New Directions in Antiplatelet Therapy

José Luis Ferreiro, MD; Dominick J. Angiolillo, MD, PhD

Atherosclerosis is a chronic inflammatory process that is known to be the underlying cause of coronary artery disease (CAD). In addition to being the first step of primary sclerotic plaque. Because atherothrombotic events are essentially platelet-driven processes, this underscores the importance of antiplatelet agents, which represent the cornerstone of treatment, particularly in the settings of patients with acute coronary syndromes (ACS) and undergoing percutaneous coronary intervention (PCI).

Currently, there are 3 different classes of antiplatelet drugs that are approved for clinical use and recommended per guidelines for the treatment and prevention of ischemic events in the settings of ACS and PCI: (1) cyclooxygenase-1 (COX-1) inhibitor: aspirin, (2) adenosine diphosphate (ADP) P2Y<sub>12</sub> receptor antagonists: ticlopidine, clopidogrel, prasugrel, and ticagrelor, and (3) glycoprotein IIb/IIIa inhibitors (GPI): abciximab, eptifibatide, and tirofiban. Currently available are only for parenteral administration, and therefore their use is limited only to the acute phase of treatment of ACS patients undergoing PCI. Oral antiplatelet agents, namely aspirin and P2Y<sub>12</sub> receptor inhibitors, are recommended for prevention of ischemic events in both the acute and long-term phases of treatment. For over a decade, dual antiplatelet therapy (DAPT) with aspirin and clopidogrel has been considered the standard of care in the setting of ACS and PCI. However, a considerable number of adverse ischemic events continue to occur with this DAPT regimen, which has led to the development of newer and more potent antiplatelet agents. The objective of the present manuscript is to provide an overview on the most recent advances of antiplatelet agents. The objective of the present manuscript is to provide an overview on the most recent advances of antiplatelet agents. The objective of the present manuscript is to provide an overview on the most recent advances of antiplatelet agents.

Currently Approved Agents

Aspirin

Aspirin exerts its action through an irreversible blockade of COX-1, the enzyme that catalyzes the synthesis of thromboxane A<sub>2</sub> (TXA<sub>2</sub>) from arachidonic acid through selective acetylation of a serine residue at position 529 (Ser529). TXA<sub>2</sub> causes changes in platelet shape and enhances recruitment and aggregation of platelets through its binding to thromboxane and prostaglandin endoperoxide (TP) receptors. Therefore, aspirin decreases platelet activation and aggregation processes mediated by TP receptor pathways.

Although the optimal dose of aspirin has been the subject of debate, the efficacy of low-dose aspirin is supported by the results of numerous studies. In these investigations, a dose-dependent risk for bleeding, particularly upper gastrointestinal bleeding, with no increase in efficacy was observed. This is in line with the overall results of the CURRENT/OASIS-7 (Clopidogrel optimal loading dose Usage to Reduce Recurrent EveNTs-Organization to Assess Strategies in Ischemic Syndromes) trial, in which ACS patients (n=25 087) scheduled to undergo angiography were assigned to high or standard dose of clopidogrel for a month, including an open-label randomization to high (300–325 mg daily) versus low dose (75–100 mg daily) of aspirin. Although no significant differences between high and low dose aspirin were found in efficacy or bleeding, a trend toward a higher rate of gastrointestinal bleeds in the high dose aspirin group (0.38% versus 0.24%; P=0.051) at 30 days was observed. Overall, these data suggest that after loading dose administration of aspirin, the use of a low maintenance dose regimen should be considered for secondary prevention of vascular events.

Several studies have observed an association between aspirin poor responsiveness and a higher risk of recurrent ischemic events. The prevalence of aspirin resistance varies among studies, which can be attributed to differences in the definition of resistance, type of assay used, dose of aspirin, and population considered. In fact, when using COX-1 specific tests (eg, determination of serum thromboxane and assays using arachidonic acid as agonist), aspirin resistance is a sporadic phenomenon (less than 5% of patients). Of note, poor patient compliance is the main cause of aspirin resistance, when assessed by COX-1 specific tests. Other possible causes that may play a role in a reduced response to aspirin include type of aspirin used (eg, enteric versus nonenteric coated), genetics (eg, COX-1 polymorphism), dosing regimen, and drug interactions (eg, ibuprofen).
P2Y12 Receptor Antagonists

Adenosine diphosphate exerts its effects on platelets via the P2Y1 and P2Y12 receptors. Although both receptors are needed for aggregation, activation of the P2Y12 pathway plays the principal role, leading to sustained platelet aggregation and stabilization of the platelet aggregate.17 P2Y12 receptor inhibitors are recommended for prevention of ischemic events in both the acute and long-term phases of treatment, as summarized in Table 1 and described in details below.

Clopidogrel

Three generations of thienopyridines (ticlopidine, clopidogrel, and prasugrel), a family of nondirect, orally administered antiplatelet agents that irreversibly block the platelet ADP P2Y12 receptor, are approved currently for clinical use. After its approval in 1997, clopidogrel soon replaced ticlopidine due to its more favorable safety profile.18 Further, clopidogrel has a pharmacological advantage over ticlopidine, as it achieves a faster onset of action through administration of a loading dose.19 Clopidogrel is a prodrug that requires metabolization in the liver through a double oxidation process mediated by several cytochrome P450 (CYP) isoforms, to be converted finally into its active metabolite, which irreversibly blocks the ADP P2Y12 platelet receptor. Due to the irreversible blockade of the P2Y12 receptor, clopidogrel effects last for the whole lifespan of the platelet (7–10 days).20,21

Dual antiplatelet therapy with aspirin and clopidogrel is recommended per guidelines for patients with ACS, including those with unstable angina (UA) or non-ST elevation acute coronary syndromes (NSTEMI), ST-elevation myocardial infarction (STEMI), and for patients undergoing PCI (Table 1).3–6 This recommendation is based on the findings of several large-scale trials that have shown a clear benefit of adjunctive treatment with clopidogrel in addition to aspirin in preventing recurrent atherothrombotic events.22–25 However, DAPT with aspirin and clopidogrel should not be recommended for primary prevention or in patients not presenting with an ACS or undergoing PCI, because it has not been proven superior to aspirin alone in this scenario.26

Despite the undisputed clinical benefit achieved with the combination of clopidogrel and aspirin in the setting of ACS or PCI, a considerable number of patients continue to experience recurrent ischemic events.22–25 This is partially due to clopidogrel’s main drawback, represented by its broad variability in platelet inhibitory effects, which includes a high percentage of patients with suboptimal antiplatelet effects. The percentage of “low responders” or “resistant” patients ranges from 5% to 40% across studies, depending on definitions, type of test used, dose of clopidogrel, and population characteristics. Genetic, cellular, and clinical mechanisms have been reported to play a role in inadequate clopidogrel responsiveness.20,21 Some of these, such as poor clopidogrel metabolizer status due to the presence of loss-of-function alleles for the CYP2C19 enzyme and the use of proton pump inhibitors interfering with CYP2C19 activity (eg, omeprazole), have prompted the Food and Drug Administration and European Medicines Agency to issue box warnings.27,28 Although the clinical relevance and the appropriateness of these warnings have been subject to controversies, the association between low responsiveness to clopidogrel and adverse ischemic outcomes, including stent thrombosis, is well established.20,21 Overall, these results emphasize the need for finding new antiplatelet strategies to achieve more potent P2Y12 receptor blockade with less variability in response (Figure 2),29 especially in high risk subsets of patients, such as those suffering an ACS or undergoing PCI.

One of the strategies suggested to overcome nonresponsiveness is the use of a higher than currently approved loading and maintenance doses of clopidogrel, which have been observed to achieve greater platelet inhibitory effects.20,21 The CURRENT/OASIS-7 trial, which assessed the efficacy of high (600 mg loading dose followed by 150 mg daily for 1 week and then 75 mg/daily until day 30) versus standard dose (300 mg loading followed by 75 mg daily until day 30) of clopidogrel for 1 month
Table 1. Guideline Recommendations for Available P2Y₁₂ Antagonists

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
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</thead>
<tbody>
<tr>
<td><strong>2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction</strong>&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Class I; Level of Evidence A</td>
<td>Class I; Level of Evidence B</td>
<td>Not FDA approved or marketed at the time of writing of Guidelines</td>
</tr>
<tr>
<td>Left Main Disease</td>
<td>Clopidogrel 300 to 600 mg should be given as early as possible before or at the time of PCI followed by 75 mg daily for at least 12 months: Class I; Level of Evidence B for duration</td>
<td>Prasugrel 60 mg should be given promptly and no later than 1 hour after PCI once coronary anatomy is defined and a decision is made to proceed with PCI, followed by 10 mg daily for at least 12 months: Class I; Level of Evidence B for duration</td>
<td>Ticagrelor 180 mg (ACS patients) followed by 90 mg twice daily for at least 12 months</td>
</tr>
<tr>
<td>NSTE-ACS&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Class I; Level of Evidence A</td>
<td>Class I; Level of Evidence B</td>
<td>Class I; Level of Evidence B</td>
</tr>
<tr>
<td>30% probability of ischemic events and no contraindications for percutaneous revascularization</td>
<td>Clopidogrel 600 mg (ACS and non-ACS patients) followed by 75 mg daily for at least 12 months</td>
<td>Prasugrel 60 mg (ACS patients) followed by 10 mg daily for at least 12 months</td>
<td>Ticagrelor (180-mg LD, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischemic events (e.g., elevated troponins), regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced)</td>
</tr>
<tr>
<td><strong>2011 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation</strong>&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Class I; Level of Evidence A</td>
<td>Class I; Level of Evidence B</td>
<td>Class I; Level of Evidence B</td>
</tr>
<tr>
<td>2010 ESC/EACTS/EAPCI Guidelines on myocardial revascularization&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Class I; Level of Evidence A</td>
<td>Class I; Level of Evidence B</td>
<td>Class I; Level of Evidence B</td>
</tr>
<tr>
<td>Elective PCI: Pretreatment with 300 mg loading dose ≥6 h before PCI (or 600 mg ≥2 h before): Class I Level of Evidence C</td>
<td>NSTE-ACS: Class Ia; Level of Evidence B</td>
<td>Ticagrelor 180-mg LD followed by 90 mg twice daily (Guidelines specify: “Depending on approval and availability. Direct comparison between prasugrel and ticagrelor is not available”</td>
<td></td>
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<tr>
<td>NSTE-ACS: 600-mg LD as soon as possible: Class I Level of Evidence C</td>
<td>NSTE-ACS: Class I; Level of Evidence B</td>
<td>Ticagrelor 180 mg (ACS) followed by 90 mg twice daily for at least 12 months</td>
<td></td>
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<tr>
<td>STEMI: 600-mg LD as soon as possible. Primarily if more efficient antiplatelet agents are contraindicated.</td>
<td>NSTE-ACS: Class I; Level of Evidence B</td>
<td>Ticagrelor 180 mg (ACS patients) followed by 90 mg twice daily for at least 12 months</td>
<td></td>
</tr>
</tbody>
</table>

<sup>*General recommendation: A loading dose of a P2Y₁₂ receptor inhibitor should be given to patients undergoing PCI with stenting: Level of Evidence A.

in ACS patients (n = 25 087) scheduled to undergo angiography, included ACS patients (n = 25 087) scheduled to undergo angiography within 72 hours of hospital arrival. In the overall study population, no benefit was derived from the high dose regimen. However, in the subgroup of patients undergoing PCI (n = 17 232), the high dose strategy was associated with a decrease in the rates of ischemic outcomes (3.9% versus 4.5%; hazards ratio [HR], 0.85; P = 0.036), and reduced the risk of stent thrombosis by 30%, at the expense, however, of a significant increase in study defined major bleedings.<sup>30</sup>

The concept of a “tailored treatment” by increasing clopidogrel dosing according to the degree of responsiveness of a given patient assessed by a platelet function assay was evaluated in the GRAVITAS (Gauging Responsiveness with a Verify Now Assay: Impact on Thrombosis And Safety) trial. In this investigation, the efficacy of high dose clopidogrel (600 mg initial dose and 150 mg daily thereafter for 6 months) versus standard dose clopidogrel (no additional loading dose and 75 mg daily) was compared in 2214 patients with high on-treatment reactivity, on the basis of Verify Now P2Y₁₂ assay measurement, 12 to 24 hours after PCI with drug-eluting stents. No differences in the rates of ischemic (2.3% versus 2.3%; HR, 1.01 [0.58–1.76]; P = 0.97) or bleeding outcomes (1.4% versus 2.3%; HR, 0.59 [0.31–1.11]; P = 0.10) were found.<sup>31</sup> Thus, a benefit of a tailored strategy with clopidogrel therapy was not observed in this trial, which may be explained by the overall low percentage of events observed and the weak increase in platelet inhibition achieved with a high dose of clopidogrel compared with standard dosing. Indeed, other strategies (Figure 2) have shown to be associated with greater pharmacodynamic effects (ie, enhanced platelet inhibition), measured by different platelet function assays, than high dose clopidogrel among patients with high on-treatment platelet reactivity as well as poor clopidogrel responders with stable coronary artery disease as shown in the TRIGGER-PCI (Testing platelet Reactivity In patients underGoing elective stent placement on clopidogrel to Guide alternative thErapy with pRasugrel) trial, in which despite the pharmacodynamic superiority of...
prasugrel, the trial was stopped prematurely for futility due to an event rate that was substantially lower than expected.32

Prasugrel
Prasugrel, a third generation thienopyridine, is an orally administered prodrug that needs hepatic biotransformation into its active metabolite to irreversibly block the P2Y12 receptor.33 Prasugrel has several pharmacological advantages over clopidogrel, because it is more effectively converted into its active metabolite and displays a faster onset of action and greater degree of platelet inhibition with less variability in response, even when compared with high dose clopidogrel.34

The TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38) trial evaluated the clinical efficacy and safety of prasugrel (60 mg loading dose followed by a 10 mg maintenance dose), compared with standard clopidogrel (300 mg loading dose followed by 75 mg daily maintenance dose) therapy in 13 608 patients with moderate to high risk ACS undergoing PCI.35 Patients pretreated with clopidogrel were not eligible for this study and patients were randomized only after coronary anatomy was established, with the exception of patients presenting with STEMI undergoing primary PCI in whom allocation to randomized treatment was allowed before coronary anatomy was known. The primary efficacy end point, which was the composite of death from cardiovascular causes, nonfatal myocardial infarction (MI), or nonfatal
initial nonfatal event, recurrent events, including mortality, were significantly reduced with prasugrel compared with clopidogrel.\(^{40}\) In contrast, no net benefit was observed in elderly patients (≥75 years) and in those weighing less than 60 kg due to an increase in bleeding complications. The Food and Drug Administration recommends using a 5 mg dose in low weight patients, although the safety of this dose, which derives from pharmacokinetic findings, has not been prospectively studied yet. In elderly patients, prasugrel is generally not recommended except in patients with diabetes or a prior MI, in whom the benefits outweighed the risks, supporting the use of prasugrel at standard dosing in the elderly with these characteristics. A net harm was found in patients with history of stroke or transient ischemic attack, and therefore prasugrel is contraindicated in these subjects. In addition, prasugrel is contraindicated at patients at high risk of bleeding. Patients who are treated with clopidogrel can switch to prasugrel without concerns of drug interactions and is associated with increased platelet inhibition.\(^{41}\) Prasugrel effects have not shown to be modulated by aspirin dose or CYP interfering drugs, including proton pump inhibitors. A washout period of 7 days is warranted for prasugrel-treated patients requiring surgery. Prasugrel is only approved for clinical use in patients with ACS undergoing PCI, and the efficacy and safety of prasugrel in medically-managed patients (n=10300) with UA/NSTEMI is currently being evaluated in the TRILOGY-ACS (TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medicallY manage Acute Coronary Syndromes) trial (NCT00699989). Further, the benefits and risks associated with prasugrel pretreatment in ACS patients (n=4100) scheduled for an invasive strategy is being evaluated in the ACCOAST (A Comparison of Prasugrel at PCI or Time of Diagnosis of Non-ST Elevation Myocardial Infarction, NCT01015287) trial.

**Ticagrelor**

Ticagrelor is an orally administered cyclopentyltriazoloopyrimidine, a new compound class, which directly and reversibly inhibits through allosteric modulation the platelet ADP \(P2Y_{12}\) receptor.\(^{42}\) Similarly to prasugrel, standard dose ticagrelor (180 mg loading dose/90 mg twice daily maintenance dose) has a faster onset of action and provides stronger and more consistent platelet inhibition than clopidogrel. Because ticagrelor has reversible binding effects and plasma half-life of 8 to 12 hours, twice daily dosing is required.\(^{43}\) Approximately 30% to 40% of ticagrelor effects are attributed to metabolites generated by the hepatic CYP3A system, which also is involved in metabolism of the drug itself.

The PLATO (Platelet Inhibition and Patient Outcomes) trial evaluated the benefit of ticagrelor (180 mg loading dose followed by 90 mg twice daily) compared with clopidogrel (300 to 600 mg loading dose followed by 75 mg daily) in preventing cardiovascular events in 18624 ACS patients.\(^{44}\) PLATO is the latest of the pivotal large-scale clinical trials evaluating the efficacy of dual antiplatelet therapy with aspirin and an orally administered \(P2Y_{12}\) receptor inhibitor in ACS patients (Table 2). In contrast to TRITON-TIMI 38, in PLATO patients pretreated with clopidogrel were eligible for enrollment, and randomization generally occurred before...
defining coronary anatomy to reflect current practice patterns. In this trial, ticagrelor therapy significantly reduced the rate of the primary end point (death from vascular causes, nonfatal MI, or nonfatal stroke) at 12 months (9.8% versus 11.7%; HR, 0.84 [0.77–0.92]; P = 0.0001). The outcomes were driven by a reduction of cardiovascular death (4.0% versus 5.1%; HR, 0.79; P = 0.001) and MI (5.8% versus 6.9%; HR, 0.84 [0.75–0.95]; P = 0.005). Ticagrelor-treated patients also experienced a reduction in definite or probable stent thrombosis (2.2% versus 3.0%; HR, 0.73 [0.57–0.94]; P = 0.014; Figure 3). Although no differences in protocol-defined major bleeding was found (11.6% versus 11.2%; HR, 1.04; P = 0.43), the rate of non-CABG major bleeding was increased significantly with ticagrelor when using both PLATO (4.5% versus 3.8%; P = 0.03) and TIMI criteria (2.8% versus 2.2%; P = 0.03).44 In addition, although fatal intracranial bleeding was significantly more frequent in the ticagrelor arm (0.1% versus 0.01%; P = 0.02), overall PLATO-defined fatal bleeding was not significantly different between arms (0.3% versus 0.3%; P = 0.66). Of note, the benefit of ticagrelor was consistent across different subgroup analyses, such as patients with an initial conservative approach with noninvasive treatment strategy,43 patients undergoing a planned invasive strategy,46 and those undergoing CABG.47 In addition, there weren’t any specific subgroups that emerged to have higher bleeding potential with ticagrelor, including patients with prior transient ischemic/ischemic stroke. Several nonhematological safety end points, which have been associated with higher discontinuation rates, have been observed with ticagrelor. These include higher rates of dyspnea and ventricular pauses, and increased levels of creatinine and uric acid during treatment compared with clopidogrel. Although the mechanisms contributing to these effects have been attributed to off-target effects of ticagrelor (eg, increased adenosine levels due to reduced erythrocyte uptake) or its metabolites, they remain elusive, and these side effect thus far have not been shown to have any significant clinical impact.48,49

Ticagrelor has been approved recently for clinical use and is indicated for the prevention of atherothrombotic events in patients with ACS, including patients managed medically and invasively. In addition to being contraindicated in patients at high risk of bleeding, ticagrelor is contraindicated in patients with prior hemorrhagic stroke and severe hepatic dysfunction. Ticagrelor-treated patients requiring surgery warrant a minimum of a 5 day washout period to minimize bleeding complications. Because ticagrelor is metabolized by CYP3A4/5 enzymes, the prescribing information for ticagrelor recommends that patients taking ticagrelor should avoid the use of strong inhibitors or inducers of CYP3A. In addition, patients taking ticagrelor should avoid simvastatin and lovastatin doses >40 mg and monitor digoxin levels with initiation of, or any change in, ticagrelor therapy. Furthermore, patients from North America participating in the PLATO trial had worse outcomes with ticagrelor compared with other geographic regions.50 This result is believed to be related to the higher doses of long-term aspirin generally administered to patients with ACS in the United States, and the prescribing information for ticagrelor includes a warning to avoid aspirin doses >100 mg in patients receiving the drug.50 The ongoing PEGASUS (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin)-TIMI 54 trial is evaluating the efficacy and safety of ticagrelor in combination with aspirin (versus aspirin plus placebo) in patients (n = 21 000) with a history of MI within 1 to 3 years (NCT01225562). The
ongoing ATLANTIC trial (A 30 Day Study to Evaluate Efficacy and Safety of Prehospital versus In-hospital Initiation of Ticagrelor Therapy in STEMI Patients Planned for Percutaneous Coronary Intervention, NCT01347580) is evaluating prehospital versus in hospital initiation of ticagrelor therapy in STEMI patients (n=1770) planned for PCI.

**Glycoprotein IIb/IIIa Inhibitors**

Three different GPIs are currently approved for clinical use: abciximab, eptifibatide, and tirofiban. These drugs are only available for intravenous use and have a rapid onset of action and a very potent inhibitory effect on platelets. However, their use is restricted to the acute phase of treatment. Importantly, the efficacy of these agents correlates directly with the severity and the risk of ACS, thus, its use is not generally recommended in low to moderate risk patients or in those in whom a conservative approach is chosen, whereas they reach their maximal benefit in high risk ACS patients undergoing PCI. Of note, many trials evaluating GPIs’ efficacy were performed before in the era in which regimens of clopidogrel that are currently being used (eg, pretreatment, high loading doses) were not part of the standard of care and the new P2Y_{12} inhibiting agents prasugrel and ticagrelor were not available. Therefore, the role of GPIs role in today’s clinical practice is diminished significantly.

The benefit of abciximab for reduction of ischemic events in ACS patients undergoing PCI after a clopidogrel 600 mg loading dose appears to be limited to high risk patients both in NSTEMACS, such as a dose with elevated troponin levels, and STEMI. However, the major limitation of GPIs is bleeding risk. Importantly, bleeding complications have shown to have important prognostic implications, including on short and long-term mortality, underscoring the need to identify safer antithrombotic treatment options. Head-to-head comparisons between GPIs and bivalirudin, a direct thrombin inhibitor, have shown bivalirudin to be noninferior in terms of reducing ischemic events, but associated with better safety as indicated by the lower rates of major bleedings compared with GPIs. Such potential advantages over COX-1 inhibition achieved with aspirin. Further, many TXA_{2} pathway inhibitors also exert inhibitory effects on TXA_{2} synthase in addition to TP receptors, allowing more comprehensive blockade TXA_{2} mediated signaling. Moreover, TPs are also expressed in inflammatory cells, the vascular wall, and in atherosclerotic plaques. Thus, TP antagonists may also exert some effect on these structures.

**Antiplatelet Agents Under Clinical Development**

There are still drawbacks of currently approved antiplatelet agents, which include (1) no effective alternative to block TXA_{2} pathway in patients with either severe allergy or inadequate response to aspirin, (2) a P2Y_{12} inhibitor intravenously administered for patients in whom absorption of oral medications is compromised (eg, intubated patients), and (3) a P2Y_{12} inhibitor with a very quick offset of action, which can be useful in patients with a bleeding event or as a bridging therapy to provide sufficient platelet inhibition in patients that need to undergo CAGB. In this section, we provide an overview on several drugs under development that may play a future role if shown to be effective for these unmet needs.

**Thromboxane A_{2} Pathway Inhibitors**

Because inhibition of TP receptors blocks the effect of TXA_{2} on platelets as well as TP activation through other ligands, such as eicosanoids and endoperoxides, blockade of TP may have potential advantages over COX-1 inhibition achieved with aspirin. Further, many TXA_{2} pathway inhibitors also exert inhibitory effects on TXA_{2} synthase in addition to TP receptors, allowing more comprehensive blockade TXA_{2} mediated signaling. Moreover, TPs are also expressed in inflammatory cells, the vascular wall, and in atherosclerotic plaques. Thus, TP antagonists may also exert some effect on these structures.

TXA_{2} pathway inhibitors include picotiamide (a combined TXA_{2} synthase inhibitor and TP receptor blocker), ridogrel (a combined TXA_{2} synthase inhibitor and TP receptor blocker), ramatroban (a TP receptor inhibitor), NCX 4016 (a nitric oxide-releasing aspirin derivative), Si8886/terutroban (a TP receptor inhibitor), and EV-077 (a combined TXA_{2} synthase inhibitor and TP receptor blocker). Some of these agents have been tested in clinical settings. In a randomized trial of patients with diabetes mellitus and peripheral artery disease (PAD), picotiamide reduced long term overall mortality, but not major cardiovascular events, compared with aspirin. Ridogrel failed to show any benefit over aspirin as adjunct therapy to thrombolysis in patients with acute MI. Terutroban (S18886) is a novel oral, selective, and reversible TP antagonist, which has shown an excellent safety profile in patients with stable PAD. However, terutroban failed to meet the primary end point of noninferiority compared with aspirin in a cohort of patients with cerebrovascular disease. At the present time, none of the above mentioned agents appear to be suitable for replacing aspirin in patients with CAD.

**P2Y_{12} Inhibitors**

Cangrelor is the P2Y_{12} inhibitor at the most advanced stage of clinical development. Cangrelor is an intravenous adenosine
triphosphate analog, which reversibly and directly, thus, not needing any biotransformation, inhibits the P2Y₁₂ receptor.⁶⁵ Cangrelor has dose dependent and, thus, predictable, pharmacodynamics effects. It achieves very potent (>90%) platelet inhibition, with immediate onset of action, and because of its ultrashort half-life (3–6 minutes), it has a very rapid offset of action, with return to baseline platelet function within 30 to 60 minutes.⁶⁵

Despite the promising results obtained in phase II studies, which showed cangrelor to be a very potent platelet inhibitor with a relatively safe profile, these findings were not corroborated in phase III studies. The CHAMPION (Cangrelor versus standard therapy to Achieve optimal Management of Platelet Inhibition) program included the CHAMPION-PCI and the CHAMPION-PLATFORM trials, which evaluated mostly ACS patients undergoing PCI and were terminated before completion because of an interim analysis showing insufficient evidence of clinical effectiveness of cangrelor (bolus 30 μg/kg plus infusion of 4 μg/kg/min for the duration of the PCI procedure, with a minimum infusion duration of 2 hours and a maximum of 4 hours).⁶⁶⁻⁶⁷ Pitfalls in trial design and definition of study end points may have contributed to failure to show superiority in terms of reduction of adverse ischemic outcomes of cangrelor over clopidogrel in CHAMPION-PCI (n=8716), and over placebo in CHAMPION-PLATFORM (n=5362) trials. In a pooled analysis of the 2 CHAMPION trials comprising a total of 13 049 patients, cangrelor had no effect on the primary end point with the original CHAMPION trials comprising a total of 13 049 patients, can-

**Table 3.** Pharmacological Properties of Currently Approved and Investigational P2Y₁₂ Inhibitors

<table>
<thead>
<tr>
<th>Group</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
<th>Cangrelor*</th>
<th>Elinogrel*</th>
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<tr>
<td>Administration</td>
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<td>Seconds</td>
<td>Seconds</td>
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<td>Yes</td>
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*Cangrelor and elinogrel are investigational agents and not approved for clinical use at the time of preparation of this manuscript. CPTP indicates cyclopentyltriazolopyrimidine; ATP, adenosine triphosphate; IV, intravenous; CYP, cytochrome P450.

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<td>Seconds</td>
</tr>
<tr>
<td>Offset of action</td>
<td>7–10 d</td>
<td>7–10 d</td>
<td>3–5 d</td>
<td>~60 min</td>
<td>50 min (IV)</td>
</tr>
<tr>
<td>CYP drug interactions</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*Cangrelor and elinogrel are investigational agents and not approved for clinical use at the time of preparation of this manuscript. CPTP indicates cyclopentyltriazolopyrimidine; ATP, adenosine triphosphate; IV, intravenous; CYP, cytochrome P450.

**Protease-Activated Receptor-1 Inhibitors**

Dual antiplatelet therapy with aspirin and a P2Y₁₂ receptor inhibitor represents the current standard of care for patients with ACS or undergoing PCI. However, aspirin and P2Y₁₂ inhibitors target the TXA₂ and ADP P2Y₁₂ platelet activation pathways and minimally affect other pathways, such as thrombin mediated platelet activation. Thrombin is an essential component of the coagulation cascade, and also a potent agonist for platelet activation.⁷³ This may help explain why patients continue to experience recurrent ischemic events despite receiving standard DAPT. A selective inhibition of
thrombin-mediated platelet activation, the most potent pathway for platelet aggregation, without other effects on hemostatic processes that involve thrombin therefore may represent an attractive strategy for patients with atherothrombotic diseases. Currently, 2 oral thrombin receptor antagonists, which selectively block the platelet protease-activated receptor-1 (PAR-1) receptor subtype, are under clinical development: vorapaxar (SCH530348) and atopaxar (E5555).

Vorapaxar is a selective and potent oral PAR-1 (the principal thrombin receptor in humans) antagonist, which has shown a good efficacy and safety profile in preclinical and phase I and II studies, in which addition of vorapaxar to DAPT with aspirin and clopidogrel, also known as triple antiplatelet therapy, was not associated with increased risk of bleeding. Vorapaxar is a selective and potent oral PAR-1 (the principal thrombin receptor in humans) antagonist, which has shown a good efficacy and safety profile in preclinical and phase I and II studies, in which addition of vorapaxar to DAPT with aspirin and clopidogrel, also known as triple antiplatelet therapy, was not associated with increased risk of bleeding. Vorapaxar is a selective and potent oral PAR-1 (the principal thrombin receptor in humans) antagonist, which has shown a good efficacy and safety profile in preclinical and phase I and II studies, in which addition of vorapaxar to DAPT with aspirin and clopidogrel, also known as triple antiplatelet therapy, was not associated with increased risk of bleeding.

The phase III clinical development of vorapaxar includes 2 large-scale trials: TRACER (Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients With Acute Coronary Syndrome) and TRA 2P (Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients With Atherosclerosis)-TIMI 50. Results of the TRACER trial, which randomized patients with NSTEACS (n = 12,944) to receive vorapaxar or placebo on top of standard antiplatelet therapy (approximately 90% on DAPT with aspirin and clopidogrel), has been published recently. Follow-up in the trial was stopped prematurely due to a safety review that observed an excess in the rates of moderate and severe bleeding in the vorapaxar arm compared with placebo (7.2% versus 5.2%; HR, 1.65 [1.16–1.58]; P < 0.001), as well as in the rates of intracranial hemorrhage (1.1% versus 0.2%; HR, 3.39 [1.78–6.45]; P < 0.001). The primary efficacy end point (composite of death from cardiovascular causes, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization) was numerically but not significantly reduced with the addition of vorapaxar to standard therapy (18.5% versus 19.9%; HR, 0.92 [0.85–1.01]; P = 0.07). In TRA 2P-TIMI 50 trial, patients who had a history of MI, ischemic stroke, or PAD (n = 26,449) were randomized to receive vorapaxar (2.5 mg daily) or placebo with a median follow-up of 30 months. Vorapaxar reduced the rates of the primary efficacy end point (composite of death from cardiovascular causes, MI, or stroke) compared with placebo (9.3% versus 10.5%; HR, 0.87 [0.80–0.94]; P < 0.001), at the cost of increasing the risk of moderate or severe bleeding (4.2% versus 2.5%; HR, 1.66 [1.43–1.93]; P < 0.001), including intracranial hemorrhage (1.0% versus 0.5%; P < 0.001). Of note, vorapaxar treatment was discontinued in patients with a prior stroke due to the risk of intracranial hemorrhage.

Atopaxar is in an earlier stage of development that has recently completed phase II testing. Two phase II studies, the LANCELOT-ACS (Lessons From Antagonizing the Cellular Effects of Thrombin-Acute Coronary Syndromes) and the LANCELOT-CAD (Lessons From Antagonizing the Cellular Effect of Thrombin-Coronary Artery Disease) recently have observed a good safety profile in terms of bleeding risk of atopaxar compared with placebo in patients with ACS and with CAD, respectively. However, dose-dependent QTc prolongation without apparent complications and transient elevation in liver transaminases were observed with the highest doses of atopaxar. Parallel findings were found in another phase II study performed in Japanese patients with ACS or high risk CAD. Larger trials are warranted to establish the real clinical value of this new agent. However, phase III investigations are not being planned for atopaxar.

**Other Antiplatelet Agents in Early Phase Clinical Development**

Several other agents that target a number of platelet signaling pathways have been evaluated in preclinical or early phase clinical studies, including inhibitors of collagen-platelet interaction, such as glycoprotein VI antagonists (kistomin, revacept) or glycoprotein Ib antagonist (6B4-Fab monoclonal antibody), serotonin receptor inhibitors (APD791), prostaglandin E receptor 3 antagonists (DG-041), nitric oxide donors (LA846, LA419), and phosphatidylinositol 3-kinase inhibitors (TGX-221). These agents need to undergo more advanced clinical testing before establishing its possible applications in clinical practice.

**Future Perspectives and Conclusions**

Dual antiplatelet therapy with aspirin and clopidogrel has been for many years the antiplatelet treatment of choice for patients with ACS and undergoing PCI. Despite the benefit of this combination, a substantial percentage of patients still present recurrent atherothrombotic events, leading to the development of newer and more potent antiplatelet agents, some of which have already been approved for clinical use, such as prasugrel and ticagrelor. Both agents support the concept that in high-risk settings more potent platelet inhibition translates into reduced risk of ischemic events at the expense of increased bleeding risk. However, because there is some overlapping in the recommendations of currently available guidelines, the choice of a particular antiplatelet strategy for a given patient may be confusing. Until more evidence derived from large scale studies is presented (eg, head-to-head comparisons between prasugrel and ticagrelor), subgroup analyses of available data might represent a reasonable option to determine the best niche for the use of each of the newer antiplatelet agents, as well as to define settings in which 1 or both of these drugs should not be used. However, clinicians must also be cautious when using subgroup data to guide therapy because these analyses are sometimes methodologically limited because they are underpowered to demonstrate a treatment effect, and the analysis is often not planned but performed post hoc. Indeed, costs remain a key decision factor for the patient on whether a novel P2Y12 receptor inhibitor will be chosen over clopidogrel, which will soon be available in a generic and less expensive formulation in most countries. Similar cost-effectiveness considerations can be made with regards on how to implement other proposed anti-thrombotic approaches, such as adding the novel oral anticoagulant rivaroxiban to standard DAPT, a strategy that was associated with a reduction in ischemic events, including reduced cardiovascular mortality using a 2.5 mg twice daily dosing regimen, albeit at the expense of increased major bleeding and intracranial hemorrhage.

Strategies of stratifying patients based on results of platelet function and genetic testing, which have been able to identify patients at increased risk of recurrent atherothrombotic events...
Despite compliance with clopidogrel therapy, have represented very important advancements in our field.\textsuperscript{20,21} These strategies may set the basis for investigations to identify patients who can potentially benefit from antiplatelet treatment strategies tailored to the individual patient, with the goal of maximizing ischemic benefit and minimizing bleeding risk.\textsuperscript{52,83} Defining a “therapeutic window” of levels of platelet reactivity associated with reduced risk of ischemic and bleeding events is indeed a promising area of research that, however, requires further investigation. However, to date, larger scale clinical studies have failed to show that modifying therapy translates into improved clinical outcomes and current guidelines do not support their routine use of platelet function and genetic testing (Table 4).\textsuperscript{3–6} Ongoing clinical trials assessing novel antiplatelet agents or treatment strategies will indeed provide the safety and efficacy information to define the best combination of antiplatelet treatment strategies to treat patients with ACS or undergoing PCI.

**Disclosures**


**References**


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**Table 4. Guideline Recommendations on the Use of Platelet Function and Genetic Testing**

<table>
<thead>
<tr>
<th>Year</th>
<th>ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction\textsuperscript{3}</th>
<th>ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention\textsuperscript{4}</th>
<th>ESC Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-segment Elevation\textsuperscript{5}</th>
<th>ESC/EACTS/EAPCI Guidelines on Myocardial Revascularization\textsuperscript{6}</th>
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</thead>
<tbody>
<tr>
<td>2011</td>
<td><strong>Class IIb; Level of Evidence B</strong> Platelet function testing to determine platelet inhibitory response in patients with UA/NSTEMI (or, after ACS and PCI) on thienopyridine therapy may be considered if results of testing may alter management.</td>
<td><strong>Class IIb; Level of Evidence B</strong> Platelet function testing may be considered in patients at high risk for poor clinical outcomes. In patients treated with clopidogrel with high platelet reactivity, alternative agents, such as prasugrel or ticagrelor, might be considered.</td>
<td>The routine clinical use of platelet function testing to screen patients treated with clopidogrel who are undergoing PCI is not recommended.</td>
<td>No recommendation</td>
</tr>
<tr>
<td>2011</td>
<td><strong>Class III; Level of Evidence C</strong> The routine clinical use of platelet function testing to screen patients treated with clopidogrel who are undergoing PCI is not recommended.</td>
<td><strong>Class III; Level of Evidence C</strong> Increasing the maintenance dose of clopidogrel based on platelet function testing is not advised as routine, but may be considered in selected cases.</td>
<td>No recommendation</td>
<td>No recommendation</td>
</tr>
</tbody>
</table>

ACS: acute coronary syndrome; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; UA: unstable angina.


Key Words: acute coronary syndrome ■ antplatelet therapy ■ percutaneous transluminal coronary angioplasty ■ pharmacology ■ platelets