

# Emerging antiplatelet agents, differential pharmacology, and clinical utility

Pranab Das<sup>1</sup>  
 Carrie S Oliphant<sup>2</sup>  
 Elizabeth Beach<sup>3</sup>  
 Rashmi Thapa<sup>4</sup>

<sup>1</sup>Assistant Professor, Division of Cardiology, Department of Internal Medicine, University of Tennessee Health Sciences Center, Memphis, Tennessee, USA; <sup>2</sup>Cardiology Clinical Pharmacy Specialist, Department of Pharmacy, Methodist University Hospital, and Assistant Professor University of Tennessee College of Pharmacy, Memphis, Tennessee, USA; <sup>3</sup>PGY-I Pharmacy Practice Resident, Department of Pharmacy, Methodist University Hospital, Memphis, Tennessee, USA; <sup>4</sup>Resident, Department of Internal Medicine, University of Tennessee Health Sciences Center, Memphis, Tennessee, USA

**Abstract:** The aspirin–clopidogrel combination is the current gold standard antiplatelet regimen following percutaneous coronary intervention and for the treatment of acute coronary syndrome. Despite the clinical benefit of this combination, patients continue to have vascular events. Another purinergic (P2Y<sub>12</sub>) receptor antagonist, prasugrel, became available last year. Although prasugrel is superior to clopidogrel in reducing clinical endpoints, a higher bleeding rate has been identified particularly in high-risk patients. Ticagrelor, a reversible P2Y<sub>12</sub> receptor antagonist currently being evaluated for approval, is also more potent than clopidogrel but has a similar bleeding risk. Two additional P2Y<sub>12</sub> antagonists are being investigated that will be available as an intravenous formulation. Apart from the P2Y<sub>12</sub> receptor antagonists, multiple other agents are being developed with unique mechanisms of platelet inhibition. These agents are being studied as an alternative to or in combination with clopidogrel. The antiplatelet agents currently under development include: thrombin receptor antagonists, phosphodiesterase inhibitors, a thromboxane–prostaglandin receptor antagonist, a serotonin receptor blocker, a platelet adhesion antagonist, nitric oxide-releasing aspirin, a glycoprotein VI antagonist, and a cyclooxygenase inhibitor. The purpose of this review is to describe the efficacy and safety profiles of the emerging antiplatelet agents and their role in the treatment of atherosclerotic cardiovascular diseases.

**Keywords:** antiplatelet agents, safety, efficacy, clinical pharmacology, clinical trials

## Introduction

Platelets have an important role in primary hemostasis and endothelial repair. In addition, by activation of their numerous surface receptors and release of several inflammatory mediators, platelets promote atherothrombosis.<sup>1</sup> Coronary artery disease (CAD), stroke, and peripheral vascular disease are known as “atherothrombotic” manifestations of atherosclerosis. Inhibition of platelet aggregation and secretion is paramount to reducing adverse outcomes in these clinical conditions associated with heightened platelet reactivity.

Aspirin, a cyclooxygenase (COX) inhibitor, has been used for centuries due to its anti-inflammatory, antipyretic, and analgesic properties. More recently, aspirin has been used as an antiplatelet agent to prevent thromboembolic vascular events. The thienopyridines are another class of antiplatelet agents that inhibit adenosine diphosphate-induced platelet aggregation via the P2Y<sub>12</sub> receptor located on the platelet surface. Adenosine diphosphate (ADP) is a very potent platelet agonist, whose signals to cause platelet aggregation are mediated via two purinergic platelet receptors, G<sub>q</sub> coupled P2Y<sub>12</sub> receptor and G<sub>i</sub> coupled P2Y<sub>12</sub> receptor.<sup>2</sup> Due to selective tissue distribution of

Correspondence: Pranab Das  
 Division of Cardiology, Department of Internal Medicine, University of Tennessee Health Sciences Center, Memphis, Tennessee, USA  
 Tel +1 901 448 5750  
 Fax +1 901 448 1123  
 Email pdas@uthsc.edu

P2Y<sub>12</sub> receptors, the thienopyridines, referred to as P2Y<sub>12</sub> receptor antagonists, are potent antiplatelet agents that are extensively used in clinical and interventional cardiology.

Ticlopidine, the first P2Y<sub>12</sub> antagonist, is approved for use with aspirin as dual antiplatelet therapy following coronary artery stenting.<sup>3</sup> However, due to serious side effects of ticlopidine, it is no longer the drug of choice having been replaced by clopidogrel, a second generation thienopyridine P2Y<sub>12</sub> antagonist with a more favorable side effect profile. Several large, randomized clinical trials have demonstrated the benefit of aspirin-clopidogrel combination in reducing death, myocardial infarction (MI), and target vessel revascularization among patients with acute coronary syndrome (ACS) including unstable angina, non-ST-segment elevation MI (NSTEMI) and ST-segment elevation MI (STEMI) with or without percutaneous coronary intervention (PCI).<sup>4-9</sup> The combination of aspirin and clopidogrel has now become the favored combination in the realm of interventional cardiology following PCI, and also in the medical management of patients with ACS.

Clopidogrel has properties that make it less than an ideal antiplatelet agent. It has a slow onset of action of at least two hours following a 600 mg oral loading dose, and between 6–15 hours after a 300 mg loading dose to achieve adequate platelet inhibition. This delayed onset of action can be problematic when quicker platelet inhibition is desired as in ACS. In addition, the irreversible blockade of platelet activity can delay coronary artery bypass graft (CABG) surgery for 5–7 days in an effort to reduce the rate of CABG-related bleeding and the need for re-operation and transfusion.

Although aspirin and clopidogrel are widely used in the management of ACS and after PCI, some patients continue to have thromboembolic events. One possible explanation is the concept of antiplatelet resistance that has been reported with both aspirin and clopidogrel.<sup>10,11</sup> The proposed mechanisms for antiplatelet resistance include, alternative signaling pathways for platelet activation, high stress conditions, genetic polymorphisms and drug interactions.<sup>10,12</sup> Variability in response to clopidogrel therapy has been recently demonstrated on platelet function assays. This phenomenon of “clopidogrel hyporesponsiveness” has been linked to increased thrombotic events which could be potentially fatal.<sup>13,14</sup> Tailoring of clopidogrel therapy based on platelet reactivity as assessed by *in vitro* platelet assays was met with initial enthusiasm, but this approach has been found to be far from ideal.<sup>15,16</sup> Genetic polymorphisms with reduced function variant alleles of the CYP2C19 hepatic cytochrome P450 isoenzyme involved in the metabolism of

clopidogrel to its active metabolite has been associated with platelet hypo-responsiveness.<sup>17</sup>

As a result of these problems associated with clopidogrel, newer agents are being developed with the hope of overcoming these shortcomings. Ideally, any agent aimed at replacing clopidogrel would have a faster onset of action and more uniform platelet inhibition without a significant increase in bleeding risk. In addition to finding a replacement for clopidogrel, some antiplatelet agents are being investigated as add-on therapy to the combination of aspirin and clopidogrel. Table 1 outlines the various classes of antiplatelet agents that are currently available or under investigation. We aim to discuss the role of emerging antiplatelet agents in atherosclerotic cardiovascular diseases.

## Newer P2Y<sub>12</sub> antagonists

While ticlopidine and clopidogrel have been used extensively ever since their inception, newer agents hold a great deal of promise due to their differential pharmacology.<sup>18</sup> Table 2 describes the various types of P2Y<sub>12</sub> antagonists that are currently in use, or in the later stages of development.

**Table 1** Classes of antiplatelet agents

Class	Drugs
Cyclooxygenase inhibitors	Aspirin Indobufen
ADP receptor antagonists (Thienopyridines)	Ticlopidine Clopidogrel Prasugrel
ADP receptor antagonists (Nonthienopyridines)	Cangrelor Ticagrelor Elinogrel
Glycoprotein IIb/IIIa inhibitors	Abciximab Tirofiban Eptifibatid Defibrotide
Phosphodiesterase inhibitors	Dipyridamole Cilostazol NT-702 (parogrelil hydrochloride, NM-702)
Protease-activated receptor (PAR-1) inhibitors (thrombin receptor inhibitor)	SCH 530348 E5555
Thromboxane A <sub>2</sub> receptor inhibitor	Terutroban (S18886)
Platelet adhesion antagonist	ARC1779 ClqTNF-related protein-1 DZ-697b
Nitric oxide releasing aspirin	NCX-4016
Collagen-platelet interaction inhibitor	PR-15 Monoclonal antibodies Aptamers Small molecule peptide inhibitors

**Abbreviation:** ADP, adenosine diphosphate.

**Table 2** P2Y<sub>12</sub> antagonists

Agent	Morphology	Mode of P2Y <sub>12</sub> inhibition	Reversibility of P2Y <sub>12</sub> blockade	Mode of administration	Dosing frequency	Approval status
Ticlopidine	Thienopyridine	Indirect	Irreversible	Oral	Twice daily	Approved
Clopidogrel	Thienopyridine	Indirect	Irreversible	Oral	Once daily	Approved
Prasugrel	Thienopyridine	Indirect	Irreversible	Oral	Once daily	Approved
Ticagrelor	Cyclo-pentyl-triazolo-pyrimidine	Direct	Reversible	Oral	Twice daily	Under review
Cangrelor	ATP analog	Direct	Reversible	Intravenous	During procedure	Phase III clinical trials
Elinogrel	–	Direct	Reversible	Oral and intravenous	Once daily	Phase II clinical trials

**Abbreviations:** ATP, adenosine triphosphate; P2Y<sub>12</sub>, purinergic.

### Prasugrel

Prasugrel is a new thienopyridine adenosine diphosphate (ADP) receptor antagonist. Like clopidogrel and ticlopidine, prasugrel is a selective and irreversible inhibitor of the platelet P2Y<sub>12</sub> receptor.<sup>19</sup> It is a pro-drug that is converted to its active metabolite R-138727 by cytochrome (CYP) P450 enzymes. The CYP3A4 and CYP2B6 enzymes are primarily responsible for metabolic conversion with CYP2C9 and CYP2C19 being secondary pathways. For prasugrel, conversion to the active metabolite requires only one CYP450 dependent oxidation step, while clopidogrel requires two enzymatic steps. As a result, prasugrel has a faster onset of action with a peak plasma concentration of the active metabolite 30 minutes post dosing.<sup>20</sup> The half life of the active metabolite of prasugrel is 7.4 hours (ranging from 2 hours to 15 hours) while the half life of the active metabolite for clopidogrel is 8 hours. Due to the differing enzymes involved in metabolic conversion of prasugrel to its active form, the drug interaction reported between clopidogrel and proton pump inhibitors does not seem to be clinically significant.<sup>21</sup> Unlike with clopidogrel, common functional CYP genetic variants do not affect active drug metabolite levels, inhibition of platelet aggregation, or clinical cardiovascular event rates in persons treated with prasugrel.<sup>22</sup>

Early Phase I and II clinical trials demonstrated prasugrel has a faster onset of action and more complete platelet inhibition compared to clopidogrel. The Joint Utilization of Medications to Block Platelets Optimally (JUMBO-TIMI 26) trial was the first Phase II study to evaluate the use of prasugrel in patients undergoing elective or urgent PCI.<sup>23</sup> In this study, 904 patients were randomized to prasugrel low dose (40 mg loading dose, 7.5 mg daily dose), intermediate dose (60 mg loading dose, 10 mg daily dose), or high dose (60 mg loading dose, 15 mg daily) or standard clopidogrel (300 mg loading dose, 75 mg daily dose) for approximately 30 days. All patients received aspirin 325 mg daily. The primary

endpoint of the study was non-CABG related significant hemorrhage, which was defined by the composite of TIMI major and minor bleeding criteria. Efficacy was measured by the incidence of major adverse coronary events. Variation was not significant in the primary endpoint between the combined prasugrel groups and clopidogrel, 1.7% and 1.2%, respectively (Hazard Ratio (HR) = 1.42 (95% confidence interval (CI) 0.40–5.08), *P* = 0.59). Major adverse coronary events occurred at a similar rate in the combined prasugrel arm (7.2%) and clopidogrel arm (9.4%) (HR = 0.76 (95% CI 0.46–1.24), *P* = 0.26). The authors concluded that the use of prasugrel resulted in similar bleeding and clinical events compared to clopidogrel.

The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation (PRINCIPLE) Thrombolysis in Myocardial Infarction (TIMI) 44 Trial was a randomized, double-blind, double-dummy, Phase II crossover trial enrolling 201 subjects.<sup>24</sup> Patients undergoing planned PCI were randomized to treatment with prasugrel or clopidogrel with administration of a loading dose within one hour of PCI. The treatment regimens were prasugrel 60 mg loading dose and 10 mg daily dose or clopidogrel 600 mg loading dose and 150 mg daily dose for 14 days. After completion of this phase of the study, patients were switched to the alternative medication for an additional 14 days. The primary end point of the loading dose phase was the degree of inhibition of platelet aggregation (IPA) at 6 hours. Prasugrel had a significantly higher degree of IPA (74.8 ± 13%) compared to clopidogrel (31.8 ± 21.1%) (*P* < 0.0001). For the maintenance phase of the study, the primary endpoint was degree of IPA at day 14. Results for this phase also demonstrated superiority of prasugrel versus clopidogrel, 61.3 ± 17.8% and 46.1 ± 21.3%, respectively (*P* < 0.0001). No TIMI major bleeding events were observed in either treatment arm during the study period. Thus, both

the loading and maintenance doses of prasugrel had a greater degree of platelet inhibition than high dose clopidogrel.

The positive results of the PRINCIPLE-TIMI 44 trial led to a Phase III clinical trial, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON-TIMI 38).<sup>25</sup> TRITON-TIMI 38 was a 13,608 patient, randomized, double-blinded, multinational Phase III clinical trial designed to assess the efficacy and safety of prasugrel versus clopidogrel. Patients with moderate to high risk ACS, including NSTEMI and STEMI, with scheduled PCI, were randomized to receive either prasugrel 60 mg loading dose followed by 10 mg daily or clopidogrel 300 mg loading dose followed by 75 mg daily for 6 to 15 months. The primary end point was the combined occurrence rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Non-CABG TIMI major bleeding, non-CABG TIMI life-threatening bleeding and TIMI major and minor bleeding were the main safety endpoints evaluated. The primary endpoint occurred in 9.9% of patients receiving prasugrel and 12.1% of patients receiving clopidogrel (HR = 0.81 (95% CI 0.73–0.90),  $P < 0.001$ ). This benefit of prasugrel over clopidogrel was seen as early as day 3, which is likely attributed to the rapid onset of action of prasugrel. This reduction in the primary endpoint was principally driven by a significant reduction in the rate of nonfatal myocardial infarction in the prasugrel arm (7.3% vs 9.5%; HR = 0.76 (95% CI 0.67–0.85),  $P < 0.001$ ). Other statistically significant endpoints favoring prasugrel included urgent target-vessel revascularization (2.5% vs 3.7%) and stent thrombosis (1.1% vs 2.4%). The overall reduction in stent thrombosis was remarkable regardless of the type of stent used. There were a significantly greater number of non-CABG TIMI major bleeding events with prasugrel than with clopidogrel, 2.4% and 1.8%, respectively (HR = 1.32 (95% CI 1.03–1.68),  $P = 0.03$ ). Additionally, there was a greater rate of non-CABG TIMI life-threatening bleeding in the prasugrel group (1.4% vs 0.9%; HR = 1.52 (95% CI 1.08–2.13),  $P = 0.01$ ), which included fatal (0.4% vs 0.1%, HR = 4.19 (95% CI 1.58–11.11),  $P = 0.002$ ) and nonfatal bleeding (1.1% vs 0.9%, HR = 1.25 (95% CI 0.87–1.81),  $P = 0.23$ ). CABG-related TIMI major bleeding was also higher in the prasugrel treated patients (13.4% vs 3.2%, HR = 4.73 (95% CI 1.90–11.82),  $P < 0.001$ ). Three subgroups, namely individuals with a history of previous stroke or transient ischemic attack (TIA), patients 75 years or older, and patients weighing 60 kg or less did not show favorable clinical benefits from prasugrel due to the increased risk of bleeding. In patients with a history

of cerebrovascular disease, prasugrel was associated with an increase in intracranial hemorrhage. Use of prasugrel in patients with ACS thus results in a decreased rate of clinical events with an increase in bleeding events. In the STEMI subgroup study from TRITON TIMI 38, patients with STEMI undergoing PCI, prasugrel was found to be more effective than clopidogrel for prevention of ischemic events, without an apparent excess in bleeding.<sup>26</sup>

Prasugrel is now indicated to reduce the rate of thrombotic cardiovascular events (including stent thrombosis) in patients with ACS with planned PCI. The US package insert contains a black box warning related to the increased risk of bleeding in special populations. The warning recommends against the use of prasugrel in patients with active bleeding, prior TIA or stroke and the need for CABG surgery. Patients 75 years or greater should not receive prasugrel unless the benefit outweighs the risk. For patients weighing 60 kg or less, the package labeling suggests considering prasugrel 5 mg daily even though this dosage was not studied in the TRITON-TIMI 38 trial. The American Heart Association and the American College of Cardiology have issued updates to the guidelines for the treatment of STEMI and PCI, which incorporated the latest clinical trial results for prasugrel.<sup>27</sup> A loading dose of prasugrel 60 mg is now recommended for primary PCI in STEMI patients as an alternative to clopidogrel. For STEMI patients undergoing nonprimary PCI, prasugrel 60 mg may be given within one hour after PCI in patients who did not receive fibrinolytic therapy and once the coronary anatomy is known to avoid using in patients who require CABG. After stenting, prasugrel 10 mg daily may be given as an alternative to clopidogrel 75 mg daily for at least 12 months regardless of stent type and can continue beyond 15 months after DES placement. In reference to patients undergoing a planned CABG, prasugrel should be held for at least 7 days prior to the procedure.

### Ticagrelor

Ticagrelor is a reversible oral P2Y<sub>12</sub> receptor antagonist, the first in a new class known as the cyclopentyltriazolopyrimidines. Since ticagrelor does not require metabolic conversion for activity, it has a rapid onset of action within 2–4 hours of administration. An active metabolite has been identified for ticagrelor, which is believed to contribute to the antiplatelet activity of the parent compound. Peak plasma concentrations are achieved in 1.5 to 3 hours with steady state being reached after 2 to 3 days. As a result of its reversible inhibition at the P2Y<sub>12</sub> receptor, the mean elimination half-life is 6 to 12 hours regardless of dose.

The pharmacodynamics, pharmacokinetics and safety profile of ticagrelor has been studied against clopidogrel in the Pharmacodynamics, pharmacokinetics and safety of the oral reversible P2Y<sub>12</sub> receptor antagonist AZD6140 with aspirin in patients with atherosclerosis trial (DISPERSE and DISPERSE-2 Phase II trials).<sup>28,29</sup> The DISPERSE trial was a dose ranging study comparing ticagrelor to clopidogrel in patients with stable atherosclerotic disease.<sup>28</sup> A total of 200 patients were randomized to receive ticagrelor (50, 100, or 200 mg twice a day or 400 mg daily) or clopidogrel 75 mg daily for a total of 28 days. Aspirin was given to all patients at a dose of 75–100 mg daily. The primary pharmacodynamic endpoint was the inhibition of ADP-induced platelet aggregation at various time points. The degree of platelet inhibition with the three highest doses of ticagrelor (100 mg and 200 mg twice daily and 400 mg daily) was greater (approximately 90%–95%) and more rapid than the lowest dose of ticagrelor and clopidogrel (approximately 60%). The extent of platelet inhibition did not differ among the three highest doses of ticagrelor. Bleeding was the most common adverse event and occurred more frequently with the higher doses of ticagrelor. Dyspnea was a unique side effect found in the ticagrelor patients, the incidence of which increased with increasing doses, and none of these events were considered serious. Ticagrelor 100 mg bid and 200 mg bid were well tolerated compared to 400 mg daily with a greater degree of platelet inhibition than clopidogrel and lower dose ticagrelor. In the DISPERSE-2 trial, a total of 990 patients with NSTEMI were randomized to receive ticagrelor or clopidogrel for up to 3 months.<sup>29</sup> The ticagrelor dose was either 90 mg or 180 mg twice daily. Patients in the clopidogrel group received a loading dose of 300 mg followed by 75 mg daily. All patients received aspirin, initially 325 mg followed by 75–100 mg daily. The primary safety endpoint of major or minor bleeding at 4 weeks did not differ among the groups, 9.8% in the 90 mg group ( $P = 0.43$  vs clopidogrel), 8.0% in the 180 mg group ( $P = 0.96$  vs clopidogrel) and 8.1% in the clopidogrel arm. The rate of bleeding in patients undergoing CABG less than 5 days after drug administration was lower in the ticagrelor arms. Numerically, the rate of myocardial infarctions was lower in the ticagrelor arms, but the rate of cardiovascular death was similar between the groups. This study lacked adequate power to assess clinical events. As was seen in the first DISPERSE study, the rate of dyspnea was higher in the ticagrelor arms, with 48% of the patients having persistent symptoms during the study. Ventricular pauses lasting greater than 2.5 seconds was also seen more frequently in the ticagrelor arms. The number of patients

with at least one pause and more than three episodes was significantly higher in the 180 mg group than clopidogrel. The authors concluded that ticagrelor demonstrated similar safety and tolerability to clopidogrel.

The Phase II ONSET/OFFSET trial evaluated the timing of the antiplatelet effect of ticagrelor versus clopidogrel in patients with stable coronary disease.<sup>30</sup> A total of 123 patients were randomized to receive ticagrelor 180 mg loading dose followed by 90 mg twice daily or clopidogrel 600 mg loading dose followed by 75 mg daily for 6 weeks. Aspirin 75–100 mg daily was given to all patients. At all time points, 0.5, 1, 2, 4, 8 and 24 hours after loading and at 6 weeks, ticagrelor had a significantly greater inhibition of platelet aggregation (IPA) ( $P < 0.0001$ , all comparisons). In addition, two hours after the loading dose was administered a greater percentage of patients in the ticagrelor arm had achieved  $>50\%$  IPA (98% vs 31%,  $P < 0.0001$ ) and  $>70\%$  IPA (90% vs 16%,  $P < 0.0001$ ). The offset of ticagrelor was also faster as evidenced by a comparable IPA result for ticagrelor at day 3 to that of clopidogrel at day 5. This study demonstrates that ticagrelor has faster onset and offset action compared to clopidogrel due its reversible nature.

The largest and latest Phase III trial of ticagrelor (platelet inhibition and patient outcomes (PLATO)) compared ticagrelor and clopidogrel in patients with or without STEMI.<sup>31</sup> A total of 18,624 patients were randomized to ticagrelor 180 mg loading dose followed by 90 mg twice daily or clopidogrel 300 mg loading dose followed by 75 mg daily. In patients who had PCI, an additional dose of assigned study drug was given, either ticagrelor 90 mg or clopidogrel 300 mg. Aspirin 75–100 mg daily was given to all patients, unless post stent, in which case 325 mg daily was permitted for six months. The primary efficacy endpoint was a composite of death from vascular causes, myocardial infarction or stroke. Safety was measured as the first occurrence of a major bleeding event using the study specific criteria. The rate of vascular events at 12 months occurred at a lower rate in the ticagrelor group (9.8%) compared to the clopidogrel group (11.7%) (HR = 0.84 (95% CI 0.77–0.92),  $P < 0.001$ ). This endpoint was driven by statistical reductions in the rate of MI and vascular death in the ticagrelor arm. Death from any cause, predefined as a secondary endpoint, occurred in 4.5% of ticagrelor patients versus 5.9% of clopidogrel patients (HR = 0.78 (95% CI 0.69–0.89),  $P < 0.001$ ). The rate of stent thrombosis in patients who received a stent during the study was lower with ticagrelor (1.3%) over clopidogrel (1.9%) (HR = 0.67 (95% CI 0.50–0.91),  $P = 0.009$ ). The rate of major bleeding events as defined by the PLATO investi-

gators, did not differ significantly between ticagrelor and clopidogrel, 11.6% and 11.2%, respectively (HR = 1.04 (95% CI 0.95–1.13),  $P = 0.43$ ). When the TIMI criteria for major bleeding were analyzed, the lack of difference between the treatment arms persisted (7.9% vs 7.7%; HR = 1.03 (95% CI 0.93–1.15),  $P = 0.57$ ). The rate of CABG-related bleeding using both the study definition and TIMI criteria was similar in both arms (both,  $P = 0.32$ ). Non-CABG related major bleeding was significantly higher with ticagrelor using the study criteria (4.5% vs 3.8%, HR = 1.19 (95% CI 1.02–1.38)) and TIMI criteria (2.8% vs 2.2%, HR = 1.25 (95% CI 1.03–1.53)) ( $P = 0.03$ , both endpoints). Other adverse events seen in the PLATO trial were similar to those seen in previous studies. Dyspnea was more commonly seen with ticagrelor, 13.8% versus 7.8% ( $P < 0.001$ ), although only 0.9% of the ticagrelor patients discontinued therapy as a result of this side effect. During the first week of therapy there was a significantly higher incidence of ventricular pauses greater than or equal to 3 seconds in the ticagrelor arm (5.8% vs 3.6%,  $P = 0.01$ ). In this study, uric acid and serum creatinine values were increased in the ticagrelor arm for the duration of treatment but similar to clopidogrel one month after discontinuing therapy. The authors concluded that ticagrelor significantly reduced the incidence of vascular events without a significant increase in the rate of major bleeding.

### Cangrelor

Cangrelor is also a reversible, nonthienopyridine P2Y<sub>12</sub> receptor antagonist. Unlike the other P2Y<sub>12</sub> inhibitors, cangrelor is being developed as an intravenous (IV) formulation. Cangrelor does not require metabolic conversion, which results in its ultra-short half-life of approximately 2.6 to 3.3 minutes. This short half-life allows the effects of cangrelor to be offset within 20–50 minutes following cessation of the infusion. Given the drug's unique properties, studies have been conducted in the setting of ACS and PCI. Cangrelor was studied in a Phase II trial compared to placebo in patients with unstable angina and non-Q wave MI.<sup>32</sup> In this study, cangrelor was well tolerated and bleeding rates were similar to placebo. The use of cangrelor in patients undergoing urgent or elective PCI was studied in a 2-part Phase II trial enrolling a total of 399 patients.<sup>33</sup> Results from the first part of the study showed cangrelor to have a similar rate of bleeding compared to placebo. The second part of the study was a head to head comparison with abciximab. Bleeding rates were comparable between cangrelor and abciximab. Platelet inhibition with cangrelor was seen within 15 minutes

of starting the infusion and platelet function returned to baseline within 15 minutes of stopping the infusion. Platelet inhibition in the abciximab arm was seen 24 hours after the infusion was terminated, as expected.

STEP-AMI (Safety, Tolerability and Effect on Patency in Acute Myocardial Infarction) examined the use of cangrelor alone or in combination with low dose alteplase (tPA) to standard dose tPA.<sup>34</sup> This study was stopped early due to a shift in drug development by the manufacturer. Preliminary results indicated improved coronary artery patency in the patients who received cangrelor and tPA over cangrelor alone but no benefit compared to tPA alone.

Two larger scale, Phase III randomized trials of cangrelor versus standard therapy to achieve optimal management of platelet inhibition (CHAMPION) were recently published.<sup>35,36</sup> These studies (CHAMPION PLATFORM and CHAMPION PCI) enrolling over 14,000 patients were terminated early by the manufacturer when interim efficacy analysis indicated no benefit of cangrelor over placebo. The study designs were similar with the exception of clopidogrel timing. In CHAMPION PCI, clopidogrel was given before PCI, whereas in CHAMPION PLATFORM, clopidogrel was given after PCI. The primary efficacy endpoint was a composite of death, MI or ischemia driven revascularization, which did not differ between cangrelor and placebo. An interesting finding was the rate of stent thrombosis, which was significantly reduced by cangrelor in the CHAMPION PLATFORM study but not the CHAMPION PCI study. The manufacturer of cangrelor has changed the focus of their research to investigate the role of cangrelor as bridge therapy when an antiplatelet therapy is needed short term, when oral drugs cannot be used, or when a short drug half-life is needed (for example, in bridging patients on drugs like clopidogrel who need to undergo surgery). The ongoing maintenance of platelet inhibition with cangrelor after discontinuation of thienopyridines in patients undergoing surgery (BRIDGE) study is investigating this strategy and will enroll approximately 200 patients.<sup>37</sup>

### Elinogrel (PRT 060128)

PRT 060128 or elinogrel is the only direct acting, reversible P2Y<sub>12</sub> antagonist with a unique structure that is being studied both as an IV and oral form. Thus it has the potential of being administered IV in the hospital, and then switched over to the oral form for continuation of therapy. Elinogrel is directly active without the need for any transformation. Most of the drug is excreted unchanged in the urine and feces. About 10%–20% of the drug is metabolized by demethylation (PRT 060301), and is the only prominent circulating metabolite in

plasma. In an initial pharmacokinetic and pharmacodynamic study, single IV doses of elinogrel between 1 and 40 mg were administered over 20 minutes to 5 groups of 8 healthy subjects (6 active, 2 placebo) in a randomized, double-blinded fashion.<sup>38</sup> Platelet aggregation with 10  $\mu$ M ADP at 6 minutes was measured. All IV doses were well tolerated with no serious or clinically significant adverse events. The increase in plasma drug concentration of elinogrel is dose related, and the degree of platelet inhibition is also proportional to plasma drug concentration. The maximum tolerated dose using a pre-defined bleeding time criteria was reached with the 40 mg dose. Average terminal half-life of the 40 mg dose of elinogrel was about 11 hours.

In an animal model (mouse model), the efficacy of PRT 060128 (PRT 128) and clopidogrel were compared by Andre et al.<sup>39</sup> Mice were administered PRT 128 (7.5, 20, 60 mg/kg) 2 hours prior to experiments or clopidogrel 50 mg/kg for 3 days with 5–10 animals per group. Bleeding times and thrombosis were measured. PRT 128 demonstrated dose-proportional anti-thrombotic activity *in vivo* at plasma concentrations which had minimal effect on tail bleeding times. At the highest concentrations of PRT 128, its antithrombotic activity was superior to clopidogrel. This finding of superior efficacy of PRT 128 was further evaluated in human subjects by Gurbel et al.<sup>40</sup> A total of 45 subjects with established coronary artery disease with previous coronary stent placement on chronic aspirin and clopidogrel therapy were screened for high platelet reactivity (HPR) defined as >43% platelet aggregation to 5  $\mu$ M ADP. A total of 20 out of these 45 patients had HPR. Following administration of single oral dose of 60 mg PRT 128, platelet function was assessed at baseline, 4 hours, 6 hours, and 24 hours post-dosing with several pharmacodynamic assays. Platelet reactivity fell within 4 hours of dosing, the earliest time point evaluated, and was reversible within 24 hours. Elinogrel thus reversibly overcomes high platelet reactivity seen as a result of nonresponsiveness to dual antiplatelet therapy with clopidogrel and aspirin. A simultaneous assessment of CYP2C19\*2 showed a more frequent association with HPR (77% versus 16%,  $P = 0.0004$ ).

The safety and feasibility of IV elinogrel before primary PCI for STEMI as an adjunctive antiplatelet therapy was studied in a Phase II trial (the Early Rapid Reversal of Platelet thrombosis with IV elinogrel before PCI to optimize reperfusion in acute myocardial infarction (ERASE MI)).<sup>41</sup> This was a pilot, randomized, placebo-controlled, dose-escalation study designed to study tolerability of single, IV elinogrel in escalating doses (10 mg, 20 mg, 40 mg, and 60 mg). All patients received aspirin, unfractionated heparin, and 600 mg

clopidogrel given after diagnostic angiogram but before PCI, and another 300 mg 4 hours after PCI. Other antithrombotic agents were not allowed while the use of glycoprotein IIb/IIIa inhibitors was strongly recommended. A total of 70 patients in four cohorts were enrolled. The primary outcome was in-hospital bleeding per the TIMI and GUSTO bleeding scales. The incidence of bleeding events was low, and similar with all doses of elinogrel versus placebo. There were no differences in serious adverse events with elinogrel compared to placebo.

A Phase II safety and efficacy study of elinogrel is currently ongoing (INNOVATE-PCI).<sup>42</sup> This is a multicenter, randomized, double-blind, triple-dummy, clopidogrel-controlled study of IV and oral PRT 060128 compared to clopidogrel in patients undergoing nonurgent (including elective) PCI. After diagnostic angiography, patients scheduled for nonurgent PCI will be randomized to clopidogrel or to one of three dose levels of elinogrel.

## Thrombin receptor antagonists

Thrombin is the main mediator of blood coagulation, first in the initial platelet activation, and then in the amplification and cleavage of fibrinogen to fibrin. Thrombin is also the most potent platelet activator, activating platelets at an extremely low concentration (lower than those required for activation of the coagulation cascade). Thrombin is not influenced by P2Y<sub>12</sub> receptor antagonists or aspirin. Selective blocking of the thrombin receptor effectively inhibits thrombin dependent platelet activation (the pathway involved in thrombosis). However, selective thrombin receptor blockade spares the collagen dependent activation of the pathway involved in hemostasis. This blockade does not affect the generation of fibrin by thrombin and thrombin's effects on coagulation factors are spared. Proteinase activated receptor-1 (PAR-1) is a high-affinity receptor for thrombin, and the key platelet thrombin receptor. Thrombin acts on PAR-1 by cleaving the N-terminal domain, and then exposing a tethered ligand that binds and activates the receptor. Thus, thrombin receptor antagonists by selectively inhibiting PAR-1 portend to cause a favorable balance of antithrombotic efficacy with less risk of bleeding. Inhibition of thrombin-mediated PAR-1 activation could add a new dimension in the domain of antiplatelet therapy. In addition, PAR-1 is also expressed in endothelial cells, cardiomyocytes, and smooth muscle cells. It acts as a modulator in acute inflammation and vascular repair. Thus, PAR-1 blockade may also be of interest in healing following PCI to reduce in-stent re-stenosis.<sup>43</sup>

SCH 530348 (also known as vorapaxar), an orally active, low-molecular weight, nonpeptide, competitive PAR-1 antagonist (tricyclic 3-phenylpyridine antagonist) potently inhibits thrombin-induced platelet aggregation without affecting measures of coagulation or increasing bleeding time. Both the association and dissociation rates of SCH 530348 with PAR-1 are slow, yet the inhibition is reversible and dose-dependent. A SCH 530348 loading dose of 20 mg achieves >80% inhibition of thrombin receptor activating peptide (TRAP)-induced platelet aggregation at 2 hours in approximately 50% of patients. With a 40 mg loading dose, nearly 70% patients had >80% inhibition after 1 hour and 96% by 2 hours. Both the 1 and 2.5 mg maintenance doses sustained >80% inhibition at 30 and 60 days in all patients tested. Recovery of platelet function to 50% of baseline after a single dose occurs slowly in a dose dependent manner (1, 2, and 3 weeks after 10, 20, and 40 mg doses respectively). In patients receiving a maintenance dose of 2.5 mg daily for 28 days, recovery of platelet function was observed 2 to 3 weeks after the last dose. SCH 530348 is rapidly absorbed, and has excellent bioavailability upon oral administration with a pharmacodynamic half life of greater than 7 days. It is metabolized and eliminated primarily by biliary and gastrointestinal routes. Renal clearance is less than 5%, thus clearance is no different among healthy and renally impaired patients. Exposure to SCH 530348 is dose dependent with an inter-individual variability of 20%–40% that does not depend on sex, ethnicity or fasting state. It is slowly, but extensively metabolized mostly via oxidation by the CYP3A4 system. Co-administration with ketoconazole and rifampin increases and decreases its exposure respectively.<sup>44,45</sup>

In the Phase II thrombin receptor antagonist – percutaneous coronary intervention (TRA-PCI) trial, the safety and efficacy of SCH 530348 among 1,031 patients undergoing nonurgent PCI or coronary angiography with intention to perform PCI were evaluated during a 60-day period.<sup>46</sup> In addition to aspirin and clopidogrel, and heparin or bivalirudin, patients were randomized to receive one of the three loading doses of SCH 530348 (10 mg, 20 mg, or 40 mg) or placebo at least 1 hour before PCI. Patients that underwent PCI (n = 573) were randomized to receive one of the three oral daily maintenance doses of SCH 530348 (0.5 mg, 1 mg, or 2.5 mg) or placebo for 60 days. The primary end point was the composite of TIMI major or minor bleeding in the PCI cohort. Overall, SCH 530348 did not cause an increase in the occurrence of the primary safety end point compared to placebo (3.3% with placebo versus 2.8% combined SCH 530348 groups).

The rates of bleeding by maintenance dose were also similar. Among patients undergoing CABG, CABG-related bleeding was similar between SCH 530348 and placebo. The secondary end point of death, major cardiovascular events or stroke was also similar between SCH 530348 and placebo.

Another Phase II clinical trial of 117 Japanese NSTEMI patients receiving aspirin, ticlopidine and heparin, found that the addition of SCH 530348 (20 mg or 40 mg loading followed by 1 mg or 2.5 mg maintenance dose) for 60 days did not cause an increase in the primary end point of TIMI major and minor bleeding compared to placebo.<sup>47</sup> Evidence from these two trials show that SCH 530348 when added to current standard of care therapy, does not cause increased bleeding, and may even offer a potential benefit of lowering thrombotic events.

Two Phase III trials are currently ongoing with SCH 530348. The Thrombin Receptor Antagonist for Secondary Prevention (TRA-2 degrees P-TIMI 50) trial is a double-blind, randomized, placebo controlled trial that will evaluate the efficacy of SCH 530348 plus standard-of-care therapies in secondary prevention with prior MI, stroke or peripheral vascular disease.<sup>45</sup> Planned enrollment will be 20,000 patients, randomized to receive SCH 530348 2.5 mg or placebo for a minimum of 1 year. The primary end point is the composite of cardiovascular death, MI, urgent coronary revascularization or stroke. The Thrombin Receptor Antagonist Clinical Event reduction in acute coronary syndrome (TRACER) is a double-blinded, placebo-controlled trial of >10,000 patients with NSTEMI that will compare 40 mg loading dose of SCH 530348 and 2.5 mg maintenance dose versus matching placebo in addition to aspirin and clopidogrel for at least 1 year.<sup>48</sup> The primary end point is the composite of cardiovascular death, MI, stroke, re-hospitalization for ACS, and urgent target revascularization during a minimum 1-year follow up. The estimated completion date is July 2011.

Another PAR-1 receptor inhibitor E5555 is currently being tested in Phase II safety studies. E5555 is a potent PAR-1 antagonist that targets the G-coupled receptor modulating thrombin-platelet-endothelial interactions. This drug was studied in a Phase II trial among healthy volunteers and patients with CAD treated with aspirin with or without clopidogrel.<sup>49</sup> Platelet activity was assessed after pre-incubation with escalating concentrations of E5555 (20 ng/ml, 50 ng/ml, and 100 ng/ml) in healthy volunteers, CAD patients treated with aspirin, and CAD patients treated with aspirin and clopidogrel combination (n = 10, for each group). E5555 inhibited a number of platelet biomarkers. Platelet

inhibition was usually moderate, and was not seemingly dose-dependent without TRAP stimulation. E5555 caused 10%–15% inhibition of ADP- and collagen-induced platelet aggregation in plasma, but not in whole blood. TRAP-induced aggregation was inhibited almost completely. E5555 potentiates the antiplatelet effects of aspirin alone, and also the combination of aspirin and clopidogrel. E5555 thus promises to be a potential addition to current antiplatelet therapy.

## Phosphodiesterase inhibitors

Cilostazol is a phosphodiesterase (PDE) III inhibitor that is currently indicated as a first line agent among patients with intermittent claudication due to its beneficial effect on increasing claudication distance.<sup>50</sup> In addition to its antiplatelet effects, it also possesses antiproliferative properties by reducing smooth muscle proliferation and intimal hyperplasia following endothelial injury. Recent studies have shown benefits of cilostazol as triple therapy in addition to aspirin and clopidogrel in reducing major cardiac adverse events in patients with acute coronary syndrome and following PCI.<sup>51,52</sup>

NT-702 (parogrelil hydrochloride), a selective phosphodiesterase (PDE)-3 inhibitor has vasodilatory as well as anti-inflammatory properties. In *in-vitro* studies, NT-702 potently and concentration-dependently inhibited human platelet aggregation induced by ADP, collagen, and thrombin. It is being studied for the treatment of claudication.<sup>53</sup>

## Thromboxane-prostaglandin receptor (TP) antagonist

TP receptor antagonists block the effects of thromboxane on platelets, monocytes, and vascular endothelium while allowing endothelial prostacyclin production via the COX-1 pathway. In addition, they also inhibit other thromboxane receptor ligands such as endoperoxidase, prostanoids, and isoprostanes. These agents thus cause vasodilation, and inhibit platelet aggregation.

Terutroban (formerly S18886) is an oral, reversible TP receptor antagonist with antithrombotic, antivasoconstrictive, and antiatherosclerotic properties.<sup>54</sup> Terutroban provides fast and potent antithrombotic effects comparable to that provided by aspirin–clopidogrel combination with a more favorable bleeding risk profile. In a pharmacokinetic–pharmacodynamic study, the maximal inhibitory effect was achieved in 1 hour after dosing in patients with peripheral arterial disease.<sup>55</sup> A large, Phase III trial (PERFORM) is currently comparing the efficacy and safety of terutroban versus aspirin in second-

ary prevention of cardiovascular and cerebrovascular events in patients with recent history of stroke or TIA.<sup>56,57</sup>

## Serotonin receptor blocker

Serotonin causes platelet aggregation and vasoconstriction. Sarpogrelate, a selective 5-hydroxytryptamine 2A (5-HT<sub>2A</sub>) receptor antagonist has been developed as an antiplatelet agent and has been used in Japan, China and Korea for many years in patients with peripheral vascular disease (PVD). In a Phase II study with this drug in Europe for intermittent claudication, this drug was well tolerated, and had shown a trend towards improving claudication distance.<sup>58</sup> This drug is shown to be noninferior and safer than aspirin in stroke patients.<sup>59</sup>

## Platelet adhesion antagonist

von Willebrand factor (vWF) is vital to platelet adhesion and aggregation. ARC-1779 is an optimized, second-generation, PEGylated aptamer that exerts a novel antithrombotic action through targeting the A1 domain of activated vWF and inhibiting the binding of platelet receptor glycoprotein Ib. It thus reduces platelet adhesion, and aggregation and thereby thrombus formation in arterial beds. ARC-1779 has potential therapeutic benefit in acute coronary syndromes and von Willebrand's disease, as well as in vWF-related platelet disorders such as thrombotic thrombocytopenic purpura (TTP) and other thrombotic microangiopathies. As an aptamer, the actions of ARC-1779, unlike other antiplatelet agents, can be readily reversed by binding to a complementary sequence of oligonucleotides; this ability offers potential therapeutic benefit in surgery.

In Phase I and II clinical trials, ARC-1779 has exhibited favorable pharmacokinetic, pharmacodynamic and safety properties in healthy individuals and patients with TTP. The first-in-human evaluation of ARC1779 has shown a dose- and concentration-dependent inhibition of vWF activity and platelet function with a duration of effect suitable for the intended clinical use in acute coronary syndromes.<sup>60</sup> Even in the setting of acute myocardial infarction, where vWF is increased, ARC1779 potently and specifically inhibits vWF activity and vWF dependent platelet function.<sup>61</sup> The study entitled, ARC1779 in Patients with acute myocardial infarction undergoing PCI (vITAL-1), has been terminated.<sup>62</sup>

## Nitric oxide-releasing aspirin

The addition of a nitric oxide-releasing moiety to aspirin would offer added benefit beyond the antiplatelet effects of aspirin since nitric oxide has a combination of antithrombotic, antiatherogenic and vasodilatory effects. NCX-4016 is a

prototype of this family of molecules. NCX-4016 undergoes first pass metabolism in the liver, and is metabolized to salicylic acid and NCX-4015. NCX 4016 has been effective in the inhibition of COX activity and also monocyte activation with tissue factor expression. In a rat model of carotid balloon injury treatment, NCX-4016 resulted in increased availability of nitric oxide and a lower rate of restenosis, when compared with that of aspirin. This effect was associated with diminished vascular smooth muscle cell proliferation. This agent also has a better gastrointestinal safety profile as compared to aspirin alone. In a prospective, randomized, single-blind, parallel-group trial among 44 patients with intermittent claudication comparing 4 weeks of therapy with NCX 4016 (800 mg BID) versus aspirin 100 mg daily, exercise induced endothelial dysfunction was prevented by NCX 4016, but not by aspirin.<sup>63</sup>

### Glycoprotein VI antagonist

After vessel wall disruption, platelets are adhered to subendothelial collagen through the glycoprotein VI (GPVI) receptors, and subsequently are activated. PR-15 is a soluble variant of GPVI receptor. It is a monoclonal antibody to GPVI receptor. It binds to exposed collagen and prevents GPVI mediated firm platelet adhesion and activation. Unlike other antiplatelet drugs, PR-15 targets receptors that are found on the activated platelets, which may potentially reduce the risk of bleeding associated with antiplatelet agents. *In vitro* studies have evaluated the ability of PR-15 to inhibit human platelet aggregation. The degree of reduction of aggregation produced was similar to the highest concentration regardless of collagen addition. PR-15 did not increase bleeding time *in vitro*. It has shown to be safe in animal models. A Phase I study of 30 healthy volunteers has been completed and the pharmacokinetics and pharmacodynamics (platelet aggregation) of six ascending single IV doses of PR-15 have been assessed.<sup>64</sup> This study has been terminated by the company and no further details are available.

### Cyclooxygenase inhibitors

Indobufen, a potent but reversible platelet COX-1 inhibitor has been shown to be effective as an antithrombotic agent. It was shown to be effective in prevention of graft occlusion after CABG and for the prevention of thromboembolic events in coronary artery disease.<sup>65</sup> Studies comparing indobufen to warfarin for prevention of stroke have not been very compelling for indobufen as it caused slightly higher stroke events.<sup>66</sup>

Table 3 details the nonpurine antagonists as they are being developed for clinical use. Table 4 enlists the pharmacological properties of promising antiplatelet agents.

### Discussion

Among the newer antiplatelet agents discussed in this review, prasugrel has already been approved for clinical use, while ticagrelor is expected to be available in the near future. Since prasugrel produces a more thorough inhibition of platelet aggregation with a faster onset of action without much variability in response, it should be the drug of choice in an ideal patient following percutaneous coronary intervention. However, prasugrel's use is somewhat limited by the fact that it causes more bleeding particularly among patients over 75 years of age, and patients weighing less than 60 kg. Prasugrel is contraindicated in patients with a prior history of stroke or TIA. Ticagrelor offers a distinct advantage over currently available P2Y<sub>12</sub> receptor antagonists, in that it is a reversible agent with a fast onset of action while not causing an increased risk of bleeding. The unique side effects of dyspnea, ventricular pauses and laboratory changes do not appear to be clinically significant, but warrant closer and long-term monitoring. While cangrelor is unique due to its IV formulation and short half-life, making it attractive for use during PCI, two Phase III trials showed no significant advantage of this drug over conventional therapy. Its role as a bridging

**Table 3** Newer antiplatelet compounds in clinical trials

Agent	Target	Phase of development	Indications
SCH530348	Thrombin receptor PAR-I	Phase III	Acute coronary syndrome Cardiovascular disease
E5555	Thrombin receptor, PAR-I	Phase II	Acute coronary syndrome
Terutroban (S18886)	Thromboxane receptor	Phase III	Stroke: secondary prevention
Cilostazol	Phosphodiesterase III	Phase IV	Approved for PVD Trials for PCI, stroke, DM
Sarpogrelate	5-HT <sub>2A</sub> serotonin inhibitor	Phase IV	Approved for PVD in Japan Trials for PCI, stroke

**Abbreviations:** DM, diabetes mellitus; PAR-I, protease-activated receptor-I; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; 5-HT<sub>2A</sub>, 5-hydroxytryptamine 2A.

**Table 4** Differential pharmacology of emerging antiplatelet agents

	Prasugrel	Cangrelor	Ticagrelor	Elinogrel	SCH 530348	Terutroban
Route of administration	PO	IV	PO	IV/PO	PO	PO
Loading dose	60 mg	4 mcg/kg/min	180 mg	80 mg IV	40 mg	10–30 mg
Maintenance dose	5–10 mg	4 mcg/kg/min	90 mg	50–150 mg BID (being defined)	2.5 mg	10–30 mg
Time to platelet inhibition	2 hrs	30 min	2 hrs	4 hrs	1 h	1 h
Half life	3.7 hrs	3–5 min	12 hrs	11 hrs	126–269 hrs	6–10 hrs

**Abbreviations:** BID, twice a day; IV, intravenous; PO, per oral.

therapy prior to surgery is being defined. Elinogrel on the other hand will be available in both an oral and IV form. If supported by the ongoing Phase II and III trials, elinogrel holds a great promise in interventional cardiology as this can be used as an IV form during PCI, transitioning to an oral form for maintenance therapy. The most ideal, and probably the most promising of all the emerging antiplatelet agents are the thrombin receptor antagonists. As these new agents have an excellent safety profile with less bleeding, a positive efficacy outcome from the ongoing trials will herald a new era in the field of antiplatelet therapy. The other agents discussed in this review await further clinical data to define their role in present atherosclerotic disease management.

## Disclosures

The authors report no conflict of interest in this work

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