopidogrel 600 mg; (3) faster and greater mean inhibition of P2Y₁₂-dependent platelet function after a 60-mg loading dose and 10-mg maintenance dose than after a 300- or 600-mg loading dose and 75- or 150-mg maintenance dose of clopidogrel; (4) no influence of the CYP genotype on its pharmacokinetics and pharmacodynamics; and (5) much lower interindividual variability in the inhibition of P2Y₁₂-dependent platelet responses and extremely low prevalence of subjects who display resistance to prasugrel.

The aforementioned more favorable pharmacokinetics and pharmacodynamics of prasugrel compared with clopidogrel result in greater clinical benefit, as shown by the results of the TRITON TIMI 38 phase III trial, a randomized, double-blind, parallel-group, multinational trial that evaluated 13 608 high-risk patients with ACS who required PCI. Patients were randomized to receive a 60-mg loading dose of prasugrel followed by 10 mg/d prasugrel or a 300-mg loading dose of clopidogrel followed by 75 mg/d clopidogrel for 6 to 15 months. Prasugrel was associated with fewer ischemic events (hazard ratio, 0.81; 95% confidence interval, 0.73 to 0.90; \( P<0.001 \)) but a higher incidence of major and fatal bleeding complications (hazard ratio, 1.32; 95% confidence interval, 1.03 to 1.68; \( P=0.03 \)). Although some limitations of TRITON-TIMI 38 have been criticized, the higher efficacy and lower safety of prasugrel compared with clopidogrel appear unquestionable. In a posthoc analysis, 3 subgroups appeared to have less net clinical benefit or greater harm: patients with previous cerebrovascular accidents, patients aged 75 years of age, and patients weighing <60 kg. Other analyses showed that prasugrel was a more effective antiplatelet drug than clopidogrel in patients with diabetes mellitus, ST-elevation myocardial infarction, coronary stents, or recurrent cardiovascular events on treatment. The benefit-to-risk ratio appeared particularly favorable in patients with diabetes mellitus, also because the incidence of TIMI major bleeding complications did not differ between the 2 treatments groups. However, it must be noted that the lack of difference in bleeding complications was not accounted for by a lower incidence in the prasugrel-treated group but rather by an increased incidence in the clopidogrel-treated group (Table 2); this finding is difficult to interpret from a biological standpoint and is likely attributable to the play of chance. Among patients treated with clopidogrel, carriers of a reduced-function CYP2C19 allele had a higher rate of MACEs than did noncarriers, whereas among those treated with prasugrel, the CYP2C19 genotype did not affect the incidence of MACEs.

### Prasugrel and Clopidogrel: Different Prodrugs but Drugs With The Same Potency

From the results of TRITON TIMI 38, prasugrel is generally considered a more potent antiplatelet agent than clopidogrel that could be used only in high-risk patients or for a short period; treatment with clopidogrel is preferred in the remaining situations. However, it is incorrect to say that prasugrel is more potent than clopidogrel because both ex vivo and in vitro studies demonstrated that the active metabolites of the 2 compounds have the same potency. Studies with a crossover design in which subjects were administered the 2 prodrugs showed that when the plasma concentrations of their active metabolites were plotted against the ex vivo inhibition of P2Y₁₂-dependent platelet function, all the points were evenly distributed along the same regression line (Figure 4). Moreover, when the active metabolites of the 2 prodrugs were added in vitro to washed human platelet suspensions, they inhibited ADP-induced platelet aggregation concentration dependently, displaying an identical IC₅₀ of 0.30 μmol/L (Figure 5). Therefore, because the different clinical efficacy of prasugrel and clopidogrel is not explained by differences in the potencies of their active metabolites, it must be explained by differences in their pharmacokinetics. As already mentioned, the metabolism of prasugrel to its active metabolite is much more efficient and consistent than that of clopidogrel. As a consequence, the vast majority of patients treated with prasugrel exhibit good inhibition of platelet function, whereas ~30% to 50% of patients treated with clopidogrel exhibit no or unsatisfactory responses. Because it can be predicted that higher inhibition of platelet function results in a lower risk of MACEs and higher risks of bleeding complications, more patients treated with prasugrel than patients treated with

### Table 2. Incidence of Non–CABG-Related TIMI Major Bleeding Events in the TRITON-TIMI 38 Study

<table>
<thead>
<tr>
<th>Patients</th>
<th>n</th>
<th>Clopidogrel, %</th>
<th>Prasugrel, %</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetics</td>
<td>3146</td>
<td>2.6</td>
<td>2.5</td>
<td>0.81</td>
</tr>
<tr>
<td>Nondiabetics</td>
<td>10 462</td>
<td>1.6</td>
<td>2.4</td>
<td>0.02</td>
</tr>
<tr>
<td>All patients</td>
<td>13 457</td>
<td>1.8</td>
<td>2.4</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Figure 4. Scatterplot of platelet reactivity index (PRI) by the VASP phosphorylation test vs area under the curve (AUC) of active metabolite after maintenance daily doses (MD) of clopidogrel 75 mg or prasugrel 10 mg. Reprinted from Wallentin et al with permission from Oxford University Press. Copyright 2008 Oxford University Press.

Downloaded from http://circ.ahajournals.org/ by guest on July 25, 2017
clopidogrel are protected from MACEs and, at the same time, are exposed to a risk of bleeding, accounting for the different incidences of clinical events observed in TRITON TIMI 38. If the relationship between the degree of inhibition of platelet function and incidence of clinical events is real, good responders to clopidogrel should also be at lower risk of MACEs and higher risk of bleeding than poor responders. In fact, many studies showed that good responders to standard or tailored doses of clopidogrel are better protected from MACEs than poor responders. The very few studies that also addressed the issue of the incidence of bleeding complications showed that good responders had a 30% to 40% increased incidence (which did not reach statistical significance because of the insufficient statistical power of these studies),9,25 which is similar to that observed in prasugrel-treated compared with clopidogrel-treated patients in TRITON TIMI 38 (Table 3).13 Therefore, the risk of bleeding and the protection from MACEs do not appear to be correlated with the type of P2Y12 antagonist but rather with the degree of platelet inhibition that is achieved independently of the drug that was used.

From the aforementioned considerations, the following can be concluded: (1) Tailored treatment fails to solve the problem of resistance to clopidogrel in all treated patients. (2) Patients who respond well to clopidogrel are at lower risk of MACEs but also appear to be at increased risk of bleeding compared with poor responders. (3) It is not true that prasugrel is more potent than clopidogrel; the real difference is that in contrast with clopidogrel, prasugrel effectively inhibits P2Y₁₂-dependent platelet function in the vast majority of treated patients. (4) Therefore, the higher efficacy and lower safety of prasugrel compared with clopidogrel are simply explained by the fact that prasugrel protects more patients from MACEs and exposes more patients to a risk of bleeding than clopidogrel. (5) It can be predicted that if tailored treatment with clopidogrel were successful in all patients displaying hyporesponsiveness to the drug, incidences of MACEs and bleeding in patients given tailored clopidogrel treatment would be very similar to those observed in patients given prasugrel.

Therefore, prasugrel appears an attractive solution to some of the problems associated with the use of clopidogrel and should be preferred to clopidogrel, although it might be safer to reduce its dose in patients >75 years of age or <60 kg body weight, who displayed high rates of bleedings in TRITON TIMI 3813 and particularly high plasma levels of the prasugrel active metabolite.26 As a matter of fact, decreasing the maintenance dose of prasugrel to 5 mg daily in patients who weigh <60 kg (Food and Drug Administration and European Medicines Agency) or are >75 years of age (European Medicines Agency) has been recommended, although there is no experimental evidence that this dose adjustment is safe and effective.

However, prasugrel does not solve the problem associated with the slow offset of action because, like clopidogrel, it causes irreversible inhibition of P2Y₁₂. In fact, the incidence of bleeding complications in patients who underwent CABG surgery in TRITON TIMI 38 was higher in prasugrel-treated patients (13.4%) than in clopidogrel-treated patients (3.2%) (hazard ratio, 4.73; 95% confidence interval, 1.90 to 11.82; P<0.001).13 In patients who are at risk of undergoing CABG surgery (or other types of surgery), inhibition of platelet aggregation by fast-acting and reversible antagonists with short half-lives might be preferable to irreversible inhibitors. Some direct P2Y₁₂ antagonists with such characteristics are currently under development.

### Direct P2Y₁₂ Inhibitors

**Cangrelor**

Cangrelor, previously known as ARC69931[MX], belongs to a family of analogs of ATP that are relatively resistant to breakdown by ectonucleotidases and display high affinity for the P2Y₁₂ receptor (Figure 6).27 Cangrelor is a potent inhibitor of ADP-induced aggregation of human washed platelets (PIC₅₀ = 9.4 with 30 μmol/L ADP), does not require conver-

---

**Table 3. Incidence of TIMI Major and Minor Bleeding Events in 3 Studies Comparing Prasugrel-Treated Patients With Clopidogrel-Treated Patients, Good Responders to Clopidogrel With Low Responders, and VASP-Guided Clopidogrel With Clopidogrel Control**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Total Patients, n</th>
<th>TIMI Major and Minor Bleeding Events, % increase in group 1 vs 2</th>
<th>P</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasugrel</td>
<td>Clopidogrel</td>
<td>13 467</td>
<td></td>
<td>0.002</td>
<td>12</td>
</tr>
<tr>
<td>Clopidogrel responders</td>
<td>Clopidogrel low responders</td>
<td>1608</td>
<td></td>
<td>0.25</td>
<td>23</td>
</tr>
<tr>
<td>VASP-guided clopidogrel</td>
<td>Control clopidogrel</td>
<td>429</td>
<td></td>
<td>0.8</td>
<td>9</td>
</tr>
</tbody>
</table>
sion to an active metabolite, and is immediately active after intravenous infusion, with a half-life of 3 to 6 minutes.

Cangrelor displays no significant affinity for other P2 receptors at concentrations >30 μmol/L, although it has been shown to be a potent (IC₅₀, 4 mmol/L), noncompetitive antagonist of P2Y₁₃, which is not expressed on the platelet membrane.²⁸,²⁹ A recent study suggested that cangrelor may also interact with an unidentified platelet G protein–coupled receptor that stimulates cAMP-mediated inhibition of platelet function.³⁰

**Clinical Pharmacology**

Intravenous infusion of cangrelor was well tolerated in healthy volunteers, resulting in dose-dependent inhibition of ADP-induced platelet aggregation²⁷ at doses up to 4 μg · kg⁻¹ · min⁻¹ and, at the highest dose, a 3.2- and 2.9-fold increase in bleeding time in men and women, respectively. Its short half-life resulted in a rapid reversal of both the platelet-inhibitory effect and the effect on bleeding time within 20 minutes after cessation of the infusion.

An open, multicenter, ascending-dose study in 39 ACS patients³¹ showed dose-dependent and predictable plasma levels of cangrelor, resulting in complete or nearly complete inhibition of 3 μmol/L ADP–induced platelet aggregation at doses ≥2 μg · kg⁻¹ · min⁻¹. Bleeding times were increased 3- to 5-fold at the 2-μg · kg⁻¹ · min⁻¹ dose and 7-fold at the 4-μg · kg⁻¹ · min⁻¹ dose. A double-blind, placebo-controlled study of cangrelor as adjunctive therapy to aspirin and either heparin or low-molecular-weight heparin in patients with non–Q-wave myocardial infarction showed that minor bleeding was increased slightly from 26% in the placebo-treated group to 38% in the cangrelor-treated group.³²

A larger, 2-part phase II study assessed the safety and pharmacodynamics of cangrelor in patients undergoing PCI.³³ The first part of the study enrolled 200 patients undergoing PCI who were randomized to an 18- to 24-hour intravenous infusion of placebo or to 1, 2, or 4 μg · kg⁻¹ · min⁻¹ cangrelor in addition to aspirin and heparin before the procedure. In the second part of the study, 199 patients were randomized to receive either cangrelor (4 μg · kg⁻¹ · min⁻¹) or the anti–glycoprotein IIb/IIa inhibitor abciximab before the procedure. The incidence of combined major and minor bleeding was not significantly higher in cangrelor-treated patients compared with placebo- or abciximab-treated patients. Mean inhibition of platelet aggregation in response to 3 μmol/L ADP was complete in both the group of patients treated with cangrelor 4 μg · kg⁻¹ · min⁻¹ and the group treated with abciximab.³³ However, after termination of drug infusion, platelet aggregation returned to baseline values much faster in the cangrelor-treated group than in the abciximab-treated group.³³

These data suggest that cangrelor may be useful during the periprocedural period in patients undergoing PCI. However, for long-term prevention, these patients should be treated with orally available agents. Steinhubl et al³⁴ demonstrated that the simultaneous administration of intravenous cangrelor with an oral 600-mg loading dose of clopidogrel prevents the expected inhibition of platelet aggregation by clopidogrel, presumably as a result of competitive interaction between cangrelor and the active metabolite of clopidogrel at the P2Y₁₂ receptor level. Therefore, it was suggested that the clopidogrel loading dose should be administered after termination of cangrelor infusion.³⁴ On the basis of the results of an in vitro study,³⁵ which need to be confirmed in an ex vivo study, a similar problem can be predicted with the use of prasugrel during cangrelor infusion.

The Safety, Tolerability and Effect on Patency in Acute Myocardial Infarction (STEP-AMI) angiographic trial assessed the safety and efficacy of cangrelor as an adjunct to tissue plasminogen activator in 92 patients with acute myocardial infarction.³⁶ All patients were treated with aspirin and heparin and were randomized to cangrelor alone (280 μg/min), full-dose tissue plasminogen activator alone (15-mg bolus followed by 0.75-mg/kg continuous infusion up to 50 mg over 30 minutes followed by 0.5 mg/kg up to 35 mg over...
ticagrelor (100 or 200 mg BID or 400 mg QD) inhibited platelet aggregation more rapidly and effectively and with less variability than clopidogrel after both the first dose and 28 days of therapy. Only 1 major, nonfatal hemorrhage occurred in a patient treated with ticagrelor 400 mg QD; the incidence of moderate and minor bleeding events was dose related (from 29% to 51%) in ticagrelor-treated patients and 32% in clopidogrel-treated patients. Other adverse events included dyspnea, dizziness, headache, and red blood cells in the urine. The incidence of dyspnea was dose related (reported in 10% of patients treated with ticagrelor 50 mg BID, in 16% of patients treated with 200 mg BID, and in 20% of patients treated with 400 mg QD). None of the incidents of dyspnea was considered to be serious, and none was associated with congestive heart failure or bronchospasm.\(^{40}\)

The DISPERSE-2 study compared the safety of ticagrelor with that of clopidogrel in 990 patients with non–ST-segment-elevation ACS treated with aspirin and standard therapy for ACS who were randomly assigned to a new formulation of ticagrelor 90 mg BID (corresponding to 100 mg of the old formulation) or 180 mg BID and clopidogrel at the approved doses (300-mg loading dose plus 75-mg QD maintenance dose) for up to 12 weeks.\(^{41}\) A statistically significant difference in the incidence of major bleedings was observed in the study groups. In a posthoc analysis of continuous electrocardiography, mostly asymptomatic ventricular pauses >2.5 seconds were more common in the group treated with ticagrelor 180 mg BID.\(^{41}\) This study confirmed that dyspnea occurs more frequently with ticagrelor than with clopidogrel. Again, the clinical impact appeared low, with few cases being considered serious or leading to discontinuation of treatment. The pathogenesis of dyspnea during ticagrelor treatment is unclear, although it has been hypothesized that it may be mediated by adenosine.\(^{42}\)

A substudy of DISPERSE-2 showed that ticagrelor inhibited platelet aggregation in a dose-dependent fashion and that both doses achieved greater levels of inhibition than clopidogrel.\(^{43}\) In addition, ticagrelor produced further suppression of platelet aggregation in patients who were currently receiving clopidogrel.

The results of Platelet Inhibition and Patient Outcomes (PLATO), a phase III randomized, double-blind, parallel-group efficacy and safety study in which ticagrelor (180-mg loading dose, 90-mg BID maintenance dose) was compared with clopidogrel (300- to 600-mg loading dose, 75-mg QD maintenance dose) for the prevention of MACEs in patients with non–ST-elevation or ST-elevation ACS,\(^{44}\) have recently been reported.\(^{45}\) About 65% of enrolled patients underwent PCI. After 12 months of follow-up, the primary end point (a composite of vascular death, myocardial infarction, or stroke) had occurred in 9.8% of patients receiving ticagrelor compared with 11.7% of patients receiving clopidogrel (Table 4). There was a higher incidence of TIMI major non–CABG-related bleeding in patients who received ticagrelor (2.8%) compared with those treated with clopidogrel (2.2%; \(P=0.03\)). However, the incidence of TIMI major CABG-related bleeding was similar in the 2 groups. Because of the rather high incidence of CABG-related bleeding in both
and pharmacodynamic parameters.46 All doses were well tolerated with no serious or clinically important adverse events. The effect was equivalent to that observed when elinogrel was used alone at 100 mg.46

Similar results were obtained in another randomized, double-blind study in which single intravenous doses of elinogrel between 1 and 40 mg were administered over 20 minutes to 5 groups of 8 healthy subjects (6 active, 2 placebo).47 Complete inhibition of P2Y$_{12}$-dependent ADP-induced platelet aggregation was observed at the 20-mg dose. Ex vivo thrombus formation on collagen-coated surfaces in a perfusion chamber was maximally inhibited by 40 mg elinogrel.47 The in vitro addition of elinogrel to blood samples from clopidogrel-treated healthy control subjects or diabetic patients undergoing coronary stent placement increased the inhibition of ADP-induced platelet aggregation and thrombus formation on collagen-coated surfaces.48

Elinogrel is currently under evaluation in 2 phase II clinical trials. The Early Rapid Reversal of Platelet Thrombosis With Intravenous PRT060128 Before PCI to Optimize Reperfusion in Acute MI (ERASE-MI, NCT00546260) is a randomized trial evaluating the safety and tolerability of adjunctive antiplatelet therapy with intravenous elinogrel (10, 20, 40, and 60 mg) before PCI in patients with ST-elevation myocardial infarction. A Phase 2 Safety and Efficacy Study of Intravenous PRT060128, a Novel Intra coronary platelet aggregation and thrombus formation on collagen-coated surfaces.48

Conclusions

The pharmacopeia of drugs inhibiting the platelet P2Y$_{12}$ receptor for ADP is rapidly expanding. Compared with ticlopidine and clopidogrel, well-known compounds of proven antithrombotic efficacy, the new thienopyridine prasugrel is characterized by faster onset of action and more consistent inhibition of platelet function in treated subjects. These characteristics account for the lower incidence of MACEs and higher incidence of bleeding among ACS patients scheduled for PCI compared with clopidogrel, as shown in the TRITON TIMI 38 randomized clinical trial.


table 4. Incidence of the Primary End Point (Composite of Vascular Death, Myocardial Infarction, or Stroke) and TIMI Major Bleeding Events in Patients Who Received Ticagrelor Versus Patients Who Received Clopidogrel in the PLATO Trial

<table>
<thead>
<tr>
<th>Events</th>
<th>Ticagrelor, n/N (%)</th>
<th>Clopidogrel, n/N (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td>864/9333 (9.8)</td>
<td>1014/9291 (11.7)</td>
<td>0.84 (0.77–0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major bleedings, TIMI criteria</td>
<td>657/9235 (7.9)</td>
<td>638/9186 (7.7)</td>
<td>1.03 (0.93–1.15)</td>
<td>0.57</td>
</tr>
<tr>
<td>Non–CABG-related major bleeding, TIMI criteria</td>
<td>221/9235 (2.8)</td>
<td>177/9186 (2.2)</td>
<td>1.25 (1.03–1.53)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

CI indicates confidence interval. The lack of a statistically significant difference in the incidence of total major bleeding in the 2 treatment groups despite the difference in non–CABG-related major bleeding is accounted for by the lack of statistically significant differences in the incidence of CABG-related major bleeding, which was prevalent and rather high in both groups (446 of 931 [47.9%] in ticagrelor-treated patients versus 476 of 968 [49.2%] in clopidogrel-treated patients). The severity of bleeding events also was evaluated using specific criteria developed by the PLATO investigators; however, this table reports the results obtained using only the TIMI criteria for better comparability with the results of other studies reported in this review.
Therefore, prasugrel appears to be a valid alternative to clopidogrel, which is ineffective in ~30% of treated patients. Both the Food and Drug Administration and European Medicines Agency suggested that the maintenance dose of prasugrel be reduced to 5 mg daily in some categories of patients (>75 years of age and <60 kg body weight), although there is no experimental evidence that this dose adjustment is safe and effective. Being an irreversible inhibitor of \( \text{P2Y}_{12} \), like the other thienopyridines, prasugrel has a slow offset of action, which represents a problem for those patients who need to undergo surgery (especially CABG) because they are at increased risk of bleeding complications. Three direct and reversible \( \text{P2Y}_{12} \) antagonists, cangrelor (which can be given intravenously), ticagrelor (which can be given orally), and elinogrel (which can be given both intravenously and orally), have very rapid onset and offset of platelet inhibition, which make them attractive alternatives to thienopyridines, especially when rapid inhibition of platelet aggregation or its quick reversal is required. Cangrelor was not proven superior to clopidogrel in preventing thrombotic events in patients undergoing PCI. However, it is still being studied as a bridge for patients who need to suspend treatment with thienopyridines to undergo surgery. Ticagrelor was recently proven superior to clopidogrel in preventing MACEs in ACS patients scheduled for PCI. Therefore, in the near future, physicians will have a panel of different \( \text{P2Y}_{12} \) inhibitors from which to choose, which will enable them to tailor the most appropriate antithrombotic therapy to the individual patient and risk situation.

**Disclosures**

Dr Cattaneo received honoraria or consulting fees from Lilly-Daiichi Sankyo, AstraZeneca, and The Medicines Co.

**References**


Key Words: acute coronary syndromes • adenosine diphosphate • antiplatelet agents • platelets
New P2Y12 Inhibitors
Marco Cattaneo

Circulation. 2010;121:171-179
doi: 10.1161/CIRCULATIONAHA.109.853069

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/121/1/171

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/